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Treatment resistant depression (TRD): epidemiology, clinic, burden and treatment

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Treatment resistant depression (TRD): epidemiology, clinic, burden and treatment

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Editorial: Treatment resistant depression (TRD): epidemiology, clinic, burden and treatment

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Editorial on the Research Topic

Treatment resistant depression (TRD): epidemiology, clinic, burden and treatment

Depressive disorders are severe mental disorders, with a lifetime prevalence of 16% in the general population, associated with a significant personal and social burden. Median age of onset, basic sociodemographic and environmental correlates, symptom profile and severity of depression are generally comparable across different countries and cultures. Depressive disorders can be episodic or recurrent, depending on clinical, personal and social variables (1, 2).

Most patients with major depression report an incomplete and inadequate clinical remission, with many residual symptoms, cognitive dysfunctions and working impairment (3, 4); up to one out of three patients do not fully respond to currently available treatments. According to the FDA and EMA, patients are considered to have treatment-resistant depression (TRD) when they fail to respond to ≥2 successive adequate trials of antidepressants in a single episode (5, 6). The terminology, definition and clinical usefulness of the concept TRD is debatable for multiple reasons (7). First, difficult-to-treat depression or (multiple) treatment failure are probably less stigmatizing terms. Second, it has been demonstrated that there are no meaningful cut-offs between patients having experienced 2, 3 or 4 consecutive failures suggesting more continuous 'staging models' of treatment failures. Third, we lack studies to scientifically guide clinicians on what to do after 1, 2, 3 or more treatment failures (guidelines are rather consensus based than evidence based). Despite these conceptual comments, TRD is a common condition, with a prevalence rate ranging from 30- to 40% of patients treated with antidepressants, and it is associated with high levels of personal and societal burden. Treatment-resistant depression is associated with a significant burden for patients, caregivers and families, increasing disability and worsening quality of life. Although several sociodemographic, contextual and psychological factors (e.g., living alone or together, being employed or unemployed, cognitive functioning) (8, 9), and several clinical factors (e.g., unipolar or

bipolar depression, lifestyle behaviors) can influence clinical outcome in persons with depression, only a few factors are considered as predictive of non-response across multiple modalities of treatment (10–12). Therefore, there is the need to carry on further studies to investigate how to improve the personalized approach to people suffering from TRD.

In recent years, the therapeutic armamentarium of clinicians for treatment of depression has been improved by innovative pharmacological and non-pharmacological/brain stimulation therapies (ECT, TMS, VNS) (13). More recently, new pharmacological approaches focusing on psychedelic-derived drugs (e.g., ketamine, esketamine, psylocibin) have been studied, providing clinicians with new treatment choices.

Our Research Topic entitled "*Treatment Resistant Depression (TRD): epidemiology, clinic, burden and treatment*" includes more than 20 papers written by researchers and clinicians coming from different world regions. While some papers deal with the topic of diagnosis, early detection and clinical features of TRD (Pettorruso et al.; Liu and Read; Baune et al.; Mancuso et al.), the vast majority address the topic of treatment options for TRD, including brain stimulation therapies, novel pharmacological agents and new treatment-delivery modalities (Dragon et al.; Aboubakr et al.). Finally, we received and accepted some systematic reviews and metanalyses dealing with the role personality disorders in moderating the effectiveness of treatment for TRD (Więdłocha et al.), the efficacy of ketamine/esketamine for unipolar and bipolar depression (Rodolico et al.), the use of neuromodulation for treating TRD (Lan et al.), which complement research-driven data with those derived from real-world trials (Chrenek et al.; Menculini et al.; Di Vincenzo et al.; Pessina et al.).

Given the high number of submissions and of accepted papers of extremely good quality, we can definitely consider that the present Research Topic has been extremely successful. However, despite a growing interest on TRD (from its definition to the diagnosis and to treatment options), information collected cannot be considered as conclusive yet, but can represent the basis for future studies. We are extremely grateful to all researchers, patients and caregivers that have participated in these studies, and we are committed to further increase the knowledge in the field.

Author contributions

AF: Writing – original draft, Writing – review & editing. KD: Writing – review & editing. VM: Writing – review & editing. GM: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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References

1. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412.

2. Sampogna G, Toni C, Catapano P, Della Rocca B, Di Vincenzo M, Luciano M, et al. New trends in personalized treatment of depression. *Curr Opin Psychiatry*. (2024) 37:3–8. doi: 10.1097/YCO.0000000000000903

3. Luciano M, Sampogna G, Della Rocca B, Simonetti A, De Fazio P, Di Nicola M, et al. The impact of affective temperaments on suicidal ideation and behaviors: results from an observational multicentric study on patients with mood disorders. *Brain Sci*. (2023) 13:117. doi: 10.3390/brainsci13010117

4. Demyttenaere K. What is treatment resistance in psychiatry? A "difficult to treat" concept. *World Psychiatry*. (2019) 18:354–5. doi: 10.1002/wps.20677

5. Food and Drug Administration. (2019). Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified (Accessed February 21, 2025).

6. European Medicine Agency. Available online at: https://www.ema.europa.eu/en/medicines/human/EPAR/spravato (Accessed February 21, 2025).

7. Demyttenaere K, Van Duppen Z. The impact of (the concept of) treatment resistant depression: an opinion review. *Int J Neuropsychopharm*. (2019) 22:85–92.

8. Di Vincenzo M, Sampogna G, Della Rocca B, Brandi C, Mancuso E, Landolfi L, et al. What influences psychological functioning in patients with mood disorders? The role of clinical, sociodemographic, and temperamental characteristics in a naturalistic study. *Ann Gen Psychiatry*. (2022) 21:51. doi: 10.1186/s12991-022-00428-9

9. Sampogna G, Di Vincenzo M, Della Rocca B, Mancuso E, Volpicelli A, Perris F, et al. Physical comorbidities in patients with severe mental disorders: a brief narrative review on current challenges and practical implications for professionals. *Riv Psichiatr*. (2022) 57:251–7. doi: 10.1708/3922.39071

10. Medeiros GC, Demo I, Goes FS, Zarate CA Jr, Gould TD. Personalized use of ketamine and esketamine for treatment-resistant depression. *Transl Psychiatry*. (2024) 14:481. doi: 10.1038/s41398-024-03180-8

11. Nobile B, Gourguechon-Buot E, Malestroit M, Olié E, Haffen E, Gorwood P, et al. Does depression with current suicidal ideation lead to treatment-resistant depression? Two large naturalistic cohorts of outpatients with depression and current suicidal ideation. *Psychiatry Res*. (2024) 342:116249.

12. La Verde M, Luciano M, Fordellone M, Sampogna G, Lettieri D, Palma M, et al. Postpartum depression and inflammatory biomarkers of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and monocyte-lymphocyte ratio: A prospective observational study. *Gynecol Obstet Invest*. (2024) 89:140–9. doi: 10.1159/000536559

13. McLachlan G. Treatment resistant depression: what are the options? *BMJ*. (2018) 363:k5354. doi: 10.1136/bmj.k5354

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Efficacy and safety of intermittent theta burst stimulation versus high-frequency repetitive transcranial magnetic stimulation for patients with treatment-resistant depression: a systematic review

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Objective: Intermittent theta-burst stimulation (iTBS), which is a form of repetitive transcranial magnetic stimulation (rTMS), can produce 600 pulses to the left dorsolateral prefrontal cortex (DLPFC) in a stimulation time of just over 3 min. The objective of this systematic review was to compare the safety and efficacy of iTBS and high-frequency (≥ 5 Hz) rTMS (HF-rTMS) for patients with treatment-resistant depression (TRD).

Methods: Randomized controlled trials (RCTs) comparing the efficacy and safety of iTBS and HF-rTMS were identified by searching English and Chinese databases. The primary outcomes were study-defined response and remission.

Results: Two RCTs ($n = 474$) investigating the efficacy and safety of adjunctive iTBS ($n = 239$) versus HF-rTMS ($n = 235$) for adult patients with TRD met the inclusion criteria. Among the two included studies (Jadad score = 5), all were classified as high quality. No group differences were found regarding the overall rates of response (iTBS group: 48.0% versus HF-rTMS group: 45.5%) and remission (iTBS group: 30.0% versus HF-rTMS group: 25.2%; all $Ps > 0.05$). The rates of discontinuation and adverse events such as headache were similar between the two groups (all $Ps > 0.05$).

Conclusion: The antidepressant effects and safety of iTBS and HF-rTMS appeared to be similar for patients with TRD, although additional RCTs with rigorous methodology are needed.

KEYWORDS

intermittent theta burst stimulation, high-frequency rTMS, treatment-resistant depression, systematic review, response

Introduction

Depression is a leading cause of disability worldwide and a major contributor to the global burden of disease; it is estimated to be the strongest contributor among developed countries by the end of 2030 (1). Major depressive disorder (MDD) has an estimated lifetime prevalence of 3.4% and a 12-month prevalence of 2.1% according to the latest national epidemiological survey from China (2). Over 700,000 people die by suicide every year, and more than half of these deaths are caused by depression (3). Currently, traditional treatments for MDD include antidepressant medication and psychotherapy, but more than one-third of patients fail to respond to either pharmacotherapy or psychotherapy (4–6). Similarly, up to 30% of patients do not achieve clinical remission (7, 8). In addition, multiple side effects of medication could lead to a poor quality of life and reduced treatment adherence (9). There is still a lack of effective strategies for addressing treatment-resistant depression (TRD). Therefore, new treatment modalities for patients with TRD are urgently needed.

Noninvasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) (10), transcranial direct current stimulation (tDCS) (11), and transcranial alternating current stimulation (tACS) (12), provide a nonpharmacological alternative for MDD. High-frequency (≥ 5 Hz) repetitive transcranial magnetic stimulation (HF-rTMS) was approved by the Food and Drug Administration (FDA) as a noninvasive brain stimulation technique for TRD in 2008 (13). Evidence for the supremacy of active rTMS over sham stimulation has been accumulating for nearly 20 years (10, 14). A recent study analyzing 81 randomized clinical trials (RCTs) found that active rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) led to a higher rate of clinical remission and response compared to sham stimulation (15). However, a retrospective study found that only 214/730 depressed patients (29.3%) obtained antidepressant response to HF-rTMS, showing that not all patients with MDD could benefit from HF-rTMS (16). In particular, the antidepressant effects of rTMS were not evident in patients with high resistance to prior antidepressant treatments (17). Given that the standard FDA-approved HF-rTMS protocol requires 37.5 min per session and a long treatment course (5 times per week and lasting 4–6 weeks) (18), this approach may increase the daily transport burden and inconvenience for full-time patients, thereby reducing the clinical feasibility of conventional rTMS (19).

New efficient strategies for enhancing the therapeutic efficiency of rTMS are a hot topic in current research and have shown significant clinical value. As a novel and potentially beneficial form of TMS, theta-burst stimulation (TBS) including continuous TBS (cTBS), intermittent TBS (iTBS), bilateral TBS (bTBS), and intermediate TBS (imTBS) have been popularly used in clinical practice (20). Notably, iTBS can produce 600 pulses in a total stimulation time of 3 min 9 s (20), which was also approved by the FDA in 2018 for the treatment of TRD (21). Previous pilot studies have shown that active iTBS is superior to sham stimulation for TRD (22–24). A retrospective study initially investigating the antidepressant outcomes of iTBS versus HF-rTMS over the left DLPFC found that 3-min iTBS protocols may be as effective as HF-rTMS protocols (25). Two randomized controlled studies (RCTs) consistently reported similar antidepressant effects and safety with iTBS and HF-rTMS as an adjunctive treatment for patients with TRD (26, 27). For example, Blumberger et al. carried out a large multicentre RCT that confirmed that iTBS over the left DLPFC as an add-on therapy was noninferior to HF-rTMS as measured by the Hamilton Rating Scale for Depression (HRSD) for the treatment of patients with TRD (26). Similarly, a recently published study showed similar response rates (36.7% versus 33.3%) and remission rates (18.5% versus 14.8%) as evaluated by the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients suffering from TRD treated with iTBS and HF-rTMS (27). The 3-min iTBS protocol seems to be an optimized solution for reducing depressive symptoms, as it saves time and improves acceptability in the treatment of TRD when compared to traditional HF-rTMS.

To date, no systematic review investigating the safety and antidepressant effects of iTBS versus HF-rTMS were published. To fill this gap, we performed this systematic review to evaluate the efficacy and safety of iTBS versus HF-rTMS in the treatment of patients with TRD. Based on the findings of Mutz et al.'s study (28), we hypothesized that iTBS has a similar antidepressant effect as HF-rTMS in adult patients with TRD.

Methods

Search strategy and screening criteria

Two researchers (X-JL and Z-JQ) systematically searched the Cochrane Library, PubMed, EMBASE, PsycINFO, Chinese Journal Net, and WanFang databases from inception to 19 November 2022 to identify relevant studies using the following search terms: "("intermittent theta-burst stimulation" OR (intermittent* AND "theta-burst stimulation") OR iTBS)" AND (trans-cranial magnetic stimulation OR transcranial magnetic stimulation OR rTMS OR TMS) AND (depress* OR dysphor* OR melanchol* OR antidepress*). Additionally, the references of identified RCTs (26, 27) and relevant articles (29, 30) were manually searched to identify missing studies on the safety and efficacy of iTBS versus HF-rTMS for TRD.

As recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines (31), any published RCTs comparing iTBS and HF-rTMS for TRD were included when they met the following inclusion criteria, which were developed based on the *PICOS* principles: *P*articipants: adult patients (more than 18 years) with a primary diagnosis of TRD defined by the respective studies; *I*ntervention: treatments as usual (TAU) plus active iTBS; *C*omparison: TAU plus HF-rTMS (≥ 5 Hz); *O*utcomes: the primary outcomes of interest were the study-defined response and study-defined remission as measured by HRSD or MADRS; secondary results were the rates of discontinuation and adverse events; *S*tudy: only published RCTs comparing the safety and efficacy of iTBS and HF-rTMS for patients with TRD were eligible for inclusion in this systematic review. Numerous studies have found that a standard run of iTBS (600 pulses/session) presents similar or more potent excitatory effects in brain regions than conventional rTMS (32–34). As recommended previously (20, 26), the 3-min protocol of iTBS has a unique advantage in reducing treatment time. Thus, only studies examining daily treatment using a standard dose of 600 pulses of iTBS were included. Studies focusing on other modalities of iTBS, such as accelerated iTBS (≥2 sessions/day) (35) and prolonged iTBS (1800 pulses per session) (36), were excluded. Review articles, meta-analyzes, and case reports or case series were also excluded.

Data extraction

Data extraction for each included RCT was conducted by two independent researchers (X-JL and Z-JQ) using a standardized Microsoft Excel sheet, focusing on the following subjects: study design, participant characteristics, parameters of iTBS and HF-rTMS, and treatment outcomes from the original research. Any differences in data entry between the two researchers (X-JL and Z-JQ) were discussed with a senior author (D-BC), if necessary. For the missing information or clarification, we would contact the author(s) by email or telephone.

Study quality assessment

Two researchers (X-JL and Z-JQ) independently assessed the quality of the included RCTs using the Jadad scale (37) and Cochrane risk of bias tool (38). RCTs with a Jadad score ≥ 3 were considered to be of high quality (39). In addition, the overall evidence level and strength for all primary and secondary outcomes were rated by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (40).

Results

Literature search

We initially retrieved 959 articles by searching the above databases. Ultimately, 2 RCTs (26, 27) met the inclusion criteria of the present systematic review. The study selection process is presented in Figure 1.

The characteristics of the included studies

Table 1 provides a summary of clinical characteristics and the detailed treatment protocols for each included RCT (26, 27). Two RCTs ($n = 474$) compared the efficacy and safety of iTBS ($n = 239$) and HF-rTMS ($n = 235$) for adult patients with TRD. In the two RCTs, the dose of iTBS (50 Hz) was 600 pulses per session, and the doses of HF-rTMS ranged from 1,600 to 3,000 pulses per session. Participants in iTBS groups experienced a total dose of 12,000 pulses in both RCTs, and the total dose of HF-rTMS varied from 32,000 to 60,000 pulses. Their mean duration of illness ranged from 19.5 to 23.3 months, and the proportion of male patients with TRD was between 31.7% and 40.6%. The treatment duration in both studies was 20 days.

Study quality assessment

Figure 2 presents the Cochrane risk of bias for the two included RCTs. Two RCTs (26, 27) were judged to be low risk regarding selection bias, blinding, attrition and reporting bias. As shown in Table 1, the Jadad scores of the two studies (26, 27) were 5 points (high quality). On the basis of the GRADE guidelines, the overall evidence level for the 17 primary and secondary outcomes of the two included RCTs (26, 27) ranged from "moderate" (5.9%, 1/17) to "high" (94.1%, 16/17; Supplementary Table S2).

Primary outcomes

As shown in Table 2, two RCTs (26, 27) reported the rates of study-defined remission and response at the intervention endpoint. Among the two RCTs, no group differences were found regarding the overall rates of response (iTBS group: 48.0% versus HF-rTMS group: 45.5%) and remission (iTBS group: 30.0% versus HF-rTMS group: 25.2%; all $Ps > 0.05$).

Secondary outcomes

No group differences were found in terms of discontinuation rates (iTBS group: 7.9% versus HF-rTMS group: 6.8%) or adverse events (e.g., headache, dizziness, nausea, and fatigue) in the two included RCTs (26, 27) (all $Ps > 0.05$). Details are presented in Supplementary Table S1.

Discussion

To the best of our knowledge, this study is the first systematic review of RCTs to investigate the efficacy and safety of iTBS versus HF-rTMS for patients suffering from TRD. As a result, only two RCTs (26, 27) involving 474 subjects were included. The two included RCTs were published within the last 5 years, suggesting that iTBS and HF-rTMS for subjects suffering from TRD is a new and clinically important topic. The following two major findings of this systematic review included: (1) the antidepressant effects of iTBS and HF-rTMS for patients with TRD were equivalent, and (2) iTBS using 600 pulses per session for patients with TRD among adults was relatively safe and well tolerated.

As reported in this systematic review, the two included RCTs (26, 27) used a standard operation of 600 pulses of unilateral iTBS over the left DLPFC for adult patients with TRD and achieved a similar rate of antidepressant response and remission when compared to HF-rTMS. One RCT (27) examining the long-term effectiveness of iTBS versus HF-rTMS in patients with TRD found that both groups had a similar significant improvement of depressive symptoms at 6 months. Similarly, a large network meta-analysis (113 trials, 6,750 participants) found that iTBS was superior to sham stimulation and had similar antidepressant effects as conventional rTMS (including HF-rTMS, low-frequency rTMS, and bilateral rTMS) (28). Interestingly, a similar antidepressant efficacy between intensive/accelerated iTBS and HF-rTMS for the treatments of patients with TRD were reported by Fitzgerald et al.'s study (41). Taken together, these findings provide initial support for the role of iTBS as a potential treatment with greater capacity in a shorter stimulation duration for patients with TRD.

As a new form of rTMS, the high-frequency stimulation of iTBS uses 50-Hz triplet bursts that mimic endogenous theta rhythms and influence brain synaptic plasticity more quickly and

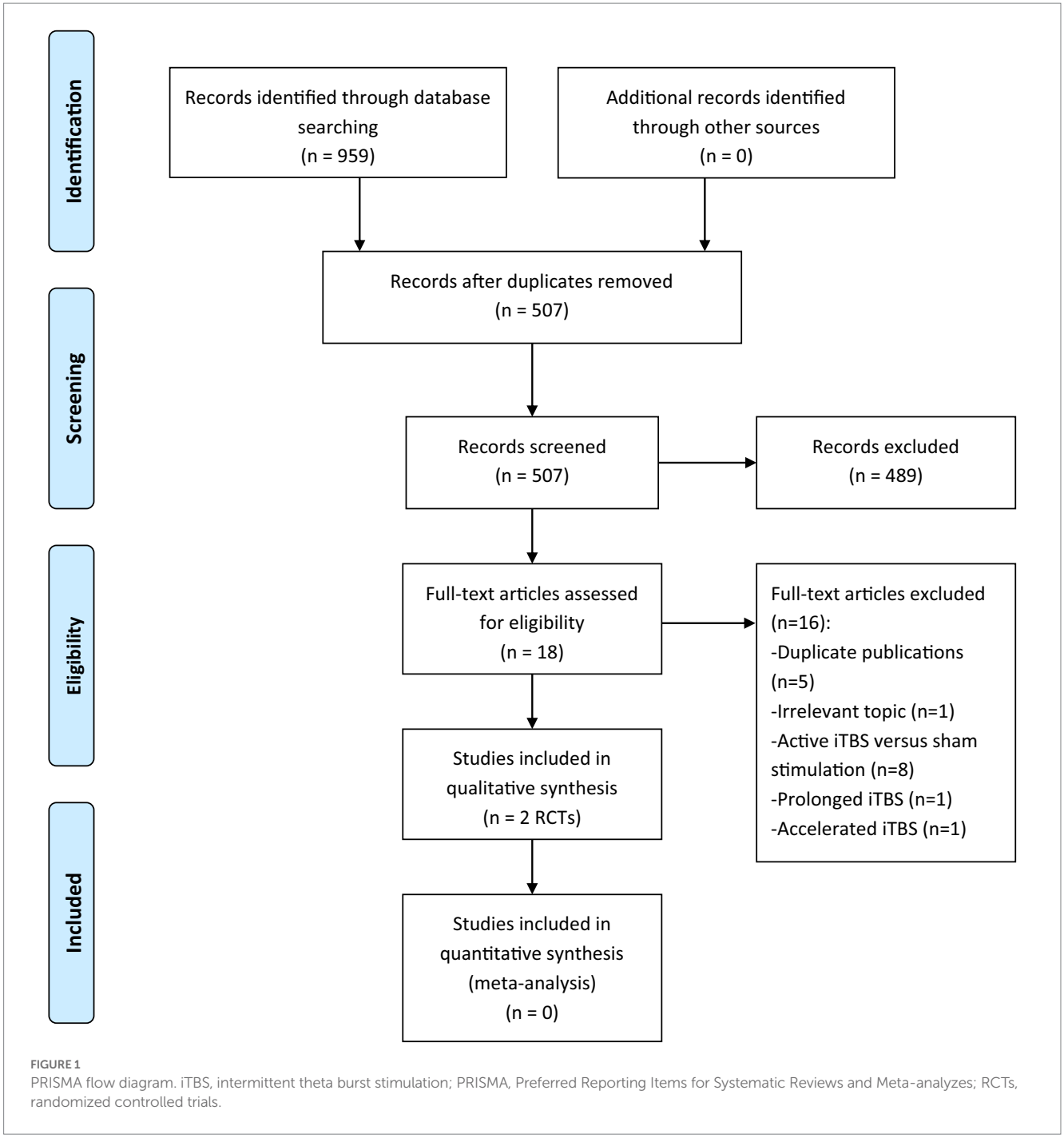

FIGURE 1
PRISMA flow diagram. iTBS, intermittent theta burst stimulation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyzes; RCTs, randomized controlled trials.

with longer-lasting effects (42). Previous preclinical studies suggested that the antidepressant effects of iTBS may be related to neuroplasticity (20). Lazzaro et al. (32) found that a 3-min iTBS treatment protocol with 600 pulses per session achieves a similar effect on neural plasticity as the 37.5-min HF-rTMS treatment. Although the recommended iTBS parameters for motor cortex experiments were 600 pulses per session (20), whether it is the optimal dosing strategy for the treatment of TRD is currently unclear. A previous study suggested that increasing the total pulses per session or the number of daily sessions of rTMS may achieve larger antidepressant efficacy (43). In contrast to the standard dose of 600 pulses of iTBS, Li et al. (36) found that a 2-week prolonged iTBS (piTBS) monotherapy with 1800 pulses per session showed the same antidepressant efficacy within a shorter treatment time when compared to the conventional 4–6 week rTMS strategy. However, an exploratory study discovered that doubling the number of iTBS pulses did not enhance the excitatory effect and may have an inhibitory effect (44). Blumberger et al. (45) compared once-daily iTBS and twice-daily iTBS for patients with TRD, finding that using more than 600

TABLE 1 Participant characteristics and HF-rTMS/iTBS parameters of each included study in this systematic review.

Study (country)	Sample size (n)[a]	-Diagnostic criteria-setting (%)-diagnosis (%)	-Illness duration (months)-male[a] (%)	Mean age[a] (range)	Medication status	-Treatment duration (days)-site (rTMS/iTBS)	-Intensity (%RMT)-frequency (Hz)		-Stimulus time/per session-train duration-intertrain duration		-Pulses per session-number of sessions-total pulses		Jadad score
							iTBS	HF-rTMS	iTBS	HF-rTMS	iTBS	HF-rTMS	
Blumberger et al. (26) (Canada)	Total: 414 iTBS: 209 HF-rTMS: 205	-DSM-IV-TR or ICD-10[b] -NR -TRD (100)	−23.3 −40.6	42.4 (18–65) years	Psychotropic allowed	−20 -L-DLPFC	−120 −50	−120 −10	−3 min 9 s −2 s −8 s	−37.5 min −4 s −26 s	−600 −20 −12,000	−3,000 −20 −60,000	5
Bulteau et al. (27) (France)	Total: 60 iTBS: 30 HF-rTMS: 30	-DSM-5 -In (5) and outpatients (95) -TRD (100)	−19.5 −31.7	52.3 (18–75) years	Psychotropic allowed	−20 -L-DLPFC	−80 −50	−110 −10	-NR -NR -NR	−20 min −4 s −28 s	−600 −20 −12,000	−1,600 −20 −32,000	5

[a]Overall number of participants.

[b]Diagnosis verified through the Mini International Neuropsychiatric Interview (MINI). DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; ICD-10, International Classification of Diseases, 10th edition; iTBS, intermittent theta burst stimulation; L-DLPFC, left dorsolateral prefrontal cortex; min, minutes; NR, not reported; rTMS, repetitive transcranial magnetic stimulation; RMT, resting motor threshold; s, seconds; TRD, treatment-resistant depression.

iTBS pulses or administering over multiple sessions per day did not produce additional benefits. Interestingly, a recent meta-analysis (5 RCTs, 239 participants) found that active accelerated iTBS (applied 2–10 sessions of iTBS daily treatment with 24,000–90,000 total pulses) achieved a larger response rate in treating major depressive episodes when compared to sham stimulation (46). To date, the heterogeneity of iTBS stimulation parameters such as treatment pulses (600–1800 pulses per session) and stimulation sessions (1–10 sessions per day) has caused some confusion in the clinical practice. Additionally, it is worth noting that prolonging the duration of iTBS stimulation or increasing the number of treatment sessions per day in a patient will be somewhat challenging for the clinical agency. Nevertheless, there is a lack of head-to-head studies comparing the safety and antidepressant effects of iTBS (daily treatment of 600 pulses) with either piTBS or accelerated iTBS for patients with TRD. Thus, further RCTs with high quality are warranted to explore the optimum protocol of iTBS in treating MDD.

Apart from the antidepressant effects, adjunctive TBS may improve the neurocognitive function of psychiatric disorders (47, 48), which has important clinical therapeutic significance. A recent meta-analysis found that iTBS shown a positive effect in enhancing neurocognitive function in healthy adults (49). The findings were consistent with a recent systematic review investigating adjunctive iTBS for neurocognitive dysfunction in elderly patients with schizophrenia (50). However, data on the neurocognitive effects of iTBS versus HF-rTMS were not reported in the two included RCTs (26, 27).

In this systematic review, similar rates of discontinuation and adverse events were observed in the two groups, indicating high clinical acceptability and feasibility of iTBS in the treatment of patients suffering from TRD. This result was consistent with a previous review that reported that iTBS as an add-on therapy was relatively safe for psychiatric disorders and found no serious adverse events except for mild side effects (e.g., headache, dizziness, nausea, and discomfort) (48). Oberman et al. (51) conducted a study focusing on the safety of TBS for the general population and found that only a few subjects suffered from mild adverse events. Similarly, studies focused on other modalities of iTBS, such as piTBS or accelerated iTBS, which were also confirmed to be safe and well tolerated in treating patients with MDD (22, 35, 36).

Overall, the primary strength of this systematic review is that two included RCTs (Jadad score = 5) were classified as high quality. However, there were several limitations in this systematic review that should be noted. First, although a comprehensive systematic search was conducted, only a relatively small number of studies (2 RCTs) met the inclusion criteria for qualitative synthesis. Second, a meta-analysis could not be conducted due to the significant heterogeneity between each included RCT. Third, a medication effect cannot be ruled out because patients remain on their ongoing pharmacological treatment. Fourth, this systematic review only included studies that used the standard dosage of 600 pulses of iTBS for daily treatment, excluding other patterns of iTBS, such as prolonged iTBS and accelerated iTBS. Fifth, all patients in the two included RCTs suffered from treatment-resistant unipolar depression, suggesting that our findings may not be generalizable to treatment-resistant bipolar depression. Finally, this systematic review has not been registered.

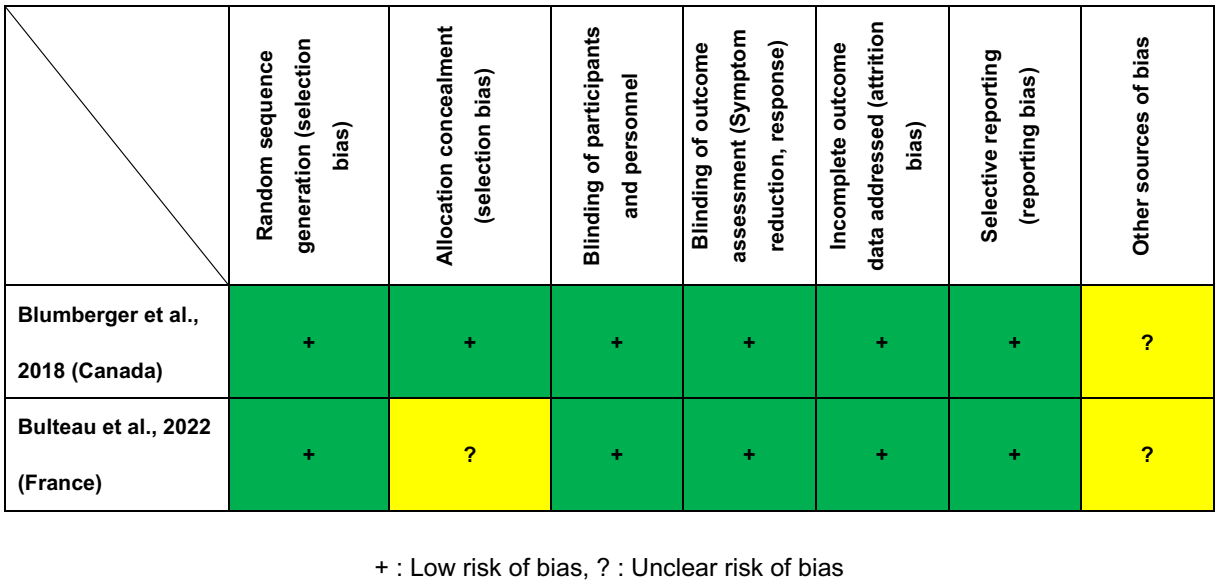

FIGURE 2
Cochrane risk of bias. +, Low risk of bias; ?, Unclear risk of bias.

TABLE 2 iTBS versus HF-rTMS for patients with TRD: study-defined response and remission.

Study	Treatment outcomes	iTBS group	HF-rTMS group	Findings[e]
Blumberger et al. (26) (Canada)	Study-defined response[a]	49.2% (95/193)	47.4% (91/192)	$p > 0.05$
Bulteau et al. (27) (France)	Study-defined response[b]	36.7% (12/30)	33.3% (10/30)	$P > 0.05$
	Total	48.0% (107/223)	45.5% (101/222)	$P > 0.05$
Blumberger et al. (26) (Canada)	Study-defined remission[c]	31.6% (61/193)	26.6% (51/192)	$P > 0.05$
Bulteau et al. (27) (France)	Study-defined remission[d]	18.5% (6/30)	14.8% (5/30)	$P > 0.05$
	Total	30.0% (67/223)	25.2% (56/222)	$P > 0.05$

[a]Defined as ≥ 50% reduction from the HRSD total score at baseline.
[b]Defined as ≥ 50% reduction from the MADRS total score at baseline.
[c]Defined as HRSD scores < 8.
[d]Defined as MADRS scores < 8.
[e]Reflect the differences between iTBS groups and HF-rTMS groups at the treatment endpoints. HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; HRSD, Hamilton Rating Scale for Depression; iTBS, intermittent theta burst stimulation; MADRS, Montgomery-Åsberg Depression Rating Scale; TRD, treatment-resistant depression.

Conclusion

The antidepressant efficacy and safety of iTBS and HF-rTMS appeared to be similar for patients with TRD, although further RCTs with rigorous methodology are needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

X-JL, Q-ML, and Z-JQ selected studies. X-JL and Z-JQ extracted the data. D-BC reviewed all the data and helped mediate disagreements. X-JL and X-HY wrote the first draft. WZ edited the manuscript. All authors contributed to the interpretation of data and approved the last manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

1. World Health Organization. *Depression and other common mental disorders: global health estimates*. Geneva: World Health Organization. (2017). Available at: https://www.who.int/key-messages#.

2. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry*. (2019) 6:211–24. doi: 10.1016/S2215-0366(18)30511-X

3. World Health Organization. *Suicide worldwide in 2019: global health estimates*. Geneva: World Health Organization. (2021). Available at: https://www.who.int/publications/i/item/9789240026643.

4. Cuijpers P, Stringaris A, Wolpert M. Treatment outcomes for depression: challenges and opportunities. *Lancet Psychiatry*. (2020) 7:925–7. doi: 10.1016/S2215-0366(20)30036-5

5. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the acnp task force on response and remission in major depressive disorder. *Neuropsychopharmacology*. (2006) 31:1841–53. doi: 10.1038/sj.npp.1301131

6. Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA. A systematic review of comparative efficacy of treatments and controls for depression. *PLoS One*. (2012) 7:e41778. doi: 10.1371/journal.pone.0041778

7. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (trd)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol*. (2007) 17:696–707. doi: 10.1016/j.euroneuro.2007.03.009

8. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a star*d report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

9. Solmi M, Fornaro M, Ostinelli EG, Zangani C, Croatto G, Monaco F, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. *World Psychiatry*. (2020) 19:214–32. doi: 10.1002/wps.20765

10. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. (2010) 67:507–16. doi: 10.1001/archgenpsychiatry.2010.46

11. Meron D, Hedger N, Garner M, Baldwin DS. Transcranial direct current stimulation (tdcs) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. *Neurosci Biobehav Rev*. (2015) 57:46–62. doi: 10.1016/j.neubiorev.2015.07.012

12. Zheng W, Cai D-B, Nie S, Chen J-H, Huang X-B, Goerigk S, et al. Adjunctive transcranial alternating current stimulation for patients with major depressive disorder: a systematic review and meta-analysis. *Front Psych*. (2023) 14:1154354. doi: 10.3389/fpsyt.2023.1154354

13. Holtzheimer PE, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. *Depress Anxiety*. (2010) 27:960–3. doi: 10.1002/da.20731

14. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. (2007) 62:1208–16. doi: 10.1016/j.biopsych.2007.01.018

15. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. *JAMA Psychiat*. (2017) 74:143–52. doi: 10.1001/jamapsychiatry.2016.3644

16. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rtms) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med*. (2014) 44:225–39. doi: 10.1017/S0033291713000512

17. Hsu JH, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Blumberger DM. Impact of prior treatment on remission with intermittent theta burst versus high-frequency repetitive transcranial magnetic stimulation in treatment resistant depression. *Brain Stimul*. (2019) 12:1553–5. doi: 10.1016/j.brs.2019.07.011

18. Cheng C-M, Li C-T, Tsai S-J. Current updates on newer forms of transcranial magnetic stimulation in major depression. *Adv Exp Med Biol*. (2021) 1305:333–49. doi: 10.1007/978-981-33-6044-0_18

19. Frey J, Najib U, Lilly C, Adcock A. Novel tms for stroke and depression (notsad): accelerated repetitive transcranial magnetic stimulation as a safe and effective treatment for post-stroke depression. *Front Neurol*. (2020) 11:788. doi: 10.3389/fneur.2020.00788

20. Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. (2005) 45:201–6. doi: 10.1016/j.neuron.2004.12.033

21. Caulfield KA. Is accelerated, high-dose theta burst stimulation a panacea for treatment-resistant depression? *J Neurophysiol*. (2020) 123:1–3. doi: 10.1152/jn.00537.2019

22. Li C-T, Chen M-H, Juan C-H, Huang H-H, Chen L-F, Hsieh J-C, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain: a. *J Neurol*. (2014) 137:2088–98. doi: 10.1093/brain/awu109

23. Cheng C-M, Juan C-H, Chen M-H, Chang C-F, Lu HJ, Su T-P, et al. Different forms of prefrontal theta burst stimulation for executive function of medication-resistant depression: evidence from a randomized sham-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*. (2016) 66:35–40. doi: 10.1016/j.pnpbp.2015.11.009

24. Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. *Int J Neuropsychopharmacol*. (2010) 13:387–93. doi: 10.1017/S1461145710000027

25. Bakker N, Shahab S, Giacobbe P, Blumberger DM, Daskalakis ZJ, Kennedy SH, et al. RTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. *Brain Stimul*. (2015) 8:208–15. doi: 10.1016/j.brs.2014.11.002

26. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (three-d): a randomised non-inferiority trial. *Lancet (London, England)*. (2018) 391:1683–92. doi: 10.1016/s0140-6736(18)30295-2

27. Bulteau S, Laurin A, Pere M, Fayet G, Thomas-Ollivier V, Deschamps T, et al. Intermittent theta burst stimulation (itbs) versus 10 Hz high-frequency repetitive transcranial magnetic stimulation (rtms) to alleviate treatment-resistant unipolar depression: a randomized controlled trial (theta-dep). *Brain Stimul*. (2022) 15:870–80. doi: 10.1016/j.brs.2022.05.011

28. Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ*. (2019) 364:l1079. doi: 10.1136/bmj.l1079

29. Blumberger DM, Mulsant BH, Thorpe KE, McClintock SM, Konstantinou GN, Lee HH, et al. Effectiveness of standard sequential bilateral repetitive transcranial magnetic stimulation vs bilateral theta burst stimulation in older adults with depression: the four-d randomized noninferiority clinical trial. *JAMA Psychiat*. (2022) 79:1065–73. doi: 10.1001/jamapsychiatry.2022.2862

30. Voigt JD, Leuchter AF, Carpenter LL. Theta burst stimulation for the acute treatment of major depressive disorder: a systematic review and meta-analysis. *Transl Psychiatry*. (2021) 11:330. doi: 10.1038/s41398-021-01441-4

31. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. (2009) 339:b2535. doi: 10.1136/bmj.b2535

32. Di Lazzaro V, Dileone M, Pilato F, Capone F, Musumeci G, Ranieri F, et al. Modulation of motor cortex neuronal networks by rtms: comparison of local and remote effects of six different protocols of stimulation. *J Neurophysiol*. (2011) 105:2150–6. doi: 10.1152/jn.00781.2010

33. Kaster TS, Downar J, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, et al. Trajectories of response to dorsolateral prefrontal rtms in major depression: a three-d study. *Am J Psychiatry*. (2019) 176:367–75. doi: 10.1176/appi.ajp.2018.18091096

34. Si Y, Wu X, Li F, Zhang L, Duan K, Li P, et al. Different decision-making responses occupy different brain networks for information processing: a study based on eeg and tms. *Cereb Cortex*. (2019) 29:4119–29. doi: 10.1093/cercor/bhy294

35. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford neuromodulation therapy (snt): a double-blind randomized controlled trial. *Am J Psychiatry*. (2022) 179:132–41. doi: 10.1176/appi.ajp.2021.20101429

36. Li C-T, Cheng C-M, Chen M-H, Juan C-H, Tu P-C, Bai Y-M, et al. Antidepressant efficacy of prolonged intermittent theta burst stimulation monotherapy for recurrent depression and comparison of methods for coil positioning: a randomized, double-blind, sham-controlled study. *Biol Psychiatry*. (2020) 87:443–50. doi: 10.1016/j.biopsych.2019.07.031

37. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4

38. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. (2011) 343:d5928. doi: 10.1136/bmj.d5928

39. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet (London, England)*. (1997) 350:834–43.

40. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. (2011) 64:401–6. doi: 10.1016/j.jclinepi.2010.07.015

41. Fitzgerald PB, Chen L, Richardson K, Daskalakis ZJ, Hoy KE. A pilot investigation of an intensive theta burst stimulation protocol for patients with treatment resistant depression. *Brain Stimul*. (2020) 13:137–44. doi: 10.1016/j.brs.2019.08.013

42. Suppa A, Huang YZ, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimul*. (2016) 9:323–35. doi: 10.1016/j.brs.2016.01.006

43. Teng S, Guo Z, Peng H, Xing G, Chen H, He B, et al. High-frequency repetitive transcranial magnetic stimulation over the left dlpfc for major depression: session-dependent efficacy: a meta-analysis. *Eur Psychiatry*. (2017) 41:75–84. doi: 10.1016/j.eurpsy.2016.11.002

44. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Exp Brain Res*. (2010) 204:181–7. doi: 10.1007/s00221-010-2293-4

45. Blumberger DM, Vila-Rodriguez F, Wang W, Knyahnytska Y, Butterfield M, Noda Y, et al. A randomized sham controlled comparison of once vs twice-daily intermittent theta burst stimulation in depression: a Canadian rTMS treatment and biomarker network in depression (cartbind) study. *Brain Stimul*. (2021) 14:1447–55. doi: 10.1016/j.brs.2021.09.003

46. Cai D-B, Qin Z-J, Lan X-J, Liu Q-M, Qin X-D, Wang J-J, et al. Accelerated intermittent theta burst stimulation for major depressive disorder or bipolar depression: a systematic review and meta-analysis. *Asian J Psychiatr*. (2023) 85:103618. doi: 10.1016/j.ajp.2023.103618

47. Zheng LN, Guo Q, Li H, Li CB, Wang JJ. Effects of repetitive transcranial magnetic stimulation with different paradigms on the cognitive function and psychotic symptoms of schizophrenia patients. *Beijing Da Xue Xue Bao*. (2012) 44:732–6. doi: 10.3969/j.issn.1671-167X.2012.05.013

48. Rachid F. Safety and efficacy of theta-burst stimulation in the treatment of psychiatric disorders: a review of the literature. *J Nerv Ment Dis*. (2017) 205:823–39. doi: 10.1097/NMD.0000000000000742

49. Pabst A, Proksch S, Médé B, Comstock DC, Ross JM, Balasubramaniam R. A systematic review and meta-analysis of the efficacy of intermittent theta burst stimulation (itbs) on cognitive enhancement. *Neurosci Biobehav Rev*. (2022) 135:104587. doi: 10.1016/j.neubiorev.2022.104587

50. Zhang X, Yang X, Shi Z, Xu R, Tan J, Yang J, et al. A systematic review of intermittent theta burst stimulation for neurocognitive dysfunction in older adults with schizophrenia. *J Pers Med*. (2023) 13:485. doi: 10.3390/jpm13030485

51. Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *J Clin Neurophysiol*. (2011) 28:67–74. doi: 10.1097/WNP.0b013e318205135f

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Biological correlates of treatment resistant depression: a review of peripheral biomarkers

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Introduction: Many patients fail to respond to multiple antidepressant interventions, being defined as "treatment-resistant depression" (TRD) patients. TRD is usually associated with increased severity and chronicity of symptoms, increased risk of comorbidity, and higher suicide rates, which make the clinical management challenging. Efforts to distinguish between TRD patients and those who will respond to treatment have been unfruitful so far. Several studies have tried to identify the biological, psychopathological, and psychosocial correlates of depression, with particular attention to the inflammatory system. In this paper we aim to review available studies assessing the full range of biomarkers in TRD patients in order to reshape TRD definition and improve its diagnosis, treatment, and prognosis.

Methods: We searched the most relevant medical databases and included studies reporting original data on possible biomarkers of TRD. The keywords "treatment resistant depression" or "TRD" matched with "biomarker," "inflammation," "hormone," "cytokine" or "biological marker" were entered in PubMed, ISI Web of Knowledge and SCOPUS databases. Articles were included if they included a comparison with healthy controls (HC).

Results: Of the 1878 papers identified, 35 were included in the present study. Higher plasma levels of IL-6 and TNF-α were detected in TRD patients compared to HC. While only a few studies on cortisol have been found, four papers showed elevated levels of C-reactive protein among these patients and four articles focused on immunological cells. Altered kynurenine metabolism in TRD patients was reported in two studies, while contrasting results were found with regard to BDNF.

Conclusion: Only a few biological alterations correlate with TRD. TNF-α seems to be the most relevant biomarker to discriminate TRD patients from both HC and treatment-responsive MDD patients. Moreover, several discrepancies among studies have been found, due to methodological differences and the lack of a standardized diagnostic definition of TRD.

KEYWORDS

major depression, treatment resistant depression, TRD, biomarker, cytokines, inflammation

Introduction

Major Depressive Disorder (MDD) is a heterogeneous severe mental disorder, deriving from the interplay between genetic, environmental and psychological factors (1). More than 280 million people suffer from MDD, which is the primary cause of disability worldwide (2) and of significant impairment in daily functioning and quality of life (3, 4). At least 80% of patients with MDD experience work difficulties, problematic social interactions, and impaired daily life activities, making difficult the achievement of a full functional recovery (5, 6). Several effective pharmacological and psychosocial interventions are available for MDD, but many patients fail to respond to multiple antidepressant interventions, being defined as "treatment-resistant depression" (TRD) patients (7).

The first conceptualization of TRD dates back to 1970s as an attempt to overcome the limitation of the construct of "refractory depression" (8). Subsequently, Ban (9) argued that failure to respond to pharmacological treatment in patients with depression might reflect a different neurobiological substrate of depressive symptoms, compared to those patients who responded adequately to antidepressants. Accordingly, resistance to antidepressants would define for a distinct clinical subtype of depression. The first clinical definition of TRD was provided only in the late 90s by Thase and Rush (10), who described a sample of depressed patients who had not responded to at least two adequate trials of antidepressant medications, revitalizing the concept of TRD. Since then, the concept of TRD has been constantly refined (11, 12).

Currently, different definitions of TRD are available. The European Medicines Agency (EMA) defined resistance as a "failure to produce significant clinical results with a treatment of at least two different antidepressants (of the same or different classes) administered at the right doses and for an adequate amount of time, with verified patients' compliance to treatment," and is widely adopted as a standard definition of TRD in research settings (13). According to the Maudsley Staging Method, TRD is defined by five domains: time-course, severity, number of drugs, augmentative strategies, and use of ECT, with a maximum score of 15 (14). However, despite efforts, the definition of treatment resistant depression still presents several critical issues. In fact, some authors pointed out that the resistance construct can lead to a sense of nihilism in both patients and mental health professionals (15), and the construct of Difficult-To-Treat Depression (DTTD) would be preferable: while TRD focuses on a trial-and-error approach to find the right treatment, DTTD recognizes the importance of tailoring treatment to the needs of individual patients and considers a more comprehensive evaluation of patient's medical history, lifestyle, and other subjective variables (16, 17). However, more complex and accurate definitions are poorly represented in clinical trials (18).

The difficulties in increasing knowledge about epidemiology, clinical management, and treatment of TRD are partially due to the lack of a univocal definition of this syndrome, which is highly needed. In fact, resistance to antidepressants is associated with greater symptom severity and chronicity, increased risk of comorbid physical (19, 20) and mental disorders, and higher suicide rates (21). Thus, TRD might represent a distinct clinical subtype of depression, yet one of the more severe, with unique treatment challenges and implications (22, 23), or a more severe form of MDD at the extreme of the affective continuum.

In order to gain deeper insights into the presence of a distinct clinical phenotype of TRD with discernible biological foundations, in this paper we have investigated biomarkers, specifically those previously documented in the literature for their associations with TRD. Biomarker can be defined as "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention" (24). Biomarkers, as measurable molecular or cellular indicators, hold the potential to unravel the intricate interplay between genetic, physiological, and environmental factors that contribute to the manifestation of unique clinical profiles. These biomarkers serve as invaluable tools, facilitating the characterization, diagnosis, and understanding of the underlying biological mechanisms associated with a specific clinical phenotype. In the field of psychiatry, the practical application of biomarkers remains notably absent in clinical practice, primarily due to the limited supporting evidence in the literature. Biomarkers have demonstrated their transformative impact in various branches of medicine, including neurology and immunology, where they have facilitated early diagnosis, disease subtyping, treatment monitoring, prognosis assessment, and drug development.

However, efforts to distinguish between patients who will respond to treatment and those who will not have been unfruitful so far (25). Several studies have tried to identify the biological, psychopathological, and psychosocial correlates of depression, with particular attention to the dysfunction of the inflammatory system (26). Compared to patients with major depression who respond to pharmacological treatments, TRD patients have increased levels of proinflammatory cytokines, which indirectly reduce serotonin availability in the central nervous system (27) and the efficacy of antidepressant medications (28). Moreover, TRD is also associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis (29). A systematic review investigating the role of C-reactive protein (CRP) as a biomarker for MDD showed a low grade of inflammation was found in a percentage of MDD patients who were less responsive to treatment, suggesting that this could represent a subgroup of depressed patients with a different etiopathogenesis (30). Another studied biomarker is the brain-derived neurotrophic factor (BDNF), whose levels are significantly reduced in TRD patients compared to MDD, suggesting that the decreased levels of BDNF may be associated with biological resistance to traditional antidepressant treatments (31).

Taken together, available data suggest that chronic neuroinflammation might be implicated in the pathogenesis of MDD, with lower evidence about possible biomarkers of TRD (32). The identification of biomarkers of TRD holds relevant implications at clinical and research level. TRD biomarker could be used in clinical practice to identify in advance patients who are at higher risk to develop treatment resistance, facilitating the early detection of difficult to treat patients. Moreover, from a clinical perspective the availability of reliable biomarkers of TRD would be useful to assess a more precise prognosis of MDD patients, and to identify personalized and integrated treatments (which include psychotherapy and other psychosocial interventions) in order to reduce the risk of treatment resistance. At research level the identification of reliable biomarkers for TRD would be useful in order to develop new treatments strategies to be used in patients with TRD.

In this paper we review available studies assessing the full range of biomarkers compared to healthy controls in order to reshape TRD definition and improve its diagnosis, treatment, and prognosis.

Methods

The keywords "treatment resistant depression" OR "TRD" matched with "biomarker," "inflammation," "hormone," "cytokine" or "biological marker" were entered in the PubMed, ISI Web of Knowledge and SCOPUS databases for papers published from inception until April 6, 2023. Studies were included in the review if they: (1) included patients with a diagnosis of TRD; (2) assessed any biological marker for TRD; (3) included a control group of healthy subjects; (4) were written in English. Studies including other subsamples of patients (i.e., those with bipolar disorder) were included only if it was possible to extrapolate data on patients with unipolar TRD. We included only papers assessing biological markers in the review. Markers of different nature, such as those based on imaging, genetics and clinical evaluations were excluded from our analysis. Moreover, articles not providing a clear definition or utilizing ambiguous terminology for TRD were excluded. Only original articles were considered for the review. Additionally, the reference lists of all included papers were checked for the identification of other possible studies (Figure 1). The full reports of potentially relevant studies were obtained, and content of each paper was extracted.

For each paper, data on study design, sample characteristics, age range of recruited patients, biomarkers detected, psychopathological and psychosocial characteristics, TRD definition, and main results were independently extracted by four authors; discrepancies were resolved by discussion.

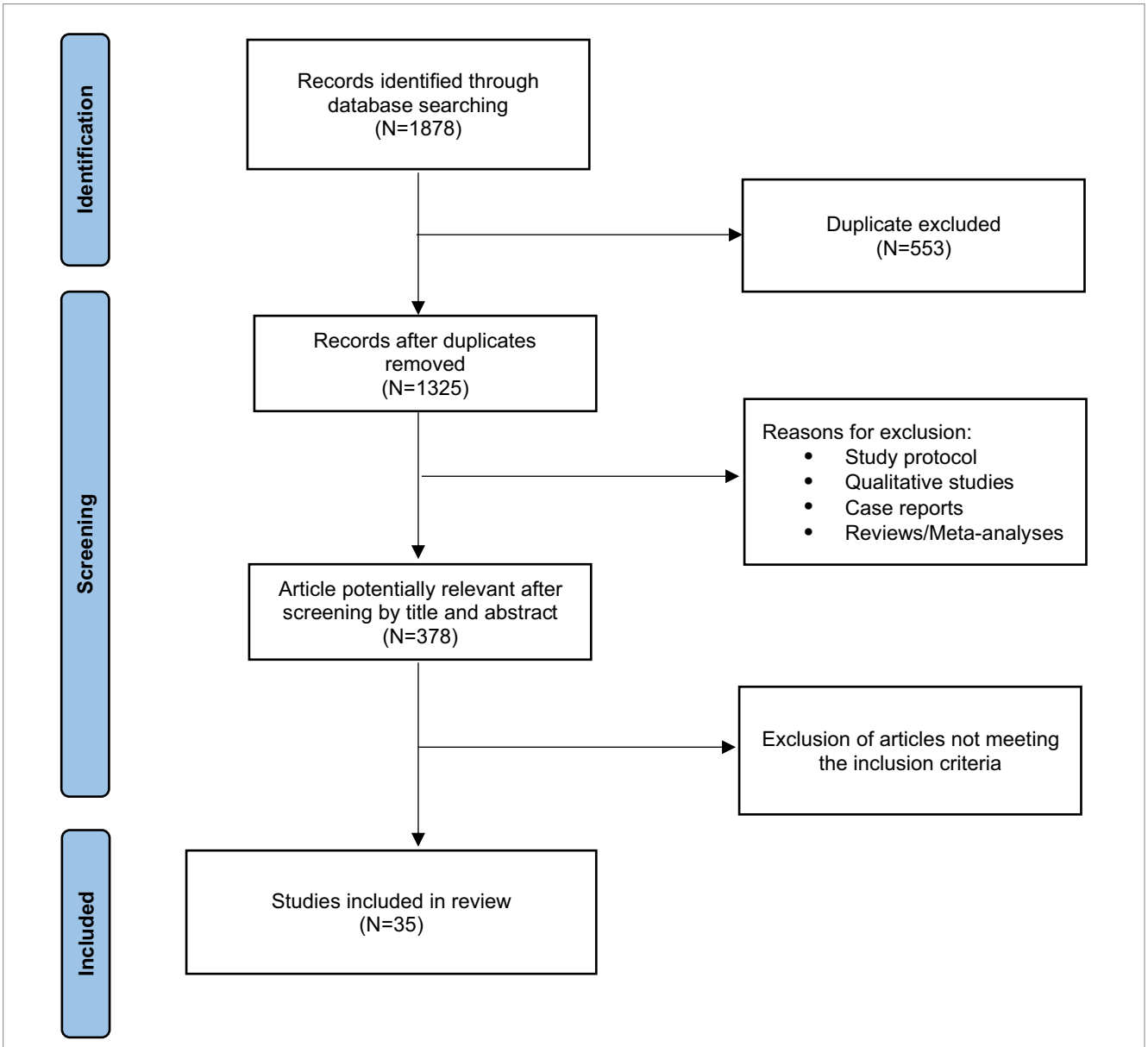

FIGURE 1
PRISMA flow diagram of selection of studies for inclusion in the review.

Results

Entering the keywords in the relevant databases, 1,878 papers were identified; 553 were duplicates and excluded. 947 further papers were eliminated after reading the abstracts because they did not meet the inclusion criteria. After reading full-text papers, 212 more papers were excluded. Therefore, our review consists of 35 papers, grouped in the following five categories according to the main investigated biological correlates: studies on cytokines; other inflammatory markers; kynurenine; Brain-Derived Neurotrophic Factor (BDNF); and other clinical parameters (Table 1).

Cytokines

With respect to IL-1, available data are still inconsistent. In fact, while Uint et al. (62) found higher IL-1b plasma levels in TRD compared to HC, Zincir et al. (67) and Wu et al. (65) found lower IL-1b levels of in TRD patients.

All available studies found increased plasma levels of IL-6 in TRD patients compared to HC (28, 49, 54, 65).

Seven studies addressed the correlation between TNF-α and TRD. Sanchez-Carro et al. (55) provided data supporting the role of TNF-α in discriminating between TRD and HC using a machine learning approach. These findings were replicated in a case–control cross-sectional study on elderly TRD patients, where TNF-α levels were significantly higher in TRD than in the HC group (65). In addition, in a double-blind, randomized, placebo-controlled trial, Strawbridge et al. (59) found that the baseline pro-inflammatory proteins, including TNF-α, were significantly higher in TRD patients than in HC, after controlling for gender, age, childhood adversity and BMI. On the other hand, one study found no difference in the production of lipopolysaccharide induced-TNF-α in peripheral blood mononuclear cells (34), while other reports (61, 67) found decreased TNF-α levels in TRD compared to HC. Interestingly, one study reported higher serum concentrations of TNF-α receptor subtype 1 (TNF-α R1) titers in TRD patients compared to HC (44).

In a randomized controlled trial, Zincir et al. (67) found higher levels of IL-10 in TRD compared to HC, while another study found no difference between TRD patients and healthy controls (59).

Other cytokines which have been explored as potential biomarkers of TRD include IL-12, IL-5, Interferon gamma (IFN-gamma), IL-8 and IL-4. Szałach et al. (61) reported lower levels of serum IL-12 and higher levels of IL-8 in TRD patients vs. HC. Strawbridge et al. (60) found higher levels of IL-8 in TRD patients compared to controls, associated with elevated titers of IL-5. Moreover, IL-4 blood levels were significantly higher in TRD than in the control group (67), while no difference in phytohemagglutinin (PHA)-induced IL-2 production has been found between patients and controls (34). One study found higher IFN-gamma titers in TRD than in the control group (67).

Other inflammatory markers

Despite consolidated evidence on cortisol levels in MDD, only a few studies have been carried out in patients with TRD. Markopoulou et al. (51) and Wu et al. (65) found higher cortisol serum levels in TRD vs. HC. Interestingly, Juruena et al. (45) found an impaired activity of glucocorticoid receptors (GRs) in TRD group compared to HC. de Menezes Galvão et al. (40) carried out a RCT on the effect of ayahuasca on the hypothalamic-pituitary-adrenal axis (HPA) and found that at baseline TRD patients exhibit blunted awakening salivary cortisol response and hypocortisolemia compared to HC.

Four studies (38, 39, 41, 59) found elevated levels of C-reactive protein (CRP) in TRD patients compared to HC, two studies reported no differences between cases and controls (44, 62), while Sanchez-Carro et al. (55) found that CRP does not discriminate between the two groups.

Four studies investigated immunological cells populations in TRD patients compared to HC. In particular, two studies found no differences in lymphocyte proliferation (34) and central populations of T cells between TRD patients and HC (61). However, in a large trial by Lauden et al. (46) on 570 TRD patients and 2,850 HC, higher levels of blood WBC, lymphocytes and platelets were found in the TRD group. Another study on lymphocyte sensitivity to dexamethasone (DEX) intake found that changes in cell redistribution after DEX administration were more prominent in TRD patients than in controls, but the effects of DEX were dependent on DEX-induced suppression of cortisol secretion (35).

Kynurenine

We found three studies on the kynurenine pathway in TRD. Zhou et al. (66) found lower serum concentrations of tryptophan (TRP), kynurenic acid (KYNA) and the KYNA/kynurenine (KYN) ratio, and a higher KYN/TRP ratio in TRD patients compared to HC. Also, Schwieler et al. (57) found an altered kynurenine metabolism in TRD patients, in particular decreased plasma levels of KYNA and significantly increased quinolinic acid/kynurenine ratio. However, one study found no difference between TRD and HC in the plasma levels of tryptophan, KYNA, and quinolinic acid (QUIN).

Brain-Derived Neurotrophic Factor

Four studies have explored the role of BDNF in TRD. In a randomized double-blinded placebo-controlled trial using a parallel-arm design of ayahuasca vs. placebo, no correlation was found between plasma levels of BDNF and TRD (41). Two studies reported lower levels of BDNF in TRD compared to HC (33, 53), while Uint et al. (62) found opposite results.

Other hematological parameters

Several other hematological parameters have been investigated in TRD patients. In particular, lower serum albumin levels were found in TRD patients compared to controls (64), while no significant difference in the levels of basal Thyroid Stimulating Hormone (TSH) and T4 were detected between major depressed patients with or without TRD and non-TRD (46, 63). One study showed lower vascular endothelial growth factor (VEGF) titers in TRD patients compared to HC (53). One study found reduced baseline levels of enzyme cofactor biopterin (involved in the synthesis of neurotransmitters like serotonin, dopamine, and norepinephrine) in

TABLE 1 Summary of studies included in the review.

Study and country	Sample size	Biomarker	Body fluid	TRD definition	Study design	Main results
Allen et al. (33), Ireland	35 TRD patients 20 HC	BDNF	Blood	Failure of two antidepressant trials	Cross-sectional	BDNF was lower in TRD patients compared to HC. sBDNF was significantly elevated only at 1 week following the first ketamine infusion in those classified as responders 1 week later. BDNF was not elevated following subsequent infusions
Bauer et al. (34), Brazil	36 TRD patients 31 HC	Salivary cortisol before and after DEX, phytohemagglutinin-induced T-cell proliferation, IL-2, TNFα, lymphocyte sensitivity to both cortisol and DEX	Saliva Blood	Failure of five different antidepressants trials	Cross-sectional	Basal morning cortisol levels from patients and controls did not differ nor did their T-cell proliferation and cytokine production. Ten out of 36 patients were classified as nonsuppressors and presented significantly higher post-DEX salivary cortisol levels than suppressors. Cells of nonsuppressors produced significantly less TNFα compared to suppressors. GC-induced suppression of lymphocyte proliferation and cytokine production were generally less marked in depressives compared with controls
Bauer et al. (35), Brazil	36 TRD patients 31 HC	Salivary cortisol and CD4+, CD8+, CD19+, CD56+, and HLADR+ cells distribution	Saliva Blood	Failure of five different antidepressants trials	Cross-sectional	No differences in basal salivary cortisol levels were found between patients and controls. Changes in cell redistribution (CD4+, CD8+, CD19+, CD56+, and HLADR+ cells) after DEX administration were more prominent in controls than in patients, but the effects of DEX varied dependent on whether patients exhibited DEX-induced suppression of cortisol secretion. Glucocorticoid-induced suppression of adhesion molecule expression was generally less marked in patients than controls
Carpenter et al. (36), USA	19 TRD patients 19 HC	Substance P	CSF	Failure to respond to at least two but not more than six antidepressant trials	Cross-sectional	Mean CSF substance P concentration was significantly lower in TRD patients on psychotropic medications than in the HC group
Cattaneo et al. (37), Italy	58 TRD patients 36 MMD responsive patients 36 MMD untreated patients 40 HC	IL-1-beta, IL-6, TNFα, MIF, glucocorticorticoid receptor, SGK1, FKBP5, P2RX7, CCL2, CXCL12, CRP, A2M, AQP4, ISG15, STAT1, and USP-18	Blood	Depressive symptoms (HDRS >13) while currently on an antidepressant at standard therapeutic dose for at least 6 weeks, plus at least one historical failure to a different antidepressant	Cross-sectional	Treatment-resistant and drug-free depressed patients had both increased inflammasome activation (higher P2RX7 and proinflammatory cytokines/chemokines mRNAs expression) and glucocorticoid resistance (lower GR and higher FKBP5 mRNAs expression), while responsive patients had an intermediate phenotype with lower CXCL12. Six mRNAs (P2RX7, IL-1-beta, IL-6, TNFα, CXCL12, and GR) distinguished treatment-resistant from responsive patients, even after adjusting for other variables that were different between groups

(Continued)

TABLE 1 (Continued)

Study and country	Sample size	Biomarker	Body fluid	TRD definition	Study design	Main results
Chamberlain et al. (38), UK	102 TRD patients 48 Responsive MMD patients 48 Untreated MMD patients 54 HC	CRP	Blood	Patients with HDRS total score > 13; currently in treatment with a monoaminergic drug for at least 6 weeks	Cross-sectional	Compared with HC, CRP was significantly elevated in TRD, but was not in the treatment-responsive and untreated groups
Congio et al. (39), Brazil	24 TRD patients 82 HC	Leptin, CRP	Blood	HDRS-17 Total score > 16, after 8 to 12-weeks of several antidepressant trials	Cross-sectional	Higher levels of leptin, hs-CRP > 3 mg/L and higher BMI were found to be associated with TRD. The TRD patients with hs-CRP > 3 mg/L presented on average higher levels of leptin for the same BMI, compared to non-TRD
de Menezes Galvão et al. (40), Brazil	28 TRD patients 43 HC	Cortisol	Saliva Blood	Failure of two antidepressant trials	Placebo controlled trial	Baseline assessment showed blunted awakening salivary cortisol response and hypocortisolemia in patients, with TRD respect to HC
Galvão-Coelho et al. (41), Brazil	28 TRD patients 45 HC	CRP, IL-6, cortisol, BDNF, GOT, GPT	Blood	Failure of two antidepressant trials	Double blind placebo controlled-trial	Higher CRP levels and similar IL-6 levels in TRD patients compared to control group, adjusting for BMI. A significant inverse correlation between CRP and cortisol levels was found in patients. No correlation between CRP and BDNF, and between IL-6 and any variable in patient group. No correlation between CRP and IL-6 in the control group
Gur et al. (42), Israel	26 TRD patients 24 MDE (both MDD and BPD) patients 30 HC	AQP4-IgG	Blood	Failure of two antidepressant trials	Longitudinal	Absence of AQP4-IgG autoantibodies in all patients
Hoekstra et al. (43), Netherlands	20 TRD patients 29 HC	Biopterin, neopterin, phenylalanine, tyrosine, TRP, isoleucine, leucine, and valine	Blood	Failure to a prior treatment with a tricyclic antidepressant, lithium addition or an irreversible monoamine oxidase inhibitor	Longitudinal	Lower plasma biopterin concentration in TRD patients compared to HC. After treatment, biopterin increased in TRD patients with psychotic features. The plasma phenylalanine/tyrosine ratio normalized after ECT. Mean tryptophan concentration was lower in TRD than in HC
Huang et al. (44), Taiwan	20 TRD patients 14 responsive MDD patients 34 HC	CPR, sIL-2R, sIL-6R, TNFα-R1	Blood	Failure of two antidepressant trials	Cross-sectional	MDD patients had higher serum concentrations of TNFα R1. Higher serum concentrations of TNFα R1 in TRD patients than in healthy controls or non-TRD group. The most significant finding from this study was the correlation of increased serum concentrations of TNFα R1 and impaired glutamatergic neurotransmission in the caudate nucleus and anterior cingulate cortex in patients with TRD

(Continued)

TABLE 1 (Continued)

Study and country	Sample size	Biomarker	Body fluid	TRD definition	Study design	Main results
Juruena et al. (45), UK	12 TRD patients 12 HC	Cortisol	Saliva	Failure of two antidepressant trials	Cross-sectional	Higher salivary cortisol levels in TRD patients compared with controls after all challenges. In these patients the provision of spironolactone did not increase cortisol compared to placebo; spironolactone with prednisolone had no effect on the suppressive effects of prednisolone. Patients with TRD had a reduction in the conversation of spironolactone to the active metabolite canrenone
Lauden et al. (46), Israel	570 TRD patients 2,850 MDD patients 2,850 HC	WBC, lymphocytes, eosinophils, basophils, platelets, MPV, glucose, TSH, CRP, ESR, C3, C4, antinuclear antibodies, RF, IgE	Blood	Presence of minimal improvement or no improvement with at least two different classes of antidepressants, at adequate doses and durations (at least 6 weeks)	Cross-sectional	Higher levels of blood WBC, lymphocytes, platelets, C-reactive protein, ESR, C3 and C4 levels in TRD patients compared controls
Maes et al. (47), Belgium	28 TRD patients 8 responsive MDD patients 15 HC	DPP IV	Blood	Failure of two antidepressant trials	Cross-sectional	Significantly lower derum DPP IV activity in major depressed subjects, irrespective of treatment resistance, than in normal volunteers; subchronic treatment with antidepressants has no significant effect on serum DPP IV activity; serum DPP IV is related to immune- as well as inflammatory markers of major depression
Maes et al. (48), Belgium	23 TRD patients 9 responsive MDD patients 15 HC	Zn and Cu	Blood	Failure of two antidepressant trials	Longitudinal	Decreased Serum Zn levels in TRD patients; treatment with antidepressants does not alter the initially lower Zn levels, although antidepressant treatment significantly reduces serum Cu levels; lower serum Zn is significantly related to immune/inflammatory markers
Maes et al. (49), Belgium	28 TRD patients 7 MDD patients 15 HC	IL-6, IL-6R, IL-1Ra, sCD8, CC16, and Zn	Blood	Treatment resistance according to Thase and Rush criteria	Cross-sectional	Significantly higher serum IL-6 levels in TRD subjects, while there were no significant differences between normal volunteers and non-TRD patients, and between patients with and without TRD
Maes et al. (50), Belgium	19 TRD patients 16 responsive MDD patients 22 HC	CoQ10	Blood	Presence of (a) failure of two antidepressant trials; (b) failure to respond to augmentation treatment; (c) point b plus failure to respond to two augmentation strategies; (d) previous stage plus non-response to ECT	Cross-sectional	Plasma CoQ10 was significantly lower in patients with TRD and with Chronic Fatigue Syndrome than in the other depressed patients. No significant correlation between plasma CoQ10 and the HDRS

(Continued)

TABLE 1 (Continued)

Study and country	Sample size	Biomarker	Body fluid	TRD definition	Study design	Main results
Markopoulou et al. (51), UK	28 TRD patients 40 HC	DHEA, cortisol	Blood	Failure of two antidepressant trials. Degree of resistance was staged according to the Thase and Rush criteria	Observational	Cortisol levels were significantly higher in patients than controls, but DHEA levels did not differ. The ratio of cortisol/DHEA was significantly elevated in patients
Nasca et al. (52), USA	11 TRD patients 26 MD patients 26 HC	LAC	Blood	History of nonresponse to at least two antidepressant trials	Cross-sectional	Compared to HC, decrease in LAC was larger in TRD patients, among whom childhood trauma and, specifically, a history of emotional neglect and being female, predicted the decreased LAC
Pisoni et al. (53), United Kingdom	36 TRD patients 36 HC	Tie2, BDNF, VEGF, VEGFC, VEGFD, PlGF, bFGF, and sFlt1	Blood	Score > 7.5 using the Maudsley Staging Method	Longitudinal	Deficit of peripheral growth factors in TRD patients. Higher Tie2 levels in TRD patients than controls, while lower VEGFC and BDNF levels in TRD participants. Levels of VEGF were not significantly different between patients and controls A decrease of VEGF 260 and VEGFC over time in TRD patients was reported. No changes were seen in levels of BDNF following antidepressant treatment. TRD patients showed significantly lower levels of VEGFD at admission compared to responders
Rengasamy et al. (54), USA	103 TRD patients 43 HC	IL-6	Blood CSF	Failure of three antidepressant trials	Cross-sectional	Higher levels of plasma IL-6 were found in TRD compared to HC
Sanchez-Carro et al. (55), Spain	59 TRD patients 32 MDD patients 80 HC	TNFα and CRP	Blood	Failure of two antidepressant trials, or non-response to the augmentation treatments	Cross-sectional	TNFα and CRP were relevant for the differentiation of the group of patients from the HC group
Sasaki et al. (56), Japan	10 TRD patients 27 MDD patients 25 HC	OXT	Blood	Failure of two antidepressant trials and not responding to at least eight sessions of cognitive behavioral therapy	Cross-sectional	Serum OXT levels in TRD patients were higher compared to HC
Schwieler et al. (57), Sweden	19 TRD patients 22 HC	IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNFα, IFN-γ, GM-CSF, KYNA, and QUIN	Blood	Patients had been adequately treated with oral antidepressant, but had not responded	Observational	Increased plasma levels of IL-6 in TRD patients compared HC. Decreased plasma levels of KYNA and significantly increased QUIN/KYNA ratio in TRD Plasma levels of tryptophan, kynurenine, and QUIN did not differ between patients and controls. There was a significant inverse correlation between symptom severity and kynurenine levels at baseline

(Continued)

TABLE 1 (Continued)

Study and country	Sample size	Biomarker	Body fluid	TRD definition	Study design	Main results
Sowa-Kucma et al. (58), Poland	42 TRD patients 72 responsive MDD patients 50 HC	IL-1α, IL-1RA, IL-2R, IL-6R, sTNF-R1, sTNF-R2, TBARS	Blood	Failure of two antidepressant trials	Cross-sectional	TRD is characterized by increased sIL-6R levels as compared with controls and depressed patients without TRD, lowered sTNF-R2 levels as compared to non-TRD patients and increased TBARS levels as compared with all other study samples
Strawbridge et al. (59), UK	129 TRD patients 28 HC	IL-6, CRP, TNFα, and IL-10	Blood	Non-responsive to at least two antidepressants	Two-arm parallel-group, double-blind, randomized, placebo-controlled trial	CRP, TNFα and IL-6 were elevated in TRD patients compared to HC. Other inflammatory proteins did not mediate or moderate treatment outcomes
Strawbridge et al. (60), UK	36 TRD patients 36 HC	CRP, IFNα, IFNγ, IL-10, IL-12, IL-12p70, IL-13, IL-15, IL-16, IL-17, IL-1α, IL1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), TNFα, TNFβ, Eotaxin (CCL11), Eotaxin-3 (CCL26), GM-CSF, IP-10 (CXCL10), MCP1 (CCL2), MCP4 (CCL13), Mip1a (CCL3), Mip1b (CCL4), SAA, sICAM1 (sCD54), sVCAM1 (sCD106), and TARC (CCL17)	Blood	TRD was assessed using the Maudsley Staging Method staging tool	Longitudinal	Patients with TRD reported higher proteomic inflammatory activity than HC; elevated inflammation is predictive of a more severe or resistant depressive illness both retrospectively (i.e., prior to inpatient treatment, in the current episode) and prospectively (predicting more severe depressive symptoms in the months after discharge)
Szałach et al. (61), Poland	20 TRD patients 13 HC	CD28, CD69, CD25, CD95, HLA-DR, IL12p70, TNFα, IL-10, IL-6, IL-1β, and IL-8	Blood	Failure of two antidepressant trials	Cross-sectional	Lower percentage of CD3 + CD4 + CD25+ and CD3 + CD8 + CD95+ cells in TRD patients than HC, lower serum levels of IL-12p70 and TNFα, and significantly higher IL-8 levels
Uint et al. (62), Brasil	34 TRD patients 43 BPD patients 41 HC	TNFα, IL-1β, IL-6, BDNF, and CRP	Blood	Failure of two antidepressant trials	Cross-sectional	BDNF and IL-1β plasma concentrations were increased in TRD compared to HC
Vandoolaeghe et al. (63), Belgium	27 TRD patients 9 responsive MDD patients 15 HC	TSH, T4	Blood	Failure of two antidepressant trials	Cross-sectional	No significant differences in basal TSH or T4 in TRD was found
Van Hunsel et al. (64), Belgium	29 TRD patients 8 responsive MDD patients 29 HC	TSP, albumin, alpha1, alpha2, beta, and gamma-globulin	Blood	Failure of two antidepressant trials	Longitudinal	Significantly lower TSP and percentage and concentration of serum albumin (Alb) and γ-globulin fraction in TRD than in HC Serum beta-globulin concentrations were significantly lower in TRD subjects than in HC

(Continued)

TABLE 1 (Continued)

Study and country	Sample size	Biomarker	Body fluid	TRD definition	Study design	Main results
Wu et al. (65) China	30 TRD patients 30 responsive MDD patients 30 HC	Cortisol, nesfatin-1, CRP, TNFα, IL-6, 1 L-1β	Blood	Ineffective treatments for 3 months with two or more different antidepressants in sufficient quantity	Cross-sectional	Serum cortisol, CRP, TNFα, and IL-6 levels were significantly higher in TRD than in HC. Serum nesfatin-1 levels in the non-TRD group were significantly lower than HC and TRD groups, and significantly higher serum IL-1β levels in the non-TRD group than in the control and TRD groups
Zhou et al. (66), China	68 TRD patients 6 HC	TRP, KYN, and KYNA	Blood	Failure of two antidepressant trials	Longitudinal	Lower serum levels of TRP and KYNA and the KYNA/KYN ratio and higher KYN/TRP ratio in TRD patients than in HC
Zincir et al. (67), Turkey	50 TRD patients 30 HC	IL-1, IL-6, TNFα, IL-10, IL-4, and IFN-gamma	Blood	Failure of two antidepressant trials	Prospective, non-randomized, controlled study	Higher levels of IL-1, TNFα, and IL-10 before treatment in TRD than in HC. No significant difference in the levels of IL-6 before and after treatment when compared to the control group

AQP4, aquaporin-4; A2M, alpha-2-macroglobulin; BDNF, brain-derived neutrophic factor; bFGF, basic fibroblast growth factor; BPD, bipolar disorder; CCL, CC motif chemokine ligand; CD, cluster of differentiation; CoQ10, Q10 Coenzyme; CRP, C-reactive protein; CSF, cerebrospinal fluid; Cu, cupper; CXCL, CXC motif chemokine ligand; C3, complement component 3; C4, complement component 4; CC16, clara cell protein; DDP IV, dipeptidyl peptidase 4; Dex, dexamethasone; DHEA, dehydroepiandrosterone; ECT, elettroconvulsive therapy; ERS, erythrocyte sedimentation rate; FKBP5, FK506 binding protein 5L GM-CSF, granulocyte-macrophage colony-stimulating factor; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HC, healthy control; HDRS, Hamilton Depression Rating Scale; HLA, human leukocyte antigen; Ig, immunoglobulin; IL, interleukin; IL1RA, IL-1 receptor antagonist; IL-2R, IL-2 receptor; INF, interferon; KYN, kynurenin; KYNA, kynurenic acid; LAC, acetyl-L-carnitine; Mcp, monocyte chemoattractant protein-1; MDD, major depressive disorder; MDE, major depressive episode; MIF, macrophage migration inhibitory factor; Mip, macrophage inflammatory protein; MPV, medium platelet volume; OXT, oxytocin; PlGF, placental growth factor; P2RX7, purinergic receptor; QUIN, quinolinic acid; RF, reumatoid factor; sFlt1, soluble fms-like tyrosine kinase-1 (VEGF receptor-1); sICAM, soluble intercellular adhesion molecules; sVCAM, soluble vascular cell adhesion molecule; sIL2R, soluble IL-2 receptor; sIL6R, soluble IL-2 receptor; sTNF-R1, soluble TNF-receptor1; sTNF-R2, soluble TNF-receptor2; TARC, thymus- and activation-regulated chemokine; TBARS, thiobarbituric acid reactive substances; Tie-2, angiopoietin-1 receptor; TNF, tumor necrosis factor; TNFαR1, tumor necrosis factor-alpha receptor subtype 1; TRD, treatment-resistant depression; TSH, thyroid stimulating hormone; TSP, total serum protein; T3, triiodothyronine; T4, thyroxine; VEGF, Vascular endothelial growth factor; WBC, white blood cells; Zn, Zinc.

TRD patients compared to HC (43). Significantly decreased serum levels of acetylating molecule acetyl-L-carnitine (LAC) were observed in TRD patients compared to HC (52). Another study reported higher serum levels of oxytocin (OXT) in a sample of adolescents with TRD compared to age-matched HC (56).

Gur et al. (42) found that TRD patients are more frequently seronegative to Aquaporin-4 (an astrocyte water channel protein) autoantibodies (AQP4-IgG) compared to HC. However, another study reported no statistical difference in the expression of AQP4 gene between TRD and HC (37).

Interestingly, two studies assessed zinc (Zn) serum levels: Maes et al. (48) found significantly lower levels of serum Zn in TRD than in HC, which were inversely correlated with IL-6 titers (49). The same authors showed a significantly lower serum activity of dipeptidyl peptidase IV (DPP IV), a serine protease with a role in cytokine production, in TRD than in HC (47), and significantly lower levels of the antioxidant Coenzyme Q10 compared to responsive-MDD patients (50). Sanchez-Carro et al. (55) reported that glutathione and 4-hydroxynonenal (HNE) could serve as variables to discriminate between TRD patients and HC. Moreover, one study investigated the role of stress-related neuropetide Substance P (SP) in the central nervous system (CNS), by means of standard lumbar puncture techniques (36). Authors reported that TRD patients taking psychotropic medications had significantly lower mean cerebrospinal fluid SP concentration than HC (53).

Discussion

The underlying biological mechanisms that contribute to development and maintenance of TRD are not yet elucidated. The identification of reliable biomarkers would allow an early identification, proper diagnosis and treatment of TRD, improving the chance of a successful outcome (68). However, only a small number of biological alterations seem to correlate with TRD, in particular some cytokines, the kynurenine pathway catabolites, CRP, BDNF and cortisol.

The role of inflammation, and in particular of cytokines, in the pathophysiology of mental disorders has been recently highlighted (69), following a new wave of studies using modern biological techniques (70, 71). While several evidence shows an involvement of the immunological systems in MDD, suggesting that the communication between immune and brain systems might be mediated by increased cytokine levels (72, 73), only a limited number of studies investigating the role of inflammation and of cytokine alteration in TRD have been found, despite the presence of low-grade neuroinflammation has been reported to be more frequently in patient with treatment resistant major depression, rather than in responders and healthy controls (74, 75).

Available evidence has reported that TNF-α, whose blood concentration has shown a significant improvement after treatments with antidepressants, is the most relevant biomarker to discriminate TRD patients from both to HC and to treatment-responsive MDD

patients (55, 74). In the Central Nervous System (CNS) TNF-α promotes serotonin metabolism and enhances the serotonin transporter's activity (76). In particular, reduced levels of TNF-α could be associated to a reduced activity of serotonin transporter, thus influencing the effectiveness antidepressants, like selective serotonin reuptake inhibitors (SSRIs) (76). Consequently, the assessment of TNF-α levels could have potential clinical relevance for TRD patients who have experienced several unsuccessful trials of antidepressant treatments (77).

Two studies found increased levels of IL-8 in TRD patients compared to healthy controls. IL-8 is produced by monocytes, macrophages, and neutrophils and exerts a pro-inflammatory action, by facilitating neutrophil migration. It is also synthetized in SNC by microglia can synthesize IL-8 in response to proinflammatory stimuli; it has also been reported that anti-inflammatory cytokines can downregulate its production and release in the SNC (20). IL-8 levels have been found to be consistently elevated in TRD patients also when they are compared to MDD responsive individuals, suggesting that this cytokine could be a potential biomarker for TRD. However, this hypothesis needs to be confirmed by further larger longitudinal studies, with standardized diagnostic criteria and treatment-specific analyzes. Additionally, a more comprehensive understanding of the role of IL-8 in TRD might come from multi-modal research approaches, integrating genetic, imaging, and clinical data. Reviewed studies are insufficient to draw any other firm consideration about the role of the other cytokines, such as IL-2, IL-5, and IL-12, in TRD pathophysiology.

The BDNF has also been assessed as a biomarker in the pathophysiology of TRD. The BDNF belongs to the family of neurotrophins, a group of growth factors that support the survival, development, and function of neurons in the brain and peripheral nervous system (78). Inflammation, which is associated with increased cytokines production, affects BDNF expression, although the exact biological pathway is not fully elucidated (79). Chronic stress induces a reduction in BDNF concentration (80), but studies analyzing serum BDNF levels in TRD conveyed conflicting results (81). In fact, while some studies reported a reduction of BDNF concentration (53, 64), others found an increase of BDNF levels (62) or no difference between TRD and healthy controls. The inconsistency of these results might be due to the fact that serum analysis of BDNF concentrations is variable and scarcely reliable, unless Polymerase Chain Reaction (PCR) is used.

Many studies reported increased cortisol levels in TRD patients (51, 65), suggesting an alteration in HPA axis. One hypothesis regarding cortisol modulation in depression indicates a form of HPA axis fatigue with an underlying hypocortisolism both in salivary and plasma samples (34, 40). In fact, chronic low levels of cortisol can cause weakness, loss of appetite and immunological dysfunctions, which are symptoms commonly associated to depression (82, 83). However, the inconsistency of results reported in studies included in the present review can be explained by the fact that antidepressant treatments can alter HPA axis functions. Therefore, in order to fully understand the role of cortisol in depression, studies comparing medicated vs. non medicated patients are needed (84).

Several studies found alterations in the number of blood immune cells. Evidence shows that TRD patients can have increased leucocytes and possibly platelets; however, the role of immune cells in TRD should be better investigated. In fact, studies including a higher number of participants reported an increase in immunological cells, such as neutrophils and platelets in TRD patients vs. healthy controls; however, these differences were not statistically significant when comparing MMD and TRD, challenging the view that they can represent different pathologies along the affective spectrum (46).

In the present review, an alteration in the kynurenine pathway (KP) has been reported in several studies. This result is of particular relevance, since the vast majority (~95%) of tryptophan (TRP) is metabolized via KP in kynurenine (KYN), quinolinic acid (QUIN) and kynuretic acid (KYNA), while only a small part of TRR is used to synthetize monoamines, implicated in the pathophysiology of MDD, including noradrenaline and serotonin (85). Enzymes of the KP, can be activated by pro-inflammatory cytokines, which may lead to TRP depletion (86). Results of the present review confirm this hypothesis, despite they need to be replicated in larger samples.

Treatment-resistant depression represents a significant challenge in mental health care, making a priority the need to identify the etiological pathways of this complex mental disorder. Numerous additional biological pathways, including biopterin, acetyl-L-carnitine, oxytocin, zinc, glutathione, nesfatin-1, and dipeptidyl peptidase IV, have been investigated in TRD. In particular, biopterin, a critical cofactor in neurotransmitter synthesis, has shown potential relevance in TRD (87). Alterations in biopterin metabolism have been associated with the dysregulation of serotonin, dopamine, and norepinephrine systems, all of them being implicated in depression (88). Similarly, Acetyl-L-carnitine, an endogenous compound involved in cellular energy metabolism and neuroprotection, has demonstrated antidepressant effects in clinical studies, indicating its potential as a therapeutic target for TRD (89). While the studies on pathways of biopterin and acetyl-L-carnitine seem promising to enhance our understanding of major depression and of TRD, others - including aquaporin-4, vascular endothelial growth factor (VEGF), and thyroid-stimulating hormone (TSH) - have yield fewer compelling results. However, the current level of evidence for these pathways is still low, and any consideration about the potential role in TRD remains speculative.

The existing literature on the biological correlates of TRD is explored by numerous studies, but the comparability of their findings and methods often proves challenging mainly due to methodological disparities and clinical characterization differences. These variations encompass the utilization of diverse laboratory techniques and the incorporation of inclusion criteria grounded in distinct conceptual definitions. As a consequence, the synthesis of this body of research faces obstacles in drawing definitive conclusions about the underlying biological mechanisms of TRD.

In the analysis of the selected articles conflicting outcomes have emerged. Nevertheless, certain cytokines, such as IL-6 and TNF-α, have demonstrated a more extensive body of supporting evidence. A significant proportion of the examined cytokines, however, lacked a sufficient number of studies for meaningful cross-comparisons, rendering the available evidence insufficient to derive preliminary conclusions. Moreover, notwithstanding the presence of evidentiary support in other domains of psychiatric pathologies, the cortisol pathway exhibited incongruent findings in the context of TRD. Additionally, the available data regarding BDNF appear challenging to compare due to methodological disparities in the analysis, which may account for the incongruity of the results.

This review is subject to several limitations, that are hereby acknowledged. First and foremost, a significant challenge in our synthesis of findings is the inconsistency in the definition of treatment-resistant depression across studies. The lack of a standardized and universally accepted definition hampers the possibility to draw definitive conclusions regarding biomarkers associated with this specific depressive phenotype. Additionally, methodological limitations within included studies, such as variations in sample collection and processing techniques, assay methodologies, and data analysis approaches, introduce potential sources of bias, reducing the comparability and generalizability of results. Another common limitation observed in available studies is represented by the relatively small sample sizes, which may limit the statistical power of studies. Therefore, caution is needed when interpreting the findings of this review, and further well-designed studies with larger and more homogeneous samples are warranted to overcome these limitations and provide more robust evidence regarding biomarkers of TRD.

In conclusion, although the notion of TRD lacks coherence and standardization (90, 91), some evidence suggests a biological alteration in TRD. However, the future perspectives for research on the biological correlates of TRD are both promising and challenging (92). To advance our understanding of TRD's biological underpinnings, it is imperative to establish a more robust conceptual framework for TRD, which include the resistance to psychotherapeutic interventions, also. Additionally, future studies should aim to include well-characterized, medication-naïve patient samples and adopt longitudinal designs to assess biomarker variations over time. Based on the findings of this review, it becomes evident that prioritizing the analysis of biomarker panels, rather that single biomarkers, is imperative. Finding a biosignature of TRD, coming from a panel of biomarkers, not only enables a more comprehensive understanding of biological processes underlying mental disorder but also offers an opportunity to develop targeted treatments able to influence it and to modify the long-term outcome of TRD. Lastly, future studies should include strategies to identify patient with pseudoresistance to pharmacological treatments (23), due to poor compliance to pharmacological treatments.

Author contributions

EM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. GS: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. AB: Writing – review & editing, Data curation. BD: Data curation, Writing – review & editing. MD: Data curation, Writing – review & editing. MVL: Methodology, Writing – review & editing. FM: Methodology, Writing – review & editing. FL: Data curation, Writing – review & editing. ML: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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References

1. Boschloo L, Hieronymus F, Cuijpers PICECA Work Group. Clinical response to SSRIs relative to cognitive behavioral therapy in depression: a symptom-specific approach. *World Psychiatry*. (2022) 21:152–3. doi: 10.1002/wps.20944

2. World Health Organization. *Depression* (2021). Available at: https://www.who.int/news-room/fact-sheets/detail/depression (Accessed April 25, 2023).

3. Miguel C, Karyotaki E, Cuijpers P, Cristea IA. Selective outcome reporting and the effectiveness of psychotherapies for depression. *World Psychiatry*. (2021) 20:444–5. doi: 10.1002/wps.20900

4. Trivedi MH. Major depressive disorder: remission of associated symptoms. *J Clin Psychiatry*. (2006) 67:27–32.

5. Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, Koenigsberg SH, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). *PharmacoEconomics*. (2021) 39:653–65. doi: 10.1007/s40273-021-01019-4

6. Steger MF. Meaning in life is a fundamental protective factor in the context of psychopathology. *World Psychiatry*. (2022) 21:389–90. doi: 10.1002/wps.20916

7. Furukawa TA, Shinohara K, Sahker E, Karyotaki E, Miguel C, Ciharova M, et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. *World Psychiatry* (2021) 20:387–96. doi: 10.1002/wps.20906

8. Murphy JA, Sarris J, Byrne GJ. A review of the conceptualisation and risk factors associated with treatment-resistant depression. *Depress Res Treat*. (2017) 2017:4176825–10. doi: 10.1155/2017/4176825

9. Ban TA. Prolegomenon to the clinical prerequisite: psychopharmacology and the classification of mental disorders. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (1987) 11:527–80. doi: 10.1016/0278-5846(87)90019-4

10. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. (1997) 58:23–9.

11. Ventriglio A, Bhugra D, Sampogna G, Luciano M, De Berardis D, Sani G, et al. From dysthymia to treatment-resistant depression: evolution of a psychopathological construct. *Int Rev Psychiatry*. (2020) 32:471–6. doi: 10.1080/09540261.2020.1765517

12. Cuijpers P, Quero S, Noma H, Ciharova M, Miguel C, Karyotaki E, et al. Psychotherapies for depression: a network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. *World Psychiatry* (2021) 20:283–93. doi: 10.1002/wps.20860

13. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of depression. (2013). Available at: https://www.ema.europa.eu/en/news/european-medicines-agency-publishes-guideline-clinical-investigation-medicines-depression (Accessed April 25, 2023).

14. Fekadu A, Wooderson S, Donaldson C, Markopoulou K, Masterson B, Poon L, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry*. (2009) 70:177–84. doi: 10.4088/jcp.08m04309

15. McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord*. (2014) 156:1–7. doi: 10.1016/j.jad.2013.10.043

16. Rush AJ, Sackeim HA, Conway CR, Bunker MT, Hollon SD, Demyttenaere K, et al. Clinical research challenges posed by difficult-to-treat depression. *Psychol Med*. (2022) 52:419–32. doi: 10.1017/S0033291721004943

17. Stein DJ, Shoptaw SJ, Vigo DV, Lund C, Cuijpers P, Bantjes J, et al. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration. *World Psychiatry*. (2022) 21:393–414. doi: 10.1002/wps.20998

18. Anderson IM. We all know what we mean by treatment-resistant depression - don't we? *Br J Psychiatry*. (2018) 212:259–61. doi: 10.1192/bjp.2018.56

19. Meng R, Yu C, Liu N, He M, Lv J, Guo Y, et al. Association of Depression with all-Cause and Cardiovascular Disease Mortality among Adults in China. *JAMA Netw Open*. (2020) 3:e1921043. doi: 10.1001/jamanetworkopen.2019.21043

20. Kim H, Turiano NA, Forbes MK, Kotov R, Krueger RF, Eaton NR, et al. Internalizing psychopathology and all-cause mortality: a comparison of transdiagnostic vs. diagnosis-based risk prediction. *World Psychiatry*. (2021) 20:276–82. doi: 10.1002/wps.20859

21. Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. *J Affect Disord*. (2018) 235:362–7. doi: 10.1016/j.jad.2018.04.016

22. Möller HJ, Seemüller F, Schennach R, Gupta RK. Treatment-resistant depression: a separate disorder – a new approach In: S Kasper and S Montgomery, editors. *Treatment-resistant depression*. London: Willey Blackwell (2013). 21–41. doi: 10.1002/9781118556719.ch2

23. Leichsenring F, Steinert C, Rabung S, Ioannidis JPA. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. *World Psychiatry*. (2022) 21:133–45. doi: 10.1002/wps.20941

24. FDA-NIH Biomarker Working Group. BEST (biomarkers, EndpointS, and other tools) resource. Silver spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US). (2006). Available at: www.ncbi.nlm.nih.gov/books/NBK326791/.

25. Owen MJ, Williams NM. Explaining the missing heritability of psychiatric disorders. *World Psychiatry*. (2021) 20:294–5. doi: 10.1002/wps.20870

26. Fisher AJ, Song J, Soyster PD. Toward a systems-based approach to understanding the role of the sympathetic nervous system in depression. *World Psychiatry*. (2021) 20:295–6. doi: 10.1002/wps.20872

27. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. (2009) 65:732–41. doi: 10.1016/j.biopsych.2008.11.029

28. Liu JJ, Wei YB, Strawbridge R, Bao Y, Chang S, Shi L, et al. Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis. *Mol Psychiatry*. (2020) 25:339–50. doi: 10.1038/s41380-019-0474-5

29. Markopoulou K, Fischer S, Papadopoulos A, Poon L, Rane LJ, Fekadu A, et al. Comparison of hypothalamo-pituitary-adrenal function in treatment resistant unipolar and bipolar depression. *Transl Psychiatry*. (2021) 11:1–8. doi: 10.1038/s41398-021-01343-5

30. Orsolini L, Pompili S, Tempia Valenta S, Salvi V, Volpe U. C-reactive protein as a biomarker for major depressive disorder? *Int J Mol Sci*. (2022) 23:1616. doi: 10.3390/ijms23031616

31. Watson D, Levin-Aspenson HF, Waszczuk MA, Conway CC, Dalgleish T, Dretsch MN, et al. Validity and utility of hierarchical taxonomy of psychopathology (HiTOP): III. Emotional dysfunction superspectrum. *World Psychiatry*. (2022) 21:26–54. doi: 10.1002/wps.20943

32. Marrie RA, Bernstein CN. Psychiatric comorbidity in immune-mediated inflammatory diseases. *World Psychiatry*. (2021) 20:298–9. doi: 10.1002/wps.20873

33. Allen AP, Naughton M, Dowling J, Walsh A, Ismail F, Shorten G, et al. Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: a comparison of ketamine and ECT. *J Affect Disord*. (2015) 186:306–11. doi: 10.1016/j.jad.2015.06.033

34. Bauer ME, Papadopoulos A, Poon L, Perks P, Lightman SL, Checkley S, et al. Altered glucocorticoid immunoregulation in treatment resistant depression. *Psychoneuroendocrinology*. (2003) 28:49–65. doi: 10.1016/s0306-4530(02)00009-4

35. Bauer M, Papadopoulos A, Poon L, Perks P, Lightman S, Checkley S, et al. Dexamethasone-induced effects on lymphocyte distribution and expression of adhesion molecules in treatment-resistant depression. *Psychiatry Res*. (2002) 113:1–15. doi: 10.1016/s0165-1781(02)00243-3

36. Carpenter LL, Bayat L, Moreno F, Kling MA, Price LH, Tyrka AR, et al. Decreased cerebrospinal fluid concentrations of substance P in treatment-resistant depression and lack of alteration after acute adjunct vagus nerve stimulation therapy. *Psychiatry Res*. (2008) 157:123–9. doi: 10.1016/j.psychres.2007.04.016

37. Cattaneo A, Ferrari C, Turner L, Mariani N, Enache D, Hastings C, et al. Whole-blood expression of inflammasome- and glucocorticoid-related mRNAs correctly separates treatment-resistant depressed patients from drug-free and responsive patients in the BIODEP study. *Transl Psychiatry*. (2020) 10:232. doi: 10.1038/s41398-020-00874-7

38. Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DNC, Drevets WC, et al. Treatment-resistant depression and peripheral C-reactive protein. *Br J Psychiatry*. (2019) 214:11–9. doi: 10.1192/bjp.2018.66

39. Congio AC, Norcia M, Urbano MR, Verri WA, Vargas Nunes SO. Association of clinical features and biomarkers with treatment-resistant depression. *Neurol Psychiatry Brain Res*. (2020) 36:32–8. doi: 10.1016/j.npbr.2020.02.004

40. de Menezes Galvão AC, de Almeida RN, Silva EADS, Freire FAM, Palhano-Fontes F, Onias H, et al. Cortisol modulation by Ayahuasca in patients with treatment resistant depression and healthy controls. *Front Psych*. (2018) 9:185. doi: 10.3389/fpsyt.2018.00185

41. Galvao-Coelho NL, de Menezes Galvao AC, de Almeida RN, Palhano-Fontes F, Braga IC, Soares BL, et al. Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca. *J Psychopharmacol*. (2020) 34:1125–33. doi: 10.1177/0269881120936486

42. Gur S, Taler M, Bormant G, Blattberg D, Nitzan U, Vaknin-Dembinsky A, et al. Lack of association between unipolar or bipolar depression and serum aquaporin-4 autoantibodies. *Brain Behav Immun*. (2020) 88:930–4. doi: 10.1016/j.bbi.2020.05.001

43. Hoekstra R, Van den Broek WW, Fekkes D, Bruijn JA, Mulder PGH, Pepplinkhuizen L. Effect of electroconvulsive therapy on biopterin and large neutral amino acids in severe, medication-resistant depression. *Psychiatry Res*. (2001) 103:115–23. doi: 10.1016/s0165-1781(01)00282-7

44. Huang MH, Chen MH, Tu PC, Bai YM, Su TP, Yang BH, et al. Elevated tumor necrosis factor-alpha receptor subtype 1 and the association with abnormal brain function in treatment-resistant depression. *J Affect Disord*. (2018) 235:250–6. doi: 10.1016/j.jad.2018.04.037

45. Juruena MF, Pariante CM, Papadopoulos AS, Poon L, Lightman S, Cleare AJ. The role of mineralocorticoid receptor function in treatment-resistant depression. *J Psychopharmacol*. (2013) 27:1169–79. doi: 10.1177/0269881113499205

46. Lauden A, Geishin A, Merzon E, Korobeinikov A, Green I, Golan-Cohen A, et al. Higher rates of allergies, autoimmune diseases and low-grade inflammation markers in treatment-resistant major depression. *Brain Behav Immun Health*. (2021) 16:100313. doi: 10.1016/j.bbih.2021.100313

47. Maes M, de Meester I, Verkerk R, de Medts P, Wauters A, Vanhoof G, et al. Lower serum dipeptidyl peptidase IV activity in treatment resistant major depression: relationships with immune-inflammatory markers. *Psychoneuroendocrinology*. (1997) 22:65–78. doi: 10.1016/s0306-4530(96)00040-6

48. Maes M, Vandoolaeghe E, Neels H, Demedts P, Wauters A, Meltzer HY, et al. Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. *Biol Psychiatry*. (1997) 42:349–58. doi: 10.1016/S0006-3223(96)00365-4

49. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine*. (1997) 9:853–8. doi: 10.1006/cyto.1997.0238

50. Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Lower plasma coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness. *Neuro Endocrinol Lett*. (2009) 30:462–9.

51. Markopoulou K, Papadopoulos A, Juruena MF, Poon L, Pariante CM, Cleare AJ. The ratio of cortisol/DHEA in treatment resistant depression. *Psychoneuroendocrinology*. (2009) 34:19–26. doi: 10.1016/j.psyneuen.2008.08.004

52. Nasca C, Bigio B, Lee FS, Young SP, Kautz MM, Albright A, et al. Acetyl-l-carnitine deficiency in patients with major depressive disorder. *Proc Natl Acad Sci U S A*. (2018) 115:8627–32. doi: 10.1073/pnas.1801609115

53. Pisoni A, Strawbridge R, Hodsoll J, Powell TR, Breen G, Hatch S, et al. Growth factor proteins and treatment-resistant depression: a place on the path to precision. *Front Psych*. (2018) 9:386. doi: 10.3389/fpsyt.2018.00386

54. Rengasamy M, McClain L, Gandhi P, Segreti AM, Brent D, Peters D, et al. Associations of plasma interleukin-6 with plasma and cerebrospinal fluid monoamine biosynthetic pathway metabolites in treatment-resistant depression. *Neurol Psychiatry Brain Res*. (2018) 30:39–46. doi: 10.1016/j.npbr.2018.05.001

55. Sánchez-Carro Y, de la Torre-Luque A, Leal-Leturia I, Salvat-Pujol N, Massaneda C, de Arriba-Arnau A, et al. Importance of immunometabolic markers for the classification of patients with major depressive disorder using machine learning. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2023) 121:110674. doi: 10.1016/j.pnpbp.2022.110674

56. Sasaki T, Hashimoto K, Oda Y, Ishima T, Yakita M, Kurata T, et al. Increased serum levels of oxytocin in 'Treatment resistant depression in adolescents (TRDIA)' group. *PLoS One*. (2016) 11:e0160767. doi: 10.1371/journal.pone.0160767

57. Schwieler L, Samuelsson M, Frye MA, Bhat M, Schuppe-Koistinen I, Jungholm O, et al. Electroconvulsive therapy suppresses the neurotoxic branch of the kynurenine pathway in treatment-resistant depressed patients. *J Neuroinflammation*. (2016) 13:51. doi: 10.1186/s12974-016-0517-7

58. Sowa-Kucma M, Styczen K, Siwek M, Misztak P, Nowak RJ, Dudek D, et al. Lipid peroxidation and immune biomarkers are associated with major depression and its phenotypes, including treatment-resistant depression and melancholia. *Neurotox Res*. (2018) 33:448–60. doi: 10.1007/s12640-017-9835-5

59. Strawbridge R, Jamieson A, Hodsoll J, Ferrier IN, McAllister-Williams RH, Powell TR, et al. The role of inflammatory proteins in anti-glucocorticoid therapy for treatment-resistant depression. *J Clin Med*. (2021) 10:784. doi: 10.3390/jcm10040784

60. Strawbridge R, Hodsoll J, Powell TR, Hotopf M, Hatch SL, Breen G, et al. Inflammatory profiles of severe treatment-resistant depression. *J Affect Disord*. (2019) 246:42–51. doi: 10.1016/j.jad.2018.12.037

61. Szałach ŁP, Cubała WJ, Lisowska KA. Changes in T-cell subpopulations and cytokine levels in patients with treatment-resistant depression-a preliminary study. *Int J Mol Sci*. (2022) 24:479. doi: 10.3390/ijms24010479

62. Uint L, Bastos GM, Thurow HS, Borges JB, Hirata TDC, França JID, et al. Increased levels of plasma IL-1b and BDNF can predict resistant depression patients. *Rev Assoc Med Bras*. (2019) 65:361–9. doi: 10.1590/1806-9282.65.3.361

63. Vandoolaeghe E, Maes M, Vandevyvere J, Neels H. Hypothalamic-pituitary-thyroid-axis function in treatment resistant depression. *J Affect Disord*. (1997) 43:143–50. doi: 10.1016/s0165-0327(96)01426-7

64. Van Hunsel F, Wauters A, Vandoolaeghe E, Neels H, Demedts P, Maes M. Lower total serum protein, albumin, and beta-and gamma-globulin in major and treatment-resistant depression: effects of antidepressant treatments. *Psychiatry Res*. (1996) 65:159–69. doi: 10.1016/s0165-1781(96)03010-7

65. Wu X, Dai B, Yan F, Chen Y, Xu Y, Xia Q, et al. Serum cortisol, Nesfatin-1, and IL-113: potential diagnostic biomarkers in elderly patients with treatment-resistant depression. *Clin Interv Aging*. (2022) 17:567–76. doi: 10.2147/CIA.S361459

66. Zhou Y, Zheng W, Liu W, Wang C, Zhan Y, Li H, et al. Antidepressant effect of repeated ketamine administration on kynurenine pathway metabolites in patients with unipolar and bipolar depression. *Brain Behav Immun*. (2018) 74:205–12. doi: 10.1016/j.bbi.2018.09.007

67. Zincir S, Öztürk P, Bilgen AE, Izci F, Yükselir C. Levels of serum immunomodulators and alterations with electroconvulsive therapy in treatment-resistant major depression. *Neuropsychiatr Dis Treat*. (2016) 12:1389–96. doi: 10.2147/NDT.S106652

68. Kendler KS. Incremental advances in psychiatric molecular genetics and nosology. *World Psychiatry*. (2022) 21:415–6. doi: 10.1002/wps.20999

69. Penninx BWJH. Psychiatric symptoms and cognitive impairment in "long COVID": the relevance of immunopsychiatry. *World Psychiatry*. (2021) 20:357–8. doi: 10.1002/wps.20913

70. Keshavan MS. Characterizing transdiagnostic premorbid biotypes can help progress in selective prevention in psychiatry. *World Psychiatry*. (2021) 20:231–2. doi: 10.1002/wps.20857

71. Wakefield JC. Klerman's "credo" reconsidered: neo-Kraepelinianism, Spitzer's views, and what we can learn from the past. *World Psychiatry*. (2022) 21:4–25. doi: 10.1002/wps.20942

72. Arango C, Dragioti E, Solmi M, Cortese S, Domschke K, Murray RM, et al. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. *World Psychiatry*. (2021) 20:417–36. doi: 10.1002/wps.20894

73. Islam MR, Sohan M, Daria S, Masud AA, Ahmed MU, Roy A, et al. Evaluation of inflammatory cytokines in drug-naïve major depressive disorder: a systematic review and meta-analysis. *Int J Immunopathol Pharmacol*. (2023) 37:3946320231198828. doi: 10.1177/03946320231198828

74. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. (2000) 22:370–9. doi: 10.1016/S0893-133X(99)00134-7

75. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am J Psychiatry*. (2014) 171:1278–86. doi: 10.1176/appi.ajp.2014.14010094

76. Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology*. (2006) 31:2121–31. doi: 10.1038/sj.npp.1301029

77. Haroon E, Daguanno AW, Woolwine BJ, Goldsmith DR, Baer WM, Wommack EC, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology*. (2018) 95:43–9. doi: 10.1016/j.psyneuen.2018.05.026

78. Krueger RF, Hobbs KA, Conway CC, Dick DM, Dretsch MN, Eaton NR, et al. Validity and utility of hierarchical taxonomy of psychopathology (HiTOP): II. Externalizing superspectrum. *World Psychiatry*. (2021) 20:171–93. doi: 10.1002/wps.20844

79. de Felice G, Luciano M, Boiano A, Colangelo G, Catapano P, Della Rocca B, et al. Can brain-derived neurotrophic factor be considered a biomarker for bipolar disorder? An analysis of the current evidence. *Brain Sci*. (2023) 13:1221. doi: 10.3390/brainsci13081221

80. Lydiard RB. Worried sick: antidepressants, stress, and inflammation. *J Clin Psychiatry*. (2007) 68:1613–4. doi: 10.4088/jcp.v68n1021

81. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience*. (2013) 246:199–229. doi: 10.1016/j.neuroscience.2013.04.060

82. Laugesen K, Farkas DK, Vestergaard M, Jørgensen JOL, Petersen I, Sørensen HT. Glucocorticoid use and risk of suicide: a Danish population-based case-control study. *World Psychiatry*. (2021) 20:142–3. doi: 10.1002/wps.20831

83. Feldman R. What is resilience: an affiliative neuroscience approach. *World Psychiatry*. (2020) 19:132–50. doi: 10.1002/wps.20729

84. Lee DH, Lee JY, Hong DY, Lee EC, Park SW, Lee YK, et al. Pharmacological treatment for Neuroinflammation in stress-related disorder. *Biomedicine*. (2022) 10:2518. doi: 10.3390/biomedicines10102518

85. Dinan TG, Cryan JF. Gut microbiota: a missing link in psychiatry. *World Psychiatry*. (2020) 19:111–2. doi: 10.1002/wps.20726

86. Zádor F, Joca S, Nagy-Grócz G, Dvorácskó S, Szűcs E, Tömböly C, et al. Pro-inflammatory cytokines: potential links between the endocannabinoid system and the kynurenine pathway in depression. *Int J Mol Sci*. (2021) 22:5903. doi: 10.3390/ijms22115903

87. Cavaleri D, Bartoli F, Capogrosso CA, Guzzi P, Moretti F, Riboldi I, et al. Blood concentrations of neopterin and biopterin in subjects with depression: a systematic review and meta-analysis. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2023) 120:110633. doi: 10.1016/j.pnpbp.2022.110633

88. Kalkman HO, Feuerbach D. Antidepressant therapies inhibit inflammation and microglial M1-polarization. *Pharmacol Ther*. (2016) 163:82–93. doi: 10.1016/j.pharmthera.2016.04.001

89. Veronese N, Stubbs B, Solmi M, Ajnakina O, Carvalho AF, Maggi S. Acetyl-L-carnitine supplementation and the treatment of depressive symptoms: a systematic review and Meta-analysis. *Psychosom Med*. (2018) 80:154–9. doi: 10.1097/PSY.0000000000000537

90. Dyck MJ. Treatment-resistant depression: a critique of current approaches. *Aust N Z J Psychiatry*. (1994) 28:34–41. doi: 10.3109/00048679409075843

91. Conway CR, George MS, Sackeim HA. Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. JAMA. *Psychiatry*. (2017) 74:9–10. doi: 10.1001/jamapsychiatry.2016.2586

92. Borsboom D, Haslbeck JMB, Robinaugh DJ. Systems-based approaches to mental disorders are the only game in town. *World Psychiatry*. (2022) 21:420–2. doi: 10.1002/wps.21004

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A narrative review of digital biomarkers in the management of major depressive disorder and treatment-resistant forms

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Introduction: Depression is the leading cause of worldwide disability, until now only 3% of patients with major depressive disorder (MDD) experiences full recovery or remission. Different studies have tried to better understand MDD pathophysiology and its resistant forms (TRD), focusing on the identification of candidate biomarkers that would be able to reflect the patients' state and the effects of therapy. Development of digital technologies can generate useful digital biomarkers in a real-world setting. This review aims to focus on the use of digital technologies measuring symptom severity and predicting treatment outcomes for individuals with mood disorders.

Methods: Two databases (PubMed and APA PsycINFO) were searched to retrieve papers published from January 1, 2013, to July 30, 2023, on the use of digital devices in persons with MDD. All papers had to meet specific inclusion criteria, which resulted in the inclusion of 12 articles.

Results: Research on digital biomarkers confronts four core aspects: (I) predicting diagnostic status, (II) assessing symptom severity and progression, (III) identifying treatment response and (IV) monitoring real-word and ecological validity. Different wearable technologies have been applied to collect physiological, activity/sleep, or subjective data to explore their relationships with depression.

Discussion: Depression's stable rates and high relapse risk necessitate innovative approaches. Wearable devices hold promise for continuous monitoring and data collection in real world setting.

Conclusion: More studies are needed to translate these digital biomarkers into actionable interventions to improve depression diagnosis, monitoring and management. Future challenges will be the applications of wearable devices routinely in personalized medicine.

KEYWORDS

major depressive disorder, digital biomarkers, wearable devices, artificial intelligence, personalized treatment, mental healthcare

Highlights

- Digital biomarkers show promise in predicting and assessing mood disorders.
- Smartphone data aids in tracking depression severity and treatment responses.
- Wearable devices enhance real-world monitoring of mood disorders.
- Artificial intelligence advances offer new diagnostic and therapeutic possibilities.
- Integration of technology improves major depressive disorder (MDD) diagnosis and personalized treatment.

1 Introduction

Globally, depression is estimated to affect 300 million individuals and is the leading cause of disability worldwide (1) and will become the leading cause of disability globally by 2030 (1). The prevalence of depressive disorders is highest among young adults aged 18 years (2–4). Onset during adolescence poses a particularly elevated risk of recurrence and long-term impairment in real-life functioning (5, 6). Despite increased accessibility of treatment over the last four decades prevalence rates have remained static (7). Even the best available treatments are largely unsuccessful at producing lasting outcomes, as approximately 40%–50% of patients relapse within 1–2 years of receiving treatment (8, 9). Symptoms of depression may manifest on multiple levels, including subjective emotional, cognitive, behavioral, and physical. In the depression field there is a strong need for monitoring clinical evolution and treatment responses in a more efficient manner to identify the treatment-resistant depression (TRD) forms. TRD is a condition characterized by persistent or recurrent depressive symptoms despite adequate treatment with one or more antidepressant medications (10). Approximately one-third of individuals with major depressive disorder (MDD) do not achieve full remission of symptoms even after trying two suitable trials of antidepressants without adequate response (11, 12). Despite its medical importance MDD is poorly defined and diagnosed since its diagnosis is mostly based on data subjectively reported by the patients themselves (13–15) and lack of objective, clinically relevant outcome measure. It is still debated whether mental disorders should be conceptualized as discrete entities (categorical approach) such as DSM or ICD or as phenomena along a continuum of severity (dimensional approach). The US National Institute of Mental Health proposed a new approach for research on mental disorders, the research domain criteria (RDoC) (16), a project aimed at re-orienting research on etiology and pathophysiology of psychopathological phenomena from category-based to dimension-based and at incorporating genetics, neuroimaging, and cognitive features into diagnostic schemes. The focus of research in mood disorders has shifted to more quantifiable metrics, while behavioral aspects have diminished markedly in importance (17). Digital biomarkers have significant value in psychiatric conditions like schizophrenia, autism, and PTSD. In schizophrenia, they assist in early diagnosis, symptom tracking, and treatment optimization, enhancing patient care. For autism, digital biomarkers are crucial for monitoring social interactions and enabling early diagnosis and personalized interventions. In PTSD, these biomarkers aid in monitoring physical and behavioral responses, supporting early intervention and symptom assessment. Digital biomarkers are defined as objective, quantifiable physiological and behavioral data that are collected and measured by means of digital devices such as portables, wearables, implantables, or ingestibles. Digital technologies offer promising tools for detecting MDD and depression-related symptoms objectively and precisely (18, 19). These technologies enable the remote collection of large volumes of clinically relevant data, which may be less burdensome than traditional in-clinic visits and more reflective of clinically relevant changes (20, 21). Wearable technologies, such as smartwatches and novel sensors, can generate valuable digital biomarkers of depression in real-world settings (22) building a digital phenotyping, defined as the moment-by-moment quantification of the individual-level human phenotypein its own environment using apps from smartphones or other personal devices (19, 23). In the recent years, several digital biomarkers have been investigated for MDD characterization and diagnosis such as measure patterns of physical activity (24, 25) features from voice samples (26, 27), light exposure measurements (25), mobile phone global positioning systems (GPS) and normal usage of smartphones such as usage duration and frequency (22).

2 Aims of this review

This review investigates how digital technologies, such as wearables and smartphone apps, are revolutionizing the assessment and treatment of major depressive disorder (MDD) and treatment-resistant depression (TRD). It anticipates that as digital mental health assessment advances and precision medicine is applied, the quality of life for individuals with MDD and TRD will improve. The review also identifies research gaps and recommends further investigation.

3 Methods

3.1 Search strategy and study eligibility criteria

To identify studies on the use of wearable devices in depression research, a literature search was performed to two major health-related databases: PubMed and APA PsycINFO, focusing on articles published from 1st of January 2013 to 30 July 2023. We searched for papers in which abstracts included the terms: Depression AND Device OR Depression AND digital tools OR Depression AND digital biomarkers OR Depression AND smartwatch OR Resistant depression AND digital biomarker OR Resistant depression AND digital biomarker OR Resistant depression AND actigraphy OR Resistant depression AND smartwatch.

Studies were chosen based on these inclusion criteria: randomized controlled trial, retrospective study, cohort study, open study, expert opinion, concerning conceptualization, diagnosis of major depressive disorder (MDD) according to DSM-5 or ICD-10, studies published in English, studies carried out in humans and studies published in journals indexed in Embase or Medline.

The exclusion criteria were meta-analysis, review, duplicates, comments, editorials, case reports/case series, theses, proceedings, letters, short surveys and notes, studies irrelevant for the topic, unavailable full-text and studies that do not meet inclusion criteria.

The PRISMA search process is presented in Figure 1.

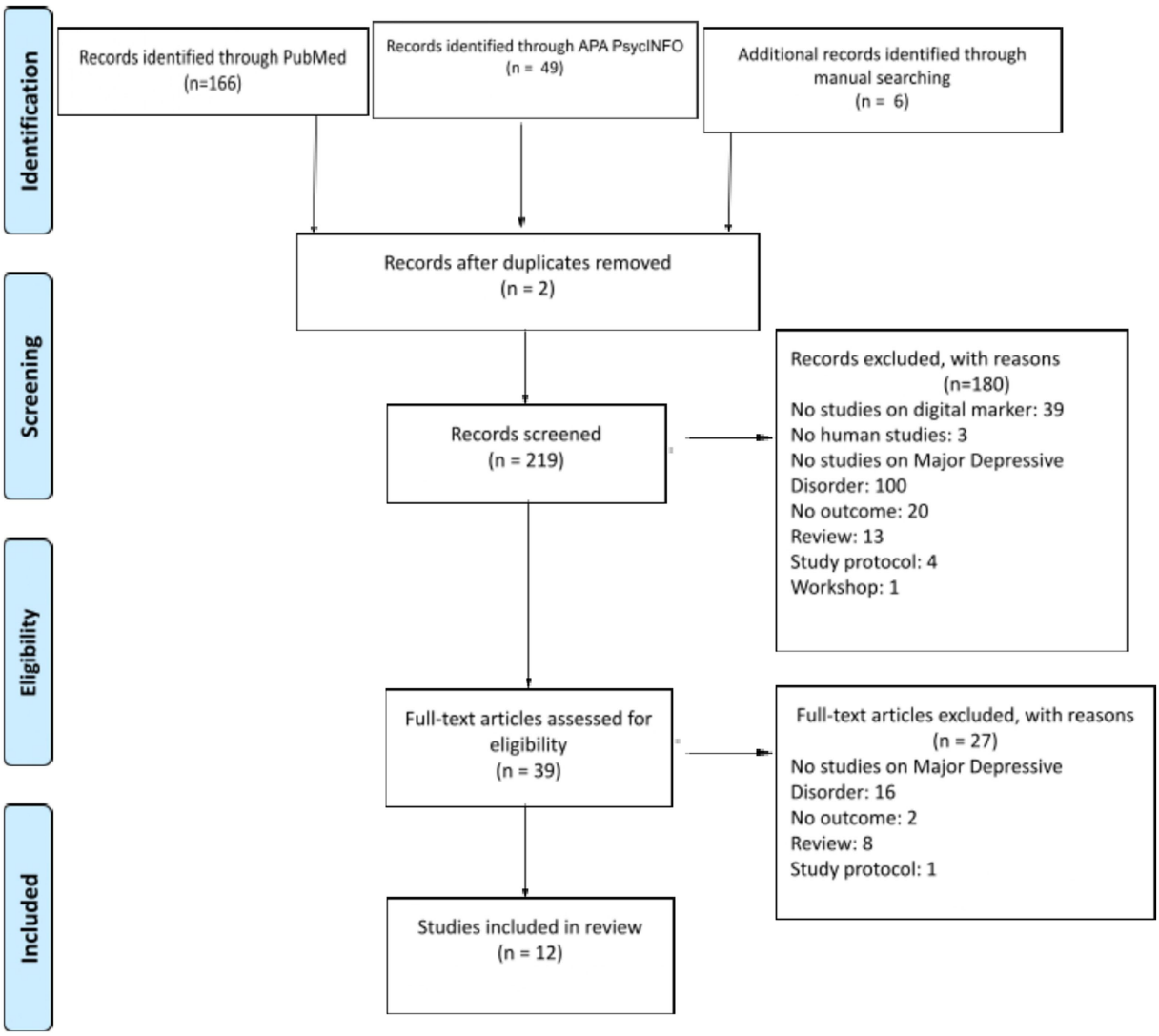

FIGURE 1
Flowchart of the study selection process. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 21. e1000097. doi: 10.1371/journal.pmed.1000097.

We collected a total of 12 studies that made use of wearable devices to assess or monitor depressive symptoms and TRD or to predict MDD (Table 1).

3.2 Study selection

The selection of studies for this review occurred in a two-stage process. Initially, two independent reviewers assessed the titles and abstracts of all the retrieved papers. In the subsequent stage, these same reviewers individually examined the full texts of the papers identified in the first phase. Any discrepancies between the two reviewers were resolved by involving a third reviewer.

3.3 Data extraction and data synthesis

Data extraction for each included study was carried out by two independent researchers, namely AV and FM, utilizing a standardized data extraction sheet in Microsoft Excel. The focus of this extraction encompassed several key subjects, including study design, participant characteristics, diagnosis of MDD, and digital device details derived from the original research.

In the event of any disparities in data entry between these two researchers, such discrepancies were thoroughly deliberated with two additional independent reviewers when deemed necessary.

4 Results

4.1 Literature search

The search across PubMed and APA PsycINFO bibliographic database produced a total of 215 records. Additionally, by conducting backward reference list checking and forward reference list checking, we discovered 6 new studies. After initial screening based on their titles and abstracts, 180 records were excluded. Out of the initial 39 references, the synthesis now comprises a total of 12 articles.

TABLE 1 Studies using digital devices in subjects with MDD and TRD.

References	Subjects	Mood disorder diagnosis	Wearable device type	Device technology brands	Methods	Study experimentation duration	Mood assessed methods	Main points
Jacobson et al. (28)	23 patients (65% with primary MDD; 30% Bipolar II and 4% Bipolar I)	SCID-I	Wrist actigraph	Actiwatch	Actigraphs were worn at all times, except when bathing. The sampling frequency was 32 Hz and movements of ≥0.05 g were recorded. Voltage of movement was recorded for each minute	2 weeks	MADRS	Participants' diagnostic group status can be predicted with a high degree of accuracy (predicted correctly 89% of the time)
Jacobson et al. (24)	15 MDD outpatients	MINI	Wrist actigraph	Actiwatch-L	Record of continuous movements (≥0.01 g) and ambient light exposure in lux every 15 min	1 week	BDI II; HAM-D	Passive movement and light data collected can be used to accurately assess both self-reported and clinician-rated depression severity
Siddi et al. (29)	510 MDD	LIDAS	Wrist-worn wearable device, and smartphone apps	Fitbit charge 2 and 3	HR was computed during the whole day (24 h) and just at night (from 00:00 to 05:59), as well as just during resting periods and during active periods separately. The average of each of the daily HR parameters was computed in the week before the PHQ-8 assessment across the follow-up	Up 2 years follow up	PHQ-8 (delivered through an app installed in an Android smartphone) every 2 weeks	During resting periods: decreases in HR variation during the day were related with an increased severity of depression. An HR at night was higher in participants with more severe depressive symptoms
Sverdlov et al. (30)	20 subjects with unipolar depression (MDD; PDD) 20 healthy controls	MINI	Smartphone apps	Android-based smartphone	During in-clinic visits three technologies were administered via mobile applications: an interactive tool for the self-assessment of mood, and a cognitive test; a passive behavioral monitor to assess social interactions and global mobility; a platform to perform voice recordings	2 weeks	HAM-D; MADRS	Correlation between various digital biomarker features and a clinical endpoint (MADRS total score) was assessed. Selected digital biomarker features (PHQ2 of Cambridge cognition; behavioral tracker features of BeHapp; neurophysiological features of Neurocart; EEG—resting state features of ElMindA Ltd. and EEG—BNA features of ElMindA Ltd.) were able to predict individual MADRS total scores, and use these models as classifiers
Abbas et al. (31)	18 MDD (11 women, 7 men)	MINI, MADRS	Smartphone apps		Video and audio captured during the smartphone assessment using the smartphone front-facing camera and microphone	4 weeks	Participants were asked by push-notification	Ability of digitally measured facial, vocal, and movement behaviors to measure depression severity and treatment response across 4 weeks of antidepressant treatment
Cormack et al. (32)	30 MDD (19 women, 11 men)	PHQ-9	Smartphone app, smartwatch	Apple iPhone, Apple Watch series 2	Cognitive and self-report assessments, heart rate and activity data	6 weeks	Complete the PHQ-8 every 2 weeks	High correspondence was observed between frequent assessments and established measures, showing moderate alignment between daily mood evaluations and validated depression questionnaires, and similar correlation for cognitive assessments with depression-sensitive tests

(Continued)

TABLE 1 (Continued)

References	Subjects	Mood disorder diagnosis	Wearable device type	Device technology brands	Methods	Study experimentation duration	Mood assessed methods	Main points
Kim et al. (33)	24 adolescents with MDD (17 girls, 7 boys), 10 HC	K-SAD -Present and Lifetime Version	Smartphone app		Smartphone usage time, physical movement distance, and the number of phone calls and text messages during the study period (STAR-DS app)	5 weeks	CDRS-R,CDI, BDI-II, C-SSRS CGI-S, CGAS, SCARED	Adolescents with MDD displayed higher call reception, possibly due to increased attention from family and friends. MDD participants exhibited extended smartphone usage, yet their usage wasn't oriented towards social communication, marking a distinction from controls. MDD participants traveled longer distances than controls.
Zhang et al. (34)	316 MDD	PHQ-8	Smartphone NBDC		Passive and active remote monitoring technology apps and an activity tracker	2 years	PHQ-8	Increased time at home, inability to work or study, and diminished social interactions are reflected in the reduced amount of the NBDC sequence. Depression also may lead to misalignment of the circadian rhythm and make people's life rhythms (such as sleep rhythms and social rhythms) more irregular
Mahendran et al. (35)	450 MDD	HAM-D	Smartwatch	Mi band—3	Gyroscope, accelerometer, heart rate monitor for recording the data from the gestures that the users make	1 week	—	The smartwatch data was used because it provided objective sensor data compared to the subjective questionnaire responses. After preprocessing and feature selection, logistic regression and random forest models were applied individually and then combined using a weighted average ensemble model. The results indicated that the weighted average ensemble performed better than the individual models, with random forest outperforming logistic regression
McNamara et al. (31)	60 MDE, 54 PC, 101 NCP	MINI for DSM-5	Sctigraphy		Daily physical activity, sleep consistency	1 week	MASQG, SHAPS	Psychiatric control groups can help to distinguish specific factors in the diagnosis of interest. Low positive emotionality is a strong differentiator of depression. Additionally, perceived sleep quality and impairment are also important predictors
Winkler et al. (36)	14 TRD	SCID-1	Actigraph	Actiwatch plus	Activity levels were measured with wrist actigraphy before and after ECT	4.1 ± 4.7 days of actigraphic measurement before ECT and 3.6 ± 2.1 days after ECT	HAM-D	Increase in light activity and circadian amplitude in patients with remission after ECT
Nishida et al. (37)	14 patients with medication resistant MDD	MINI	Actigraph	FS-750	Patients were instructed to wear the FS-750 system for a period of 7 days before the initiation of rTMS treatment and until rTMS treatment was completed	Actigraphic data were evaluated at baseline and in the first (rTMS sessions 1–3), second (rTMS sessions 4–7), and third (rTMS sessions 8–10) sections	HAM-D; PSQI	Sleep variables assessed by actigraphy did not show significant changes. A daytime physical activity response to rTMS occurred in early sessions

BDI-II, Beck Depression Inventory II; CDI, Children's Depression Inventory; CDRS-R, Children's Depression Rating Scale—Revised; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impressions-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; ECT, Electroconvulsive Therapy; EEG-BN, Electroencephalography Brain Network; HAM-D, Hamilton Depression Rating Scale; HR, Heart Rate; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; LIDAS, Lifetime Depression Assessment Self-Report; MASQ-GD, Mood and Anxiety Symptom Questionnaire—Short Form general distress subscale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; MINi, Mini—International Neuropsychiatric Interview; NBDC, Nearby Bluetooth Device Count; NCP, No Current Psychopathology; PC, Psychiatric Control; PDD, Persistent Depressive Disorder; PHQ-2, Patient Health Questionnaire-2; PHQ-8, Patient Health Questionnaire-8; PSQI, Pittsburgh Sleep Quality Index; rTMS, Repetitive transcranial magnetic stimulation; SCARED, Screen for Child Anxiety Related Emotional Disorders; SCID-I, Structured Clinical Interview; SHAPS, Snaith-Hamilton Pleasure Scale; STAR-D, Sequenced Treatment Alternatives to Relieve Depression.

4.2 General description of included studies

Among the various studies examining wearable devices for individuals with MDD, approximately one- third employed actigraph units, while the rest utilized commercial wearable devices not originally designed for medical purposes. These included devices such as the Fitbit® (Fitbit®, Inc., San Francisco, CA, United States), the Apple Watch (Apple Inc., Cupertino, CA, United States), and the Mi Smartwatch (Xiaomi Corporation, China). In addition, some studies relied on mobile applications (Apps).

Through a narrative synthesis of various reviews and in agreement with several authors' perspectives, we have pinpointed specific domains where the integration of tools and digital markers significantly enhances clinicians' capabilities in predicting, diagnosing, and providing care and treatment for individuals grappling with MDD and TRD.

The reviewed studies focused on gathering specific physiological, activity/sleep, or subjective data from individuals through digital devices, with the aim of exploring the relationship between these parameters and depression.

4.2.1 Predictive modeling of diagnostic status

Multiple studies have showcased the promise of digital biomarkers, encompassing factors like movement intensity, light exposure, and smartphone usage patterns, in forecasting the diagnostic status of individuals grappling with mood disorders (19, 22, 38). Jacobson et al. (28) conducted a study to identify digital biomarkers for MDD and bipolar disorder (BD) and track symptom changes over 2 weeks. By analyzing movement patterns, they used extreme gradient boosting to achieve an 89% accuracy in predicting diagnostic groups and monitoring symptom changes. Combining MDD and BD data revealed potential transdiagnostic traits. Movement and light data were found relevant for detecting mood disorders and correlated with behaviors like energy levels, psychomotor activity, and sleep disturbances during mood episodes. Two studies focus on data analysis to identify important predictors in different contexts (35, 39). In their study Mahendran et al. (35), researchers used cardiac monitoring data, which included questionnaire responses and smartwatch sensor data. They then trained machine learning models such as logistic regression and random forest, and the results showed that the ensemble of models performed better than individual implementations, with random forest standing out. McNamara et al. (39), used a wide range of data, including demographic data, biobehavioral measurements, and self-report questionnaires to identify predictors of depression. The results revealed that psychosocial predictors such as negative self-referential thinking, rumination, self- reported sleep quality, and functional distress were important in predicting depression.

4.2.2 Assessment of symptom severity and progression

Digital phenotyping has emerged as a valuable tool for evaluating the severity and trajectory of mood disorder symptoms. In the realm of assessing depression severity and treatment response in individuals with MDD, researchers have explored the utilization of digital biomarkers and technologies. Four notable studies shed light on this area: in the study conducted by Jacobson et al. (24), passive movement and light exposure data were analyzed in 15 medicated outpatients with MDD over a week. The study demonstrated that passive movement and light data could effectively gauge depression severity, even in cases of high severity. However, while modern lifestyles often drive the development of technology tailored for personal fitness, such as Fitbit® and various apps that monitor vital signs like heart rate and body temperature, many devices used in research are repurposed for the advancement of mental health applications. Abbas et al. (31), used the AiCure smartphone app to track digital biomarkers associated with MDD under antidepressant therapy (ADT). These markers included voice, facial expressions, and movement indicators. The study found that monoamine ADTs, such as SSRIs and SNRIs, had a significant impact on digital biomarker with a reduction in symptom severity as assessed by the MADRS evaluation, indicating an improvement in motor functioning and a decrease in depression severity due to these treatments. Indeed, in Sverdlov et al. (30), the authors points out that common efficacy scales like HAM-D and MADRS are subjective and prone to bias. Digital technologies offer objective tools for depression symptom detection. Mobile apps and wearables can generate digital biomarkers in real-world settings. The study assessed seven digital technologies in individuals with unipolar depression and healthy controls, aiming to distinguish between them, build accurate classifiers, and explain variation in MADRS scores. Technologies were evaluated to identify digital biomarkers revealing correlations between different digital Importantly, selected digital biomarker features demonstrated predictive capabilities for individual. Therefore, Siddi et al. (29) in their study with up to 2 years follow up, based on data from the RADAR-MDD study involving 600 individuals with MDD, examined the relationship between heart rate (HR) parameters using a Fitbit® device and the severity of depression. The findings showed that individuals with higher depression severity tended to have a lower resting HR variation throughout the day, and this association remained significant even after accounting for individual characteristics. The research indicates that passive behaviors, which are indicative of depression, are more common in individuals with greater depression severity, particularly during the nighttime when HR may be elevated due to the sleep problems often seen in those with MDD.

4.2.3 Treatment response monitoring

Assessing treatment responses in the context of mood disorders constitutes a pivotal research domain. Abbas et al. (31) showcased the capacity of digital biomarkers, encompassing motor function, to accurately monitor shifts in depression severity throughout the course of antidepressant therapy. In a parallel attempt, Kim et al. (33) used smartphone data to prognosticate treatment outcomes among adolescents grappling with MDD, shedding light on the prospect of personalized treatment strategies through the avenue of digital phenotyping. In their research, Winkler et al. (36) investigated the impact of electroconvulsive therapy (ECT) on rest-activity patterns in patients with TRD. They studied 15 individuals with TRD who received ECT and used wrist actigraphy to measure their activity levels before and after treatment. They observed that Individuals who reached remission experienced notable enhancements in light activity, overall activity, and circadian amplitude and ECT had a limited impact on the timing of peak activity or actigraphic sleep measurements. In 2016, Nishida et al. (37) conducted an open-label pilot study on 14 medication-resistant MDD patients to assess the impact of rTMS on their rest-activity cycle and sleep disturbances. They administered 10 rTMS sessions targeting the

bilateral dorsolateral prefrontal cortex and used waist actigraphy to measure changes in the rest- activity cycle. The results showed significant improvements in depression symptoms and sleep quality measured by rating scales, but actigraphy-based sleep measures did not exhibit substantial changes. Digital therapeutics are under study and represent a potential future clinical vista in this population (18). These findings, coupled with advancements in the realm of digital biomarkers and the refinement of neurostimulation parameters, hold potential for improving overall health results and the cost efficiency of MDD and TRD treatment.

4.2.4 Real-world monitoring and ecological validity

Incorporating wearable devices into depression research offers several benefits. Wearable technology allows for ongoing and unbiased observation of individuals in their everyday environments. This enables the objective tracking of real-time changes and enhances the precision of monitoring treatment outcomes. Cormack et al. (32), involving individuals with MDD, explored the use of wearable technology for high-frequency cognitive and mood assessments over 6 weeks. The study found that daily assessments were practical and showed meaningful correlations with established measures of mood and cognition. While there was some improvement in mood, it varied among participants, highlighting the complexity of depression. In Kim et al. (33) paper, data from a smartphone app called "STAR-DS" was used to predict depressive symptoms and treatment responses in adolescents. The study found that call-related features, smartphone usage duration, and movement distance were important predictors of MDD. Call duration was especially significant in predicting treatment responses. Adolescents with MDD had different smartphone usage patterns compared to controls. This study emphasized the potential of smartphone behaviors in forecasting depression outcomes. Remote measurement technologies were used to monitor individuals with MDD in real-world settings. The study of Zhang et al. (34), found that Bluetooth device count (NBDC) data was correlated with depressive symptoms. Lower PHQ-8 scores were associated with increased social activities. Changes in NBDC data were linked to fluctuations in depressive manifestations and behaviors, including reduced social engagement, impaired work, or study performance, and disrupted circadian rhythms. This research highlighted the feasibility of using NBDC for monitoring individuals with MDD in real-life contexts.

5 Discussion

The review of the selected studies on predictive modeling, assessment of symptom severity and progression, treatment response monitoring, and real-world monitoring with ecological validity showcases the remarkable potential of digital biomarkers and technologies in advancing our understanding and management of MDD and TRD. The ability to predict diagnostic status with a high degree of accuracy using digital biomarkers is may be a transformative breakthrough. The integration of movement, light exposure, and smartphone data has not only enabled accurate predictions but has also revealed common features across mood disorders, highlighting the existence of transdiagnostic traits. This is in line with the research domain criteria (RDoC) criteria and opens new prospective for understanding the underlying mechanisms of mood disorders (35, 39). Assessing symptom severity and progression may be significantly enhanced by digital phenotyping, although this kind of technology is rapidly improving and the validity of these measurements need more strong confirmations. The use of passive movement and light exposure data, often repurposed from personal fitness technology, demonstrates the adaptability and versatility of digital biomarkers in assessing depression severity. Moreover, the impact of antidepressant therapies on digital biomarkers related to motor function may provides valuable insights into the mechanisms of action of these treatments. The ability to predict individual depression severity scores are groundbreaking advancements in the field, digital biomarkers potential role in predicting individual depression severity may be a groundbreaking advancement, once confirmed and replicated in larger populations studies, providing clinicians with even more personalized assessment instruments (29, 30). Monitoring treatment responses, especially in cases of treatment-resistant depression (TRD), is crucial for improving patient outcomes. These advancements, coupled with the refinement of neurostimulation parameters, hold the potential to enhance overall health outcomes and the cost-effectiveness of TRD care. This suggests that approaches, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), have the potential to positively impact the rest-activity cycle in TRD patients who achieve remission. The demonstrated effectiveness of digital biomarkers, including motor function, in tracking shifts in depression severity during treatment is a significant step forward (33, 36). Additionally, the potential for personalized treatment strategies through smartphone data analysis among adolescents with MDD holds promise for tailoring interventions to individual needs. Real-world monitoring with ecological validity using wearable technology and smartphone apps represents a paradigm shift in depression research. The ability to conduct daily assessments in natural environments provides a more comprehensive understanding of mood fluctuations and cognitive changes. Smartphone behaviors and Bluetooth device count data offer exciting prospects for predicting MDD and treatment responses. These findings underscore the dynamic nature of depression and the importance of considering real-world factors in assessment and treatment planning (33, 34).

6 Conclusion

This narrative review highlights the diverse research areas that underscore the versatility and potential of digital biomarkers and technologies in the diagnosis, assessment, and treatment of mood disorders. In this review, we delve into the technologies, available research findings, and implementation challenges most pertinent to the integration of digital psychiatry within MDD and its resistant forms. The integration of wearable devices with smart devices, such as mobile phones, has gained widespread acceptance due to their convenience and style (20). Notably, our review is the first in the literature to focus on wearable devices targeting depression assessed using DSM-5 or ICD-10 criteria. Although the different wearable device technologies were examined, the review falls short of reporting the effectiveness measure values, and therefore does not assess performance. This review underscores the potential for remote diagnosis and prediction using these devices. Future trends are anticipated with the emergence of new wearable devices that will introduce innovative diagnostic and therapeutic approaches like motion

capture, speech analysis, and portable light therapy. These developments hold the promise of fundamental changes in the diagnosis and treatment of depression, potentially enabling early and precise diagnosis, personalized treatment for depression patients, and preventive measures for at-risk groups (40, 41). Digital psychiatry encompasses various aspects of healthcare, including delivery, illness surveillance, disease management, and treatment. Advances in artificial intelligence and machine learning are expected to serve as a crucial bridge for translating new data into clinically relevant digital biomarkers (22, 38).

Wearable devices are poised to play a critical role in medicine, particularly in the context of personalized telemedicine. Future research endeavors should continue to explore these areas, enhancing the precision and efficacy of digital phenotyping in mental healthcare, ultimately leading to an improved quality of life for individuals affected by MDD.

Author contributions

AV: Conceptualization, Data curation, Methodology, Project administration, Resources, Writing – original draft. FM: Conceptualization, Methodology, Project administration, Writing – original draft. CP: Writing – review & editing. MP: Writing – review & editing. FF: Writing – review & editing. GP: Writing – review & editing. RS: Writing – review & editing. AM: Writing – review & editing. JS: Writing – review & editing. MS: Writing – review & editing. GC: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. World Health Organization. *World mental health report: transforming mental health for all* World Health Organization (2022).

2. Maj M. Validity and clinical utility of the current operational characterization of major depression. *Int Rev Psychiatry*. (2012) 24:530–7. doi: 10.3109/09540261.2012.712952

3. Maj M. Development and validation of the current concept of major depression. *Psychopathology*. (2012) 45:135–46. doi: 10.1159/000329100

4. Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Mol Psychiatry*. (2022) 27:281–95. doi: 10.1038/s41380-021-01161-7

5. Bains N, Abdijadid S. Major Depressive Disorder. StatPearls. Treasure Island (FL). (2023).

6. Yalin N, Young AH. Pharmacological treatment of bipolar depression: what are the current and emerging options? *Neuropsychiatr Dis Treat*. (2020) 16:1459–72. doi: 10.2147/NDT.S245166

7. Ormel J, Kessler RC, Schoevers R. Depression: more treatment but no drop in prevalence: how effective is treatment? And can we do better? *Curr Opin Psychiatry*. (2019) 32:348–54. doi: 10.1097/YCO.0000000000000505

8. Dobson KS, Hollon SD, Dimidjian S, Schmaling KB, Kohlenberg RJ, Gallop RJ, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. *J Consult Clin Psychol*. (2008) 76:468–77. doi: 10.1037/0022-006X.76.3.468

9. Vittengl JR, Clark LA, Dunn TW, Jarrett RB. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. *J Consult Clin Psychol*. (2007) 75:475–88. doi: 10.1037/0022-006X.75.3.475

10. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment- resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412. doi: 10.1002/wps.21120

11. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

12. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. *Neuropsychiatr Dis Treat*. (2020) 16:221–34. doi: 10.2147/NDT.S198774

13. Fried EI. Moving forward: how depression heterogeneity hinders progress in treatment and research. *Expert Rev Neurother*. (2017) 17:423–5. doi: 10.1080/14737175.2017.1307737

14. Fried EI. The 52 symptoms of major depression: lack of content overlap among seven common depression scales. *J Affect Disord*. (2017) 208:191–7. doi: 10.1016/j.jad.2016.10.019

15. Taliaz D, Spinrad A, Barzilay R, Barnett-Itzhaki Z, Averbuch D, Teltsh O, et al. Optimizing prediction of response to antidepressant medications using machine learning and integrated genetic, clinical, and demographic data. *Transl Psychiatry*. (2021) 11:381. doi: 10.1038/s41398-021-01488-3

16. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *Am J Psychiatry*. (2014) 171:395–7. doi: 10.1176/appi.ajp.2014.14020138

17. Insel TR. Digital phenotyping: technology for a new science of behavior. *JAMA*. (2017) 318:1215–6. doi: 10.1001/jama.2017.11295

18. McIntyre RS, Greenleaf W, Bulaj G, Taylor ST, Mitsi G, Saliu D, et al. Digital health technologies and major depressive disorder. *CNS Spectr*. (2023) 1-12:1–12. doi: 10.1017/S1092852923002225

19. Lee S, Kim H, Park MJ, Jeon HJ. Current advances in wearable devices and their sensors in patients with depression. *Front Psychiatry*. (2021) 12:672347. doi: 10.3389/fpsyt.2021.672347

20. Ahmed A, Aziz S, Alzubaidi M, Schneider J, Irshaidat S, Abu Serhan H, et al. Wearable devices for anxiety & depression: a scoping review. *Comput Methods Programs Biomed Update*. (2023) 3:100095. doi: 10.1016/j.cmpbup.2023.100095

21. Ahmed A, Hassan A, Aziz S, Abd-Alrazaq AA, Ali N, Alzubaidi M, et al. Chatbot features for anxiety and depression: a scoping review. *Health Informatics J*. (2023) 29:14604582221146719. doi: 10.1177/14604582221146719

22. Torous J, Wisniewski H, Liu G, Keshavan M. Mental health mobile phone app usage, concerns, and benefits among psychiatric outpatients: comparative survey study. *JMIR Ment Health*. (2018) 5:e11715. doi: 10.2196/11715

23. Rajagopalan A, Shah P, Zhang MW, Ho RC. Digital platforms in the assessment and monitoring of patients with bipolar disorder. *Brain Sci*. (2017) 7:150. doi: 10.3390/brainsci7110150

24. Jacobson NC, Weingarden H, Wilhelm S. Using digital phenotyping to accurately detect depression severity. *J Nerv Ment Dis*. (2019) 207:893–6. doi: 10.1097/NMD.0000000000001042

25. Tonon AC, Fuchs DFP, Barbosa Gomes W, Levandovski R, de Almeida P, Fleck M, et al. Nocturnal motor activity and light exposure: objective actigraphy-based marks of melancholic and non-melancholic depressive disorder. Brief report. *Psychiatry Res*. (2017) 258:587–90. doi: 10.1016/j.psychres.2017.08.025

26. Mundt JC, Snyder PJ, Cannizzaro MS, Chappie K, Geralts DS. Voice acoustic measures of depression severity and treatment response collected via interactive voice response (IVR) technology. *J Neurolinguistics*. (2007) 20:50–64. doi: 10.1016/j.jneuroling.2006.04.001

27. Zhang L, Duvvuri R, Chandra KKL, Nguyen T, Ghomi RH. Automated voice biomarkers for depression symptoms using an online cross-sectional data collection initiative. *Depress Anxiety*. (2020) 37:657–69. doi: 10.1002/da.23020

28. Jacobson NC, Weingarden H, Wilhelm S. Digital biomarkers of mood disorders and symptom change. *NPJ Digit Med*. (2019) 2:3. doi: 10.1038/s41746-019-0078-0

29. Siddi S, Bailon R, Gine-Vazquez I, Matcham F, Lamers F, Kontaxis S, et al. The usability of daytime and night-time heart rate dynamics as digital biomarkers of depression severity. *Psychol Med*. (2023) 53:3249–60. doi: 10.1017/S0033291723001034

30. Sverdlov O, Curcic J, Hannesdottir K, Gou L, De Luca V, Ambrosetti F, et al. A study of novel exploratory tools, digital technologies, and central nervous system biomarkers to characterize unipolar depression. *Front Psychiatry*. (2021) 12:640741. doi: 10.3389/fpsyt.2021.640741

31. Abbas A, Sauder C, Yadav V, Koesmahargyo V, Aghjayan A, Marecki S, et al. Remote digital measurement of facial and vocal markers of major depressive disorder severity and treatment response: a pilot study. *Front Digit Health*. (2021) 3:610006. doi: 10.3389/fdgth.2021.610006

32. Cormack F, McCue M, Taptiklis N, Skirrow C, Glazer E, Panagopoulos E, et al. Wearable technology for high-frequency cognitive and mood assessment in major depressive disorder: longitudinal observational study. *JMIR Ment Health*. (2019) 6:e12814. doi: 10.2196/12814

33. Kim JS, Wang B, Kim M, Lee J, Kim H, Roh D, et al. Prediction of diagnosis and treatment response in adolescents with depression by using a smartphone app and deep learning approaches: usability study. *JMIR Form Res*. (2023) 7:e45991. doi: 10.2196/45991

34. Zhang Y, Folarin AA, Sun S, Cummins N, Ranjan Y, Rashid Z, et al. Predicting depressive symptom severity through individuals' nearby Bluetooth device count data collected by mobile phones: preliminary longitudinal study. *JMIR Mhealth Uhealth*. (2021) 9:e29840. doi: 10.2196/29840

35. Mahendran N, Vincent DR, Srinivasan K, Chang CY, Garg A, Gao L, et al. Sensor-assisted weighted average ensemble model for detecting major depressive disorder. *Sensors*. (2019) 19:4822. doi: 10.3390/s19224822

36. Winkler D, Pjrek E, Lanzenberger R, Baldinger P, Eitel D, Kasper S, et al. Actigraphy in patients with treatment-resistant depression undergoing electroconvulsive therapy. *J Psychiatr Res*. (2014) 57:96–100. doi: 10.1016/j.jpsychires.2014.06.006

37. Nishida M, Kikuchi S, Nisijima K, Suda S. Actigraphy in patients with major depressive disorder undergoing repetitive transcranial magnetic stimulation: an open label pilot study. *J ECT*. (2017) 33:36–42. doi: 10.1097/YCT.0000000000000352

38. Torous J, Lipschitz J, Ng M, Firth J. Dropout rates in clinical trials of smartphone apps for depressive symptoms: a systematic review and meta-analysis. *J Affect Disord*. (2020) 263:413–9. doi: 10.1016/j.jad.2019.11.167

39. McNamara ME, Shumake J, Stewart RA, Labrada J, Alario A, Allen JJB, et al. Multifactorial prediction of depression diagnosis and symptom dimensions. *Psychiatry Res*. (2021) 298:113805. doi: 10.1016/j.psychres.2021.113805

40. Moshe I, Terhorst Y, Philippi P, Domhardt M, Cuijpers P, Cristea I, et al. Digital interventions for the treatment of depression: a meta-analytic review. *Psychol Bull*. (2021) 147:749–86. doi: 10.1037/bul0000334

41. Moshe I, Terhorst Y, Opoku Asare K, Sander LB, Ferreira D, Baumeister H, et al. Predicting symptoms of depression and anxiety using smartphone and wearable data. *Front Psychiatry*. (2021) 12:625247. doi: 10.3389/fpsyt.2021.625247

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Cariprazine augmentation in patients with treatment resistant unipolar depression who failed to respond to previous atypical antipsychotic add-on. A case-series

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Among individuals receiving an adequate pharmacological treatment for Major Depressive Disorder (MDD), only 30% reach a full symptom recovery; the remaining 70% will experience either a pharmacological response without remission or no response at all thus configuring treatment resistant depression (TRD). After an inadequate response to an antidepressant, possible next step options include optimizing the dose of the current antidepressant, switching to a different antidepressant, combining antidepressants, or augmenting with a non-antidepressant medication. Augmentation strategies with the most evidence-based support include atypical antipsychotics (AAs). Few data are available in literature about switching to another antipsychotic when a first augmentation trial has failed. We present a case-series of patients with unipolar treatment resistant depression who were treated with a combination of antidepressant and low dose of cariprazine after failing to respond to a first augmentation with another AA. We report data about ten patients affected by unipolar depression, visited at the outpatients unit of Mental Health Department of ASL CN2 of Bra and NA1 of Napoli (Italy). All patients failed to respond to conventional antidepressant therapy. A low dose of AA (aripiprazole, risperidone or brexpiprazole) was added for one month to the ongoing antidepressant treatment without clinical improvement. A second augmentation trial was then made with cariprazine. Seven out of ten patients were responders at the end of period, of them 1 patient reached responder status by week 2. HAM-D mean scores decreased from 23.9 $\pm$ 3.9 (baseline) to 14.8 $\pm$ 5.3 (4 weeks). Cariprazine was well tolerated, no severe side effect was observed during the trial. Our sample of treatment resistant unipolar patients showed good response to augmentation with cariprazine. Failure to a first AA-augmentation trial does not preclude response to a second one. This preliminary result requires confirmation through more rigorous studies conducted over greater samples.

KEYWORDS

major depression, treatment resistance, cariprazine, augmentation, atypical antipsychotic

Introduction

Despite the availability of many pharmacological treatment options, nearly about a half of patients affected by Major Depression Disorder (MDD) do not adequately responds to antidepressant (AD) treatment (1, 2). Treatment resistant depression (TRD) is a serious and disabling illness with significant impact on social and occupational outcomes (3). Current strategies to treat patients who do not respond to first-line antidepressant monotherapy include switching AD (either within or between classes) or combining different drugs (4). After failure of 2 AD treatments, current guidelines indeed suggest augmentation strategies (5). Effective agents to add on to ongoing AD, according to literature, could be chosen between mood stabilizers, ADs, thyroid hormones, ketamine or atypical antipsychotic (AA) (5–7). Aripiprazole (8, 9), olanzapine (10, 11), quetiapine (12, 13) and risperidone (14, 15) showed efficacy in augmentation trial for patients affected by TRD. More recently brexpiprazole (16–18) and cariprazine (19–21) also demonstrated their efficacy for TRD. Not withstanding various studies that show efficacy of AAs as dd-on strategy to ameliorate depressive symptoms in TRD, there is a lack of literature, to our knowledge, about efficacy of a second trial with an AA in those patients who failed to respond to a first augmentation trial with antipsychotic. We report a case series of TRD patients who failed to respond to an augmentation with a first AA to their ongoing AD and were subsequently treated with low dose cariprazine (CPZ) as add-on. Cariprazine is a partial agonist of dopamine D2/D3 receptors (preferring D3) and serotonin 5HT1A/5Ht2A receptors (22). This unique receptor profiles may play a role in its efficacy and tolerability and are believed to be involved in the antipsychotic, antidepressant, antianhedonic and pro-cognitive effects (23, 24). FDA has approved cariprazine as an adjunctive treatment for unipolar depression (1.5–3 mg/day) however in Europe it has been approved only for schizophrenia (25).

Materials and methods

Clinical records of inpatients and outpatients with a diagnosis of Major Depressive Disorder according to DSM-5 criteria treated in the Mental Health Department of Alba and Bra (Italy) and Mental Health Department of Napoli 1 (Italy) from July 2022 and March 2023 were analyzed. All patients presented with some form of treatment resistance that was defined according to operational criteria provided by Sourey et al. (26). All patients were treated with a AA (aripiprazole, risperidone or brexpiprazole) added to ongoing AD therapy for 4 weeks without response estimated as reduction of Hamilton Depression Rating Scale (HAM-D) (27) score of at least 50% from the beginning of the augmentation. After a wash-out period from the first AA of 2 weeks maintaining the ongoing AD treatment unchanged, patients underwent a second augmentation trial of 4 weeks with cariprazine. Cariprazine starting dose was 1.5 mg/day for all patients. Dosage changes were established according to clinical judgment (no specific guidelines were followed. Dosage variation was established according to efficacy observed and tolerability). AD dose was maintained unchanged during the weeks of add-on.

All subjects referred to our Service did sign a written informed consent to have their clinical data potentially used for teaching or search purposes, anonymously treated. Written consent was also collected for off-label treatment. Socio-demographic, clinical and safety information were collected for each subject from medical reports. Patients underwent control visits according to clinical practice. All psychiatric diagnoses and clinical assessment were made by psychiatrist with several years of experience. Due to the frequent presence of bipolar spectrum features in TRD patients, careful screening was made by psychiatrist for this diagnosis also by mean of Mood Disorder Questionnaire (MDQ). For the purpose of this report, medical records have been analyzed at the start of treatment with cariprazine, after 2 weeks and after 4 weeks. Clinical symptoms of depression were assessed by means of HAM-D. The effectiveness of cariprazine was assessed evaluating the change of HAM-D scores from baseline to endpoint (4 weeks). Due to exiguity of the sample no statistical analysis was performed.

Results

We report on a case series of 10 patients. 6 patients (60.0%) were female. The mean age of the sample was 52.3 ± 6.2 years. The mean age at onset of Major depressive disorder was 25.4 ± 4.1 years. 4 patients (40.0%) had at least one suicidal attempt lifetime. About two-thirds of patients (60%) had other comorbid psychiatric disorders. All socio-demographic and clinical characteristics of the patients are shown in Table 1, including the AA used in the first augmentation trial. Mean doses of antipsychotic in the first trial were, respectively, 4.4 ± 1.2 mg/day for aripiprazole, 1 ± 0 mg/day for brexpiprazole and 0.8 ± 2.3 mg/day for risperidone (risperidone in add on ranged from 0.5 to 1.5 mg/day). Table 2 reports duration of the single episode of treatment resistant depression, the AD combined with cariprazine and its dosage. All patients completed the 4 weeks period of cariprazine add-on, 7 patients (70.0%) experienced at least one adverse event (AE) (see Table 3). HAM-D mean scores decreased from 23.9 ± 3.9 (baseline) to 14.8 ± 5.3 (4 weeks) (Figure 1). 7/10 patients were responders at the end of period, of them 1 patient reached responder status by week 2. No patient met the criteria for remission. Dosage of cariprazine was increased to 3 mg/d in 4 patients. Table 3 summarizes dosage, timing of response and reported AEs in the sample of 10 patients.

Discussion

To the best of our knowledge this is the first study focusing on the efficacy and tolerability of cariprazine as add-on agent in TRD real-world patients who failed a previous trial of AA augmentation of their AD therapy. Treating TRD is a clinical challenge due to its cost in terms of continuing disability, consequence for patients' functioning and quality of life as well as resource utilization (1, 2, 28).

Although not licensed in all countries, cariprazine is one of the so called third generation antipsychotics that showed evidence in treatment of depression. In a phase 2 study flexible –dose cariprazine in adults with MDD and inadequate response to ongoing AD treatment, change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) total score was significantly greater with cariprazine 2–4.5 mg/day compared with placebo (19). In a more recent phase 3 study adjunctive 1.5 mg/day of cariprazine demonstrated efficacy in reducing depressive symptoms in adults with

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TABLE 1 Demographic and clinical characteristics of the sample.

Parameters		*N* = 10
Age, years (mean ± SD)		52.3 ± 6.2
Sex, *n* (%)	Male	4 (40.0)
	Female	6 (60.0)
Marital status, *n* (%)	Single	1 (10.0)
	Married	9 (90.0)
Educational level, years (mean ± SD)		11.3 ± 3.4
Working for pay, *n* (%)	Yes	5 (50.0)
	No	5 (50.0)
Age at onset, years (mean ± SD)		25.4 ± 4.1
Number of episodes, (mean ± SD)		3.6 ± 1.3
Suicide attempts lifetime, *n* (%)	Yes	4 (40.0)
	No	6 (60.0)
Psychiatirc comorbidities, *n* (%)	Yes	6 (60.0)
	No	4 (40.0)
Type of psychiatric comorbities, *n* (%)	OCD	3 (30.0)
	Anxiety disorders	3 (30.0)
	SUD	2 (20.0)
Class of antidepressant, *n* (%)	SSRI	5 (50.0)
	SNRI	2 (20.0)
	TCA	3 (30.0)
Previous augmenting AA, *n* (%)	Aripiprazole	4 (40.0)
	Brexpiprazole	3 (30.0)
	Risperidone	3 (30.0)
HAM-D scores, (mean ± SD)		23.9 ± 3.9

AA: Atypical Antipsychotic; HAM-D: Hamilton Depression Rating Scale; OCD: Obsessive-Compulsive Disorder; SUD: Substance Use Disorder; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; TCA: Tricyclic Antidepressant.

TABLE 2 Duration of of depressive episode, antidepressant treatment and dosage in the sample.

Patient	Duration of depressive episode (weeks)	AD combined with cariprazine	Daily dosage of AD during the add on
1	8	Fluvoxamine	300 mg
2	10	Sertraline	200 mg
3	11	Fluvoxamine	300 mg
4	12	Clomipramine	225 mg
5	12	Duloxetine	60 mg
6	14	Clomipramine	300 mg
7	24	Duloxetine	90 mg
8	15	Paroxetine	60 mg
9	22	Clomipramine	225 mg
10	28	Sertraline	200 mg

AD: antidepressant.

MDD and inadequate response to AD alone (21). Although unipolar and bipolar depression are distinct illnesses, previously published bipolar studies showed positive results with cariprazine add-on (29–31) also when added to mood stabilizers and AD in patients with resistant bipolar depression (32). Collectively these studies support the efficacy of adjunctive cariprazine in reducing depressive symptoms. Our preliminary results show that cariprazine can reduce depressive symptoms in real-world TRD patients in the short-term period also in the sub-population of patients that already failed a first augmentation trial with another AA (in our sample risperidone, aripiprazole or brexpiprazole). At the end of the 4 weeks of observation seven out of ten patients met the criteria for a clinical response, one patient showed response already at week 2, However exiguity of the sample and descriptive nature of our study do not allow a comparison

TABLE 3 Response, timing and adverse events in the sample.

Patient	Ham-D score			Responder	Final CPZ dose Mg/day	AEs
	Baseline	2 weeks	4 weeks			
1	16	17	18	No	3	Akathisia
2	20	20	21	No	3	–
3	24	14	12	Within week 4	1.5	–
4	29	18	14	Within week 4	1.5	Nausea
5	21	11	8	Within week 4	3	Tremor
6	24	12	9	Within week 2	1.5	Headache
7	26	23	23	No	3	Agitation
8	27	21	10	Within week 4	1.5	Xerostomia
9	27	18	13	Within week 4	1.5	–
10	25	23	20	No	3	Xerostomia

HAM-D: Hamilton Depression Rating Scale; CPZ: cariprazine; AEs: Adverse events.

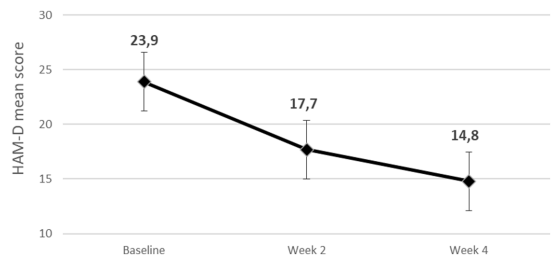

FIGURE 1
Mean reduction of Hamilton Depression Rating Scale (HAM-D) scores during the 4 weeks observation period.

with literature about cariprazine add on. In Durgam et al. (19) rate of responders according to MADRS scores was 48% with cariprazine 1–2 mg/day and 50% with cariprazine 2–4,5 mg/day. In Sachs et al. (21) responders to cariprazine 1.5 mg/day added to ongoing AD therapy were 40.9 and 41% when dosage was 3 mg/day. In our sample most patients responded to a dosage of cariprazine of 1.5 mg/day. These data are congruent with previous observation that lower dose of this antipsychotic seem to be more effective in reducing depressive symptoms (21). In our sample there was no drop-out due to adverse events and there was no severe adverse event reported. In our samples cariprazine was associated with favorable tolerability profiles, low discontinuation rates as previously observed in other study (21). It should be noted that no patients of our study discontinued the previous AA added as augmenting agent, due to side effects but only to lack of efficacy.

In conclusion, our case series suggests that adding low dose cariprazine to AD therapy in TRD patients who failed a previous AA augmentation trial could be an efficacious strategy to ameliorate depressive symptoms and this seems to be true also in real-world patients with other psychiatric comorbidities. To the best of our knowledge this is the first observation in this direction. Our results suffer for several limitations, first the retrospective observational nature of the study and the exiguity of the sample. Further confirmation in larger population and in prospective studies is needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EP: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. AM: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. FR: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. VM: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am*. (1996) 19:179–200. doi: 10.1016/s0193-953x(05)70283-5

2. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. (2006) 163:28–40. doi: 10.1176/appi.ajp.163.1.28

3. Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. *Curr Med Res Opin*. (2010) 26:2475–84. doi: 10.1185/03007995.2010.517716

4. American Psychiatric Association. *Practice guidelines for the treatment of patients with major depressive disorder*. *3rd* ed. Washington, DC: American Psychiatric Association (2010).

5. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the Management of Adults with major depressive disorder: section 3. Pharmacological treatments. *Can J Psychiatr*. (2016) 61:540–60. doi: 10.1177/0706743716659417

6. Gelenberg AJ. A review of the current guidelines for depression treatment. *J Clin Psychiatry*. (2010) 71:e15. doi: 10.4088/JCP.9078tx1c

7. Nuñez NA, Joseph B, Pahwa M, Kumar R, Resendez MG, Prokop LJ, et al. Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. *J Affect Disord*. (2022) 302:385–400. doi: 10.1016/j.jad.2021.12.134

8. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. (2007) 68:843–53. doi: 10.4088/jcp.v68n0604

9. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. (2008) 28:156–65. doi: 10.1097/JCP.0b013e31816774f9

10. Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. (2006) 23:364–72. doi: 10.1002/da.20130

11. Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. *CNS Drugs*. (2010) 24:131–61. doi: 10.2165/11530280-000000000-00000

12. McIntyre A, Gendron A, McIntyre A. Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. *Depress Anxiety*. (2007) 24:487–94. doi: 10.1002/da.20275

13. El-Khalili N, Joyce M, Atkinson S, Buynak RJ, Datto C, Lindgren P, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*. (2010) 13:917–32. doi: 10.1017/S1461145710000015

14. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. (2009) 166:980–91. doi: 10.1176/appi.ajp.2009.09030312

15. Rafeyan R, Papakostas GI, Jackson WC, Trivedi MH. Inadequate response to treatment in major depressive disorder: augmentation and adjunctive strategies. *J Clin Psychiatry*. (2020) 81:OT19037BR3. doi: 10.4088/JCP.OT19037BR3

16. Fava M, Ménard F, Davidsen CK, Baker RA. Adjunctive Brexpiprazole in patients with major depressive disorder and irritability: an exploratory study. *J Clin Psychiatry*. (2016) 77:1695–701. doi: 10.4088/JCP.15m10470

17. Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *J Clin Psychiatry*. (2015) 76:1224–31. doi: 10.4088/JCP.14m09688

18. Thase ME, Youakim JM, Skuban A, Hobart M, Zhang P, McQuade RD, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. (2015b) 76:1232–40. doi: 10.4088/JCP.14m09689

19. Durgam S, Earley W, Guo H, Li D, Németh G, Laszlovszky I, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *J Clin Psychiatry*. (2016) 77:371–8. doi: 10.4088/JCP.15m10070

20. Earley WR, Guo H, Németh G, Harsányi J, Thase ME. Cariprazine augmentation to antidepressant therapy in major depressive disorder: results of a randomized, double-blind, placebo-controlled trial. *Psychopharmacol Bull*. (2018) 48:62–80.

21. Sachs GS, Yeung PP, Rekeda L, Khan A, Adams JL, Fava M. Adjunctive Cariprazine for the treatment of patients with major depressive disorder: a randomized, double-blind, placebo-controlled phase 3 study. *Am J Psychiatry*. (2023) 180:241–51. doi: 10.1176/appi.ajp.20220504

22. Stahl SM. Mechanism of action of cariprazine. *CNS Spectr*. (2016) 21:123–7. doi: 10.1017/S1092852916000043

23. Gyertyán I, Sághy K, Laszy J, Elekes O, Kedves R, Gémesi LI, et al. Subnanomolar dopamine D3 receptor antagonism coupled to moderate D2 affinity results in favourable antipsychotic-like activity in rodent models: II. Behavioural characterisation of RG-15. *Naunyn Schmiedeberg's Arch Pharmacol*. (2008) 378:529–39. doi: 10.1007/s00210-008-0311-x

24. Duric V, Banasr M, Franklin T, Lepack A, Adham N, Kiss B, et al. Cariprazine exhibits anxiolytic and dopamine D3 receptor-dependent antidepressant effects in the chronic stress model. *Int J Neuropsychopharmacol*. (2017) 20:788–96. doi: 10.1093/ijnp/pyx038

25. European medicines agency reagila assessment report (2017). European medicines agency. Available at: https://www.ema.europa.eu/en/documents/overview/reagila-epar-summary-public_en.pdf

26. Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria. *Eur Neuropsychopharmacol*. (1999) 9:83–91. doi: 10.1016/s0924-977x(98)00004-2

27. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

28. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

29. Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Németh G, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of Cariprazine in patients with bipolar I depression. *Am J Psychiatry*. (2016) 173:271–81. doi: 10.1176/appi.ajp.2015.15020164

30. Earley W, Burgess MV, Rekeda L, Dickinson R, Szatmári B, Németh G, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. *Am J Psychiatry*. (2019) 176:439–48. doi: 10.1176/appi.ajp.2018.18070824

31. Earley WR, Burgess MV, Khan B, Rekeda L, Suppes T, Tohen M, et al. Efficacy and safety of cariprazine in bipolar I depression: a double-blind, placebo-controlled phase 3 study. *Bipolar Disord*. (2020) 22:372–84. doi: 10.1111/bdi.12852

32. Teobaldi E, Pessina E, Martini A, Cattateno CI, De Berardis D, Martiadis V, et al. Cariprazine augmentation in treatment-resistant bipolar depression: data from a retrospective observational study. *Curr Neuropharmachol*. (2023).

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Stanford neuromodulation therapy for treatment-resistant depression: a systematic review

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Objective: This systematic review of randomized controlled studies (RCTs) and observational studies evaluated the efficacy and safety of stanford neuromodulation therapy (SNT) for patients with treatment-resistant depression (TRD).

Methods: A systematic search (up to 25 September, 2023) of RCTs and single-arm prospective studies was conducted.

Results: One RCT ($n = 29$) and three single-arm prospective studies ($n = 34$) met the study entry criteria. In the RCT, compared to sham, active SNT was significantly associated with higher rates of antidepressant response (71.4% versus 13.3%) and remission (57.1% versus 0%). Two out of the three single-arm prospective studies reported the percentage of antidepressant response after completing SNT, ranging from 83.3% (5/6) to 90.5% (19/21). In the three single-arm prospective studies, the antidepressant remission rates ranged from 66.7% (4/6) to 90.5% (19/21). No severe adverse events occurred in all the four studies.

Conclusion: This systematic review found SNT significantly improved depressive symptoms in patients with TRD within 5 days, without severe adverse events.

KEYWORDS

stanford neuromodulation therapy, treatment-resistant depression, response, remission, systematic review

Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide (1), and up to 55% of patients suffering from MDD fulfill the criteria of treatment-resistant depression (TRD) (2). Accumulating evidence has found that ketamine (3) and esketamine (4) had a rapid antidepressant, antisuicidal effects on TRD. Esketamine nasal spray has been approved as the first therapeutic agent for TRD (5). Furthermore, a real-world study found a significant reduction of depressive symptoms in patients suffering from TRD after receiving esketamine nasal spray (5). Apart from antidepressant medication, strategies such as vagus nerve stimulation (6), electroconvulsive therapy (7, 8), transcranial alternating current stimulation (9), and transcranial magnetic stimulation (TMS) [e.g., deep TMS (10), accelerated TMS (11), intermittent theta-burst stimulation (iTBS) (12), accelerated iTBS (13), bilateral TBS (14), and

continuation TBS (15)], have been developed as a nonpharmacological alternative for the treatment of MDD.

iTBS has been approved in many countries in the treatment of TRD. However, efficiency has been less than desired and another treatment protocol (number and spacing of individual treatments) may provide a better outcome (16). Stanford neuromodulation therapy (SNT), a neuroscience-informed accelerated iTBS protocol, had been investigated as a solution to these limitations (17). For example, Cole et al. reported significant superiority of active SNT over sham stimulation in improving depressive symptoms in TRD (17). We conducted this systematic review of randomized controlled studies (RCTs) and single-arm prospective studies to examine the efficacy and safety of SNT for patients with TRD.

Method

Inclusion criteria

Following PICOS acronym, studies were selected and screened by three investigators (XJL, ZJQ and QML) for inclusion in this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (18). Participants: patients with TRD based on study-defined diagnostic criteria. For example, TRD was defined as failure to responding to at least two antidepressants from different classes at adequate dosages (19). Intervention vs. Comparison: active SNT plus antidepressants or antidepressants free versus sham SNT plus antidepressants or antidepressants free in RCTs; or SNT added to antidepressants or antidepressants free in single-arm prospective studies. Outcomes: Coprimary outcomes were study-defined response and remission. A secondary outcome was adverse events. Study: only published RCTs or single-arm prospective studies on the efficacy and safety of SNT, using resting-state functional connectivity Magnetic Resonance Imaging (fcMRI) to target high-dose iTBS (10 sessions of iTBS daily, 18,000 pulses/day, 5 consecutive days, and 90,000 total pulses), as an adjunctive treatment for TRD were considered. High-dose iTBS studies with different intervals between sessions, such as 50-min or 60-min, were approved. Studies on patients without TRD were excluded (20). Systematic reviews, retrospective studies, and case reports/series were not included.

Study selection

We performed a systematic review of relevant literature from inception to 25 September, 2023, based on the Cochrane Library, PubMed, EMBASE and PsycINFO databases and reference lists from retrieved studies (16, 17, 21) to identify RCTs and single-arm prospective studies (single-group and before-after design) that examined the antidepressant effects of SNT for TRD. The following search terms were used: ("Stanford neuromodulation therapy" OR "Stanford accelerated intelligent neuromodulation therapy" OR SNT OR "High-dose spaced theta-burst stimulation") AND (depress* OR dysphor* OR dysthymi* OR melanchol* OR antidepress* OR bipolar OR MDD). Study selection was performed independently by three investigators (XJL, ZJQ and QML).

Data extraction

Data extraction was performed independently by three investigators (XJL, ZJQ, and QML). If there were discrepancies, consensus was achieved between the investigators and then discussion was conducted with a senior investigator (WZ). Additionally, the first and/or corresponding authors were contacted as necessary to acquire any pertinent information that was missing.

Quality assessment

For RCTs and single-arm prospective studies, the Cochrane risk of bias (22) and Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) (23) were, respectively, used to assess the study quality independently by the three investigators (XJL, ZJQ, and QML).

Results

As shown in Figure 1, 107 potentially relevant articles were identified, and finally one RCT (17) and three single-arm prospective studies (16, 21, 24) met the study entry criteria (Table 1). Four studies ($n = 63$) (16, 17, 21, 24) examined the efficacy and safety of adjunctive SNT for adult patients with TRD. The risk of bias of included studies is summarized in Tables 2, 3. Based on the Cochrane risk of bias tool, the double-blind RCT (17) was rated as low risk with regard to attrition bias and reporting bias (Table 2). In the RCT, compared to sham, active SNT was significantly associated with higher rates of antidepressant response (71.4% versus 13.3%) and remission (57.1% versus 0%) (17). Two out of the three single-arm prospective studies reported the rates of antidepressant response after completing SNT, ranging from 83.3% (5/6) (21) to 90.5% (19/21) (16). In the three single-arm prospective studies, the antidepressant remission rates ranged from 66.7% (4/6) (21), 83.3% (5/6) (24) to 90.5% (19/21) (16). Furthermore, Cole et al. found 70% of patients with TRD continued to fulfill response criteria at 1-month follow-up (16). Poydasheva et al. reported that 40% of patients with TRD met the criteria for both response and remission at the 3-month follow-up assessment (24). No severe adverse events occurred in the four studies (16, 17, 21).

Discussion

This systematic review found SNT, using resting-state fcMRI to target high-dose iTBS, could significantly improve depressive symptoms in patients with TRD within 5 days, without severe adverse events. The rate of antidepressant remission (66.7–90.5%) reported in the included studies is higher than the corresponding figures for ketamine treatment (8.3%) (25), electroconvulsive therapy (48.0%) (26) and standard FDA-approved repetitive transcranial magnetic stimulation (rTMS) protocols (5.9%) (27). However, Lan et al. found that iTBS (one sessions/day) and high-frequency rTMS appeared to be equally effective in alleviating depressive symptoms for patients with TRD (10). A recent meta-analysis of RCTs ($n = 239$) found that the study-defined response

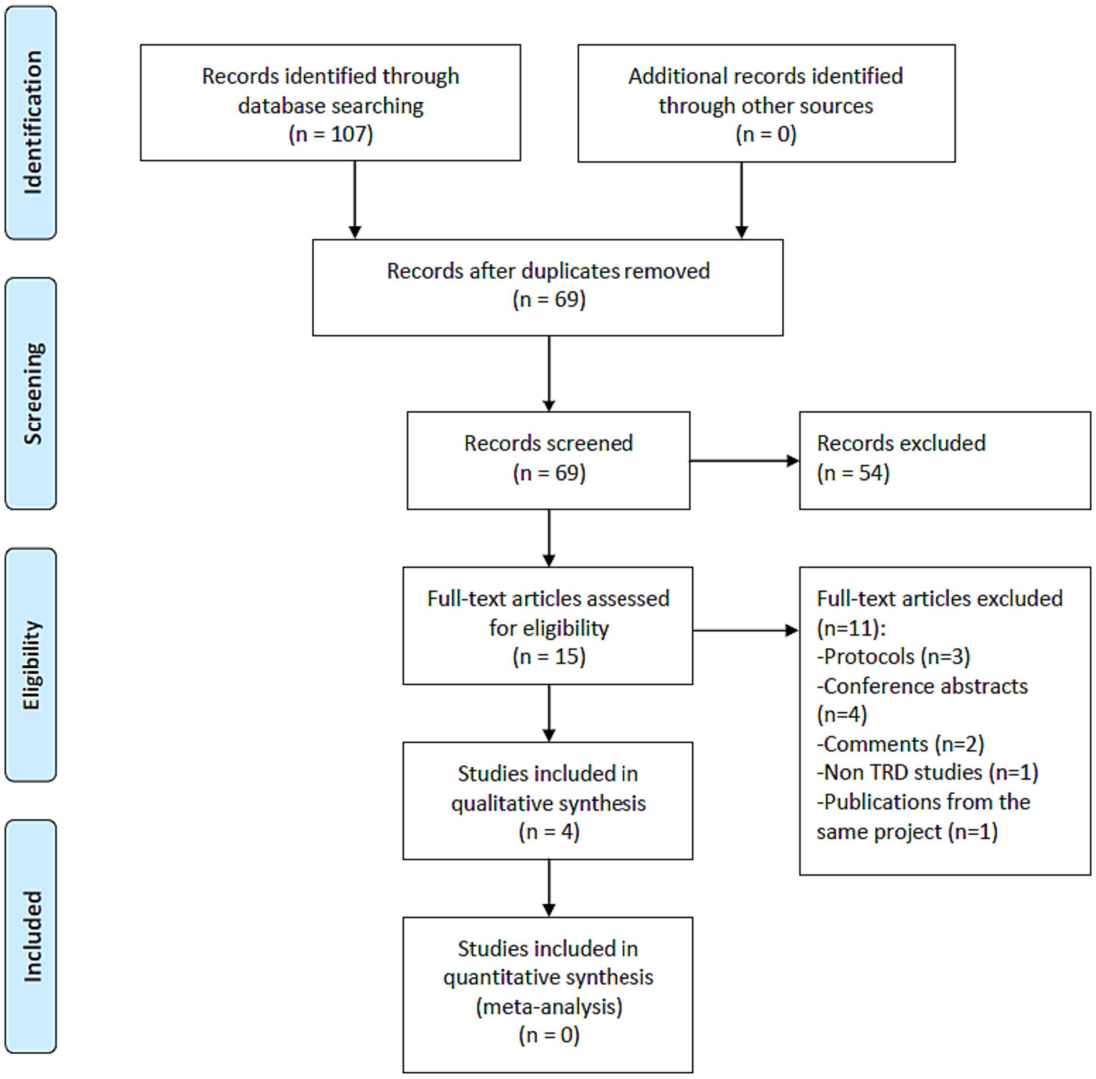

FIGURE 1
PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCTs, randomized controlled trials; TRD, treatment-resistant depression.

was greater for active accelerated iTBS (≥2 sessions of iTBS daily) than sham stimulation (13).

The short duration protocol (5 days) of SNT is a non-invasive brain stimulation with proven efficacy in TRD which could be used in emergency or inpatient settings where rapid-acting treatments are needed. As previously described (16, 17, 21), this protocol for SNT consisted of 5 consecutive days (90,000 total pulses) with ten iTBS sessions per day (18,000 pulses/day and a 50-min intersession interval per session) delivered to the region of the left dorsolateral prefrontal cortex (DLPFC). This protocol was designated SNT, to distinguish it from other accelerated iTBS protocols which do not have a high overall pulse dose of stimulation (SNT versus standard iTBS protocols: 90,000 versus 18,000 pulses) and individualized targeting using fcMRI (28, 29). This systematic review of studies with iTBS at high doses involved different intersession intervals per session. Therefore, one single-arm prospective study with its protocol for SNT consisting of 5 consecutive days (18,000 pulses/day, 90,000 total pulses and a 60-min intersession interval per session) was also included (24). However, the individual contribution of each element in the improvement of TRD outcomes is unclear, and this should be further examined.

As a rapid therapeutic intervention for TRD, SNT seems to be comparable to glutamatergic modulators like esketamine (the S-enantiomer of ketamine) (30), exhibiting a greater affinity for the N-methyl-d-aspartate receptor compared to the R-enantiomer (31). The administration of esketamine via intravenous (32) or intranasal (31) routes has a rapid onset of antidepressant effects. For example, Daly et al. found that esketamine administered intranasally at doses of 28, 56, and 84 mg appeared to be effective in treating TRD (31). A retrospective study found that accelerated high-frequency rTMS (four times daily for five consecutive days over the left DLPFC) appears to be more effective than intranasal esketamine (33). However, there are currently no head-to-head comparison studies on TMS and esketamine in treating TRD.

TABLE 1 Summary of studies included in this systematic review.

Study (country)	Sample size (n)[a]	Design: -Blinding -Setting (%) -Treatment duration (days)	Participants: -Diagnosis (%) -Diagnostic criteria -Illness duration[c] (yrs)	-Mean age[c] (yrs) (range) -Sex: male (%)	-TRD criteria -Clinical effects	SNT therapeutic frequency and ADs dosages (mg/day); Number of patients (n)	-Stimulation target (active/sham)[b] -Intensity (%rMT)	-Pulses/day (total pulses) -Intersession interval per session -Number of sessions (n/day)	Depressive symptoms measured by MADRS or HRSD (Pre/Post-SNT and follow-up at any time)	Response and remission rate (Post-SNT and follow-up at any time)
Cole et al., 2020 (USA)	22	-Observational study -Outpatients −5	-MDD (90.5) and BD (9.5) -DSM-5 −23.0	−44.9 (19–78) −9 (42.9)	-≥ 1 ADs -MADRS	Active SNT (50 Hz) + ADs (NR); *n* = 21[c]	-Left DLPFC −90	−18,000 (18,000*5 days = 90,000) −50 min −50 (10/day)	Pre-SNT: 34.86 ± 5.29 Post-SNT: 5.0 ± 6.37; 1-month follow-up: 10.95 ± 11.76	90.5 and 90.5% (Post-SNT); 70 and 60% (1-month follow-up)
Cole et al., 2022 (USA)	29	-DB -NR −5	-MDD (100) -DSM-5 −23.4	−50.6 (22–80) −19 (65.5)	-NR -MADRS	1. Active SNT (50 Hz) + ADs (NR) or ADs free; *n* = 14 2. Sham SNT (no active stimulation) + ADs (NR) or ADs free; *n* = 15	-Left DLPFC −90	−18,000 (18,000*5 days = 90,000) −50 min −50 (10/day)	Pre-SNT: 31.0 ± 4.0 Post-SNT: NR Pre-sham: 35.0 ± 6.0 Post-sham: NR	Active SNT: 71.4 and 57.1% (Post-SNT); 77.8 and 66.7% (1-week follow-up); 84.6 and 53.8% (2-week follow-up); 69.2 and 61.5% (3-week follow-up); 69.2 and 46.2% (4-week follow-up) Sham SNT: 13.3 and 0% (Post-sham); 20.0 and 10.0% (1-week follow-up); 7.1 and 7.1% (2-week follow-up); 7.1 and 7.1% (3-week follow-up); 7.1 and 0% (4-week follow-up)
Poydasheva et al., 2022 (Russia)	6	-Observational study -NR −5	-MDD (33.3) and BD (66.7) -ICD-10 −21.2	−40.2 (21–66) −3 (50)	-NR -MADRS	Active SNT (50 Hz) + ADs (NR); *n* = 6	-Left DLPFC −120	−18,000 (18,000*5 days = 90,000) −1 h −50 (10/day)	Pre-SNT: 19.83 ± NR Post-SNT: NR	NR and 83.3% (Post-SNT); NR and 20% (1-month follow-up)[d]; 80 and 60% (2-month follow-up)[d]; 40 and 40% (3-month follow-up)[d]
Williams et al., 2018 (USA)	6	-Observational study -NR −5	-MDD (83.3) and BD (16.7) -DSM-5 −32.0	−56.0 (38–69) −2 (33.3)	-NR -HRSD	Active SNT (50 Hz) + ADs (NR); *n* = 6	-Left DLPFC −90	−18,000 (18,000*5 days = 90,000) −50 min −50 (10/day)	Pre-SNT: 28.8 ± 6.0 Post-SNT: 7.0 ± 4.7	83.3 and 66.7% (Post-SNT); 33.3 and 0% (2-week follow-up); 0 and 0% (4-week follow-up)

[a]Overall number of participants.

[b]The left DLPFC functional target was localized for each participant using the Localite Neuronavigation System.

[c]It was extracted from the available data of each study.

[d]The follow-up data was analyzed from a cohort of five patients, as one patient withdrew from the study after the stimulation completion.

ADs, antidepressants; APs, Antipsychotics; BD, bipolar disorder; DB, double blind; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; DLPFC, dorsolateral prefrontal cortex; HRSD, Hamilton Rating Scale for Depression; h, hour; ICD-10, International Classification of Diseases, 10th edition; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; min, minutes; NR, not reported; rMT, resting motor threshold; SNT, Stanford Neuromodulation Therapy; TRD, treatment-resistant depression; yrs, years.

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TABLE 2 Cochrane risk of bias.

	Random sequence generation (selection bias)	*Allocation concealment (selection bias)*	*Blinding of participants and personnel*	*Blinding of outcome assessment (Symptom reduction, response)*	*Incomplete outcome data addressed (attrition bias)*	*Selective reporting (reporting bias)*	*Other sources of bias*
Cole et al., 2022 (USA)	?	?	+	+	+	+	?

+, Low risk of bias; –, High risk of bias; ?, Unclear risk of bias; nd, not determined.

TABLE 3 Risk of bias in single-arm prospective studies of SNT for TRD with ROBINS-I tool.

Study (country)	Bias due to confounding	Bias in selection of patients into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk
Cole et al., 2020 (USA)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Poydasheva et al., 2022 (Russia)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Williams et al., 2018 (USA)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Notes: A study was assigned moderate risk if the study was judged to be at low or moderate risk for all domains. A study was assigned critical risk if 1 or more of domains was rated as critical risk. ROBINS-I, Risk Of Bias In Non-randomized Studies – of Interventions; SNT, Stanford neuromodulation therapy; TRD, treatment-refractory depression.

This systematic review has several limitations. First, only one RCT (17) was detected and the total sample size of the included studies ($n = 63$) was relatively small. Second, of the included four studies, three (16, 17, 21) were conducted by the same team at a single site, limiting generalizability of these findings. Third, the systematic review was not registered as this is not compulsory in most academic journals. Fourth, long-term follow up period (e.g., longer than 3 months) was not adopted in included studies, although the persistence of the antidepressant effect remains an important issue for TMS treatments, with several studies emphasizing the urgency of developing maintenance protocols to prevent potential relapses (34). Despite these limitations, this systematic review preliminarily found that SNT protocol appeared to be effective and well tolerated by patients with TRD. SNT is distinct from standard once daily TMS. An advantage of standard once daily TMS (treatment time 40 min) is that it allows time for supportive care to be provided by staff. Accelerated treatment offers considerable alternative advantages which will call for reorganization and reorientation of treatment centers. Future research is warranted to confirm and expand the utilization of SNT as an adjunctive treatment for TRD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

X-JL: Data curation, Writing – original draft. D-BC: Data curation, Writing – original draft. Q-ML: Data curation, Writing – original draft. Z-JQ: Writing – original draft. SP: Writing – review & editing. WZ: Writing – original draft. Y-TX: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Friedrich MJ. Depression is the leading cause of disability around the world. *JAMA*. (2017) 317:1517. doi: 10.1001/jama.2017.3826

2. Thomas L, Kessler D, Campbell J, Morrison J, Peters TJ, Williams C, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. *Br J Gen Pract*. (2013) 63:e852–8. doi: 10.3399/bjgp13X675430

3. Marcantoni WS, Akoumba BS, Wassef M, Mayrand J, Lai H, Richard-Devantoy S, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009 - January 2019. *J Affect Disord*. (2020) 277:831–41. doi: 10.1016/j.jad.2020.09.007

4. McIntyre RS, Carvalho IP, Lui LMW, Majeed A, Masand PS, Gill H, et al. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. *J Affect Disord*. (2020) 276:576–84. doi: 10.1016/j.jad.2020.06.050

5. Martinotti G, Vita A, Fagiolini A, Maina G, Bertolino A, Dell'Osso B, et al. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. (2022) 319:646–54. doi: 10.1016/j.jad.2022.09.043

6. Zhang X, Guo YM, Ning YP, Cao LP, Rao YH, Sun JQ, et al. Adjunctive vagus nerve stimulation for treatment-resistant depression: a preliminary study. *Int J Psychiatry Clin Pract*. (2022) 26:337–42. doi: 10.1080/13651501.2021.2019789

7. İlhan Atagün M, Atay CÖ. A systematic review of the literature regarding the relationship between oxidative stress and electroconvulsive therapy. *Alpha Psychiatry*. (2022) 23:47–56. doi: 10.5152/alphapsychiatry.2021.21584

8. Zheng W, Li XH, Zhu XM, Cai DB, Yang XH, Ungvari GS, et al. Adjunctive ketamine and electroconvulsive therapy for major depressive disorder: a meta-analysis of randomized controlled trials. *J Affect Disord*. (2019) 250:123–31. doi: 10.1016/j.jad.2019.02.044

9. Zheng W, Cai DB, Nie S, Chen JH, Huang XB, Goerigk S, et al. Adjunctive transcranial alternating current stimulation for patients with major depressive disorder: a systematic review and meta-analysis. *Front Psych*. (2023) 14:1154354. doi: 10.3389/fpsyt.2023.1154354

10. Lan XJ, Yang XH, Qin ZJ, Cai DB, Liu QM, Mai JX, et al. Efficacy and safety of intermittent theta burst stimulation versus high-frequency repetitive transcranial magnetic stimulation for patients with treatment-resistant depression: a systematic review. *Front Psych*. (2023) 14:1244289. doi: 10.3389/fpsyt.2023.1244289

11. Zheng W, Zhang XY, Xu R, Huang X, Zheng YJ, Huang XB, et al. Adjunctive accelerated repetitive transcranial magnetic stimulation for older patients with depression: a systematic review. *Front Aging Neurosci*. (2022) 14:1036676. doi: 10.3389/fnagi.2022.1036676

12. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet*. (2018) 391:1683–92. doi: 10.1016/s0140-6736(18)30295-2

13. Cai DB, Qin ZJ, Lan XJ, Liu QM, Qin XD, Wang JJ, et al. Accelerated intermittent theta burst stimulation for major depressive disorder or bipolar depression: a systematic review and meta-analysis. *Asian J Psychiatr*. (2023) 85:103618. doi: 10.1016/j.ajp.2023.103618

14. Qin ZJ, Huang SQ, Lan XJ, Shi ZM, Huang XB, Ungvari GS, et al. Bilateral theta burst stimulation for patients with acute unipolar or bipolar depressive episodes: a systematic review of randomized controlled studies. *J Affect Disord*. (2023) 340:575–82. doi: 10.1016/j.jad.2023.08.065

15. Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain*. (2014) 137:2088–98. doi: 10.1093/brain/awu109

16. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. *Am J Psychiatry*. (2020) 177:716–26. doi: 10.1176/appi.ajp.2019.19070720

17. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry*. (2022) 179:132–41. doi: 10.1176/appi.ajp.2021.20101429

18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097

19. Demyttenaere K, Van Duppen Z. The impact of (the concept of) treatment-resistant depression: an opinion review. *Int J Neuropsychopharmacol*. (2019) 22:85–92. doi: 10.1093/ijnp/pyy052

20. Tang NL, Chen YH, Wang WY, Sun CZ, Wu D, Sun L, et al. A preliminary study of precise treatment for major depression patients with suicide ideation by individualized targeted robot assisted Stanford accelerated intelligent neuromodulation therapy (in Chinese). *Chinese J. Psychiatry*. (2022) 55:14–23. doi: 10.3760/cma.j.cn113661-20210527-00173

21. Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, et al. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. *Brain*. (2018) 141:e18. doi: 10.1093/brain/awx379

22. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. (2011) 343:d5928. doi: 10.1136/bmj.d5928

23. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. (2016) 355:i4919. doi: 10.1136/bmj.i4919

24. Poydasheva AG, Bakulin IS, Sinitsyn DO, Zabirova AH, Suponeva NA, Maslenikov NV, et al. Experience of stanford neuromodulation therapy in patients with treatment-resistant depression. *Bull Russian State Med Univ*. (2022) 4:31–7. doi: 10.24075/brsmu.2022.044

25. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. *J Psychopharmacol*. (2019) 33:494–501. doi: 10.1177/0269881119827811

26. Heijnen WT, Birkenhäger TK, Wierdsma AI, van den Broek WW. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *J Clin Psychopharmacol*. (2010) 30:616–9. doi: 10.1097/JCP.0b013e3181ee0f5f

27. Taylor SF, Bhati MT, Dubin MJ, Hawkins JM, Lisanby SH, Morales O, et al. A naturalistic, multi-site study of repetitive transcranial magnetic stimulation therapy for depression. *J Affect Disord*. (2017) 208:284–90. doi: 10.1016/j.jad.2016.08.049

28. Desmyter S, Duprat R, Baeken C, Van Autreve S, Audenaert K, van Heeringen K. Accelerated intermittent theta burst stimulation for suicide risk in therapy-resistant depressed patients: a randomized, sham-controlled trial. *Front Hum Neurosci*. (2016) 10:480. doi: 10.3389/fnhum.2016.00480

29. Duprat R, Desmyter S, Rudi de R, van Heeringen K, Van den Abbeele D, Tandt H, et al. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission? *J Affect Disord*. (2016) 200:6–14. doi: 10.1016/j.jad.2016.04.015

30. d'Andrea G, Pettorruso M, Lorenzo GD, Mancusi G, McIntyre RS, Martinotti G. Rethinking ketamine and esketamine action: are they antidepressants with mood-stabilizing properties? *Eur Neuropsychopharmacol*. (2023) 70:49–55. doi: 10.1016/j.euroneuro.2023.02.010

31. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. (2018) 75:139–48. doi: 10.1001/jamapsychiatry.2017.3739

32. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biol Psychiatry*. (2016) 80:424–31. doi: 10.1016/j.biopsych.2015.10.018

33. Pettorruso M, d'Andrea G, Di Carlo F, De Risio L, Zoratto F, Miuli A, et al. Comparing fast-acting interventions for treatment-resistant depression: an explorative study of accelerated HF-rTMS versus intranasal esketamine. *Brain Stimul*. (2023) 16:1041–3. doi: 10.1016/j.brs.2023.06.003

34. d'Andrea G, Mancusi G, Santovito MC, Marrangone C, Martino F, Santorelli M, et al. Investigating the role of maintenance TMS protocols for major depression: systematic review and future perspectives for personalized interventions. *J Pers Med*. (2023) 13:697. doi: 10.3390/jpm13040697

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Use of ketamine for treatment resistant depression: updated review of literature and practical applications to a community ketamine program in Edmonton, Alberta, Canada

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Background: Though intravenous (IV) ketamine and intranasal (IN) esketamine are noted to be efficacious for treatment-resistant depression (TRD), access to each of these treatments within healthcare systems is limited due to cost, availability, and/or monitoring requirements. IV ketamine has been offered at two public hospital sites in Edmonton, Canada since 2015. Since then, demand for maintenance ketamine treatments has grown. This has required creative solutions for safe, accessible, evidence-based patient care.

Objectives: Aims of this paper are twofold. First, we will provide a synthesis of current knowledge with regards to the clinical use of ketamine for TRD. Consideration will be given regarding; off-label racemic ketamine uses versus FDA-approved intranasal esketamine, populations treated, inclusion/exclusion criteria, dosing, assessing clinical response, concomitant medications, and tolerability/safety. Second, this paper will describe our experience as a community case study in applying evidence-based treatment. We will describe application of the literature review to our clinical programming, and in particular focus on cost-effective maintenance treatments, long-term safety concerns, routes of ketamine administration other than via intravenous, and cautious prescribing of ketamine outside of clinically monitored settings.

Methodology: We conducted a literature review of the on the use of ketamine for TRD up to June 30, 2023. Key findings are reviewed, and we describe their application to our ketamine program.

Conclusion: Evidence for the use of ketamine in resistant depression has grown in recent years, with evolving data to support and direct its clinical use. There is an increasing body of evidence to guide judicious use of ketamine in various clinical circumstances, for a population of patients with a high burden of suffering and morbidity. While large-scale, randomized controlled trials, comparative studies, and longer-term treatment outcomes is lacking, this community case study illustrates that currently available evidence can be applied to real-world clinical settings with complex patients. As cost is often a significant barrier to accessing initial and/or maintenance IV or esketamine treatments, public

ketamine programs may incorporate SL or IN ketamine to support a sustainable and accessible treatment model. Three of such models are described.

KEYWORDS

ketamine, non-intravenous ketamine, maintenance ketamine, community ketamine use, depression, treatment-resistant depression

1 Introduction

Treatment-resistant depression (TRD) has been estimated to affect 30–55% of individuals with Major Depressive Disorder (MDD) (1). Though definitions of TRD vary in the literature, one accepted definition is a failure to respond to two (or more) first-line antidepressant agents with adequate dose and duration, and it has been noted that nearly a third of individuals with MDD do not remit with the first or second treatment step (2). Ketamine is an NMDA-antagonist that has demonstrated rapid efficacy as a novel antidepressant in numerous systematic reviews and meta-analyses (3–7). Note that for the purposes of this paper, discussion will center around the pharmacologic use of ketamine for depression, and exclude any discussion of ketamine assisted psychotherapy.

In 2015, due to an unmet need, the Gray Nuns and Misericordia Hospitals (Covenant Health, Edmonton, Canada) began offering limited, publicly funded intravenous (IV) ketamine treatments as a novel treatment option for selected patients with severe treatment resistant unipolar or bipolar depression. Due to its limited evidence at that time, our programs initially treated only patients who had exhausted all other treatment options. Early patients in our program were considered to have ultra-resistant depression (URD), with 90% of patients failing to respond to electroconvulsive therapy (ECT) and an average of 8.1 prior antidepressant trials (8). This represents a greater level of treatment resistance than the typical patients included in IV ketamine studies. Based on chart review of these first 50 patients treated in our program, 50% had unipolar depression, 40% had bipolar depression, and 10% were unspecified. 44% responded within 8 IV treatments of ketamine and 16% remitted. Controlled studies have since corroborated that reduced (but still meaningful) efficacy is still likely to occur in patients with similarly high degrees of treatment resistance (9–11).

Data on the safety and efficacy of ketamine for depression has subsequently grown substantially. In Canada, due to the largest body of evidence available, IV racemic ketamine has been acknowledged as a 3rd line treatment for both bipolar depression and adults with unipolar TRD (12, 13). While the majority of studies have involved unipolar (or mixed unipolar/bipolar) TRD, a recent review confirmed similar efficacy and tolerability in studies with exclusively bipolar depression (14). Similarly, intranasal (IN) esketamine has been approved in Canada and the United States for TRD with the above definition (15). As a result, our inclusion criteria were broadened in 2020 to include "less" treatment resistant individuals. These local protocols served as the basis for a broader provincial IV ketamine protocol for depression to be used in Alberta, Canada (16). Due to high cost and lack of public coverage for most, IN esketamine, though indicated for TRD is not used by our program. As such, this review focuses on the use of racemic ketamine for depression as has been used in our programs.

With burgeoning evidence and increasing mass media popularity, the demand for ketamine treatment has risen, and there has been a rapid increase in the number of clinics and hospital sites that are using ketamine for TRD (17). It would follow that these programs have addressed, or will need to address clinical issues that arise, such as issues around maintenance treatments and ways to increase access as IV ketamine programs become saturated. As the literature is rapidly growing, our group sought to review current literature to ensure best practices in our program. We do not intend to provide an exhaustive review of the literature, although the findings of several recent systematic reviews and meta-analysis will be described in this paper.

This document will review key questions that we have evaluated, and how it has been applied to our program. We will also discuss the models of non-parenteral ketamine use we have considered as options to increase overall access to ketamine treatment for depression within public healthcare systems.

2 Methods

The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2020 Ketamine Task force update was considered a comprehensive systematic review on ketamine for depression as a baseline. As this paper's literature search covered to Jan 31, 2020, we conducted a review of the literature from January 1, 2020 – June 30, 2023. This search was done via OVID search platform, MEDLINE database. The keyword terms 'ketamine' or 'esketamine' were used; combined with 'depression' or 'bipolar" or 'TRD' or 'treatment resistant depression'. Age groups were selected for 19 years and older, with studies limited to humans. Case reports, clinical trials, comparative studies, practice guidelines, meta-analysis, multicentre studies, observational studies, randomized controlled trials, reviews, and systematic reviews were considered. Reference lists of papers were also scanned for additionally relevant items. Papers were discussed among authors, and key items were brought to the interdisciplinary ketamine team for further review. Other notable studies outside of these parameters or suggested by peer reviewers between the end of our literature review and final manuscript acceptance were considered and added when felt to add value to the manuscript. Literature has been synthesized in the following discussion along with the authors' suggested applications to clinical practice.

3 Clinical considerations

3.1 What are our considerations in choosing between IV ketamine or in esketamine?

IN esketamine (SPRAVATO) was approved by Health Canada for TRD in 2020, while off-label, IV ketamine was previously acknowledged as an effective adjunct for TRD. While there is more robust clinical trial data for IN esketamine, its high cost frequently precludes its use. In terms of efficacy, head-to-head RCTs between IV ketamine and IN esketamine are lacking, but metanalyses of observational studies have compared efficacy of both treatments. One meta-analysis showed no difference in efficacy up to 1 month (18). However, two recent studies suggest that while each had similar rates of response/remission, IV ketamine required fewer treatments to achieve this outcome (19, 20).

Regardless, as racemic IV ketamine is not prohibitive in cost to the patients in our program (it is covered by public healthcare), it is the standard of treatment we use and will be the focus of discussion.

3.2 What population should be treated with IV ketamine?

Our protocol currently applies only to individuals with TRD (unipolar or bipolar), defined as failure to respond to two or more trials of appropriate pharmacotherapy. Our program treats adult patients ages 18 and over, including adults over 65, as there is early data for efficacy and safety with ketamine (21, 22) in older adults, and even more data with esketamine (23). Though not part of our patient population, one randomized control trial (RCT) in adolescents with TRD has also had favorable results (24).

Our population of adult patients with TRD is largely heterogeneous in terms of comorbidities, illness severity/duration, and levels of treatment resistance. More treatment-resistant patients have been reported as less likely to fully remit, but not less likely to respond to treatment (17). A recent study demonstrated that clinical features including severe anhedonia, anxious distress, mixed symptoms and/or bipolarity were more highly associated with response/remission (25). Efficacy of IV ketamine in individuals has been reported in two meta-analyses as either slightly inferior, or not different from ECT (26, 27). Evidence for functional improvement with ketamine treatment is lacking, but data supports the general notion that psychosocial functioning improves (28). Qualitatively, we have seen numerous cases of resistant patients who respond to treatment in a functionally meaningful way that improves quality of life and merits consideration for ongoing treatment. While there is preliminary evidence for use of ketamine in obsessive-compulsive disorder, social anxiety, post-traumatic stress disorder, psychosis, and comorbid substance use disorders (29), none were considered robust enough for inclusion in a regular protocol.

3.3 What is the inclusion/exclusion criteria for IV ketamine?

The presence of psychiatric comorbidities (including borderline personality disorder) does not significantly affect treatment outcomes or efficacy in a meaningful way (30, 31). Exclusion criteria include a primary psychotic disorder, uncontrolled hypertension, central aneurysmal disease, significant valvular disease, recent cardiovascular event (within 6 weeks), and class 3 heart failure (New York Heart Association) as per CANMAT recommendations (32).

Pregnancy and breastfeeding are considered contraindications to IV ketamine. While brief exposure to ketamine in the context of general anesthesia is unlikely to have negative effects, ketamine is known to cross the placenta (33) and exposure to repeated doses has not been studied. Animal models also suggest potential for adverse events with exposure to fetuses and infants (34).

Exclusion criteria have been made relative, rather than absolute, in keeping with longtime considerations to determine eligibility for ECT. Medical and/or second consultation with a psychiatrist is sought when appropriate to aid in assessment of risk/benefit. Decisions are made on a case-by-case basis.

3.4 Dosing regimens for IV ketamine

Meta-analysis of 79 studies (2,665 patients) reported variable but significant and conclusive efficacy for both response and remission rates with single and repeated ketamine dosing (35). With repeated treatments, ketamine's antidepressant effect was maintained, and appears to offer greater efficacy and more prolonged benefit compared to single infusion (36).

The standard acute course in our program is 8 treatments, typically administered two times weekly. Though three-times weekly treatments are no more effective than twice-weekly (37), some patients in our program may receive 1 or 3 treatments in a week depending on scheduling availability.

A dose of 0.5 mg/kg has been previously recommended (12), as lower doses have not been found to be as effective (38). A higher single dose of 1.0 mg/kg was found similarly safe, but not more effective than 0.5 mg/kg. There was a trend toward a longer duration of response at the higher dose, however.

The starting dose for IV ketamine in our program is 0.5 mg/kg, infused over 40 min. Given the safety data for higher doses, and data above that suggested a longer duration of response, we began increasing doses to 0.75 mg-1.0 mg/kg for patients who were tolerating infusions but had little or no response to 0.5 mg/kg. In our clinical experience, we have observed several patients who do not respond until the dose is increased, and data looking at superiority of 1.0 mg/kg versus 0.5 mg/kg was based only on a single infusion. Based on this, combined with clinical experience, Figure 1 highlights a suggested treatment algorithm. In cases where a patient only begins to respond to higher doses late in the course of 8 treatments, it is left to clinical discretion to consider extending the acute course.

3.5 How should clinical response be assessed?

A lack of dissociation is not correlated with reduced antidepressant response and should not be a factor in dosing decisions (39). The antidepressant response should eventually extend well beyond the treatment day, particularly after 5–8 treatments. If positive effects continue to wear off within 1–3 days, sustained antidepressant

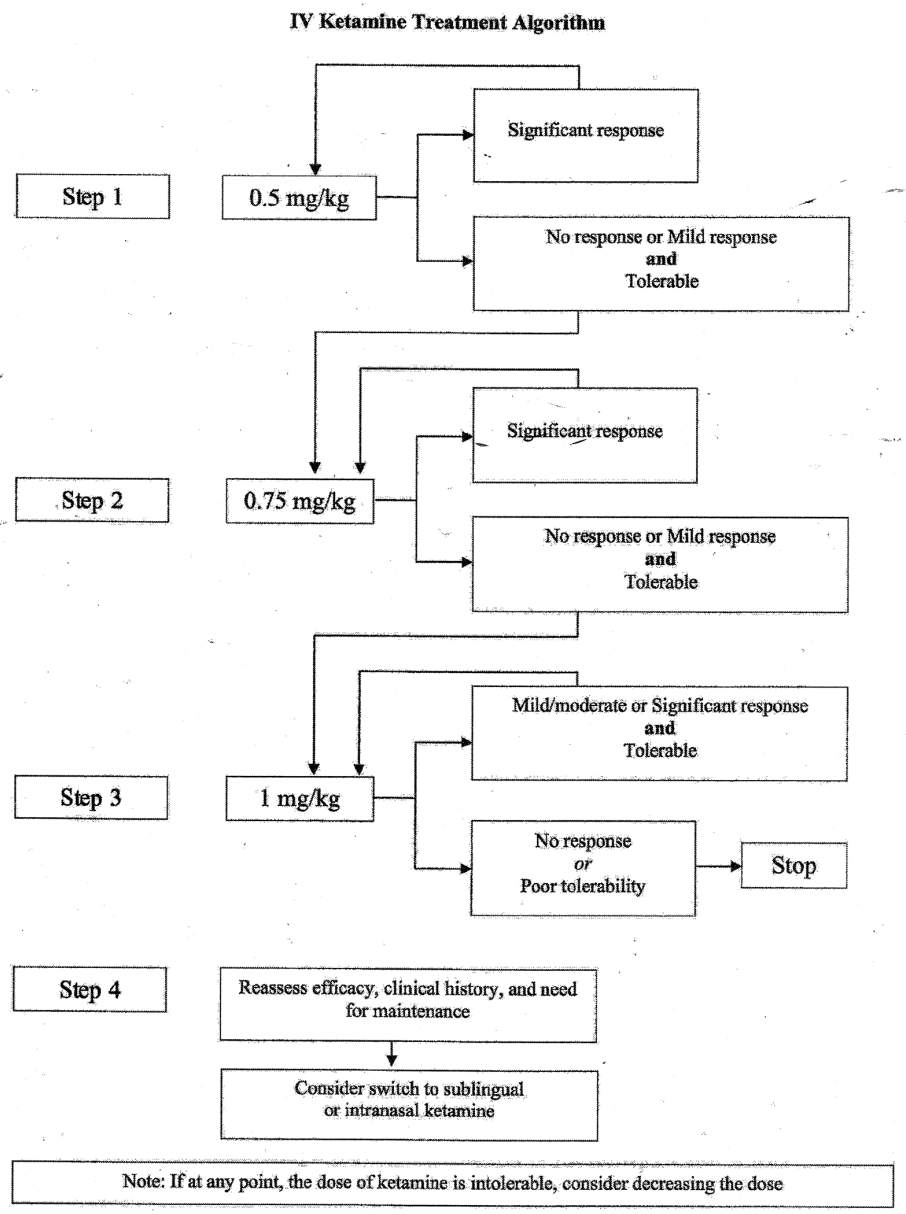

FIGURE 1
Suggested treatment algorithm for IV ketamine prescribing. If any point, the dose of ketamine is intolerable, consider decreasing the dose.

response with ketamine is unlikely and other treatment options should be considered.

It is important to ensure that there are clinical improvements in core symptoms of depression between treatments, and that the patient is not simply "liking" the dissociative effects of the treatment experience or enjoying a brief "escape" from their depression, not unlike those who abuse substances.

Along with clinical assessment, patient reported outcomes measures (PROMS) such as the Quick Inventory of Depressive Symptoms (QIDS) have been helpful to track progress. Traditional mood rating scales may not always capture rapid improvements, and another option would be the McIntyre and Rosenblat Rapid Response Scale (MARRRS), developed specifically as a tool to detect improvement with rapid acting antidepressants (40). Functional rating scales and quality of life scales may also be of benefit.

3.6 Which concomitant medications should be avoided?

There is mixed literature as to whether certain concomitant psychotropic medications may prevent antidepressant effects of ketamine. Though it has been suggested that benzodiazepines and other drugs acting on the Gamma-Aminobutyric Acid (GABA) systems may interfere with treatment response, a large meta-analysis found that concomitant benzodiazepine use had no overall effect (35).

Though no consistent effect is found, interference has been shown with high dose benzodiazepines such as delayed response and increased likelihood of relapse (41), with delayed response also observed with benzodiazepine use in esketamine treatment. Our program recommends to reduce or discontinue benzodiazepines if possible, or to use agents with shorter half-lives and simpler metabolism. Patients are advised not to take their benzodiazepine the morning of treatment and the evening prior. Higher doses or longer courses of ketamine may be required for individuals who continue benzodiazepines.

Co-administration of a single dose of naltrexone reduced antidepressant response to ketamine in one placebo-controlled study, raising questions as to whether naltrexone should be avoided during ketamine treatment (42). Though other reports have not replicated this finding (43, 44), the uncertainty surrounding this topic suggests that the decision to continue naltrexone could be made on a case-by-case basis.

Though lamotrigine has been reported to diminish dissociative effects of ketamine, antidepressant response is still elicited, supporting the concept that dissociation is not required for pharmacologically induced antidepressant effects of ketamine (45). A systematic review concluded that there was no evidence to support a negative interaction between lamotrigine and ketamine in clinical populations (46).

It has generally been considered safe to co-administer antidepressants and mood stabilizers with ketamine, but caution has been advised with MAOIs (12). Several case reports describe safe use of esketamine and MAOIs (47), as well as ketamine with MAOIs (48). Though to be used with caution, IV ketamine has been useful as a bridging treatment during an antidepressant washout prior to starting an MAOI, and during the first few weeks of MAOI treatment.

3.7 What are the common acute side effects of IV ketamine?

Ketamine is a safe and well-tolerated medication when administered at antidepressant doses. Common side effects noted in literature are transient and may include psychotomimetic and dissociative experiences, blurred vision, dizziness, anxiety, irritability, headaches, nausea, tachycardia, and elevated blood pressure (6, 49, 50). Side effects peak within 30–60 min, and abate within 1–2 h. Adverse events are almost always dose-dependent (51). Patients in our program are provided this information prior to giving consent to treatment.

3.8 How should ketamine-induced hypertension be managed?

Ketamine is known to transiently raise blood pressure, with a mean maximum increase of 9-19 mmHg, returning to normal in 2–4 h (52). Early recommendations, based on expert consensus suggested not to proceed with IV ketamine if baseline blood pressure was over 140/90, and to pause the infusion if blood pressure exceeded 160/100 (12). A recent report suggested that up to 20% of ketamine infusions may require anti-hypertensives (51).

Conversely, transient hypertension is not treated in an emergency medicine scenario unless there are symptoms of hypertensive emergency which include crushing chest pressure, syncope, severe abdominal pain, decreased (not just altered) level of consciousness, or shortness of breath (53). Risks associated with treating asymptomatic transient hypertension have also been noted, and it could be argued that the above guidance is overzealous.

Our protocol has been updated to better align with the emergency medicine approach to management of transient hypertension. Blood pressure is measured at baseline and post-treatment. Measurements are to be taken during the infusion only if there are signs/symptoms of hypertensive emergency as noted above. Patients in our program must undergo a complete history and physical examination prior to starting a course of IV ketamine infusions. Active medical issues or untreated hypertension are considered relative exclusion criteria to be considered on an individual risk/benefit basis.

Although the aim is for chronic hypertension to be sufficiently treated prior to ketamine treatments, if baseline blood pressure is elevated on the day of treatment, the decision to proceed is made on a case-by-case basis. Otherwise healthy individuals can tolerate slight elevation in blood pressure without adverse consequences, not unlike increases seen during exercise, which is known to transiently increase systolic blood pressure to levels greater than seen with IV ketamine treatment (greater than 200 mmHg) (54). Patients with risk factors for subarachnoid hemorrhage (SAH), such as pre-existing aneurysm or arterio-venous malformation (85% of SAH clinical presentations) (55), or other medical conditions felt to be at risk with transient blood pressure elevations, would necessitate medical consultation for advice on a more cautious approach. Of note, pre-treatment with clonidine has been reported to mitigate pressor effects of ketamine without causing rebound hypertension, so this may be an option for patients where blood pressure increases may pose reason for concern (56). Use of beta blockers or calcium channel blockers has also been suggested when blood pressure is a concern (57).

3.9 What setting and staff are required for IV ketamine?

Though no consistent standard is in place, the Canadian Ketamine Task Force suggested that IV ketamine should be administered in a facility equipped to handle both storage of a controlled substance and ability to deal with medical emergencies. While an anesthetist need not be present to administer a subanesthetic dose, staff administering ketamine should be medical professionals with appropriate training (12). Our ketamine programs are based in acute care hospitals, which have a rapid response team available in case of an emergency. This rapid response service has never been required since the program began in 2015, with at least 10,000 infusions performed. A nurse trained in advanced airway management administers the ketamine infusion, and a physician can be reached by telephone if there are nursing concerns. Treatments are provided in the unit's neuromodulation recovery room, or in individual patient rooms. As sensory perception is often amplified during treatment, our program aims to provide a calm environment with reduced stimuli.

Consistent nursing staff dedicated specifically to IV ketamine is beneficial, to be familiar with what to expect and how to support patients through treatments. At times, dissociative effects include tearfulness, rumination and having intrusive thoughts or memories, which may prompt nursing staff to intervene, redirect and/or support

the patient. This is not considered to be a form of ketamine-assisted psychotherapy, but a supportive psychiatric nursing intervention as required. Patients are kept on the unit for approximately 90 min post-infusion, which is based on a 15-min half-life of IV ketamine, with a total time of elimination being approximately 75 min (58). If patients continue to feel dissociative effects, they are kept longer at nursing discretion. Patients require a ride home after treatment.

3.10 What is an approach to maintenance treatment?

Once remission is reached with a traditional antidepressant, continued treatment for a minimum of 9–12 months (or longer if it is a repeat episode or severe illness) is recommended to minimize relapse risk (59). Similarly, following a successful course of ECT, maintenance ECT reduces relapse significantly compared to pharmacotherapy alone (60). Similarly, repeated doses of IV ketamine have demonstrated efficacy in maintaining response (61). A recent systematic review included 3 RCTs, 8 open-label trials, and 30 case series with a total of 1,495 patients with bipolar or unipolar depression (62). Routes of administration varied and included IV (18 studies), IN (3), IN esketamine (5), oral (10), and intramuscular (3). There were several reports of transitioning IV ketamine patients to other dosage forms (SL, IN, oral) for ketamine maintenance treatment. The five largest (N = 11–94) studies of IV ketamine maintenance used dose ranges from 0.5–1.2 mg/kg. Dose frequency was variable, ranging anywhere from weekly to every 12 weeks. Important findings in this review included reports of sustained efficacy for many individuals lasting greater than 1 year, and no new safety signals with prolonged treatment.

The most robust data for maintenance ketamine comes from a large RCT of 802 patients using maintenance IN esketamine over 1 year. There was a 51% reduction in relapse with treatment-remitters, and a 70% reduction in relapse with treatment-responders, when given with conventional antidepressant compared to antidepressant plus placebo (63). The population in this report included individuals with TRD who had failed to respond to two or more antidepressants. The largest IV ketamine maintenance study to date (open-label) reported on more highly resistant individuals who had already failed to respond to ECT. Of these, 94/150 (63%) of these patients responded to IV ketamine, and with maintenance treatment of variable dose and frequency, nearly two-thirds of these highly treatment-resistant responders showed a sustained response (64).

Meta-analysis data suggests that ketamine response is less robust and of shorter duration for individuals with a higher level of treatment resistance, thus it may be these individuals for whom maintenance ketamine is a more inevitable consideration (65). Physicians in our program decide whether to offer maintenance ketamine based the degree of ketamine response, level of treatment resistance, accessibility of ongoing IV ketamine treatments, and/or patient suitability for alternate forms of ketamine use, which will be further discussed.

3.11 What is the long-term safety of ketamine?

There is growing but still limited data on long-term use of ketamine for depression. The previously mentioned systematic review of 1,495 patients receiving ketamine for up to 18 months did not identify safety concerns (62). A recently published survey of 6,630 patients in the United States treated with repeated or maintenance parenteral ketamine reported that discontinuation rates for adverse events was 0.7% (66). 0.5% of patients discontinued for psychological distress. There were three cases reported "bladder dysfunction," no reports of cognitive issues, two reports of psychosis, and one report of hypomania. While the study was unable to assess causality of the adverse events, the overall incidence of these is reassuringly low. Similarly, Janssen's esketamine clinical program reported data from a 4-year follow-up among 1,006 patients continuing to receive maintenance esketamine with no new safety signals demonstrated (67).

3.11.1 Urinary effects

High dose, chronic ketamine use among ketamine abusers has been associated with ulcerative urinary cystitis and dilated common bile ducts mimicking choledochal cysts (68–71). This has not yet been reported in the literature with clinical IV ketamine treatment for depression, but we have occasionally seen patients develop transient urinary symptoms. Periodic screening for any urinary symptoms and urinalysis to screen for microscopic hematuria should be done periodically in patients using maintenance ketamine. If symptoms develop, the risk/benefit of continuing ketamine should be assessed, with urologic consultation.

3.11.2 Cognition

While neurocognitive impairment has been reported with chronic ketamine abuse (72), a review of 5 IV ketamine studies with objective measurements of cognition noted either a neutral effect or an improvement in cognition, with no domains showing impairment (73). The improvement in cognition typically correlated with the degree of antidepressant response. In our program, a study of 40 patients found improved cognition over a course of 8 IV ketamine treatments as measured by a Digit Span Substitution Test (DSST) and patients perceived their overall cognition as improved when self-rated with a Perceived Deficits Questionnaire (PDQ) (74).

3.11.3 Ketamine abuse/misuse

Ketamine abuse often occurs with other substance use, more confounding health variables, and consumption at significantly higher and more frequent doses than is used for depression (75, 76). Though ketamine abuse rates are substantially higher in Eastern countries (Hong Kong, Taiwan) (34), its prevalence In North America is low; estimated at 0.4% in college students over a 1 year period (77), While preclinical studies suggested a theoretical abuse potential for ketamine, two reviews of clinical literature find no suggestion for ketamine misuse or abuse when prescribed for depression (78). Real world-studies have also replicated these findings with esketamine (79, 80).

A retrospective survey of patients in our program with patients prescribed ketamine outside of clinically monitored settings did not find any indication of misuse. Drug-liking, was variable, with a number of patients indicating a dislike for the dissociative effects of ketamine. Overall risk level appeared low, but not negligible (81). Similarly, there is only one case report of drug seeking behavior and craving in a single patient treated with esketamine (82). Similar to other medications with abuse, caution in prescribing should be exercised, but its use should not be stigmatized and potentially discourage access. Suggestions for judicious use have been previously summarized by another group that included two of our coauthors and will be reviewed in following sections (83).

3.12 When IV ketamine is not an option, are other routes of administration possible?

Ketamine may be administered in a variety of different routes, including IV, IM, subcutaneous (SC), IN, SL, and oral (PO), but each has different rates of bioavailability (Table 1) and pharmacokinetics (84, 85). Clinically, these differences may affect efficacy and tolerability. A pharmacokinetic study demonstrated that equal doses of IM, SC, and 40-min IV ketamine infusions achieve similar peak plasma levels and clearance rates (86). Systematic reviews have not demonstrated significantly different side effect or tolerability profiles regardless of the route of administration, though it has been suggested that side effects are most likely correlated with total plasma levels achieved regardless of the route delivered (35, 87).

Small studies have demonstrated similar effectiveness/tolerability with IM ketamine at similar doses to IV ketamine in both single and repeat doses (88, 89). A recent RCT (45 patients) also demonstrated equal effectiveness in repeat treatments comparing IM ketamine (0.5 mg/kg), oral ketamine (1 mg/kg), and ECT (90). A systematic review of SC ketamine for depression found safety and efficacy at doses of 0.1–0.5 mg/kg, though studies were noted to be heterogenous in nature (91). A recent RCT (174 patients) investigated SC ketamine, with a more highly treatment-resistant group (more than 5 failed antidepressant trials, 24% failing ECT). Compared to active control (midazolam), doses of 0.6–0.9 mg/kg (but not 0.5 mg/kg) were superior, with a favorable side effect profile (92). Although IM and SC ketamine may offer a more efficient use of resources, saving the time required for IV insertion and infusion, our program has not yet incorporated their use given the comparative lack of studies.

Non-parenteral forms of ketamine including IN, PO and SL ketamine are also reported as safe and efficacious (18). Though less evidence-based than IV ketamine, they may offer improved access due to reduced cost and potentially less monitoring required, which will be later discussed. In our community, expertly-compounded IN or SL racemic ketamine costs $100–150 per month, a significant decrease in treatment cost compared to IN esketamine. While balancing considerations of patient access, safety, and limitations of evidence base for these treatments, concepts have been applied to a paradigm to treat patients with these modalities (83), and physicians in our program have utilized IN and SL ketamine at times for both acute and maintenance treatment. The clinical context of the patient (including degree of illness, previous treatments, treatment setting, resource availability) should be considered in balance with potential side effects/risks. Suggested criteria for offering non parenteral ketamine are highlighted in Table 2.

TABLE 1 Routes and bioavailability of ketamine.

Route	Bioavailability %
Intravenous	95–100
Intramuscular	64–95
Subcutaneous	64–95
Intranasal	30–50
Sublingual	20–30
Oral	10–20

3.13 What doses should be used for non-parenteral forms of ketamine?

Though parenteral doses of ketamine in studies have been relatively consistent, evidence for optimal dosing of non-parenteral ketamine remains limited. Though meta-analysis supports safety and efficacy of IN ketamine, most of this data is derived from IN esketamine trials. One report on racemic IN ketamine suggested tolerability concerns (93), but several others support its use. A small, randomized cross-over study found efficacy and favorable tolerability of a single 50 mg dose (94), and a retrospective case series with repeated doses of 100-150 mg noted positive results in the majority of patients with no instances of discontinuation for adverse side effects or concerning safety signals (95). A subsequent retrospective study reported benefit and tolerability for 50 or 75 mg of IN ketamine in psychiatric inpatients with TRD (96). An international consensus paper suggests that compounded racemic IN ketamine could be used in doses ranging from 50 to 150 mg once or twice weekly (29).

Though meta-analysis data is positive for PO and SL ketamine (97), reported doses and frequencies varied widely, ranging from 0.5–1.25 mg/kg (or 50-300 mg for studies which reported total doses only) used multiple times per day to once a month. A recent large ($N = 664$) retrospective report of SL ketamine (300-450 mg) used off-label at home demonstrated nearly identical results to IV ketamine when administered as a series of 6 treatments (98).

As data regarding dosing is limited, we have elected to dose based on bioavailability of the chosen formulation in comparison to IV dosing (100% bioavailable) of 0.5–1.0 mg/kg (Table 3). Though it is a crude estimate that is unable to account for varying pharmacokinetic factors, it has been a useful clinical guideline. If used for acute treatment in our program, IN or SL ketamine is typically given 2–3 times weekly, modeling IV ketamine and IN esketamine schedules. For an initial course to ketamine-naive individuals, patients are started at the minimum effective dose of the calculated dose range.

Some prescribers instead choose not to dose by weight and start ketamine-naïve patients conservatively at 50-100 mg SL or IN, titrating the dose up as tolerated to efficacy. One recent report successfully started ketamine-naïve patients at 300 mg SL and increased as tolerated to 450 mg (98), but our approach to date has been more conservative. A recent chart review of a sample of patients from our program found SL ketamine was generally started at 50-200 mg, though the most common starting doses were 100 mg and 150 mg. Subsequent increases went as high as 300 mg (81). IN ketamine was typically started at 100 mg and increased as high as 150 mg. Starting doses near the higher range would typically be patients transitioned to SL ketamine for maintenance, following a course of IV ketamine. Optimal dosing to maximize the balance between efficacy and tolerability requires further research.

3.14 In what setting can patients use SL or in ketamine?

While Health Canada requires IN esketamine to be administered and monitored a health care setting, this mandate is not aligned with the drug's side effect and risk profile, so should not set a standard SL or IN racemic ketamine use. Significant adverse events have not been reported with esketamine, including issues related to transient

TABLE 2 Clinical scenarios to consider for non-IV forms of ketamine for acute or maintenance treatment.

Individuals reasonable to consider for an acute course (8 treatments) of non-IV ketamine would be those with both 1. Major depressive episode (unipolar or bipolar), refractory to trials of 2 or more antidepressants/mood stabilizers, and adjunctive agents with a greater evidence base, AND 2. Unable to access more evidence-based ketamine treatments such as IV ketamine and IN esketamine.
Individuals reasonable to consider for maintenance non-IV ketamine treatments would include those with: 1. Major depressive episode (unipolar or bipolar), considered to have exhausted other treatment options with trials of multiple antidepressants, adjuncts, and mood-stabilizing medications from different classes, *but have had positive response to an acute course of either IV or SL/IN ketamine*, AND 2. Unable to access maintenance IV ketamine or IN esketamine treatments. Where patients continue to have coverage and access to IN esketamine following an index series of IN esketamine treatments, we would suggest continuing with IN esketamine for maintenance as it is most strongly supported by the literature at this time in terms of efficacy and safety.

TABLE 3 Suggested dosing for intranasal and sublingual ketamine.

Mode of administration	Intravenous	Intranasal	Sublingual
Bioavailability (%)	100	30–50	20–30
Minimum effective dose (mg/kg)	0.5	1.0	1.5
Maximal effective dose (mg/kg)	1.0	3.0	5
Conversion/multiplier factor from previously given IV ketamine dose	N/A	2–3	3–5

hypertension or dissociative side effects. Similarly, long term IN esketamine use has not been associated with safety concerns. Concerns for addiction potential, misuse, or diversion may prompt the tight control around IN esketamine, but it has been previously noted that regulatory policies do not align with expert consensus regarding risks (99). Potential harms of ketamine have been assessed as similar to stimulants or benzodiazepines, all of which are lower than alcohol. Placing ketamine on a more restrictive access and monitoring schedule than other psychotropics with abuse potential stigmatizes this treatment, and limits access for individuals with TRD.

Initially, patients in our program were monitored in office for their first SL or IN treatment, with potential for subsequent treatments to be used at home. However, our critical assessment of risks and benefits concludes that in office monitoring need not be routinely required. As discussed above, blood pressure need not be monitored as asymptomatic hypertension should not be treated. Patients typically report dissociative effects to be less than experienced in with IV ketamine treatments, and with appropriate psychoeducation, dissociative experiences are rarely a concern. Non parenteral forms of ketamine may be safely prescribed for home use, to the appropriate patient, in the appropriate clinical scenario.

TABLE 4 Clinical factors that would support eligibility for less supervised ketamine use.

High level of treatment resistance – patients who have exhausted other treatment options - Severe symptoms - Significant disability - Suicidality - Has required usage of other off-label treatments in the past
No drug misuse history – Substance abuse/misuse screen
No previous history of antisocial/illegal activity/drug diversion
Previous positive response to ketamine
Limited ability to access ketamine treatments with stronger evidence base (IV ketamine or IN esketamine)
Reliable to attend follow-up appointments
Medically suitable for ketamine treatment, including stable cardiovascular status and controlled baseline blood pressure
Compliant with side effect monitoring
Significant experience with side effects of psychotropics and good judgment on reporting these to the clinician

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Suggested considerations for prescribing ketamine for home use have previously been raised and are summarized in Table 4. If home administration is chosen to be a suitable alternative, other authors have also made practical suggestions for judicious prescribing. These are noted in Table 5. Our program follows these suggestions, and requests patients to return used intranasal devices to the pharmacy for disposal of any remaining ketamine in the device.

4 Future directions

Future directions in ketamine treatment could include consideration of 3 treatment models we refer to as: (1) step-down approach, (2) step-up approach, and (3) clinical-matching approach. The common aim of all is to find a complementary way to integrate use of SL or IN ketamine into the IV ketamine treatment paradigm. Our program organically evolved into using the "step-down" approach where a course of IV ketamine is administered for acute treatment, and if maintenance treatment is needed, "stepping down" to IN or SL ketamine. This has been done either with a direct transition from an acute course of IV ketamine to SL or IN ketamine at varying intervals or has been done to support an IV ketamine taper, continuing SL or IN treatments once or twice weekly, in between biweekly, every 3 week and then monthly IV treatments, with an eventual goal to transition off IV treatments entirely. While there is no data to support superiority for either mode, a recent report of transition to IN esketamine to maintain the response of IV ketamine provides comparative support for a step-down model (100).

The "step-up" approach is an alternative that could be considered, particularly by new ketamine programs. In this model, a referral criterion for IV ketamine could include a previous failed trial of SL or IN ketamine in the community. This model also evolved organically for during the COVID-19 pandemic, during a time that our IV programs were not operating, and patients were reluctant to come for treatment in a health care setting. SL or IN compounded ketamine was prescribed to ketamine naïve patients with several patients responding well and not requiring IV treatment. This approach could reduce wait

TABLE 5 Practical suggestions for judicious prescribing of ketamine as an antidepressant for home use.

Obtain and document informed consent – potential risks/benefits
Consider the use of patient contracts
Prescribe in limited quantities and limited refills (for example, provide 2–4 weeks supply depending on frequency of dosing)
Prescriber experience with ketamine - Affiliation with a more intensive ketamine program (for further assessment/ referral/case discussions)
Consider observing first treatments or dose changes in office to monitor blood pressure in medically at-risk patients, and dissociation in ketamine-naïve individuals
Educate patients on dissociative symptoms
Advise patients not to drive until next day after use Dose at night when used at home • Advise a quiet calm environment • For ketamine-naïve patients, consider the presence of another responsible adult for the first several doses, if not observed in office • Wait until dissociative/sedative effects of ketamine dissipate before using other potentially sedating bedtime medications
Screen for bladder toxicity - Check urinalysis at baseline and q3-6 months for signs of microscopic hematuria - Ask about urinary symptoms (for example, frequency, urgency, hematuria)
Monitor for drug liking/signs or symptoms of misuse - lost prescriptions - requests for early refills - requests for dose escalation or increased frequency despite stable psychiatric status
Consider that non-IV forms may require higher doses due to reduced bioavailability, and that documented bioavailability of each formulation is to be considered a rough estimate and may vary
Prescribing clinicians should be informed of current literature and continue medical education on ketamine to learn and adjust prescribing practices as new data become available

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lists and reserve IV ketamine treatments for more treatment-resistant individuals. Adopting this "step-up" paradigm could be of particular use in smaller centers with limited IV ketamine availability.

A third "clinical-matching" model would involve making decisions regarding what form of ketamine is appropriate based on patient profile. The patients with TRD that meet criteria for IV ketamine are a heterogeneous group in terms of symptom severity and chronicity, comorbid conditions, and the number of previous treatments tried. While this model has not been used to date in our program, theoretically, IV ketamine could be reserved for only the most treatment resistant patients, such as our original URD population. Other patients who meet "minimum" TRD criteria may respond favorably to SL or IN ketamine treatment. While our clinical experience supports the notion that the "less" treatment resistant patient may respond to SL or IN ketamine alone, further research is needed in this area.

Continued challenges with any of these paradigms include lack of data regarding optimal dosing and frequency for SL and IN ketamine. A clear limitation in our approach is the extrapolation of IV ketamine and IN esketamine data. A review of clinicaltrials.gov indicates that several studies involving racemic IN ketamine are in various stages of progress, so further data to guide its use may be on the horizon. Larger controlled trials with IN/SL ketamine, and comparative studies with IV ketamine or IN esketamine would be of great value to guide future treatment.

5 Conclusion

As the evidence for IV ketamine and IN esketamine for TRD has increased, the availability and accessibility of these treatments has been a financial and logistical challenge for many, preventing access to evidence-based treatments with much promise. This community case study has described the evolution of a public ketamine program, including the application of a recent literature review to clinical programming. Sites starting an IV ketamine program must be aware of limitations, particularly in consideration for how maintenance treatment may be offered to those who require it. Without the ability to offer maintenance ketamine in some form, offering this treatment to patients who may respond well, only to relapse again raises questions surrounding the ethics of offering short term treatment only. As we have shared in this community case study, the use of SL and IN ketamine in Edmonton, Canada has facilitated increased access to ketamine treatment, and allowed us to address this issue.

Though awareness of potential risks of ketamine use is essential, it need not be stigmatized as an overly dangerous treatment when considering highly ill and treatment-resistant patients. Rare, but serious adverse events can occur with any treatment, and there is no suggestion that the risks of ketamine are out of keeping with other medications commonly used in psychiatry. The ability to prescribe SL and IN ketamine provides psychiatrists with more options to offer to patients with TRD. Clinicians who elect to offer these treatments must be aware of the limitations in the guiding body of literature. Aspects such as patient selection, regular follow up, and ongoing assessment of risk/benefit for the individual patient are essential. Future research to better elucidate optimal prescribing of ketamine will support physicians and patients in making treatment decisions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the studies involving humans because this paper contains no original data. It reviews previously reported research on human populations. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/ next of kin in accordance with the national legislation and institutional

requirements because there were no participants. Data presented has been reported elsewhere and is reviewed.

Author contributions

CC: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Data curation, Resources, Software, Visualization. BD: Conceptualization, Data curation, Visualization, Writing – review & editing. AK: Conceptualization, Visualization, Writing – review & editing. CM: Conceptualization, Writing – review & editing. RT: Conceptualization, Writing – review & editing. JS: Conceptualization, Writing – review & editing, Methodology, Project administration, Supervision, Writing – original draft.

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Conflict of interest

CC has received honoraria from Abbvie. AK has received honoraria from Abbvie, Bausch Health, Eisai, Elvium, Takeda, Lundbeck, Otsuka, Sunovion, Jazz, Paladin and has served as a medical advisor for the Newly Institute, a private clinic that utilizes SL ketamine. RT has received honoraria from Abbvie, Lundbeck, Otsuka, Takeda, Sunovion, Janssen, Bloom Psychedelics, Sunovion, and Eisai. JS has received honoraria from Abbvie, Bausch Health, Eisai, Janssen, Lundbeck, Otsuka, and has served as a medical advisor for the Newly Institute, a private clinic that utilizes SL ketamine.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412. doi: 10.1002/wps.21120

2. Rush A, Fava M, Wisniewski S, Lavori PW, Trivedi MH, Sackeim HA, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. (2004) 25:119–42. doi: 10.1016/S0197-2456(03)00112-0

3. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Hum Psychopharmacol*. (2015) 30:152–63. doi: 10.1002/hup.2475

4. McGirr A, Berlim MT, Bond DJ, Neufeld NH, Chan PY, Yatham LN, et al. A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: efficacy and tolerability. *J Psychiatr Res*. (2015) 62:23–30. doi: 10.1016/j.jpsychires.2015.01.003

5. Fond G, Loundou A, Rabu C, Macgregor A, Lançon C, Brittner M, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology*. (2014) 231:3663–76. doi: 10.1007/s00213-014-3664-5

6. Serafini G, Howland RH, Rovedi F, Girardi P, Amore M. The role of ketamine in treatment-resistant depression: a systematic review. *Curr Neuropharmacol*. (2014) 12:444–61. doi: 10.2174/1570159X12666140619204251

7. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of short and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Res*. (2015) 230:682–8. doi: 10.1016/j.psychres.2015.10.032

8. Thomas RK, Baker G, Lind J, Dursun S. Rapid effectiveness of intravenous ketamine for ultra-resistant depression in a clinical setting and evidence for baseline anhedonia and bipolarity as clinical predictors of effectiveness. *J Psychopharmacol*. (2018) 32:1110–7. doi: 10.1177/0269881118793104

9. Cusin C, Ionescu DF, Pavone KJ, Akeju O, Cassano P, Taylor N, et al. Ketamine augmentation for outpatients with treatment-resistant depression: preliminary evidence for two-step intravenous dose escalation. *Aust N Z J Psychiatry*. (2017) 51:55–64. doi: 10.1177/0004867416631828

10. Ionescu DF, Bentley KH, Eikermann M, Taylor N, Akeju O, Swee MB, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. *J Affect Disord*. (2019) 243:516–24. doi: 10.1016/j.jad.2018.09.037

11. McIntyre RS, Rodrigues NB, Lee Y, Lipsitz O, Subramaniapillai M, Gill H, et al. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian rapid treatment Center of Excellence. *J Affect Disord*. (2020) 274:903–10. doi: 10.1016/j.jad.2020.05.088

12. Swainson J, McGirr A, Blier P, Brietzke E, Richard-Devantoy S, Ravindran N, et al. The Canadian network for mood and anxiety treatments (CANMAT) task force recommendations for the use of racemic ketamine in adults with major depressive disorder: recommendations. *Can J Psychiatr*. (2021) 66:113–25. doi: 10.1177/0706743720970860

13. Yatham L, Kennedy S, Parikh S, Schaffer A, Bond DJ, Frey BN, et al. Canadian network for mood and anxiety treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorder*. (2018) 20:97–170. doi: 10.1111/bdi.12609

14. Jawad MY, Qasim S, Ni M, Guo Z, di Vincenzo JD, d'Andrea G, et al. The role of ketamine in the treatment of bipolar depression: a scoping review. *Brain Sci*. (2023) 13:909. doi: 10.3390/brainsci13060909

15. U.S. Food and Drug Administration. (2019). *Press Release: FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic [press release]*. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632761.htm

16. Alberta Health Services. *Intravenous Ketamine for the Treatment of Adult Depression*. (2021). Available at: https://extranet.ahsnet.ca/teams/policydocuments/1/clp-amh-ahs-iv-ketamine-amh-10-01.pdf (Accessed March 25, 2021).

17. Wilkinson ST, Toprak M, Turner MS, Levine SP, Katz RB, Sanacora G. A survey of the clinical, off-label use of ketamine as a treatment for psychiatric disorders. *Am J Psychiatry*. (2017) 174:695–6. doi: 10.1176/appi.ajp.2017.17020239

18. McIntyre RS, Carvalho IP, Lui LMW, Majeed A, Masand PS, Gill H, et al. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. *J Affect Disord*. (2020) 276:576–84. doi: 10.1016/j.jad.2020.06.050

19. Singh B, Kung S, Pazdernik V, Schak KM, Geske J, Schulte PJ, et al. Comparative effectiveness of intravenous ketamine and intranasal Esketamine in clinical practice among patients with treatment-refractory depression: an observational study. *J Clin Psychiatry*. (2023) 84:14548. doi: 10.4088/JCP.22m14548

20. Nikayin S, Rhee TG, Cunningham ME, de Fontnouvelle CA, Ostroff RB, Sanacora G, et al. Evaluation of the trajectory of depression severity with ketamine and Esketamine treatment in a clinical setting. *JAMA Psychiatry*. (2022) 79:736–8. doi: 10.1001/jamapsychiatry.2022.1074

21. Lipsitz O, di Vincenzo JD, Rodrigues NB, Cha DS, Lee Y, Greenberg D, et al. Safety, tolerability, and real-world effectiveness of intravenous ketamine in older adults with treatment-resistant depression: a case series. *Am J Geriatr Psychiatry*. (2021) 29:899–913. doi: 10.1016/j.jagp.2020.12.032

22. Oughli H, Gebara M, Ciarleglio A, Lavretsky H, Brown PJ, Flint AJ, et al. Intravenous ketamine for late-life treatment-resistant depression: a pilot study of tolerability, safety, clinical benefits, and effect on cognition. *Am J Geriatr Psychiatry*. (2023) 31:210–21. doi: 10.1016/j.jagp.2022.11.013

23. d'Andrea G, Chiappini S, McIntyre RS. Investigating the effectiveness and tolerability of intranasal esketamine among older adults with Treatment-Resistant Depression (TRD): A Post-hoc Analysis from the REAL-ESK Study Group. *Am J Psychiatry*. (2023) 31:1032–41.

24. Dwyer JB, Landeros-Weisenberger A, Johnson JA, Londono Tobon A, Flores JM, Nasir M, et al. Efficacy of intravenous ketamine in adolescent treatment-resistant depression: a randomized midazolam-controlled trial. *Am J Psychiatry*. (2021) 178:352–62. doi: 10.1176/appi.ajp.2020.20010018

25. Pettorruso M, Guidotti R, d'Andrea G. Predicting outcome with Intranasal Esketamine treatment: A machine-learning, three-month study in Treatment-Resistant Depression (ESK-LEARNING). *Psychiatry Res*. (2023) 115378. doi: 10.1016/j.psychres.2023.115378

26. Menon V, Varadharajan N, Faheem A, Andrade C. Ketamine vs electroconvulsive therapy for major depressive episode: a systematic review and Meta-analysis. *JAMA Psychiatry*. (2023) 80:639–42. doi: 10.1001/jamapsychiatry.2023.0562

27. Rhee TG, Shim SR, Forester BP, Nierenberg AA, McIntyre RS, Papakostas GI, et al. Efficacy and safety of ketamine vs electroconvulsive therapy among patients with major depressive episode: a systematic review and Meta-analysis. *JAMA Psychiatry*. (2022) 79:1162–72. doi: 10.1001/jamapsychiatry.2022.3352

28. Ng J, Rosenblat JD, Lui LMW, Teopiz KM, Lee Y, Lipsitz O, et al. Efficacy of ketamine and esketamine on functional outcomes in treatment-resistant depression: a systematic review. *J Affect Disord*. 202. (2021) 293:285–94. doi: 10.1016/j.jad.2021.06.032

29. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatr*. (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

30. Danayan K, Chisamore N, Rodrigues NB, Vincenzo JDD, Meshkat S, Doyle Z, et al. Real world effectiveness of repeated ketamine infusions for treatment-resistant depression with comorbid borderline personality disorder. *Psychiatry Res*. (2023) 323:115133–3. doi: 10.1016/j.psychres.2023.115133

31. Martinotti G, Vita A, Fagiolini A, et al. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. (2022) 319:646–54.

32. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. (2017) 74:399–405. doi: 10.1001/jamapsychiatry.2017.0080

33. Product Information. *KETALAR(R) intravenous, intramuscular injection, ketamine HCl intravenous, intramuscular injection*. Chestnut Ridge, NY: Par Pharmaceutical (Per FDA) (2020).

34. Nikayin S, Murphy E, Krystal J, Wilkinson ST. Long-term safety of ketamine and esketamine in treatment of depression. *Expert Opin Drug Saf*. (2022) 21:777–87. doi: 10.1080/14740338.2022.2066651

35. Alnefeesi Y, Chen-Li D, Krane E, Jawad MY, Rodrigues NB, Ceban F, et al. Real-world effectiveness of ketamine in treatment-resistant depression: a systematic review and meta-analysis. *J Psychiatr Res*. (2022) 151:693–709. doi: 10.1016/j.jpsychires.2022.04.037

36. Kryst J, Kawalec P, Mitoraj AM, Pilc A, Lasoń W, Brzostek T. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. *Pharmacol Rep*. (2020) 72:543–62. doi: 10.1007/s43440-020-00097-z

37. Singh JB, Fedgchin M, Daly EJ, de Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry*. (2016) 173:816–26. doi: 10.1176/appi.ajp.2016.16010037

38. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol Psychiatry*. (2020) 25:1592–603. doi: 10.1038/s41380-018-0256-5

39. Grabski M, Borissova A, Marsh B, Morgan CJA, Curran HV. Ketamine as a mental health treatment: are acute psychoactive effects associated with outcomes? A systematic review. *Behav Brain Res*. (2020) 392:112629–1129. doi: 10.1016/j.bbr.2020.112629

40. McIntyre RS, Rodrigues NB, Lipsitz O, Lee Y, Cha DS, Gill H, et al. Validation of the McIntyre and Rosenblat rapid response scale (MARRRS) in adults with treatment-resistant depression receiving intravenous ketamine treatment. *J Affect Disord*. (2021) 288:210–6. doi: 10.1016/j.jad.2021.03.053

41. Andrashko V, Novak T, Brunovsky M, Klirova M, Sos P, Horacek J. The antidepressant effect of ketamine is dampened by concomitant benzodiazepine. *Front Psych*. (2020) 11:844. doi: 10.3389/fpsyt.2020.00844

42. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am J Psychiatry*. (2018) 175:1205–15. doi: 10.1176/appi.ajp.2018.18020138

43. Yoon G, Petrakis IL, Krystal JH. Association of combined naltrexone and ketamine with depressive symptoms in a case series of patients with depression and alcohol use disorder. *JAMA Psychiatry*. (2019) 76:337–8. doi: 10.1001/jamapsychiatry.2018.3990

44. Marton T, Barnes DE, Wallace A, Woolley JD. Concurrent use of buprenorphine, methadone, or naltrexone does not inhibit ketamine's antidepressant activity. *Biol Psychiatry*. (2019) 85:e75–6. doi: 10.1016/j.biopsych.2019.02.008

45. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of n-methyl-d-aspartate receptor antagonists. *Arch Gen Psychiatry*. (2000) 57:270–6. doi: 10.1001/archpsyc.57.3.270

46. Wilkowska A, Wiglusz MS, Jakuszkowiak-Wojten K, Cubała WJ. Ketamine and lamotrigine combination in psychopharmacology: systematic review. *Cells*. (2022) 11:645. doi: 10.3390/cells11040645

47. Ludwig VM, Sauer C, Young AH, Rucker J, Bauer M, Findeis H, et al. Cardiovascular effects of combining subcutaneous or intravenous Esketamine and the MAO inhibitor tranylcypromine for the treatment of depression: a retrospective cohort study. *CNS Drugs*. (2021) 35:881–92. doi: 10.1007/s40263-021-00837-6

48. Wang JCC, Swainson J. The concurrent treatment with intravenous ketamine and an irreversible monoamine oxidase inhibitor for treatment-resistant depression without hypertensive crises. *J Clin Psychopharmacol*. (2020) 40:515–7. doi: 10.1097/JCP.0000000000001244

49. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database Syst Rev*. (2015):CD011612. doi: 10.1002/14651858.CD011612.pub2

50. Wan L, Levitch CF, Perez AM, Brallier JW, Iosifescu DV, Chang LC, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry*. (2015) 76:247–52. doi: 10.4088/JCP.13m08852

51. Rodrigues NB, McIntyre RS, Lipsitz O, Lee Y, Cha DS, Nasri F, et al. Safety and tolerability of IV ketamine in adults with major depressive or bipolar disorder: results from the Canadian rapid treatment center of excellence. *Expert Opin Drug Saf*. (2020) 19:1031–40. doi: 10.1080/14740338.2020.1776699

52. Szarmach J, Cubała WJ, Włodarczyk A, Wiglusz MS. Short-term ketamine administration in treatment-resistant depression: focus on cardiovascular safety. *Psychiatr Danub*. (2019) 31:585–90.

53. Yip R, Swainson J, Khullar A, McIntyre RS, Skoblenick K. Intravenous ketamine for depression: a clinical discussion reconsidering best practices in acute hypertension management. *Front Psych*. (2022) 13:7504. doi: 10.3389/fpsyt.2022.1017504

54. Daida H, Allison TG, Squires RW, Miller TD, Gau GT. Peak exercise blood pressure stratified by age and gender in apparently healthy subjects. *Mayo Clin Proc*. (1996) 71:445–52. doi: 10.4065/71.5.445

55. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet*. (2017) 389:655–66. doi: 10.1016/S0140-6736(16)30668-7

56. Lenze EJ, Farber NB, Kharasch E, Schweiger J, Yingling M, Olney J, et al. Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: a pilot randomised controlled trial. *World J Biol Psychiatry*. (2016) 17:230–8. doi: 10.3109/15622975.2016.1142607

57. Ceban F, Rosenblat JD, Kratiuk K, Lee Y, Rodrigues NB, Gill H, et al. Prevention and Management of Common Adverse Effects of ketamine and Esketamine in patients with mood disorders. *CNS Drugs*. (2021) 35:925–34. doi: 10.1007/s40263-021-00846-5

58. FDA. *Drug Monograph: KETALAR (ketamine hydrochloride) injection*. Access Data FDA. (2023). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016812s040lbl.pdf (Accessed August 24, 2023).

59. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the Management of Adults with major depressive disorder. *Can J Psychiatr*. (2016) 61:540–60. doi: 10.1177/0706743716659417

60. Navarro V, Gastó C, Torres X, Masana G, Penadés R, Guarch J, et al. Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. *Am J Geriatr Psychiatry*. (2008) 16:498–505. doi: 10.1097/JGP.0b013e318170a6fa

61. McMullen EP, Lee Y, Lipsitz O, Lui LMW, Vinberg M, Ho R, et al. Strategies to prolong Ketamine's efficacy in adults with treatment-resistant depression. *Adv Ther*. (2021) 38:2795–820. doi: 10.1007/s12325-021-01732-8

62. Smith-Apeldoorn SY, Veraart J, Spijker J, Kamphuis J, Schoevers RA. Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and tolerability. *Lancet Psychiatry*. (2022) 9:907–21. doi: 10.1016/S2215-0366(22)00317-0

63. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant for relapse prevention in patients with treatment-resistant depression. *JAMA Psychiatry*. (2019) 76:893–903. doi: 10.1001/jamapsychiatry.2019.1189

64. Dale RM, Bryant KA, Thompson NR. Metabolic syndrome rather than body mass index is associated with treatment response to ketamine infusions. *J Clin Psychopharmacol*. (2020) 40:75–9. doi: 10.1097/JCP.0000000000001149

65. Levinta A, Meshkat S, McIntyre RS, Ho C, Lui LMW, Lee Y, et al. The association between stage of treatment-resistant depression and clinical utility of ketamine/esketamine: a systematic review. *J Affect Disord*. (2022) 318:139–49. doi: 10.1016/j.jad.2022.08.050

66. Feifel D, Dadiomov D, Lee KC. Safety of repeated Administration of Parenteral Ketamine for depression. *Pharmaceuticals (Basel)*. (2020) 13:151. doi: 10.3390/ph13070151

67. Zaki N, Fu DJ, Daly E, et al. Long-term safety of esketamine nasal spray in adults with treatment-resistant depression: a subgroup analysis of the ongoing SUSTAIN-3 study. Poster presented at: Neuroscience Education Institute (NEI) Congress; November 4–7, 2021; Colorado Springs, CO. (2021).

68. Wong SW, Lee KF, Wong J, Ng WW, Cheung YS, Lai PB. Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. *Hong Kong Med J*. (2009) 15:53–6.

69. Chen LY, Chen KP, Huang MC. Cystitis associated with chronic ketamine abuse. *Psychiatry Clin Neurosci*. (2009) 63:591. doi: 10.1111/j.1440-1819.2009.01972.x

70. Chang T, Lin CC, Lin ATL, Fan YH, Chen KK. Ketamine-induced uropathy: a new clinical entity causing lower urinary tract symptoms. *Low Urin Tract Symptoms*. (2012) 4:19–24. doi: 10.1111/j.1757-5672.2011.00101.x

71. Morgan CJ, Curran HVIndependent Scientific Committee on Drugs. Ketamine use: a review. *Addiction*. (2012) 107:27–38. doi: 10.1111/j.1360-0443.2011.03576.x

72. Strous JFM, Weeland CJ, van der Draai FA, Daams JG, Denys D, Lok A, et al. Brain changes associated with long-term ketamine abuse: A systematic review. *Front Neuroanat*. (2022) 16:231. doi: 10.3389/fnana.2022.795231

73. Gill H, Gill B, Rodrigues NB, Lipsitz O, Rosenblat JD, el-Halabi S, et al. The effects of ketamine on cognition in treatment-resistant depression: a systematic review and priority avenues for future research. *Neurosci Biobehav Rev*. (2021) 120:78–85. doi: 10.1016/j.neubiorev.2020.11.020

74. Yan R, Chubbs B, Malkin M, et al. *Effects of intravenous ketamine on sleep, cognition, and anxiety in patients with treatment resistant depression poster presented at European congress of Neuropsychopharmacology*. Vienna, Austria, p. 100933. (2022).

75. Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biol Psychiatry*. (2013) 73:1133–41. doi: 10.1016/j.biopsych.2013.03.026

76. Singh I, Morgan C, Curran V, Nutt D, Schlag A, McShane R. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. *Lancet Psychiatry*. (2017) 4:419–26. doi: 10.1016/S2215-0366(17)30102-5

77. Bokor G, Anderson PD. Ketamine: an update on its abuse. *J Pharm Pract*. (2014) 27:582–6. doi: 10.1177/0897190014525754

78. Le TT, Cordero IP, Jawad MY, Swainson J, Di Vincenzo JD, Jaberi S, et al. The abuse liability of ketamine: a scoping review of preclinical and clinical studies. *J Psychiatr Res*. (2022) 151:476–96. doi: 10.1016/j.jpsychires.2022.04.035

79. Samalin L, Rothärmel M, Mekaoui L, Gaudré-Wattinne E, Codet MA, Bouju S, et al. Esketamine nasal spray in patients with treatment-resistant depression: the real-world experience in the French cohort early-access programme. *Int J Psychiatry Clin Pract*. (2022) 26:352–62. doi: 10.1080/13651501.2022.2030757

80. Chiappini S, d'Andrea G, De Filippis S, et al. Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: A viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study. *Eur Neuropsychopharmacol*. (2023) 74:15–21.

81. Chubbs B, Wang J, Archer S, Chrenek C, Khullar A, Wolowyk M, et al. A survey of drug liking and cravings in patients using sublingual or intranasal ketamine for treatment-resistant depression: a preliminary evaluation of real-world addictive potential. *Front Psych*. (2022) 13:439. doi: 10.3389/fpsyt.2022.1016439

82. Orsolini L, Salvi V, Volpe U. Craving and addictive potential of esketamine as side effects? *Expert Opin Drug Saf*. (2022) 21:803–12. doi: 10.1080/14740338.2022.2071422

83. Swainson J, Klassen LJ, Brennan S, Chokka P, Katzman MA, Tanguay RL, et al. Non parenteral ketamine for depression: a practical discussion on addiction potential and recommendations for judicious prescribing. *CNS Drugs*. (2022) 36:239–51. doi: 10.1007/s40263-022-00897-2

84. Zanos P, Moaddel R, Morris P, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacol Rev*. (2018) 70:621–60. doi: 10.1124/pr.117.015198

85. Abuhelwa AY, Somogyi AA, Loo CK, Glue P, Barratt DT, Foster DJR. Population pharmacokinetics and pharmacodynamics of the therapeutic and adverse effects of ketamine in patients with treatment-refractory depression. *Clin Pharmacol Ther*. (2022) 112:720–9. doi: 10.1002/cpt.2640

86. Loo C, Gálvez V, O'Keefe E, Mitchell PB, Hadzi-Pavlovic D, Leyden J, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand*. (2016) 134:48–56. doi: 10.1111/acps.12572

87. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*. (2018) 5:65–78. doi: 10.1016/S2215-0366(17)30272-9

88. Bonnett CJ, Jain R, Ross CN, Wallington DA, Schock TR. Intramuscular ketamine to treat major depressive disorder: a case series of forty patients. *J Psychiatry Ment Heal*. (2021) 6:1–4. doi: 10.16966/2474-7769.145

89. Mikellides G, Michael P, Psalta L, Schuhmann T, Sack AT. A retrospective naturalistic study comparing the efficacy of ketamine and repetitive transcranial magnetic stimulation for treatment-resistant depression. *Front Psych*. (2022) 12:1–9. doi: 10.3389/fpsyt.2021.784830

90. Kheirabadi D, Kheirabadi GR, Mirlohi Z, Tarrahi MJ, Norbaksh A. Comparison of rapid antidepressant and Antisuicidal effects of intramuscular ketamine, Oral ketamine, and electroconvulsive therapy in patients with major depressive disorder: a pilot study. *J Clin Psychopharmacol*. (2020) 40:588–93. doi: 10.1097/JCP.0000000000001289

91. Cavenaghi VB, Da Costa LP, Lacerda ALT, Hirata ES, Miguel EC, Fraguas R. Subcutaneous ketamine in depression: a systematic review. *Front Psych*. (2021) 12:513068. doi: 10.3389/fpsyt.2021.513068

92. Loo C, Glozier N, Barton D, Baune BT, Mills NT, Fitzgerald P, et al. Efficacy and safety of a 4-week course of repeated subcutaneous injections for treatment-resistant depression (KADS study): randomized double-blind active-controlled trail. *Br J Psychiatry*. (2023) 2023:1–9. doi: 10.1192/bjp.2023.79

93. Gálvez V, Li A, Huggins C, Glue P, Martin D, Somogyi AA, et al. Repeated intranasal ketamine for treatment-resistant depression - the way to go? Results from a pilot randomised controlled trial. *J Psychopharmacol*. (2018) 32:397–407. doi: 10.1177/0269881118760660

94. Lapidus K, Levitch C, Perez A, Brallier JW, Parides MK, Soleimani L, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry*. (2014) 76:970–6. doi: 10.1016/j.biopsych.2014.03.026

95. Lee V, Archer S, Chrenek C, Swainson J. A response to: repeated intranasal ketamine for treatment-resistant depression: the way to go? Results from a pilot randomised controlled trial. *J Psychopharmacol*. (2019) 33:258–9. doi: 10.1177/0269881118822160

96. Peters EM, Halpape K, Cheveldae I, Wanson A. Intranasal racemic ketamine for patients hospitalized with treatment-resistant depression: a retrospective analysis. *Exp Clin Psychopharmacol*. (2022) 31:593–8. doi: 10.1037/pha0000627

97. Meshkat S, Haikazian S, di Vincenzo JD, Fancy F, Johnson D, Chen-Li D, et al. Oral ketamine for depression: an updated systematic review. *World J Biol Psychiatry*. (2023) 24:545–57. doi: 10.1080/15622975.2023.2169349

98. Hassan K, Struthers WM, Sankarabhotla A, Davis P. Safety, effectiveness and tolerability of sublingual ketamine in depression and anxiety: a retrospective study of off-label, at-home use. *Front Psych*. (2022) 13:624. doi: 10.3389/fpsyt.2022.992624

99. Nutt D, King LA, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet*. (2007) 369:1047–53. doi: 10.1016/S0140-6736(07)60464-4

100. d'Andrea G, Pettorruso M, Rhee TG. Exploring the potential of a bridge therapy: Synergistic approach integrating intravenous ketamine and intranasal esketamine for treatmentresistant depression. *Acta Psychiatr Scand*. (2023) 148:382–97.

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An integrated precision medicine approach in major depressive disorder: a study protocol to create a new algorithm for the prediction of treatment response

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Major depressive disorder (MDD) is the most common psychiatric disease worldwide with a huge socio-economic impact. Pharmacotherapy represents the most common option among the first-line treatment choice; however, only about one third of patients respond to the first trial and about 30% are classified as treatment-resistant depression (TRD). TRD is associated with specific clinical features and genetic/gene expression signatures. To date, single sets of markers have shown limited power in response prediction. Here we describe the methodology of the PROMPT project that aims at the development of a precision medicine algorithm that would help early detection of non-responder patients, who might be more prone to later develop TRD. To address this, the project will be organized in 2 phases. Phase 1 will involve 300 patients with MDD already

recruited, comprising 150 TRD and 150 responders, considered as extremes phenotypes of response. A deep clinical stratification will be performed for all patients; moreover, a genomic, transcriptomic and miRNomic profiling will be conducted. The data generated will be exploited to develop an innovative algorithm integrating clinical, omics and sex-related data, in order to predict treatment response and TRD development. In phase 2, a new naturalistic cohort of 300 MDD patients will be recruited to assess, under real-world conditions, the capability of the algorithm to correctly predict the treatment outcomes. Moreover, in this phase we will investigate shared decision making (SDM) in the context of pharmacogenetic testing and evaluate various needs and perspectives of different stakeholders toward the use of predictive tools for MDD treatment to foster active participation and patients' empowerment. This project represents a proof-of-concept study. The obtained results will provide information about the feasibility and usefulness of the proposed approach, with the perspective of designing future clinical trials in which algorithms could be tested as a predictive tool to drive decision making by clinicians, enabling a better prevention and management of MDD resistance.

KEYWORDS

major depressive disorder (MDD), treatment resistant depression (TRD), antidepressant treatment response, genomics, transcriptomics, predictive algorithm, patient empowerment, shared decision making (SDM)

1 Introduction

The World Health Organization (WHO) declared that "there is no health without mental health." Mental health is a state of well-being in which an individual is aware of his or her own abilities, can cope with the normal stress of life, can work productively and is able to contribute to his or her community. Major depressive disorder (MDD) is the most common psychiatric disease worldwide and represents a leading cause of years lived with disability. In turn, this leads to an enormous socio-economic impact. Indeed, MDD represents the costliest psychiatric disorder in Europe (1). Moreover, it has been largely demonstrated that women are nearly twice as likely as men to be diagnosed with MDD. Different biological and environmental factors seem to increase the risk of depression in women; however, this issue remains largely unknown (2).

The main goal of treating MDD is to achieve remission and to maintain the therapeutic effects over time. Despite the availability of different classes of antidepressant drugs, the success of pharmacological treatment is still unsatisfactory, and matching a patient to his/her optimal treatment generally requires multiple trials of different treatments administered adequately in terms of doses and timing, with the sobering observation that the more treatments tried without success, the less likely a successful outcome. Only about 30 and 40% of patients experience remission after the first and second treatment course, respectively, and up to one third of them are classified as resistant to treatment (Treatment-Resistant Depression, TRD) (3, 4). This causes suffering for patients and their families and significantly contributes to pushing up costs for healthcare services.

The observation that TRD occurs despite the high variety of pharmacological drugs acting through different mechanisms of action suggests a possible common mechanism in resistant depression. This is consistent with evidence from studies that combine pharmacology, genetics, and brain imaging data, showing that non-response to a wide range of treatments share common etiology and common neuronal mechanisms that still need to be investigated (5).

Several clinical variables are associated with an unfavorable treatment outcome in MDD, such as earlier disease onset, greater severity, presence of psychiatric comorbidity, suicidal behaviors, and early life adversity (6). From a biological perspective, TRD is associated with specific molecular underpinnings, which are only partly known. Concerning transcriptomics, there is evidence of distinct patterns of gene expression, both in the central nervous system and in peripheral tissues, such as blood (7). Moreover, expression alterations of both coding genes and microRNAs (small non-coding RNAs that regulate gene expression) have been related to the lack of response to antidepressant treatment (8). In addition, several studies also indicated the existence of a genetic vulnerability to non-response to antidepressant drugs and TRD (7, 9). In animal models, RNA-seq on different brain regions after antidepressant treatments showed largely distinct gene changes associated with treatment response (10). Moreover, accumulating evidence shows that transcriptional changes seen across several brain regions in animal models of depression coincide with genetic risk factors in depressed human patients. This indicates the likelihood that peripheral changes in gene expression might reflect to some extent some aspects of brain function (11).

In this context, the identification of predictive markers will help the early detection of non-responder patients, who may be more prone to later develop TRD. However, the use of single sets of markers (either clinical or molecular) have shown limited predictive power and low replicability, indicating that the etiology of MDD in non-responder patients remains to be better understood. Through multi-omics integration, machine learning methods have the potential to model the interactions between several molecular layers (such as DNA or

RNA) to predict a clinical endpoint using a holistic model (12). It is conceivable that the integration of diverse sets of predictors might increase the accuracy in the identification of non-responder and TRD patients.

The overall objective of the PROMPT ("Toward PrecisiOn Medicine for the Prediction of Treatment response in major depressive disorder through stratification of combined clinical and -omics signatures") consortium, which is funded by the European ERA PerMed funding scheme, is to apply an integrated precision medicine approach in MDD through the combination of clinical, genomic, transcriptomic and sex-related data. The core objective is to create a new algorithm for the prediction of treatment response, which could be tested and validated in future clinical trials. This algorithm might represent a new tool for clinicians to drive decision-making, based not only on patients' clinical features, but also on their genetic and transcriptomic background. An additional objective is to evaluate the potential use of a predictive pharmacogenetic tool in clinical practice from different perspectives and needs of various stakeholders involved in MDD treatment. Moreover, it is important to stress that the development of such an innovative precision medicine tool is central, but only part of the process to advance MDD treatment. Considering the later clinical application is crucial, and shared decision making (SDM) is increasingly viewed as the gold standard in patient-healthcare professional communication (13). SDM is a patient-centered approach that aids empowerment by supporting patients to actively take part in developing an informed decision about further treatment jointly with healthcare professionals based on clinical options as well as a patient's individual preferences (14–16). Although SDM has been reported to lead to better decisions, increased patient participation, patient satisfaction, and treatment adherence and avoidance of overtreatment, its application in the mental health field is still rare (16, 17). Furthermore, multiple factors have been reported to influence SDM. This includes personal characteristics of the engaging parties, such as sex, age, clinical knowledge, years of experience, spoken language, or the level of education, factors relating to the interaction process, such as providing information or establishing a trustful relationship, and factors concerning broader structures of the healthcare system, for example, time constraints (18). In PROMPT, we consider application and SDM from the beginning and seek to identify factors that might come into play when patients and healthcare professionals come together to decide specifically about using the developed algorithm in clinical practice.

2 Methodology

2.1 Study design

The overall methodology of the project is based on a two-phase design (Figure 1). In the first phase (training phase, retrospective design), 300 already recruited MDD patients, including 150 TRD and 150 responders considered as extremes phenotypes of response, will undergo a deep clinical and omics profiling. These data will be exploited to develop an innovative integrative algorithm for the prediction of MDD treatment outcome.

In the second phase (testing phase, prospective observational design), a new naturalistic cohort of 300 MDD patients will be recruited, and omics profiled to assess the predictive reliability of the algorithm under real-world conditions. Furthermore, in the second phase of the project, surveys involving the general population, patients as well as health care professionals, integrated with focus groups, will be performed on the topic of personalized, tool-assisted, and shared decision making processes. This will permit soundly to take into account the patients' perspective, their needs on the use of predictive tools for MDD treatment and will support the process of patient empowerment in Personalized Psychiatry.

2.2 Phase 1: training phase

In this first project phase, two groups of clinically well-characterized MDD patients (TRD and responders), already recruited in the context of ongoing projects, will be selected considering them as extreme phenotypes of response allowing to train models on a dichotomous outcome. All patients will be profiled with genomic, pharmacogenetic, transcriptomic and miRNomic high-throughput technologies to create an integrative machine learning (ML) algorithm discriminating between the two groups.

2.2.1 Study participants and clinical assessment

Three hundred MDD patients were already recruited from one unit participating in PROMPT consortium (IRCCS Fatebenefratelli, Brescia, Italy): half were classified as TRD and the other 150 as responders. For all of them, diagnosis of moderate to severe MDD according to the DSM-IV was confirmed using the Italian version of the SCID-I diagnostic scale. The diagnosis of personality disorders was made on the basis of clinical symptoms evaluation in agreement with the DSM-IV. Exclusion criteria were the following: (a) a lifetime history of schizophrenic, schizoaffective, or bipolar disorder; (b) personality disorder, substance abuse, alcohol abuse or dependency, obsessive compulsive disorder (OCD), or post-traumatic stress disorder (PTSD) as the primary diagnosis; (c) comorbidity with an eating disorders; (d) comorbidity with alcohol and substance dependence; (e) intellectual disability and cognitive impairment; (f) neurological disorders (i.e., Parkinson's disease, multiple sclerosis, Alzheimer's and other dementias, epilepsy, strokes, brain tumors, traumatic conditions of the nervous system); (g) comorbidity with other severe medical illness and severe autoimmune diseases (i.e., cancers, Crohn's Disease, Rheumatoid Arthritis (RA), Lupus, Scleroderma, Psoriasis, Myasthenia gravis, Sjögren syndrome, Systemic lupus erythematosus); (h) pregnancy.

On the basis of clinical evaluation, TRD was defined as a failure of treatment to produce response or remission for patients after two or more treatment attempts of adequate and recommended dose and duration. Based on clinical judgment by the treating psychiatrists, MDD patients were classified as responders when they achieved response or remission in terms of a reduction in symptomatology with the first antidepressant treatment attempt of adequate dose and duration. For all patients, detailed socio-demographic (such as, age, sex, working and marital status) and clinical information (such as, age of onset, severity, psychiatric and physical comorbidities) was collected. Symptom evaluations were made using Montgomery-Åsberg Depression Rating Scale (MADRS) at the presentation of the patients to psychiatric services or hospital, in concomitance with the blood collection.

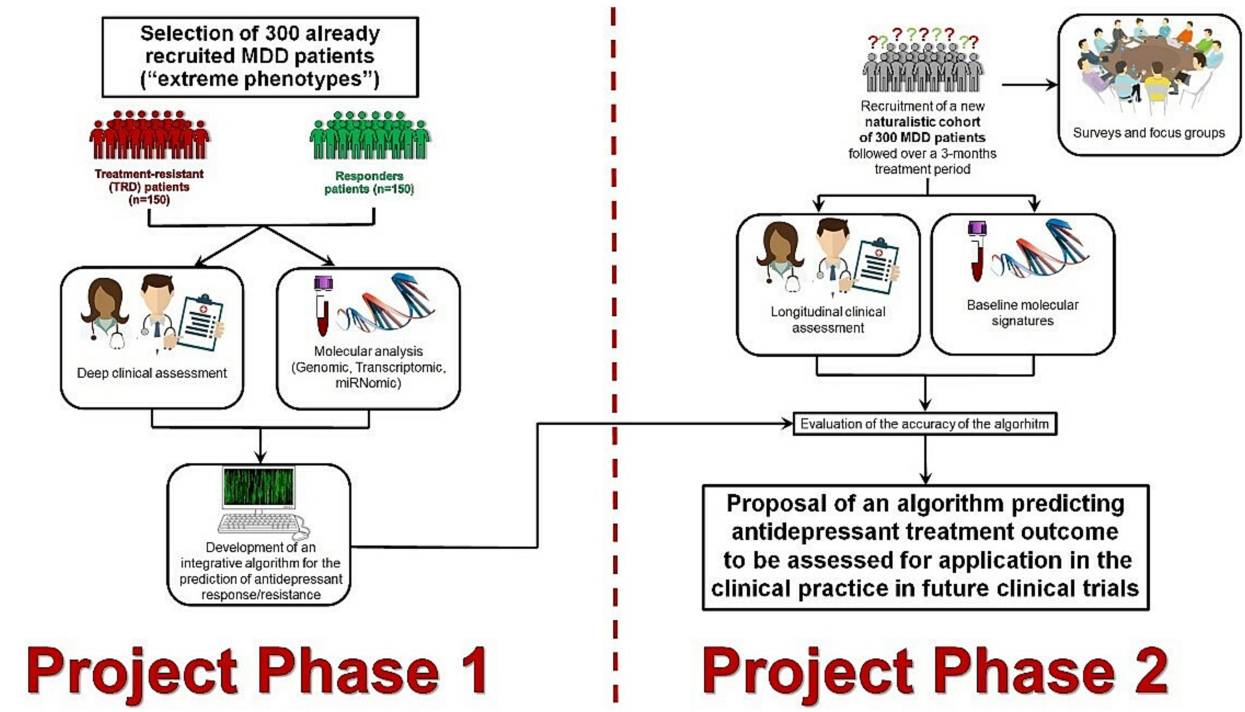

FIGURE 1
Study design phases of PROMPT project.

2.2.2 Omics profiling

DNA and RNA extracted from peripheral blood samples are prepared for genomic, pharmacogenetic, transcriptomic and miRNomic profiling. DNA is extracted from whole blood samples using the Gentra Puregene Blood kit (Qiagen), according to the manufacturer's instructions. Total RNA is extracted from blood already collected in PAXGene tubes and stored at −80°C with the PAXGene Blood miRNA Kit (Qiagen), designed for the simultaneous isolation of small and large RNAs. RNA is quantified and quality-checked through the Agilent 2,100 Bioanalyzer system and aliquots are sent to the involved project partners for transcriptomic and miRNomic profiling.

2.2.3 Genomic and pharmacogenetic profiling

All the patients are genotyped through the GWAS array Infinium PsychArray-24 v1.3 BeadChip. In addition, all of them are genotyped with customized TaqMan OpenArray plates on a QuantStudio 12 K Flex Real-Time PCR System (Applied Biosystems, Foster City, California, United States) to obtain pharmacogenomics profile that include the following single-nucleotide polymorphisms (SNPs) in relative genes (15 in *CYP2D6*, 10 in *CYP2C19*, 4 in *CYP2B6*, 2 in *CYP2C9*, 8 in *CYP1A2*, 8 in *CYP3A4*, 11 in *ABCB1*). We also genotype the 5-HTTLPR (short/long allele) and rs25531 polymorphisms (A/G genotype) in the *SLC6A4* gene.

2.2.4 Transcriptomic profiling

Abundant RNAs such as ribosomal and beta globin transcripts are removed starting from 10 ng total RNA using the Illumina Stranded total RNA Prep with Ribo-Zero Plus kit. RNA library preparation is performed following manufacturer's recommendations. Final samples pooled library preparations are sequenced on a Novaseq 6,000 ILLUMINA, at a depth of 2x30Millions of 100bases reads per sample after demultiplexing (19).

2.2.5 MiRNomic (+ other small RNA) profiling

MiRNomic (+ other small RNA) profiling is conducted by small RNA-Seq. The NEBNext® Small RNA Library Prep Set for Illumina® kit is used with minor modifications. Adaptor ligation, first strand cDNA synthesis, and PCR enrichment are performed. Library amplification utilizes custom Unique Dual Indexes (UDIs). Purification steps involve AgenCourt AMPure XP beads, and library analysis is done using Agilent Bioanalyzer. Size selection is performed using 6% Novex TBE PAGE Gels, and quantification is carried out with the KAPA Library Quantification Kit. Sequencing yields 20–30 million single-end 50 bp reads per sample on a NextSeq2000 (Illumina).

2.2.6 Bioinformatic analysis

Quality assessment is done with FastQC, and reads are trimmed using Cutadapt before mapping. For miRNOmic data, sequences with length < 16 nucleotides are discarded. Reads are aligned to the reference genome (hg38 and miRBase v22 for RNASeq and miRNOmic, respectively) with STAR. Counts table is generated using featureCounts, filtered for lowly expressed genes, and analyzed using linear models (limma) for differential expression analysis. Functional analysis utilizes available annotations in functional genomics resources. Network-based approaches are employed to visualize miRNA-target connections and perform gene ontology (GO) analyses. STRINGdb is used for protein–protein interaction retrieval, igraph for network analysis,

and clusterProfiler for GO and pathway enrichment analyses. Differential expression of miRNAs is validated by qPCR.

2.2.7 Sample size calculations

Power analyses were assessed using Bioconductor R packages ssizeRNA (20), ssize.fdr (21) and ssize (22). Parameters were obtained from seven publications of expression data in MDD patients (23–29). In cases where adjusted *p*-values were not reported, we adjusted them using the function p.adjust, with the FDR method. Dispersion of genes was not specified in the seven publications so we considered a 0.3 for all of them. Assessed experiments vary considerably in conditions, methods and results, which resulted in sample size estimations per group ranging between 11 and 121. Hence, we aim at a sample size of 150 per group, which exceeds the largest sample size calculated because we want to be conservative for the multi-omic nature of the study, but is also realistic considering our recruitment capacity.

2.2.8 Integration of clinical and – omics data

With the purpose of understanding the molecular mechanisms of TR and identifying potential biomarkers to be used as features in a predictive model of treatment response (TR), we use multi-staged strategies such as differential gene/miRNA expression (limma), knowledge-driven miRNA-target analysis and Weighted Gene Co-expression Network Analysis (WGCNA), as explained previously. Nonetheless, given that we have three different omics layers (DNA, RNA miRNA), we also take advantage of meta-dimensional methodologies, which involve analyzing all omics layers simultaneously. These methodologies are especially powerful to capture complex interactions between the individual molecular layers and possibly identify new integrated molecular features (reduced dimensionality) that explain the phenotype. These new features are then being assessed, as features for a predictive model. We will employ different methods including iClusterPlus, which uses penalized likelihood approach with lasso penalty to associate a genomic feature with a phenotype, multi-omics factor analysis (MOFA), which infers an interpretable low-dimensional data representation as hidden factors or the partial least squares discriminant analysis (PLS-DA), implemented in mixOmics, which has increasingly been used in omics research as a supervised version of PCA that preserves in its first PC as much covariance as possible between the original data and its labeling (30). To avoid overfitting of the algorithm, this discovery analysis is done on two thirds of the Phase 1 data, keeping one third unseen from any training process.

Importantly, given the high relevance of the sex dimension in TR, we will stratify all analyses according to sex. This might as well help to further decipher the influence of sex on TRD. We also clinically assessed anxiety disorders in comorbidity, more frequently present in women, and will be analyzed with respect to omics data and putative sex effect.

2.2.9 Development of the predictive algorithm

We will combine the multi-omic features identified to play a role in TR to generate a predictive model for TRD on Phase 1 data using state-of-the art statistical and machine learning methods for classification. We favor tree-based methods such as random forests or extreme gradient boosting over traditional regression models because they are not equipped to identify complex interacting risk structures empirically and have failed to model sex-specific associations (31). Standard methods of internal validation (e.g., bootstrap or cross-validation) will be used to estimate performance, to avoid over-fitting and to ensure reproducibility of the model. To select between models, we will use standard metrics such as Accuracy and F-measure on the validation set. Potential biases that may affect the inclusiveness of the models (e.g., sex or ethnicity issues) will be carefully considered.

2.3 Phase 2: testing phase

In the second phase of the project, the developed algorithm from phase 1 will be tested in a newly recruited naturalistic cohort of 300 patients to assess, under real-world conditions, the ability of the algorithm to correctly discriminate patients according to treatment response. Moreover, in the context of the new recruitment, patients' focus groups and surveys will be set to assess perspectives and needs about predictive tools in precision medicine.

2.3.1 Study participants and clinical assessment

A naturalistic cohort of 300 MDD patients is being recruited to assess, in real-world conditions, the capability of the algorithm to correctly predict the treatment outcomes. Patients are recruiting by the Department of Psychiatry at the University of Münster (Germany), by the Department of Medical Sciences and Public Health in Cagliari (Italy) and by the Department of Adult Psychiatry at Poznan (Poland). The broad inclusion criterion is a diagnosis of moderate to severe MDD and an age over 18 years. The exclusion criteria for Phase 2 are the following: (a) a lifetime history of schizophrenic, schizoaffective, or bipolar disorder; (b) personality disorder, drug abuse disorder, alcohol misuse and abuse disorder, OCD, PTSD as primary diagnosis; (c) comorbidity with alcohol and substance dependence; (d) severe neurological disorders (e.g., multiple sclerosis, Parkinson, dementia; intellectual disability; debilitating medical disorders). Diagnoses are confirmed according to the DSM-5 using the SCID-5-CV (clinical version) and the SCID-5-PD (personality disorders) diagnostic scale. At the baseline (T0), the Childhood Trauma Questionnaire (CTQ) is administered.

Patients are treated with antidepressant (AD) in monotherapy or with complex psychopharmacology such as two ADs or AD associated with other drugs (second-generation antipsychotics, mood stabilizers, lithium, FT3/FT4). Combination with diverse types of ongoing psychotherapy is accepted, if initiated prior to baseline.

Clinical assessment will be performed at 5 time points: baseline (T0), 2 (T1), 4 (T2), 8 (T3), and 12 (T4) weeks, using the MADRS, the Beck Depression Inventory II (BDI-II), the Beck Anxiety Inventory (BAI), the Columbia-Suicide Severity Rating Scale (C-SSRS) and the UKU Side Effects Rating Scale. At all time-points except the T1, the Functioning Assessment Short Test 24 items (FAST), the Quality of Life Questionnaire (SF-36) and the Perceived Stress Scale-10 (PSS-10) are administered. Moreover, at T0 and at T3 the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) are applied for the evaluation of cognitive symptoms in MDD patients.

This study involving human participants was reviewed and approved by the Ethics Committee "Ethik-Kommission Westfalen-Lippe" (Münster, Germany, registration number: 2021-103-f-S). Based on the German ethics approval, local ethics approval was obtained at the other clinical trial sites. The patients/participants provided their

written informed consent to participate in this study. The study protocol was registered on ClinicalTrials.gov as NCT05537558.

2.3.2 Biospecimens

Fasting blood samples are collected at T0, T2, T3, and T4 in each clinical recruitment center, which perform the first pre-processing steps. One EDTA Tube for DNA extraction and PAXGene Blood RNA Tube collected at T0 are sent to the same unit (IRCCS Fatebenefratelli, Brescia, Italy) that performed the DNA and RNA extractions for phase 1 to have uniform laboratory standards and reduce biases using the same methods described above in phase 1. The omics profiling (genomic, pharmacogenetic, transcriptomic, miRNomic) are carried out in the same sites and with the same methods described in phase 1. All remaining samples of unused biospecimens [EDTA tube, PAXGene Blood RNA, plasma, serum collected at each time point as well as peripheral blood mononuclear cell (PBMC)] (collected at T0 and T3) are stored locally at the recruitment sites and at the end of the project will be sent to Coordinator site in Münster, where the PROMPT Consortium biobank will be established using Centraxx standards.

2.3.3 Outcomes

Our study has three major outcomes. The primary outcome is symptom improvement at week 8, as measured by the percent change in the MADRS score from baseline. Secondary outcomes include response and remission rates at 4, 8, and 12 weeks according to the MADRS. Tertiary outcomes include: (1) changes in scores of self-reported depressive symptoms at 2, 4, 8, and 12 weeks compared with baseline, as measured by the BDI; (2) response and remission rate at 4, 8, and 12 weeks according to BDI-II; (3) changes in scores of anxiety symptoms at 2, 4, 8, and 12 weeks compared with baseline, as measured by the BAI; (4) changes in scores of suicidal risk at 2, 4, 8 and 12 weeks compared with baseline, as measured by the C-SSRS; (5) changes in scores of perceived stress at 4, 8 and 12 weeks compared with baseline, as measured by the PSS-10; (6) changes in scores of psychosocial functioning at 4, 8 and 12 weeks compared with baseline, as measured by the FAST and Quality of Life Questionnaire (SF-36); (7) changes in scores of cognitive symptoms at 8 weeks compared with baseline, as measured by the RBANS; (8) and side effects at 4, 8, and 12 weeks, as assessed by the UKU Side Effect Rating Scale.

The response is defined as a $\geq$ 50% decrease in the assessment of interest (MADRS, BDI-II) at weeks 4, 8, and 12 compared with the baseline. Remission is defined as a score of $\leq$9 for MADRS and $\leq$ 9 for BDI-II. Moreover, the response to treatment is also computed at each time point considering different thresholds of symptom reduction (>20, >50, and > 80%) on the MADRS total score, as well as on the BDI-II total score. This approach allows defining fast responders (>20% after 2 weeks), partial responders (>50%) and full responders (>80%) after 8 weeks as compared to non-responders (<50% change in MADRS score) at week 8.

2.3.4 Sample size calculations

Considering an Area Under Receiver Operating Characteristic (AUROC) Curve of 0.8, given a proportion of 0.3 of TRD, a confidence interval width of 0.125 at 0.95 confidence level, we computed that a sample size of at least 272 MDD patients will be enough to validate the predictive algorithm developed in the phase 1 of the PROMPT project.

2.3.5 Data management

The data management process is the responsibility of the project coordinator. Clinical and biological data collection, analysis, storage, security, and sharing are consistent with the standard operating procedures that ensure patient pseudonymization.

Several data sets are generated, stored and shared during the project, including clinical data and omics data (genomic, transcriptomic, miRNomic, methylomic, and metabolomic).

We use data and metadata standard for file names and directories, clinical data and omics data. Access to data is restricted to qualified members of the project team. During the project, each data set is locally stored (secure servers, controlled access and backup copies). Secure protocols for data transfer such as sftp in concordance with national and European GDPR regulations are being used. For after the project, raw omics data and associated clinical metadata will be anonymized and hosted at the European Genome-Phenome Archive (EGA), following the MINSEQE standards. Codes and scripts will be deposited in software repositories (e.g., GitHub).

2.3.6 Data integration and testing of the algorithm and predictive accuracy

Phase 2 data will be used to externally validate the model. This new naturalistic cohort will be different in the nature of patients as well as their provenance. We will assess the performance of the model using different measures such as C-index, accuracy, true positive rate and false positive rate. We will compute these measures for the whole cohort as well as in stratified groups by sex, ethnicity, and country of origin to assess potential biases of the model.

We also want to address the challenge of designing algorithms and tools that are both usable and effective, which are the two main obstacles in the clinical application of advanced statistical and ML models based on multi-omics data. Interpretability, intended as the ability to appropriately explain the reasoning behind the predictions, will be considered as a mandatory component of the model and can be achieved by using intrinsically interpretable models like random forests, by evaluating the model structure and importantly the feature importance, for instance through model agnostic techniques such as SHAP (SHapley Additive exPlanations) (32).

2.4 Perspectives and perceptions about predictive testing in the treatment of depression

This part of the PROMPT project seeks to identify perspectives and perceptions that may play a role when patients and professionals engage in a shared decision making (SDM) process on the question whether to apply an algorithm to aid decision making on the use of antidepressants. SDM requires engagement of health care professionals and facilitates patient empowerment by taking a patient's wishes, values, beliefs, attitudes and perspectives into account (14–16). We approach this question on the possible value of an algorithm in treatment settings by employing two methodological approaches, qualitative focus groups and quantitative (online) surveys. Taken together, these two approaches will allow us to learn about the perspectives of different stakeholders participating in MDD treatment toward the assumed use of a treatment decision-aiding algorithm. It is

anticipated that these results have the potential to foster translation into clinical practice, especially shared decision making processes.

2.4.1 MDD patients focus group

Employing an experience-driven bottom-up approach, patient focus groups will be conducted at all patient-recruiting PROMPT sites (Munster – Germany, Cagliari – Italy, Poznan – Poland) to learn about the perspectives of MDD patients toward the algorithm in a rather hypothesis-freeway (33, 34). Using a pre-developed protocol, MDD patients meeting the criteria for participation in the PROMPT phase 2 will be invited to take part in a 90 min group discussion together with 3–4 fellow patients of different sex, age, and MDD history. Trained moderators will lead through the three-step procedure. After a short introduction to share previous experiences with depression treatment, participating patients learn about the algorithm and are encouraged to freely voice and discuss their thoughts, concerns, hopes and perspectives before the session concludes with an overall summery. Details about the algorithm are provided by means of a graphical representation and moderators are instructed to seek a broad exploration of the issues raised by the participants and to employ a series of follow up questions targeting specific areas of potential relevance. All focus groups will be audio recorded. Patient anonymity is maintained by choosing pseudonyms during the discussion and by removing private information from the subsequently generated transcripts. Following transcription of all audio recordings, anonymized transcripts will be further translated into English. Qualitative content analysis is conducted upon both, native language transcripts and English translations using MAXQDA®. Drawing on a transcript-based classification scheme, two different coders will analyze patients' statements, focusing particularly on hopes or concerns associated with the algorithm, as well as on issues related to the decision-making process when deciding for or against the application of the decision-aiding algorithm that is being developed in the PROMPT project. To gain a broad understanding of the patient's perspective on the algorithm and its application, we plan to conduct 4–5 focus groups at each site.

2.4.2 Online surveys

Employing a theory-driven top-down approach, we will further develop surveys to learn about the perspectives of MDD patients, psychiatrists, neurologists, general practitioners, scientists, and the general population in a more hypothesis-driven way. These surveys contain items presented to any participant group as well as target group specific items. For example, all participants are asked to complete a hypothetical decision-making scenario. In this scenario, the algorithm is introduced and participants have to choose. In case patients are addressed in the survey, they are asked whether they would agree to undergo testing. In case health care professionals are addressed, they would be asked whether they would recommend the use of a testing tool for their patients with depression. Completing the surveys, all participants are further asked to rate perceived importance of a set of SDM related variables for this particular decision scenario and to fill in scales meant to operationalize participants' attitudes, beliefs or perspectives about genetics more generally. All surveys will be provided in English and in the different native languages of the PROMPT-Consortium participating countries and distributed either as a link to a REDCap based online version or as a paper version at all PROMPT Sites (French, German, Italian, Polish and Spanish). Using the R statistical environment (35), we will run linear mixed effect models on a pre-processed and random forest imputed dataset (36). Analyses will be conducted for each participant group, as a whole and in sex-specific manner.

3 Summary and conclusions

Our project aims at the development of a clinically useful algorithm model that integrates clinical data (wide range of symptomatology assessment, treatment side effects, presence of childhood trauma) and -omics data (genomic, pharmacogenetic, transcriptomic and miRNomic profiling) for the prediction of treatment response in MDD patients. The study results are framed in the context of precision psychiatry and personalized psychiatry to enable the tailoring of the right therapeutic strategy for the right person at the right time. To account for sex-specific MDD outcomes, all analyses in the project will be stratified according to sex to better understand the sex dimension of treatment response both in relation to biological factors, sex-related lifestyle and environmental factors. Moreover, our project deepens the knowledge and experience of the shared decision making process when using predictive algorithms to aid decision making in Psychiatry. Both, predictive computational tools and shared decision making processes constitute key components of the Personalized Psychiatry concept. The definition of TRD that we used is the commonly accepted clinical definition of two or more failed pharmacological treatments. Unfortunately, the absence of a validated definition of TRD is a major limitation from the viewpoints of translational research, treatment development, as well as clinical and policy decision-making. Indeed, for example neurostimulation techniques and evidence-based psychotherapy are not considered in the definition of TRD, which is a limitation of this definition. TRD patients should include particularly the non-remitters and recurrent MDD patients having a high probability to have a poor prognosis of the disorder. The pathway toward more targeted treatments in psychiatry requires a more precise delineation of the phenotype being evaluated, and this represents an important goal for current and future research in psychiatry.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Ethik-Kommission Westfalen-Lippe der Ärztekammer Westfalen-Lippe, Münster, Germany (registration number: 2021-103-f-S). Based on the German ethics approval, local ethics approval was obtained at the other clinical trial sites. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BB: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. AM: Funding acquisition, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. BC: Writing – review & editing, Funding acquisition, Supervision. MC: Investigation, Resources, Writing – review & editing. JDB: Writing – review & editing, Data curation, Formal analysis. CD: Data curation, Writing – review & editing, Project administration. EF-R: Project administration, Writing – review & editing, Investigation, Resources. RG: Investigation, Resources, Writing – review & editing. BK: Writing – review & editing, Data curation, Project administration. PK: Data curation, Project administration, Writing – review & editing. GK: Writing – review & editing, Investigation, Resources. DK: Investigation, Resources, Writing – review & editing. MML: Resources, Writing – review & editing, Data curation, Project administration. PM: Writing – review & editing, Formal analysis. M-AM: Formal analysis, Writing – review & editing. VM: Writing – review & editing, Investigation, Resources. PP: Investigation, Resources, Writing – review & editing. JPB: Resources, Writing – review & editing, Formal analysis, Writing – original draft. GP: Resources, Writing – review & editing, Investigation. FP: Writing – review & editing, Investigation, Resources. MP: Investigation, Resources, Writing – review & editing. CP: Investigation, Resources, Writing – review & editing. CS: Investigation, Resources, Writing – review & editing, Project administration. IS: Investigation, Resources, Writing – review & editing. VW: Investigation, Resources, Writing – review & editing. LX: Resources, Writing – review & editing, Formal analysis. JZ: Writing – review & editing, Formal analysis, Investigation, Resources, Writing – original draft. MG: Writing – review & editing, Conceptualization, Funding acquisition, Supervision. MM: Investigation, Project administration, Resources, Writing – review & editing. AS: Investigation, Resources, Writing – review & editing, Project administration. M-CP: Conceptualization, Funding acquisition, Writing – review & editing, Investigation, Resources, Writing – original draft. FR: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. FS: Conceptualization, Funding acquisition, Writing – review & editing, Supervision. MD: Conceptualization, Funding acquisition, Investigation, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

BB received speaker/consultation fees from: AstraZeneca, Lundbeck, Pfizer, Takeda, Servier, Bristol Myers Squibb, Otsuka, LivaNova, Boehringer-Ingelheim, Biogen and Janssen-Cilag.

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References

1. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. (2018) 75:336–46. doi: 10.1001/jamapsychiatry.2017.4602

2. Carvalho Silva R, Pisanu C, Maffioletti E, Menesello V, Bortolomasi M, PROMPT consortium, et al. Biological markers of sex-based differences in major depressive disorder and in antidepressant response. *Eur Neuropsychopharmacol*. (2023) 76:89–07. doi: 10.1016/j.euroneuro.2023.07.012

3. Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M. The STAR*D study: treating depression in the real world. *Cleve Clin J Med*. (2008) 75:57–66. doi: 10.3949/ccjm.75.1.57

4. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatr*. (2007) 52:46–54. doi: 10.1177/070674370705200108

5. Wise T, Cleare AJ, Herane A, Young AH, Arnone D. Diagnostic and therapeutic utility of neuroimaging in depression: an overview. *Neuropsychiatr Dis Treat*. (2014) 10:1509–22. doi: 10.2147/NDT.S50156

6. Perlis RH. A clinical risk stratification tool for predicting treatment resistance in major depressive disorder. *Biol Psychiatry*. (2013) 74:7–14. doi: 10.1016/j.biopsych.2012.12.007

7. Fabbri C, Corponi F, Souery D, Kasper S, Montgomery S, Zohar J, et al. The genetics of treatment-resistant depression: a critical review and future perspectives. *Int J Neuropsychopharmacol*. (2019) 22:93–04. doi: 10.1093/ijnp/pyy024

8. Belzeaux R, Lin R, Ju C, Chay M-A, Fiori LM, Lutz P-E, et al. Transcriptomic and epigenomic biomarkers of antidepressant response. *J Affect Disord*. (2018) 233:36–44. doi: 10.1016/j.jad.2017.08.087

9. Porcelli S, Drago A, Fabbri C, Gibiino S, Calati R, Serretti A. Pharmacogenetics of antidepressant response. *J Psychiatry Neurosci*. (2011) 36:87–13. doi: 10.1503/jpn.100059

10. Xicota L, De Toma I, Maffioletti E, Pisanu C, Squassina A, Baune BT, et al. Recommendations for pharmacotranscriptomic profiling of drug response in CNS disorders. *Eur Neuropsychopharmacol*. (2022) 54:41–53. doi: 10.1016/j.euroneuro.2021.10.005

11. Bagot RC, Cates HM, Purushothaman I, Lorsch ZS, Walker DM, Wang J, et al. Circuit-wide transcriptional profiling reveals brain region-specific gene networks regulating depression susceptibility. *Neuron*. (2016) 90:969–83. doi: 10.1016/j.neuron.2016.04.015

12. Sathyanarayanan A, Mueller TT, Ali Moni M, Schueler K, Baune BT, Lio P, et al. Multi-omics data integration methods and their applications in psychiatric disorders. *Eur Neuropsychopharmacol*. (2023) 69:26–46. doi: 10.1016/j.euroneuro.2023.01.001

13. Hauser K, Koerfer A, Kuhr K, Albus C, Herzig S, Matthes J. Outcome-relevant effects of shared decision making. *Deutsches Arzteblatt international*. (2015) 112:665–71. doi: 10.3238/arztebl.2015.0665

14. Drake RE, Cimpean D, Torrey WC. Shared decision making in mental health: prospects for personalized medicine. *Dialogues Clin Neurosci*. (2009) 11:455–63. doi: 10.31887/DCNS.2009.11.4/redrake

15. Slade M. Implementing shared decision making in routine mental health care. *World Psychiatry*. (2017) 16:146–53. doi: 10.1002/wps.20412

16. Hopwood M. The shared decision-making process in the pharmacological Management of Depression. *Patient*. (2020) 13:23–30. doi: 10.1007/s40271-019-00383-w

17. Patel SR, Bakken S, Ruland C. Recent advances in shared decision making for mental health. *Curr Opin Psychiatry*. (2008) 21:606–12. doi: 10.1097/YCO.0b013e32830eb6b4

18. Alsulamy N, Lee A, Thokala P, Alessa T. Views of stakeholders on factors influencing shared decision-making in the eastern Mediterranean region: a systematic review. *East Mediterr Health J* (2021) 27:300–11. doi: 10.26719/emhj.20.139

19. Xicota L, Ichou F, Lejeune F-X, Colsch B, Tenenhaus A, Leroy I, et al. Multi-omics signature of brain amyloid deposition in asymptomatic individuals at-risk for Alzheimer's disease: the INSIGHT-preAD study. *EBioMedicine*. (2019) 47:518–28. doi: 10.1016/j.ebiom.2019.08.051

20. Bi R, Liu P. Sample size calculation while controlling false discovery rate for differential expression analysis with RNA-sequencing experiments. *BMC Bioinform*. (2016) 17:146. doi: 10.1186/s12859-016-0994-9

21. Orr M, Liu P. Sample size estimation while controlling false discovery rate for microarray experiments using the ssize.Fdr package. *R J*. (2009) 1:47–53. doi: 10.32614/RJ-2009-019

22. Warnes GR, Liu P, Li F. Estimate microarray sample size. (2018). Available at:https://bioconductor.statistik.tu-dortmund.de/packages/3.6/bioc/manuals/ssize/man/ssize.pdf (Accessed June 26, 2023).

23. Minelli A, Magri C, Giacopuzzi E, Gennarelli M. The effect of childhood trauma on blood transcriptome expression in major depressive disorder. *J Psychiatr Res*. (2018) 104:50–4. doi: 10.1016/j.jpsychires.2018.06.014

24. Pettai K, Milani L, Tammiste A, Võsa U, Kolde R, Eller T, et al. Whole-genome expression analysis reveals genes associated with treatment response to escitalopram in major depression. *Eur Neuropsychopharmacol*. (2016) 26:1475–83. doi: 10.1016/j.euroneuro.2016.06.007

25. Belzeaux R, Lin C-W, Ding Y, Bergon A, Ibrahim EC, Turecki G, et al. Predisposition to treatment response in major depressive episode: a peripheral blood gene coexpression network analysis. *J Psychiatr Res*. (2016) 81:119–26. doi: 10.1016/j.jpsychires.2016.07.009

26. Guilloux J-P, Bassi S, Ding Y, Walsh C, Turecki G, Tseng G, et al. Testing the predictive value of peripheral gene expression for nonremission following citalopram treatment for major depression. *Neuropsychopharmacology*. (2015) 40:701–10. doi: 10.1038/npp.2014.226

27. Hennings JM, Uhr M, Klengel T, Weber P, Pütz B, Touma C, et al. RNA expression profiling in depressed patients suggests retinoid-related orphan receptor alpha as a biomarker for antidepressant response. *Transl Psychiatry*. (2015) 5:e538. doi: 10.1038/tp.2015.9

28. Mamdani F, Berlim MT, Beaulieu M-M, Turecki G. Pharmacogenomic predictors of citalopram treatment outcome in major depressive disorder. *World J Biol Psychiatry*. (2014) 15:135–44. doi: 10.3109/15622975.2013.766762

29. Ju C, Fiori LM, Belzeaux R, Theroux J-F, Chen GG, Aouabed Z, et al. Integrated genome-wide methylation and expression analyses reveal functional predictors of response to antidepressants. *Transl Psychiatry*. (2019) 9:254. doi: 10.1038/s41398-019-0589-0

30. Subramanian I, Verma S, Kumar S, Jere A, Anamika K. Multi-omics data integration, interpretation, and its application. *Bioinform Biol Insights*. (2020) 14:99051. doi: 10.1177/1177932219899051

31. Gradus JL, King MW, Galatzer-Levy I, Street AE. Gender differences in machine learning models of trauma and suicidal ideation in veterans of the Iraq and Afghanistan wars. *J Trauma Stress*. (2017) 30:362–71. doi: 10.1002/jts.22210

32. Markus AF, Kors JA, Rijnbeek PR. The role of explainability in creating trustworthy artificial intelligence for health care: a comprehensive survey of the terminology, design choices, and evaluation strategies. *J Biomed Inform*. (2021) 113:103655. doi: 10.1016/j.jbi.2020.103655

33. Bender DE, Ewbank D. The focus group as a tool for health research: issues in design and analysis. *Health Transit Rev*. (1994) 4:63–80.

34. Powell RA, Single HM, Lloyd KR. Focus groups in mental health research: enhancing the validity of user and provider questionnaires. *Int J Soc Psychiatry*. (1996) 42:193–06. doi: 10.1177/002076409604200303

35. R Core Team R: a language and environment for statistical computing. (2017). Available at:https://www.R-project.org/ (Accessed May 31, 2023).

36. Wright MN, Ziegler A. ranger: a fast implementation of random forests for high dimensional data in C++ and R. *J Stat Softw*. (2017) 77:1–17. doi: 10.18637/jss.v077.i01

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Vagus nerve stimulation allows to cease maintenance electroconvulsive therapy in treatment-resistant depression: a retrospective monocentric case series

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Context: The use of vagus nerve stimulation (VNS) to reduce or stop electroconvulsive therapy (ECT) in treatment-resistant depression seems promising. The aim of this study was to investigate the efficacy of VNS on the reduction of ECT sessions and mood stabilization.

Methods: We conducted a monocentric retrospective case series of patients who suffered from treatment-resistant depression, treated with ECT and referred to our center for VNS. We investigated the number and the frequency of ECT sessions before and after VNS implantation. Secondary criteria consisted in the Montgomery Åsberg Depression Rating Scale (MADRS) score, number of medical treatments, dosage of the main treatment and length of hospital stays before and after VNS. Additionally, we sent an anonymous survey to psychiatrists and other physicians in our institution to investigate their knowledge and perception of VNS therapy to treat treatment-resistant depression.

Results: Seven patients benefited from VNS: six (86%) were female (mean age of 51.7 +/− 16.0 years at surgery), and five (71%) suffered from bipolar depression (three type I and two type II). All patients were followed up at least 2 years post-implantation (range: 27–68 months). Prior to VNS, six patients were treated by maintenance ECT. After VNS, three (43%) patients did not require maintenance ECT anymore, and three (43%) patients required less frequent ECT session with a mean 14.7 +/− 9.8 weeks between sessions after VNS vs. 2.9 +/− 0.8 weeks before VNS. At last follow-up, 4 (57%) patients had stopped ECT. Five (71%) patients implanted with VNS were

good responders (50% decrease relative to baseline MADRS). According to the survey, psychiatrists had a significantly better perception and knowledge of ECT, but a worse perception and knowledge of VNS compared to other physicians.

Conclusion: VNS is a good option for treatment-resistant depression requiring maintenance ECT dependence. Larger on-going studies will help broaden the implanted patients while strengthening psychiatrists' knowledge on this therapy.

KEYWORDS

drug resistance, electric stimulation therapy, treatment outcome, safety, perception

Introduction

According to the World Health Organization (WHO), over 300 million people are estimated to suffer from depression, equivalent to 4.4% of the world's population (1). Approximately 30% of depressive patients are treatment-resistant (2, 3). Electroconvulsive therapy (ECT) is the standard treatment for treatment-resistant depression (4). It is recognized as efficient for mood stabilization but is associated with several issues, such as its long-term side effects (headaches, memory loss), a poor acceptability, and a high rate of relapse after ECT interruption (5–8). The necessity for maintenance ECT is challenging in terms of hospital resources and costs. More recently, Abrupt discontinuation of maintenance ECT during COVID-19 pandemic lead to relapses and highlighted the need for alternative therapy (9–11).

Vagus Nerve Stimulation (VNS) has been approved by the FDA as a treatment option for treatment-resistant depression since 2005 in the US and long-term follow-up of large cohorts revealed its efficacy in treatment-resistant depression (12). It is possible to perform ECT while having a VNS device and a previous case series described VNS as a potential relay to progressively cease maintenance ECT (13).

In France, VNS is still not recommended for treatment-resistant depression: it remains only offered to a few patients in tertiary care centers based on humanitarian exemptions. The referral of potential candidates to VNS remains a challenge, which makes VNS hardly accessible to most patient suffering treatment resistant depression (14). The main goal of this study was to assess the efficacy of VNS on maintenance ECT weaning and on depressive mood stabilization in treatment-resistant depression. The GHU PARIS Hospital (Paris, France) was born after the merger of the Sainte Anne Hospital, the Maison Blanche Hospital, and the Perray-Vaucluse Hospital in 2019. Due to its large coverage of the Ile de France region (representing approximatively 20% of the French population), GHU PARIS Hospitals takes care of approximatively 1 people on 40 in that region. If there is a large majority of psychiatrists, the GHU PARIS hospital medical population also includes general care practitioners, intensive care specialists, neurologists, neuroradiologists, specialists of physical and functional rehabilitation, and neurosurgeons with a tradition of multidisciplinary dialogue (15).

The main objective of the study was to retrospectively collected data concerning efficacy and safety of VNS for treatment-resistant depression after maintenance ECT. The second objective was to review psychiatrists and non-psychiatrists' knowledge and perception of ECT and VNS as treatment options for depression using an anonymous online survey, in order to understand the low number of patients referred to VNS surgery after maintenance ECT.

Methods

Study design – settings and timeframes

This study is a retrospective, monocentric case series (tertiary care center, GHU PARIS Hospital, France). One investigator (O.A) collected clinical, imaging, surgical, treatment-related and follow-up data for all patients who underwent VNS surgery for treatment-resistant depression using a protocol designed for this study. This case series has been reported in line with the Preferred Reporting Of CasE Series in Surgery (PROCESS) Guidelines (16). The period of interest was from January 2015 to January 2020. Post January 2020, the COVID pandemic stopped these compassionate surgeries. The GHU PARIS Hospital (France) is a tertiary care center with a dedicated functional neurosurgery team and a dedicated psychiatry team.

Participants – registration

Inclusion criteria were: (1) patients older than 18 at surgery; (2) treatment resistant depression (unipolar or bipolar); (3) implantation with a VNS system; (4) available data. Exclusion criteria were: (1) patients lost to follow-up (no contact with the medical team from GHU PARIS Sainte Anne during the last year); (2) follow-up shorter than 2 years.

The collected data included patient demographics (sex, profession, age at diagnosis, personal and family medical history), clinical characteristics (symptoms at diagnosis, number and severity of episodes, hospital stays, suicide attempts), imaging data when available, medical treatment details in particular dosage of main therapy, ECT details, surgical and post operative data.

All patients filled a signed informed consent concerning the use of their de-identified data for scientific purpose. The study was conducted in accordance with the Declaration of Helsinki. The local institutional review board approved the study protocol (IRB00011687).

Intervention

Patients who were referred by their psychiatry team to a functional neurosurgeon for a neuromodulation treatment option were assessed and implanted with a VNS device (Demi-Pulse®, LivaNova, United States) on the left side. The surgical technique was previously described (17). Briefly, the patients were under general anesthesia on supine position, the vagus nerve dissection and placing the helical coils around the nerve were performed under optical magnification. Stimulation was activated between 1- to 16 weeks after the operation at the standard parameters used for treatment resistant epilepsy. The intensity of stimulation was gradually increased to maximize its efficacy while minimizing sides effects.

Follow-up and efficacy assessment

Follow-up was conducted jointly by the psychiatry and the neurosurgery team through clinical consultations. Patients were followed between 2 and 5 years post-operatively with repeated measurements of the MontgomeryÅsberg Depression Rating Scale (MADRS). It is a ten-item diagnostic scale for depression, designed to be sensitive to treatment effect, validated in several languages including French and widely used (18, 19).

The interruption or reduction of ECT sessions after VNS activation was the primary outcome. Secondary outcomes were: 2/ difference between MADRS scores obtained in the month preceding VNS activation and at last follow-up; 3/the number of medications and changes in dosage of the main treatment in the month preceding VNS activation and at last follow-up; 4/length of hospitalization in a psychiatric Department before and since VNS activation (measured in days) until last follow-up.

Survey

An anonymous survey was sent to psychiatrists and other physicians (general practitioners, neurologists, neurosurgeons, and intensive care specialists) working at GHU PARIS Hospital via Google Forms. This 13-items questionnaire was designed by a multidisciplinary team including 2 senior neurosurgeons, and 3 senior psychiatrists (see Supplementary Table S1). A paired Likert score ensured proper comparability between answers. A scale ranging from 1 to 4 was used, with 1 corresponding to "Very good," and 4 "Bad." There was no neutral proposition (forced answers). The questionnaire included: 5 items concerning individual participants and local organization (specialization of the participants, awareness of the multidisciplinary meeting, etc.), 8 items concerning the neuromodulation procedure (knowledge and perception) dealing with ECT, VNS but also repetitive trans magnetic stimulation (rTMS) and deep brain stimulation (DBS). A free comment section was provided at the end of the questionnaire. Answers were binarized into positive answers for 1 & 2 ("very good" and "good," respectively) and negative answers for 3 & 4 ("mediocre" and "bad," respectively).

The questionnaire was sent by e-mail to 587 physicians working at GHU PARIS Hospital. Reminder e-mails were sent 2 weeks and 4 weeks after the initial email.

Measurements and analysis

Categorical variables were described as number and percentages. Continuous variables were described as mean ± standard deviation. Univariate analyses were carried out using the chi-square test after converting Likert's scale data into binary variables when required. A value of p of less than 0.05 was considered significant. Analyses were performed using Jamovi (20).

Results

Patients' characteristics

Table 1 summarizes patients' characteristics.

Since March 2017, seven patients were implanted with VNS for treatment-resistant depression (five bipolar and two unipolar) at GHU PARIS Hospital's Neurosurgery department. Patients' characteristics are detailed in Table 1. Six patients were female, the mean age at implantation was 51 years (range 22–74). Three patients were also diagnosed with other psychiatric conditions (anorexia, generalized anxiety disorder and substance abuse disorder). Five patients have a close family history of psychiatric disorder (mood disorders, substance abuse disorder, suicide). Four patients have attempted suicide at least once. One patient happens to also have epilepsy (VNS surgery for treatment-resistant depression only).

The median delay to surgery was equal to 13 years (range 5–23 years) between diagnosis and referral for VNS. At surgery, all patients had received several medical treatments consisting in antidepressants, mood regulators and neuroleptics (four out of seven had received more than 10 different drugs). Two patients had received a treatment by clozapine and three patients had tried ketamine intravenous perfusions. As for non-pharmaceutical treatments, all patients had received ECT, and two patients had also received repetitive rTMS. Six patients were on maintenance ECT at the time of surgery.

All patients were followed up at least 2 years post-implantation (mean: 43.9 +/− 14.3 months, range: 27–68 months). After VNS implantation, one patient experienced a short-term complication (transitory voice alteration) and two patients experienced long term complications (Supplementary Figures S3, S4; Supplementary Video 1): sternocleidomastoid muscle contraction likely caused by the involuntary stimulation of the superior root of the ansa cervicalis (21), and severe sinus bradycardia, a rare complication of VNS (22–25), respectively. Muscle contraction disappeared after a revision surgery with lead replacement for the first patient whereas the implantation of a pacemaker allowed to restart VNS for the second one. The median activation period was 36 months (range 12–64). At last follow-up, six VNS devices were still activated. The only deactivated stimulator was deactivated at the patient's request (chest discomfort without dyspnea).

Efficacy of VNS on decreasing the use of ECT

Figure 1 presents the results of VNS on several efficacy criteria.

Since all patients received ECT before being referred to neurosurgery for VNS, we documented the number of sessions they received in the 2 years before VNS and in the 2 years following VNS activation (Figure 1A).

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TABLE 1 Patients' characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gender	F	F	F	F	F	F	M
Age (years)	43	22	53	74	58	54	58
Diagnosis	Bipolar disorder, type I	Bipolar disorder, type II	Depression disorder	Depression disorder	Bipolar disorder, type II	Bipolar disorder, type I	Bipolar disorder, type I
Comorbidities	Generalized Anxiety Disorder	Epilepsy	Anorexia		Anorexia Substance abuse disorder		
Clinical course before VNS (years)	14	9	5		12	22	23
Number of medications	>10	>10	>10	3	4	>10	2
Clozapine	Yes	No	No	No	No	Yes	No
ECT	Yes	Yes	Yes	Yes	Yes	Yes	Yes
rTMS	Yes	No	No	No	No	Yes	No
Ketamine perfusions	Yes	Yes	Yes	No	No	No	No
Time since VNS intervention (years)	2	3	4	4	2	2	4
VNS activation status	On	On	On	On	On	Off	On
Short term complications	No	No	No	No	No	No	Yes (dysphonia)
Long term complications	Yes	No	No	No	Yes	No	No
Second surgery	Yes				No		No

ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; VNS, Vagus nerve stimulation.

Three (43%) patients did not require any ECT in the 2 years following VNS activation. Three (43%) patients could reduce ECT frequency in the 2 years following VNS activation with a mean 14.9 +/− 9.8 weeks between ECT sessions vs. 2.9 +/− 0.8 weeks in the 2 years before VNS. Only one patient received 19 ECT sessions in the 2 years following VNS activation vs. 0 in the 2 years before VNS: it was the patient suffering from the severe sinus bradycardia with a deactivated VNS. At last follow-up, 4 (67%) patients had stopped ECT and the patient requiring a pacemaker implantation showed a favorable evolution after VNS activation. No adverse effect occurred during ECT sessions after VNS implantation.

Efficacy of VNS on mood stabilization

Regarding VNS efficacy based on MADRS score, five patients showed a positive response with a reduction of their MADRS score (Figure 1B). Four patients (1, 2, 4, and 7) are currently in clinical remission (MADRS ≤4), euthymic and living at home. Patient 3 is receiving outpatient intravenous ketamine perfusions for a mild recurrent depressive episode (MADRS = 8 vs. 36 before VNS). Patients 5 and 6 are hospitalized in a psychiatry Department for a recurrent depressive episode.

We observed a reduction of the total number of medications prescribed for all but one patient who has been consistently prescribed 2 medications (Theralite and Carbamazepine) before and after VNS activation (Figure 1C). The mean reduction was of 1.4 +/− 0.8 treatment with a decrease in dosage of the main treatment of 38.3% +/− 35.1 (4 patients took Lithium, 2 anti-psychotic medications, and 1 a dopamine agonist).

There was a general trend towards less hospitalized days in a psychiatric department after the VNS activation in comparison with the baseline period (Figure 1D), but with important individual variations: for instance, patient 1 spent 36 days hospitalized after VNS surgery vs. 176 before whereas patient 3 was hospitalized 135 days after VNS surgery vs. 136 before.

There were no suicide following VNS activation and one episode of self-harm in a patient suffering from numerous self-harm episodes prior to VNS activation.

GHU PARIS medical population survey: psychiatrists and other physicians' knowledge and perception of ECT and VNS

Figure 2 summarize the results of survey analysis.

Response rate to the survey was 13.5% 50 psychiatrists and 19 other physicians (2 general practitioners, 2 intensive care specialists, 7 neurologists, and 8 neurosurgeons).

Regarding ECT, 94% of psychiatrists vs. 10% of other physicians reported a good (very good + good) knowledge of the procedure ($p < 0.001$) and 96% of psychiatrists had a good perception of ECT vs. 79% of other physicians ($p = 0.027$). By contrast, 72% of psychiatrists vs. 58% of other physicians reported a bad (mediocre + bad) knowledge of VNS and 54% of psychiatrists had a bad perception of VNS vs. 11% of other physicians ($p < 0.001$). Psychiatrists had a significantly poorer knowledge of VNS compared to ECT ($p < 0.001$). Their perception of VNS was the worse among the four investigated neuromodulation techniques ($p < 0.001$ vs. ECT). The results for deep brain stimulation (DBS) and repetitive trans magnetic (rTMS) are reported in Supplementary Figure S5.

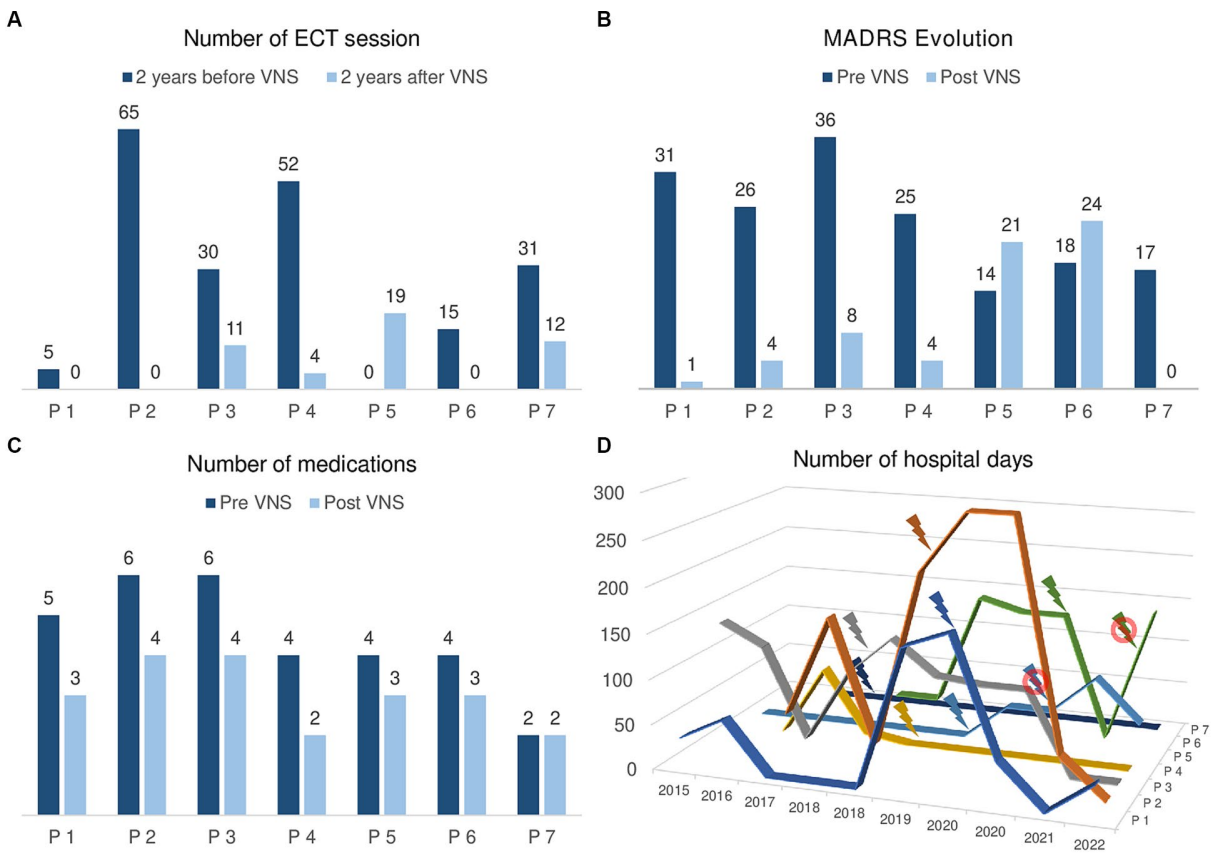

FIGURE 1
Efficacy of VNS on mood stabilization in the case of 7 patients stimulated at GHU PARIS Hospital. **(A)** Number of ECT sessions in the 2 years before VNS activation and in the 2 years after VNS activation. Patients 1, 2, 3, 4, 6, and 7 required less ECT sessions in the 2 years after VNS activation. Only patient 5 received 19 sessions in the 2 years after VNS versus 0 in the 2 years before. **(B)** MADRS score before VNS activation and at last follow-up. Patients 1, 2, 3, 4, and 7 show a reduction of their MADRS score and are in remission (MADRS ≤9). Clinically, patients 1, 2, 4, and 7 are in remission and patient 3 is experiencing a mild depressive episode. Patients 5 and 6 show a higher MADRS score at last follow-up than before VNS. Clinically, they are hospitalized in a psychiatry ward for a recurrent depressive episode. **(C)** Number of medications prescribed before VNS activation and at last follow-up. Patient 7 has been consistently prescribed 2 medications and all the other patients take less medications at last follow-up. **(D)** Number of days per year spent in a psychiatric ward in the 2 years before and after VNS activation. Of note, patient 7 has never been admitted to psychiatry. Patients 1 to 4 show a tendency towards less hospitalizations since VNS activation. Patients 5 and 6 are currently hospitalized in a psychiatry ward.

Discussion

Key results

This study showed that: 1/VNS could contribute to cease or reduce the frequency of maintenance ECT, 2/after VNS, the majority of patients had fewer medications and/or fewer recurrences and/or shorter hospital stays, 3/VNS in treatment-resistant depression, unipolar or bipolar, was successful in mood stabilization according to MADRS, 4/psychiatrists at a tertiary care center had a poor knowledge and perception of VNS and in general of invasive neuromodulation therapies.

Interpretation

About 50% of patients with major depression relapse within 1 year of treatment with ECT but maintenance ECT remains discussed, due to neurocognitive adverse effects of ECT (26, 27). During COVID-19 pandemic, nearly 60% of the patients requiring maintenance ECT relapsed after abrupt discontinuation (9–11). It has been reported that VNS can help to decrease frequency or to stop maintenance ECT (13, 28, 29). Our results were in line with these results: all the patients with the VNS activated at least 2 years after the implantation performed less ECT session than before VNS implantation and 4 out 5 totally stopped maintenance ECT. Moreover, maintenance ECT has a significant cost: reducing the frequency of ECT session at the cost of a VNS implantation is economically sound (28). As previously described, none complication occurred during ECT session after VNS implantation: it is another argument to propose VNS in front of an ECT dependence (29, 30).

The link between maintenance ECT and VNS is not evident. Mechanisms of action of both techniques are not fully understood (31, 32). Some directions could be: the role of the neuro-endocrine system as ECT and VNS both exert an effect on it (31, 33); the need to disturb causal depression network as VNS is known to perturb epileptic aberrant network (34, 35); the effect of neurogenesis with an increase in hippocampal volume after VNS or after ECT (36, 37). It is probably the conjunction of several mechanisms of action that explained the therapeutic effect of both techniques.

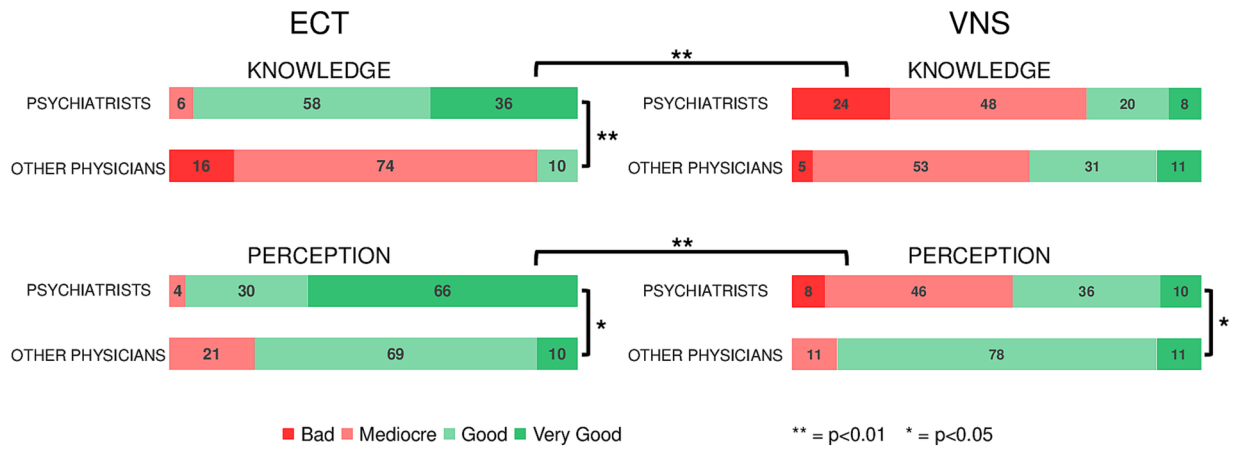

FIGURE 2
Results of the anonymous survey sent to psychiatrists and other physicians working at GHU PARIS Hospital, assessing their knowledge and perception of neuromodulation treatments for depression (ECT and VNS). 94% of psychiatrists vs. 10% of other physicians report a good (very good + good) knowledge of ECT ($p < 0.001$) and 96% of psychiatrists have a good perception of ECT vs. 79% of physicians ($p = 0.027$). 28% of psychiatrists vs. 42% of physicians report a good knowledge of VNS ($p = 0.268$) whereas 46% of psychiatrists vs. 89% of physicians have a good perception of VNS ($p = 0.007$). Psychiatrists have a significantly worse knowledge of VNS compared to ECT ($p < 0.001$). Their perception of VNS was the worse among the four investigated neuromodulation techniques ($p < 0.001$ vs. ECT).

This cases series was another step towards the confirmation of VNS efficacy for treatment resistant depression: five patients had favorable outcomes after VNS activation despite being considered after the failure of more than 4 different medications and the bad tolerance, non-response, exhaustion, reliance on ECT treatment. Apart from MADRS score, length of hospitalization, number of medication and number of ECT sessions were globally reduced. This is in line with other studies and should be confirmed by larger studies (12, 38–42). There were no suicide following VNS activation and one episode of self-harm in a patient suffering from numerous self-harm episodes prior to VNS activation. The other complications rate was higher compared to previous literature, probably due to the small sample size (12). It should be stressed that the VNS efficacy and tolerance was correct in a population mainly made up of patients suffering from bipolar disorder, making VNS a potential treatment of choice for this subpopulation (12).

The paucity of patients suffering from treatment-resistant depression referred to VNS surgery was in line with previous results (43, 44). Beside the difficult definition of treatment-resistance in psychiatry, several reasons could be provided: the psychiatrists' residency offers only limited contact with neuromodulation, only few hospitals have enough resources to take care of treatment-resistant psychiatric patients, perception of medical invasiveness is highly variable, psychiatrists have little knowledge on current neurosurgical procedures, and literature is not straightforward (45–47). The anonymous survey provided additional evidence that psychiatrists working at a tertiary care center did not have enough knowledge on invasive neuromodulation such as VNS whereas ECT was well-known. There was a significant difference between psychiatrists and other physicians in term of invasive neuromodulation perception, even if their knowledge was not significantly different. There is a need for better teaching of psychiatric neurosurgery for both residents and seniors physicians (46, 48, 49).

Limitations

These findings should be interpreted with caution, given the retrospective and monocentric design, the lack of a control group, all limiting the generalizability of the results. The specific medical population and the low response rate weaken the survey analysis. Further confirmatory analyses are required to reproduce the present results.

Conclusion

This case series adds to the growing literature concerning VNS usefulness in case of maintenance ECT. VNS did not preclude to perform ECT sessions after the implantation but help to reduce the frequency or even to stop maintenance ECT. Large ongoing studies, such as the RECOVER study, on VNS in treatment-resistant depression will help to precise the appropriate place of VNS in the treatment algorithm for treatment-resistant depression and will ease the referral of patients to surgery (50).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Campus de Neurochirurgie – IRB00011687. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the

participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

OA: Data curation, Investigation, Writing – original draft, Writing – review & editing. PDo: Data curation, Investigation, Validation, Writing – original draft, Writing – review & editing. IH: Data curation, Investigation, Writing – original draft, Writing – review & editing. RG: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. AG-R: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. RC: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. PDu: Methodology, Writing – original draft, Writing – review & editing. PG: Formal analysis, Writing – original draft, Writing – review & editing. FV: Investigation, Writing – original draft, Writing – review & editing. JP: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

MZ reports a relationship with LivaNova PLC that includes: travel reimbursement. RC reports a relationship with LivaNova PLC that includes: speaking and lecture fees and travel reimbursement. PDo reports a relationship with LivaNova PLC that includes: speaking and lecture fees and travel reimbursement.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1305603/full#supplementary-material

References

1. World Health Organization. Depression and other common mental disorders: Global Health estimates. Geneva: World Health Organization (2017). Available at: https://iris.who.int/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf?sequence=1 (Accessed November 26, 2023).

2. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: challenges and strategies. *Neuropsychiatr Dis Treat*. (2020) 16:221–34. doi: 10.2147/NDT.S198774

3. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. (2003) 53:649–59. doi: 10.1016/S0006-3223(03)00231-2

4. The UK ECT Review Group.Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. (2003) 361:799–808. doi: 10.1016/S0140-6736(03)12705-5

5. Andrade C, Arumugham SS, Thirthalli J. Adverse effects of electroconvulsive therapy. *Psychiatr Clin North Am*. (2016) 39:513–30. doi: 10.1016/j.psc.2016.04.004

6. Moksnes KM, Ilner SO. Electroconvulsive therapy – efficacy and side-effects. *Tidsskr Den Nor Legeforening*. (2010) 130:2460–4. doi: 10.4045/tidsskr.09.1102

7. MacQueen G, Parkin C, Marriott M, Bégin H, Hasey G. The long-term impact of treatment with electroconvulsive therapy on discrete memory systems in patients with bipolar disorder. *J Psychiatry Neurosci*. (2007) 32:241–9.

8. Petrides G, Tobias KG, Kellner CH, Rudorfer MV. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. *Neuropsychobiology*. (2011) 64:129–40. doi: 10.1159/000328943

9. Lambrichts S, Vansteelandt K, Crauwels B, Obbels J, Pilato E, Denduyver J. Relapse after abrupt discontinuation of maintenance electroconvulsive therapy during the COVID-19 pandemic. *Acta Psychiatr Scand*. (2021) 144:230–7. doi: 10.1111/acps.13334

10. Martínez-Amorós E, Serra P, Bassa A, Palao DJ, Cardoner N. Discontinuation of maintenance electroconvulsive therapy: lessons learned from the COVID-19 pandemic. *Rev Psiquiatr Salud Ment*. (2022) 15:154–5. doi: 10.1016/j.rpsm.2021.07.005

11. Van de Velde N, Geerts P-J, Tandt H, Vanderhasselt M-A, Titeca K. Discontinuation of continuation or maintenance electroconvulsive therapy caused by the COVID-19 pandemic: a naturalistic study investigating relapse in patients with major depressive disorder. *J ECT*. (2021) 37:230–7. doi: 10.1097/YCT.0000000000000785

12. Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD. A 5-year observational study of patients with treatment-resistant depression treated with Vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. *Am J Psychiatry*. (2017) 174:640–8. doi: 10.1176/appi.ajp.2017.16010034

13. Aaronson ST, Goldwaser EL, Kutzer DJ, McAllister-Williams RH, Sackeim HA. Vagus nerve stimulation in patients receiving maintenance therapy with electroconvulsive therapy: a series of 10 cases. *J ECT*. (2021) 37:84. doi: 10.1097/YCT.0000000000000724

14. McAllister-Williams RH, Bulmer S, Newton K, Heath K, Cousins DA, Currie A. Assessment for vagus nerve stimulation in patients with difficult-to-treat depression: a model from the Newcastle regional affective disorders service (RADS). *J Affect Disord*. (2021) 280:315–8. doi: 10.1016/j.jad.2020.11.020

15. Zanello M, Pallud J, Baup N, Peeters S, Turak B, Krebs MO. History of psychosurgery at Sainte-Anne hospital, Paris, France, through translational interactions between psychiatrists and neurosurgeons. *Neurosurg Focus*. (2017) 43:E9. doi: 10.3171/2017.6.FOCUS17250

16. Agha RA, Fowler AJ, Rajmohan S, Barai I, Orgill DP. Preferred reporting of case series in surgery; the PROCESS guidelines. *Int J Surg Lond Engl*. (2016) 36:319–23. doi: 10.1016/j.ijsu.2016.10.025

17. Hamdi H, Spatola G, Lagarde S, McGonigal A, Paz-Paredes A, Bizeau A. Use of polyvinyl alcohol sponge cubes for vagal nerve stimulation: a suggestion for the wrapping step. *Oper Neurosurg Hagerstown*. (2020) 18:487–95. doi: 10.1093/ons/opz227

18. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. (1979) 134:382–9. doi: 10.1192/bjp.134.4.382

19. Huijbrechts IP, Haffmans PMJ, Jonker K, Van DA, Hoencamp E. A comparison of the Hamilton rating scale for depression and the Montgomery-Asberg depression rating scale. *Acta Neuropsychiatr*. (1999) 11:34–7. doi: 10.1017/S0924270800036358

20. The jamovi project. Jamovi (version 2.3) [computer software], (2023), Available at: https://www.jamovi.org

21. Gopalakrishnan CV, Kestle JRW, Connolly MB. The "vagal ansa": a source of complication in vagus nerve stimulation. *J Neurosurg Pediatr*. (2015) 15:535–8. doi: 10.3171/2014.10.PEDS14259

22. Clark AJ, Kuperman RA, Auguste KI, Sun PP. Intractable episodic bradycardia resulting from progressive lead traction in an epileptic child with a vagus nerve

stimulator: a delayed complication. *J Neurosurg Pediatr* (2012) 9:389–393. doi: 10.3171/2011.12.PEDS11124

23. Iriarte J, Urrestarazu E, Alegre M, Macías A, Gómez A, Amaro P. Late-onset periodic asystolia during vagus nerve stimulation. *Epilepsia*. (2009) 50:928–32. doi: 10.1111/j.1528-1167.2008.01918.x

24. Shankar R, Olotu VO, Cole N, Sullivan H, Jory C. Case report: vagal nerve stimulation and late onset asystole. *Seizure*. (2013) 22:312–4. doi: 10.1016/j.seizure.2012.12.011

25. Ratajczak T, Blank R, Parikh A, Wase A. Late-onset asystolic episodes in a patient with a vagal nerve stimulator. *Hear Case Rep*. (2018) 4:314–7. doi: 10.1016/j.hrcr.2018.04.004

26. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology*. (2007) 32:244–54. doi: 10.1038/sj.npp.1301180

27. Jelovac A, Kolshus E, McLoughlin DM. Relapse following successful electroconvulsive therapy for major depression: a Meta-analysis. *Neuropsychopharmacology*. (2013) 38:2467–74. doi: 10.1038/npp.2013.149

28. Warnell RL, Elahi N. Introduction of vagus nerve stimulation into a maintenance electroconvulsive therapy regimen: a case study and cost analysis. *J ECT*. (2007) 23:114–9. doi: 10.1097/YCT.0b013e3180616647

29. Burke MJ, Husain MM. Concomitant use of vagus nerve stimulation and electroconvulsive therapy for treatment-resistant depression. *J ECT*. (2006) 22:218–22. doi: 10.1097/01.yct.0000230364.04240.52

30. Santermans L, Vanderbruggen N, Zeeuws D, Baeken C. Successful ECT treatment after relapse during VNS therapy. *Psychiatr Danub*. (2010) 22:S166.

31. Carron R, Roncon P, Lagarde S, Dibué M, Zanello M, Bartolomei F. Latest views on the mechanisms of action of surgically implanted cervical vagal nerve stimulation in epilepsy. *Neuromodulation J Int Neuromodulation Soc*. (2022) 26:498–506. doi: 10.1016/j.neurom.2022.08.447

32. Bolwig TG. How does electroconvulsive therapy work? Theories on its mechanism. *Can J Psychiatry Rev Can Psychiatr*. (2011) 56:13–8. doi: 10.1177/070674371105600104

33. Haskett RF. Electroconvulsive Therapy's mechanism of action: neuroendocrine hypotheses. *J ECT*. (2014) 30:107. doi: 10.1097/YCT.0000000000000143

34. Bartolomei F, Bonini F, Vidal E, Trébuchon A, Lagarde S, Lambert I. How does vagal nerve stimulation (VNS) change EEG brain functional connectivity? *Epilepsy Res*. (2016) 126:141–6. doi: 10.1016/j.eplepsyres.2016.06.008

35. Siddiqi SH, Schaper FLWVJ, Horn A, Hsu J, Padmanabhan JL, Brodtmann A. Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. Nat. *Hum Behav*. (2021) 5:1707–16. doi: 10.1038/s41562-021-01161-1

36. Argyelan M, Deng Z-D, Ousdal OT, Oltedal L, Angulo B, Baradits M. Electroconvulsive therapy-induced volumetric brain changes converge on a common causal circuit in depression. *Mol Psychiatry*. (2023) 2:1–9. doi: 10.1038/s41380-023-02318-2

37. Perini GI, Toffanin T, Pigato G, Ferri G, Follador H, Zonta F. Hippocampal gray volumes increase in treatment-resistant depression responding to Vagus nerve stimulation. *J ECT*. (2017) 33:160. doi: 10.1097/YCT.0000000000000424

38. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM. A one-year comparison of Vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. (2005) 58:364–73. doi: 10.1016/j.biopsych.2005.07.028

39. Conway CR, Kumar A, Xiong W, Bunker M, Aaronson ST, Rush AJ. Chronic Vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. *J Clin Psychiatry*. (2018) 79:22269. doi: 10.4088/JCP.18m12178

40. Christmas D, Steele JD, Tolomeo S, Eljamel MS, Matthews K. Vagus nerve stimulation for chronic major depressive disorder: 12-month outcomes in highly treatment-refractory patients. *J Affect Disord*. (2013) 150:1221–5. doi: 10.1016/j.jad.2013.05.080

41. Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med*. (2008) 38:651–61. doi: 10.1017/S0033291707001924

42. Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimulat*. (2013) 6:631–40. doi: 10.1016/j.brs.2012.09.013

43. Ramasubbu R, Golding S, Williams K, Mackie A, MacQueen G, Kiss ZHT. Recruitment challenges for studies of deep brain stimulation for treatment-resistant depression. *Neuropsychiatr Dis Treat*. (2021) 17:765–75. doi: 10.2147/NDT.S299913

44. Filkowski MM, Mayberg HS, Holtzheimer PE. Considering eligibility for studies of deep brain stimulation for treatment-resistant depression: insights from a clinical trial in unipolar and bipolar depression. *J ECT*. (2016) 32:122–6. doi: 10.1097/YCT.0000000000000281

45. Bluhm R, Cortright M, Achtyes ED, Cabrera LY. They are invasive in different ways: stakeholders perceptions of the invasiveness of psychiatric electroceutical interventions. *AJOB Neurosci*. (2021) 14:1. doi: 10.1080/21507740.2021.1958098

46. Cormier J, Iorio-Morin C, Mathieu D, Ducharme S. Psychiatric neurosurgery: a survey on the perceptions of psychiatrists and residents. *Can J Neurol Sci*. (2019) 46:303–10. doi: 10.1017/cjn.2019.5

47. Brem A-K, Lehto SM. Stuck between bench and bedside: why non-invasive brain stimulation is not accessible to depressed patients in Europe. *Front Hum Neurosci*. (2017) 11:39. doi: 10.3389/fnhum.2017.00039

48. LY C, GR N, AM MC, E A, R B. A qualitative study of key stakeholders' perceived risks and benefits of psychiatric electroceutical interventions. *Health Risk Soc*. (2021) 23:217–35. doi: 10.1080/13698575.2021.1979194

49. Naesström M, Blomstedt P, Hariz M, Bodlund O. Deep brain stimulation for obsessive-compulsive disorder: knowledge and concerns among psychiatrists, psychotherapists and patients. *Surg Neurol Int*. (2017) 8:298. doi: 10.4103/sni.sni_19_17

50. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV. Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults: IV. Neurostimulation therapies. *J Affect Disord*. (2009) 117:S44–53. doi: 10.1016/j.jad.2009.06.039

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Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression: an overview of systematic reviews with meta-analysis

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Background: Unipolar and bipolar depression present treatment challenges, with patients sometimes showing limited or no response to standard medications. Ketamine and its enantiomer, esketamine, offer promising alternative treatments that can quickly relieve suicidal thoughts. This Overview of Reviews (OoR) analyzed and synthesized systematic reviews (SRs) with meta-analysis on randomized clinical trials (RCTs) involving ketamine in various formulations (intravenous, intramuscular, intranasal, subcutaneous) for patients with unipolar or bipolar depression. We evaluated the efficacy and safety of ketamine and esketamine in treating major depressive episodes across various forms, including unipolar, bipolar, treatment-resistant, and non-resistant depression, in patient populations with and without suicidal ideation, aiming to comprehensively assess their therapeutic potential and safety profile.

Methods: Following PRIOR guidelines, this OoR's protocol was registered on Implasy (ID:202150049). Searches in PubMed, Scopus, Cochrane Library, and Epistemonikos focused on English-language meta-analyses of RCTs of ketamine or esketamine, as monotherapy or add-on, evaluating outcomes like suicide risk, depressive symptoms, relapse, response rates, and side effects. We included studies involving both suicidal and non-suicidal patients; all routes and formulations of administration (intravenous, intramuscular, intranasal) were considered, as well as all available comparisons with control interventions. We excluded meta-analysis in which the intervention was used as anesthesia for electroconvulsive therapy or with a randomized ascending dose design. The selection, data extraction, and quality assessment of studies were carried out by pairs of reviewers in a blinded manner. Data on efficacy, acceptability, and tolerability were extracted.

Results: Our analysis included 26 SRs and 44 RCTs, with 3,316 subjects. The intervention is effective and well-tolerated, although the quality of the included SRs and original studies is poor, resulting in low certainty of evidence.

Limitations: This study is limited by poor-quality SRs and original studies, resulting in low certainty of the evidence. Additionally, insufficient available data prevents differentiation between the effects of ketamine and esketamine in unipolar and bipolar depression.

Conclusion: While ketamine and esketamine show promising therapeutic potential, the current evidence suffers from low study quality. Enhanced methodological rigor in future research will allow for a more informed application of these interventions within the treatment guidelines for unipolar and bipolar depression.

Systematic review registration: [https://inplasy.com/inplasy-2021-5-0049/], identifier (INPLASY202150049).

KEYWORDS

unipolar depression, bipolar depression, ketamine, esketamine, suicidal ideation, treatment resistance, Overview of Reviews

1 Introduction

Major Depressive Disorder (MDD) is a psychiatric condition with a prevalence of 4.4% worldwide (1). The text revision of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) defines the MDD as a minimum of 2 weeks of low mood or loss of interest in daily activities, accompanied by vegetative, motor, and cognitive symptoms. Depressed individuals may also have suicidal thoughts or tendencies (2). Bipolar disorder (BD) is characterized by alternating depressive and (hypo)manic episodes. In accordance with the DSM-5-TR, while the depressive phase of BD shares the same criteria as MDD, the manic and hypomanic phases are characterized by an elevation in mood, increased psychomotor activity, inflated self-esteem, risky behaviors, and reduced need for sleep. In more severe cases (mania), psychotic or more severe symptoms may also be present, leading to a decline in functioning or necessitating hospitalization (2). BD affects approximately 40 million individuals in the general population and has a significant impact on an individual's quality of life, relationships, and occupational functioning (3).

The pathogenesis of MDD in both unipolar and bipolar depression is very complex and still partly unknown, due to the interaction between both genetic and environmental factors (4). The monoaminergic hypothesis, which postulates deficits in neurotransmission as the cause of depression, has historically been considered to explain depressive pathophysiology. In particular, dysfunctions in norepinephrine, serotonin, and dopamine neurotransmissions are implicated in the disorder (5). Treatment with antidepressants that increase serotonin levels alone is not recommended for BD, as it exposes the patient to the risk of a (hypo) manic switch. The preferred treatment involves the use of mood stabilizers, such as lithium or antiepileptic drugs, which exert their effect by stabilizing neurotransmission, and second-generation antipsychotics with a specific antagonistic action on the 5-HT_{2A} receptor (6). This antagonism would lead to an increase in the release of serotonin in the synaptic cleft, combined with the blockade of dopamine receptors to prevent potential bipolar switches (7). In general, the monoaminergic hypothesis does not provide a full understanding of neurochemistry of major depressive episode and alterations in γ-amino-butyric acid (GABA), glutamatergic and opioid endogenous neurotransmission may be also implied (8). As a result, multiple medications have been developed with varying degrees of specificity toward these neurotransmitter systems.

The most prescribed antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs) with a more favorable balance between effectiveness and tolerability (9). The basic mechanism of action of SSRIs involves inhibition of the reuptake of serotonin released by neurons. Other antidepressant drugs also promote noradrenergic (norepinephrine and serotonine reuptake inhibitors, SNRIs) and dopaminergic (norepinephrine and dopamine reuptake inhibitors, NDRIs, i.e., bupropion) neurotransmission (5). On the other hand, the management of BD involves a combination of pharmacotherapy, psychotherapy, and lifestyle modifications (10), as well as several non-pharmacological approaches (11). While there are also other molecules with antidepressant action, which altogether would theoretically allow even more specific intervention toward individual depressive symptoms (12), still many patients achieve partial response or become resistant to treatment (13, 14). The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) defines the treatment resistant depression (TRD) as a non-response to ≥2 antidepressant trials prescribed with adequate dose and duration (≥ 6 weeks) (15, 16). TRD can be also treated with the augmentation strategies as a second-generation antipsychotic or lithium (17).

In recent years, ketamine and its levogyre enantiomer, esketamine, have demonstrated a promising rapid antidepressant and anti-suicidal effect, particularly in individuals resistant to other medications (18). They were also remarkable for their status as the first antidepressants purportedly able to alleviate depression and, notably, suicidal ideation within hours for many patients (19). Intravenously administered ketamine is a racemic mixture of the R and S enantiomers, both of which have overlapping actions on the glutamatergic N-methyl-D-aspartic acid (NMDA) receptor contributing to its antidepressant action as well as on the σ1 receptor (20). Recently, the use of

intranasally administered levogyre enantiomer of ketamine (i.e., esketamine) has been approved in TRD (21), resulting also a favorable alternative pharmacological approach for BD, especially in those cases resistant to traditional medications (22). Moreover, intranasal administration route has made clinical management more convenient by eliminating the need for intravenous infusion sessions. Specifically, the intranasal spray can be administered on a weekly or biweekly basis after an initial phase of twice-weekly administration (23).

Several clinical studies were conducted to test efficacy and tolerability of ketamine and derivatives in unipolar and bipolar depression (24). Consequently, a plethora of meta-analyses have been produced to synthesize the available data. Writing systematic reviews with meta-analysis involves the application of standard criteria (25), which are not always met (26). However, this is significant, both for clinicians and researchers, because, when available, guidelines that inform clinical practice rely heavily on meta-analyses (27). The study design suitable for synthesizing multiple systematic reviews is the Overview of Reviews (OoR) (28). In 2021, de Mendonça Lima and collaborators produced an OoR on the efficacy and tolerability of ketamine in the treatment of depression (29), whereas Shamabadi and colleagues produced an OoR on ketamine effect on suicidality (30). Given the number of new systematic reviews with meta-analysis to date produced, the aim of this study is to consolidate the rapidly growing body of literature on the efficacy and safety of ketamine and esketamine on unipolar and bipolar depression using standard criteria (31). By offering a comprehensive and cohesive overview of the existing evidence, this study is aimed to support evidence-based decision-making for clinicians, researchers, and policymakers in the field.

2 Materials and methods

2.1 Eligibility criteria

Only systematic reviews containing at least one meta-analysis on randomized clinical trials, which were either cluster type (where groups of individuals are randomized) or non-cluster (where individuals are randomized) have been included. Only English-language studies, published in indexed journals, without any restriction on publication date were retained. To be eligible for inclusion, meta-analyses had to analyze original studies involving human patients with unipolar, bipolar, resistant, or non-resistant major depressive episode, regardless of the diagnostic criteria used. We included studies involving both suicidal and non-suicidal patients. The study must have focused on the use of ketamine or its levogyre enantiomer (esketamine) as a treatment, administered via any route and formulation (either intravenous, intramuscular, intranasal, or subcutaneous), either as monotherapy or in combination with other drugs. The study must have included a comparator treatment, such as another antidepressant agent, an active or inactive placebo; finally, the included reviews had to contain at least one of the following outcomes: suicide risk, depressive symptomatology, relapse rate, treatment response rate, dropout rate, dissociative or psychotic symptomatology as side effects.

We excluded meta-analyses that included original studies investigating the effect of ketamine as an anesthetic treatment before electroconvulsive therapy, as well as studies with a randomized ascending dose design that did not report data separately for each time-point. The latter category of studies is designed to determine the optimal dose for efficacy and safety and often interrupts the control treatment during the trial. To include only those meta-analyses that met these inclusion/exclusion criteria, we read and extracted the original studies included in the individual meta-analyses, but we did not include or analyze any study not covered in the included systematic reviews. We followed the definition of systematic review proposed by the Cochrane Handbook, i.e., studies that are designed to "collate evidence that fits pre-specified eligibility criteria in order to answer a specific research question" (32).

2.2 Information sources and search strategy

The study search is updated to December 31, 2022. We searched two bibliographic databases (Scopus and MEDLINE via PubMed) and two systematic review databases (Cochrane Database of Systematic Reviews [CDSR] and Epistemonikos). We checked the references of the included systematic reviews, including any that did not appear in the search. We used the following search string: ('ketamine' OR 'n-methylketamine' OR 's-ketamine' OR (('n-methylaspartate' OR 'nmda') AND antagonist)). We used the official PubMed filter for systematic reviews and meta-analyses (systematic[sb]) (33) and adapted it to limit the search to reviews in Scopus. In Epistemonikos, the results were filtered by systematic reviews and in CDSR, only systematic reviews were considered.

2.3 Selection and data collection process

The Rayyan website was used for the title/abstract screening process. This website allows for semi-automatic deduplication of studies. Authors (PC, ADF, LR, AN) screened in pairs the studies to be included by checking their title and abstract. The same authors, again in pairs, selected the potentially candidate studies by checking their full text by using Airtable relational database. At each step, whenever disagreement emerged among the authors, a third author (AR) resolved it. The whole process was blinded, except in cases of disagreement. All reviews that met the predefined criteria were included, regardless of the degree of overlap in the populations involved or the interventions compared. Furthermore, systematic reviews with identical inclusion criteria were also retained.

To provide an overview of the overlap between different systematic reviews, we created multiple citation matrices categorized by the diagnosis of the patients included. These matrices indicated not only the presence of the study in the specific meta-analysis, but also the outcomes for which it had been considered. The authors (PC, ADF, LR, AN, GC) extracted the data contained in the studies independently and in a blind manner. The procedure was done using the relational database (Airtable) that automatically identified if there was disagreement in the extracted data, so that a final unique database was generated.

2.4 Data items

For each systematic review, we extracted the following study variables: search engines used, date of last search, inclusion and exclusion criteria of individual reviews, potential authors' conflict of interest, project funding, diagnosis of included patients, drug(s) investigated, dose of interventional drug, and comparator(s). In addition, the following outcomes were extracted: response (as defined

by the authors), remission (as defined by the authors), depressive symptoms, total dropouts, suicidality risk scales, all available adverse events (e.g., dissociative, psychotic, gastroenteric, neurological, etc.).

Regardless of the time points suggested in the individual meta-analyses, we grouped the time points as follows: ≤60 min, 61–90 min, 91–120 min, 121–240 min, 24–48 h, 3–6 days, 7–13 days, 14–28 days, >28 days. Time points that did not fall into these categories were adjusted. Endpoint data were collected. For each meta-analysis, when possible, statistical model adopted, type of effect size and its measure, with respective low and high confidence intervals, *p* value of statistical significance of comparisons, heterogeneity of the meta-analysis, the test used to measure it, and the statistical significance of the test were collected.

2.5 Quality assessment of the systematic reviews

The methodological quality of the included systematic reviews was assessed using the AMSTAR-2 (34). It is a widely used tool for conducting rapid, reliable, and reproducible critical quality assessment of RCT reviews on the effectiveness of health care interventions. The tool assesses the presence of any critical issues, distinguishing them into minor and major, thereby identifying the reliability of the review. A systematic review is considered having a high reliability if no more than one minor criticality is present, moderate if more than one minor criticality is present, low in the presence of at least one major criticality, and very low if multiple major critical elements are present. Each author used this tool independently and separately, blindly from each other. Reviewers in couples evaluated all studies. After blinding was broken, a final decision on AMSTAR-2 scoring was reached through discussion. If necessary, a third author (AR) was involved. Due to the absence of a specific tool to apprise the quality network meta-analyses, we adapted the AMSTAR-2 for this scope.

2.6 Confidence in results assessment

We took the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scores (35) of the systematic reviews whenever reported. GRADE is a widely used system for grading the quality of evidence of systematic reviews and meta-analyses to pose clinical recommendations. There are four distinct levels of evidence according to this framework, which can be very low, low, moderate, or high. These four levels of certainty correspond to the progressively increasing degree of fit between the estimated effect and the true effect. The scoring process considers the assessment of the risk of bias of the included studies, the degree of imprecision of the effect estimate, the degree of inconsistency among studies, the degree of correspondence between the measure being investigated and the instruments used to measure it (indirectness), and the impact of missing evidence (publication bias).

2.7 Risk of bias and reporting bias assessment

Where reported in the various systematic reviews, the risk of bias of the individual original studies was extracted. We've also synthesized the risk of bias to allow for a comparison of outcomes between the original and the 2.0 version of the tool, as well as between ketamine and esketamine. If present, the reporting bias, the statistical tool used to measure it and its statistical significance were also extracted from the reviews.

2.8 Synthesis methods

The data was summarized in descriptive tables, which were grouped by outcome and distinguished by the type of depression studied, including unipolar or bipolar depression, and TRD or non-TRD. In addition, data were summarized in a narrative manner. In the summary, the data presented do not distinguish between ketamine and its racemic formulation. However, where noteworthy differences arose, these were explicitly stated. In the extraction process, all sensitivity and subgroup analysis relevant to the clinical question of this paper (unipolar vs. bipolar; resistant vs. non-resistant; current suicidal ideation present vs. no suicidal ideation) were extracted separately and tabulated. Any discrepancy between systematic reviews was reported.

3 Results

3.1 Study selection

As reported in the PRISMA flowchart (Supplementary Figure 1), the search produced a total of 2,256 studies, reduced to 1,770 after the deduplication process. Thus, through the title/abstract screening process, 1,715 records were excluded. The full texts of the remaining 55 studies were viewed and 29 studies were excluded, which are shown in the Supplementary Table 1. Thirty-one reviews with meta-analysis were considered, of those two were updates of previous meta-analysis by the same group of authors (36, 37) and one had been retracted (38), thus the final number of individual independent reviews corresponded to 26 (Supplementary Table 1) and 44 RCTs (reported in the Supplementary Table 2) with a total of 3,316 subjects. Among the included studies, there were two network meta-analyses involving ketamine as intervention, one about all available medications for acute bipolar depression (36), and the other on TRD drugs (39). We excluded meta-analyses that contained original studies from the systematic reviews that did not meet the inclusion criteria for this overview. The specific individual original studies that were excluded are listed in the Supplementary Table 3.

3.2 Characteristics of included studies

Supplementary Table 1 shows the characteristics of the included systematic reviews. Most of the reviews used MEDLINE as a scientific search engine. Other commonly used engines were Embase and PsycINFO. The most recent scientific databases search of the included reviews was dated December 1, 2021. As per the inclusion criteria, all studies were on parallel or crossover RCTs. Most of the included studies indistinctly involved patients with unipolar and bipolar depression (40–50), with some exceptions, where only patients with unipolar (39, 51–56) or bipolar depression (36, 57, 58) were included.

Only four reviews (39, 58–60) involved patients who had previously shown resistance to antidepressant treatment by inclusion criterion. Fifteen reviews considered any route of administration of the intervention (39, 41, 42, 44, 46, 47, 49, 50, 54, 55, 57–59, 61, 62). Three reviews considered only intravenous ketamine administration (36, 45, 60), whereas some others considered also the intranasal use (40, 41, 46, 51–53, 56, 63, 64). One of the included reviews considered only oral ketamine use (48). The majority of the reviews included in this OoR incorporated studies that used saline solution as the comparator for ketamine and esketamine (40, 45–47, 50, 51, 54, 56, 59, 63). Conversely, in other reviews, alternative comparators such as midazolam, diclofenac, and electroconvulsive therapy (ECT), were also included.

Regarding funding sources, nine studies reported public funding (41–45, 51, 56, 57, 62), one study reported private funding (39), and one study reported combined public and private fundings (55). Nine studies reported no funding (36, 40, 46, 52, 54, 58, 60, 63, 64), whereas information about funding was not available for six studies (47–50, 53, 59). In sixteen studies the authors reported conflict of interest (39–42, 45–49, 52, 53, 55, 57, 58, 63, 64). In eight studies the authors explicitly denied any conflicts of interest (44, 50, 51, 54, 56, 59, 60, 62). In one study, information about conflicts of interest was not reported (43).

3.3 Primary studies overlap

The citation matrices (Supplementary File 4) display the included studies and the outcomes analyzed in each meta-analysis. The most frequently included studies in the meta-analyses were Diazgranados et al. (65), Murrough et al. (66), Sos et al. (67), Zarate et al. (68), and Zarate et al. (69). The inclusion of the other studies was less consistent, across the various meta-analyses.

3.4 Risk of bias of included studies

AMSTAR-2 was applied on all systematic reviews. Most of the studies (23 of 26) had critically low quality. The remaining three studies had low quality (42, 57, 60). The scoring is given in more detail in Supplementary Table 2. Out of the 26 studies that were analyzed for quality scoring, only 5 of them (42, 48, 57, 58, 62) had a written protocol in advance. Additionally, only 6 studies (42, 46, 51, 57, 58, 60) included the list of the excluded studies, while 11 out of 26 studies argued in the discussion about the risk of bias of the included studies (36, 41–43, 46, 53, 54, 57, 59, 62, 70). In half of the studies (13 out of 26) (36, 42–45, 48, 53, 56–58, 60, 62, 63) a comprehensive literature search was performed and, in 15 out of 26 studies (36, 40, 41, 43–46, 49, 50, 53, 56, 59, 60, 63, 64), the authors explored how publication bias affected the outcomes of their meta-analysis. Although it is considered a minor issue in the scoring of AMSTAR-2, it should be noted that all but one (45) of the studies did not report data on the funding of the original studies included in the reviews.

3.5 Summary of results

Supplementary Table 3 provides a depiction of the meta-analyses, categorized by diagnosis and time points. A comprehensive report of the meta-analyses can be found in the Supplementary Table 5.

3.5.1 Depressive symptoms

The intervention group shows greater reduction in depressive symptoms compared to the control group at all time points, up to 3–6 days. However, for patients with BD, there is no difference between the intervention and the comparator from 7 to 13-day time point. The lack of efficacy for BD primarily stems from meta-analyses on ketamine, not esketamine. For patients with MDD, the intervention's efficacy persists in most of the analyses at later time points.

3.5.2 Remission rate

Despite the absence of differences in the remission rate between the intervention and comparator groups at the 60-min time-point, the intervention arm generally displayed superiority over the control group in subsequent time-points, up until 3–6 days. Notably, the effectiveness of ketamine at the 24–48 h time-point revealed inconsistency, with half of the studies indicating no efficacy, irrespective of diagnosis and comparator. In the time-points exceeding 3–6 days, the differences in patients with MDD were not always consistent, with some meta-analyses showing the experimental arm superior to the control, while others did not. Conversely, no superiority of the intervention over control was observed in meta-analyses solely involving patients with BD. Even though results beyond 3–6 days generally did not favor the intervention, all meta-analyses on esketamine, which exclusively involved patients with unipolar depression, suggested a greater efficacy compared to the control arm.

3.5.3 Response rate

Regarding the response rate, the intervention proved to be superior to the control arm for all time points, from <60 min to the 24–48-h range, except for one meta-analysis (57). Subsequently, analyses involving patients with unipolar depression demonstrated a substantial superiority of the intervention arm over control, except for a few meta-analyses, while those involving only patients with BD did not show any difference. It's important to note that all available data on esketamine involve only patients with unipolar depression and consistently suggest greater efficacy in respect to the comparator. On the other hand, data on ketamine, involving both unipolar and bipolar depression patients, present less homogeneous results.

3.5.4 Suicide scales

The suicide scales did not show any difference between the intervention and control groups at less than 60 min time point. There were no data available for the time points of 60–90 and 90–120 min. Meta-analyses showed that the intervention was more effective than the placebo from the time point of 120–240 min to 3–6 days. Only one meta-analysis, including patients with BD has been conducted (57); evaluating the outcome at the 24–48-h time point no difference between the two groups was found. While the available data for esketamine are consistent, favoring the intervention over the control, it is not the case for some time-points for ketamine, where the data for this outcome are scarce. Moreover, no data are available for esketamine beyond the 24–48 h.

3.5.5 Dropout rates

Both the intervention, including both ketamine and esketamine, and control groups had similar dropout rates in all meta-analyses. This data was provided at >28 day time-point and at endpoints.

3.5.6 Tolerability (adverse effects)

Ten reviews have thoroughly investigated the tolerability of treatment (41, 42, 45–48, 50, 51, 53, 56). Dissociative symptoms were investigated in three reviews (45–47) by using Clinician-Administered Dissociative States Scale (CADSS), revealing no notable discrepancies between intervention and control groups, aside from the results at the <60-min time-point, where the intervention group demonstrated higher scores. There is no data available for CADSS solely on esketamine, while data is available from meta-analyses solely on ketamine and from mixed meta-analyses. On the other hand, four reviews (41, 42, 53, 56) assessed the presence or absence of dissociation, challenging CADSS data and indicating an elevated occurrence of dissociative events at the 14–28 day and > 28-day periods. The only available data for ketamine, coming from a small number of patients, suggests no difference between ketamine and saline solution at the endpoint. A different result is found for esketamine, where dissociative symptoms persist even in the long term.

No differences were found between patients receiving the intervention or comparator for most of the other side effects, except for blurred vision, confusion, diplopia, dizziness, dysgeusia, emotional blunting, feeling abnormal, feeling drunk, hypoesthesia, headache, oral hypoesthesia, increased blood pressure, lethargy, paresthesia, postural dizziness, sedation, somnolence, throat irritation, vertigo, nausea, and vomiting. There were no obvious differences between the side effects for the different formulations, apart from a few exceptions. Dizziness did not vary between ketamine and the control at 7–13 days. Headache was typically the same for both groups, though one study found it to be slightly more common after 28 days with esketamine. Lastly, esketamine resulted in more nausea and vomiting compared to control, a trend not observed with ketamine.

3.5.7 Data heterogeneity

Overall, heterogeneity data were reported unsystematically. Often statistical tests excluded its presence in meta-analyses. The only outcomes showing some statistical heterogeneity were depressive symptoms (36, 40, 43, 51, 54), response (36, 51, 56, 58), suicide scales (63), BPRS (50), and CADSS (45).

3.6 Reporting biases

A very small number of systematic reviews reported the presence of publication bias which, in most cases, was visually investigated with funnel plots. Moreover, those were often used non-canonically, as they included fewer than 10 original studies (71). In any case, of the few studies reporting the information, the data were discordant and inconclusive for most outcomes.

3.7 Risk of bias of original studies and outcomes certainty of evidence

3.7.1 Risk of bias of original studies

A complete report of the risk of bias of the included studies is detailed in the Supplementary Table 6. Study quality was measured in most of the included reviews. Four studies did not perform any Risk of Bias measurement (44, 47, 50, 52). The most used tool was the Cochrane's Risk of Bias in its original version, while Risk of Bias 2.0 was used in four recent reviews (40, 49, 53, 63). In addition, the Jadad score (72) and the Downs and Black checklist (73) have only been used in three systematic reviews (56, 60, 64).

From the 16 systematic reviews that used the original Risk of Bias tool, it emerges that most studies performed randomization adequately. However, in several reviews, authors noted that there was a high risk of bias in the included studies for failure to allocate concealment and inadequate blinding of recruiting staff and assessors' blinding domains. Additionally, original studies suffered from incomplete outcome reporting and selective reporting. For the Risk of Bias 2.0 domains, there was generally a satisfactory randomization process, although some studies exhibited a higher risk of bias due to possible deviations from the intervention and incomplete data reporting. Nevertheless, outcomes were overall adequately measured and there was no data selection bias detected. Regarding the presence of other biases in the studies, many reviews found a high risk of bias, but this category encompasses diverse information. In comparing ketamine and esketamine within the original Risk of Bias (RoB) framework, we find that the two treatments exhibit largely similar characteristics across the various domains. The notable exception is in the performance domain where esketamine studies received more "Some concerns" ratings than ketamine studies. Despite not having conducted a detailed analytical comparison, the other differences between esketamine and ketamine studies do not appear to be significantly distinct. Results from Jadad score and Downs & Black Checklist are limited, and their overall scoring may not always be consistent with the outcomes derived from Cochrane's Risk of Bias assessment.

3.7.2 Outcomes certainty of evidence

Except for Cochrane systematic reviews, almost all studies did not estimate the level of certainty of the evidence. Specifically, the studies measured the degree of certainty of the evidence as follows: Dean et al. (57) reported a low and very low degree of certainty for the response at 24–48 h when comparing ketamine vs. saline and ketamine vs. midazolam, respectively. The study also found a very low certainty of evidence for depressive symptoms at 24–48 h and 7–13 day time points, as well as a very low confidence level for total dropouts at endpoint and remission at both 24–48 h and 7–13 days. Caddy et al. (42) identified a low level of certainty for the response measure at the 24–48 h, 3–6 day, and 7–13 day time points, as well as a low level of evidence for depressive symptoms at the 24–48 h time point and emotional blunting at endpoint. Witt et al. (62) discovered a moderate degree of evidence for suicide rate at two time points: <60 min and 14–28 days. Finally, Zheng et al. (56) found a high level of evidence at endpoints for response, remission, and nearly all investigated adverse effects.

4 Discussion

4.1 Main findings

To the best of our knowledge, this OoR is the most comprehensive to date available, encompassing a total of 26 studies. In comparison to previous OoRs (29, 30), a particularly accurate selection process for

reviews based on the original included studies was employed. Consequently, we excluded some outcomes or entire meta-analyses that did not meet the inclusion criteria, thus resulting in an enhanced methodological and data homogeneity.

As a whole, existing data confirm the rapid efficacy of antidepressant treatment of ketamine on affective symptoms and suicidal ideation, though the effect on the latter decreases at later time points. There is no available data on depressive symptoms separately for patients with unipolar and bipolar depression for the time points < 60 min, 60–90 min, and 90–120 min. Combined meta-analyses of patients with unipolar and bipolar depression indicate greater efficacy of the intervention compared to the control group. For subsequent time points, the intervention maintains good efficacy for patients with unipolar depression, whereas its efficacy declines after 2 weeks in patients with bipolar depression.

Regarding tolerability and acceptability, data is limited. Nevertheless, no significant difference emerges between intervention and control groups, except for adverse effects. Overall, however, the quality of the original studies included in the meta-analyses is poor.

Of note, all meta-analyses focusing solely on esketamine, which often shows to be more effective than the control across several outcomes, only include patients with unipolar depression. Conversely, the data for ketamine, which can display more inconsistent efficacy results, considers both patients with unipolar and bipolar depression. This leaves unresolved the question of efficacy between ketamine and its enantiomer. Indeed, the solitary study that directly contrasts esketamine and ketamine echoes this deficiency in data, reporting no substantial differences in either efficacy or tolerability between the two treatments (74). An analysis of study quality revealed that ketamine and esketamine have comparable Risk of Bias across most domains. One exception is the allocation concealment, where esketamine outperforms due to its differing administration route. However, preliminary data show no efficacy differences between ketamine and esketamine in patients with MDD, when both are administered intravenously in a triple-blind study (75).

4.2 Evidence in context

The available evidence for the treatment of TRD and for patients at suicidal risk offers viable alternatives (76–80); however, its prevalence and burden remain high (81). Our meta-summary highlighted the efficacy of the use of ketamine/esketamine in these clinical contexts, although the quality of the evaluated evidence is low. Despite its potential as a promising intervention, there are notable challenges associated with its use, including the requirement for hospital visits for administration and the restriction on driving after receiving the treatment. Additionally, the substantial costs involved in initiating and maintaining the treatment, which impact the healthcare system, should be considered. Indeed, according to NICE guidelines, the use of esketamine would have a too much high incremental cost-effectiveness ratio, leading to discontinuation of this approach even when adopted as a third-line intervention (82). Additionally, other studies showed how other therapeutic options had a better cost-effectiveness ratio in the treatment of patients with TRD, such as electroconvulsive therapy (83).

4.3 Limitations of the evidence

The available evidence does not allow to draw conclusions with a high level of confidence. Specifically, no available meta-analysis holds up to high quality criteria. In addition, almost all the included original studies had various methodological limitations, leading few studies to have a low risk of bias. In addition, few meta-analyses investigated the long-term efficacy of ketamine, thus leaving an evidence gap.

4.4 Implication for practice, policy and future research

At present, no guidelines recommend ketamine or esketamine as a treatment for depression, except as a third-line intervention, due to the limited available data. Consequently, in clinical practice, it is crucial to carefully consider the use of ketamine or esketamine against other interventions with a higher certainty of evidence. However, given the potential of ketamine treatment, especially for TRD and high suicidal risk cases, further research in ketamine is warranted. The two key priorities should be: (i) more methodologically rigorous studies, and (ii) long-term data on treatment efficacy.

4.5 Strengths and limitations of the overview

To our knowledge, the present OoR is the most extensive available evidence on ketamine for the treatment of depression. As such, this work has some strengths: (i) it is based on current standards regarding the preparation of OoRs, setting it apart from previous studies; (ii) it not only draws from bibliographic search engines, but also from aggregators of systematic reviews; (iii) we reviewed the individual studies included in various meta-analyses to improve the methodological homogeneity of the reported data; additionally, we performed a comprehensive and detailed representation of the data related to the side effects; and (iv) we also tried to synthesize the available data clearly and transparently, reporting both the excluded and included material.

This OoR has also limitations: (i) the literature review was not conducted on multiple search engines, although, compared to previous similar works, we included more than twice the number of studies; (ii) we only included studies written in English during the selection process; (iii) the attempt to be more comprehensive may have led to the possibility of combining heterogeneous reviews on one hand and having studies with similar inclusion criteria on the other, thus raising the risk of duplicated information; during this process, however, particular attention has been paid to disentangle the different research questions, to provide the reader with as much useful information as possible for clinical practice and to improve future research based on the present data; and (iv) we have not undertaken a detailed comparison of esketamine and ketamine's effectiveness or tolerability. Nevertheless, our findings suggest esketamine has a more consistent advantage over control treatments. However, this conclusion should be interpreted cautiously due to the smaller number of studies pertaining to esketamine compared to those on ketamine. Interestingly, despite esketamine studies having undergone a rigorous registration process, the quality of these studies did not significantly surpass that of ketamine research which has not been subject to such

stringent scrutiny. At present, the scarce esketamine-specific meta-analyses, the similar study quality between ketamine and esketamine research, and the variability within the ketamine data, collectively impede drawing any definitive conclusions regarding their comparative efficacy and tolerability, at least for patients with unipolar depression.

5 Conclusion and future outlooks

Although literature data suggest that ketamine and its derivatives is effective for treating depression, the available literature remains qualitatively limited. The production of evidence synthesis studies has been prolific; however, it has not improved the overall quality of the original studies, which remains poor. Additionally, concerns about long-term treatment efficacy data persist. Higher quality original studies are needed, particularly with improvements to allocation concealment and assessor blinding in future research. Though the quantity of available data for esketamine is lesser than that for ketamine, it's crucial not to disregard its apparent consistent efficacy. This effectiveness could be attributed to the selection of a more uniform patient group, specifically those diagnosed with unipolar disorder. Future studies are also warranted to investigate the effectiveness of (es)ketamine in the treatment of major depressive episode with mixed features which appear to be burdened with a higher suicidal risk than pure depressive forms (84). The pharmacological management of mixed states during major depressive episode has always been a challenge for the clinicians not only for their insidious course but also due to the lack of robust evidence (85), that is slowly growing (86). Authors should also enhance data reporting and avoid to selectively present results. Furthermore, it is beneficial for future systematic reviews with meta-analyses to be pre-planned and have registered protocols. Addressing the risk of bias and publication bias in future reviews will provide more valid information on the reliability of the results. Lastly, given the commercial interest in these products for treating depression, the funding of original studies should not be overlooked. In a few words, only when the quality of evidence will reach a sufficient level of evidence, firm conclusions will be drawn about the benefit of using ketamine for the treatment of resistant depression and for patients at suicidal risk.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. PC: Data curation, Investigation, Methodology, Writing – original draft. ADF: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. AA: Writing – original draft. GC: Investigation, Writing – original draft. CC: Writing – original draft. AC: Writing – original draft. AF: Supervision, Writing – review & editing. GL: Writing – original draft. LM: Writing – original draft. AN: Investigation, Writing – original draft. LR: Investigation, Writing – original draft. AP: Supervision, Writing – original draft. MS: Project administration, Supervision, Writing – review & editing. EA: Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. World Health Organization. *Depression and other common mental disorders: global health estimates*. Geneva: World Health Organization (2017).

2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5-TR*. Washington D.C: American Psychiatric Association Publishing (2022).

3. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Psychiatry*. (2022) 9:137–50. doi: 10.1016/S2215-0366(21)00395-3

4. Lopizzo N, Chiavetto LB, Cattane N, Plazzotta G, Tarazi FI, Pariante CM, et al. Gene-environment interaction in major depression: focus on experience-dependent biological systems. *Front Psych*. (2015) 6:68. doi: 10.3389/fpsyt.2015.00068

5. Dean J, Keshavan M. The neurobiology of depression: an integrated view. *Asian J Psychiatr*. (2017) 27:101–11. doi: 10.1016/j.ajp.2017.01.025

6. McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. *Lancet*. (2020) 396:1841–56. doi: 10.1016/S0140-6736(20)31544-0

7. Altamura AC, Lietti L, Dobrea C, Benatti B, Arici C, Dell'Osso B. Mood stabilizers for patients with bipolar disorder: the state of the art. *Expert Rev Neurother*. (2011) 11:85–99. doi: 10.1586/ern.10.181

8. Sarawagi A, Soni ND, Patel AB. Glutamate and GABA homeostasis and neurometabolism in major depressive disorder. *Front Psych*. (2021) 12:637863. doi: 10.3389/fpsyt.2021.637863

9. Marasine NR, Sankhi S, Lamichhane R, Marasini NR, Dangi NB. Use of antidepressants among patients diagnosed with depression: a scoping review. *Biomed Res Int*. (2021) 2021:6699028. doi: 10.1155/2021/6699028

10. Concerto C, Chiarenza C, di Francesco A, Natale A, Privitera I, Rodolico A, et al. Neurobiology and applications of inositol in psychiatry: a narrative review. *Curr Issues Mol Biol*. (2023) 45:1762–78. doi: 10.3390/cimb45020113

11. Spampinato C, Aguglia E, Concerto C, Pennisi M, Lanza G, Bella R, et al. Transcranial magnetic stimulation in the assessment of motor cortex excitability and treatment of drug-resistant major depression. *IEEE Trans Neural Syst Rehabil Eng*. (2013) 21:391–403. doi: 10.1109/TNSRE.2013.2256432

12. Tomlinson A, Furukawa TA, Efthimiou O, Salanti G, de Crescenzo F, Singh I, et al. Personalise antidepressant treatment for unipolar depression combining individual choices, risks and big data (PETRUSHKA): rationale and protocol. *Evid Based Ment Health*. (2020) 23:52–6. doi: 10.1136/ebmental-2019-300118

13. Sousa RD, Gouveia M, Nunes da Silva C, Rodrigues AM, Cardoso G, Antunes AF, et al. Treatment-resistant depression and major depression with suicide risk-the cost of illness and burden of disease. *Front Public Health*. (2022) 10:898491. doi: 10.3389/fpubh.2022.898491

14. Elsayed OH, Ercis M, Pahwa M, Singh B. Treatment-resistant bipolar depression: therapeutic trends, challenges and future directions. *Neuropsychiatr Dis Treat*. (2022) 18:2927–43. doi: 10.2147/NDT.S273503

15. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of depression. (2013). Available at: https://www.fda.gov/media/113988/download.

16. Food and Drug Administration. *Major depressive disorder: developing drugs for treatment, guidance for industry', DRAFT GUIDANCE. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), revision 1*. Rome: Food and Drug Administration (2018).

17. Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. (2015) 29:459–525. doi: 10.1177/0269881115581093

18. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and Esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

19. Johnston JN, Kadriu B, Kraus C, Henter ID, Zarate CA Jr. Ketamine in neuropsychiatric disorders: an update. *Neuropsychopharmacology*. (2024) 49:23–40. doi: 10.1038/s41386-023-01632-1

20. Wei Y, Chang L, Hashimoto K. A historical review of antidepressant effects of ketamine and its enantiomers. *Pharmacol Biochem Behav*. (2020) 190:172870. doi: 10.1016/j.pbb.2020.172870

21. Singh JB, Daly EJ, Mathews M, Fedgchin M, Popova V, Hough D, et al. Approval of esketamine for treatment-resistant depression. *Lancet Psychiatry*. (2020) 7:232–5. doi: 10.1016/S2215-0366(19)30533-4

22. Martinotti G, Dell'Osso B, di Lorenzo G, Maina G, Bertolino A, Clerici M, et al. Treating bipolar depression with esketamine: safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. *Bipolar Disord*. (2023) 25:233–44. doi: 10.1111/bdi.13296

23. Kasper S, Cubała WJ, Fagiolini A, Ramos-Quiroga JA, Souery D, Young AH. Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: basic science, evidence-based knowledge and expert guidance. *World J Biol Psychiatry*. (2021) 22:468–82. doi: 10.1080/15622975.2020.1836399

24. Kraus C, Rabl U, Vanicek T, Carlberg L, Popovic A, Spies M, et al. Administration of ketamine for unipolar and bipolar depression. *Int J Psychiatry Clin Pract*. (2017) 21:2–12. doi: 10.1080/13651501.2016.1254802

25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

26. Matthias K, Rissling O, Pieper D, Morche J, Nocon M, Jacobs A, et al. The methodological quality of systematic reviews on the treatment of adult major depression needs improvement according to AMSTAR 2: a cross-sectional study. *Heliyon*. (2020) 6:e04776. doi: 10.1016/j.heliyon.2020.e04776

27. Schünemann HJ. Using systematic reviews in guideline development: the GRADE approach. systematic reviews in health research: meta-analysis in context. *Res Synth Methods*. (2022) 22:424–48. doi: 10.1002/9781119099369.ch22

28. Hunt H, Pollock A, Campbell P, Estcourt L, Brunton G. An introduction to overviews of reviews: planning a relevant research question and objective for an overview. *Syst Rev*. (2018) 7:39. doi: 10.1186/s13643-018-0695-8

29. Lima TM, Visacri MB, Aguiar PM. Use of ketamine and esketamine for depression: an overview of systematic reviews with meta-analyses. *Eur J Clin Pharmacol*. (2022) 78:311–38. doi: 10.1007/s00228-021-03216-8

30. Shamabadi A, Ahmadzade A, Hasanzadeh A. Ketamine for suicidality: an umbrella review. *Br J Clin Pharmacol*. (2022) 88:3990–4018. doi: 10.1111/bcp.15360

31. Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. *BMJ*. (2022) 378:e070849. doi: 10.1136/bmj-2022-070849

32. Chandler JCM, Thomas J, Higgins JPT, Deeks JJ, Clarke MJ. Chapter I: introduction In: JPT Higgins, J Chandler, M Cumpston, T Li, MJ Page and VA Welch, editors. *Cochrane handbook for systematic reviews of interventions version 6.3* (2022).

33. National Library of Medicine. *Search strategy used to create the PubMed systematic reviews filter*. (2019). Available at: https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html (Accessed January 18, 2024).

34. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. (2017) 358:j4008. doi: 10.1136/bmj.j4008

35. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. (2008) 336:924–6. doi: 10.1136/bmj.39489.470347.AD

36. Bahji A, Ermacora D, Stephenson C, Hawken ER, Vazquez G. Comparative efficacy and tolerability of adjunctive pharmacotherapies for acute bipolar depression: a systematic review and network meta-analysis. *Can J Psychiatr*. (2021) 66:274–88. doi: 10.1177/0706743720970857

37. McCloud TL, Caddy C, Jochim J, Rendell JM, Diamond PR, Shuttleworth C, et al. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. *Cochrane Database Syst Rev*. (2015) 9:CD011611. doi: 10.1002/14651858.CD011611.pub2

38. PARSAIK AK, SINGH B, KHOSH-CHASHM D, MASCARENHAS SS. Efficacy of ketamine in bipolar depression: systematic review and meta-analysis. *J Psychiatr Pract*. (2015) 21:427–35. doi: 10.1097/PRA.0000000000000106

39. Papadimitropoulou K, Vossen C, Karabis A, Donatti C, Kubitz N. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis. *Curr Med Res Opin*. (2017) 33:701–11. doi: 10.1080/03007995.2016.1277201

40. McIntyre RS, Carvalho IP, Lui LMW, Majeed A, Masand PS, Gill H, et al. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. *J Affect Disord*. (2020) 276:576–84. doi: 10.1016/j.jad.2020.06.050

41. Bahji A, Zarate CA, Vazquez GH. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *Expert Opin Drug Saf*. (2022) 21:853–66. doi: 10.1080/14740338.2022.2047928

42. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database Syst Rev*. (2015) 9:CD011612. doi: 10.1002/14651858.CD011612.pub2

43. Fond G, Loundou A, Rabu C, Macgregor A, Lançon C, Brittner M, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology*. (2014) 231:3663–76. doi: 10.1007/s00213-014-3664-5

44. Han Y, Chen J, Zou D, Zheng P, Li Q, Wang H, et al. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. *Neuropsychiatr Dis Treat*. (2016) 12:2859–67. doi: 10.2147/NDT.S117146

45. Kishimoto T, Chawla JM, Hagi K, Zarate CA Jr, Kane JM, Bauer M, et al. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med*. (2016) 46:1459–72. doi: 10.1017/S0033291716000064

46. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med*. (2015) 45:693–704. doi: 10.1017/S0033291714001603

47. Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. (2015) 172:950–66. doi: 10.1176/appi.ajp.2015.15040465

48. Nuñez NA, Joseph B, Pahwa M, Seshadri A, Prokop LJ, Kung S, et al. An update on the efficacy and tolerability of oral ketamine for major depression: a systematic review and meta-analysis. *Psychopharmacol Bull*. (2020) 50:137–63.

49. Rhee TG, Shim SR, Forester BP, Nierenberg AA, McIntyre RS, Papakostas GI, et al. Efficacy and safety of ketamine vs electroconvulsive therapy among patients with major depressive episode: a systematic review and meta-analysis. *JAMA Psychiatry*. (2022) 79:1162–72. doi: 10.1001/jamapsychiatry.2022.3352

50. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Res*. (2015) 230:682–8. doi: 10.1016/j.psychres.2015.10.032

51. An D, Wei C, Wang J, Wu A. Intranasal ketamine for depression in adults: a systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials. *Front Psychol*. (2021) 12:648691. doi: 10.3389/fpsyg.2021.648691

52. Hock RS, Feeney A, Iovieno N, Murrough JW, Mathew SJ, Iosifescu DV, et al. Rapidity of symptom improvement with intranasal esketamine for major depressive disorder: a systematic review and meta-analysis. *J Clin Psychiatry*. (2022) 84:21r14086. doi: 10.4088/JCP.21r14086

53. Jawad MY, di Vincenzo JD, Ceban F, Jaberi S, Lui LMW, Gillissie ES, et al. The efficacy and safety of adjunctive intranasal esketamine treatment in major depressive disorder: a systematic review and meta-analysis. *Expert Opin Drug Saf*. (2022) 21:841–52. doi: 10.1080/14740338.2022.2058488

54. Kryst J, Kawalec P, Mitoraj AM, Pilc A, Lasoń W, Brzostek T. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. *Pharmacol Rep*. (2020) 72:543–62. doi: 10.1007/s43440-020-00097-z

55. Xu Y, Hackett M, Carter G, Loo C, Gálvez V, Glozier N, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. (2016) 19:pyv124. doi: 10.1093/ijnp/pyv124

56. Zheng W, Cai DB, Xiang YQ, Zheng W, Jiang WL, Sim K, et al. Adjunctive intranasal esketamine for major depressive disorder: a systematic review of randomized double-blind controlled-placebo studies. *J Affect Disord*. (2020) 265:63–70. doi: 10.1016/j.jad.2020.01.002

57. Dean RL, Marquardt T, Hurducas C, Spyridi S, Barnes A, Smith R, et al. Ketamine and other glutamate receptor modulators for depression in adults with bipolar disorder. *Cochrane Database Syst Rev*. (2021) 2021:CD011611. doi: 10.1002/14651858.CD011611.pub3

58. Fornaro M, Carvalho AF, Fusco A, Anastasia A, Solmi M, Berk M, et al. The concept and management of acute episodes of treatment-resistant bipolar disorder: a systematic review and exploratory meta-analysis of randomized controlled trials. *J Affect Disord*. (2020) 276:970–83. doi: 10.1016/j.jad.2020.07.109

59. Lee EE, Della Selva MP, Liu A, Himelhoch S. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. *Gen Hosp Psychiatry*. (2015) 37:178–84. doi: 10.1016/j.genhosppsych.2015.01.003

60. Marcantoni WS, Akoumba BS, Wassef M, Mayrand J, Lai H, Richard-Devantoy S, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009 - January 2019. *J Affect Disord*. (2020) 277:831–41. doi: 10.1016/j.jad.2020.09.007

61. Fond G, Bennabi D, Haffen E, Brunel L, Micoulaud-Franchi JA, Loundou A, et al. A Bayesian framework systematic review and meta-analysis of anesthetic agents effectiveness/tolerability profile in electroconvulsive therapy for major depression. *Sci Rep*. (2016) 6:19847. doi: 10.1038/srep19847

62. Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry*. (2020) 54:29–45. doi: 10.1177/0004867419883341

63. Xiong J, Lipsitz O, Chen-Li D, Rosenblat JD, Rodrigues NB, Carvalho I, et al. The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: a systematic review and meta-analysis. *J Psychiatr Res*. (2021) 134:57–68. doi: 10.1016/j.jpsychires.2020.12.038

64. Papakostas GI, Salloum NC, Hock RS, Jha MK, Murrough JW, Mathew SJ, et al. Efficacy of Esketamine augmentation in major depressive disorder: a meta-analysis. *J Clin Psychiatry*. (2020) 81:19r12889. doi: 10.4088/JCP.19r12889

65. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. (2010) 67:793–802. doi: 10.1001/archgenpsychiatry.2010.90

66. Murrough JW, Iosifescu DV, Chang LC, al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392

67. Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol Lett*. (2013) 34:287–93.

68. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856

69. Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. (2012) 71:939–46. doi: 10.1016/j.biopsych.2011.12.010

70. Anderson IM, Blamire A, Branton T, Clark R, Downey D, Dunn G, et al. Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (ketamine-ECT): a multicentre, double-blind, randomised, parallel-group, superiority trial. *Lancet Psychiatry*. (2017) 4:365–77. doi: 10.1016/S2215-0366(17)30077-9

71. Sterne JA, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. (2011) 343:d4002. doi: 10.1136/bmj.d4002

72. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4

73. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. (1998) 52:377–84. doi: 10.1136/jech.52.6.377

74. Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. *J Affect Disord*. (2020) 264:527–34. doi: 10.1016/j.jad.2019.11.086

75. Lii TR, Smith AE, Flohr JR, Okada RL, Nyongesa CA, Cianfichi LJ, et al. Randomized trial of ketamine masked by surgical anesthesia in depressed patients. *medRxiv*. (2023). doi: 10.1101/2023.04.28.23289210 [Preprint].

76. Gabriel FC, Stein AT, Melo DO, Fontes-Mota GCH, dos Santos IB, Rodrigues CS, et al. Guidelines' recommendations for the treatment-resistant depression: a systematic review of their quality. *PLoS One*. (2023) 18:e0281501. doi: 10.1371/journal.pone.0281501

77. Scott F, Hampsey E, Gnanapragasam S, Carter B, Marwood L, Taylor RW, et al. Systematic review and meta-analysis of augmentation and combination treatments for early-stage treatment-resistant depression. *J Psychopharmacol*. (2023) 37:268–78. doi: 10.1177/02698811221104058

78. Li H, Cui L, Li J, Liu Y, Chen Y. Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials. *J Affect Disord*. (2021) 287:115–24. doi: 10.1016/j.jad.2021.03.019

79. Hung YY, Yang LH, Stubbs B, Li DJ, Tseng PT, Yeh TC, et al. Efficacy and tolerability of deep transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *Prog Neuro Psychopharmacol Biol Psychiatry*. (2020) 99:109850. doi: 10.1016/j.pnpbp.2019.109850

80. D'Anci KE, Uhl S, Giradi G, Martin C. Treatments for the prevention and management of suicide: a systematic review. *Ann Intern Med*. (2019) 171:334–42. doi: 10.7326/M19-0869

81. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. *J Clin Psychiatry*. (2021) 82:20m13699. doi: 10.4088/JCP.20m13699

82. National Institute for Health and Care Excellence. Esketamine nasal spray for treatment-resistant depression [TA854]. (2022). Available at: https://www.nice.org.uk/guidance/ta854.

83. Degerlund Maldi K, Asellus P, Myléus A, Norström F. Cost-utility analysis of esketamine and electroconvulsive therapy in adults with treatment-resistant depression. *BMC Psychiatry*. (2021) 21:610. doi: 10.1186/s12888-021-03601-8

84. Mineo L, Rodolico A, Spedicato GA, Aguglia A, Bolognesi S, Concerto C, et al. Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria. *Bipolar Disord*. (2022) 24:530–8. doi: 10.1111/bdi.13166

85. Natale A, Mineo L, Fusar-Poli L, Aguglia A, Rodolico A, Tusconi M, et al. Mixed depression: a mini-review to guide clinical practice and future research developments. *Brain Sci*. (2022) 12:92. doi: 10.3390/brainsci12010092

86. McIntyre RS, Lipsitz O, Rodrigues NB, Lee Y, Cha DS, Vinberg M, et al. The effectiveness of ketamine on anxiety, irritability, and agitation: implications for treating mixed features in adults with major depressive or bipolar disorder. *Bipolar Disord*. (2020) 22:831–40. doi: 10.1111/bdi.12941

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Treating depression at home with transcranial direct current stimulation: a feasibility study

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Introduction: Treating major depressive disorder (MDD) with transcranial direct current stimulation (tDCS) devices at home has various logistic advantages compared to tDCS treatment in the clinic. However, preliminary (controlled) studies showed side effects such as skin lesions and difficulties in the implementation of home-based tDCS. Thus, more data are needed regarding the feasibility and possible disadvantages of home-based tDCS.

Methods: Ten outpatients (23–69 years) with an acute depressive episode were included for this one-arm feasibility study testing home-based tDCS. All patients self-administered prefrontal tDCS (2 mA, 20 min, anodal left, cathodal right) at home on 30 consecutive working days supported by video consultations. Correct implementation of the home-based treatment was analyzed with tDCS recordings. Feasibility was examined by treatment compliance. For additional analyses of effectiveness, three depression scores were used: Hamilton depression rating scale (HDRS-21), Major Depression Inventory (MDI), and the subscale depression of the Depression-Anxiety-Stress Scale (DASS). Furthermore, usability was measured with the user experience questionnaire (UEQ). Tolerability was analyzed by the number of reported adverse events (AEs).

Results: Eight patients did not stick to the protocol. AEs were minimal. Four patients responded to the home treatment according to the MDI. Usability was judged positive by the patients.

Conclusions: Regular video consultations or other safety concepts are recommended regardless of the number of video sessions actually conducted. Home-based tDCS seems to be safe and handy in our feasibility study, warranting further investigation.

KEYWORDS

non-invasive, transcranial direct current stimulation, tDCS, home treatment, feasibility

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (NIBS) technique that induces a weak constant direct current (1–2 mA) via electrodes that are placed on the scalp. Thus, cortical excitability can be modulated by changing the resting membrane potential (1). Treatment over several weeks has the potential to alter pathological cortical plasticity in various psychiatric diseases (2). Conventionally, a tDCS device has an anodal electrode, which increases the excitability of the underlying cortex, and a cathodal electrode, which decreases the excitability of the underlying cortex (1). For treating major depressive disorder (MDD), the anode is placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode is placed over the right DLPFC (3). The rationale for investigating tDCS as a treatment for depression is based on considerations of hypometabolism of the left DLPFC and right prefrontal hypermetabolism as well as dysfunction of brain plasticity, characterized by an alteration of long-term potentiation for depression (4). Thus, by simultaneously increasing the neuronal activity on the left and decreasing the activity on the right side of the DLPFC, antidepressant effects can be achieved (5). A meta-analysis by Razza et al. (6) has already shown that the effects of active tDCS are superior to sham conditions, but with rather small to medium effect sizes. Furthermore, Brunoni et al. (7) have shown that therapeutic effects of tDCS may be mediated by pharmacological modulation of neurons associated with depression in deep brain structures, although they are not directly affected by superficial current flow generated by tDCS stimulation. Nevertheless, tDCS is a promising therapy option for more than one-third of patients who do not achieve remission after multiple treatment trials (7, 8).

To date, tDCS treatment is typically applied at a medical facility by trained medical staff (3). However, daily preparation and the application of the tDCS stimulation itself (20–30 min) take time and staff capacity (9). Daily arrivals at the clinic require additional resources and limit its applicability for patients living far away from a treatment center.

Home-based tDCS treatment has been proposed and investigated for several years (3) as tDCS devices are small, portable, and relatively low-cost and have a favorable side effect profile. Specific devices for home treatment were developed that can be programmed in the clinic beforehand so that patients can use them at home just by activating the stimulation device (9). Although antidepressant treatment at home is possible with a portable tDCS device, an implementation at home can have some disadvantages, like incorrect placement of the electrodes or the risk of overstimulation (10). In order to minimize such adverse events (AEs) and to ensure correct training and supervision of the patients, the first measurement in our study was carried out at the hospital. Additionally, all patients received a comprehensive introduction to the device. Another disadvantage that might come with home-based treatment is the lack of contact with researchers, which might positively impact depressive symptoms due to social interaction (11). In order to ensure contact nonetheless and to supervise regular implementation and the documentation of possible side effects (headaches, etc.) regular video calls with medical staff were implemented. Although patients using home-based tDCS no longer have any travel costs, the use of accessible home-based tDCS devices is still costly due to license fees for tele-therapy; room costs (heating, etc.), data protection processing programs, and staff workload are still comparable for treatment in a clinic (12).

Nevertheless, deploying tDCS treatment at home comes with many advantages, such as reaching more patients (13). Moreover, outpatients who suffer from a depressive episode with pronounced avolition are not required to travel to the clinic for daily treatment (3). Additionally, given the COVID-19 pandemic in which frequent personal contact was avoided anyway, depression treatment with NIBS could take place continuously (14, 15). Hence, the number of studies concerning tDCS home-based treatment for depression is increasing (13). According to the review by Kumpf et al. (9), to date, nine previous studies that primarily targeted home-based tDCS on depressive symptoms of 231 patients have shown a trend towards good antidepressant effectiveness, i.e., amelioration of symptoms in uncontrolled trials. According to Woodham et al. (16), in an open-label trial of 4 weeks, Alonzo et al. (3) found a response rate of 38% (n = 33) and Borrione et al. (17) found a response rate of 80% (n = 5) using a tDCS protocol combined with an app-based psychological intervention. Most of the few sham-controlled studies have not found a significant difference between active and placebo stimulation so far [Mota et al. (18), Lee et al. (19)]. One sham-controlled home-based tDCS trial by Oh et al. (20) has found a significant difference between active and sham tDCS, but 13/58 participants did not complete the study and all participants were additionally prescribed escitalopram 5–20 mg/day. Furthermore, Kumpf et al. (9) have shown that home-based tDCS trials for depression vary strongly in treatment parameters such as electrode positioning, current intensity, or number of sessions. Thus, more research regarding the implementation of home-based tDCS treatment for depression is needed (9).

Here, we conducted a one-arm feasibility study to determine the feasibility of video monitoring and related tDCS parameters of a 6-week home-based tDCS treatment for patients suffering from MDD. Additionally, we investigated clinical outcome measures. The time frame of 6 weeks was chosen because similar in-clinic protocols yield the best effects (10).

Methods and materials

Subjects and study design

The study protocol, patient information, and consent forms were approved by the local ethics committee of the University of Regensburg (20-2091-101). The trial was registered at the U.S. National Institutes of Health Database (www.clinicaltrials.gov) accessible with the identifier code NCT05123872. All patients gave written informed consent to the study. Recruitment took place via a pool of outpatients of the Bezirksklinikum Regensburg (Germany) and via outpatients of psychotherapists of Regensburg. Outpatients of both sexes were eligible for the study if they (1) were

aged 18–70 years, (2) suffered from a depressive episode relating to unipolar or bipolar depression as identified by ICD-10 criteria (21) and/or (3) had a score of at least 21 points in the 21-item Hamilton depression rating scale (HDRS 21), (4) had stable psychotropic medication for at least 2 weeks, and (5) had internet connection at home and used the provided video -call set-p. Exclusion criteria were (1) contraindication for treatment with tDCS (e.g., electronic implants, cardiac pacemakers, or dermatological diseases), (2) neurological diseases (e.g., history of seizures), (3) simultaneous participation in a different study, and (4) pregnancy or lactation period.

Ten outpatients were recruited from fall 2020 to fall 2021. For a better overview, the original numbering was maintained (Pat 1–10). One male patient was treated erroneously with a current of only 1 mA (Pat 2, see below) and was therefore excluded from further analyses. Thus, we recruited one additional male patient in spring 2023 (Pat 11). Additionally, because of more than 50% missing data and delayed return of the tDCS device, data from one female patient (Pat 10, see below) had to be excluded from analyses.

At baseline, week 3, and week 6 (end of treatment), the severity of depressive symptoms was assessed with three different questionnaires as not to miss any possible effects on different clinical aspects. Observer-based ratings were assessed with the 21-item Hamilton Depression Rating Scale (HDRS-21; 22), which scores from 0 to 66. Self-reported symptoms were assessed with the Major Depression Inventory (MDI; 23), which scores from 0 to 50. Weekly surveys were covered with the Depression-Anxiety-Stress Scale (DASS; 24). Here, we focused on the changes in the depression subscale, which scores from 0 to 21. In all three questionnaires, higher scores indicate more depressive symptoms. At week 3, the HDRS-21 was assessed via video consultation (see below). For additional analyses, patients completed at these time points the Pittsburgh Sleep Quality Index (PSQI; 25) and an abbreviated version of the WHO quality-of-life scale (WHOQOL-BREF; 26), which is divided into four domains: physical health (domain 1), psychological health (domain 2), social relationships (domain 3), and environment (domain 4). In order to investigate the subjective impression of the users toward home treatment, patients completed at week 6 the user experience questionnaire (UEQ), which is based on the open-source evaluation method by Schrepp et al. (27). The questionnaire is divided into six scales, which measure the classical usability aspects as well as user experience aspects. The six scales include Attractiveness (Overall impression of the product), Perspicuity (Is it easy to get familiar with the product)?, Efficiency (Can users solve their tasks without unnecessary effort)?, Dependability (Does the user feel in control of the interaction)?, Stimulation (Is it exciting and motivating to use the product)?, and Novelty (Is the design of the product creative)? (https://www.ueq-online.org/; access: 2024-01-30). Higher UEQ scores correspond to better evaluation. Additionally, clinicians completed the seven-level scale Clinical Global Impression Scales (CGI-Severity and CGI-Improvement; 28) for quantifying and tracking the patient's treatment response over the course of the trial (see Figure 1).

tDCS: home treatment

Two hospital visits were mandatory for study participation: one pre-treatment and one post-treatment (Figure 1). The initial visit, conducted at the Bezirksklinikum Regensburg outpatient clinic, involved both the first tDCS treatment and comprehensive patient training for home sessions. A medical technical assistant meticulously instructed participants on electrode placement and treatment protocol, ensuring accurate and safe self-administration upon discharge. During the subsequent at-home phase, adherence and treatment safety were monitored via daily video consultations, facilitated by the CLICKDOC software (version 5.9.1, La-Well Systems GmbH), a clinically approved platform. These consultations verified proper electrode placement, confirmed treatment initiation, and monitored for any AEs that were noted on a treatment protocol. Only participants demonstrating consistent adherence and correct electrode positioning without any further instruction needed were permitted to undergo unsupervised treatment sessions as long as they did not report any side effect in the first five consecutive sessions. Treatment parameters remained consistent throughout the study: On 30 consecutive weekdays with video consultations once a day, each session delivered a 2-mA current for 20 min using a prefrontal montage. The CE-certified DC-Stimulator Mobile (Neuroconn, Ilmenau, Germany) was employed for all stimulations and could be activated by the study participants at any time.

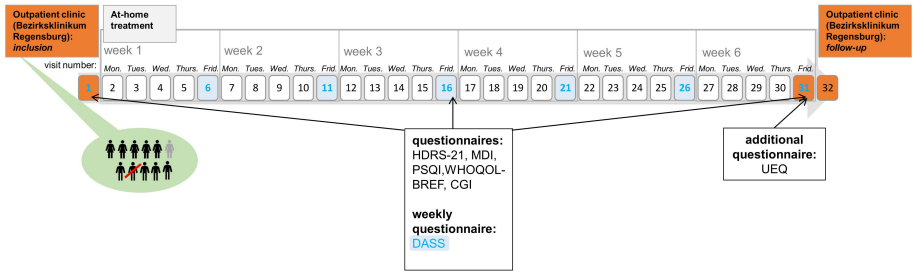

FIGURE 1
Course of the trial. This figure shows the course of the study. Inclusion, visit 31, and visit 32 (follow up measures) took place in the hospital (orange). Home-based treatment is depicted in gray. The Depression-Anxiety-Stress Scale was completed every Friday (blue).

At the initial visit, participants received a personalized tDCS kit composed of the stimulation device, two 5×7 cm rubber electrodes, color-coded sponges (anode: red, cathode: blue), NaCl 0.9% solution for sponge soaking, and an instruction manual with detailed illustrations. This standardized protocol, coupled with daily monitoring and adherence checks, aimed to ensure the safety of home-based tDCS treatment for all participants (see Figure 2).

Statistical analysis

We used descriptive statistics to summarize the clinical and demographic characteristics of the sample and the completion rates.

Since we focused on the tDCS treatment outside of a clinical setting, we analyzed the tDCS data (regularity of implementation without video consultation, number of video consultations, etc.) as primary outcome. For this purpose, the tDCS recordings (mean amperage, mean voltage, mean time of treatment, etc.) were extracted from the output neuroConn LogFiles and mean scores were calculated within Microsoft Excel. Subjective rating of the treatment usability (UEQ) was analyzed as primary outcome, on a descriptive level. Any AEs that occurred were coded if reported at any intensity or duration. AE occurrences were estimated by the number of participants reporting an AE in at least one of their tDCS sessions.

In accordance with our registry at clinicaltrials.gov (see above), all depression questionnaires (HDRS-21, MDI, and DASS) were also defined as primary outcome measures. The number of responders was defined by ≥50% reduction in the mean scores after the treatment duration of 6 weeks (efficiency) according to the HDRS-21. Collected follow-up data (after 18 weeks, visit 32) was not further analyzed due to >50% missing data. Thus, the planned secondary outcome measures (changes of the HDRS-21, MDI, CGI-I, PSQI, WHOQOL-BREF, and DASS between baseline and week 18) could not be calculated. Accordingly, outcome measures were calculated for a time frame of 6 weeks. Thus, repeated-measures analysis of variance (ANOVA) with time as within factor (three levels: baseline vs. week 3 vs. week 6) were used for the estimation of secondary treatment effects. For the weekly DASS data, another ANOVA for the subscale *depression* with time as within factor (seven levels: baseline vs. week 1 vs. week 2 vs. week 3 vs. week 4 vs. week 5 vs. week 6) was calculated, despite 44% missing data for this questionnaire. Subsequent paired samples *t*-tests were calculated for *post-hoc* analyses. Regarding the feasibility, both patient reports and log files of the used tDCS devices were analyzed. All 10 patients are listed corresponding to the time of the first treatment. All statistical analyses were conducted with SPSS version 28.0 (IBM SPSS, Chicago, IL).

Due to the use of three depression measurements, threshold level of significance was adjusted for multiple comparisons by Bonferroni's correction (p = 0.017). Mean (M) and standard deviation (SD) are reported. The mean values of the PSQI and WHOQOL-BREF were conducted with Microsoft Excel sheets. The mean values of the UEQ were analyzed with Microsoft Excel (ueq-online.org), by Schrepp et al. (27).

Results

Demographics

All patients suffered from an acute depressive episode (ICD-10: F32.1, F33.1, and F33.2). Our sample consisted of one full-time employee, two half-time employees, three students, one early pensioner, one pensioner, and two unemployed patients. Two patients were single, and eight were in a relationship. Eight patients were high school graduates, one patient did not have an academic degree, and one educational information was missing.

Further demographic and clinical characteristics of the enrolled patients are provided in Tables 1, 2.

Feasibility

All participants performed an average of 29.6 stimulation sessions over the course of 6 weeks (Table 3). Most of the patients conducted the treatments in the morning or at noon. Eight patients did not stick to the protocol, meaning that according to the tDCS log

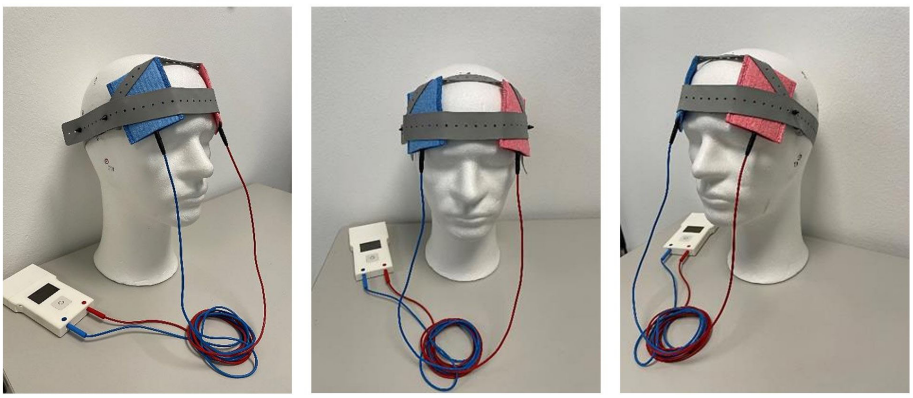

FIGURE 2
Prefrontal setup of the tDCS device for home treatment.

TABLE 1 Clinical data at baseline of the present sample.

General variables	
Age: M (SD)	37.40 (14.14)
Age: range	23 - 69
Gender: m/f (*N*)	4/6 (10)
Questionnaire scores at baseline: M (SD)	
HDRS-21(0–65)	18.90 (4.04)
MDI (0–50)	32.50 (6.54)
DASS, depression subscale (0–12)	11.25 (4.92)
WHOQOL-BREF physical health subdomain (4–20)	11.77 (3.22)
WHOQOL-BREF psychological subdomain (4–20)	10.43 (1.56)
WHOQOL-BREF social subdomain (4–20)	12.67 (2.61)
WHOQOL-BREF environment subdomain (4–20)	14.60 (2.01)
PSQI total sum (0–21)	8.78 (5.49)
CGI (1–7)	4.44 (.53)

Questionnaire scores at baseline were calculated without patient 10. HDRS-21, Hamilton Depression Scale 21 items. MDI, Major Depression Inventory. WHOQOL-BREF, World Health Organization Quality of Life Questionnaire short version; higher scores indicate better quality of life. PSQI, Pittsburgh Sleep Quality Index. CGI, Clinical Global Impression; ordinal scale.

TABLE 2 Clinical data per patient.

Patient	Comorbid psychiatric diagnoses (ICD-10)	Comorbid diseases	Psychiatric medication (dosage)
1		Tinnitus	Escitalopram (10 mg), tebonin (120 mg), doxepin (20 mg)
3	Borderline personality disorder (F60.31), ADHD (F90.0), adjustment disorder (F43.2)		sertralin (100 mg), olanzapin (7.5 mg), sumatriptan (100 mg)
4			
5	ADHD (F90.0)		Atomoxetin (60 mg)
6			
7			Agomelatin (u.d.)
8			Trimipramin (25 mg)
9			Escitaloptam (5 mg)
10		Hypothyreosis	
11		arterial hypertension, arthosis	Venlaflaxin (75 mg), hydrochlorothiazide (20 mg), zanipress (20 mg)

ADHD, attention deficit/hyperactivity disorder. u.d.: unknown dosage. Patients were taking daily antidepressants. Doses were not changed throughout the study.

files, some patients conducted the treatment not only on working days but also, for example, even on holidays or on weekends. For example, patient 11 conducted the treatment every day. In four patients, the time of treatment was highly variable: patient 4 underwent treatment between 7:16 a.m. and 10:57 p.m. and patient 7 underwent treatment between 7:30 a.m. and 4:16 p.m. Patient 10 underwent treatment three times at night. Patient 11 underwent treatment at 7:00 a.m. during supervision and at 7:00 p.m. without supervision. Only two participants underwent the treatment regularly at the same time as instructed.

Usability and tolerability

Based on the evaluation method by Schrepp et al. (27), all patients evaluated the treatment as follows: the scales *Attractiveness* (M = 0.89, SD = 0.81) and *Stimulation* (M = 0.97, SD = 0.93) were rated "below average". *Efficiency* was rated "above average" (M =1.06, SD = 0.79). The scales *Perspicuity* (M = 1.83, SD = 1.56), *Novelty* (M = 1.14, SD = 0.38), and *Dependability* (M = 1.53, SD = 0.85) were rated "good" (Figure 3).

No serious AEs occurred in any of the patients. Side effects were noted as free text by the medical staff on the treatment protocol: 2/10 patients indicated mild headaches after treatment during the first week. One patient felt tingling over the course of the entire treatment. Another patient felt tingling during the first week of treatment. One of ten patients indicated mild redness on the left side of his head after treatment 5 and 6. The number of side effects was not related to the number of sessions.

Additional analyses: effectiveness

Each level of all within-subjects factors, regarding the HDRS-21 and MDI data, was approximately normally distributed, as assessed by the Shapiro–Wilk test, $p > 0.05$.

Table 4 provides all results concerning depression measurements in the course of the trial. There was a statistically significant reduction (change in %) of the mean MDI scores after treatment compared to baseline ($\frac{(\text{week 6}-\text{Baseline})}{\text{Baseline}}$). In contrast, no significant reduction of the mean HDRS-21 scores was found.

Five participants responded to the treatment confirmed by the HDRS-21, corresponding to 55.5% of the sample. Four of these five participants additionally responded to the treatment confirmed by the MDI, which corresponds to 44.4% of the sample (see Table 4).

Concerning the MDI scores, *post-hoc* analyses revealed significant reductions after week 3 [$t(8) = 2.86$, $p = 0.021$] and week 6 [$t(8) = 5.03$, $p = 0.001$] compared to baseline.

Because of high correlations among the seven measurements concerning the DASS data, the Greenhouse–Geisser correction was used: Over the course of the trial, no significant reduction in the depression subscale of the DASS was found [$F(2.5,10.2) = 1.89$, $p = 0.197$, partial $\eta^2 = 0.321$] (Figure 4). In analyses of the DASS data, there were four responders: Pat 5 (−80%), Pat 9 (−100%), Pat 8 (−80%), and Pat 1 (−100%).

TABLE 3 Mean values for the tDCS data.

Patient	Amperage (mA)	Electrical voltage (V)	Average time of treatment	Days of treatment	Days without supervision
1	1.981	4.565	11:44 a.m.	28	0
3	1.982	5.308	12:43 p.m.	29	1
4	1.979	4.926	12:16 p.m.	28	10
5	1.993	4.657	7:58 a.m.	31	5
6	1.982	5.605	1:29 p.m.	28	3
7	1.985	5.321	11:16 a.m.	30	4
8	1.980	4.766	12:47 p.m.	34	3
9	1.979	6.277	9:06 a.m.	29	2
10	1.982	5.115	8:06 a.m.	23	9
11	1.982	6.416	3:32 p.m.	36	22

Days of treatment include first visit at hospital. Patients 10 and 11 ended two treatments a few seconds before the regular ending of the stimulation after 20 min. Patient 11 had to restart the treatment 11 times due to "cancellation by error" by the device itself.

Regarding the CGI-I measurements, equivalent improvements were found for two of the same patients: The third patient's illness was estimated as improved (score: 2) by the clinicians after week 6. Patient 5 was considered as improved already after week 3 (Figure 5).

Repeated-measures ANOVAs for secondary outcome measures revealed no significant improvement of the patients sleep regarding the PSQI scores. However, there was a statistically significant improvement in the psychological subdomain of the WHOQOL-BREF over the course of the study [95% CI: 9.53 to 13.23; $F(2,16) = 4.71$, $p = 0.025$, partial $\eta^2 = 0.371$]. In the physical health subdomain, there was also a statistically significant increase in quality of life [95% CI: 9.35 to 15.37; $F(2,16) = 3.76$, $p = 0.046$, partial $\eta^2 = 0.320$]. Regarding the social and environment subdomain, there were no significant changes (Figure 6) ($ps > 0.157$).

Discussion

The present one-arm feasibility study investigated in a small sample of patients different aspects regarding tDCS treatment of depression at home. The study revealed possible difficulties in carrying out a tDCS treatment outside of a clinical setting (e.g., tertiary care hospital), despite the support of regularly planned video consultations. Additionally, we provide further data regarding clinical outcome measurements for home-based tDCS treatment.

Although we had the impression with a few participants that after a certain number of monitored sessions they could perform the tDCS treatments on their own, we found from analyzing the tDCS data recordings that more than half of the study participants did not adhere to the pre-discussed treatment protocol (e.g., treatment on holidays or weekends). As an example, patient 10 forgot the treatment (and video consultations) three times and performed the stimulation at nighttime without supervision and with a short interval to next day's treatment. Thus, if certain patients failed to attend the scheduled video call, then they performed the treatment without video supervision and presumably not entirely correctly. Further results showed that patients 3, 5, and 11, all treatment responders, restarted the treatment on their own if there was any problem with the tDCS device or if their recording was uncompleted. This highlights the need for daily video calls to check the correct implementation or that the device is programmed in a way that it can only be switched on at a certain time, because even though those 3 patients were able to restart the stimulation on their own and completed the treatment correctly, it

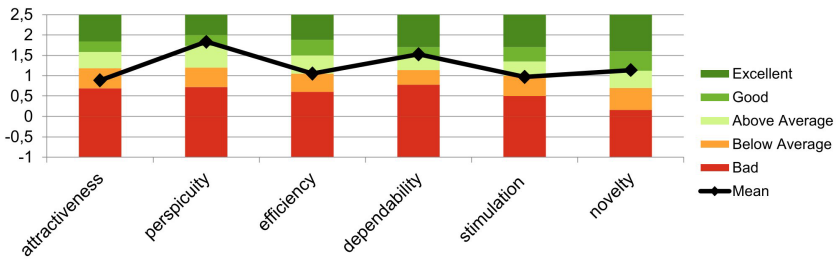

FIGURE 3
Mean evaluation of the user experience based on the evaluation method by Schrepp et al. (27). This graph shows the mean scores and SDs of the six factors of the user experience questionnaire (UEQ) across the sample.

TABLE 4 Sum scores for all participants over the course of the trial for two of the depression measurements.

	BL	Week 3	Week 6	Change (%)	95% CI lower	95% CI upper	
HDRS-21							
Pat 1	14.00	15.00	21.00	+50.0			
Pat 3	27.00	15.00	9.00	−66.6			
Pat 4	18.00	14.00	12.00	−33.3			
Pat 5	17.00	6.00	8.00	−53.0			
Pat 6	19.00	16.00	18.00	−5.3			
Pat 7	16.00	16.00	22.00	+37.5			
Pat 8	22.00	12.00	11.00	−50.0			
Pat 9	22.00	20.00	5.00	−77.3			
Pat 11	14.00	-99	7.00	−50.0			
Total (SD)	19.38 (4.14)	14.25 (4.03)	13.25 (6.32)		13.76	17.68	F (2,14) = 3.13, partial η^2 = 0.309, p = 0.075
MDI							
Pat 1	20.00	19.00	16.00	−20.0%			
Pat 3	39.00	32.00	15.00	−61.5%			
Pat 4	32.00	34.00	25.00	−21.9%			
Pat 5	25.00	8.00	8.00	−68.0%			
Pat 6	41.00	37.00	36.00	−12.2%			
Pat 7	37.00	30.00	27.00	−27.0%			
Pat 8	37.00	26.00	20.00	−45.9%			
Pat 9	34.00	5.00	6.00	−82.4%			
Pat 11	31.00	25.00	7.00	−77.4%			
Total (SD)	32.89 (6.81)	24.00 (11.27)	17.78 (10.22)		18.53	31.24	F (2,16) = 14.28, partial η^2 = 0.641, p< 0.001

Responders are shown in orange. BL, Baseline. +: increase in the depression measurement (%). −99: missing data. SD are shown for the present sample.

highlights the risk of overstimulation for incautious patients. Previous studies have shown that the number and interval of sessions are critical concerning safety. With higher numbers of sessions and shorter intervals, the risk of side effects increases (29, 30). In our study, one patient had a comorbid borderline personality disorder that comes with a high risk of self-harming behavior (31). As already stated in a review by Kumpf et al. (9), regular supervision of home-based treatment and technical control of the device are

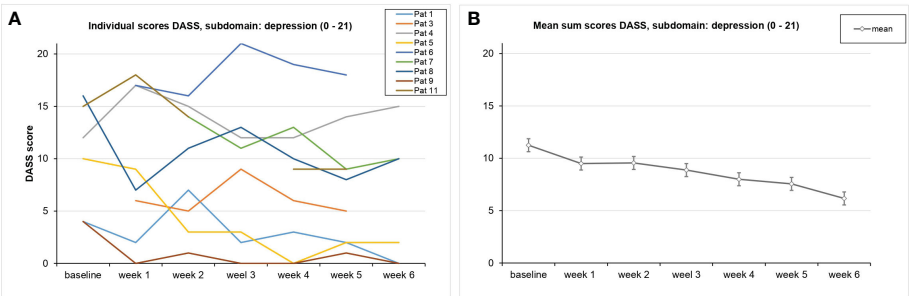

FIGURE 4
Course of the DASS values on average **(A)** and for each patient **(B)** This graph shows the DASS scores for the subscale *depression* over the course of the trial for each participant. SDs are not plotted for presentational purposes. Missing values are not replaced. Responders are shown in orange.

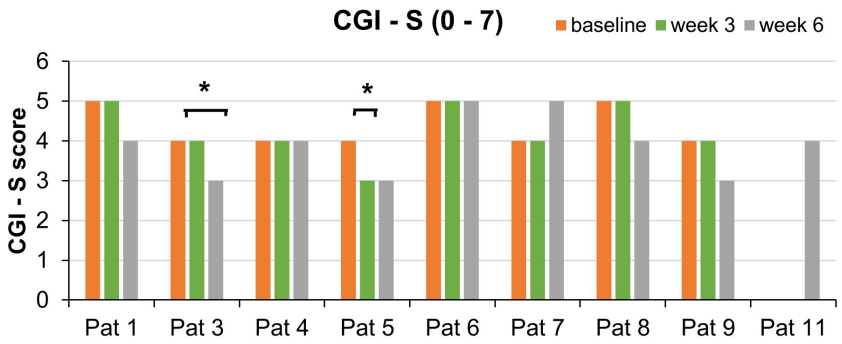

FIGURE 5
Course of the CGI-S scores for each patient split by week 3 and week 6. This bar graph shows the CGI-S scores over the course of the trial. *Significant improvement of the global impression as measured by the CGI-I (score: 2). SDs are not plotted for presentational purposes. Missing values are not replaced.

important in order to minimize possible side effects and risks of deliberated self-harm. Our results show that a home-based tDCS device has to be remotely adjusted, because although the clinicians in this study saw no need for real-time video consultation, there were some subjects who did not adhere to the protocol. Future studies should consider a security system to permit daily use for 20 min with a minimal interval of 12 h between sessions, as, e.g., in Carvalho et al. (12). The use of pre-programmed home-based tDCS would allow patients to choose what time of day to receive the treatment, therefore accommodating patients' schedules and minimizing possible side effects. Future studies with real-life video consultations should at least consider a fast-track contact line. This would ensure that patients could report any side effects or get help with technical problems. Another option would be to resort to daily written feedback to clinicians, which would allow them to decide whether to contact respective patients. Although we only found minimal deviations from the protocol, future studies should ensure that patients comply to agreed arrangements.

Furthermore, our results show that for patient 2, the device was incorrectly set, because he was stimulated with a very low mean amperage of 0.995 mA. This problem was only detected after study finalization. This highlights the need for corresponding training of the instructing staff. A recent investigation concerning another NIBS, home-based tES (transcranial electrical stimulation), showed that an educational program for remote training and supervision at home could facilitate further research (32).

Our study participants evaluated the treatment as not hard to learn (UEQ factor: Perspicuity). However, the overall impression of the product (UEQ factor: Attractiveness) and the excitement/motivation to use the product (UEQ factor: Stimulation) were both rated low ("below average"). Overall, home-based tDCS seems to be moderately user-friendly when using the Neuroconn home-based tDCS system the way this study did. According to previous studies, we registered no serious adverse effects and only few minor side effects (subjective sensations of tingling or headaches/pain during the first treatments and/or mild skin

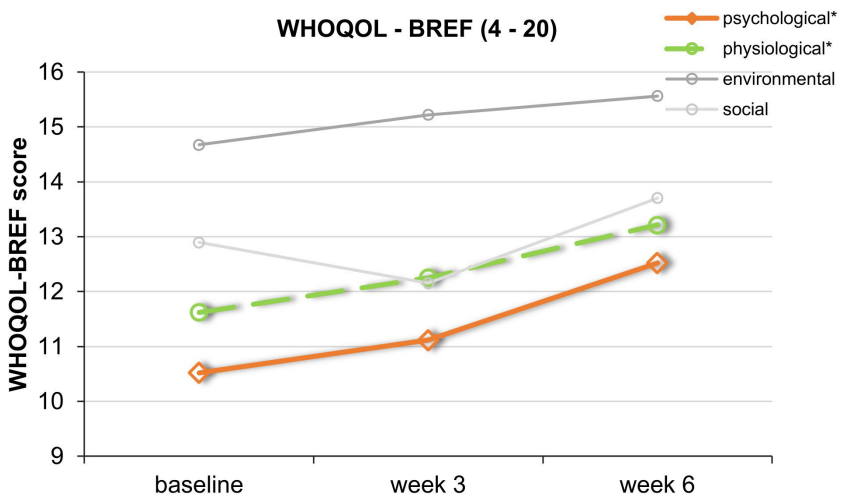

FIGURE 6
Course of the mean values of the 4 subdomains of the WHOQOL-BREF. This graph shows WHOQOL-BREF mean scores over the course of the trial. *Significant improvement for the physical (green) and psychological (orange) subdomains. SDs are not plotted for presentational purposes.

redness), confirming that tDCS is a tolerable treatment method (13)—even at home. This is in contrast to a recent published study by Kumpf et al. (9), where their home-based trial had to be prematurely terminated due to an accumulation of skin lesions. These findings highlight the need for careful and active side effect monitoring before and after stimulation, e.g., in the form of a safety questionnaire, as MDD patients may be impaired in their ability to proactively report side effects (9).

As this one-arm study did not include a control condition and because of a small sample size, our additional analyses regarding effectiveness have to be interpreted cautiously. Our patients had a statistically significant score reduction in self-reported symptoms (MDI). There was no significant reduction in the HDRS-21 or in the subscale *depression* of the DASS. A reason for a lack of significant result regarding the DASS might be the fact that there were 44% missing data for the weekly filled-out questionnaire. Regarding the HDRS and MDI, it has to be noted that observer-rated instruments benefit from clinician expertise and are argued to be more "objective", while self-rated questionnaires may capture better subjective experience (33). In a study by Leuchter et al. (34), changes induced with another NIBS, repetitive transcranial magnetic stimulation (rTMS), were better captured by self-report scales. In their study, the HDRS also had the lowest response rates. Nevertheless, the authors stated that a better outcome on a self-report scale might be conceived as a "false positive" benefit with the HDRS as the more accurate measurement (34). Thus, we cannot exclude or determine the extent of placebo effects regarding the MDI data. Available randomized controlled trials of home-based tDCS for depression have not found significant differences in active relative to sham tDCS treatment. Only one single-blinded study by Oh et al. (20) found that active tDCS resulted in a significantly higher reduction of Beck Depression Inventory (BDI-I) scores, which also represents a self-report scale, compared to sham treatment. Therefore, further controlled studies are needed to demonstrate that active home-based tDCS exceeds placebo effects. Nevertheless, half of our patients fulfilled response criteria in all three questionnaires. Our results regarding response rates (MDI: 44.4%) go in line with a study by Alonzo et al. (3) who found a response rate of 38% for observer-rated symptoms (Montgomery Asperg Rating Scale) after 6 weeks of self-administered tDCS stimulation. Another study, by Borrione et al. (17), who used app-based psychological interventions in combination with home-based tDCS, found a response rate (HAMD-17) of 80%. Possible influences (additional app-based intervention, psychiatric medication, etc.) on respective response rates must be taken into account as, e.g., Brunoni et al. (35) found that antidepressants can lead to increased tDCS effects.

Additionally, it is noticeable that non-response was sometimes related to a lower rate of video supervised sessions. This phenomenon might be explained by the positive impact that daily contact with researchers has on depressive symptoms due to social interaction (11). Future sham-controlled studies should consider to investigate the connection between the number of video consultations and depressive outcome in the course of a tDCS treatment.

In the whole sample, physical and psychological quality of life was improved with a large effect size, whereas the environmental and social domain as well as sleep quality remained unchanged. The result regarding the psychological domain goes in line with previous literature that anodal tDCS over left DLPFC improves the processing of positive affective stimuli and reduces the selective attention for negative affective stimuli, thus increasing the psychological domain of life quality (36). An improvement in the physical domain might be correlated with an amelioration of the somatic symptoms of depression, e.g., lack of motivation, over the course of the trial (ICD-10). Home-based tDCS did not improve the social and environmental domains, which might be explained by conducting the treatment at home alone without, e.g., augmented group therapy (37). Moreover, many of our patients forgot the video consultations or implemented further treatment on their own, whereby they had no positive effect from a social interaction with our clinicians. In contrast to a study by Zhou et al. (15) that treated insomnia patients with tDCS at a hospital, improvement of sleep quality was not found in our study (15). The lack of improvement of the sleep quality in our study may be due to the fact that the authors treated patients who suffered from insomnia and thus had worse pre-treatment PSQI scores than ours. Another explanation could be that regular video consultations cannot be compared with controlled sleep times in a sleep laboratory that might have had a positive effect on the sleep quality of the author's patients. With respect to the follow-up data, we have to notice that more than 50%, mostly non-responders, of our patients were not reachable after termination of the study. Thus, we refrained from an evaluation of the follow-up data because the focus of this study was not on long-lasting antidepressant effects. Study limitations refer to the lack of attrition and/or adherence rates. Future studies should consider including these parameters in order to make potential difficulties regarding the implementation at home statistically comparable.

Conclusions

Our results show that regular video consultations are needed to ensure good adherence to a predefined protocol (e.g., once a day at 24-h intervals) and to minimize the occurrence of side effects. Nevertheless, in the event that the clinical impression arises that a patient can continue the treatment without further video consultations, other safety concepts should be used in such cases. Furthermore, the present one-armed study on the topic of tDCS at home for depressive disorders provides further evidence regarding usability, tolerability, and effectiveness.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethikkommission der Universität Regensburg. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KD: Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. MA: Investigation, Writing – review & editing. FW: Investigation, Writing – review & editing. MH: Formal analysis, Writing – review & editing. LE: Formal analysis, Writing – review & editing. BL: Conceptualization, Investigation, Project administration, Supervision, Writing – review & editing. TH: Investigation, Writing – review & editing. MS: Conceptualization, Investigation, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declare that this study received three home-tDCS devices free of charge from Neuroconn Illmenau, Germany. The company was not involved in the study design, collection, analysis, interpretation of the data, the writing or editing of this article or the decision to submit it for publication.

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References

1. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol.* (2000) 527:633. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

2. Kuo M-F, Chen P-S, Nitsche MA. The application of tDCS for the treatment of psychiatric diseases. *Int Rev Psychiatry.* (2017) 29:146–67. doi: 10.1080/09540261.2017.1286299

3. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *J Affect Disord.* (2019) 252:475–83. doi: 10.1016/j.jad.2019.04.041

4. Samara Z, Evers EA, Peeters F, Uylings HB, Rajkowska G, Ramaekers JG, et al. Orbital and medial prefrontal cortex functional connectivity of major depression vulnerability and disease. Biological Psychiatry. *Cogn Neurosci Neuroimaging.* (2018) 3:348–57. doi: 10.1016/j.bpsc.2018.01.004

5. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). [Review]. *Clin Neurophysiol.* (2017) 128:56–92. doi: 10.1016/j.clinph.2016.10.087

6. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. *Depression Anxiety.* (2020) 37:594–608. doi: 10.1002/da.23004

7. Brunoni AR, Júnior RF, Kemp AH, Lotufo PA, Benseñor IM, Fregni F. Differential improvement in depressive symptoms for tDCS alone and combined with pharmacotherapy: an exploratory analysis from the Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Study. *Int J Neuropsychopharmacol.* (2014) 17:53–61. doi: 10.1017/S1461145713001065

8. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *Am J Psychiatry.* (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

9. Kumpf U, Palm U, Eder J, Ezim H, Stadler M, Burkhardt G, et al. TDCS at home for depressive disorders: an updated systematic review and lessons learned from a prematurely terminated randomized controlled pilot study. *Eur Arch Psychiatry Clin Neurosci.* (2023) 273:1–18. doi: 10.1136/bmj.n71

10. Kumpf U, Ezim H, Stadler M, Burkhardt G, Palm U, Dechantsreiter E, et al. Transcranial direct current stimulation as treatment for major depression in a home treatment setting (HomeDC trial): study protocol and methodology of a double-blind, placebo-controlled pilot study. *Pilot Feasibility Stud.* (2023) 9:1–13. doi: 10.1186/s40814-023-01423-x

11. Elmer T, Stadtfeld C. Depressive symptoms are associated with social isolation in face-to-face interaction networks. *Sci Rep.* (2020) 10:1444. doi: 10.1038/s41598-020-58297-9

12. Carvalho F, Brietzke AP, Gasparin A, Dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. *JoVE (J Visual Exp).* (2018) 137:e57614. doi: 10.3791/57614

13. Pilloni G, Vogel-Eyny A, Lustberg M, Best P, Malik M, Walton-Masters L, et al. Tolerability and feasibility of at-home remotely supervised transcranial direct current stimulation (RS-tDCS): single-center evidence from 6,779 sessions. *Brain Stimul*. (2022) 15:707–16. doi: 10.1016/j.brs.2022.04.014

14. Bikson M, Hanlon CA, Woods AJ, Gillick BT, Charvet L, Lamm C, et al. Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. *Brain Stimul*. (2020) 13:1124–49. doi: 10.1016/j.brs.2020.05.010

15. Zhou Q, Yu C, Yu H, Zhang Y, Liu Z, Hu Z, et al. The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. *Sleep Med*. (2020) 70:17–26. doi: 10.1016/j.jad.2017.08.024

16. Woodham RD, Rimmer RM, Young AH, Fu CH. Adjunctive home-based transcranial direct current stimulation treatment for major depression with real-time remote supervision: An open-label, single-arm feasibility study with long term outcomes. *J Psychiatr Res*. (2022) 153:197–205. doi: 10.1016/j.jpsychires.2022.07.026

17. Borrione L, Klein I, Razza LB, Suen P, Brunoni AR. Use of app-based psychological interventions in combination with home-use transcranial direct current stimulation for the treatment of major depressive disorder: a case series. *Journal of affective disorders*. (2021) 288:189–90. doi: 10.1016/j.jad.2021.04.013

18. Mota SM, Amaral de Castro L, Riedel PG, Torres CM, Bragatti JA, Brondani R, et al. Home-based transcranial direct current stimulation for the treatment of symptoms of depression and anxiety in temporal lobe epilepsy: a randomized, double-blind, sham-controlled clinical trial. *Front Integr Neurosci*. (2021) 51:753995. doi: 10.3389/fnint.2021.753995

19. Lee J, Lee CW, Jang Y, You JS, Park YS, Ji E, et al. Efficacy and safety of daily home-based transcranial direct current stimulation as adjunct treatment for bipolar depressive episodes: double-blind sham-controlled randomized clinical trial. *Front Psychiatry*. (2022) 13:969199. doi: 10.3389/fpsyt.2022.969199

20. Oh J, Jang KI, Jeon S, Chae JH. Effect of self-administered transcranial direct stimulation in patients with major depressive disorder: A randomized, single-blinded clinical trial. *Clin Psychopharmacol Neurosci*. (2022) 20:87. doi: 10.9758/cpn.2022.20.1.87

21. Dilling H, Dittmann V. Die psychiatrische Diagnostik nach der 10. Revision der internationalen Klassifikation der Krankheiten (ICD-10) [Psychiatric diagnosis following the 10th revision of the International Classification of Diseases (ICD-10)]. *Nervenarzt*. (1990) 61:259–70.

22. Hamilton MAX. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. (1967) 6:278–96. doi: 10.1111/j.2044-8260.1967.tb00530.x

23. Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord*. (2001) 66:159–64. doi: 10.1016/S0165-0327(00)00309-8

24. Nilges P, Essau C. Die depressions-angst-stress-skalen. *Der Schmerz*. (2015) 29:649–57. doi: 10.1007/s00482-015-0019-z

25. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

26. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *psychol Med*. (1998) 28:551–8. doi: 10.1017/S0033291798006667

27. Schrepp M, Hinderks A, Thomaschewski J. Construction of a benchmark for the user experience questionnaire (UEQ). *Int J Interactive Multimedia Artif Intell*. (2017) 4:39–45. doi: 10.9781/ijimai.2017.445

28. Guy WBRR. Clinical global impressions scale. *ECDEU Assessment manual*. (1976), 218–22. doi: 10.1037/t48216-000

29. Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, et al. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection and reporting practices. *Brain Stimul*. (2012) 5:435–53. doi: 10.1016/j.brs.2011.10.001

30. Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols. *Front Syst Neurosci*. (2015) 9:26. doi: 10.3389/fnsys.2015.00026

31. Reichl C, Kaess M. Self-harm in the context of borderline personality disorder. *Curr Opin Psychol*. (2021) 37:139–44. doi: 10.1016/j.copsyc.2020.12.007

32. Cappon D, den Boer T, Yu W, LaGanke N, Fox R, Brozgol M, et al. An educational program for remote training and supervision of home-based transcranial electrical stimulation: feasibility and preliminary effectiveness. *Neuromodulation: journal of the International Neuromodulation Society*. (2023), S1094-7159(23)00671-2. doi: 10.1016/j.neurom.2023.04.477

33. Zimmerman M, Walsh E, Friedman M, Boerescu DA, Attiullah N. Are self-report scales as effective as clinician rating scales in measuring treatment response in routine clinical practice? *J Affect Disord*. (2018) 225:449–52. doi: 10.1016/j.jad.2017.08.024

34. Leuchter MK, Citrenbaum C, Wilson AC, Tibbe TD, Jackson NJ, Krantz DE, et al. A comparison of self-and observer-rated scales for detecting clinical improvement during repetitive transcranial stimulation (rTMS) treatment of depression. *Psychiatry Res*. (2023) 330:115608. doi: 10.1016/j.psychres.2023.115608

35. Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio PS, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: findings from a naturalistic study. *Eur Psychiatry*. (2013) 28:356–61. doi: 10.1016/j.eurpsy.2012.09.001

36. Mondino M, Thiffault F, Fecteau S. Does non-invasive brain stimulation applied over the dorsolateral prefrontal cortex non-specifically influence mood and emotional processing in healthy individuals? *Front Cell Neurosci*. (2015) 9:399. doi: 10.3389/fncel.2015.00399

37. Bajbouj M, Aust S, Spies J, Herrera-Melendez AL, Mayer SV, Peters M, et al. PsychotherapyPlus: Augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. *Eur Arch Psychiatry Clin Neurosci*. (2018) 268:797–808. doi: 10.1007/s00406-017-0859-x

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Risk factors for suicidal attempts in a sample of outpatients with treatment-resistant depression: an observational study

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Introduction: Treatment-resistant depression (TRD) is commonly defined as the failure of at least two trials with antidepressant drugs, given at the right dose and for an appropriate duration. TRD is associated with increased mortality, compared to patients with a simple major depressive episode. This increased rate was mainly attributed to death from external causes, including suicide and accidents. The aim of our study is to identify socio-demographic and psychopathological variables associated with suicidal attempts in a sample of outpatients with TRD.

Material and methods: We performed a monocentric observational study with a retrospective design including a sample of 63 subjects with TRD referred to an Italian outpatient mental health centre. We collected socio-demographic and psychopathological data from interviews and clinical records.

Results: 77.8% of the sample (N=49) were females, the mean age was 49.2 (15.9). 33.3% (N=21) of patients had attempted suicide. 54% (N=34) of patients had a psychiatric comorbidity. Among the collected variables, substance use (p=0.031), psychiatric comorbidities (p=0.049) and high scores of HAM-D (p=0.011) were associated with the occurrence of suicide attempts. In the regression model, substance use (OR 6.779), psychiatric comorbidities (OR 3.788) and HAM-D scores (OR 1.057) were predictive of suicide attempts. When controlling for gender, only substance use (OR 6.114) and HAM-D scores (OR 1.057) maintained association with suicide attempts.

Conclusion: The integrated treatment of comorbidities and substance abuse, which involves different mental health services, is fundamental in achieving the recovery of these patients. Our study supports the importance of performing a careful clinical evaluation of patients with TRD in order to identify factors associated with increased risk of suicide attempts.

KEYWORDS

treatment-resistant depression, suicide risk, suicidal attempt, antidepressant therapy, clinical assessment

1 Introduction

All over the world about 300 million people suffer from major depressive disorder (MDD) (1). The World Health Organization (WHO) has identified MDD as the primary cause of disability burden, leading to reduced productivity, heightened healthcare expenses, and, most significantly, hindrances in achieving a fulfilling and enriching life (2). The advent of antidepressant medications has brought about a transformative shift in the treatment of major depression. Unfortunately, however, about 60% of patients do not show an adequate response to first line pharmacological treatments and 30% respond poorly to different trials with various antidepressants (3). The extreme variability in antidepressant treatment response is likely due to neurobiological and environmental factors (4).

Treatment-resistant depression (TRD) is commonly defined by the lack of positive response to at least two types of antidepressant medication, administered at the correct dosage and for a suitable duration (5). However, experts still do not agree on the definition of appropriate dose and appropriate treatment duration (6) and a consensus definition of TRD has not yet been reached. There is also little consensus about the best tools to diagnose TRD and measure its outcomes. These limitations hampered the possibility to compare and summarize study results, thus limiting the possibility to define clinical guidelines (7).

Several studies have reported that TRD could be associated with increased mortality (8, 9), although the sample sizes were small and follow-up times have been relatively short. A Swedish population-based study considering 118,774 individuals diagnosed with depression reported an overall mortality 1.35 times higher among patients with TRD compared to individuals with MDD (10). The increased rate was mainly attributed to external causes, including suicide and accidents.

A systematic review of suicidality in TRD found an overall incidence of completed suicides of 0.47 per 100 patients/year and of attempted suicides of 4.66 per 100 patients/year (95% CI: 3.53-6.23) (11). These are respectively twice and ten times greater than those found in non-resistant patients: 0.22 completed and 0.43 attempted suicides per 100 patients/year (12). In general, several studies pointed out that 30% of patients with TRD had one or more suicide attempts (13). Another recent study (14) dealing with suicidality in the context of major depression found that individuals with TRD had higher suicide rates compared to those who were diagnosed with MDD. Previous studies also highlighted that suicide related mortality in TRD was higher than in MDD even when depressive symptoms were classified as "mild" (15, 16). Furthermore, most authors underlined that the type of suicide attempt, which can be classified in impulsive, frequent or well-planned (17), is almost never reported. This hampers the study of underlying moderators of the high suicide risk observed in TRD. For example, suicide attempts classified as impulsive may indicate a decreased impulse control in TRD patients or an increase of impulsiveness that might be responsive to a different treatment. Another possible interpretation is that TRD patients could be aware of the limited therapeutic options for future improvement, which could lead to a higher proportion of well-planned suicide attempts, compared to non-resistant patients.

Patients with TRD often have comorbid personality disorders and this comorbidity could represent the underlying moderator of frequent suicide attempts in this subset of TRD patients. In a recent review article (18) a significant impact to development of TRD is determined by the co-occurring diagnosis of a personality disorder, as personality disorders in general respond poorly to pharmacological treatment. In particular, borderline personality disorder is characterised by high levels of impulsivity, unstable self-image, feeling of emptiness and extreme mood instability. It has been reported that depressive disorder with comorbid borderline personality disorder (BPD) shows greater treatment resistance and worse functional impairment (19).

Based on these premises, our study aims to identify which socio-demographic and psychopathological data are associated with suicidal attempts in a sample of TRD outpatients.

2 Materials and methods

2.1 Characteristics of the study

We performed a monocentric observational study with a retrospective design including 63 outpatients aged between 19 and 79 years diagnosed with major depression (ICD-10 criteria). Patients were in charge of an Italian mental health outpatient centre. Subjects were labelled as "treatment resistant" based on their psychopharmacological history. We accepted the definition of TRD as the failure of at least two antidepressants prescribed at an appropriate dose and duration (5).

2.2 Assessment instruments

Personal and clinical data were collected during interviews. The content of each clinical interview, as part of the general clinical practice, is reported in the patient's personal clinical record.

We considered the following clinical data: age, gender, occupational and marital status, family history of psychiatric disorders, present and past psychopharmacological therapies, substance and/or alcohol use disorder, presence of comorbid personality disorders, number of suicide attempts, duration of current and past depressive episode.

Psychopathology, with an emphasis on mood symptoms, was assessed by means of the following scales, administered at baseline, as a test battery specific for patients diagnosed with TRD: the Montgomery-Asberg Depression Rating Scale (MADRS) (20), the Hamilton Rating Scale for Anxiety (HAM-A) (21) and Depression (HAM-D) (22), the Brief Psychiatric Rating Scale (BPRS) (23), the Koukopoulos Mixed Depression Rating Scale (KMDRS) (29). The diagnosis of personality disorder was established using the Structured Clinical Interview (SCID II, 24).

2.2.1 Montgomery-Asberg depression rating scale

This clinician-rated scale is designed to measure depression severity and detect changes due to antidepressant treatments. The scale consists of 10 items, scored from 0 (symptom not present or normal) to 6 (severe or continuous presence of the symptom), for a maximum total score of 60. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts (25).

2.2.2 Hamilton rating scale for anxiety

HAM-A is represented by 14 items. Every item individually encompasses a group of symptoms. This scale estimates both psychic anxiety and somatic anxiety including mental agitation and psychological distress; and physical complaints related to anxiety, respectively. The item score ranges from 0 to 4. The higher the score, the more severe the anxiety. The total score ranges from 0 to 56. In this scale, score < 17 indicates mild severity, 18-24 represents mild to moderate severity, and 25-30 refers to moderate to severe condition (26).

2.2.3 Hamilton rating scale for depression

The HAM-D (22) is a clinical interview for the severity of depressive symptoms and one of the most frequently used outcome measures of depression in adults. We used the 17-item form (assessing depressed mood, suicide, insomnia initial - middle – delayed, work and interests, retardation, agitation, anxiety psychic – somatic, somatic gastrointestinal, somatic general – genital, hypochondriasis, insight, loss of weight). Items are scored from 0 to 4 or 0 to 2 depending on the symptom assessed, with higher scores indicating greater symptom pathology (27).

2.2.4 Brief psychiatric rating scale

The Brief Psychiatric Rating Scale (BPRS) was developed to measure changes in a comprehensive set of psychopathologic symptoms present in major psychiatric diagnoses. The items assess the following symptom domains: 1. somatic concern, 2. anxiety, 3. emotional withdrawal, 4. conceptual disorganization, 5. feelings of guilt, 6. tension, 7. mannerisms and posturing, 8. grandiosity, 9. depressive mood, 10. hostility, 11. suspiciousness, 12. hallucinatory behavior, 13. motor retardation, 14. uncooperativeness, 15. unusual thought content, 16. blunted affect, 17. excitement, and 18. disorientation. Each item is rated on a seven-point Likert scale, ranging from “1” (not present) to “7” (extremely severe). Thus, the sum score ranges between 18 and 126, with a higher score indicating more severe symptomatology (28).

2.2.5 Koukopoulos mixed depression rating scale

The Koukopoulos Mixed Depression Rating Scale (KMDRS) is a scale specifically created to assess mixed depression. Koukopoulos and collaborators developed and validated specific criteria such as the presence of a depressive episode plus absence of retardation, talkativeness, psychic agitation on inner tension, description of suffering from spells of weeping, racing or crowded thoughts, irritability or unproved rage, mood lability or marked reactivity, early insomnia. It includes 14 items. Items 1-4, 6, 8-11, 13-14 are evaluated according to a Likert-type scale whose scores range from 0 to 3; items 5, 7 and 12 have a score range from 0 to 6. In each item, 0 indicates the absence of the symptom relating to the single item, while 3 or 6, depending on the item, represents the maximum severity level of the relevant item. Therefore, the scale ranges from a minimum of 0 to a maximum of 51 (29).

2.3 Statistical analysis

First, descriptive analyses of the variables considered were carried out. Chi-square test was performed for the nominal variables. Paired sample t-test or Mann-Whitney were performed (according to the type of distribution) for the quantitative and ordinal variables, according to the presence or absence of suicidal attempts. A two-tailed p value <0.05 was regarded as statistically significant. For the variables in which statistical significance was found, we performed regression analyses with suicidal attempts as outcome variable and the retrieved variables as the independent predictors. Data were analysed using the Jamovi program (Version 2.3, 30).

3 Results

Clinical characteristics of the sample are presented in Table 1. 77.8% of the sample (N=49) were females, and the mean age was 49.2 years (SD 15.9). 47.6% of the sample (N=30) were in treatment with Esketamine. In our sample, 21 (33.3%) patients attempted suicide. 32 patients (50.8%) had a psychiatric comorbidity. Of these, 23 patients (36.5% of the sample) had a personality disorder. Detailed treatment regimens of each patient included in the study are described in Supplementary Table 1.

Univariate analyses are described in Table 2. Substance use, personality disorder, psychiatric comorbidity and higher HAM-D scores were significantly more frequent among suicide attempters. All other variables were not significantly different between the two groups.

We then constructed a regression model using suicidal attempts as the dependent variable and all other variables as independent predictors (Table 3). The resulting model explained 34.8% of the variance (R^2N=0.348, AIC=70.0, p<0.001). The independent predictors were the presence of a psychiatric comorbidity, substance use and HAM-D scores (Table 3). We also performed a regression model with the same variables and gender as a controlling factor (Table 4). In this model, the explained variance was also slightly increased and substance use and HAM-D were the only predictive variables for suicidal attempts (R^2N=0.354, AIC 71.7 p<0.001).

4 Discussion

Our research focused on identifying the risk factors associated with suicide attempts among individuals diagnosed with

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TABLE 1 General characteristics of the sample.

Socio-demographic and psychopathological variables features of the sample (N=63)	
Gender	49 F (77.8%), 14 M (22.2%)
Age (Mean, SD, range)	49.2 (15.9), 19-79
Marital status	single 31 (49.2%) married/in a relationship 32 (50.8%)
Children	Yes 34 (56%) No 29 (46%)
Education	Primary school 4 (6.3%) Secondary school 20 (31.7%) High school 31 (49.2%), University degree 8 (12.7%)
Employment status	Unemployed 22 (34.9%) Employed 26 (41.3%) Student 5 (7.9%) Retired 10 (15.9%)
Familiar history for mental disorders	Yes 32 (50.8%) No 31 (49.2%)
Age of first depressive episode (Mean, SD, range)	34.2 (17.2) 11-79
Psychiatric Comorbidities	Yes 34 (54%) No 29 (46%)
Psychiatric Comorbidities (ICD-10 or SCID-II criteria)	None 29 (46%) Personality disorder 23 (36.5%): borderline 10, narcissistic 2, histrionic 1, dependent 2, obsessive-compulsive 1, NOS 7 Eating disorder 3 (4.8%) Bipolar disorder 3 (4.8%) PTSD 1(1.6%) Autism spectrum disorder 1 (1.6%) Generalised anxiety disorder 1 (1.6%) Cyclothymic disorder (1.6%) OCD 1 (1.6%)
Substance use	Yes 27 (42.9%) No 36 (57.1%)
Suicide attempts	Yes 21 (33.3%) No 42 (66.7%)
Main antidepressant prescribed	Sertraline 7 (11.1%) Venlafaxine 6 (9.5%) Vortioxetine 6 (9.5%) Trazodone 3 (4.8%) Duloxetine 2 (3.2%) Fluoxetine 2 (3.2%) Escitalopram 2 (3.2%) Paroxetine 2 (3.2%) Mirtazapine 1 (1.6%) Citalopram 1 (1.6%) Clomipramine 1 (1.6%) Esketamine 30 (47.6%)
Concomitant therapies: antipsychotics	Yes 44 (69.8%) No 19 (27.3%)
Concomitant therapies: mood stabilisers	Yes 35 (55.6%) No 28 (44.4%)
MADRS (baseline)	27.0 (13.7)
HAM-A (baseline)	25.2 (15.9)
HAM-D (baseline)	22.6 (17.6)
BPRS (baseline)	47.3 (16.7)
KMDRS (baseline)	13.6 (6.75)

Treatment-Resistant Depression (TRD) who were receiving care at an outpatient mental health facility in Italy. We observed that substance use was associated with a higher rate of suicide attempts. Additionally, psychiatric comorbidities, namely borderline personality disorder, were also associated with a higher rate of suicide attempts.

Notably, about 30% of individuals with TRD make suicide attempts at least once in their lifetime, as reported by several studies, twice as much as in non-resistant depression (31, 32). This datum is in line with the percentage registered in our sample (33%, n=21). This underscores the need of vigilant clinical monitoring of TRD patients, considering that a close psychiatric follow-up following a suicide attempt has demonstrated an antisuicidal protective effect (33).

In our sample, 77.8% were female patients. This prevalence is higher than in previous studies, but in line with generally higher prevalence of TRD in females (34), as well as in MDD in general (35, 36). For example, Herlein and colleagues identified a 62.3% prevalence of females in their sample, while another study recorded a female prevalence rate of 52.6% (37). In our sample, patients who have attempted suicide are on average younger (44.2 vs 51.6 years old), as previous research has already outlined (38).

The association between substance use and suicidal attempts that we observed is in line with previous research: one nested case-control study (39) based on a Swedish nation-wide register of TRD patients observed a correlation of substance use disorders, personality disorders, and anxiety disorders with attempted suicides. Our hypothesis is that substance use disorder may be a proxy of impulsiveness which could result in suicide attempts. Our findings emphasise the importance of implementing primary and secondary prevention strategies regarding psychoactive substance use, as well as to enhance cooperation between general psychiatry and addiction mental health services (40).

In our study, psychiatric comorbidities have been associated with suicide attempts. In a recent study, patients with TRD, compared to patients with MDD have a higher rate of psychiatric comorbidities, a longer duration of depressive episodes and three times the number of inpatient bed-days (41). These findings stress the importance of early identification of patients with MDD and high risk of TRD, in order to target health care efforts (42). Taking into account the HAM-D rating scale, we found that higher scores (i.e. worse depressive symptomatology) were associated with suicide attempts. This datum has been already highlighted by previous studies (43, 44). In the same way, it has been demonstrated that patients with TRD have on average higher HAM-D scores than

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TABLE 2 Univariate analysis.

Variable		Suicidal Attempt (No) N=42	Suicidal Attempt (Yes) N=21	P	Chi-square/U di Mann-Whitney
Gender	F	31	18	0.284	1.15*
	M	11	3		
Marital status	Single	21	10	0.86	0.031*
	Married/in a relationship	21	11		
Children	Yes	22	12	0.721	0.128*
	No	20	9		
Age (mean, SD, range)		51.6 (15.3) range 22-79	44.2 (16.1) range 16-72	0.092	325^
Education	Primary School	4	0	0.059	7.43*
	Secondary school	12	8		
	High school	18	13		
	Degree	8	0		
Occupation	Unemployed	15	7	0.319	3.52*
	Employed	15	11		
	Retired	9	1		
	Student	3	2		
Substance use	Yes	14	13	**0.031**	**4.67***
	No	28	8		
Psychiatric comorbidity	Yes	19	15	**0.049**	**3.87***
	No	23	6		
Personality disorder	Yes	11	12	**0.016**	**5.79***
	No	31	9		
Personality disorder (type)	Borderline	4	6	0.563	4.72*
	Narcissistic	1	1		
	Histrionic	1	0		
	Dependent	1	1		
	Obsessive-compulsive	1	0		
	NOS	3	4		
Previous major depressive episodes (N, SD)		4.22 (4.72)	4.05 (4.40)	0.897	0.130^
Family history for mental disorders	Yes	21	11	0.931	0.008*
	No	20	10		
Concomitant therapies: antipsychotics	Yes	29	15	0.846	0.038*
	No	13	6		
Concomitant therapies: mood stabilisers	Yes	22	13	0.473	0.514*
	No	20	8		
HAM-A		23.0 (14.6)	29.8 (17.9)	0.111	-1.162^
HAM-D		18.7 (13.4)	30.4 (22.4)	**0.012**	**-2.59^**

(Continued)

TABLE 2 Continued

Variable	Suicidal Attempt (No) N=42	Suicidal Attempt (Yes) N=21	P	Chi-square/U di Mann-Whitney
MADRS	25.7 (12.4)	29.6 (15.9)	0.289	-1.07^
BPRS	46.4 (16.8)	48.9 (17.3)	0.579	-0.558^
KMDRS	14.4 (6.67)	12.3 (6.86)	0.249	1.16^

*chi-square test; ^t- test or Mann-Whitney test. Bold characters indicate statistically significant values (p<0.05).

patients with major depression, as well as a longer duration of illness (45).

Furthermore, we found an association between personality disorders and suicidal attempts. This finding has been already outlined by Reutfors et al. (39), who found as independent risk factors for suicidal attempts a history of suicide attempts, substance abuse, personality disorders, and somatic comorbidity. This finding implies a careful assessment of personality disorders through evidence-based instruments, as well as an adequate treatment with a targeted psychotherapy (46, 47). As far as our sample is concerned, the most represented among personality disorders was borderline personality disorder (BPD, n=10, 15.9% of the total sample and 43.5% of personality disorders, respectively). Depressive disorder and borderline personality disorder are often comorbid. The high impulsivity and the poor mentalizing skills that are core feature of BPD often lead to self-injurious behaviours and suicide attempts. As well as TRD, borderline personality disorder responds poorly to conventional pharmacological treatments. However, we didn't find a specifical association between BPD and suicidal attempts, since patients with BPD were nearly equally distributed in the two categories. This may also be related to the relatively small sample size of our study, and study with a bigger sample could better define this association.

The topic of suicidality among patients with a primary diagnosis of treatment-resistant depression necessitates meticulous investigation, given the heightened prevalence of suicidal thoughts, attempts, and completed suicides in individuals with TRD as opposed to those with Major Depressive Disorder (MDD) (48). TRD represents a clinical challenge in psychiatry, since it is associated with a loss of quality of life, a lower productivity, more hospitalizations and higher healthcare costs (49, 50).

Some pharmacological therapies have shown promising results in treating TRD. For example, esketamine, the levo enantiomer of ketamine, has been approved for the treatment of TRD and can be administered as a nasal spray. This drug has proven generally safe and well tolerated and has provided meaningful and rapid impact on reducing depressive symptoms and suicide ideation (51). A possible beneficial effect on suicidal behaviour in TRD patients has also been suggested for lithium. In a meta-analysis by Cipriani and colleagues (52) authors found that lithium helped reducing suicide risk in patients with mood disorders. It was hypothesised that it may exert its antisuicidal effects by reducing relapse of mood disorder and also by decreasing aggression and possibly impulsivity, which might be another mechanism mediating the antisuicidal effect. Regarding TRD, evidence about lithium's antisuicidal effects is still poor.

As far as non-pharmacological treatments are concerned, various studies have focused on Repetitive Transcranial Magnetic Stimulation (rTMS) that is a non-invasive brain stimulation technique used to treat mood disorders, including TRD, but also other mental illnesses such as obsessive-compulsive disorder (OCD) and borderline personality disorder (BPD). A recent meta-analysis by Chen et al. (53) found that rTMS significantly reduced suicidal ideation and improved depressive symptoms. Focusing on suicidal ideation, this was reduced after rTMS in patients with major depressive disorder but not in those with TRD.

Our study has several limitations. First of all, the sample size was quite small, thus limiting the generalizability of the results. In this regard, future studies with larger sample sizes and a prospective design could provide a more precise insight into our findings. Moreover, our study did not collect other relevant parameters related to suicidal attempts, such as the number of hospitalizations and the modality of attempted suicide, which is known to be a relevant diagnostic and prognostic factor (54). Secondly, we did not use a specific appropriate assessment instrument for suicidal ideation (48, 55). These limitations are mainly due to the research design which was carried out at a public mental healthcare facility, in a "real world" setting. Therefore, assessments were not specifically designed to investigate specific psychopathological domains. A larger sample size and a more careful assessment of these features could lead to more accurate results. Lastly, we did not perform a psychopathological assessment at follow-up with the rating scales

TABLE 3 Predictors of suicidal attempts-model 1.

Predictor	SE	Z	P	OR	95% CI	
Psychiatric comorbidity	1.332	**2**	**0.046**	3.788	1.026	13.994
Substance use	0.021	**2.72**	**0.007**	6.779	1.705	13.994
HAM-D	0.0212	**2.62**	**0.009**	1.057	1.014	1.102

chi-square test; ^t- test or Mann-Whitney test. Bold characters indicate statistically significant values (p<0.05).

TABLE 4 Predictors of suicidal attempts-model 2.

Predictor	SE	Z	P	OR	95% CI	
Psychiatric comorbidity	0.678	1.847	0.065	3.495	0.926	13.188
Substance use	0.720	**2.514**	**0.012**	6.114	1.49	25.088
HAM-D	0.0213	**2.631**	**0.009**	1.057	1.014	1.103
Gender	0.933	-0.571	0.568	0.587	0.094	3.654

Bold characters indicate statistically significant values ($p<0.05$).

performed at baseline. Such finding would have allowed us to highlight symptomatic changes at follow-up and any correlations with suicidal behaviors. In future research, it could be interesting, as we found an association between HAM-D scores and suicide attempts, to analyze separately every single item of this scale with respect to suicidality in a more dimensional approach. Indeed, the National Institute of Mental Health Collaborative Depression study highlighted three group of symptoms (1, anhedonia, hopelessness; 2, anxiety, agitation, panic; 3, aggression, impulsivity) as more predictive of suicide than either diagnoses or syndrome (56).

Our study supports the importance of performing a careful clinical evaluation of patients with treatment-resistant depression and of raising awareness among clinicians to prevent pseudo-resistance and to identify factors associated with increased severity of symptoms. In this regard, it would be useful to insert standardised evaluation such as the HAM-D scale (which is overall not time-consuming) in clinical practice. Additionally, assessment of personality disorders as well as potential dysfunctional personality traits deserve a place in clinical practice (57). On the other hand, clinicians should strictly adhere to pharmacological guidelines, following the correct doses of each medication and the adequate duration of the treatment in order to identify TRD correctly and perform a differential diagnosis between TRD and refractory depression, that is a form of depressive disorder that has not shown adequate response to any treatment (58). For a more personalised and targeted therapy, pharmacogenomic tests hold great promise for future routine clinical practice but now they are mostly limited to specialised services (59). In conclusion, clinical practice should incorporate personalized medicine principles in order to choose more effective pharmacological and psychosocial therapeutic strategies.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The dataset includes privacy-related information. Requests to access these datasets should be directed to Filippo Besana; filippo.besana01@universitadipavia.it.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

SC: Formal analysis, Writing – original draft, Writing – review & editing, Data curation, Software. FB: Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization. GM: Data curation, Writing – original draft, Writing – review & editing. FM: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. VA: Data curation, Writing – original draft, Writing – review & editing. PP: Supervision, Visualization, Writing – original draft, Writing – review & editing. NB: Formal analysis, Supervision, Writing – original draft, Writing – review & editing. MO: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1371139/full#supplementary-material

References

1. Ferrari AJ, Charlson FJ, Norman RE, Flaxman AD, Patten SB, Vos T, et al. The epidemiological modelling of major depressive disorder: application for the Global Burden of Disease Study 2010. *PloS One*. (2013) 8:e69637. doi: 10.1371/journal.pone.0069637

2. Patel V, Chisholm D, Parikh R, Charlson FJ, Degenhardt L, Dua T, et al. Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *Lancet*. (2016) 387:1672–85. doi: 10.4103/0971-9962.193189

3. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence*. (2012) 6:369–88. doi: 10.2147/ppa.s29716

4. Coplan JD, Gopinath S, Abdallah CG, Berry BR. A neurobiological hypothesis of treatment-resistant depression - mechanisms for selective serotonin reuptake inhibitor non-efficacy. *Front Behav Neurosci*. (2014) 8:189. doi: 10.3389/fnbeh.2014.00189

5. McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord*. (2014) 156:1–7. doi: 10.1016/j.jad.2013.10.043

6. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, et al. Defining treatment-resistant depression. *Depress Anxiety*. (2020) 37:134–45. doi: 10.1002/da.22968

7. Li CT. Overview of treatment-resistant depression. *Prog Brain Res*. (2023) 278:1–23. doi: 10.1016/bs.pbr.2023.03.007

8. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry*. (2009) 166:410–7. doi: 10.1176/appi.ajp.2008.08081239

9. Scherrer JF, Chrusciel T, Garfield LD, Freedland KE, Carney RM, Hauptman PJ, et al. Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. *Br J Psychiatry*. (2012) 200:137–42. doi: 10.1192/bjp.bp.111.096479

10. Reutfors J, Andersson TM, Brenner P, Brandt L, DiBernardo A, Li G, et al. Mortality in treatment-resistant unipolar depression: A register-based cohort study in Sweden. *J Affect Disord*. (2018) 238:674–9. doi: 10.1016/j.jad.2018.06.030

11. Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. *J Affect Disord*. (2018) 235:362–7. doi: 10.1016/j.jad.2018.04.016

12. Braun C, Bschor T, Franklin J, Baethge C. Suicides and suicide attempts during long-term treatment with antidepressants: A meta-analysis of 29 placebo-controlled studies including 6,934 patients with major depressive disorder. *Psychother Psychosom*. (2016) 85:171–9. doi: 10.1159/000442293

13. Orsolini L, Latini R, Pompili M, Serafini G, Volpe U, Vellante F, et al. Understanding the complex of suicide in depression: from research to clinics. *Psychiatry Investig*. (2020) 17:207–21. doi: 10.30773/pi.2019.0171

14. Kern DM, Canuso CM, Daly E, Johnson JC, Fu DJ, Doherty T, et al. Suicide-specific mortality among patients with treatment-resistant major depressive disorder, major depressive disorder with prior suicidal ideation or suicide attempts, or major depressive disorder alone. *Brain Behav*. (2023) 13. doi: 10.1002/brb3.3171

15. Dold M, Bartova L, Fugger G, Kautzky A, Souery D, Mendlewicz J, et al. Major depression and the degree of suicidality: results of the European Group for the Study of Resistant Depression (GSRD). *Int J Neuropsychopharmacol*. (2018) 21:539–49. doi: 10.1093/ijnp/pyy009

16. Li G, Fife D, Wang G, Sheehan JJ, Bodén R, Brandt L, et al. All-cause mortality in patients with treatment-resistant depression: a cohort study in the US population. *Ann Gen Psychiatry*. (2019) 18:23. doi: 10.1186/s12991-019-0248-0

17. Lopez-Castroman J, Nogue E, Guillaume S, Picot MC, Courtet P. Clustering suicide attempters: impulsive-ambivalent, well-planned, or frequent. *J Clin Psychiatry*. (2016) 77:e711–8. doi: 10.4088/JCP.15m09882

18. Young M. Treatment-resistant depression: the importance of identifying and treating co-occurring personality disorders. *Psychiatr Clin North Am*. (2018) 41:249–61. doi: 10.1016/j.psc.2018.01.003

19. Bellino S, Patria L, Paradiso E, Di Lorenzo R, Zanon C, Zizza M, et al. Major depression in patients with borderline personality disorder: a clinical investigation. *Can J Psychiatry*. (2005) 50:234–8. doi: 10.1177/070674370505000407

20. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. (1979) 134:382–9. doi: 10.1192/bjp.134.4.382

21. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x

22. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

23. Overall JE. The Brief Psychiatric Rating Scale in psychopharmacology research. In: Pichot P, Olivier-Martin R, editors. *Psychological measurements in psychopharmacology*. Basel, Switzerland: S. Karger (1974). doi: 10.1159/000395069

24. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. *Structured clinical interview for DSM-IV axis II personality disorders, (SCID-II)*. Washington, DC: American Psychiatric Association (1997).

25. Hudgens S, Floden L, Blackowicz M, Jamieson C, Popova V, Fedgchin M, et al. Meaningful change in depression symptoms assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Åsberg Depression Rating Scale (MADRS) among patients with treatment resistant depression in two, randomized, double-blind, active-controlled trials of esketamine nasal spray combined with a new oral antidepressant. *Affect Disord*. (2021) 281:767–75. doi: 10.1016/j.jad.2020.11.066

26. Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Efficacy and safety of Ashwagandha (Withania somnifera) root extract in insomnia and anxiety: A double-blind, randomized, placebo-controlled study. *Cureus*. (2019) 11. doi: 10.7759/cureus.5797

27. Imboden C, Gerber M, Beck J, Holsboer-Trachsler E, Pühse U, Hatzinger MJ. Aerobic exercise or stretching as add-on to inpatient treatment of depression: similar antidepressant effects on depressive symptoms and larger effects on working memory for aerobic exercise alone. *Affect Disord*. (2020) 276:866–76. doi: 10.1016/j.jad.2020.07.052

28. Hofmann AB, Schmid HM, Jabat M, Brackmann N, Noboa V, Bobes J, et al. Utility and validity of the Brief Psychiatric Rating Scale (BPRS) as a transdiagnostic scale. *Psychiatry Res*. (2022) 314:114659. doi: 10.1016/j.psychres.2022.114659

29. Koukopoulos AE, De Chiara L, Simonetti A, Kotzalidis GD, Janiri D, Manfredi G, et al. The Koukopoulos mixed depression rating scale (KMDRS) and the assessment of mixed symptoms during the perinatal period. *J Affect Disord*. (2021) 281:980–8. doi: 10.1016/j.jad.2020.08.080

30. The jamovi project. jamovi. (Version 2.3) (2022). Available online at: https://www.jamovi.org.

31. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depressionJ. *Clin Psychiatry*. (2006) 67:688–95. doi: 10.4088/JCP.v67n0501

32. Hantouche E, Angst J, Azorin JM. Explained factors of suicide attempts in major depression. *J Affect Disord*. (2010) 127:305–8. doi: 10.1016/j.jad.2010.04.032

33. Bostwick JM, Pabbati C, Geske JR, McKean AJ. Suicide attempt as a risk factor for completed suicide: even more lethal than we knew. *Am J Psychiatry*. (2016) 173:1094–100. doi: 10.1176/appi.ajp.2016.15070854

34. Liu X, Mukai Y, Furtek CI, Bortnichak EA, Liaw KL, Zhong W. Epidemiology of treatment-resistant depression in the United States. *J Clin Psychiatry*. (2021) 83:21m13964. doi: 10.4088/JCP.21m13964

35. Albert PR. Why is depression more prevalent in women? *J Psychiatry Neurosci*. (2015) 40:219–21. doi: 10.1503/jpn.150205

36. Picco L, Subramaniam M, Abdin E, Vaingankar JA, Chong SA. Gender differences in major depressive disorder: findings from the Singapore Mental Health Study. *Singapore Med J*. (2017) 58:649–55. doi: 10.11622/smedj.2016144

37. Martinotti G, Vita A, Fagiolini A, Maina G, Bertolino A, Dell'Osso B, et al. Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. (2022) 319:646–54. doi: 10.1016/j.jad.2022.09.043

38. Buerke M, Galfalvy H, Keilp JG, Sheftall AH, Burke AK, Bridge JA, et al. Age effects on clinical and neurocognitive risk factors for suicide attempt in depression - Findings from the AFSP lifespan study. *J Affect Disord*. (2021) 295:123–30. doi: 10.1016/j.jad.2021.08.014

39. Reutfors J, Andersson TM, Tanskanen A, DiBernardo A, Li G, Brandt L, et al. Risk factors for suicide and suicide attempts among patients with treatment-resistant depression: nested case-control study. *Arch Suicide Res*. (2021) 25:424–38. doi: 10.1080/13811118.2019.1691692

40. McGinty EE, Presskreischer R, Han H, Barry CL. Psychological distress and loneliness reported by US adults in 2018 and April 2020. *JAMA*. (2020) 324:93–4. doi: 10.1001/jama.2020.9740

41. Lundberg J, Cars T, Löövˇ SÅ, Söderling J, Sundström J, Tiihonen J, et al. Association of treatment-resistant depression with patient outcomes and health care resource utilization in a population-wide study. *JAMA Psychiatry*. (2023) 80:167–75. doi: 10.1001/jamapsychiatry.2022.3860

42. Ekman M, Granström O, Omérov S, Jacob J, Landén M. The societal cost of depression: evidence from 10,000 Swedish patients in psychiatric care. *J Affect Disord*. (2013) 150:790–7. doi: 10.1016/j.jad.2013.03.003

43. Shen Y, Wu F, Zhou Y, Ma Y, Huang X, Ning Y, et al. Association of thyroid dysfunction with suicide attempts in first-episode and drug naïve patients with major depressive disorder. *J Affect Disord*. (2019) 259:180–5. doi: 10.1016/j.jad.2019.08.067

44. Ma YJ, Zhou YJ, Wang DF, Li Y, Wang DM, Liu TQ, et al. Association of lipid profile and suicide attempts in a large sample of first episode drug-naive patients with major depressive disorder. *Front Psychiatry*. (2020) 11:543632. doi: 10.3389/fpsyt.2020.543632

45. Buoli M, Capuzzi E, Caldiroli A, Ceresa A, Esposito CM, Posio C, et al. Clinical and biological factors are associated with treatment-resistant depression. *Behav Sci (Basel)*. (2022) 12:34. doi: 10.3390/bs12020034

46. Choi-Kain LW, Finch EF, Masland SR, Jenkins JA, Unruh BT. What works in the treatment of borderline personality disorder. *Curr Behav Neurosci Rep*. (2017) 4:21–30. doi: 10.1007/s40473-017-0103-z

47. Kramer U, Eubanks CF, Bertsch K, Herpertz SC, McMain S, Mehlum L, et al. Future challenges in psychotherapy research for personality disorders. *Curr Psychiatry Rep*. (2022) 24(11):613–22. doi: 10.1007/s11920-022-01379-4

48. Corral R, Alessandria H, Agudelo Baena LM, Ferro E, Duque X, Quarantini L, et al. Suicidality and quality of life in treatment-resistant depression patients in Latin America: secondary interim analysis of the TRAL study. *Front Psychiatry*. (2022) 13:812938. doi: 10.3389/fpsyt.2022.812938

49. Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, Burton WN, et al. Cost burden of treatment resistance in patients with depression. *Am J Manag Care*. (2010) 16(5):370–7.

50. Olchanski N, McInnis Myers M, Halseth M, Cyr PL, Bockstedt L, Goss TF, et al. The economic burden of treatment-resistant depression. *Clin Ther*. (2013) 35(4):512–22. doi: 10.1016/j.clinthera.2012.09.001

51. Hong JP, Malek AZA, Li CT, Paik JW, Sulaiman AH, Madriaga G, et al. Efficacy and safety of esketamine nasal spray in addition to standard of care in patients with major depressive disorder who have active suicidal ideation with intent: A subgroup analysis of the Asian cohort of ASPIRE I (a randomized, double-blind, placebo-controlled study). *Asia Pac Psychiatry*. (2023) 15:e12548. doi: 10.1111/appy.12548

52. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. (2013) 27:f3646. doi: 10.1136/bmj.f3646

53. Chen GW, Hsu TW, Ching PY, Pan CC, Chou PH, Chu CS. Efficacy and tolerability of repetitive transcranial magnetic stimulation on suicidal ideation: A systemic review and meta-analysis. *Front Psychiatry*. (2022) 13:884390. doi: 10.3389/fpsyt.2022.884390

54. Kim SH, Kim HJ, Oh SH, Cha K. Analysis of attempted suicide episodes presenting to the emergency department: comparison of young, middle aged and older people. *Int J Ment Health Syst*. (2020) 14:46. doi: 10.1186/s13033-020-00378-3

55. Salvi J. Calculated decisions: columbia-suicide severity rating scale (C-SSRS). *Emerg Med Pract*. (2019) 21:CD3–4.

56. Fawcett J, Busch KA, Jacobs D, Kravitz HM, Fogg L. Suicide: a four-pathway clinical-biochemical model. *Ann N Y Acad Sci*. (1997) 836:288–301. doi: 10.1111/j.1749-6632.1997.tb52366.x

57. Westen D, Muderrisoglu S. Assessing personality disorders using a systematic clinical interview: evaluation of an alternative to structured interviews. *J Pers Disord*. (2003) 17:351–69. doi: 10.1521/pedi.17.4.351.23967

58. Oliveira-Maia AJ, Bobrowska A, Constant E, Ito T, Kambarov Y, Luedke H, et al. Treatment-resistant depression in real-world clinical practice: A systematic literature review of data from 2012 to 2022. *Adv Ther*. (2024) 41:34–64. doi: 10.1007/s12325-023-02700-0

59. van Schaik RHN, Müller DJ, Serretti A, Ingelman-Sundberg M. Pharmacogenetics in psychiatry: an update on clinical usability. *Front Pharmacol*. (2020) 11:575540. doi: 10.3389/fphar.2020.575540

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Development of a multivariate prediction model for antidepressant resistant depression using reward-related predictors

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Introduction: Individuals with depression who do not respond to two or more courses of serotonergic antidepressants tend to have greater deficits in reward processing and greater internalizing symptoms, yet there is no validated self-report method to determine the likelihood of treatment resistance based on these symptom dimensions.

Methods: This online case-control study leverages machine learning techniques to identify differences in self-reported anhedonia and internalizing symptom profiles of antidepressant non-responders compared to responders and healthy controls, as an initial proof-of-concept for relating these indicators to medication responsiveness. Random forest classifiers were used to identify a subset from a set of 24 reward predictors that distinguished among serotonergic medication resistant, non-resistant, and non-depressed individuals recruited online (N = 393). Feature selection was implemented to refine model prediction and improve interpretability.

Results: Accuracies for full predictor models ranged from .54 to .71, while feature selected models retained 3-5 predictors and generated accuracies of .42 to .70. Several models performed significantly above chance. Sensitivity for non-responders was greatest after feature selection when compared to only responders, reaching .82 with 3 predictors. The predictors retained from feature selection were then explored using factor analysis at the item level and cluster analysis of the full data to determine empirically driven data structures.

Discussion: Non-responders displayed 3 distinct symptom profiles along internalizing dimensions of anxiety, anhedonia, motivation, and cognitive function. Results should be replicated in a prospective cohort sample for predictive validity; however, this study demonstrates validity for using a limited anhedonia and internalizing self-report instrument for distinguishing between antidepressant resistant and responsive depression profiles.

KEYWORDS

depression, treatment-resistant, antidepressants, SSRI, anhedonia, internalizing, reward, machine learning

Introduction

Major Depressive Disorder (MDD) is a heterogeneous disorder with widespread effects (1). Serotonergic antidepressants (e.g. selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors; SSRIs and SNRIs) are standard first-line treatment for MDD, but have high non-response rates and a 6-8 week latency for symptom reduction (2, 3). There is currently no standard set of self-report items for prediction of response likelihood to SSRI/SNRIs in a clinical setting. Patients are often asked to complete extensive questionnaires and multiple self-report scales upon intake, which increases treatment and diagnostic burden. Therefore, we aim to identify a limited set of self-report items that can be administered with minimal burden to clinicians and patients for identifying pre-morbid treatment resistance to serotonergic antidepressants. In this study, we provide a proof-of-concept by first identifying a set of scales related to reward processing that differentiate between individuals with depression (MDD), antidepressant-resistant depression (ARD), and non-depressed adults. We intend to use this set of items in future research to determine their predictive validity for ARD.

Anhedonia is a symptom frequently present in individuals with depression following the administration of serotonergic antidepressants, and presence of anhedonia at pre-treatment predicts poorer response to these medications (4–11). Anhedonia arises from impairments in reward processing (12–14). It is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (15) as low interest in and hedonic pleasure for reward. Alternative depression treatments such as esketamine and neuromodulatory therapies are used after non-response to multiple rounds of serotonergic medication has been established, and these treatments often specifically target anhedonia via the dopaminergic reward system (16–19). There is strong empirical evidence that traditional antidepressants such as SSRI/SNRIs can induce emotional blunting and apathy in individuals with depression (20–23). Fatigue and lack of concentration have also been reported as persistent residual symptoms post-treatment (24, 25), which can both be mechanistically linked to reward processing as they arise due to dopamine and norepinephrine deficiencies (26–28). Anhedonia in MDD is multifaceted (12), leading to a need for identifying the combination of anhedonia subcomponents with the greatest validity for discriminating between non-resistant MDD and ARD. We aim to balance discriminant validity with clinical utility by identifying a set of items that are practical to administer.

The National Institute of Mental Health has incorporated research delineating the function of reward processing into a framework of transdiagnostic neurobiological and behavioral mechanisms. This Research Domain Criteria framework posits that the domain of Positive Valence Systems is composed of reward responsiveness, reward valuation, and reward learning. These also map onto neural models of anticipatory vs. consummatory anhedonia proposed and validated by Berridge (29) such that anticipation maps onto "wanting" and consummation maps onto "liking". Berridge found these processes to be governed by disparate brain networks and to operate somewhat independently of each other (29–31). Recent studies have presented a more detailed chain of neural signaling in reward processing: (1) incentive salience (internally cued desire; wanting), (2) anticipation (readiness for reward), (3) motivation (effort to obtain the reward), (4) hedonic response (consummation of reward, or liking), and (5) feedback integration (learning) (32–34). Additionally, personality traits such as extraversion have been shown to modulate sensitivity to reward (35).

In line with recent efforts to define the dimensional structure underlying psychopathology (36–38), we recognize anhedonia as part of a broader transdiagnostic endophenotype of internalizing symptomatology (39, 40). An internalizing spectrum of psychopathology has been well established and includes depressive disorders, general anxiety disorder, social anxiety disorder, and panic disorder, all of which are characterized by high levels of mood and cognitive disturbances (41–43). A common internalizing mechanism may help explain high rates of comorbidity between these disorders. Empirical research converges with a model of internalizing factors consisting of low positive affect in the form of loss of motivation and interest (anhedonia) and high negative affect in the form of anxious arousal and apprehension (39, 40). Thus, comprehensive measurement is needed to gain information about the type(s) of anhedonia and related impairments present in ARD.

To advance research, it is necessary to first identify where the greatest differences exist in individuals with ARD versus antidepressant responsive MDD, and how these vary from more general differences between individuals with and without depression. Machine learning methods have been increasingly used for complex biological models with limited sample sizes and have demonstrated utility in finding patterns, especially within high dimensional data (44–48). For a detailed account of the advantages to using machine learning methods over traditional regression, please see Supplementary Materials.

In the current paper, we rely on Random Forests, a non-parametric statistical technique. Non-parametric statistical techniques make no assumptions about the underlying distribution of the data, and similarly, non-parametric machine learning models do not assume a pre-specified form. Non-parametric classification algorithms have been used in large naturalistic MDD studies such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), Combining Medications to Enhance Depression Outcomes (CO-MED), Genome-based Therapeutic Drugs for Depression (GENDEP) and the German Research Network on Depression (GRND) databases to predict treatment outcomes using sets of clinical and sociodemographic predictors, with reported accuracy rates ranging between.5 to.8 (44, 49–53). However, criticisms of using such models for treatment prognosis include their complexity, requiring comprehensive symptom and treatment data on each patient. In addition, they have a "black box" methodology where the process of prediction is either hidden or uninterpretable. Thus, machine learning techniques have been leveraged at the basic and translational research phases but require more simplification and transparency to be useful in clinical application. To date there has been limited work on using findings generated from basic and translational research to develop a practical instrument for predicting antidepressant medication prognosis.

We will use supervised machine learning methods to differentiate individuals who are ARD and medication responsive using a limited but comprehensive set of phenomenological predictors related to reward. We aim to provide an initial proof-of-concept for a practical self-report instrument to identify individuals with ARD based on a limited set of anhedonia and related items, which can then be refined and validated longitudinally. Additionally, we will use unsupervised machine learning to explore empirical patterns in the subset of significant predictors. To be useful in clinical practice, this proto-instrument will need to distinguish individuals with ARD from a population of potential patients who either (1) have depression or (2) do not have depression. Therefore, unlike previous machine learning studies that draw only from a population of patients with depression, this study will assess 3 groups of individuals: ARD, non-resistant depression (MDD), and non-depressed healthy controls (HC). In line with recent work using a wider range of clinical and sociodemographic variables for predicting treatment-resistance (52), it is hypothesized that we will be able to identify a set of measures and items to discriminate between groups at clinically meaningful levels (44, 54).

Materials and methods

Participants

The methods for this study, including sample size and analyses, were registered prior to viewing any collected data (55). Participants (N = 399, $female_{prop}$ = .49) aged 18 or older were recruited using Prolific and ResearchMatch from a population pool within the United States between the months of April-December 2022. The number of participants deviated from the preregistered sample size of N = 600, although are achieved sample size is adequate for Random Forests. Recent evidence suggests a rule of thumb of 5 - 10 events per predictor variable, with the upper end recommended for samples with 30 events or fewer (56, 57). In this study, the event of interest was presence of ARD (N = 164), and classification models used up to 24 predictors, thus falling within in the acceptable range.

ResearchMatch is a national health volunteer registry funded by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program. ResearchMatch volunteers have consented to be contacted by researchers about health studies for which they may be eligible. Prolific is an online research platform with behavioral and diagnostic filtering capabilities that helps researchers post studies and recruit from a general population. Our sample consisted of a similar proportion of participants recruited from Prolific (51%) and ResearchMatch (49%). The proportion of individuals within each group by platform is provided in Supplementary Materials (S0).

Inclusion criteria were adults fluent in English, who have a self-identified diagnosis of unipolar depression with either symptom improvement from at least 1 full course (> 4 weeks) of SSRI/SNRI medication) or non-improvement with at least 2 full courses of SSRI/SNRIs. Clinicians frequently use subjective report when defining depression treatment response (58). This study's use of self-classification aligns with previous research methodology for identifying treatment resistance and uses the definition of inadequate response published by the US Food and Drug Administration (59) and European Medicines Agency (60). Clinical records were not obtained as we tried to minimize risk to participants of identification by collecting anonymous data. We additionally recruited a non-depressed control sample who have never been diagnosed with depression and scored ≤ 3 on the Patient Health Questionnaire-2 (PHQ-2) (61). *Exclusion criteria* were individuals with bipolar depression, psychosis, ADHD, and any personality disorder, to minimize confounding variables due to different treatments for these disorders. We also excluded individuals regularly taking bupropion, stimulant medications, pramipexole, or L-dopa medication due to their direct effects on the dopamine reward system. However, we did not exclude individuals on the basis of substances of abuse.

We recruited participants who were not treatment naïve so they could identify whether antidepressants worked for them. This was a cross sectional study aimed at investigating the differences in reward processing for individuals with and without ARD, and determining the predictive validity of these reward measures was out of the scope of this study. To confirm that minimal or no effects of serotonergic medication on anhedonia existed in our sample, we conducted moderation analyses for reported presence of medication on the effect of group on each anhedonia metric with the intent to exclude measures moderated by presence of medication.

Screening for individuals recruited from ResearchMatch was implemented online via the REDCap (Research Electronic Data Capture; 62, 63) platform hosted at the University of Southern California. On Prolific, screening was implemented via a study where participants were compensated based on average time spent. Screening measures included an author-constructed questionnaire of depression diagnosis and treatment history for recruitment of the 2 depression groups and the PHQ-2 (61) for recruitment of the healthy control group. Screening was also used to balance ARD vs. MDD groups. Review and approval for this study and all procedures was obtained from the institutional review board at the University of Southern California.

Procedure

Participants were administered a battery of validated scales measuring depression, reward anticipation and hedonic experience, motivation, and personality via the online survey platform "Psytoolkit" (64, 65). This platform does not allow surveys to be saved and returned to at a later time. Survey items were grouped and displayed across 3 pages, and participants were told that they must reach the end of the study to be compensated. However, survey items were not mandatory and participants were able to navigate back and forth across pages. Validated scales were chosen to represent all stages of reward processing and stable traits related to reward. Scales were selected for inclusion if they contained items measuring a distinct component of anhedonia. Inter-item reliabilities for the scales are reported in Table 1 and ranged from acceptable to high. Summary statistics of item means

TABLE 1 Inter-item reliabilities for each scale.

Scale	Cronbach's α
PHQ-9	.87
MEI	.91
TEPS	.82
MASQ	.90
BFAS	.74
DASS	.97
BIS	.74
BAS	.85
ACIPS	.92

and standard deviations (SD) for each of the 24 subscales are displayed in Table 2.

Instrumentation

Depression measure

1. Patient health questionnaire-9 (PHQ-9) (66): 9 item 4-point Likert-based scale on frequency of depression symptomatology over the past 2 weeks. The PHQ-9 was validated against the mental health professional interview in a sample of 3000 patients, with a reported sensitivity of 75% and a specificity of 90% for major depression.

Reward processing measures

1. Inventory of depression and anxiety symptoms expanded version (IDAS-II) (67) The dysphoria subscale (IDASdy) contains items related to depressed mood, worthlessness, and guilt. The lassitude subscale (IDASla) contains items reflecting low energy. This study only administered the subset of items contained in these 2 subscales.
2. Temporal experience of pleasure scale (TEPS) (68): 18 item 6-point Likert-based scale consisting of two subscales measuring consummatory (TEPSc) and anticipatory (TEPSa) experience of pleasure.
3. Motivation and energy inventory (MEI) (69): 30-item Likert-based questionnaire with subscales for mental energy (MEIme), physical energy (MEIpe), and social motivation (MEIsm). The MEIme subscale is composed of cognitive functioning items, such as memory, concentration, and decision-making. The MEIpe subscale is composed of physical energy items. The MEIsm subscale is composed of items related to both interest and frequency of social activity and motivation for recreational activities. Each MEI subscale significantly distinguished between responders and non-responders in an 8-week antidepressant vs placebo trial ($p < .001$ for all pairwise t-tests).
4. Mood and anxiety symptoms questionnaire short adaptation (MASQ-D30) (70): 30-item 5-point Likert-based short form of the MASQ (71) used to assess trait symptomatology based on Clark and Watson's Tripartite Model (41) of psychopathology, with 10 items each loading onto general distress (MASQgd), anxious arousal (MASQaa), and anhedonic depression (MASQad) factors.
5. Depression anxiety stress scale (DASS) (72): 42-item 4-point Likert-based scale designed to assess functioning using 3 subscales: depression (low positive affect and hopelessness; DASSd), anxiety (arousal and hyperarousal; DASSa), and stress (agitation or negative affect; DASSs).
6. Anticipatory and consummatory interpersonal pleasure scale (ACIPS) (73): 17 item 6-point Likert-based scale consisting of 7 anticipatory and 10 consummatory social pleasure items. Three subscales indicating anhedonia toward intimate social interactions (ACIPSis), group social interactions (ACIPSgs), and social bonding and making connections (ACIPSsb).

Trait measures

1. Behavioral inhibition activation scale (BIS/BAS) (74): 24 item 4-point Likert-based scale consisting of 4 subscales mapping onto behavioral inhibition (BIS), drive (BASd), reward responsiveness (BASr), and fun-seeking (BASf). The latter 3 were found to strongly load onto a second order factor of behavioral activation.
2. Big five aspect scale (BFAS) (75): 100-item 5-point Likert scale assessing two factor components of each of the big five personality constructs. In this study only items related to extraversion and neuroticism were used, as these traits are most related to a diathesis for depression. Extraversion is composed of the enthusiasm (BFASee) and assertiveness (BFASea) subscales. Neuroticism is composed of the withdrawn (BFASnw) and emotional volatility (BFASnv) subscales. Each subscale consists of 10 items for a total of 40 items.

Analysis

Supervised machine learning algorithms are used to solve prediction problems where data is labeled (a dependent variable is specified). The full set of observations is split into training and test datasets, and the algorithm uses labels in the training set to improve accuracy while balancing generalizability to the test set. Random forest (RF) is a supervised classifier composed of an ensemble of decision trees; each of which is grown on a bootstrapped sample with a randomly selected subset of predictors, where results are aggregated by majority voting (76). In our pre-registration, we specified use of regularized regression methods, which can be used for continuous outcomes. However, RF is widely used for classification due to its

TABLE 2 Summary statistics of predictor means by group. Pre-imputed statistics are calculated from the non-missing items for each subscale.

Raw Data Summary Statistics by Diagnostic Group					
Predictor	HC, N = 100[1]	MDD, N = 129[1]	ARD, N = 164[1]	p-value[2]	q-value[3]
MEIme	7.32 (1.93)	6.10 (2.25)	5.13 (2.01)	<.001	<.001
MEIpe	6.18 (1.77)	4.38 (2.33)	4.54 (2.14)	<.001	<.001
MEIsm	8.35 (2.85)	6.83 (3.01)	7.04 (3.10)	<.001	.001
TEPSc	4.09 (.84)	4.34 (.91)	4.08 (.83)	.014	.023
TEPSa	3.84 (.67)	3.81 (.75)	3.59 (.76)	.052	.063
MASQaa	2.04 (.91)	2.15 (.89)	2.57 (.90)	<.001	<.001
MASQad	3.37 (.69)	3.77 (.87)	3.72 (.98)	<.001	<.001
MASQgd	2.54 (.77)	2.77 (.96)	3.21 (.81)	<.001	<.001
BFASnw	3.01 (.69)	3.35 (.77)	3.47 (.66)	<.001	<.001
BFASnv	2.77 (.77)	3.03 (.85)	3.08 (.73)	.008	.013
BFASee	3.00 (.66)	3.02 (.83)	2.72 (.65)	.004	.007
BFASea	2.94 (.69)	2.84 (.84)	2.92 (.75)	.500	.500
IDASdy	2.42 (.73)	2.77 (.93)	3.21 (.78)	<.001	<.001
IDASla	2.48 (.79)	3.01 (.89)	3.23 (.87)	<.001	<.001
DASSd	.97 (.67)	1.19 (.76)	1.59 (.73)	<.001	<.001
DASSa	.84 (.76)	.85 (.72)	1.18 (.68)	<.001	<.001
DASSs	1.06 (.69)	1.13 (.68)	1.47 (.62)	<.001	<.001
BIS	2.84 (.46)	3.00 (.47)	2.94 (.47)	.021	.030
BASd	2.45 (.61)	2.34 (.70)	2.54 (.64)	.025	.033
BASr	2.96 (.58)	3.02 (.65)	2.86 (.60)	.051	.063
BASf	2.65 (.55)	2.49 (.66)	2.63 (.65)	.200	.200
ACIPSgs	4.00 (1.08)	4.12 (1.34)	3.74 (1.16)	.021	.030
ACIPSis	3.99 (.90)	4.13 (1.07)	3.86 (.93)	.063	.072
ACIPSsb	3.88 (.94)	4.04 (1.11)	3.90 (1.01)	.200	.200

[1]Mean (SD).
[2]Kruskal-Wallis rank sum test.
[3]False discovery rate correction for multiple testing.

robustness against skewed distributions, outliers, and data transformations (77). It has been shown to perform well in previous depression studies predicting treatment outcomes on large datasets (52).

Model performance was assessed using the following metrics. "Accuracy" refers to the proportion of cases correctly classified across all classes. "Sensitivity" refers to the proportion of cases within a specified class that were correctly classified (e.g.: the proportion of ARD observations that were predicted to be ARD by the model). "Specificity" refers to the proportion of cases not within a specified class that were correctly classified (e.g.: ARD specificity refers to the proportion of MDD and HC cases not classified as ARD by the model). As we are interested in the generalizability of models to new data, hypothesis testing was employed to assess whether test set prediction accuracy was significantly different from chance using the "no-information rate", which is the prevalence of the largest class (78). Out-of-bag (OOB) accuracy was reported for each model, which is defined as 1 minus the average error of all predictions made using the training observations not within the bootstrapped sample. Sensitivity and specificity for training and test sets are reported for all models.

RF classifiers were implemented using the "RandomForest" (79) and "caret" (78) packages for the statistical software R (version 4.2.2) (80). Data were first divided using a pseudorandom 70/30 train/test split maintaining similar proportions of group sizes in each set (n_{train} = 276, n_{test} = 119). To avoid leakage, missing data for the train and test sets were imputed separately using predictive mean matching with the "Multiple Imputation by Chained Equations" (mice) (81) package for R. 133 observations contained at least 1 item missing in the predictor set, however total proportion of missingness in the data was low, at.4%. The variables with the highest percent missing were BFAS item 39 (2.02%), BFAS item 33 (1.77%), and BFAS item 34 (1.77%).

A multiclass target variable (all three groups) and two binarized target variables (ARD vs. non-ARD and ARD vs. MDD) were used as labels for separate models. For the first binary model, data were dummy-coded to compare ARD vs. both non-ARD groups. This model was used to generate a subset of items for distinguishing ARD from non-ARD in the general population. The other binary model was built using only the 2 depression groups. It was used to generate another subset of items for distinguishing ARD from MDD in patients with depression. Thus, the variables retained from this selection process were hypothesized to have the greatest discriminability for ARD specifically.

We defined "full models" as classifiers that included all items from the validated scales except PHQ-9, where item means were computed within each subscale (p = 24; where p is the number of predictors). Feature selection was applied separately to each model using the "VarSelRF" (82, 83) package for R, with initial number of trees = 5000 and number of trees for additional forests = 2000 (default suggested values). The algorithm uses backward elimination to drop a portion (.2) of the least important variables from the previous iteration. Using a similar process to Kautzky et al. (52), we repeated the feature selection procedure with random seeds of 1 to 500. Only those predictors retained in ≥ 80% of the results were used in "small models".

The hyperparameter "m_{try}" represents the number of predictors to be randomly sampled for each split. It is set by the experimenter and can be tuned to optimize model accuracy. We used grid search to tune m_{try} separately from feature selection with values ranging from 1 to p-1 using 10-fold cross-validation with 3 repeats of 500 trees each. Small models were trained and tuned separately using this method for each target variable.

Lastly, we used unsupervised methods (factor analysis and cluster analysis) to explore empirical patterns at the item level with only items from the subscales driving highest RF model accuracy. This study benefitted from empirically driven analysis due to the exploratory nature of using a novel combination of validated self-report subscales. We first conducted an exploratory factor analysis to assess if further dimension reduction would be plausible. The number of factors to extract was determined using parallel analysis (84). Factor analysis was carried out using the "psych" package for R (85) using an oblique "oblimin" rotation for factor extraction and a minimum item loading cutoff of.3. Next, k-means was used to explore empirical groupings of individuals (86). K-means is a method of clustering observations into an experimenter defined number of clusters k. This analysis was carried out using the "kmeans" function in the "stats" package for R, which is part of the R base code (80). K was determined by optimizing for within cluster sum-of-squares (WSS) using the "factoextra" package for R (87) and the "NbClust" package (88), which provides 30 indices for determining the number of clusters to use and proposes the best cluster number by majority vote. From this function, the majority of indices proposed 2 to 4 clusters. The 2-cluster solution was deemed trivial as one cluster was composed of individuals with fewer depression symptoms and the other composed of individuals with more severe depression. 3 and 4 clusters were computed for analysis and discussion.

Data exclusion

3 subjects were excluded for failed attention checks. An additional 2 subjects were excluded due to missing multiple items comprising 1 or more subscales (predictor variable) to be used for learning, and 1 subject was excluded based on missing the target group variable. The resulting dataset comprised 393 subjects [49.0% female, mean (SD) age = 34.6(11.0)].

Results

393 observations were included in the analysis, of which 41.7% were self-identified individuals with ARD. Unimputed PHQ-9 depression score for the full dataset significantly differed across groups (F = 24.58, p <.001), with post-hoc Tukey-corrected comparisons revealing significant differences between ARD vs. MDD ($M_{diff(ARD - MDD)}$ = .32, *adjusted-p* <.001), ARD vs. HC ($M_{diff(ARD - HC)}$ = .53, *adjusted-p* <.001) and MDD vs. HC ($M_{diff(MDD - HC)}$ = .21, *adjusted-p* = .030; see Supplementary Figure S1 for distribution of PHQ-9 score across groups).

78.1% of the MDD group and 67.7% of the ARD group reported taking an SSRI or SNRI for greater than 4 weeks at the time of this study. Of these individuals, 52.7% in the ARD group and 53.9% in the MDD group were taking an SSRI, 14.3% in the ARD and 20.6% in the MDD medicated group were taking an SSRI with augmentation, and 24.11% in the ARD and 18.63% in the MDD medicated group reported taking an SNRI. 24 logistic regression analyses examining the interaction effect of medication with each predictor variable regressed on group were evaluated using the generalized linear models ("glm") function in base R (80). After correcting for multiple comparisons by controlling for a false discovery rate of <.05 using the Benjamini-Hochberg adjustment (89), no interaction effects remained significant. Therefore, no predictors were removed from the analysis. Please see Supplementary Table S2 for mean predictor scores by group and medication status as well as their BH-adjusted p-values.

Supervised learning

Multiclass target variable

The first RF model predicted group membership using the full variable set for all groups and the specified 70/30 train/test split resulting in 276 training observations with 116 events of interest (for accuracy metrics see Table 3). In this multiclass model, the test set accuracy (.54) was significantly higher than the no-information rate of.42 (p = .004). The model had the highest sensitivity for the ARD group (.71) and the highest specificity for the HC group (.86). Test sensitivity was similar to training sensitivity for all groups.

Next, feature selection was implemented, and 5 variables retained for small model classification. The variables meeting criteria were: DASSa, MASQaa, IDASdy, MEIme, and MEIpe. These variables describe anxiety, dysphoria, as well as mental and physical energy. The ARD group had higher mean DASSa scores than the MDD group ($M_{diff(ARD - MDD)}$ = .33) and a greater

TABLE 3 Multiclass full vs. small model metrics.

		Full Model	Small Model	3-P Model	6-P Model
Train	Optimal m_{try}	5	1	1	1
	OOB Accuracy	.57	.59	.51	.52
	HC sensitivity	.54	.59	.37	.34
	HC specificity	.89	.89	.83	.87
	MDD sensitivity	.42	.48	.49	.44
	MDD specificity	.77	.77	.72	.72
	ARD sensitivity	.70	.67	.61	.68
	ARD specificity	.68	.69	.69	.65
Test	Accuracy	.54**	.42	.47	.53*
	95% CI	(.45,.63)	(.33,.52)	(.38,.57)	(.43,.62)
	HC sensitivity	.45	.33	.27	.47
	HC specificity	.86	.80	.81	.85
	MDD sensitivity	.38	.28	.36	.33
	MDD specificity	.80	.78	.76	.73
	ARD sensitivity	.71	.59	.69	.71
	ARD specificity	.62	.52	.62	.68

*p <.05.
**p <.01.
The full model was specified on all 24 predictors. Small model specification used only the feature selected predictors trained on the multiclass variable. 3-P and 6-P models were specified using feature selection on the binarized target variables. The no-information rate of the test set was.42.

difference than the MDD vs. HC groups ($M_{diff(MDD - HC)}$ = .01) groups. The ARD and MDD groups had a greater difference in MASQaa score ($M_{diff(ARD - MDD)}$ = .42) than between MDD and HC groups ($M_{diff(MDD - HC)}$ = .11). The ARD group had a higher IDASdy mean score and a greater difference in score with the MDD group ($M_{diff(ARD - MDD)}$ = .44) than the MDD and HC groups ($M_{diff(ARD - MDD)}$ = .35). MEIme ($M_{diff(ARD - MDD)}$ = -.97; $M_{diff(MDD - HC)}$ = -1.22) and MEIpe ($M_{diff(ARD - MDD)}$ = .16; $M_{diff(MDD - HC)}$ = -1.80) were both substantially greater in the HC group than the two depression groups.

A small model was subsequently fit using 10-fold cross validation to tune m_{try} on the training set observations with only the subset of predictors found using feature selection. Accuracy slightly improved in the training data for HC (sensitivity = .59) and MDD (.48) but decreased in test (HC sensitivity = .33; MDD sensitivity = .28; see Table 3); furthermore, no improvements were seen in ARD train or test sensitivity over the full model. Therefore, this small model variable set was rejected as a candidate for prediction of ARD.

Binarized target variables

ARD vs. non-ARD

This model also used 276 training observations with 116 events of interest. OOB accuracy for the full predictor set (.71) was similar to test accuracy (.65). Sensitivity was slightly higher in the test set for predicting ARD instances (.58) than the train set (.55). Full accuracy metrics for the binary target variables are reported in Table 4.

Feature selection of the ARD vs. non-ARD target variable retained 5 variables. All the DASS subscales were retained in addition to IDASdy and MEIme. The difference in mean score for these subscales (except MEIme, which had similarly large differences between all groups) were greater between ARD vs. MDD than MDD vs. HC (DASSd: $M_{diff(ARD - MDD)}$ = .40; $M_{diff(MDD - HC)}$ = .22; DASSs: $M_{diff(ARD - MDD)}$ = .34; $M_{diff(MDD - HC)}$ = .07). Fitting a 10-fold cross validated model for m_{try} on the small set of variables resulted in improved overall test accuracy and a significant p-value for the hypothesis test of accuracy evaluated against the no-information rate of.58 (accuracy = .70, p = .005). Sensitivity (.63) and specificity (.75) for ARD improved moderately in the small model.

ARD vs. MDD

This model was specified on 205 training observations and 116 events of interest. OOB accuracy on the full predictor set was.69 and.66 for test accuracy. Sensitivity for ARD cases in the cross-validated train data reached.79, however the model did not generalize as well (ARD test sensitivity = .65). Feature selection resulted in only 2 variables retained under pre-defined criteria: DASSd and MEIsm. The MEIsm subscale was surprisingly greater in the ARD group than the MDD group ($M_{diff(ARD - MDD)}$ = .21). Test accuracy (.61) and ARD sensitivity (.71) were somewhat improved in this model. In the interest of finding a set of variables with improved discriminability for ARD, we also computed a 3-predictor (3-P) model including the next most frequent variable selected (48% of random seed iterations): DASSa. This model demonstrated a significantly greater test accuracy over the no-information rate of.56 (accuracy = .67, p = .020) with a test sensitivity for ARD of.82 and specificity of.49. Both the 2-P and 3-P small models had the same specificity (.49) for ARD; thus the 3-P model substantially increased accuracy of classifying ARD cases, but not at the expense of MDD accuracy.

Generalization of binarized feature selection on multiclass target variable

The set of predictors resulting in the greatest sensitivity to ARD included: DASSd, DASSa, and MEIsm. This set was used to generate predictions for the other target variables. Using the 3-predictor (3-P) model to train on the multiclass target variable resulted in lower sensitivities for HC (.27) and MDD (.36) in the test set, but slightly

TABLE 4 Binarized target variables' full vs. small model metrics.

		ARD vs. non-ARD			ARD vs. MDD		
		Full Model	Small Model	3-P Model	Full Model	2-P Model	3-P Model
Train	Optimal m_{try}	3	1	1	2	1	1
	OOB Accuracy	.71	.70	.67	.69	.68	.67
	ARD Sensitivity	.55	.59	.57	.79	.77	.74
	ARD Specificity	.83	.78	.75	.57	.57	.59
Test	Test Accuracy	.65	.70**	.64	.66*	.61	.67*
	95% CI	(.56,.74)	(.61,.78)	(.55,.73)	(.55,.76)	(.50,.72)	(.56,.77)
	ARD Sensitivity	.57	.63	.59	.86	.71	.82
	ARD Specificity	.71	.75	.68	.41	.49	.49

*p <.05.
**p <.01.
The m_{try} hyperparameter was optimized on accuracy, which is the proportion of correct categorizations. OOB accuracy represents the proportion of correct cases not within each bootstrapped sample for all classes. Test accuracy represents the proportion of correctly classified cases in the test set for all classes. Sensitivity represents correctly classified cases of the selected class. Specificity represents correctly classified cases not of the selected class. Full model specification included all 24 predictor variables. Small model specification included only the variables meeting selection criteria when trained on the corresponding target variable's training set. 3-P and 2-P models were specified using the feature selection procedure with the ARD vs. MDD target variable.

improved sensitivity for ARD (.69). However, sensitivity did not improve in the ARD vs. non-ARD target variable using this test set.

We also tested a combined 6-predictor (6-P) model using predictors retained from both binarized target variables' feature selection processes on the multiclass variable. This resulted in a small increase in overall test accuracy, which was significant over the no-information rate (p = .010). ARD test sensitivity (.71) was improved over the other multiclass models, however MDD (.33) and HC (.47) sensitivity remained low. Full results are reported in Table 3.

Unsupervised learning

In the following, only individual items from the 6-P model subscales were analyzed: DASSd, DASSa, DASSs, MEIme, MEIsm, and IDASdy. Only a very small percentage of observations were missing from this subset (.03%). Therefore, to increase clarity of data interpretation without a large risk of introducing bias, predictive mean matching was used to impute missing data based only on this subset of items using the "mice" package (81).

Exploratory factor analysis

We used exploratory factor analysis to confirm whether the factor structure at the item level would be retained when combining items from multiple validated scales. Parallel analysis suggested 6 factors in the item-level data. The 6-factor solution item loadings are reported in Supplementary Table S3. Most items grouped into their theoretically proposed subscales. We interpret the factors in their order of extraction. The first factor was composed of anhedonia items (mostly DASSd: "*I couldn't seem to experience any positive feeling at all*"). The second factor was composed mostly of somatic anxiety items (DASSa: "*I had a feeling of faintness*") and some DASSs items ("*I was in a state of nervous tension*"). Factor 3 was composed of cognitive function items (MEIme: "*During the past 4 weeks, how often did you have problems concentrating?*"). Factor 4 was composed solely of DASSs items related to distress ("*I found myself getting upset by quite trivial things*"). Factor 5 was composed almost solely of MEIsm items ("*During the past 4 weeks, to what extent were you interested in talking with others?*"). Factor 6 was composed of 4 IDAS dysphoria items related to self-worth and guilt ("*I felt inadequate*"). However, other items from the IDASdy subscale loaded onto the first 3 factors. Only one item did not have a loading >.3 onto any factors (MEIsm: "*During the past 4 weeks, how often did you avoid social conversations with others?*").

Cluster analysis

We performed cluster analysis of individuals using the subset of individual items within the 6-P model using 4 clusters, determined from optimizing for WSS. A cluster by WSS graph is presented in Figure 1. Due to our sample having 3 diagnostic groups, we also computed a 3-cluster solution. In the 3-cluster solution: cluster 1 was composed mostly of individuals from the MDD and ARD groups. Cluster 2 consisted mostly of the ARD group, and cluster 3 consisted mostly of HC and MDD groups. In the 4-cluster solution: cluster 1 consisted of mostly HC and ARD individuals. Clusters 2 and 3 consisted of mostly the MDD and ARD groups, while cluster 4 was mostly the HC and MDD groups. Cluster by group frequencies are shown in Figure 2 for the k = 4 solution.

To characterize differences in symptom profiles across clusters, we computed means of the standardized item scores for each of the 6 factor-analyzed dimensions. Results are summarized in Table 5.

3-cluster solution

The first cluster in the k = 3 solution can be interpreted as capturing the similarities between the 2 depression groups ($n_{HC/MDD/ARD}$ = 15/47/63). This cluster had the lowest motivation and above average levels of anhedonia and dysphoria as well as below

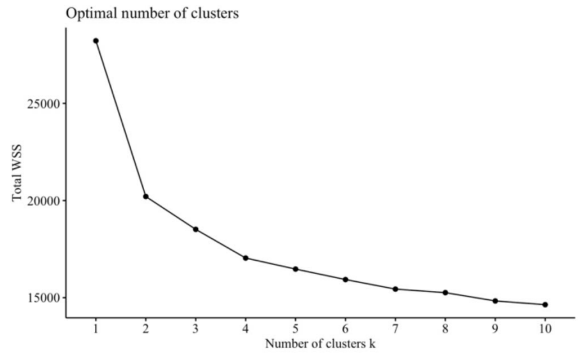

FIGURE 1
Number of clusters. Total WSS is plotted by number of clusters. Beyond *k* = 4, the WSS incrementally decreases at a decreasing rate. Therefore, a 4-cluster solution was chosen to prevent unnecessary complexity and inaccuracies to data modeling and interpretation.

average anxiety. The second cluster ($n_{HC/MDD/ARD}$ = 36/30/72) was composed of mostly the ARD group. This cluster displayed the highest anxiety, anhedonia, distress, and dysphoria coupled with the lowest cognitive functioning. Interestingly, this cluster also displayed above average social motivation. The 3rd cluster ($n_{HC/MDD/ARD}$ = 49/52/29) was composed mostly of the HC group, and displayed low anhedonia, anxiety, distress, and dysphoria along with above average cognitive functioning and motivation.

4-cluster solution

The first cluster ($n_{HC/MDD/ARD}$ = 36/22/56) in the k = 4 solution was composed mostly of commonalities between ARD and HC groups. This cluster was characterized by the highest anxiety of all clusters, along with above average anhedonia, distress, and dysphoria and below average mental functioning. Similar to cluster 2 in the 3-cluster model, this cluster also had high motivation. Cluster 2 ($n_{HC/MDD/ARD}$ = 29/49/59) was composed mostly of commonalities between MDD and ARD groups, and displayed low anhedonia, anxiety, distress and dysphoria along with low motivation. Cluster 3 ($n_{HC/MDD/ARD}$ = 3/27/37) was composed of mostly ARD individuals and displayed the highest levels of anhedonia and the lowest levels of motivation and cognitive functioning. This group also had the highest levels of dysphoria and above average distress and anxiety. Cluster 4 ($n_{HC/MDD/ARD}$ = 32/31/12) represented similarities between HC and MDD groups, and displayed the lowest levels of anhedonia, anxiety, distress, and dysphoria. This group also had above average motivation and cognitive functioning. See Figure 3 for graphical depiction of cluster profiles.

Discussion

Random forest classification models built using anhedonia and other internalizing predictors reached accuracy levels ranging from.42-.71. Sensitivity for ARD ranged from.55-.86 and specificity ranged from.49 -.83 (proportion of ARD individuals in the total sample = .42 and in the depression only groups = .56). Model performance based on anhedonia and related predictors was comparable to results reported from other studies using comprehensive sets of demographic, socioeconomic and clinical predictors from cohort depression databases (44, 49, 52, 90, 91). Several models including the full multiclass comparison reached test accuracy levels significantly above chance. The small model with best overall accuracy and sensitivity for ARD contained 6 predictors and factor analyzed into 6 symptom dimensions at the item level. Cluster analyses revealed 3-4 empirical groupings varying in affective and cognitive disturbance along these 6 dimensions.

Optimal m_{try} varied between 1-5 and was generally smaller for each cross-validated model than the recommended rule of thumb (m_{try} = √predictors; for a plot of accuracy by m_{try} values for the multiclass variable full model, see Supplementary Figure S4). Larger values of this hyperparameter generate more optimized forests, as the best predictor can more often be chosen for each split. However, this can also lead to overfitting. Smaller m_{try} values lead to a weaker but more diverse forest as only a few predictors are tested at a time, and models can generalize better when making predictions for test set observations. All small models performed best with m_{try} = 1.

Feature selection of the binarized comparisons (the 6-P model) resulted in a set of variables with greater discriminability for ARD. The 6-P model performed better in test sensitivity/specificity for ARD in the multiclass comparison than the set of selected variables specified using the multiclass target variable itself. These variables encompassed the measurement of low pleasure ("*I couldn't seem to experience any positive feeling at all*"), motivation ("*During the past 4 weeks, how often did you engage in recreational activities or*

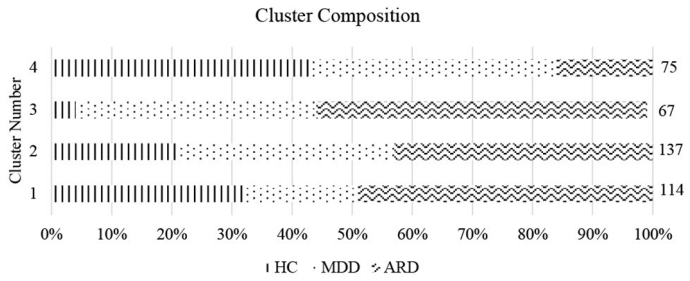

FIGURE 2
Cluster composition by group. Cluster number and proportion by group (% of total cluster) are shown for *k* = 4. Size of each cluster is indicated on the right vertical axis.

TABLE 5 Factor means by cluster. Standardized item score factor mean and SDs by cluster are reported for k = 3 (top) and k = 4 (bottom).

6-Factor Standardized Item Scores by Cluster: k = 3					
Factor	1, N = 125[1]	2, N = 138[1]	3, N = 130[1]	p-value[2]	q-value[3]
Anhedonia	.15 (.64)	.65 (.47)	-.84 (.40)	<.001	<.001
Anxiety	-.18 (.38)	.84 (.34)	-.72 (.32)	<.001	<.001
Cognitive	-.09 (.31)	-.22 (.28)	.32 (.28)	<.001	<.001
Distress	.00 (.53)	.73 (.42)	-.77 (.44)	<.001	<.001
Motivation	-.44 (.43)	.24 (.72)	.16 (.60)	<.001	<.001
Dysphoria	.33 (.73)	.40 (.64)	-.74 (.65)	<.001	<.001

[1] Mean (SD).
[2] Kruskal-Wallis rank sum test.
[3] False discovery rate correction for multiple testing.

6-Factor Standardized Item Scores by Cluster: k = 4						
Factor	1, N = 114[1]	2, N = 137[1]	3, N = 67[1]	4, N = 75[1]	p-value[2]	q-value[3]
Anhedonia	.48 (.35)	-.32 (.43)	.98 (.54)	-1.04 (.36)	<.001	<.001
Anxiety	.83 (.34)	-.35 (.36)	.30 (.56)	-.90 (.18)	<.001	<.001
Cognitive	-.19 (.28)	.04 (.32)	-.22 (.30)	.41 (.25)	<.001	<.001
Distress	.69 (.36)	-.27 (.46)	.48 (.64)	-.99 (.37)	<.001	<.001
Motivation	.52 (.48)	-.21 (.46)	-.75 (.38)	.26 (.65)	<.001	<.001
Dysphoria	.19 (.54)	-.11 (.61)	1.08 (.46)	-1.06 (.52)	<.001	<.001

[1] Mean (SD).
[2] Kruskal-Wallis rank sum test.
[3] False discovery rate correction for multiple testing.
Positive means denote above-average levels and negative means denote below-average levels of each factor. The anhedonia factor describes low pleasure and interest and was composed mostly of DASSd items. The anxiety factor was composed mostly of DASSa and DASSs items and describes somatic symptoms of nervousness. The cognitive factor describes cognitive functioning (i.e. focus, memory and decision-making), and was composed mostly of MEIme items. The distress factor was composed of DASSs items related to emotional upset. The motivation factor was composed of MEIsm items related to social and recreational motivation, and the dysphoria factor was composed of IDASdy items related to guilt and self-worth.

hobbies?"), cognitive function ("*During the past 4 weeks, how often did you have trouble making minor decisions?*"), stress ("*I found myself getting upset rather easily*"), and anxiety ("*I felt that I was using a lot of nervous energy*"), whereas the set of items specified using the multiclass target contained predictors related more to somatic anxiety and physical energy. Therefore, somatic symptoms may be more important in identifying any depression whereas anhedonia and cognitive symptoms may be more important for specifically identifying individuals with ARD.

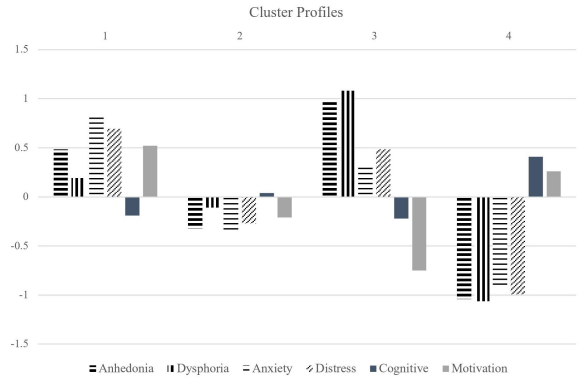

FIGURE 3
Anhedonia factor cluster profiles. (from left to right) The first 4 factors are negatively valenced. The last 2 factors are positively valenced (cognitive functioning and motivation) and depicted using solid bars.

Cognitive function as measured by MEIme and cognitive distress as measured by IDASdy displayed similarly large differences across ARD vs. MDD and MDD vs. HC groups. Cognitive impairment in the areas of attention, executive function, and memory are considered core markers of major depression and have been found to persist even after depression remission (92, 93). Dysphoria, being the opposite of euphoria, was composed of items representing thoughts of worthlessness, hopelessness and guilt. It may be related to emotion dysregulation, and has been associated with depressive episodes and cognitive impairment (94, 95). These findings suggest that individuals with ARD are much more cognitively impaired than non-depressed individuals and are more likely to suffer from disordered thinking and worry. Untreated, this may lead to greater risk for recurrent depressive episodes.

The anxiety and stress scores displayed greater differences between ARD vs. MDD than MDD vs. HC. This aligns with previous studies finding comorbid anxiety to be a clinical predictor of treatment resistance (90, 96, 97). The importance of anxiety measurement is highlighted again when distinguishing

solely between ARD and MDD groups. In this comparison, the full model performed significantly above chance whereas the 2-P model (using only items representing depressed mood and social motivation) did not. However, the 3-P model performed comparably to the full model in terms of test sensitivity and specificity for ARD. Adding an anxiety subscale improved predictive sensitivity for ARD without sacrificing specificity. According to these results, high negative emotionality is equally important as anhedonia (low positive emotionality) for ARD discriminability.

Reported physical energy (MEIpe: "*During the past 4 weeks, how much of the time did you feel physically tired during the day?*") was much higher in healthy controls; HC vs. MDD had a substantially greater difference in mean score than MDD vs. ARD. Similarly, the MEIsm mean score was much greater in HC than the 2 depression groups. This subscale captured more than just social motivation; it also contained items related to interest in recreational activities and projects. Thus, a physical component of anhedonia may be more important for distinguishing individuals with and without depression. Physical activity is a well-established strategy for management of depression symptoms, and frequently recommended for prevention of depression (98–100). Furthermore, exercise has been found to be beneficial in the treatment of anxiety, and in a non-clinically depressed population for improvement of depression symptoms (101, 102). Individuals with ARD report low physical energy coupled with high anxiety. Therefore, these individuals may stand to gain the most from physical activities, but paradoxically may have the most trouble implementing a regular exercise protocol.

This study demonstrates the viability of using a limited set of self-report predictors relating to one broad symptom dimension for classification of antidepressant response. The range of sensitivity achieved for ARD in this study (.55-.86) was comparable to other naturalistic machine learning studies using a more diverse set of sociodemographic, diagnostic and medical history, genetic and self-report clinical predictors (.55 -.82) (49–52). Such comprehensive information can be impractical to gather for every patient and not readily available in real-life clinical practice. Additionally, unlike the previously cited studies leveraging national depression databases, we included a control sample of individuals with no reported depression diagnosis or treatment history. Therefore, this study was not limited in scope to binary comparisons of response vs. non-response and achieved classification accuracy at levels significantly above chance with a multiclass comparison. Furthermore, the feature selection process elucidated the existence of distinct differences in anhedonia profiles within a depression group and between individuals with and without depression. This study contributes to our understanding of the nature of SSRI/SNRI treatment resistance and highlights a novel pathway for clinical application.

Few prior studies using machine learning to predict treatment outcomes have examined the meaning of variable and model selection results for improving our understanding of clinical phenotypes. In this study we used unsupervised methods to reveal data-driven insights on the symptom profile(s) of ARD. Exploratory factor analysis mostly retained the 6-P scale dimensions, except IDASdy. Dysphoria is a multifaceted component of depression and represents a general dissatisfaction and unease toward life. The IDASdy subscale was composed of items capturing distress, worry, low self-worth, hopelessness, and guilt (67). Therefore, several items were split among the other dimensions of anxiety, anhedonia, and cognitive impairment. However, 4 items loaded together to form a low self-worth and hopelessness factor ("I felt discouraged about things"; "I blamed myself for things"), which retained the name dysphoria.

These dimensions were then examined across empirically determined data clusters. The 4-cluster solution found 2 large (capturing around 2/3 of the total cases) and 2 smaller clusters (approx. 1/3 of the total cases combined) such that ARD was evenly distributed across the 2 large clusters and dominated one of the smaller clusters. The first large cluster resembled the symptom profile of an anxious depression subtype, with greater reported levels of anxiety and distress than anhedonia and dysphoria. This cluster also displayed above average levels of motivation, presumably because motivation can be derived from anxious avoidance of aversive events or end states (41, 103, 104). This cluster was composed of proportionally more HC and ARD as well as fewer MDD individuals than the second large cluster. The second large cluster was composed of a low-disturbance profile characterized by slightly below average anxiety, distress, anhedonia, motivation, and dysphoria. The symptom profile of this cluster suggests a successfully treated group of participants. The third cluster was a small group consisting of mostly ARD participants. The symptom profile of this cluster was characterized by exceedingly high anhedonia, dysphoria, low motivation, plus moderate cognitive impairment, and above average anxiety and distress. However, unlike cluster 1, the anhedonia and dysphoria in this cluster was greater than the anxiety and distress symptom dimensions, while motivation was much more impaired. Cluster 4 was composed mainly of the HC and MDD groups. This cluster scored below average on the negatively valenced symptom dimensions (anhedonia, dysphoria, anxiety, and distress) and above average on the positively valenced dimensions (cognitive function and motivation). Therefore, we found 4 clusters of participants based on internalizing symptom profiles, loosely resembling the subtypes (cluster 1) anxious-depression, (cluster 2) low-disturbance/treated, (cluster 3) anhedonic, and (cluster 4) non-depressed.

These findings suggest the presence of symptom heterogeneity even in just individuals with ARD, varying along dimensions of anxiety, anhedonia, and cognitive disturbance. Some of the variation in profiles may have been driven by the presence of antidepressant medication. In both the 3- and 4-cluster solution, a similar low anxiety depression profile was present and contained the greatest proportion of the non-resistant MDD group. This may reflect the robust anxiolytic effects of SSRI/SNRI medication; indeed, several SSRIs are indicated for treatment of anxiety disorders, post-traumatic stress disorder, and obsessive-compulsive disorder (105–107). Additionally, emotional blunting is a commonly reported side-effect of this type of medication (108–110).

Previous evidence has suggested a mechanistic difference underlying the interest and the pleasure facets of reward processing (19, 32, 34). The TEPSa, BFASee, and BASd subscales all reflect the interest component of anhedonia related to function of the dopaminergic reward circuit. To be in line with recent evidence for the successful treatment of anhedonia using neural stimulation of reward circuit regions, we would expect much larger differences between these subscales for the ARD vs. MDD groups (111–113). However, to the extent that this can be captured in self-report data, we did not find differences in anticipatory anhedonia and apathy between ARD and MDD to be robust at the level of granularity posited. We did, however, find the importance of a broad internalizing dimension composed of affective and cognitive disturbances in contributing to prediction of a treatment-resistant phenotype.

Lastly, it is important to note that the majority of individuals with depression in both the MDD and ARD groups were taking some form of serotonergic medication, and SSRIs were the most common treatment even for individuals who self-identified as ARD. This demonstrates the pervasiveness of serotonergic medication use in depression treatment, even as its high non-response rate is widely accepted (58). The dominant narrative of the monoamine hypothesis of depression was a major limiting factor for identifying new treatment mechanisms (114). Additionally, current perspectives on alternative treatments are that they carry greater risks; for example, deep brain stimulation and electroconvulsive therapy are well-established for treating non-responsive depression (16, 115, 116), but use invasive surgical techniques. Esketamine and other pharmacotherapies are nascent treatments with promise for efficacy, but some researchers still question long-term safety and tolerability (117). However, there is increasing acknowledgment of the heterogeneity in major depression, and many recognize the need for diversification and individualization of treatment protocols (118).

Limitations

Several limitations were present due to the cross-sectional nature of this study. First, treatment at time of study adds a complex confound to the interpretation of these results, as people were prescribed varying doses of medications from different antidepressant classes and may augment with differing classes of medications or alternative therapies. However, the overwhelming majority of participants who were on medication listed an antidepressant within the SSRI/SNRI pharmacological classes, and these medications are ineffective at reducing anhedonia (7). Similarly, chronic use of recreational substances and drugs of abuse may contribute another confound. The survey items generally measured across multiple days or weeks and trait-level effects, which may somewhat reduce bias from acute substance use. Yet these are two sources of bias that must be considered when interpreting findings.

A second limitation arises from the online case-control study design and self-diagnosed group labels. Reliance on online self-report modality is a simple way to streamline large-scale data collection from a broad geographical area with a greater level of confidentiality for participants. However, it can impact internal validity due to the inability to verify accuracy of self-reporting and standardize phenomenological measurement. Furthermore, there may be impacts to external validity and generalizability to patient populations who do not participate in online research platforms. Therefore, more extensive research is needed to validate these findings through both verification of patient records and in-person data collection across several geographic locations.

Clinicians frequently use subjective reports of symptom improvement when making treatment modifications. However, in this study the measure of improvement from medication was not standardized and must be interpreted with caution. We were not able to measure pre to post change in depression, as we only captured respondents at one time point. Because of these limitations, we are not able to draw conclusions about pre-treatment anhedonia profile. In our data, there were large ranges for depression severity in each self-identified group; distributions can be seen in Supplementary Figure S1. Despite efforts to limit the presence of depression in the HC group by pre-screening based on PHQ-2, a substantial portion of this group still averaged a moderate score on the PHQ-9 and reported presence of other internalizing symptoms such as anxiety on the other measures. Therefore, the HC group had somatic and cognitive symptoms (as only affective symptoms are assessed by PHQ-2). This suggests a substantial portion of the population may express anxious depression symptoms while not considering themselves depressed or not seeking a diagnosis. This may be due to (1) a component of alexithymia that may be present in mood disorders, or (2) lack of general knowledge around the heterogeneity of depression criteria and failure to recognize the somatic and cognitive impairments that define both depression and anxiety. In addition, the MDD group appeared to have a bimodal distribution on PHQ-9 scores, and some also reported various internalizing symptoms based on the cluster analysis. Therefore, some individuals may have self-identified as responding to medication while contending with residual symptoms, due to the heterogeneous nature of depression symptom dimensions they may have felt improvement in some domains while remaining static in others. This demonstrates a limitation of self-identified diagnosis; significant variability exists in these groups.

Third, Random Forests is limited in its use outside the bounds of this dataset because it cannot extrapolate predictions for new values. Therefore, it is bound by the largest and smallest values of predictors in the training set. Additionally, sample size differences across classes can sometimes contribute to variation in sensitivity and specificity for the models, with sensitivity skewed toward the larger class. In the multiclass models, ARD sensitivity was generally greater than the other 2 groups. The sample size of the ARD group was slightly greater than the HC (1.64:1) and MDD (1.27:1) groups. The binarized models performed better in accuracy than the multiclass, with the ARD vs. non-ARD model performing better for classifying non-ARD cases and the ARD vs. MDD model better at classifying ARD cases. In the first binarized model, the combined sample size for the HC and MDD groups was slightly larger than the ARD group (1.4:1), while the sample size in the second binarized model was slightly larger in the ARD group (.8:1). Data balancing is sometimes used with RF classifiers to prevent this issue, and can be performed by a combination of under-sampling the majority class and over-sampling the minority class (119). However, this can

introduce some bias in the data; therefore, it is commonly used for extremely unbalanced data (minority class prevalence < 10%). The results are thus better interpreted by comparing full to small model accuracy across all groups. To address these limitations, results should be replicated in a sample of pre-treatment individuals with depression who are followed longitudinally from pre- to post-treatment and assessed by a clinician for depression improvement.

Conclusions

These findings highlight the efficacy of using a limited set of self-reported anhedonia and internalizing predictors to evaluate SSRI/SNRI treatment-resistance. This case-control study attained comparable model performance to prior naturalistic cohort studies exploiting a broader range of sociodemographic and clinical predictors without using a non-depressed control group. Specific components of internalizing symptomatology (i.e. depressed mood) were found to have greater importance for distinguishing ARD in particular, whereas other components (i.e. physical energy) were more relevant for distinguishing any presence of depression. Furthermore, an abridged set of items relating to anxiety, anhedonia, and cognitive function were found to differentiate ARD from non-ARD individuals at levels significantly above chance. This study found (1) the qualitative components of anhedonia differ when comparing across treatment response groups vs. overall presence of disorder, and (2) produced a reasonable sized set of items consisting of the DASS, MEI mental energy and social motivation subscales, and IDAS dysphoria subscale for practical clinical use. Self-report items are easy to administer, standardized, and cost friendly. To enhance usability by clinicians as a predictive tool for ARD in pre-treatment individuals, further study should aim to replicate results in a prospective cohort sample.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by University of Southern California Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – original draft. SR: Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1349576/full#supplementary-material

References

1. Ettman CK, Cohen GH, Abdalla SM, Sampson L, Trinquart L, Castrucci BC, et al. Persistent depressive symptoms during COVID-19: a national, population-representative, longitudinal study of U.S. adults. *Lancet Reg Health – Am.* (2022) 5:100091. doi: 10.1016/j.lana.2021.100091

2. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. (2003) 53:649–59. doi: 10.1016/S0006-3223(03)00231-2

3. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv.* (2009) 60:1439–45. doi: 10.1176/ps.2009.60.11.1439

4. McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor

treatment–resistant depression. *J Am Acad Child Adolesc Psychiatry*. (2012) 51:404–11. doi: 10.1016/j.jaac.2012.01.011

5. Nutt D, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacol (Oxf)*. (2007) 21:461–71. doi: 10.1177/0269881106069938

6. Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry*. (2015) 28:7–12. doi: 10.1097/YCO.0000000000000122

7. Klein ME, Grice AB, Sheth S, Go M, Murrough JW. Pharmacological treatments for anhedonia. In: Pizzagalli DA, editor. *Anhedonia: Preclinical, Translational, and Clinical Integration*. Springer International Publishing, Cham (2022). p. 467–89. Current Topics in Behavioral Neurosciences. doi: 10.1007/7854_2022_357

8. Spijker J, Bijl RV, Graaf RD, Nolen WA. Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand*. (2001) 103:122–30. doi: 10.1034/j.1600-0447.2001.103002122.x

9. Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, et al. Reduced reward learning predicts outcome in major depressive disorder. *Biol Psychiatry*. (2013) 73:639–45. doi: 10.1016/j.biopsych.2012.10.014

10. Vinckier F, Gourion D, Mouchabac S. Anhedonia predicts poor psychosocial functioning: Results from a large cohort of patients treated for major depressive disorder by general practitioners. *Eur Psychiatry*. (2017) 44:1–8. doi: 10.1016/j.eurpsy.2017.02.485

11. Fawcett J, Clark DC, Scheftner WA, Gibbons RD. Assessing anhedonia in psychiatric patients. *Arch Gen Psychiatry*. (1983) 40:79–84. doi: 10.1001/archpsyc.1983.01790010081010

12. Borsini A, Wallis ASJ, Zunszain P, Pariante CM, Kempton MJ. Characterizing anhedonia: A systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cognit Affect Behav Neurosci*. (2020) 20:816–41. doi: 10.3758/s13415-020-00804-6

13. Höflich A, Michenthaler P, Kasper S, Lanzenberger R. Circuit mechanisms of reward, anhedonia, and depression. *Int J Neuropsychopharmacol*. (2019) 22:105–18. doi: 10.1093/ijnp/pyy081

14. Treadway MT, Zald DH. Parsing anhedonia: translational models of reward-processing deficits in psychopathology. *Curr Dir Psychol Sci*. (2013) 22:244–9. doi: 10.1177/0963721412474460

15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington, D.C.: American Psychiatric Publishing (2013). doi: 10.1176/appi.books.9780890425596

16. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry*. (2010) 67:110–6. doi: 10.1016/j.biopsych.2009.09.013

17. Lally N, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA. Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol (Oxf)*. (2015) 29:596–607. doi: 10.1177/0269881114568041

18. Martin JLR, Barbanoj MJ, Schlaepfer TE, Thompson E, Pérez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression: Systematic review and meta-analysis. *Br J Psychiatry*. (2003) 182:480–91. doi: 10.1192/bjp.182.6.480

19. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. (2008) 33:368–77. doi: 10.1038/sj.npp.1301408

20. Christensen MC, Ren H, Fagiolini A. Emotional blunting in patients with depression. Part I: clinical characteristics. *Ann Gen Psychiatry*. (2022) 21:10. doi: 10.1186/s12991-022-00387-1

21. Goodwin GM, Price J, De Bodinat C, Laredo J. Emotional blunting with antidepressant treatments: A survey among depressed patients. *J Affect Disord*. (2017) 221:31–5. doi: 10.1016/j.jad.2017.05.048

22. Ma H, Cai M, Wang H. Emotional blunting in patients with major depressive disorder: A brief non-systematic review of current research. *Front Psychiatry*. (2021) 12:792960. doi: 10.3389/fpsyt.2021.792960

23. Masdrakis VG, Markianos M, Baldwin DS. Apathy associated with antidepressant drugs: a systematic review. *Acta Neuropsychiatr*. (2023) 35:189–204. doi: 10.1017/neu.2023.6

24. Fava M, Graves LM, Benazzi F, Scalia MJ, Iosifescu DV, Alpert JE, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *J Clin Psychiatry*. (2006) 67:1754–9. doi: 10.4088/JCP.v67n1113

25. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med*. (2011) 41:1165–74. doi: 10.1017/S0033291710001911

26. Zajecka J, Kornstein SG, Blier P. Residual symptoms in major depressive disorder: prevalence, effects, and management. *J Clin Psychiatry*. (2013) 74:18127. doi: 10.4088/JCP.12059ah1

27. Stahl SM, Zhang L, Damatarca C, Grady M. Brain circuits determine destiny in depression: a novel approach to the psychopharmacology of wakefulness, fatigue, and executive dysfunction in major depressive disorder. *J Clin Psychiatry*. (2003) 64 (Suppl 14):6–17.

28. Ghanean H, Ceniti AK, Kennedy SH. Fatigue in patients with major depressive disorder: prevalence, burden and pharmacological approaches to management. *CNS Drugs*. (2018) 32:65–74. doi: 10.1007/s40263-018-0490-z

29. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. *Curr Opin Pharmacol*. (2009) 9:65–73. doi: 10.1016/j.coph.2008.12.014

30. Berridge KC, Robinson TE. Parsing reward. *Trends Neurosci*. (2003) 26:507–13. doi: 10.1016/S0166-2236(03)00233-9

31. Peciña S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? *J Neurosci Off J Soc Neurosci*. (2005) 25:11777–86. doi: 10.1523/JNEUROSCI.2329-05.2005

32. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci*. (2018) 19:470–84. doi: 10.1038/s41583-018-0029-9

33. Kring AM, Barch DM. The motivation and pleasure dimension of negative symptoms: Neural substrates and behavioral outputs. *Eur Neuropsychopharmacol*. (2014) 24:725–36. doi: 10.1016/j.euroneuro.2013.06.007

34. Rizvi S. Anhedonia in major depressive disorder: exploration of a predictive clinical phenotype. [Thesis]. University of Toronto. (2015) Available at: https://tspace.library.utoronto.ca/handle/1807/69447.

35. Blain SD, Sassenberg TA, Xi M, Zhao D, DeYoung CG. Extraversion but not depression predicts reward sensitivity: Revisiting the measurement of anhedonic phenotypes. *J Pers Soc Psychol*. (2021) 121:e1–18. doi: 10.1037/pspp0000371

36. Conway CC, Forbes MK, Forbush KT, Fried EI, Hallquist MN, Kotov R, et al. A hierarchical taxonomy of psychopathology can transform mental health research. *Perspect Psychol Sci*. (2019) 14:419–36. doi: 10.31234/osf.io/wsygp

37. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. (2010) 167:748–51. doi: 10.1176/appi.ajp.2010.09091379

38. Insel TR, Cuthbert BN. Endophenotypes: Bridging genomic complexity and disorder heterogeneity. *Biol Psychiatry*. (2009) 66:988–9. doi: 10.1016/j.biopsych.2009.10.008

39. Nitschke JB, Heller W, Imig JC, McDonald RP, Miller GA. Distinguishing dimensions of anxiety and depression. *Cognit Ther Res*. (2001) 25:1–22. doi: 10.1016/j.jad.2011.10.005

40. Snyder HR, Silton RL, Hankin BL, Smolker HR, Kaiser RH, Banich MT, et al. The dimensional structure of internalizing psychopathology: relation to diagnostic categories. *Clin Psychol Sci*. (2023) 11(6):1044-63. doi: 10.1177/21677026221119483

41. Clark LA, Watson D. Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Abnorm Psychol*. (1991) 100:316–36. doi: 10.1037//0021-843X.100.3.316

42. Watson D. Rethinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. *J Abnorm Psychol*. (2005) 114:522–36. doi: 10.1037/0021-843X.114.4.522

43. Kovacs M, Devlin B. Internalizing disorders in childhood. *J Child Psychol Psychiatry*. (1998) 39:47–63. doi: 10.1017/S0021963097001765

44. Cohen ZD, DeRubeis RJ. Treatment selection in depression. *Annu Rev Clin Psychol*. (2018) 14:209–36. doi: 10.1146/annurev-clinpsy-050817-084746

45. Goodwin NL, Nilsson SRO, Choong JJ, Golden SA. Toward the explainability, transparency, and universality of machine learning for behavioral classification in neuroscience. *Curr Opin Neurobiol*. (2022) 73:102544. doi: 10.1016/j.conb.2022.102544

46. Iniesta R, Stahl D, McGuffin P. Machine learning, statistical learning and the future of biological research in psychiatry. *Psychol Med*. (2016) 46:2455–65. doi: 10.1017/S0033291716001367

47. Libbrecht MW, Noble WS. Machine learning applications in genetics and genomics. *Nat Rev Genet*. (2015) 16:321–32. doi: 10.1038/nrg3920

48. Yarkoni T, Westfall J. Choosing prediction over explanation in psychology: lessons from machine learning. *Perspect Psychol Sci*. (2017) 12:1100–22. doi: 10.1177/1745691617693393

49. Chekroud AM, Zotti RJ, Shehzad Z, Gueorguieva R, Johnson MK, Trivedi MH, et al. Cross-trial prediction of treatment outcome in depression: a machine learning approach. *Lancet Psychiatry*. (2016) 3:243–50. doi: 10.1016/S2215-0366(15)00471-X

50. Iniesta R, Malki K, Maier W, Rietschel M, Mors O, Hauser J, et al. Combining clinical variables to optimize prediction of antidepressant treatment outcomes. *J Psychiatr Res*. (2016) 78:94–102. doi: 10.1016/j.jpsychires.2016.03.016

51. Iniesta R, Hodgson K, Stahl D, Malki K, Maier W, Rietschel M, et al. Antidepressant drug-specific prediction of depression treatment outcomes from genetic and clinical variables. *Sci Rep*. (2018) 8:5530. doi: 10.1038/s41598-018-23584-z

52. Kautzky A, Möller HJ, Dold M, Bartova L, Seemüller F, Laux G, et al. Combining machine learning algorithms for prediction of antidepressant treatment response. *Acta Psychiatr Scand*. (2021) 143:36–49. doi: 10.1111/acps.13250

53. Mehltretter J, Rollins C, Benrimoh D, Fratila R, Perlman K, Israel S, et al. Analysis of features selected by a deep learning model for differential treatment selection in depression. *Front Artif Intell*. (2020) 2. doi: 10.3389/frai.2019.00031

54. Uher R, Tansey KE, Malki K, Perlis RH. Biomarkers predicting treatment outcome in depression: what is clinically significant? *Pharmacogenomics*. (2012) 13:233–40. doi: 10.2217/pgs.11.161

55. AsPredicted. Available online at: https://aspredicted.org/blind.php?x=56J_LDS.

56. Baeza-Delgado C, Cerdá Alberich L, Carot-Sierra JM, Veiga-Canuto D, Martínez de Las Heras B, Raza B, et al. A practical solution to estimate the sample size required for clinical prediction models generated from observational research on data. *Eur Radiol Exp*. (2022) 6:22. doi: 10.1186/s41747-022-00276-y

57. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol*. (2007) 165:710–8. doi: 10.1093/aje/kwk052

58. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412. doi: 10.1002/wps.21120

59. U.S. Food and Drug Administration. *Major depressive disorder: developing drugs for treatment*. Silver Spring: U.S: Food and Drug Administration: Center for Drug Evaluation and Research (2018).

60. European Medicines Agency. *Guideline on clinical investigation of medicinal products in the treatment of depression - Revision 2*. Amsterdam: European Medicines Agency (2013).

61. Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. (2003) 41:1284–92. doi: 10.1097/01.MLR.0000093487.78664.3C

62. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J BioMed Inform*. (2009) 42:377–81. doi: 10.1016/j.jbi.2008.08.010

63. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. *J BioMed Inform*. (2019) 95:103208. doi: 10.1016/j.jbi.2019.103208

64. Stoet G. PsyToolkit: A software package for programming psychological experiments using Linux. *Behav Res Methods*. (2010) 42:1096–104. doi: 10.3758/BRM.42.4.1096

65. Stoet G. PsyToolkit: A novel web-based method for running online questionnaires and reaction-time experiments. *Teach Psychol*. (2017) 44:24–31. doi: 10.1177/0098628316677643

66. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. (1999) 282:1737–44. doi: 10.1001/jama.282.18.1737

67. Watson D, O'Hara MW, Naragon-Gainey K, Koffel E, Chmielewski M, Kotov R, et al. Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment*. (2012) 19:399–420. doi: 10.1177/1073191112449857

68. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: A scale development study. *J Res Personal*. (2006) 40:1086–102. doi: 10.1016/j.jrp.2005.11.001

69. Fehnel SE, Bann CM, Hogue SL, Kwong WJ, Mahajan SS. The development and psychometric evaluation of the Motivation and Energy Inventory (MEI). *Qual Life Res Int J Qual Life Asp Treat Care Rehabil*. (2004) 13:1321–36. doi: 10.1023/B:QURE.0000037502.64077.4d

70. Wardenaar KJ, van Veen T, Giltay EJ, de Beurs E, Penninx BWJH, Zitman FG. Development and validation of a 30-item short adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ). *Psychiatry Res*. (2010) 179:101–6. doi: 10.1016/j.psychres.2009.03.005

71. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, O'McCormick RA, et al. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *J Abnorm Psychol*. (1995) 104(1):3–14. doi: 10.1037//0021-843x.104.1.3

72. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther*. (1995) 33:335–43. doi: 10.1016/0005-7967(94)00075-U

73. Gooding DC, Pflum MJ. The assessment of interpersonal pleasure: Introduction of the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) and preliminary findings. *Psychiatry Res*. (2014) 215:237–43. doi: 10.1016/j.psychres.2013.10.012

74. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *J Pers Soc Psychol*. (1994) 67:319–33. doi: 10.1037//0022-3514.67.2.319

75. Deyoung C, Quilty L, Peterson J. Between facets and domains: 10 aspects of the big five. *J Pers Soc Psychol*. (2007) 93:880–96. doi: 10.1037/0022-3514.93.5.880

76. Breiman L. Random forests. *Mach Learn*. (2001) 45:5–32. doi: 10.1023/A:1010933404324

77. Cutler A, Cutler DR, Stevens JR. Random forests. In: Zhang C, Ma Y, editors. *Ensemble Machine Learning: Methods and Applications*. MA: Springer US, Boston (2012). p. 157–75. doi: 10.1007/978-1-4419-9326-7_5

78. Kuhn M. Building predictive models in R using the caret package. *J Stat Software*. (2008) 28:1–26. doi: 10.18637/jss.v028.i05

79. Liaw A, Wiener M. Classification and regression by randomForest. *Forest*. (2001) 23:18–22.

80. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing (2013). Available at: http://www.R-project.org/.

81. Buuren Sv, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Software*. (2011) 45:1–67. doi: 10.18637/jss.v045.i03

82. Diaz-Uriarte R. GeneSrF and varSelRF: a web-based tool and R package for gene selection and classification using random forest. *BMC Bioinf*. (2007) 8:328. doi: 10.1186/1471-2105-8-328

83. Díaz-Uriarte R, Alvarez de Andrés S. Gene selection and classification of microarray data using random forest. *BMC Bioinf*. (2006) 7:3. doi: 10.1186/1471-2105-7-3

84. Horn JL. A rationale and test for the number of factors in factor analysis. *Psychometrika*. (1965) 30:179–85. doi: 10.1007/BF02289447

85. Revelle WR. psych: procedures for personality and psychological research(2017). Available online at: https://CRAN.R-project.org/package=psych.

86. Hartigan JA, Wong MA. A K-means clustering algorithm. *J R Stat Soc Ser C Appl Stat*. (1979) 28:100–8. doi: 10.2307/2346830

87. Kassambara A. Factoextra: extract and visualize the results of multivariate data analyses(2016). Available online at: http://www.sthda.com/english/rpkgs/factoextra.

88. Charrad M, Ghazzali N, Boiteau V, Niknafs A. NbClust: an R package for determining the relevant number of clusters in a data set. *J Stat Software*. (2014) 61:1–36. doi: 10.18637/jss.v061.i06

89. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

90. Kautzky A, Dold M, Bartova L, Spies M, Vanicek T, Souery D, et al. Refining prediction in treatment-resistant depression: results of machine learning analyses in the TRD III sample. *J Clin Psychiatry*. (2018) 79:16m11385. doi: 10.4088/JCP.16m11385

91. Riedel M, Möller HJ, Obermeier M, Adli M, Bauer M, Kronmüller K, et al. Clinical predictors of response and remission in inpatients with depressive syndromes. *J Affect Disord*. (2011) 133:137–49. doi: 10.1016/j.jad.2011.04.007

92. Perini G, Ramusino MC, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: Recent advances and novel treatments. *Neuropsychiatr Dis Treat*. (2019) 15:1249–58. doi: 10.2147/NDT

93. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med*. (2014) 44:2029–40. doi: 10.1017/S0033291713002535

94. Guesdon A, Lejeune FX, Rotgé JY, George N, Fossati P. Mind-wandering changes in dysphoria. *Front Psychiatry*. (2020) 11:544999. doi: 10.3389/fpsyt.2020.544999

95. Messerotti Benvenuti S, Mennella R, Buodo G, Palomba D. Frontal theta activity as an EEG correlate of mood-related emotional processing in dysphoria. *J Psychopathol Behav Assess*. (2017) 39:241–52. doi: 10.1007/s10862-016-9572-8

96. Cepeda MS, Reps J, Ryan P. Finding factors that predict treatment-resistant depression: Results of a cohort study. *Depress Anxiety*. (2018) 35:668–73. doi: 10.1002/da.2018.35.issue-7

97. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Res*. (2016) 240:421–30. doi: 10.1016/j.psychres.2016.04.034

98. Hu MX, Turner D, Generaal E, Bos D, Ikram MK, Ikram MA, et al. Exercise interventions for the prevention of depression: a systematic review of meta-analyses. *BMC Public Health*. (2020) 20:1255. doi: 10.1186/s12889-020-09323-y

99. Morres ID, HatziGeorgiadis A, Stathi A, Comoutos N, Arpin-Cribbie C, Krommidas C, et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depress Anxiety*. (2019) 36:39–53. doi: 10.1002/da.22842

100. Pascoe MC, Parker AG. Physical activity and exercise as a universal depression prevention in young people: A narrative review. *Early Interv Psychiatry*. (2019) 13:733–9. doi: 10.1111/eip.12737

101. Bellón JÁ, Conejo-Cerón S, Sánchez-Calderón A, Rodríguez-Martín B, Bellón D, Rodríguez-Sánchez E, et al. Effectiveness of exercise-based interventions in reducing depressive symptoms in people without clinical depression: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry*. (2021) 219:578–87. doi: 10.1192/bjp.2021.5

102. Saeed SA, Cunningham K, Bloch RM. Depression and anxiety disorders: benefits of exercise, yoga, and meditation. *Am Fam Physician*. (2019) 99:620–7.

103. Lockwood P, Jordan CH, Kunda Z. Motivation by positive or negative role models: Regulatory focus determines who will best inspire us. *J Pers Soc Psychol*. (2002) 83:854–64. doi: 10.1037//0022-3514.83.4.854

104. Higgins ET. Beyond pleasure and pain. *Am Psychol*. (1997) 52:1280–300. doi: 10.1037//0003-066X.52.12.1280

105. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA, et al. Selective serotonin reuptake inhibitors and adverse effects: A narrative review. *Neurol Int*. (2021) 13:387–401. doi: 10.3390/neurolint13030038

106. Jakubovski E, Johnson JA, Nasir M, Müller-Vahl K, Bloch MH. Systematic review and meta-analysis: Dose–response curve of SSRIs and SNRIs in anxiety disorders. *Depress Anxiety*. (2019) 36:198–212. doi: 10.1002/da.2019.36.issue-3

107. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs Context*. (2015) 4:212290. doi: 10.7573/17404398

108. Barnhart WJ, Makela EH, Latocha MJ. SSRI-induced apathy syndrome: A clinical review. *J Psychiatr Pract*. (2004) 10:196. doi: 10.1097/00131746-200405000-00010

109. Opbroek A, Delgado PL, Laukes C, McGahuey C, Katsanis J, Moreno FA, et al. Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *Int J Neuropsychopharmacol*. (2002) 5:147–51. doi: 10.1017/S1461145702002870

110. Price J, Cole V, Goodwin GM. Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. *Br J Psychiatry*. (2009) 195:211–7. doi: 10.1192/bjp.bp.108.051110

111. Cash RFH, Weigand A, Zalesky A, Siddiqi SH, Downar J, Fitzgerald PB, et al. Using brain imaging to improve spatial targeting of transcranial magnetic stimulation for depression. *Biol Psychiatry*. (2021) 90:689–700. doi: 10.1016/j.biopsych.2020.05.033

112. Fenoy AJ, Quevedo J, Soares JC. Deep brain stimulation of the "medial forebrain bundle": a strategy to modulate the reward system and manage treatment-resistant depression. *Mol Psychiatry*. (2022) 27:574–92. doi: 10.1038/s41380-021-01100-6

113. Ryan J, Pouliot JJ, Hajcak G, Nee DE. Manipulating reward sensitivity using reward circuit–targeted transcranial magnetic stimulation. *Biol Psychiatry Cognit Neurosci Neuroimaging*. (2022) 7:833–40. doi: 10.1016/j.bpsc.2022.02.011

114. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: A paradigm shift for depression research and treatment. *Neuron*. (2019) 101:774–8. doi: 10.1016/j.neuron.2019.02.005

115. Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. A meta-analysis of electroconvulsive therapy efficacy in depression. *J ECT*. (2003) 19:139. doi: 10.1097/00124509-200309000-00005

116. Dandekar MP, Fenoy AJ, Carvalho AF, Soares JC, Quevedo J. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. *Mol Psychiatry*. (2018) 23:1094–112. doi: 10.1038/mp.2018.2

117. Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sánchez E, Gutiérrez-Rojas L, Meana JJ. Antidepressant efficacy and tolerability of ketamine and esketamine: A critical review. *CNS Drugs*. (2018) 32:411–20. doi: 10.1007/s40263-018-0519-3

118. Arns M, van Dijk H, Luykx JJ, van Wingen G, Olbrich S. Stratified psychiatry: Tomorrow's precision psychiatry? *Eur Neuropsychopharmacol*. (2022) 55:14–9. doi: 10.1016/j.euroneuro.2021.10.863

119. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE: synthetic minority over-sampling technique. *J Artif Intell Res*. (2002) 16:321–57. doi: 10.1613/jair.953

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Depression with comorbid borderline personality disorder - could ketamine be a treatment catalyst?

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Borderline personality disorder (BPD) is diagnosed in 10-30% of patients with major depressive disorder (MDD), and the frequency of MDD among individuals with BPD reaches over 80%. The comorbidity of MDD and BPD is associated with more severe depressive symptoms and functional impairment, higher risk of treatment resistance and increased suicidality. The effectiveness of ketamine usage in treatment resistant depression (TRD) has been demonstrated in numerous studies. In most of these studies, individuals with BPD were not excluded, thus given the high co-occurrence of these disorders, it is possible that the beneficial effects of ketamine also extend to the subpopulation with comorbid TRD and BPD. However, no protocols were developed that would account for comorbidity. Moreover, psychotherapeutic interventions, which may be crucial for achieving a lasting therapeutic effect in TRD and BPD comorbidity, were not included. In the article, we discuss the results of a small number of existing studies and case reports on the use of ketamine in depressive disorders with comorbid BPD. We elucidate how, at the molecular and brain network levels, ketamine can impact the neurobiology and symptoms of BPD. Furthermore, we explore whether ketamine-induced neuroplasticity, augmented by psychotherapy, could be of use in alleviating core BPD-related symptoms such as emotional dysregulation, self-identity disturbances and self-harming behaviors. We also discuss the potential of ketamine-assisted psychotherapy (KAP) in BPD treatment. As there is no standard approach to the application of ketamine or KAP in individuals with comorbid TRD and BPD, we consider further research in the field as imperative. The priorities should include development of dedicated protocols, distinguishing subpopulations that may benefit most from such treatment and investigating factors that may influence its effectiveness and safety.

KEYWORDS

ketamine, esketamine, depression, treatment resistant depression (TRD), borderline personality disorder, ketamine-assisted psychotherapy (KAT)

Introduction

Borderline personality disorder (BPD) is diagnosed in 10-30% patients with major depressive disorder (MDD), whereas the incidence of MDD in BPD individuals ranges from 71% to 83% (1–3). Comorbidity of BPD and MDD negatively affects prognosis of both disorders and is associated with more severe depressive symptoms and functional impairment, delayed time to remission and shorter time to relapse (4, 5). Moreover, available treatment options such as antidepressants, electroconvulsive therapy, and psychotherapy are far less effective in such individuals (6–8). In this article we elucidate how, at the molecular and brain network levels, ketamine can impact the neurobiology and symptoms of BPD. We also discuss the results of existing studies and case reports on the use of ketamine/esketamine in BPD or depressive disorders with comorbid BPD. Furthermore, we explore whether ketamine-induced, psychotherapy-augmented neuroplasticity, augmented by psychotherapy, could prove effective in alleviating core BPD-related symptoms. Moreover, we discuss the potential of ketamine-assisted psychotherapy (KAP) in MDD with comorbid BPD.

Clinical outline

According to International Classification of Diseases 11th Revision (ICD-11) borderline personality is a pattern specifier used in combination with a personality disorder category or a personality difficulty. It may be applied to individuals whose personality disturbance is characterized by a pervasive instability of interpersonal relationships, self-image, affects and marked impulsivity (9). Subjects with BPD experience profound mood disturbances, persistent negative affect and excessive emotional reactions especially in response to social rejection and abandonment (10, 11). Both MDD and BPD highly correlate with non-suicidal self-injuries (NSSI) (12). NSSI is common in BPD patients (50-80% of cases) and approximately 40% of patients committed more than 50 self-mutilations (13). It is estimated that 40 to 85% of BPD individuals attempt suicide, usually multiple times, and up to 10% die as a result (13, 14). Soloff et al. found that comorbidity of BPD with MDD increases the number and severity of suicide attempts (15). A recent study supported findings that comorbid BPD plays crucial role as a risk factor for suicide attempts in depression (16).

Other core features of BPD include impulsivity, emotional dysregulation and disturbed self-identity (17–19). Impulsive behavior in BPD is closely linked to emotional suffering and low distress tolerance (20). Emotional dysregulation is related to heightened negative affect, sensitivity, low self-awareness and deficits in applying regulation strategies (18). Instead of adaptive regulation, maladaptive coping mechanisms are present. These include ruminations, NSSI, impulsive suicidal behaviors and substance abuse (11). Soloff et al. observed that negative affectivity is linked with clinical severity of suicide attempts and reduced inhibitory control (21). A high percentage of patients exhibit stress-related dissociative experiences such as derealization and depersonalization, which, along with the desire to reduce emotional tension, are the main driving factors for self-harm in BPD (20).

Self-identity disturbances in BPD manifest as an inconsistent, non-integrated sense of self and unstable, usually negative self-esteem (20). Individuals with BPD experience high levels of self-criticism, low self-compassion, strongly impaired self-reflection and disoriented life narratives (19, 22). These disturbances result in distrust in their own judgment and long-term difficulties with self- and goal-oriented behavior (20). Moreover, high self-criticism and low self-compassion are related to NSSI (23).

In patients with MDD and BPD, the prevalence of post-traumatic stress disorder (PTSD) is significantly higher than in patients without BPD diagnosis (24). It is estimated that 22-24% of subjects with primary diagnosis of PTSD have comorbid BPD, whereas the prevalence of PTSD in BPD population ranges from 33 to 79% (25, 26). Thus, the comorbidity of BPD and PTSD, as well as BPD with PTSD and MDD seems to be relatively frequent. It is perhaps unsurprising given that BPD is considered a potential risk factor for PTSD (24). In comparison with single-disorder groups, these patients often experienced greater exposure to trauma and more severe mood instability (27). Traumatic or disturbed early relationship experiences may result in insecure attachment patterns and impaired emotional processing (28). It is worth mentioning that complex PTSD (cPTSD), a diagnostic category added recently to ICD-11, in addition to PTSD symptoms, is characterized by disturbances in self-organization, which are conceptualized similarly to BPD symptoms (9).

Potential neurobiological background of BPD symptoms

In BPD brain dysfunction centers around hypoactive anterior cingulate cortex (ACC), hyperactive amygdala and insula, as well as functional dysconnectivity within and between large brain networks (11). Although recent meta-analysis showed no consistent pattern of alterations in brain activity, it reported a dysfunction of amygdala and ACC during processing of emotional stimuli (29). Goldstein et al. found that BPD subjects, when exposed to repeated negative stimuli, exhibit amplified amygdala response. This evidences impaired amygdala habituation (30). Extensive response to negatively valenced information is associated with higher anxiety, aggression and affective instability levels (11). Hyperresponsiveness of amygdala may prompt individuals to excessively process negative affective stimuli. For BPD subjects, painful stimuli were proven to normalize stress levels and amygdala activity, which may explain frequent NSSI (31, 32).

Baczkowski et al. demonstrated that in BPD, an increase in connectivity resulting from performing emotional regulation tasks does not occur in regions essential for effortful emotional regulation, such as prefrontal cortex (PFC). As a result, cognitive control, which enables reinterpretation of meaning of emotional stimuli, is impaired (33). Frontolimbic dysconnectivity hypothesis, which includes deficient top-down control and enhanced bottom-

up regulation, explains the neural mechanism of affective instability in BPD, as well as preoccupation with negative ideation in MDD (11, 34). Reduced top-down regulatory activity in brain regions supporting cognitive control such as dorsolateral PFC (dlPFC) and dorsal ACC (dACC) may result in the inability to suppress distracting emotional influences (35). On the other hand, abnormal bottom-up regulation is linked with increased amygdala activity. It results in excessive responses to emotional stimuli that dysregulate cognitive control (34).

A growing body of evidence based on resting state functional magnetic resonance (rs-fMRI), supports the presence of alterations in functional network connectivity in BPD. Aguilar-Ortiz et al. showed failures in deactivation in key regions of default mode network (DMN), such as medial frontal cortex and the precuneus (36). Activity within DMN is related to internally directed, self-referential processes and ruminations (37). O'Neil et al. reported increased connectivity between precuneus and frontal regions, which are responsible for processing of self-referential thoughts and information (38). Ruminative thinking triggered by negative affect influences severity of BPD symptoms (39). Van Schie et al. indicated that in BPD individuals, altered activity of temporolimbic areas and precuneus leads to focusing on negative feedback which maintains their negative self-esteem (40). Heightened sensitivity to social exclusion may be significantly associated with precuneus and insula activation (41). Abnormal activation of the insula, one of the key salience network (SN) nodes, during affective and pain regulation is believed to be one of neural mechanisms underlying NSSI in BPD patients (42). In BPD, hyperconnectivity within SN nodes (amygdala and insula with dACC) is associated with emotional hypersensitivity, whereas reduced connectivity between SN and frontoparietal regions of central executive network (CEN) contributes to impaired control over emotional reactions (43).

Among neurobiological alterations present in BPD, opioid neurotransmission disturbances are also of interest. Low basal opioid concentration may manifest as chronic dysphoria and a lack of sense of wellbeing. Low opioid levels along with compensatory higher sensitivity of μ-opioid receptors may explain repetitive NSSI as a behavior which leads to increase in opioid neurotransmission (44). Adverse experiences, such as childhood abuse, common in BPD, are thought to result in modulation of the opioid system (45). Importantly, intrapsychic pain, same as the physical, is regulated by opioids and the neural network comprising e.g. ACC, insula, amygdala, hypothalamus and nucleus accumbens (46). Opioid disturbances in BPD can contribute to emotional suffering related to social rejection or exclusion manifesting in self-harm and suicide (47).

Current BPD treatment outlook

There is no approved pharmacological treatment for BPD (20). Additionally, meta-analyses have shown that no pharmacotherapy appears to be effective for the overall severity of BPD symptoms (48, 49). However, some agents prove to be beneficial in several types of BPD symptoms, thus a symptom-targeted pharmacotherapy is a common strategy in clinical practice (50). Selective serotonin (SSRIs) and serotonin and norepinephrine (SNRI) reuptake inhibitors may be beneficial in reducing impulsivity, affective lability, irritability and somatic symptoms, although there is no conclusive evidence that they may contribute to consistent reduction of the severity of BPD (51, 52). According to American Psychiatric Association (APA) guidelines, SSRI or SNRI should be a first-line pharmacological treatment of affective dysregulation and impulsive-behavioral dyscontrol symptoms in BPD (53). On the other hand, in a more recent review, Bohus et al. conclude, that there is no sufficient evidence to support SSRI use in the treatment of BPD psychopathology, unless antidepressant effect is required (20). Low-certainty, limited evidence suggests that anticonvulsants such as valproate, lamotrigine and topiramate can be beneficial in anger, aggression, and affective lability associated with BPD (51). However, as APA guidelines indicate, mood stabilizers (lithium, valproate or carbamazepine) may be considered as a second-line or adjunctive treatment of symptoms within the above domains (53). Second generation antipsychotics have been reported to reduce anger, affective instability, impulsivity, paranoid ideation, dissociative symptoms and anxiety in BPD (52). APA guidelines recommend those particularly in treatment of cognitive-perceptual BPD symptoms, whereas The National Institute for Health and Care Excellence (NICE) guidelines state that antipsychotics can be considered only as a crisis treatment, prescribed for no longer than 1 week (54). A recently published comparative effectiveness research study, indicated that among all pharmacotherapies employed in BPD patients, only the treatment with attention deficit hyperactivity disorder medication was associated with a reduced risk of suicidal behaviors (55). Some authors suggest that therapy of BPD needs to be prioritized when BPD and depression co-occur (1). It seems more accurate however, that non-BPD disorder (i.e. MDD) should be managed in parallel with BPD-oriented psychotherapy (20).

Among BPD-specific psychotherapies, dialectical behavior therapy (DBT) and mentalization-based treatment (MBT) have been studied most extensively. Transference-focused psychotherapy (TFP) and schema-focused therapy (SFT) are also established psychotherapeutic strategies for BPD (56). DBT focuses on symptoms of emotional dysregulation, MBT – difficulties in identifying oneself and others mental states, TFP – unintegrated, undifferentiated images and representations of oneself and others, often following early-experienced trauma, while SFT - dysfunctional life schemas and thinking patterns (20). BPD-specific approaches were shown to support improvements in BPD symptoms and psychological well-being, but their effectiveness is reported to be moderate. Additionally, they do not fulfil the need for rapid symptom reduction, have limited accessibility and high dropout rate (57, 58). A recent review of 28 studies of various modalities psychotherapy in BPD (with DBT as the most frequent) indicated that approximately half of the patients did not respond to treatment and over a quarter of patients dropped out (56). A meta-analysis of DBT studies regarding its impact on suicidality revealed reduced self-directed violence and frequency of crisis services interventions with no significant improvement in suicidal thoughts (59). A recent Cochrane review of psychotherapies applied in BPD found no improvement in interpersonal and

psychosocial functioning, fear of abandonment, affective instability and feeling of emptiness at 6 to 12 months after the end of treatment (49).

Antidepressant and antisuicidal efficacy of ketamine

Ketamine administration in MDD and treatment resistant depression (TRD) is widely researched, with its efficacy evidenced in numerous double-blind, randomized clinical trials (RCT) (60–67). It is regarded as fast-acting antidepressant (68–70). Kryst et al. have shown that a single infusion may result in a significant antidepressive effect lasting for up to 7 days, which can be sustained by repeated infusions (70). The vast majority of RCTs of ketamine in MDD did not exclude patients with comorbid BPD (60–67). In a midazolam-controlled study on MDD individuals with significant suicidal ideation, 28% of participants met the diagnostic criteria for BPD, with ketamine proving to be superior in reduction of depressive symptoms and suicidal ideation within 24 hours after the single infusion. The authors reported that clinical improvement was maintained for up to 6 weeks (71). Given the high co-occurrence of MDD and BPD, it is possible that the beneficial effects of ketamine can also extend to the subpopulation with BPD. However, no protocols were developed that would account for this comorbidity. Additionally, many of the esketamine randomized clinical trials excluded individuals with BPD (72–75). Notwithstanding, real-world study of esketamine in TRD including 15% of individuals with comorbid personality disorders, indicated significant reduction of depressive symptoms and suicidal thoughts (76). Three months after beginning of treatment, clinical response and remission rates were high - 64,2% and 40,6%, respectively. Moreover, no differences in efficacy of esketamine were found among patients with and without comorbid personality disorders.

Both ketamine and esketamine are proven to rapidly decrease suicidal thoughts. Chen et al. assessed the antisuicidal effect of ketamine as 'large' or 'medium-large' (after 4-6 and 24 hours after infusion, respectively), whereas the effect of intranasal esketamine was reported as 'small-medium' (77). Ketamine-induced decrease in suicidal thoughts may be partially independent of the improvement in depressive symptoms (71). Lengvenyte et al. suggested that ketamine may be particularly useful in patients with stress-induced suicidal ideation, which is common in BPD (47).

Ketamine's mechanisms of antidepressant action

Ketamine is a racemic mixture of two enantiomers, esketamine and arketamine (78). It is a nonselective, noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist, which binds to the phencyclidine site of this receptor (78). Importantly, ketamine preferentially blocks NMDAR on the inhibitory gamma-aminobutyric acid (GABA) interneurons. This preferential action of ketamine leads to pyramidal cell disinhibition and an increase in overall excitatory glutamatergic neurotransmission, especially the prefrontal cortex and cortico-limbic regions, which are associated with mood regulation (79). Ketamine is hypothesized to inhibit extra-synaptic GluN2B-NMDAR. Their activation results in suppression of protein synthesis. Therefore, the blockade of GluN2B-NMDAR de-suppresses protein synthesis, which may induce antidepressant action via a mechanistic target of rapamycin (mTOR)-dependent pathway (80). However, it seems that blocking NMDAR may not be the main mechanism of ketamine's therapeutic effect, as studies of other NMDAR antagonists did not show their antidepressant efficacy (68, 81). Meta-analysis of placebo-controlled trials using racemic ketamine or esketamine did not show greater antidepressant efficacy of esketamine, even though esketamine has a 3-4 times greater affinity for NMDAR than arketamine (69). In turn, arketamine, despite its lower affinity for NMDAR showed a greater antidepressant effect in preclinical studies (82, 83). (2R, 6R)-hydroxynorketamine, a metabolite of arketamine with low affinity for NMDAR, also showed a rapid antidepressant effect in rodents. It has been proposed that this metabolite might be a key component of ketamine's antidepressant effectiveness (83). However, it was not confirmed in studies on patients with depression, as higher level of hydroxynorketamine was associated with less significant clinical improvement (84, 85).

The aforementioned prefrontal cortex disinhibition is thought to be associated with an increase in dopaminergic, serotoninergic and noradrenergic transmissions in cortical and subcortical brain regions (79). In the region of lateral habenula, regarded as an 'anti-reward center' because of its engagement in negative emotion coding, ketamine inhibits NMDA dependent neuronal bursting activity (86). Subsequently, the downstream monoaminergic reward centers in ventral tegmental area and dorsal raphe nucleus become disinhibited, the reward processing is restored and pleasure perception increases (47).

Ketamine increases activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) which play crucial role in long-term potentiation (LTP). LTP is one of phenomena underlying synaptic plasticity, that results in a persistent strengthening of synapses (87). AMPAR activation leads to the release of the brain derived neurotrophic factor (BDNF) and enhances the availability of its tropomyosin kinase B (TRKB) receptor (87, 88). Neuroplasticity is considered as a key mechanism of ketamine antidepressive action. Meta-analysis on the potential biomarkers of ketamine efficacy indicated that patients who exhibited increased BDNF levels during treatment were more likely to become responders (89).

Furthermore, ketamine and esketamine are thought to share several mechanisms of action with mood stabilizers and act as cellular membrane stabilizers, as well as modulators of neuronal excitability. Acting on GluN2D NMDAR subunits reduces the influx of Ca2+ ions, which leads to restoration of membrane potential which subsequently alters protein translation and availability which finally results in neuroplasticity enhancement (90). Preclinical studies revealed that ketamine and, to a greater extent, esketamine may also inhibit the voltage-gated sodium channels (VGSC) and reduce the influx of Na+, which in turn

decreases the excitatory neurotransmission (91). Importantly, this mechanism of action forms a molecular basis of therapeutic effect of several mood stabilizers such as valproate, carbamazepine and lamotrigine (92). On the other hand, ketamine, similarly to lithium, inhibits the glycogen synthase kinase 3β (GSK-3β) pathways (through GSK-3β phosphorylation), which is considered as possible significant mechanism contributing to its antidepressant and neuroplastic effect (93). As mood stabilizers are reported to be, to a certain extent, effective in reducing impulsivity, aggression and anger in BPD, the above molecular effects of ketamine may also prove to be advantageous in treatment of depression with comorbid BPD. Interestingly, McIntyre et al. indicated that ketamine may be effective in treatment-resistant MDD or bipolar disorder with mixed features such as anxiety, irritability and agitation (94).

Influence that ketamine exerts on the opioid system may prove beneficial in BPD, in which opioid neurotransmission seems to be disturbed. Ketamine as an agonist of opioid receptors increases basal opioid levels (83). Research indicates that blocking the opioid receptors with naltrexone reduces both antidepressant and antisuicidal effects (95). Moreover, it is suggested that dynorphins, as an endogenic agonist of κ-opioid receptors, may mediate emotional pain, dysphoria and promote self-harm behaviors (96). Ketamine is thought to cause down-regulation of κ-opioid receptors and resolve imbalance between 'hedonic' μ- and 'dysphoric' κ-opioid receptors activity (97). We speculate that ketamine modulatory effect on opioid neurotransmission may contribute to reduction in negative affect and autodestructive tendencies in BPD individuals.

Ketamine-induced alterations in brain activity

Numerous studies indicate that remitters treated with ketamine exhibit normalization in intra- and inter-network functional connectivity (67, 98, 99). ACC-related circuit modulation is thought to be crucial in ketamine antidepressant and antisuicidal action (100). Alexander speculates that ketamine acute effects on subgenual ACC reflect in shutting down emotional pain network and alleviating affective pain, whereas sustained effects on neuroplastic modulation in DMN contribute to resolving of ruminative thinking patterns (97). Similarly to serotoninergic psychedelics, ketamine has been shown to acutely disintegrate functional connectivity in DMN and decrease activity within this network (101, 102).

Evans et al. indicated normalization of the interaction between DMN and SN in MDD individuals after ketamine infusion (103). Ketamine also increases connectivity between DMN and CEN nodes (104–108). It could prove beneficial for both MDD and BPD patients as such increase facilitates shifting attention from internal, self-referential thought processes towards external, goal-directed tasks (109). Vasavada et al. indicated that repeated ketamine administrations lead to increased top-down control of emotional processes and restored top-down regulation of ventral limbic structures (110). Sterpenich et al. have reported that ketamine application resulted in decreased amygdala, insula and dACC responses to negative stimuli during an emotional recognition task (111). Normalization of these SN nodes overactivity is thought to play an important role in the antidepressant effect (43, 112).

Ketamine is also reported to alleviate stress-related symptoms by enhancing neuroplasticity particularly in medial PFC (mPFC). Norbury et al. revealed that post-traumatic stress disorder (PTSD) symptoms improvement in ketamine group was associated with increased prefrontal top-down inhibition of amygdala in response to social signs of a threat. Moreover, individuals with lower baseline mPFC inhibition of amygdala showed greater clinical improvement as a result of ketamine treatment (113). The effect could also prove beneficial in BPD treatment, given that PTSD and BPD both exhibit reduced activation of executive-related frontal regions and hyperactivation of the emotion-related limbic regions.

Frontostriatal and interlimbic connectivity normalization caused by ketamine is thought to facilitate regaining cognitive control over emotional activity (101). It may prove significant for patients with comorbid depression and BPD who exhibit abnormalities in top-down and bottom-up processing. We speculate that ketamine impact on intra- and inter-network connectivity induces long-lasting cognitive and psychological flexibility, which in turn contributes to improvement in BPD-related negative self-schema and disturbed social cognition. Enhancement of neuroplasticity between limbic regions and networks essential for emotional regulation, self-awareness, goal-oriented and social behaviors may meaningfully impact treatment of TRD with comorbid BPD.

On the other hand, it was also reported that serial ketamine infusions result in significant decrease in activation of brain regions associated with response inhibition and inhibitory control network, which is related to improvement in depressive symptoms (114). Such normalization, while beneficial in TRD, may result in increased impulsivity and self-harming behaviors in comorbid BPD.

Stone et al. reported reduced activation in the left superior temporal cortex after ketamine infusion, which is associated with impaired self-monitoring (115). Hyperactive self-monitoring is considered to be a part of depression mindset, thus its reduction may be beneficial for MDD patients (116). However, in BPD individuals reduced ability to self-monitor may disrupt already low emotional awareness.

Ketamine/esketamine trials and case studies in BPD

Danyan et al. evaluated the therapeutic effect of ketamine (4 intravenous infusions in 2 weeks, 0,5-0,75mg/kg) in TRD patients with and without comorbid BPD. Both groups showed comparable improvement in depressive and anxiety symptoms, as well as in intensity of suicidal ideations. Reduction in depressive and BPD symptoms (measured with Borderline Symptom List, BSL-23) and

positive correlation between these improvements was indicated. The antidepressant effect of ketamine was more pronounced in patients with more severe baseline suicidal ideation. Moreover, improvements in social, family and work functionality scores were observed. Dissociative symptoms were mild and transient in both groups. Relevant limitations of the study included retrospective and open-label design and short (1 week) follow-up after final infusion (117).

In an open-label study Chen et al. explored the effectiveness and safety of single intravenous infusion (0,5mg/kg) in MDD individuals with or without elevated BPD features. Improvements in depressive symptoms as well as suicidal ideation were significant and comparable in both groups within 3 and 24h after infusion. In group encompassing MDD subjects with BPD features, the response after 14 days was of greater magnitude. Dissociative symptoms were mild, but more pronounced in BPD group 24h after infusion. Brief Psychiatric Rating Scale (BPRS) scores, reflecting the severity of psychotic symptoms, were very low at all times. It must be noted, however, that the study was not specifically focused on BPD and the groups were differentiated post-hoc (118).

A double blind, randomized, midazolam-controlled pilot study tested the effects of single ketamine infusion (0,5mg/kg) in a small sample of BPD individuals. It revealed no significant changes in suicidal ideation, depression, anxiety or BPD symptoms. A greater decrease in suicidality and depressive symptoms in ketamine group was found, but it was not statistically significant. However, the study indicated improvement in socio-occupational functioning in the ketamine group. Ketamine was well tolerated, no serious adverse events occurred. It is worth noting though, that two participants of the ketamine group experienced acute distress and suicidal ideations in 4th week after infusion - one was discharged after overnight evaluation and the other received further ketamine infusions as a part of inpatient treatment (119).

Nandan et al. published a case report of an 27-year old female with TRD and BPD, hospitalized after a suicide attempt. After initial stabilization in inpatient setting, intranasal esketamine treatment was started in the outpatient setting in conjunction with citalopram and buspirone. Initial esketamine dose equaled 56 mg administered twice a week in four weeks timespan, followed by 56 mg administered once per week, which was further increased to 84 mg once per week. Authors reported significant improvement in depressive symptoms and suicidality, as well as in core BPD symptoms within 4-5 weeks. Esketamine treatment was continued for the next two years with significant improvement observed in depressive symptoms, impulsivity, affective instability and psychosocial functioning. Frequency of self-harm attempts decreased. Nandan et al. reported patient's full compliance with treatment plan, with it being poor during previous therapies. Notably, the authors indicated the importance of maintenance treatment - when esketamine administration was omitted (due to the unavailability of medication), resurgence of affective instability and self-harm attempts occurred (120).

Another case report refers to 22-year old female with MDD, social phobia, BPD and frequent past NSSI. After two ketamine infusions (0,5mg/kg) during hospitalization, robust improvement in depressive symptoms, suicidal ideation, social functioning, emotional and behavioral dysregulation was observed. Subsequently, the treatment was continued in outpatient setting. During the last follow-up, half a year after first infusion, reduction in depressive and BPD symptoms was observed. The patient completed a 3-month inpatient DBT treatment during this time. Authors speculated that ketamine modulatory effect on neuroplasticity contributed substantially to the satisfactory result of DBT that followed (121).

Galuszko-Węgielnik et al. presented a case report of 26-year old female with BPD and bipolar treatment resistant depression, who was planned to receive 8 intravenous infusions of ketamine (0,5mg/kg). The patient experienced severe dissociative symptoms as a consequence of infusions and the third one was followed by increased suicidal ideation, impulsive behavior and NSSI. No improvement in depression was observed, therefore ketamine treatment was discontinued (122).

Vanicek et al. presented a case report of a 20-year old female with MDD and BPD, who received 5 intravenous infusions of esketamine (25-50mg) within 2 weeks. Initially, a rapid improvement in depressive symptoms and suicidal ideation was observed, but over the course of treatment disinhibition symptoms occurred. Increased emotional responsivity and decreased cognitive control contributed to an impulsive suicide attempt after fifth ketamine infusion. Due to deterioration of patient's mental condition, ketamine treatment was discontinued (123).

Research suggests that ketamine/esketamine treatment may be beneficial and safe for BPD or BPD with comorbid MDD patients. On the other hand, reports indicate that acute ketamine effects such as dissociation and altered perception of reality and oneself may increase affective instability and impulsive suicidal behaviors. It is worth noting though, that no psychotherapy or psychedelic integration parallel to ketamine/esketamine administrations have been attempted in any of the discussed trials and case studies except for Rogg et al. (121). The psychedelic effect of ketamine may evoke difficult experiences, therefore psychotherapeutic integration may prove essential for individuals with MDD and BPD during ketamine treatment (124).

Ketamine-assisted psychotherapy

In a recently published systematic review, KAP application was examined in a range of disorders including MDD, PTSD, substance abuse, obsessive-compulsive disorder, generalized anxiety disorder and neuropathic pain. Most studies were focused on cognitive-behavioral therapy (CBT) and mindfulness-based psychotherapy but some involved motivational enhancement therapy, exposure therapy, existentially oriented psychotherapy and functional analytic psychotherapy. Importantly, in most of the KAP-related studies individuals with comorbid BPD weren't excluded. Definite conclusions and recommendations were not formulated due to differences in psychotherapeutic approaches and research methodologies. It was evidenced however, that incorporation of psychotherapy throughout the course of ketamine treatment may give rise to and maintain clinical improvement by reducing depression, anxiety and pain (125). Dore et al. proved that with

KAP incorporation the higher baseline suicidality levels, the greater decrease in affective symptoms (126). Krupitsky et al. applied KAP in individuals with alcohol use disorder, which resulted in improvements in emotional dysregulation and personality characteristics linked to self-criticism (127). Application of KAP in depression with comorbid BPD has not been explored yet.

Wilkinson et al. proposed that ketamine-induced enhancement of neuroplasticity may open a window of opportunity, where cognitive flexibility and learning potential are increased. Authors suggested that ketamine may increase sensitivity within key brain regions (such as mPFC and hippocampus) and induce neuroplastic changes similar as in the use of CBT. It was shown that responders to ketamine exhibited rapid improvement in cognitive control, with CBT strengthening and maintaining that improvement, which in turn may result in reversal of disrupted information processing and maladaptive behaviors (128). Ketamine may also facilitate emotional learning and improvement of negative self-schema, which is one of the core cognitive aspects of both depression and BPD (125, 129). Moreover, ketamine-induced alteration in DMN activity is thought to enable subsequent revision of mental representations of self (102).

Most research involving application of ketamine in the treatment of mental disorders regards acute ketamine-induced symptoms as side effects, with their severity monitored using dissociative and psychotic symptoms scales (most commonly Clinician-Administered Dissociative States Scale and BPRS) (130). However, several studies point out that the quality of subjective experience during ketamine administration may substantially contribute to the overall therapeutic effect. Sumner et al. proved that a greater antidepressant response to ketamine correlated with higher scores in Alerted States of Consciousness (ASC) questionnaire. The study suggests that the psychedelic experience itself may play a significant role in ketamine's antidepressant properties (124). Aust et al. underpinned importance of considering subjective quality of ketamine induced psychological effects, indicating that anxiety-related experiences may be linked to the absence of the antidepressant effect (131). Subjective experiences were reported as significantly contributing to the therapeutic effect of ketamine not only in MDD. Mystical experiences were associated with improvement in cocaine and alcohol use disorder (132, 133). Krupitsky et al. pointed out, that in addiction treatment ketamine may provide transformative experiences. After being subjected to KAP patients with heroin use disorder rated their sense of control as significantly more 'internal', which resulted in a better outcome in heroin abstinence (134). Research also indicates that the transpersonal experience of ketamine may bring on personal insights and stimulate reframing of beliefs (125). Marguilho et al. suggested that psychedelic-assisted psychotherapy efficacy is most accurately predicted by questionnaires assessing subjective psychedelic experience, which involve ego-dissolution, emotional breakthrough and mystical experiences (102). Dore et al. argue that psychedelic and dissociative experiences are an integral part of KAP and should be supported in a psychotherapeutic context (126).

The influence that ketamine has on restructuring of traumatic memories is another potentially important effect in relation to psychotherapeutic treatment in TRD with comorbid BPD. Given the importance of traumatic experiences in BPD development, the conclusions inferred from studying KAP in PTSD are potentially applicable in BPD. Better access to traumatic memories and extinction of previously paired pain-related memories are among potential processes enabling efficacy of ketamine in PTSD treatment (135). Taking into consideration that ketamine's molecular and neural mechanisms of action are also involved in memory reconsolidation, Fattore et al. speculated that application of ketamine few hours prior to memory retrieval may trigger a metaplastic cascade. Increased synaptic plasticity and alterations in neural connectivity facilitate destabilization of memories and increases receptiveness to non-pharmacological interventions (136). Although there are concerns regarding increased risk of self-harm and suicidal behavior following trauma-focused treatments in BPD patients, a systematic review of psychotherapeutic approaches for comorbid BPD and PTSD treatment indicated that trauma-focused therapies may reduce both PTSD and BPD symptoms, whereas BPD-specific psychotherapies do not alleviate PTSD symptoms (137). Identifying and tying together past experiences and current symptoms may be helpful in understanding how trauma is reflected in patient's present problems. Integrating ketamine with evidence-based psychotherapy requires further exploration in populations with comorbid depression, BPD and PTSD. Interestingly, a study on 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in PTSD revealed that the effect of the intervention extended beyond specific PTSD symptomatology and resulted in long-term personality changes such as increased openness and decreased neuroticism (138).

Researchers also point out positive aspects of pairing ketamine with psychotherapy such as reduction in defensiveness and promoting recollection of emotionally arousing past experiences. Moreover, it is suggested that ketamine's rapid antidepressant and anxiolytic effects may enhance treatment adherence and engagement in building of the therapeutic alliance (125). This may result in considerable progress in BPD treatment, where compliance is low and drop-out rates are significant.

Limitations and risks of ketamine treatment in TRD patients with comorbid BPD

Increased emotional sensitivity, as well as cognitive and emotional overload during ketamine treatment may be overwhelming for BPD patients, especially in the absence of a therapeutic process. Dissociative symptoms in BPD individuals with a history of dissociation may be exacerbated after ketamine exposure (119). These may lead to self-harm, deterioration in emotional learning and weak psychotherapy response (139–141). Moreover, psychotic-like experiences may be traumatizing for vulnerable individuals. Similarly, reliving traumatic memories, especially outside of the psychotherapeutic context, may be linked with increased risk of self-harm and suicidal behaviors. Taking into

account BPD-related low tolerance of frustration and impulsivity, the risk of suicide may greatly increase in the absence of noticeable, rapid antidepressive effect of ketamine that the patient was expecting.

Additionally, the risk of addiction in BPD patients cannot be ignored. In a review of 70 studies, Trull et al. reported that approximately half of BPD patients exhibit at least one substance use disorder (SUD) (with alcohol being the most common), whereas approximately 25% of individuals with SUD also meet criteria for BPD (142). Notwithstanding, in research involving ketamine/esketamine in MDD no substantial risks related to its use in a controlled medical setting were reported, however no studies were performed with a focus on BPD patients, in which substance abuse is a common symptom of behavioral dysregulation (143). Recently, Chiappini et al. provided preliminary insights of effectiveness and safety of intranasal esketamine among TRD patients with comorbid substance use disorder. Antidepressant effect was significant and no cases of abuse of esketamine were reported. Despite significant methodological limitations, the authors considered esketamine as effective and safe in TRD patients with comorbid SUD (144).

Mitigating risks and improving results of ketamine treatment

NSSI and suicide risk assessment and management strategies, such as development of safety plan based on DBT interventions, should become integral part of the treatment process. In BPD, psychotherapy remains a first line treatment and its incorporation into ketamine treatment protocols appears to be necessary for patients safety and efficacy improvement. Given that exposure to ketamine may provoke strong emotional reactions and trigger maladaptive defense mechanisms in BPD patients, involvement of experienced therapists is critical. It is suggested that more frequent psychotherapeutic sessions and longer duration of psychotherapy leads to increase in the efficacy of KAP (125).

A realistic goal setting is an important theme during preparation to KAP. Introducing patient to various levels of ketamine action (e.g. neurobiological, psychological) may help setting reasonable expectations. Psychoeducation regarding the procedure may decrease the risk of anxiety occurrence and aid with immersion into the psychedelic experience.

The presence of qualified personnel is required to supervise patients physical safety and assist in navigating psychological distress (125). Additionally, the setting of treatment should facilitate relaxation and help with involvement in the psychedelic experience. Ketamine administration should be followed by psychedelic integration session in order for the patient to understand and accept the experience. Psychedelic integration, although variably defined, involves reflection, validation and making meaning of psychedelic experiences and ideally should lead to incorporation of the insights into everyday life (145).

Suggested direction of future studies

We recommend controlled trials of ketamine/esketamine treatment and assisted psychotherapy in patients with TRD with comorbid BPD to assess efficacy and safety of various protocols in that population. According to available data, we conclude that TRD patients with comorbid BPD are viable candidates for clinical trials when at least 2 adequate pharmacotherapies and psychotherapy turned out to be ineffective. Research involving patients at high suicide risk (e.g. multiple or recent suicide attempts), with frequent NSSI or severe dissociative symptoms should be performed in inpatient setting, where continuous, intensified medical and psychological care is available. In the course of trials it is vital to research whether the suicide ideations and substance abuse risks constitute a major obstacle in ketamine introduction to treatment strategies. Taking into consideration BPD symptoms persistence and their susceptibility to environmental conditions, trials that would include longer lasting follow-up seem to be of most value. Additionally, it is needed to establish the optimal frequency of ketamine administration and psychotherapeutic sessions, duration of treatment, as well as psychotherapeutic modality used in KAP. Some studies suggest superiority of higher doses of ketamine in KAP, thus it is also important to assess the effects of different dosing in TRD with comorbid BPD (126, 132).

Current state of research suggests that severe personality disorders, including BPD, may constitute contraindication to ketamine treatment. Criteria of personality disorders severity included in ICD-11 and DSM-5 are comparable to Kernberg's level of personality organization approach based on assessment of presence of psychological defense mechanisms, extent of reality testing the level of identity integration and the control of aggression. According to this model, more frequent use of primitive defense mechanisms to cope with stressors and conflicts, low ability to distinguish intrapsychic from external sources of stimuli, poor sense of self, highly disintegrated identity, inability to understand or accept ordinary social criteria of reality, as well as cognitive and affective inadequacy to the psychosocial situations, are considered as indicators of psychotic level of personality organization, reflecting severe personality disorder (146). In our opinion, TRD individuals with comorbid BPD who exhibit such severity of intrapsychic functioning disturbances, should not be qualified for ketamine treatment or KAP.

As the available research is insufficient to distinguish subpopulations that could benefit the most from the ketamine introduction, further research should focus on psychological and neurobiological predictors of the therapy outcome to distinguish clusters of TRD patients with comorbid BPD. Cluster differentiation could be centered around the efficacy and safety of ketamine/esketamine and KAP application in treating patients exhibiting varying intensity of personality traits typically present in BPD such as emotional lability, anxiousness, separation insecurity, depressivity, impulsivity, risk taking and hostility. Potential impact of severity of suicidal ideations, substance abuse and the

presence of common comorbid disorders such as PTSD, cPTSD, SUD, ADHD on the treatment outcome should also be of consideration.

As some reports suggest that ketamine and other psychedelics may affect personality traits, further studies are needed to evaluate the impact KAP has on personality dimensions (127, 138). The quality of subjective experience and psychedelic effect should be considered (measured by, for instance, ASC questionnaire) when evaluating clinical outcomes related to both depressive and BPD-specific symptoms such as suicidal ideation, fear of abandonment and feeling of emptiness.

Summary

BPD is a common comorbidity of TRD and it negatively affects the course, treatment, outcome and prognosis. Moreover, it was shown that in contrast to behavioral symptoms, BPD core affective dysfunctions persist into later course of disorder (147). Interpersonal stressors are known triggers of an affective dysregulation cascade in BPD, which may result in suicidal ideations and attempts (148). Efficacy of the available pharmacological and psychotherapeutic treatments is not sufficient, thus novel therapeutic approaches are needed. Ketamine, which is evidenced to have significant antidepressant and antisuicidal effect, may become one of those. It should be emphasized though, that in vast majority of ketamine trials in MDD, patients with comorbid BPD were not excluded, yet they were not treated as a distinct group. Therefore, the efficacy and safety of the treatment has not yet been evaluated for that population.

What is more, in MDD trials, as well as in a few studies focused on BPD patients, the administration of ketamine was paired with neither psychotherapy nor psychedelic integration. Taking into account the risk of affective decompensation following ketamine exposure, these processes should form a basis of a treatment strategy. Therapeutic interventions may also help with immersion into the ketamine experience, which subjective quality seems to be important for treatment results. Additionally, enhanced neuroplasticity occurring after ketamine administration may increase cognitive flexibility and emotional learning. This can lead to improved responses to psychotherapy.

On a neurobiological level, ketamine-induced changes seem to refer to alterations reported in BPD and result in revision of mental representations of self, as well as in improvements in cognitive control and emotional regulation. It is worth researching whether ketamine-induced normalization in top-down control and bottom-up regulation processes observed in MDD and PTSD could be applicable in MDD with BPD-related emotion dysregulation.

Considering the above, we emphasize the need for extensive research of efficacy and safety of ketamine treatment with assisted psychotherapy in patients suffering from TRD with comorbid BPD. This is a crucial need and a key direction, especially in the absence of effective pharmacotherapy for BPD.

Author contributions

MW: Conceptualization, Data curation, Investigation, Project administration, Writing – original draft. PM: Investigation, Writing – original draft, Data curation. JK: Conceptualization, Investigation, Writing – original draft. MM: Writing – original draft. WD: Writing – review & editing. MD: Writing – review & editing. AS: Supervision, Writing – review & editing.

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Conflict of interest

Authors MW and PM were employed by the company KeyClinic, a commercial mental health center which provides ketamine treatment, as one of many services. Author AS was employed by the company MindHealth, a commercial psychiatric center. AS was also a member of Janssen Cilag Advisory Board and gave lectures for Janssen Cilag.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Rao S, Broadbear J. Borderline personality disorder and depressive disorder. *Australas Psychiatry*. (2019) 27:573–7. doi: 10.1177/1039856219878643

2. Biskin RS, Frankenburg FR, Fitzmaurice GM, Zanarini MC. Pain in patients with borderline personality disorder. *Pers Ment Health*. (2014) 8:218–27. doi: 10.1002/pmh.1265

3. Shah R, Zanarini MC. Comorbidity of borderline personality disorder: current status and future directions. *Psychiatr Clin North Am*. (2018) 41:583–93. doi: 10.1016/j.psc.2018.07.009

4. Bellino S, Patria L, Paradiso E, Di Lorenzo R, Zanon C, Zizza M, et al. Major depression in patients with borderline personality disorder: a clinical investigation. *Can J Psychiatry*. (2005) 50:234–8. doi: 10.1177/070674370505000407

5. Gunderson JG, Stout RL, Shea MT, Grilo CM, Markowitz JC, Morey LC, et al. Interactions of borderline personality disorder and mood disorders over 10 years. *J Clin Psychiatry*. (2014) 75:829–34. doi: 10.4088/JCP.13m08972

6. Newton-Howes G, Tyrer P, Johnson T. Personality disorder and the outcome of depression: meta-analysis of published studies. *Br J Psychiatry*. (2006) 188:13–20. doi: 10.1192/bjp.188.1.13

7. Ceresa A, Esposito CM, Buoli M. How does borderline personality disorder affect management and treatment response of patients with major depressive disorder? A comprehensive review. *J Affect Disord*. (2021) 281:581–9. doi: 10.1016/j.jad.2020.11.111

8. Nicolini AP, Sienaert P. Borderline personality disorder and outcome of electroconvulsive therapy in patients with depression: A systematic review. *J ECT*. (2023) 39:74–80. doi: 10.1097/YCT.0000000000000900

9. (2023). Available online at: https://icd.who.int/en.

10. Comtois KA, Carmel A. Borderline personality disorder and high utilization of inpatient psychiatric hospitalization: concordance between research and clinical diagnosis. *J Behav Health Serv Res*. (2016) 43:272–80. doi: 10.1007/s11414-014-9416-9

11. Perez-Rodriguez MM, Bulbena-Cabre A, Bassir Nia A, Zipursky G, Goodman M, New AS. The neurobiology of borderline personality disorder. *Psychiatr Clin North Am*. (2018) 41:633–50. doi: 10.1016/j.psc.2018.07.012

12. Peters EM, John A, Baetz M, Balbuena L. Examining the role of borderline personality traits in the relationship between major depression and nonsuicidal self-injury. *Compr Psychiatry*. (2018) 86:96–101. doi: 10.1016/j.comppsych.2018.07.008

13. Oumaya M, Friedman S, Pham A, Abou Abdallah T, Guelfi JD, Rouillon F. [Borderline personality disorder, self-mutilation and suicide: literature review]. *Encephale*. (2008) 34:452–8. doi: 10.1016/j.encep.2007.10.007

14. Paris J, Zweig-Frank H. A 27-year follow-up of patients with borderline personality disorder. *Compr Psychiatry*. (2001) 42:482–7. doi: 10.1053/comp.2001.26271

15. Soloff PH, Lynch KG, Kelly TM, Malone KM, Mann JJ. Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: a comparative study. *Am J Psychiatry*. (2000) 157:601–8. doi: 10.1176/appi.ajp.157.4.601

16. Soderholm JJ, Socada JL, Rosenstrom TH, Ekelund J, Isometsa E. Borderline personality disorder and depression severity predict suicidal outcomes: A six-month prospective cohort study of depression, bipolar depression, and borderline personality disorder. *Acta Psychiatr Scand*. (2023) 148:222–32. doi: 10.1111/acps.13586

17. Terzi L, Martino F, Berardi D, Bortolotti B, Sasdelli A, Menchetti M. Aggressive behavior and self-harm in Borderline Personality Disorder: The role of impulsivity and emotion dysregulation in a sample of outpatients. *Psychiatry Res*. (2017) 249:321–6. doi: 10.1016/j.psychres.2017.01.011

18. Carpenter RW, Trull TJ. Components of emotion dysregulation in borderline personality disorder: a review. *Curr Psychiatry Rep*. (2013) 15:335. doi: 10.1007/s11920-012-0335-2

19. Gad MA, Pucker HE, Hein KE, Temes CM, Frankenburg FR, Fitzmaurice GM, et al. Facets of identity disturbance reported by patients with borderline personality disorder and personality-disordered comparison subjects over 20 years of prospective follow-up. *Psychiatry Res*. (2019) 271:76–82. doi: 10.1016/j.psychres.2018.11.020

20. Bohus M, Stoffers-Winterling J, Sharp C, Krause-Utz A, Schmahl C, Lieb K. Borderline personality disorder. *Lancet*. (2021) 398:1528–40. doi: 10.1016/S0140-6736(21)00476-1

21. Soloff PH, Chowdury A, Diwadkar VA. Affective interference in borderline personality disorder: The lethality of suicidal behavior predicts functional brain profiles. *J Affect Disord*. (2019) 252:253–62. doi: 10.1016/j.jad.2019.04.050

22. Jorgensen CR, Berntsen D, Bech M, Kjolbye M, Bennedsen BE, Ramsgaard SB. Identity-related autobiographical memories and cultural life scripts in patients with Borderline Personality Disorder. *Conscious Cognit*. (2012) 21:788–98. doi: 10.1016/j.concog.2012.01.010

23. Hasking P, Boyes ME, Finlay-Jones A, McEvoy PM, Rees CS. Common pathways to NSSI and suicide ideation: the roles of rumination and self-compassion. *Arch Suicide Res*. (2019) 23:247–60. doi: 10.1080/13811118.2018.1468836

24. Frias A, Palma C. Comorbidity between post-traumatic stress disorder and borderline personality disorder: a review. *Psychopathology*. (2015) 48:1–10. doi: 10.1159/000363145

25. Pagura J, Stein MB, Bolton JM, Cox BJ, Grant B, Sareen J. Comorbidity of borderline personality disorder and posttraumatic stress disorder in the U.S. population. *J Psychiatr Res*. (2010) 44:1190–8. doi: 10.1016/j.jpsychires.2010.04.016

26. Sack M, Sachsse U, Overkamp B, Dulz B. [Trauma-related disorders in patients with borderline personality disorders. Results of a multicenter study]. *Nervenarzt*. (2013) 84:608–14. doi: 10.1007/s00115-012-3489-6

27. Jowett S, Karatzias T, Albert I. Multiple and interpersonal trauma are risk factors for both post-traumatic stress disorder and borderline personality disorder: A systematic review on the traumatic backgrounds and clinical characteristics of comorbid post-traumatic stress disorder/borderline personality disorder groups versus single-disorder groups. *Psychol Psychother*. (2020) 93:621–38. doi: 10.1111/papt.12248

28. Mikulincer M, Shaver PR. An attachment perspective on psychopathology. *World Psychiatry*. (2012) 11:11–5. doi: 10.1016/j.wpsyc.2012.01.003

29. Degasperi G, Cristea IA, Di Rosa E, Costa C, Gentili C. Parsing variability in borderline personality disorder: a meta-analysis of neuroimaging studies. *Transl Psychiatry*. (2021) 11:314. doi: 10.1038/s41398-021-01446-z

30. Goldstein KE, Feinberg A, Corniquel MB, Szeszko JR, New AS, Haznedar MM, et al. Anomalous amygdala habituation to unpleasant stimuli among unmedicated individuals with borderline personality disorder and a history of self-harming behavior. *J Pers Disord*. (2021) 35:618–31. doi: 10.1521/pedi_2020_34_495

31. Willis F, Kuniss S, Kleindienst N, Naoum J, Reitz S, Boll S, et al. The role of nociceptive input and tissue injury on stress regulation in borderline personality disorder. *Pain*. (2017) 158:479–87. doi: 10.1097/j.pain.0000000000000787

32. Reitz S, Kluetsch R, Niedtfeld I, Knorz T, Lis S, Paret C, et al. Incision and stress regulation in borderline personality disorder: neurobiological mechanisms of self-injurious behaviour. *Br J Psychiatry*. (2015) 207:165–72. doi: 10.1192/bjp.bp.114.153379

33. Baczkowski BM, van Zutphen L, Siep N, Jacob GA, Domes G, Maier S, et al. Deficient amygdala-prefrontal intrinsic connectivity after effortful emotion regulation in borderline personality disorder. *Eur Arch Psychiatry Clin Neurosci*. (2017) 267:551–65. doi: 10.1007/s00406-016-0760-z

34. Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD, et al. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biol Psychiatry*. (2008) 63:377–84. doi: 10.1016/j.biopsych.2007.06.012

35. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage*. (2004) 23:483–99. doi: 10.1016/j.neuroimage.2004.06.030

36. Aguilar-Ortiz S, Salgado-Pineda P, Vega D, Pascual JC, Marco-Pallares J, Soler J, et al. Evidence for default mode network dysfunction in borderline personality disorder. *Psychol Med*. (2020) 50:1746–54. doi: 10.1017/S0033291719001880

37. Carhart-Harris RL, Friston KJ. The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. *Brain*. (2010) 133:1265–83. doi: 10.1093/brain/awq010

38. O'Neill A, D'Souza A, Samson AC, Carballedo A, Kerskens C, Frodl T. Dysregulation between emotion and theory of mind networks in borderline personality disorder. *Psychiatry Res*. (2015) 231:25–32. doi: 10.1016/j.pscychresns.2014.11.002

39. Baer RA, Sauer SE. Relationships between depressive rumination, anger rumination, and borderline personality features. *Pers Disord*. (2011) 2:142–50. doi: 10.1037/a0019478

40. van Schie CC, Chiu CD, Rombouts S, Heiser WJ, Elzinga BM. Stuck in a negative me: fMRI study on the role of disturbed self-views in social feedback processing in borderline personality disorder. *Psychol Med*. (2020) 50:625–35. doi: 10.1017/S0033291719000448

41. Wrege JS, Ruocco AC, Euler S, Preller KH, Busmann M, Meya L, et al. Negative affect moderates the effect of social rejection on frontal and anterior cingulate cortex activation in borderline personality disorder. *Cognit Affect Behav Neurosci*. (2019) 19:1273–85. doi: 10.3758/s13415-019-00716-0

42. Niedtfeld I, Schmitt R, Winter D, Bohus M, Schmahl C, Herpertz SC. Pain-mediated affect regulation is reduced after dialectical behavior therapy in borderline personality disorder: a longitudinal fMRI study. *Soc Cognit Affect Neurosci*. (2017) 12:739–47. doi: 10.1093/scan/nsw183

43. Shafie M, Shahmohamadi E, Cattarinussi G, Sanjari Moghaddam H, Akhondzadeh S, Akhondzadeh S, et al. Resting-state functional magnetic resonance imaging alterations in borderline personality disorder: A systematic review. *J Affect Disord*. (2023) 341:335–45. doi: 10.1016/j.jad.2023.09.001

44. Prossin AR, Love TM, Koeppe RA, Zubieta JK, Silk KR. Dysregulation of regional endogenous opioid function in borderline personality disorder. *Am J Psychiatry*. (2010) 167:925–33. doi: 10.1176/appi.ajp.2010.09091348

45. Lutz PE, Gross JA, Dhir SK, Maussion G, Yang J, Bramoulle A, et al. Epigenetic regulation of the kappa opioid receptor by child abuse. *Biol Psychiatry*. (2018) 84:751–61. doi: 10.1016/j.biopsych.2017.07.012

46. Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An FMRI study of social exclusion. *Science*. (2003) 302:290–2. doi: 10.1126/science.1089134

47. Lengvenyte A, Olie E, Courtet P. Suicide has many faces, so does ketamine: a narrative review on Ketamine's antisuicidal actions. *Curr Psychiatry Rep*. (2019) 21:132. doi: 10.1007/s11920-019-1108-y

48. Lieb K, Vollm B, Rucker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *Br J Psychiatry*. (2010) 196:4–12. doi: 10.1192/bjp.bp.108.062984

49. Stoffers-Winterling J, Storebo OJ, Lieb K. Pharmacotherapy for borderline personality disorder: an update of published, unpublished and ongoing studies. *Curr Psychiatry Rep*. (2020) 22:37. doi: 10.1007/s11920-020-01164-1

50. American Psychiatric Association Practice G. Practice guideline for the treatment of patients with borderline personality disorder. American Psychiatric Association. *Am J Psychiatry*. (2001) 158:1–52.

51. Gartlehner G, Crotty K, Kennedy S, Edlund MJ, Ali R, Siddiqui M, et al. Pharmacological treatments for borderline personality disorder: A systematic review and meta-analysis. *CNS Drugs*. (2021) 35:1053–67. doi: 10.1007/s40263-021-00855-4

52. Del Casale A, Bonanni L, Bargagna P, Novelli F, Fiasche F, Paolini M, et al. Current clinical psychopharmacology in borderline personality disorder. *Curr Neuropharmacol*. (2021) 19:1760–79. doi: 10.2174/1570159X19666210610092958

53. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Borderline Personality Disorder (2010). Available online at: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bpd.pdf.

54. National Collaborating Centre for Mental Health (UK). *Borderline Personality Disorder: Treatment and Management*. Leicester (UK: British Psychological Society (UK (2009).

55. Lieslehto J, Tiihonen J, Lahteenvuo M, Mittendorfer-Rutz E, Tanskanen A, Taipale H. Comparative effectiveness of pharmacotherapies for the risk of attempted or completed suicide among persons with borderline personality disorder. *JAMA Netw Open*. (2023) 6:e2317130. doi: 10.1001/jamanetworkopen.2023.17130

56. Woodbridge J, Townsend M, Reis S, Singh S, Grenyer BF. Non-response to psychotherapy for borderline personality disorder: A systematic review. *Aust N Z J Psychiatry*. (2022) 56:771–87. doi: 10.1177/00048674211046893

57. Kroger C, Harbeck S, Armbrust M, Kliem S. Effectiveness, response, and dropout of dialectical behavior therapy for borderline personality disorder in an inpatient setting. *Behav Res Ther*. (2013) 51:411–6. doi: 10.1016/j.brat.2013.04.008

58. Storebo OJ, Stoffers-Winterling JM, Vollm BA, Kongerslev MT, Mattivi JT, Jørgensen MS, et al. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst Rev*. (2020) 5:CD012955. doi: 10.1002/14651858.CD012955.pub2

59. DeCou CR, Comtois KA, Landes SJ. Dialectical behavior therapy is effective for the treatment of suicidal behavior: A meta-analysis. *Behav Ther*. (2019) 50:60–72. doi: 10.1016/j.beth.2018.03.009

60. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. (2013) 74:250–6. doi: 10.1016/j.biopsych.2012.06.022

61. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety*. (2014) 31:335–43. doi: 10.1002/da.2014.31.issue-4

62. Hu YD, Xiang YT, Fang JX, Zu S, Sha S, Shi H, et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. *Psychol Med*. (2016) 46:623–35. doi: 10.1017/S0033291715002159

63. Li CT, Chen MH, Lin WC, Hong CJ, Yang BH, Liu RS, et al. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: A randomized controlled study. *Hum Brain Mapp*. (2016) 37:1080–90. doi: 10.1002/hbm.23085

64. Su TP, Chen MH, Li CT, Lin WC, Hong CJ, Gueorguieva R, et al. Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. *Neuropsychopharmacology*. (2017) 42:2482–92. doi: 10.1038/npp.2017.94

65. Zehong C, Chin-Teng L, Weiping D, Mu-Hong C, Cheng-Ta L, Tung-Ping S. Identifying ketamine responses in treatment-resistant depression using a wearable forehead EEG. *IEEE Trans BioMed Eng*. (2019) 66:1668–79. doi: 10.1109/TBME.10

66. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol Psychiatry*. (2020) 25:1592–603. doi: 10.1038/s41380-018-0256-5

67. Nugent AC, Ballard ED, Gould TD, Park LT, Moaddel R, Brutsche NE, et al. Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. *Mol Psychiatry*. (2019) 24:1040–52. doi: 10.1038/s41380-018-0028-2

68. Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, et al. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med*. (2016) 46:1459–72. doi: 10.1017/S0033291716000064

69. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *J Affect Disord*. (2021) 278:542–55. doi: 10.1016/j.jad.2020.09.071

70. Kryst J, Kawalec P, Mitoraj AM, Pilc A, Lason W, Brzostek T. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. *Pharmacol Rep*. (2020) 72:543–62. doi: 10.1007/s43440-020-00097-z

71. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. *Am J Psychiatry*. (2018) 175:327–35. doi: 10.1176/appi.ajp.2017.17060647

72. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*. (2019) 76:893–903. doi: 10.1001/jamapsychiatry.2019.1189

73. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry*. (2020) 81(3):19m12891. doi: 10.4088/JCP.19m12891

74. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol*. (2019) 22:616–30. doi: 10.1093/ijnp/pyz039

75. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *Am J Psychiatry*. (2019) 176:428–38. doi: 10.1176/appi.ajp.2019.19020172

76. Martinotti G, Vita A, Fagiolini A, Maina G, Bertolino A, Dell'Osso B, et al. Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. (2022) 319:646–54. doi: 10.1016/j.jad.2022.09.043

77. Chen CC, Zhou N, Hu N, Feng JG, Wang XB. Acute effects of intravenous sub-anesthetic doses of ketamine and intranasal inhaled esketamine on suicidal ideation: A systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. (2023) 19:587–99. doi: 10.2147/NDT.S401032

78. Zhang Y, Ye F, Zhang T, Lv S, Zhou L, Du D, et al. Structural basis of ketamine action on human NMDA receptors. *Nature*. (2021) 596:301–5. doi: 10.1038/s41586-021-03769-9

79. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

80. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. (2018) 23:801–11. doi: 10.1038/mp.2017.255

81. Zarate CA Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856

82. Zhang JC, Li SX, Hashimoto K. R (-)-ketamine shows greater potency and longer lasting antidepressant effects than S (+)-ketamine. *Pharmacol Biochem Behav*. (2014) 116:137–41. doi: 10.1016/j.pbb.2013.11.033

83. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*. (2016) 533:481–6. doi: 10.1038/nature17998

84. Farmer CA, Gilbert JR, Moaddel R, George J, Adeojo L, Lovett J, et al. Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression. *Neuropsychopharmacology*. (2020) 45:1398–404. doi: 10.1038/s41386-020-0663-6

85. Grunebaum MF, Galfalvy HC, Choo TH, Parris MS, Burke AK, Suckow RF, et al. Ketamine metabolite pilot study in a suicidal depression trial. *J Psychiatr Res*. (2019) 117:129–34. doi: 10.1016/j.jpsychires.2019.08.005

86. Shabel SJ, Proulx CD, Trias A, Murphy RT, Malinow R. Input to the lateral habenula from the basal ganglia is excitatory, aversive, and suppressed by serotonin. *Neuron*. (2012) 74:475–81. doi: 10.1016/j.neuron.2012.02.037

87. Aleksandrova LR, Phillips AG. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. *Trends Pharmacol Sci*. (2021) 42:929–42. doi: 10.1016/j.tips.2021.08.003

88. Hess EM, Riggs LM, Michaelides M, Gould TD. Mechanisms of ketamine and its metabolites as antidepressants. *Biochem Pharmacol*. (2022) 197:114892. doi: 10.1016/j.bcp.2021.114892

89. Medeiros GC, Gould TD, Prueitt WL, Nanavati J, Grunebaum MF, Farber NB, et al. Blood-based biomarkers of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis. *Mol Psychiatry*. (2022) 27:3658–69. doi: 10.1038/s41380-022-01652-1

90. Stahl SM, De Martin S, Mattarei A, Bettini E, Pani L, Guidetti C, et al. Esmethadone (REL-1017) and other uncompetitive NMDAR channel blockers may improve mood disorders via modulation of synaptic kinase-mediated signaling. *Int J Mol Sci*. (2022) 23(20):12196. doi: 10.3390/ijms232012196

91. Haeseler G, Tetzlaff D, Bufler J, Dengler R, Munte S, Hecker H, et al. Blockade of voltage-operated neuronal and skeletal muscle sodium channels by S(+)- and R (-)-ketamine. *Anesth Analg*. (2003) 96:1019–26. doi: 10.1213/01.ANE.0000052513.91900.D5

92. Sills GJ, Rogawski MA. Mechanisms of action of currently used antiseizure drugs. *Neuropharmacology*. (2020) 168:107966. doi: 10.1016/j.neuropharm.2020.107966

93. Costemale-Lacoste JF, Guilloux JP, Gaillard R. The role of GSK-3 in treatment-resistant depression and links with the pharmacological effects of lithium and ketamine: A review of the literature. *Encephale*. (2016) 42:156–64. doi: 10.1016/j.encep.2016.02.003

94. McIntyre RS, Lipsitz O, Rodrigues NB, Lee Y, Cha DS, Vinberg M, et al. The effectiveness of ketamine on anxiety, irritability, and agitation: Implications for treating mixed features in adults with major depressive or bipolar disorder. *Bipolar Disord*. (2020) 22:831–40. doi: 10.1111/bdi.12941

95. Williams NR, Heifets BD, Bentzley BS, Blasey C, Sudheimer KD, Hawkins J, et al. Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism. *Mol Psychiatry*. (2019) 24:1779–86. doi: 10.1038/s41380-019-0503-4

96. Valentino RJ, Volkow ND. Untangling the complexity of opioid receptor function. *Neuropsychopharmacology*. (2018) 43:2514–20. doi: 10.1038/s41386-018-0225-3

97. Alexander L, Jelen LA, Mehta MA, Young AH. The anterior cingulate cortex as a key locus of ketamine's antidepressant action. *Neurosci Biobehav Rev*. (2021) 127:531–54. doi: 10.1016/j.neubiorev.2021.05.003

98. Gilbert JR, Yarrington JS, Wills KE, Nugent AC, Zarate CA. Glutamatergic signaling drives ketamine-mediated response in depression: evidence from dynamic causal modeling. *Int J Neuropsychopharmacol*. (2018) 21:740–7. doi: 10.1093/ijnp/pyy041

99. Reed JL, Nugent AC, Furey ML, Szczepanik JE, Evans JW, Zarate CA Jr. Ketamine normalizes brain activity during emotionally valenced attentional processing in depression. *NeuroImage Clin*. (2018) 20:92–101. doi: 10.1016/j.nicl.2018.07.006

100. Chen MH, Lin WC, Tu PC, Li CT, Bai YM, Tsai SJ, et al. Antidepressant and antisuicidal effects of ketamine on the functional connectivity of prefrontal cortex-related circuits in treatment-resistant depression: A double-blind, placebo-controlled, randomized, longitudinal resting fMRI study. *J Affect Disord*. (2019) 259:15–20. doi: 10.1016/j.jad.2019.08.022

101. Zavaliangos-Petropulu A, Al-Sharif NB, Taraku B, Leaver AM, Sahib AK, Espinoza RT, et al. Neuroimaging-derived biomarkers of the antidepressant effects of ketamine. *Biol Psychiatry Cognit Neurosci Neuroimaging*. (2023) 8:361–86. doi: 10.1016/j.bpsc.2022.11.005

102. Marguilho M, Figueiredo I, Castro-Rodrigues P. A unified model of ketamine's dissociative and psychedelic properties. *J Psychopharmacol*. (2023) 37:14–32. doi: 10.1177/02698811221140011

103. Evans JW, Szczepanik J, Brutsche N, Park LT, Nugent AC, Zarate CA Jr. Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. *Biol Psychiatry*. (2018) 84:582–90. doi: 10.1016/j.biopsych.2018.01.027

104. Siegel JS, Palanca BJA, Ances BM, Kharasch ED, Schweiger JA, Yingling MD, et al. Prolonged ketamine infusion modulates limbic connectivity and induces sustained remission of treatment-resistant depression. *Psychopharmacol (Berl)*. (2021) 238:1157–69. doi: 10.1007/s00213-021-05762-6

105. Gartner M, Aust S, Bajbouj M, Fan Y, Wingenfeld K, Otte C, et al. Functional connectivity between prefrontal cortex and subgenual cingulate predicts antidepressant effects of ketamine. *Eur Neuropsychopharmacol*. (2019) 29:501–8. doi: 10.1016/j.euroneuro.2019.02.008

106. Mkrtchian A, Evans JW, Kraus C, Yuan P, Kadriu B, Nugent AC, et al. Ketamine modulates fronto-striatal circuitry in depressed and healthy individuals. *Mol Psychiatry*. (2021) 26:3292–301. doi: 10.1038/s41380-020-00878-1

107. Rivas-Grajales AM, Salas R, Robinson ME, Qi K, Murrough JW, Mathew SJ. Habenula connectivity and intravenous ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol*. (2021) 24:383–91. doi: 10.1093/ijnp/pyaa089

108. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, et al. Ketamine treatment and global brain connectivity in major depression. *Neuropsychopharmacology*. (2017) 42:1210–9. doi: 10.1038/npp.2016.186

109. Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. Resting-state functional connectivity in major depressive disorder: A review. *Neurosci Biobehav Rev*. (2015) 56:330–44. doi: 10.1016/j.neubiorev.2015.07.014

110. Vasavada MM, Loureiro J, Kubicki A, Sahib A, Wade B, Hellemann G, et al. Effects of serial ketamine infusions on corticolimbic functional connectivity in major depression. *Biol Psychiatry Cognit Neurosci Neuroimaging*. (2021) 6:735–44. doi: 10.1016/j.bpsc.2020.06.015

111. Sterpenich V, Vidal S, Hofmeister J, Michalopoulos G, Bancila V, Warrot D, et al. Increased reactivity of the mesolimbic reward system after ketamine injection in patients with treatment-resistant major depressive disorder. *Anesthesiology*. (2019) 130:923–35. doi: 10.1097/ALN.0000000000002667

112. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. *Neurosci Biobehav Rev*. (2013) 37:152–63. doi: 10.1016/j.neubiorev.2012.11.015

113. Norbury A, Rutter SB, Collins AB, Costi S, Jha MK, Horn SR, et al. Neuroimaging correlates and predictors of response to repeated-dose intravenous ketamine in PTSD: preliminary evidence. *Neuropsychopharmacology*. (2021) 46:2266–77. doi: 10.1038/s41386-021-01104-4

114. Sahib AK, Loureiro JR, Vasavada MM, Kubicki A, Wade B, Joshi SH, et al. Modulation of inhibitory control networks relate to clinical response following ketamine therapy in major depression. *Transl Psychiatry*. (2020) 10:260. doi: 10.1038/s41398-020-00947-7

115. Stone JM, Abel KM, Allin MP, van Haren N, Matsumoto K, McGuire PK, et al. Ketamine-induced disruption of verbal self-monitoring linked to superior temporal activation. *Pharmacopsychiatry*. (2011) 44:33–48. doi: 10.1055/s-0030-1267942

116. Ionescu DF, Felicione JM, Gosai A, Cusin C, Shin P, Shapero BG, et al. Ketamine-associated brain changes: A review of the neuroimaging literature. *Harv Rev Psychiatry*. (2018) 26:320–39. doi: 10.1097/HRP.0000000000000179

117. Danayan K, Chisamore N, Rodrigues NB, Vincenzo JDD, Meshkat S, Doyle Z, et al. Real world effectiveness of repeated ketamine infusions for treatment-resistant depression with comorbid borderline personality disorder. *Psychiatry Res*. (2023) 323:115133. doi: 10.1016/j.psychres.2023.115133

118. Chen KS, Dwivedi Y, Shelton RC. The effect of IV ketamine in patients with major depressive disorder and elevated features of borderline personality disorder. *J Affect Disord*. (2022) 315:13–6. doi: 10.1016/j.jad.2022.07.054

119. Fineberg SK, Choi EY, Shapiro-Thompson R, Dhaliwal K, Neustadter E, Sakheim M, et al. A pilot randomized controlled trial of ketamine in Borderline Personality Disorder. *Neuropsychopharmacology*. (2023) 48:991–9. doi: 10.1038/s41386-023-01540-4

120. Nandan NK, Soni PK, Parsaik A, Hashmi A. "Esketamine" in borderline personality disorder: A look beyond suicidality. *Cureus*. (2022) 14:e24632. doi: 10.7759/cureus.24632

121. Rogg H, Avram M, Muller F, Junghanns K, Borgwardt S, Zurowski B. Ketamine as a treatment option for severe borderline personality disorder: A case report. *J Clin Psychopharmacol*. (2023) 43:64–5. doi: 10.1097/JCP.0000000000001642

122. Galuszko-Wegielnik M, Jakuszkowiak-Wojten K, Wilkowska A, Cubala WJ. Short term ketamine treatment in patient with bipolar disorder with comorbidity with borderline personality disorder: Focus on impulsivity. *World J Biol Psychiatry*. (2023) 24:849–53. doi: 10.1080/15622975.2023.2227901

123. Vanicek T, Unterholzner J, Lanzenberger R, Naderi-Heiden A, Kasper S, Praschak-Rieder N. Intravenous esketamine leads to an increase in impulsive and suicidal behaviour in a patient with recurrent major depression and borderline personality disorder. *World J Biol Psychiatry*. (2022) 23:715–8. doi: 10.1080/15622975.2022.2031287

124. Sumner RL, Chacko E, McMillan R, Spriggs MJ, Anderson C, Chen J, et al. A qualitative and quantitative account of patient's experiences of ketamine and its antidepressant properties. *J Psychopharmacol*. (2021) 35:946–61. doi: 10.1177/0269881121998321

125. Drozdz SJ, Goel A, McGarr MW, Katz J, Ritvo P, Mattina GF, et al. Ketamine assisted psychotherapy: A systematic narrative review of the literature. *J Pain Res*. (2022) 15:1691–706. doi: 10.2147/JPR.S360733

126. Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs*. (2019) 51:189–98. doi: 10.1080/02791072.2019.1587556

127. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs*. (1997) 29:165–83. doi: 10.1080/02791072.1997.10400185

128. Wilkinson ST, Rhee TG, Joormann J, Webler R, Ortiz Lopez M, Lopez M, et al. Cognitive behavioral therapy to sustain the antidepressant effects of ketamine in treatment-resistant depression: A randomized clinical trial. *Psychother Psychosom*. (2021) 90:318–27. doi: 10.1159/000517074

129. Hasler G, Suker S, Schoretsanitis G, Mihov Y. Sustained improvement of negative self-schema after a single ketamine infusion: an open-label study. *Front Neurosci*. (2020) 14:687. doi: 10.3389/fnins.2020.00687

130. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*. (2018) 5:65–78. doi: 10.1016/S2215-0366(17)30272-9

131. Aust S, Gartner M, Basso L, Otte C, Wingenfeld K, Chae WR, et al. Anxiety during ketamine infusions is associated with negative treatment responses in major depressive disorder. *Eur Neuropsychopharmacol*. (2019) 29:529–38. doi: 10.1016/j.euroneuro.2019.02.005

132. Dakwar E, Nunes EV, Hart CL, Hu MC, Foltin RW, Levin FR. A sub-set of psychoactive effects may be critical to the behavioral impact of ketamine on cocaine use disorder: Results from a randomized, controlled laboratory study. *Neuropharmacology*. (2018) 142:270–6. doi: 10.1016/j.neuropharm.2018.01.005

133. Rothberg RL, Azhari N, Haug NA, Dakwar E. Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial. *J Psychopharmacol*. (2021) 35:150–8. doi: 10.1177/0269881120970879

134. Krupitsky E, Burakov A, Romanova T, Dunaevsky I, Strassman R, Grinenko A. Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *J Subst Abuse Treat*. (2002) 23:273–83. doi: 10.1016/S0740-5472(02)00275-1

135. Keizer BM, Roache JD, Jones JR, Kalpinski RJ, Porcerelli JH, Krystal JH. Continuous ketamine infusion for pain as an opportunity for psychotherapy for PTSD: A case series of ketamine-enhanced psychotherapy for PTSD and pain (KEP-P2). *Psychother Psychosom*. (2020) 89:326–9. doi: 10.1159/000507095

136. Fattore L, Piva A, Zanda MT, Fumagalli G, Chiamulera C. Psychedelics and reconsolidation of traumatic and appetitive maladaptive memories: focus on cannabinoids and ketamine. *Psychopharmacol (Berl)*. (2018) 235:433–45. doi: 10.1007/s00213-017-4793-4

137. Zeifman RJ, Landy MSH, Liebman RE, Fitzpatrick S, Monson CM. Optimizing treatment for comorbid borderline personality disorder and posttraumatic stress disorder: A systematic review of psychotherapeutic approaches and treatment efficacy. *Clin Psychol Rev*. (2021) 86:102030. doi: 10.1016/j.cpr.2021.102030

138. Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski , et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. *J Psychopharmacol*. (2017) 31:967–74. doi: 10.1177/0269881117711712

139. Perez S, Lorca F, Marco JH. "Dissociation, posttraumatic stress symptoms, emotional dysregulation, and invalidating environments as correlates of NSSI in

borderline personality disorder patients". *J Trauma Dissociation*. (2020) 21:520–35. doi: 10.1080/15299732.2020.1719262

140. Kleindienst N, Limberger MF, Ebner-Priemer UW, Keibel-Mauchnik J, Dyer A, Berger M, et al. Dissociation predicts poor response to Dialectial Behavioral Therapy in female patients with Borderline Personality Disorder. *J Pers Disord*. (2011) 25:432–47. doi: 10.1521/pedi.2011.25.4.432

141. Ebner-Priemer UW, Mauchnik J, Kleindienst N, Schmahl C, Peper M, Rosenthal MZ, et al. Emotional learning during dissociative states in borderline personality disorder. *J Psychiatry Neurosci*. (2009) 34:214–22.

142. Trull TJ, Freeman LK, Vebares TJ, Choate AM, Helle AC, Wycoff AM. Borderline personality disorder and substance use disorders: an updated review. *Borderline Pers Disord Emot Dysregul*. (2018) 5:15. doi: 10.1186/s40479-018-0093-9

143. Smith-Apeldoorn SY, Veraart JK, Spijker J, Kamphuis J, Schoevers RA. Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and tolerability. *Lancet Psychiatry*. (2022) 9:907–21. doi: 10.1016/S2215-0366(22)00317-0

144. Chiappini S, d'Andrea G, De Filippis S, Di Nicola M, Andriola I, Bassetti R, et al. Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: A viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study. *Eur Neuropsychopharmacol*. (2023) 74:15–21. doi: 10.1016/j.euroneuro.2023.04.011

145. Gren J, Gorman I, Ruban A, Tyls F, Bhatt S, Aixala M. Call for evidence-based psychedelic integration. *Exp Clin Psychopharmacol*. (2024) 32(2):129–35. doi: 10.1037/pha0000684

146. Unoka Z, Csaky-Pallavicini K, Horvath Z, Demetrovics Z, Maraz A. The Inventory of Personality Organization: A valid instrument to detect the severity of personality dysfunction. *Front Psychiatry*. (2022) 13:995726. doi: 10.3389/fpsyt.2022.995726

147. Choi-Kain LW, Zanarini MC, Frankenburg FR, Fitzmaurice GM, Reich DB. A longitudinal study of the 10-year course of interpersonal features in borderline personality disorder. *J Pers Disord*. (2010) 24:365–76. doi: 10.1521/pedi.2010.24.3.365

148. Kaurin A, Dombrovski AY, Hallquist MN, Wright AGC. Momentary interpersonal processes of suicidal surges in borderline personality disorder. *Psychol Med*. (2022) 52:2702–12. doi: 10.1017/S0033291720004791

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Facts and myths about use of esketamine for treatment-resistant depression: a narrative clinical review

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Introduction and aims: Treatment-resistant depression (TRD) occurs when at least two different antidepressants, taken at the right dosage, for adequate period of time and with continuity, fail to give positive clinical effects. Esketamine, the S-enantiomer of ketamine, was recently approved for TRD treatment from U.S. Food and Drug Administration and European Medicine Agency. Despite proved clinical efficacy, many misconceptions by clinicians and patients accompany this medication. We aimed to review the most common "false myths" regarding TRD and esketemine, counterarguing with evidence-based facts.

Methods: The keywords "esketamine", "treatment resistance depression", "depression", "myth", "mythology", "pharmacological treatment", and "misunderstanding" were entered in the main databases and combined through Boolean operators.

Results: Misconceptions regarding the TRD prevalence, clinical features and predictors have been found. With respect of esketamine, criteria to start treatment, dissociative symptoms, potential addiction and aspects of administration and monitoring, were found to be affected by false beliefs by clinicians and patients.

Discussion and conclusion: TRD represents a challenging condition, requiring precise diagnosis in order to achieve patient's full recovery. Esketamine has been proved as an effective medication to treat TRD, although it requires precautions. Evidence can inform clinical practice, in order to offer this innovative treatment to all patients with TRD.

KEYWORDS

treatment-resistant depression, esketamine, major depressive disorder, recovery, remission

Background

Major Depressive Disorder (MDD) is a severe mental disorder affecting approximately 280 million people worldwide and representing globally the leading cause of disability. MDD has been conceptualized as a syndrome characterized by depressed mood, loss of pleasure and interest, and other affective, cognitive and somatic symptoms persisting for more than two weeks (1–3). Moreover, MDD impairs psychosocial functioning and quality of life (4, 5). A clinical characterization of the individual patient is necessary in order to develop personalized treatment plan with the final aim of reaching the full recovery (6–9). People with MDD report many physical comorbidities, with a negative impact on the long-term quality of life and reducing their life expectancy (10).

Patients suffering from MDD can report a recurrent course of the disorder, with up to 50% of them not experiencing a full recovery after the first episode, and up to 35% experience more than one episode (11). Therefore, based on the longitudinal course of the disorder, several authors have proposed to distinguish difficult to treat depression from treatment-resistant depression (TRD). In particular, it is a clinical condition characterized by lack of response to appropriate treatment. The construct of TRD is very complex, as witnessed by the fact that several definitions have been proposed (12). A consensus definition is still not available, with implications on epidemiology, policy decision-making and clinical utility (13, 14). No single biomarker has been identified so far which can be considered as a benchmark for depression (15, 16) and for TRD, reflecting a common difficulty in findings biomarkers for mental disorders (17–19).

The European Medicine Agency (EMA) defined TRD as a "failure to produce significant clinical results with a treatment of at least two different antidepressants (of the same or different classes) administered at the right doses and for an adequate amount of time, with verified patients' compliance to treatment" (20). Although this definition focuses only on pharmacological aspects and does not consider psychotherapy as a strategy for mild conditions, it is widely applied in the context of research (21, 22).

Consistently to this conceptualization, EMA approved intranasal esketamine in combination with an SSRI or a SNRI for the treatment of adults with TRD in December 2019 (23), following the lead of U.S. Food and Drug Administration (24). The approval of esketamine for treating TRD has introduced an antidepressant drug with an innovative mechanism of action into clinicians' armamentarium. According to recent guidelines for managing TRD, several strategies have been suggested, including the combination or switch of antidepressants; augmentation with antipsychotic and/or mood stabilizers (25); administration of intravenous/intranasal ketamine (26) and neurostimulation techniques (electroconvulsive therapy, deep brain stimulation, vagal nerve stimulation, repetitive transcranial stimulation) (27–29).

Esketamine is the S-enantiomer of ketamine, working as non-selective, non-competitive antagonist of N-methyl-D-aspartate (NDMA) receptor (30). Subsequent downstream of glutamate release stimulates the activation of AMPA receptors, by initiating intracellular signaling cascades, resulting in the activation of mammalian target of rapamycin (mTOR) and increase of brain-derived neurotrophic factor (BDNF) levels, with positive effects on synaptic plasticity (31, 32). In terms of pharmacokinetics, intranasal esketamine has mean bioavailability of about 48%, its peak is reached until to 40 minutes from last spray, presents biphasic half-life and undergoes metabolism through CYP-2B6, -3A4, -2C9, -2C19, hydroxylation and glucuronidation (33).

Esketamine may be associated with craving behavior and additional potential (34). Indeed, dissociative state is characterized by depersonalization and derealization (24), while hallucinations have been reported as a consequence of the recreational use of ketamine, not for esketamine (35, 36). In this regard, resistance by clinicians may be encountered to the detriment of proved clinical effectiveness in TRD. Based on such premises, we carried out a narrative review of the available literature on the most common "misconceptions" and "stereotypes" associated with esketamine use; for each false myth, we provide a list of "good reasons" for disconfirming such stereotypes.

Methods

The keywords "esketamine", "treatment resistant depression", "depression", "myth", "mythology", "pharmacological treatment", and "misunderstanding" were entered in PubMed, ISI Web of Knowledge, Scopus and Medline. Terms and databases were combined using the Boolean search technique, which consists of a logical information retrieval system (two or more terms combined to make searches more restrictive or detailed). The search strategy has been limited from March 2019, when the US Food and Drug Administration (FDA) approved the use of esketamine for the treatment of treatment-resistance depression (TRD), to March 2024. The following criteria were considered for including papers in the present narrative review: 1) papers written in English; 2) papers focused on the use of esketamine as add-on treatment for TRD patients; 3) focus on prevalence of TRD and/or on side effects of esketamine treatment and/or risk of addiction due to esketamine use and/or rules of clinical practice needed for administering esketamine.

Results from the narrative clinical review

Based on the search strategy, selected studies were used for counteracting the common false myths reported in clinical practice about the use of esketamine for the treatment of patients with TRD.

The most common false myths are the following: 1) the prevalence of TRD is low in clinical practice; 2) no specific clinical features characterize the individual patient with TRD; 3) TRD cannot be predicted before its clinical manifestation; 4) patient candidate to esketamine treatment must have reported nonresponse to either SSRIs or SNRIs; 5) patient candidate to esketamine treatment must be affected only from MDD; 6) patient treated

with esketamine will report side effects, including dissociation and agitation; 7) esketamine is associated with high risk of addiction; 8) esketamine treatment requires long period of observation, with adequate room and many healthcare professionals involved in the administration procedure (Table 1).

Myth 1: The prevalence of TRD is low

Fact 1: TRD is a common clinical condition

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (37) found a cumulative remission rate of 67% throughout four acute treatment steps, while a TRD prevalence of up to 55% was detected in a cross-sectional study focused on primary care in United Kingdom (38). In more recent years, Liu et al. (39) found lower rates (5.8% and 6.0%) by analyzing data from two large databases encompassing almost 600,000 patients taking medications for depression in the United States, where a 12-month prevalence of 30.9% was also found in four claims studies (40). A similar French research detected 25.8 people suffering from TRD per 10,000 patients (41). Furthermore, TRD proportion was estimated to be 4.2% in Italy (42), 24.4% in Israel (43) and 19.6% in Thailand (44). Although prevalence data are heterogeneous, the common element is that TRD is quite frequent in ordinary clinical practice. Clinicians should be aware of the characteristics of TRD as well as of the different therapeutic strategies for managing patients suffering from TRD.

However, exact prevalence rate of TRD cannot be estimated due to the lack of a consensus definition and due to the different settings where patients can be treated (i.e., primary care, outpatient units, inpatient unit, academia) (14, 45, 46).

Myth 2: No specific clinical features characterize the individual patient with TRD

Fact 2: The individual patient with TRD has specific clinical characteristics

TRD is a clinical condition associated with high levels of social and personal burden (47), requiring half of expenditure for medical treatment of major depression in the United States (about $92.7 billion per year) (40). Patients with TRD experience significant impairment in psychosocial functioning, poor levels of quality of life, and adverse health outcomes (48–52). Hospitalization rate and emergency department utilization were found to be more than twice in TRD patients in comparison with general population (50, 53), with also significantly longer hospital stay (36% more) and higher costs (54). When compared with treatment-responding subjects, TRD patients reported more prevalent hypertension, hypothyroidism and chronic pulmonary disease (55), as well as substance use, anxiety, insomnia and pain (49). TRD patients have higher level of brain aging compared to responders (56). Furthermore, higher mortality risk (7-16 deaths per 1000 patients in 5 years) and mortality rates have been found (57–60). Compared with treatment-responsive patients, individuals with TRD are twice as likely to attempt suicide, showing a rate of 30% (61, 62).

Myth 3: TRD cannot be predicted before its clinical manifestations

Fact 3: Numerous clinical predictors allow to detect patients at high risk of TRD

Several variables have been studied as potential predictors of TRD. A European multicentric study performed on 702 patients with depression (63) detected significant association between TRD and comorbid panic disorder (OR: 3.2), anxiety (OR: 2.6), suicidal risk (OR: 2.2), social phobia (OR: 2.1), young age of onset (OR: 2.0), personality disorder (OR: 1.7), symptom severity (OR: 1.7), history of multiple hospitalizations (OR: 1.6), nonresponse to the first antidepressant taken (OR: 1.6), melancholia (OR: 1.5), and recurrent episodes (OR: 1.5). Severity and length of depressive episode, risk of suicide, psychotic symptoms, comorbid anxiety, non-response to previous antidepressants, recurrence and hospitalization were confirmed in association with TRD (64, 65), alongside with antidepressants at higher doses (66). Moreover, among physical health problems cardiovascular disease, pain and thyroid problems were most commonly reported to be associated, as well as female gender among sociodemographic variables (67). Few studies also tested the association between TRD and specific candidate genetic factors, but no specific biomarkers have been identified so far (68).

Myth 4: Patient eligible to esketamine treatment must have reported nonresponse to either SSRIs or SNRIs

TABLE 1 The most common false myths and facts regarding TRD and esketamine treatment.

Myths	Facts
The prevalence of TRD is low	TRD is a common clinical condition
No specific clinical features characterize the individual patient with TRD	The individual patient with TRD has specific clinical characteristics
TRD cannot be predicted before its clinical manifestation	Numerous clinical predictors allow to detect patients at high risk of TRD
Patient eligible for esketamine treatment must have reported nonresponse to either SSRIs or SNRIs	Patient eligible for esketamine treatment can be nonresponse to any class of antidepressants
Patient candidate to esketamine treatment must be affected only from depression	No psychiatric comorbidity can contraindicate esketamine treatment
Patient treated with esketamine will report side effects, including dissociation and agitation	Dissociation is not very frequent among side effects
Esketamine is associated with high risk of addiction	Potential addiction of esketamine is not commonly experienced by most part of patients
Esketamine treatment requires long period of observation, with adequate room and many healthcare professionals involved in the administration procedure	Esketamine treatment can be managed in outpatient unit, with the assistance of a few professionals

Fact 4: Patient eligible for esketamine treatment can be nonresponse to any class of antidepressants

Both FDA (24) and EMA (23) approved esketamine treatment for patients with depression who had tried at least two different antidepressants without gaining benefits. In this regard, there is no specific mention of SSRIs and/or SNRIs in both approval release documents, so that failure of antidepressant treatment should be intended in general, also involving other classes (e.g., tricyclics, monoamine oxidases inhibitors, or dopamine/norepinephrine modulators, atypical antidepressants). Instead, it is worth mentioning that a SSRI or SNRI is specifically required to be used in combination with esketamine treatment. In a comparative study conducted in Italy (69), more than half of unipolar and bipolar TRD patients were taking other antidepressants besides SSRIs or SNRIs before starting esketamine. As well, no specification of class was provided regarding antidepressants taken by TRD subjects enrolled by Estrade et al. (70).

Myth 5: Patient candidate to esketamine treatment must be affected only from depression

Fact 5: No psychiatric comorbidity is a contraindication to esketamine treatment

TRD is a clinical condition often occurring with other comorbid psychiatric disorders, such as anxiety, obsessive compulsive disorder, attention-deficit/hyperactivity disorder, substance use disorder as well as self-harm behavior, fatigue, chronic pain, and insomnia (58, 71–74). In the real world, clinicians deal with patients suffering from TRD with other symptoms in comorbidity, which might benefit from esketamine treatment. No contraindications have been pointed out in release documents issued by FDA and EMA (23, 24). Furthermore, esketamine's effectiveness was investigated in TRD patients with comorbid anxiety (75), post-traumatic stress disorder (76), and substance use disorder (77). The use of esketamine for treating patients with TRD and comorbid obsessive-compulsive disorder (78) and anorexia nervosa (79) has been described as well. Esketamine combined with an oral antidepressant has been approved in the United States for managing depression with acute suicidal ideation or behavior (80, 81), and in Europe for dealing with psychiatric emergencies in adults affected from depression.

Myth 6: Patient treated with esketamine will definitely experience dissociation and agitation

Fact 6: Dissociation is not very frequent among side effects

Dissociation is a complex construct defined as a "disruption and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior" (1). It encompasses depersonalization, derealization, illusions and distortion of time, which may be experienced within a few hours and mostly at a non-severe degree by 11.1-31.4% of people treated with esketamine (28). The meta-analysis by Yang et al. (82) found an overall relative risk of developing dissociation of 4.54 (p<.00001) among patients using esketamine when compared with placebo group. This value resulted almost twice (RR: 8.06, p<.00001) in the subgroup taking the dosage of 56 mg. The SUSTAIN-2 trial (83) reported dissociation rate of 23.4% during the 4-week induction period and of 18.7% during the 48-week maintenance phase. A *post-hoc* analysis found a prevalence of dissociation of 14.3% in patients forty minutes later the administration of the first dose of esketamine (84). The findings from the SUSTAIN-3 trial (85) showed dissociation in 24.4% of participants, 99.8% of whom resolved this condition during the same day of drug administration. In the real world, dissociative symptoms were detected in 39.7% of subjects (86). Causal role of dissociation in improving depressive symptoms was not consistently found (87–89). Trait dissociation, assessed through the *Dissociative Experience Scale (DES)* (90), was proved to be a significant predictor for the development of dissociation as side effect. Therefore, the DES should be used as potential screening tool for identifying patients at higher risk for developing dissociation.

Psychomotor agitation is not commonly reported as a side effect of esketamine treatment. In the REAL-ESK study (86), only one case of severe agitation was recorded among 116 treated subjects. Furthermore, a case report referring to a patient experiencing agitation and dissociation due to esketamine was described by Pereira and colleagues (91), who managed this condition throughout non-pharmacological approach.

Myth 7: Esketamine is associated with high risk of addiction

Fact 7: Potential addiction of esketamine is not commonly experienced by majority of patients

Potential addiction induced by intranasal esketamine is similar to that derived from intravenous racemic ketamine in non-dependent drug users (92). Although this aspect represents a concern for clinicians, lack of validated quantitative assessment of potential addiction in TRD patients treated with esketamine has contributed to limit evidence. Wang et al. (93) developed a visual analog scale for assessing esketamine craving and drug likeability, intended as a predictor of potential addition (94). The risk of esketamine addiction does not affect all patients equally (95). Moreover, slow de-tritation of esketamine and combined use of bupropion were suggested for managing drug-seeking and craving behaviors (34).

Myth 8: Esketamine treatment requires long period of observation, with adequate room and many healthcare professionals involved in the administration procedure

Fact 8: Esketamine treatment can be managed in outpatient unit, with the assistance of a few professionals

Esketamine treatment requires some specific conditions to be met to ensure patients monitoring and comfort. Administration should be performed in a peaceful room of hospital or outpatient unit, in which bed or chair allows patients to rest. The possibility to adjust the lighting also would be an optimal option. Sphygmomanometer and handkerchiefs are essential tool to have available. Patients have to come in the morning on an empty stomach. Esketamine is auto-administered through a nasal spray device containing 28 mg per 200 µl of vehicle solution (2 sprays). Before administration, patients are asked to clean their nose and recline their head to 45°. Blood pressure monitoring is required before and forty minutes after the last administration (20). People suffering from high blood pressure (more than 140/90 mmHg in

adults; more than 150/90 mmHg in the elderly) have to be treated previously, as esketamine treatment can only start when blood pressure levels are within normal range. After monitoring by 60-90 minutes, in the absence of any problems patients can be discharged. Although they can also go home alone, they are advised not to drive the car until the next day.

Discussion

The present narrative review aims at counteracting false myths regarding TRD and esketamine treatment by providing the most recent and updated evidence available.

TRD represents a complex clinical condition as confirmed by the lack of a consensus definition and clear epidemiological data (14, 96–99). According to EMA conceptualization (23), depression can be defined "resistant to treatment" if at least two antidepressants failed to improve depressive symptoms, despite their use at right dose, for adequate period and with adequate patient's compliance. Therefore, many clinical conditions labelled as "depressions difficult to treat" do not fully satisfy criteria for TRD and they may not benefit from treatments approved for TRD. Some clinical features might be useful in detecting real condition of TRD, and the identification of clear predictors of TRD can be helpful for optimizing diagnosis and subsequently therapy. It has to be noted that esketamine is approved for treatment-resistant depression (TRD) and emergency suicidality only. However, recent trials have confirmed its efficacy also in patients suffering from bipolar disorder, with an actual depressive phase (69), but this use remains off-label and clinicians should carefully evaluate the risk/benefit ratio in administering such medication to patients with different clinical conditions. Although these positive results are encouraging, further longitudinal studies, designed with a rigorous methodology, are required.

Esketamine represents an additional tool in the clinicians' therapeutic armamentarium for treating MDD and TRD. Clinical efficacy has been proved both in experimental and real-world settings. Superiority of esketamine combined with oral antidepressant compared to placebo plus oral antidepressant was found in the short-term by Popova et al. (100), unlike Fedgchin et al. (101) and Ochs-Ross et al. (102). In the long-term treatment, esketamine is effective in terms of significant reduction of depressive symptoms (83). Moreover, in the long-term maintenance study, adult patients with TRD treated with a continue use of esketamine report a significant delay in time to relapse compared with placebo, both considering stable remitters and stable responders (103). It is relevant to consider that no potential risk for abuse has been detected in the long-term treatment (i.e., up to one year from treatment) (104).

In the real world, significant improvements in terms of depressive symptoms and remission rates were reported after three months from the start of treatment (86), also in subjects affected by bipolar TRD (69), and in elder patients who however showed high levels of side effects (105).

Esketamine represents an important novelty among pharmacological treatments for patients with MDD, having an innovative mechanism of action (106). Indeed, depression has traditionally been conceptualized as a disorder underlying by an alteration in the neurotransmission pathways of serotonin, norepinephrine and dopamine pathways. Esketamine works as non-selective, non-competitive antagonist of NDMA receptor, determining subsequent activation of AMPA and intracellular cascades (31, 32). Higher levels of BDNF and synaptic plasticity represent positive effects. Therefore, esketamine has a specific target on a new pathway, which is represented by the glutamatergic system. However, given its similar pharmacological profile and the extensive literature on its safety and tolerability, it is crucial to briefly mention ketamine (107). Many randomized controlled trials have confirmed the acute efficacy of ketamine in patients with TRD, although only a few data come from the real-world practice. A recent systematic review (26) found that ketamine has a substantial antidepressant effect, although its effectiveness varies significantly across patients. Moreover, a recent study by Gałuszko-Węgielnik et al. (108) found that ketamine is an effective add-on treatment to standard of care for people with treatment-resistant depression presenting psychotic features. Ketamine is administered as intravenous infusion and the subsequent monitoring revealed no exacerbation of psychotic symptoms in short and long-term observation, while stable remission and fast antisuicidal effect was found. However, these data should be carefully considered since the rates of recreational use of ketamine is increasing and the potential addiction to ketamine shares the same neurobiological pathway of its clinical effectiveness in treating patients suffering from TRD (109).

Taking esketamine requires a safe setting, where healthcare professionals can monitor patient's response in terms of side effects for up to 90 minutes. Dizziness, nausea, dissociation, headache, dysgeusia, vertigo, somnolence, hypoesthesia and vomiting were reported as common side effects (110). Usually, they appear at mild or moderate degree of severity, are dose-dependent, and last only in the same day of esketamine administration. When they are severe, adjunctive treatments, and/or treatment pause or interruption should be considered (111–113). Discontinuation rate due to adverse effects in clinical trials has been estimated in about 5% of cases (85). The most relevant limitation is using esketamine is related to patients at high risk of aneurysm, and those with history of cerebral bleeding or heart attack (20). Assisted administration and monitored setting may also be helpful to promptly detect any potential risk of addiction.

Basing on patients' age, recommended dosage consists of one or two puffs in each nostril at day 1, while up to three sprays per nostril can be administered twice a week during the following 4 weeks. Depending on patient's conditions, treatment can be performed once a week for 4 weeks and once or two times per week up to 6 months. This strict schedule may appear a limitation for patients, but real-world study does not mention this aspect among the reasons of esketamine discontinuation (69).

Intranasal administration is unusual in psychiatric setting. Indeed, consolidated use of tablets, capsules and drops formulations has allowed the patient to take antidepressant therapy in comfort and autonomy. Furthermore, repeated and intermittent nasal sprays encouraged researchers to investigate

olfactory functionality and nasal mucosa of patients, who seem to well tolerate this practice also in the long term (114, 115).

Dissociative effects and the potential addictive effects of esketamine treatment are among the main concerns related to the use of esketamine in clinical practice.

As regards dissociative effects, these are experienced as feelings of disconnection from the reality, and are reporting in up to 40% of subjects taking esketamine in the real world setting, resolving within the same day of administration. Although a causal role of dissociation in improving depressive symptoms could be hypothesized, Ballard and Zarate (87) showed that it is not necessary to determine antidepressant effects of ketamine and derived medication. Moreover, the potential addiction from this drug resulted to involve patients treated with esketamine (95).

The present study has some limitations, which must be acknowledged. First, this is not a systematic review, but rather a narrative review which is more in line with the scope of the paper. It may be that relevant studies on esketamine have been omitted, but this was due to the need to identify papers related to the false myths addressed here. In fact, narrative reviews are a specific type of review in which researchers can pursue an extensive description and interpretation of previously published papers on a chosen topic. The description of the search strategy and selection criteria should be considered a major strength of the present paper. We believe that this approach has been appropriate for the topic of "myth and facts" related to the use of esketamine in ordinary routine clinical practice.

Another limitation is the inclusion of papers published in English only, which may have led to the exclusion of some papers/clinical experiences carried out in different countries with different languages.

Conclusions

TRD represents a challenging clinical condition, which needs to be adequately identified and diagnosed in order to achieve patient's full recovery. Esketamine has been proved as an effective medication to treat TRD, although it requires precautions. Evidence can inform clinical practice, in order to offer this innovative treatment to all patients with TRD.

Although esketamine is an innovative treatment for the management of TRD patients, available data clearly confirm the efficacy, safety and good tolerability profile of this medication.

Author contributions

MDV: Investigation, Writing – original draft. VM: Conceptualization, Writing – review & editing. BDR: Methodology, Writing – review & editing. EA: Methodology, Writing – review & editing. AD'A: Methodology, Writing – review & editing. AV: Investigation, Writing – original draft. ML: Methodology, Writing – review & editing. GS: Conceptualization, Writing – original draft. AF: Supervision, Writing – original draft, Writing – review & editing.

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References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. 5th edition*. Washington, DC: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596

2. Stein DJ, Shoptaw SJ, Vigo DV, Lund C, Cuijpers P, Bantjes J, et al. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration. *World Psychiatry*. (2022) 21:393–414. doi: 10.1002/wps.20998

3. World Health Organization. (2022). Available online at: https://icd.who.int/.

4. Malhi GS, Mann JJ. Depression. *Lancet*. (2018) 392:2299–312. doi: 10.1016/S0140-6736(18)31948-2

5. Fusar-Poli P, Estradé A, Stanghellini G, Esposito CM, Rosfort R, Mancini M, et al. The lived experience of depression: a bottom-up review co-written by experts by experience and academics. *World Psychiatry*. (2023) 22:352–65. doi: 10.1002/wps.21111

6. Rush AJ, Thase ME. Improving depression outcome by patient-centered medical management. *Am J Psychiatry*. (2018) 175:1187–98. doi: 10.1176/appi.ajp.2018.18040398

7. Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry*. (2020) 19:269–93. doi: 10.1002/wps.20771

8. Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, Koenigsberg SH, et al. The economic burden of adults with major depressive disorder in the United States, (2010 and 2018). *Pharmacoeconomics*. (2021) 39:653–65. doi: 10.1007/s40273-021-01019-4

9. Maj M. Understanding depression beyond the "mind-body" dichotomy. *World Psychiatry*. (2023) 22:349–50. doi: 10.1002/wps.21142

10. Berk M, Köhler-Forsberg O, Turner M, Penninx BWJH, Wrobel A, Firth J, et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World Psychiatry*. (2023) 22:366–87. doi: 10.1002/wps.21110

11. Eaton WW, Shao H, Nestadt G, Lee HB, Bienvenu OJ, Zandi P. Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry*. (2008) 65:513–20. doi: 10.1001/archpsyc.65.5.513

12. Murphy JA, Sarris J, Byrne GJ. A review of the conceptualisation and risk factors associated with treatment-resistant depression. *Depress Res Treat*. (2017) 2017:4176825. doi: 10.1155/2017/4176825

13. Fava M. The challenges of defining and managing treatment-resistant depression in research and practice. *World Psychiatry*. (2023) 22:350–1. doi: 10.1002/wps.21128

14. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412. doi: 10.1002/wps.21120

15. Abi-Dargham A, Moeller SJ, Ali F, DeLorenzo C, Domschke K, Horga G, et al. Candidate biomarkers in psychiatric disorders: state of the field. *World Psychiatry*. (2023) 22:236–62. doi: 10.1002/wps.21078

16. Mayberg HS, Dunlop BW. Balancing the beautiful and the good in pursuit of biomarkers for depression. *World Psychiatry*. (2023) 22:265–7. doi: 10.1002/wps.21081

17. Tamminga CA. Discovering informative biomarkers in psychiatry. *World Psychiatry*. (2023) 22:270–1. doi: 10.1002/wps.21084

18. Yatham LN. Biomarkers for clinical use in psychiatry: where are we and will we ever get there? *World Psychiatry*. (2023) 22:263–4. doi: 10.1002/wps.21079

19. Kumar R, Nuñez NA, Joshi N, Joseph B, Verde A, Seshadri A, et al. Metabolomic biomarkers for (R, S)-ketamine and (S)-ketamine in treatment-resistant depression and healthy controls: A systematic review. *Bipolar Disord*. (2024) 00:1–10. doi: 10.1111/bdi.13412

20. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of depression (2013). Available online at: https://www.ema.europa.eu/en/news/european-medicines-agency-publishes-guideline-clinical-investigation-medicines-depression (Accessed April 25, 2023).

21. Parker G. Treatment-resistant depression invites persistent reflection. *World Psychiatry*. (2023) 22:414–5. doi: 10.1002/wps.21135

22. Thase ME. Recent developments pertaining to treatment-resistant depression: a 40-year perspective. *World Psychiatry*. (2023) 22:413–4. doi: 10.1002/wps.21134

23. European Medicine Agency. Available online at: https://www.ema.europa.eu/en/medicines/human/EPAR/spravato.

24. Food and Drug Administration. (2019). Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified.

25. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. *Pharmacol Treatment Can J Psychiatry*. (2016) 61(9):540–60. doi: 10.1177/0706743716659417

26. Alnefeesi Y, Chen-Li D, Krane E, Jawad MY, Rodrigues NB, Ceban F, et al. Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. *J Psychiatr Res*. (2022) 151:693–709. doi: 10.1016/j.jpsychires.2022.04.037

27. McLachlan G. Treatment resistant depression: what are the options? *BMJ*. (2018) 363:k5354. doi: 10.1136/bmj.k5354

28. Swainson J, Thomas RK, Archer S, Chrenek C, MacKay M-A, Baker G, et al. esketamine for treatment resistant depression. *Expert Rev Neurother*. (2019) 19:899–911. doi: 10.1080/14737175.2019.1640604

29. Howes OD, Baxter L. The drug treatment deadlock in psychiatry and the route forward. *World Psychiatry*. (2023) 22:2–3. doi: 10.1002/wps.21059

30. Stahl S. Esketamine. In: *Prescriber's guide: stahl's essential psychopharmacology*. Cambridge University Press, Cambridge (2020). p. 275–80. doi: 10.1017/9781108921275.046

31. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. (2012) 338:68–72. doi: 10.1126/science.1222939

32. Duman RS, Aghajanian GK, Sanacora G. et al: Synaptic plasticity and depression: new insights from stress and rapid-acting antide- pressants. *Nat Med*. (2016) 22:238–49. doi: 10.1038/nm.4050

33. Bahr R, Lopez A, Rey JA. Intranasal esketamine (SpravatoTM) for use in treatment-resistant depression in conjunction with an oral antidepressant. *P T*. (2019) 44:340–75.

34. Orsolini L, Salvi V, Volpe U. Craving and addictive potential of esketamine as side effects? *Expert Opin Drug Saf*. (2022) 21:803–12. doi: 10.1080/14740338.2022.2071422

35. Goodwin GM. The psychedelic experience and treatment-resistant depression. *World Psychiatry*. (2023) 22:420–2. doi: 10.1002/wps.21140

36. Weissman MM. Does treatment-resistant depression need psychotherapy? *World Psychiatry*. (2023) 22:417–8. doi: 10.1002/wps.21137

37. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

38. Thomas L, Kessler D, Campbell J, Morrison J, Peters TJ, Williams C, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. *Br J Gen Pract*. (2013) 63:e852–8. doi: 10.3399/bjgp13X675430

39. Liu X, Mukai Y, Furtek CI, Bortnichak EA, Liaw KL, Zhong W. Epidemiology of treatment-resistant depression in the United States. *J Clin Psychiatry*. (2021) 83 (1):21m13964. doi: 10.4088/JCP.21m13964

40. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. *J Clin Psychiatry*. (2021) 82:20m13699. doi: 10.4088/JCP.20m13699

41. Bosco-Lévy P, Grelaud A, Blin P, Astruc B, Falissard B, Llorca PM, et al. Treatment resistant depression incidence and prevalence using the French nationwide claims database. *Pharmacoepidemiol Drug Saf*. (2021) 30:169–77. doi: 10.1002/pds.5082

42. Perrone V, Sangiorgi D, Andretta M, Ducci G, Forti B, PC FM, et al. Assessment of patients affected by treatment-resistant depression: findings from a Real-World Study in Italy. *J Psychiatry Psychiatr Disord*. (2020) 4:104–17. doi: 10.26502/jppd.2572-519X0098

43. Sharman Moser S, Chodick G, Gelerstein S, Barit Ben David N, Shalev V, Stein-Reisner O. Epidemiology of treatment resistant depression among major depressive disorder patients in Israel. *BMC Psychiatry*. (2022) 22:541. doi: 10.1186/s12888-022-04184-8

44. Prasartpornsirichoke J, Pityaratstian N, Poolvoralaks C, Sirinimnualkul N, Ormtavesub T, Hiranwattana N, et al. The prevalence and economic burden of treatment-resistant depression in Thailand. *BMC Public Health*. (2023) 23:1541. doi: 10.1186/s12889-023-16477-y

45. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. (1997) 58 Suppl 13:23–9.

46. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry*. (2007) 68 Suppl 8:17–25.

47. Keitner GI, Mansfield AK. Management of treatment-resistant depression. *Psychiatr Clin North Am*. (2012) 35:249–65. doi: 10.1016/j.psc.2011.11.004

48. Dibernardo A, Lin X, Zhang Q, Xiang J, Lu L, Jamieson C, et al. Humanistic outcomes in treatment resistant depression: A secondary analysis of the STAR*D study. *BMC Psychiatry [Electronic Resource]*. (2018) 18:352. doi: 10.1186/s12888-018-1920-7

49. Cepeda MS, Reps J, Fife D, Blacketer C, Stang P, Ryan P. Finding treatment-resistant depression in real-world data: How a data- driven approach compares with expert-based heuristics. *Depression Anxiety*. (2018) 35:220–8. doi: 10.1002/da.22705

50. Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. *BMC Psychiatry*. (2019) 19:247. doi: 10.1186/s12888-019-2222-4

51. Johnston KM, Powell LC, Anderson IM, Szabo S, Cline S. The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. *J Affect Disord*. (2019) 242:195–210. doi: 10.1016/j.jad.2018.06.045

52. Halaris A, Sohl E, Whitham EA. Treatment-resistant depression revisited: A glimmer of hope. *J Pers Med*. (2021) 11:155. doi: 10.3390/jpm11020155

53. Knoth RL, Bolge SC, Kim E, Tran QV. Effect of inadequate response to treatment in patients with depression. *Am J Manag Care*. (2010) 16:e188–96.

54. Lin J, Szukis H, Sheehan JJ, Alphs L, Menges B, Lingohr-Smith M, et al. Economic burden of treatment-resistant depression among patients hospitalized for major depressive disorder in the United States. *Psychiatr Res Clin Pract*. (2019) 1:68–76. doi: 10.1176/appi.prcp.20190001

55. Amos TB, Tandon N, Lefebvre P, Pilon D, Kamstra RL, Pivneva I, et al. Direct and indirect cost burden and change of employment status in treatment-resistant depression: A matched-cohort study using a US commercial claims database. *J Clin Psychiatry*. (2018) 79:17m11725. doi: 10.4088/JCP.17m11725

56. Dintica CS, Habes M, Erus G, Simone T, Schreiner P, Yaffe K. Long-term depressive symptoms and midlife brain age. *J Affect Disord*. (2023) 320:436–41. doi: 10.1016/j.jad.2022.09.164

57. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry*. (2009) 166:410–7. doi: 10.1176/appi.ajp.2008.08081239

58. Reutfors J, Andersson TML, Brenner P, Brandt L, DiBernardo A, Li G, et al. Mortality in treatment-resistant unipolar depression:aregister-basedcohortstudyin Sweden. *J Affect Disord*. (2018) 238:674–9. doi: 10.1016/j.jad.2018.06.030

59. Li G, Fife D, Wang G, Sheehan JJ, Bodén R, Brandt L, et al. All-cause mortality in patients with treatment-resistant depression: a cohort study in the US population. *Ann Gen Psychiatry*. (2019) 18:23. doi: 10.1186/s12991-019-0248-0

60. Brenner P, Reutfors J, Nijs M, Andersson TM. Excess deaths in treatment-resistant depression. *Ther Adv Psychopharmacol*. (2021) 11:20451253211006508. doi: 10.1177/20451253211006508

61. Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. *J Affect Disord*. (2018) 235:362–7. doi: 10.1016/j.jad.2018.04.016

62. Gronemann FH, Jørgensen MB, Nordentoft M, Andersen PK, Osler M. Treatment-resistant depression and risk of all-cause mortality and suicidality in Danish patients with major depression. *J Psychiatr Res*. (2021) 135:197–202. doi: 10.1016/j.jpsychires.2021.01.014

63. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry*. (2007) 68:1062–70. doi: 10.4088/jcp.v68n0713

64. Kautzky A, Dold M, Bartova L, Spies M, Kranz GS, Souery D, et al. Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. *Acta Psychiatr Scand*. (2019) 139:78–88. doi: 10.1111/acps.12959

65. Bartova L, Dold M, Kautzky A, Fabbri C, Spies M, Serretti A, et al. Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further

research and clinical practice. *World J Biol Psychiatry*. (2019) 20:427–48. doi: 10.1080/15622975.2019.1635270

66. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Res*. (2016) 240:421–30. doi: 10.1016/j.psychres.2016.04.034

67. O'Connor SJ, Hewitt N, Kuc J, Orsini LS. Predictors and risk factors of treatment-resistant depression: A systematic review. *J Clin Psychiatry*. (2023) 85 (1):23r14885. doi: 10.4088/JCP.23r14885

68. Fabbri C, Corponi F, Souery D, Kasper S, Montegomery S, Zohar J, et al. The genetics of treatment-resistant depression: a critical review and future perspectives. *Int J Neuropsychopharmacol*. (2019) 22(2):93–104. doi: 10.1093/ijnp/pyy024

69. Martinotti G, Dell'Osso B, Di Lorenzo G, Maina G, Bertolino A, Clerici M, et al. Treating bipolar depression with esketamine: Safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. *Bipolar Disord*. (2023) 25:233–44. doi: 10.1111/bdi.13296

70. Estrade I, Petit AC, Sylvestre V, Danon M, Leroy S, Perrain R, et al. Early effects predict trajectories of response to esketamine in treatment-resistant depression. *J Affect Disord*. (2023) 342:166–76. doi: 10.1016/j.jad.2023.09.030

71. Cepeda MS, Reps J, Ryan P. Findingfactorsthat predict treatment-resistant depression: results of a cohort study. *Depress Anxiety*. (2018) 35:668–73. doi: 10.1002/da.22774

72. Fabbri C, Hagenaars SP, John C, Williams AT, Shrine N, Moles L, et al. Genetic and clinical characteristics of treatment-resistant depression using primary care records in two UK cohorts. *Mol Psychiatry*. (2021) 26:3363–73. doi: 10.1038/s41380-021-01062-9

73. Brendle M, Ahuja S, Valle MD, Moore C, Thielking P, Malone DC, et al. Safety and effectiveness of intranasal esketamine for treatment-resistant depression: a real-world retrospective study. *J Comp Eff Res*. (2022) 11:1323–36. doi: 10.2217/cer-2022-0149

74. Lundberg J, Cars T, Lööv SÅ, Söderling J, Sundström J, Tiihonen J, et al. Association of treatment-resistant depression with patient outcomes and health care resource utilization in a population-wide study. *JAMA Psychiatry*. (2023) 80:167–75. doi: 10.1001/jamapsychiatry.2022.3860

75. Daly EJ, Turkoz I, Salvadore G, Fedgchin M, Ionescu DF, Starr HL, et al. The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder. *Depression Anxiety*. (2021) 38:1120–30. doi: 10.1002/da.23193

76. Rothärmel M, Benosman C, El-Hage W, Berjamin C, Ribayrol D, Guillin O, et al. Efficacy and safety of intranasal esketamine in patients with treatment-resistant depression and comorbid chronic post-traumatic stress disorder: open-label single-arm pilot study. *Front Psychiatry*. (2022) 13:865466. doi: 10.3389/fpsyt.2022.865466

77. Chiappini S, d'Andrea G, De Filippis S, Di Nicola M, Andriola I, Bassetti R, et al. Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: A viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study. *Eur Neuropsychopharmacol*. (2023) 74:15–21. doi: 10.1016/j.euroneuro.2023.04.011

78. Marcatili M, Cristian P, Laura M, Federico M, Chiara R, Lorenzo G, et al. The use of esketamine in comorbid treatment resistant depression and obsessive compulsive disorder following extensive pharmacogenomic testing: a case report. *Ann Gen Psychiatry*. (2021) 20:1–7. doi: 10.1186/s12991-021-00365-z

79. Keeler JL, Treasure J, Himmerich H, Brendle M, Moore C, Robison R. Case report: Intramuscular ketamine or intranasal esketamine as a treatment in four patients with major depressive disorder and comorbid anorexia nervosa. *Front Psychiatry*. (2023) 14:1181447. doi: 10.3389/fpsyt.2023.1181447

80. Johnson&Johnson. Available online at: https://www.jnj.com/janssen-announces-u-s-fda-approval-of-spravato-esketamine-ciii-nasal-spray-to-treat-depressive-symptoms-in-adults-with-major-depressive-disorder-with-acute-suicidal-ideation-or-behavior.

81. Pompili M. Intranasal esketamine and current suicidal ideation with intent in major depression disorder: beat the clock, save a life, start a strategy. *Front Psychiatry*. (2020) 11:325. doi: 10.3389/fpsyt.2020.00325

82. Yang S, Wang J, Li X, Wang T, Xu Z, Xu X, et al. Adverse effects of esketamine for the treatment of major depression disorder: findings from randomized controlled trials. *Psychiatr Q*. (2022) 93:81–95. doi: 10.1007/s11126-020-09871-x

83. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry*. (2020) 81(3):19m12891. doi: 10.4088/JCP.19m12891

84. Williamson D, Turkoz I, Wajs E, Singh JB, Borentain S, Drevets WC. Adverse events and measurement of dissociation after the first dose of esketamine in patients with TRD. *Int J Neuropsychopharmacol*. (2023) 26:198–206. doi: 10.1093/ijnp/pyac081

85. Zaki N, Chen LN, Lane R, Doherty T, Drevets WC, Morrison RL, et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. *Neuropsychopharmacology*. (2023) 48:1225–33. doi: 10.1038/s41386-023-01577-5

86. Martinotti G, Vita A, Fagiolini A, Maina G, Bertolino A, Dell'Osso B, et al. Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. (2022) 319:646–54. doi: 10.1016/j.jad.2022.09.043

87. Ballard ED, Zarate CA Jr. The role of dissociation in ketamine's antidepressant effects. *Nat Commun*. (2020) 11:6431. doi: 10.1038/s41467-020-20190-4

88. Chen G, Chen L, Zhang Y, Li X, Lane R, Lim P, et al. Relationship between dissociation and antidepressant effects of esketamine nasal spray in patients with treatment-resistant depression. *Int J Neuropsychopharmacol*. (2022) 25:269–79. doi: 10.1093/ijnp/pyab084

89. Mathai DS, Nayak SM, Yaden DB, Garcia-Romeu A. Reconsidering "dissociation" as a predictor of antidepressant efficacy for esketamine. *Psychopharmacology*. (2023) 240:827–36. doi: 10.1007/s00213-023-06324-8

90. Bernstein EM, Putnam FW. Development, reliability, and validity of a dissociation scale. *J Nerv Ment Dis*. (1986) 174:727–35. doi: 10.1097/00005053-198612000-00004

91. Pereira S, Brennan E, Patel A, Moran M, Wallier J, Liebowitz MR. Managing dissociative symptoms following the use of esketamine nasal spray: a case report. *Int Clin Psychopharmacol*. (2021) 36:54–7. doi: 10.1097/YIC.0000000000000327

92. Janssen Research & Development. *Crossover study to evaluate the abuse potential of intranasal esketamine compared to racemic intravenous ketamine in nondependent, recreational drug users. Clinical trial registration: 108104*. Raritan, NJ: Janssen Research & Development (2017).

93. Wang J, Khullar A, McIntyre RS, Swainson J. The Drug Liking and Craving Questionnaire (DLCQ) to evaluate addiction risk for ketamine and esketamine. *Psychiatry Res Commun*. (2022) 2:100018. doi: 10.1016/j.psycom.2021.100018

94. Food and Drug Administration. *U.S. Department of health and human services, food and drug administration, center for drug evaluation and research. Assessment of abuse potential of drugs guidance for industry* (2017). Available online at: https://www.fda.gov/media/116739/download (Accessed June 15, 2022).

95. Chubbs B, Wang J, Archer S, Chrenek C, Khullar A, Wolowyk M, et al. A survey of drug liking and cravings in patients using sublingual or intranasal ketamine for treatment resistant depression: A preliminary evaluation of real world addictive potential. *Front Psychiatry*. (2022) 13:1016439. doi: 10.3389/fpsyt.2022.1016439

96. Cuijpers P. From treatment resistance to sequential treatments of depression. *World Psychiatry*. (2023) 22:418–9. doi: 10.1002/wps.21138

97. Furukawa TA. Complexities of treatment-resistant depression: cautionary notes and promising avenues. *World Psychiatry*. (2023) 22:419–20. doi: 10.1002/wps.21139

98. Rush AJ. Challenges of research on treatment-resistant depression: a clinician's perspective. *World Psychiatry*. (2023) 22:415–7. doi: 10.1002/wps.21136

99. Souery D. Treatment-resistant depression: where to find hope? *World Psychiatry*. (2023) 22:422–3. doi: 10.1002/wps.21141

100. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *Am J Psychiatry*. (2019) 176:428–38. doi: 10.1176/appi.ajp.2019.19020172

101. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol*. (2019) 22:616–30. doi: 10.1093/ijnp/pyz039

102. Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM-3. *Am J Geriatr Psychiatry*. (2020) 28:121–41. doi: 10.1016/j.jagp.2019.10.008

103. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*. (2019) 76:893–903. doi: 10.1001/jamapsychiatry.2019.1189

104. Jeon HJ, Ju PC, Sulaiman AH, Aziz SA, Paik JW, Tan W, et al. Long-term safety and efficacy of esketamine nasal spray plus an oral antidepressant in patients with treatment-resistant depression- an asian sub-group analysis from the SUSTAIN-2 study. *Clin Psychopharmacol Neurosci*. (2022) 20:70–86. doi: 10.9758/cpn.2022.20.1.70

105. d'Andrea G, Chiappini S, McIntyre RS, Stefanelli G, Carullo R, Andriola I, et al. Investigating the effectiveness and tolerability of intranasal esketamine among older adults with treatment-resistant depression (TRD): A *post-hoc* analysis from the REAL-ESK study group. *Am J Geriatr Psychiatry*. (2023) 31:1032–41. doi: 10.1016/j.jagp.2023.06.016

106. Leichsenring F, Steinert C, Rost F, Abbass A, Heim N, Ioannidis JPA. A critical assessment of NICE guidelines for treatment of depression. *World Psychiatry*. (2023) 22:43–5. doi: 10.1002/wps.21039

107. Serafini G, Howland RH, Rovedi F, Girardi P, Amore M. The role of ketamine in treatment-resistant depression: a systematic review. *Curr Neuropharmacol*. (2014) 12:444–61. doi: 10.2174/1570159X12666140619204251

108. Gałuszko-Węgielnik M, Chmielewska Z, Jakuszkowiak-Wojten K, Wiglusz MS, Cubała WJ. Ketamine as add-on treatment in psychotic treatment-resistant depression. *Brain Sci*. (2023) 13:142. doi: 10.3390/brainsci13010142

109. Kokane SS, Armant RJ, Bolaños-Guzmán CA, Perrotti LI. Overlap in the neural circuitry and molecular mechanisms underlying ketamine abuse and its use as an antidepressant. *Behav Brain Res*. (2020) 384:112548. doi: 10.1016/j.bbr.2020.112548

110. Sapkota A, Khurshid H, Qureshi IA, Jahan N, Went TR, Sultan W, et al. Efficacy and safety of intranasal esketamine in treatment-resistant depression in adults: A systematic review. *Cureus*. (2021) 13:e17352. doi: 10.7759/cureus.17352

111. Ceban F, Rosenblat JD, Kratiuk K, Lee Y, Rodrigues NB, Gill H, et al. Prevention and management of common adverse effects of ketamine and esketamine in patients with mood disorders. *CNS Drugs*. (2021) 35:925–34. doi: 10.1007/s40263-021-00846-5

112. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

113. Swainson J, McGirr A, Blier P, Brietzke E, Richard-Devantoy S, Ravindran N, et al. The Canadian Network for Mood and Anxi- ety Treatments (CANMAT) Task Force recommendations for the use of racemic ketamine in adults with major depressive disorder: recommandations Du Groupe De Travail Du Reíseau Canadien Pour Les Traitements De L'humeur Et De L'anxieíteí (Canmat) Concernant L'utilisation de la Keítamine Raceímique Chez Les Adultes Souffrant De Trouble Deípressif Majeur. *Can J Psychiatry*. (2021) 66:113–25. doi: 10.1177/07067437

114. Doty RL, Popova V, Wylie C, Fedgchin M, Daly E, Janik A, et al. Effect of esketamine nasal spray on olfactory function and nasal tolerability in patients with treatment-resistant depression: results from four multicenter, randomized, double-blind, placebo-controlled, phase III studies. *CNS Drugs*. (2021) 35:781–94. doi: 10.1007/s40263-021-00826-9

115. Kasper S, Cubała WJ, Fagiolini A, Ramos-Quiroga JA, Souery D, Young AH. Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: Basic science, evidence-based knowledge and expert guidance. *World J Biol Psychiatry*. (2021) 22:468–82. doi: 10.1080/15622975.2020.1836399

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Major challenges in youth psychopathology: treatment-resistant depression. A narrative review

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Major depressive disorder (MDD) represents a major health issue in adolescents and young adults, leading to high levels of disability and profoundly impacting overall functioning. The clinical presentation of MDD in this vulnerable age group may slightly differ from what can be observed in adult populations, and psychopharmacological strategies do not always lead to optimal response. Resistance to antidepressant treatment has a prevalence estimated around 40% in youths suffering from MDD and is associated with higher comorbidity rates and suicidality. Several factors, encompassing biological, environmental, and clinical features, may contribute to the emergence of treatment-resistant depression (TRD) in adolescents and young adults. Furthermore, TRD may underpin the presence of an unrecognized bipolar diathesis, increasing the overall complexity of the clinical picture and posing major differential diagnosis challenges in the clinical practice. After summarizing current evidence on epidemiological and clinical correlates of TRD in adolescents and young adults, the present review also provides an overview of possible treatment strategies, including novel fast-acting antidepressants. Despite these pharmacological agents are promising in this population, their usage is expected to rely on risk-benefit ratio and to be considered in the context of integrated models of care.

KEYWORDS

major depressive disorder, treatment-resistant depression, adolescents, youth psychopathology, fast-acting antidepressants, ketamine, esketamine, glutamate

1 Introduction: major depressive disorder in youth populations

Major depressive disorder (MDD) is a serious psychiatric disorder with a relevant impact on quality of life and overall functioning. According to the World Health Organization (WHO), MDD represents the main cause of years lived with disability worldwide, leading to decreased involvement in social and work activities and to increased medical comorbidities and health resource use (1). The lifetime prevalence of MDD may reach up to 30% in special populations (2), and is usually higher among women (3).

Depressive disorders, and particularly MDD, also represent a relevant health issue in adolescents and young adults, with an overall prevalence estimated around 2-3% (4, 5), reaching up to 20% at the end of puberty (6). The incidence of MDD during adolescence is estimated about 7.5% (2.3% for serious forms of the disorder) (7), with higher prevalence rates among young women (8). A meta-analysis of 80,879 youths conducted during the first year of the Coronavirus disease 2019 (COVID-19) pandemic concluded that the global prevalence of youths experiencing clinically significant depressive symptoms increased to 25% (9). Adolescence is a vulnerable period for developing mental health issues, and particularly depression, due to the interaction of different factors encompassing biological, environmental, and social determinants (10). Indeed, the onset of puberty, together with the exposure to social media, bullying and cyber-bullying episodes and education-related issues, make this life period extremely prone to the onset of psychopathology (11). Adolescents and young adults experience a number of symptoms during depressive episodes, including persistent sadness, irritability, weight change, loss of energy, and insomnia (12). The emergence of MDD during adolescence is associated with significant functional impairment and higher comorbidity rates (11), including medical diseases (13), as well as with an increase in substance abuse (14). More than 30% of youths suffering from MDD experience suicidal ideation, and over 10% attempt suicide, the latter being the second cause of death among youths aged 15-24 (15). Studies conducted among university students highlighted that MDD could seriously impact academic performances and lead to impaired social relationships and low self-esteem (16). Moreover, the onset of MDD during youth may lead to higher recurrence and relapse rates during the following years (17). Despite the relevance of MDD among youths under a clinical and epidemiological point of view, young people suffering from this disorder are often not likely to seek help. Hence, according to recent reports, only 35% of adolescents suffering from this condition accessed mental health resources and only 33% received adequate treatment (8).

In this narrative review, we decided to focus on one of the major challenges posed by MDD, which is treatment-resistance. Since a considerable percentage of MDD first episodes occur during adolescence or young adulthood, we believe that the appropriate identification of difficult-to-treat conditions is crucial to prevent functional impairment and chronicization during the following years. As a consequence, the main aim of this paper is to critically summarize evidence concerning treatment-resistant depression (TRD) in youths, with specific focus on: definition, epidemiology, impact, clinical correlates (including differential diagnosis issues), and possible treatment strategies, with particular interest in novel antidepressant strategies. To this attempt, we performed a literature review, variously combining the following keywords in PubMed, Scopus, and Web of Science databases: “major depressive disorder”, “depressive disorders”, “treatment-resistant depression”, “treatment resist*”, “youth*”, “adolescent*”, “young adult*”.

2 Treatment-resistant depression in youth populations: clinical challenges and impact

The currently accepted definition of TRD refers to a condition in which subjects do not respond, or reach remission, after treatment with at least two antidepressants at adequate dose and for an adequate period of time (18). Using this definition, the prevalence of TRD is estimated about 20-30% among subjects suffering from MDD (19), but rates vary from 12% to 55% (20). This huge variability is mainly due to the lack of homogenous criteria for TRD, as well as to various staging models that consider different number of failed antidepressant trials and different possible treatments, e.g., variably including also psychotherapies and electro-convulsant therapy (ECT) (21). Despite consensus has not been reached yet, most studies consider response as a reduction in depressive symptoms of at least 50%, as evaluated by well-validated rating scales (22). The minimum duration of antidepressant treatment should be 4 weeks (23), with a variable range of 4-12 weeks (24). Overall, subjects with MDD who undergo adequate treatment usually reach remission in 30% cases. Out of the remaining 70%, about 20% respond to treatment without reaching remission, while 50% do not respond at all (25). To note, the possibility for reaching remission significantly decreases after the second and third treatment strategy, as detected in the wide multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (26). Furthermore, in a relevant percentage of cases where a response is observed, residual symptoms may be present and impact overall quality of life of affected individuals (27).

TRD represents a complex clinical entity, underpinning different depression subtypes, as well as psychiatric and medical comorbidities (28). This condition should be conceptualized as a phenomenon that lies on a continuum ranging from partially responsive depression to multi-treatment resistant MDD (29). As we will elucidate later, TRD is also a multifaceted phenomenon, since several factors lead to reduced treatment effectiveness in MDD. Among possible risk factors for TRD, psychiatric comorbidities, particularly anxiety disorders (30, 31), psychotic features (18), and poor treatment adherence (32) have pointed out as the most common ones.

In youth populations, no specific criteria for TRD have been suggested, and research on the topic is scant (33, 34). A broad

definition proposed for TRD in adolescents is a depressive disorder that does not respond to a two-month antidepressant treatment, namely a drug prescribed at a dose equivalent to 40 mg of fluoxetine and/or 8-16 sessions of cognitive-behavioral or interpersonal therapy (35, 36). Psychopharmacological treatment efficacy should be evaluated at intervals of at least four weeks, increasing doses in case of incomplete response (37). The main strength of this definition is the inclusion of psychotherapy among possible treatment strategies, which lacks in most adult TRD definitions (21). Indeed, psychotherapy demonstrated its efficacy in youth depression, alone or associated with pharmacological interventions, and is mentioned in the majority of treatment guidelines for this population (37–40). On the other hand, the different response to antidepressants in adolescents is not taken into account and the doses are similar to those advised for adults. It has anyway been largely demonstrated that young populations can develop activation symptoms, mood lability, and irritability in response to conventional antidepressant treatments, possibly leading to worsening of depression and suicidality (35). This is a major issue that experts should consider when defining TRD in adolescent and young adults, possibly reaching a more population-specific and comprehensive definition.

Based on the currently accepted description, a consistent percentage of adolescents and young adults with MDD – estimated around 40% - fail to respond to treatment with an antidepressant medication or evidence-based psychotherapy (33, 41), resulting in what is commonly referred to as TRD (34). To note, there is also a proportion of patients – about one third – initially reaching remission who do not maintain this outcome in the long-term (42). The impact of TRD on overall well-being has widely been recognized (43), together with the significant increase in mortality risk among affected individuals (44, 45). These aspects are particularly meaningful in youth populations. Indeed, TRD is associated with cognitive impairment (46), reduced coping abilities (47), and higher risk of developing medical diseases (48, 49), resulting in greater overall severity, poorer outcomes, and reduced functioning in different areas (50–52). High mortality rates are linked to comorbidities and to increased suicide risk (53). In most cases, TRD leads to higher use of healthcare resources, with subsequent increased health costs (54–56), which is even more relevant if we focus on young populations at their very first working experiences. As a result, quality of life is significantly impaired in adolescents and young adults suffering from TRD (57).

3 Clinical correlates of TRD in youth populations

The clinical presentation of MDD in youths, and particularly adolescents, can significantly differ from what can be observed in adult populations, although diagnostic criteria are the same. Depressive symptoms can sensitively be different across the lifespan, which lead to low diagnostic validity of traditional nosographic categories in this population (58). In early and mid-adolescents some features, particularly irritability, somatic symptoms, and anxiety, can be ever more prevalent than low mood and sadness, while in older adolescents and young adults affective and cognitive symptoms are prominent and closely resemble those observed in adults (59). Among youths, somatic and autonomic symptoms - including eating and sleep disturbances – could in some cases prevail on cognitive features and anhedonia and may lead to increased duration and severity of the depressive episode (36). Moreover, different clinical pictures may be observed also based on possible pathways leading to the development of depressive symptoms and depressive disorders. The impact that substance abuse, as well as the co-occurrence of behavioral addictions, e.g., pathological internet and social media use, can exert on the clinical picture may indeed be crucial. Sex differences have also been described, including a higher prevalence of eating and body image disorders in females, while somatic symptoms, attention deficits, restlessness, and anhedonia are more frequent in males, increasing the risk of developing conduct disorders and substance use (59). Another not negligible influence is represented by cultural and societal determinants, since the development of depression may be affected by specific factors, e.g., belonging to a minority or being culturally vulnerable in challenging environments, such as huge urban contexts (60, 61). This is a crucial points if we consider the progressive increase of migrant families belonging to ethnic minorities in European countries and the high prevalence of mood disorders in this population (62), with major challenges for psychiatric care. Indeed, symptom presentation significantly vary across cultures, as demonstrated for most psychiatric disorders, and thus require more time to be adequately identified. Moreover, adolescents coming from socially disadvantaged groups may encounter major barriers in accessing mental health care (63), which summed up to internal and external stigma-related issues determines reduced rates of help-seeking and possibly influences the emergence of treatment-resistance due to delay in symptom recognition. Cultural differences may also be experienced when it comes to how depression is perceived among youths belonging to different contexts and could influence crucial aspects such as the acceptance of the proposed treatments and the risk of drop-out, which significantly impacts the efficacy of treatment strategies (64).

Depressive episodes in youth populations are not of univocal interpretation and should be treated with particular attention especially in case of treatment resistance. Frequently, TRD during adolescence underpins the presence of an underlying bipolar diathesis. Indeed, most subjects who suffer from early onset bipolar disorder (BD) present a depressive polarity at their first episode, and it has been argued that up to 28% of young patients who are at first diagnosed with MDD develop subsequent hypomanic or manic episodes within 5-10 years (65). To note, bipolar depression is usually resistant to antidepressant treatment, which can also lead to a shift towards manic symptoms (66) and worsening of depression (67). Treatment strategies may differ significantly in case of a bipolar diathesis, since antidepressants should be used with caution in subjects suffering from, or at-risk for, BD, evaluating the risk/benefit ratio (68). In younger patients, bipolar depression may be difficult to distinguish from MDD, due to the depressive onset and the absence of previous episodes of opposite polarity. Some clinical features may anyway be evaluated as possible “red flags” and should thus be always considered. The main factor suggesting underlying bipolarity in youths with

a depressive episode is positive familiar history for BD, which already suggests the presence of an at-risk state for BD according to previously proposed criteria (69). A positive history of psychotic disorders and suicide among first-grade relatives should also be taken into account, as well as illness characteristics, since higher severity and younger age at onset could be more frequently associated with the emergence of BD among offsprings (39). As already stated, hypomanic episodes are often under-reported or considered as ego syntonic in this population. The presence of under-threshold hypomanic symptoms should anyway be systematically investigated, and clinicians should screen patients for the presence of short periods – usually, less than four days – during which clinical features such as increased self-esteem, decreased need for sleep, talkativeness, distractibility, and increased goal-directed activity occurred (69). Course characteristics of the current depressive episode should also be considered, particularly early and abrupt onset and a positive history for recurrent depressive episodes that, as already stated, fail in responding to antidepressant treatment or present worsening of depression (39, 67). Finally, further potential predictors of underlying BD include atypical or mixed features, psychotic symptoms, psychomotor retardation, and catatonia, as well as the comorbidity with substance abuse (70–72).

When TRD occurs in early onset mood disorders, it may underpin biological, clinical, and social correlates representing possible risk factors for this condition. The first point is that depression during youth may result from altered connectivity in brain regions, e.g., amygdala, involved in emotional-affective processing and regulation, during a period when they are still under development. This can result in aberrant responses to classical antidepressant treatments, even when administered for a long period of time. Genetics plays a key role in resistance to psychopharmacotherapy, as shown by previous studies on lithium response (73, 74). The main alleles involved in TRD include those encoding for steroid hormone receptors, e.g., FKBP5 (75) and for serotonin transporter (76). Being a fast metabolizer has also been associated with a reduced response to pharmacological treatment (77). Neurometabolic alterations, such as GTP cyclohydrolase deficiency, represent additional risk factors for TRD and were thus pointed out as potentially treatable causes of this condition (78, 79). Biological sex also seems to affect response to antidepressants, since girls present higher risk of experiencing recurrence and treatment resistance (80). Neurodevelopmental disorders, such as attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), represent additional risk factors for TRD in the young (81–84). This may be due to different reasons. First, the presence of untreated ADHD can reduce functioning, self-esteem, and treatment compliance, directly contributing to the development of depressive symptoms. In addition, the presence of ADHD is a risk factor for substance abuse, which further contributes to TRD. ADHD should thus be investigated in youths presenting with treatment-resistant mood disorders, since its clinical management can improve functioning, depressive symptoms, and treatment compliance, also reducing the risk for substance abuse. It was also reported that people with ASD are four times more likely to experience depression, especially in case of high functioning (85): however, autistic children and adolescents treated with selective serotonin reuptake inhibitors (SSRI) may have a higher risk of side effects, such as impulsive or irritable behavior and trouble sleeping (86). Other clinical factors that may contribute to the development of TRD are represented by overall greater illness severity during a depressive episode, high levels of anxiety, and suicidality (87–90). Psychiatric comorbidities, such as eating disorders and personality disorders, contribute to treatment resistance in youths who suffer from depression (36, 59). Moreover, adolescent depression is associated with a higher prevalence of substance-related disorders when compared to the general population (91), leading to increased disease severity and higher risk of TRD, especially in males (80, 92). The use of specific pharmacological agents and combinations, such as trazodone in association with fluoxetine, has been pointed out as a potential contributor to treatment resistance or symptom worsening in depressed young patients, but different confounding factors, e.g., pharmacokinetic interactions, make this findings anecdotical (93). Among comorbid medical conditions, early onset thyroid disorders may also cause depressive symptoms and contribute to TRD in the young (94). Finally, social factors including parental depression, early adversity or trauma, and belonging to a minority, have been identified as more prevalent in TRD young patients (95–99).

4 Treatment strategies in youth TRD

The issue of treating TRD in adolescents and young adults is challenging, due to different reasons. Indeed, no psychopharmacological treatment has specifically been approved for TRD in this population and no univocal guidelines have been reached yet. It should also be underlined that, despite some antidepressant drugs – e.g., SSRIs – are approved and considered as first-line treatments in youth depression, their use is controversial and data on their efficacy is limited. Previous literature highlighted that not only SSRIs, but also tricyclic antidepressants (TCA), present reduced effectiveness in the treatment of MDD in adolescents when compared to adult populations (100–105). Similarly, third-generation antidepressants, such as serotonin and noradrenaline reuptake inhibitors (SNRI) and mirtazapine, did not show higher efficacy when compared to placebo (101, 105). It should also be underlined that treatment indications for this age range should transcend general approaches. Indeed, there is huge variability in the clinical manifestations of depressive disorders among youths, which suggests that a precision psychiatry methodology should always be used and treatments should target symptom dimensions rather than diagnostic categories (106).

In case of non-response to the first antidepressant trial, and after considering all the factors that may impact treatment outcomes, e.g., physical and medical comorbidities (107), one possible strategy is switching to another antidepressant, usually another SSRI on a SNRI. These two treatment options showed similar response rates in previous studies (47% vs 48%, p=0.83), despite SNRIs and particularly venlafaxine presented greater effects on blood pressure and heart rates (33) In case of switching to another antidepressant, the long latency of action may represent a crucial limitation (108). As a consequence, combination and

augmentation strategies are often chosen, especially in case of a partial response to the first prescribed treatment (36). As a result, adolescents with TRD frequently receive numerous psychotropic medications, including multiple drugs acting on monoaminergic systems, mood stabilizers, particularly lithium (36, 109), and atypical antipsychotics (80), but remission rates remain low and many experience adverse effects (110). The use of combination strategies in youth TRD may also present major issues in the long-term. Indeed, despite lithium appears to be a promising treatment in this population, also due to its effects in reducing self-harm and suicidality in adults (111), its clinical use in adolescents is limited by the narrow therapeutic window and by potential adverse effects, mainly those on kidney and thyroid function (36). Similarly, long-term use of second generation antipsychotics is burdened by the considerable risk of weight gain and metabolic syndrome (112), which limits their tolerability in this population.

Previous research also focused on non-pharmacological treatments, which could limit drug-related safety issues, with the strongest evidence supporting the use of cognitive behavioral therapy (CBT) in youth populations. Indeed, the efficacy of CBT has been demonstrated even in monotherapy, with evidence on its possible usefulness in relapse prevention (113, 114). As for the effectiveness of CBT as add-on treatment in TRD, it has been suggested that it should be added to psychotropic agents as early as possible, and possibly at least after one treatment failure, representing the gold standard in this population (115). On the other hand, there are also trials supporting poor response to combined CBT-antidepressant treatment, which suggests that the profile of young patients responding to psychotherapy for depressive episodes should be better characterized (116). Despite CBT being the approach with strongest literature evidence (33, 117, 118), interpersonal therapy (IPT) also demonstrated its efficacy in adolescents with TRD (119). The effectiveness of IPT for the treatment of depression arises from its focus on social and interpersonal stressors that may trigger depressive episodes and can be significantly impactful in youth populations. Due to encouraging results in adult depression, adolescent-focused IPT protocols were designed and showed to be effective (120), despite more comparative studies would be needed. Promising results were also reported for further approaches, e.g., short-term psychoanalytic psychotherapy (121), and it was thus suggested that youths failing to respond to one first trial should switch to another approach (36).

As for non-pharmacological treatments that specifically target TRD, preliminary evidence is available for physical therapies, such as transcranial magnetic stimulation (TMS), which demonstrated to be safe and tolerable in this population acting on both depressive and anxiety symptoms (122, 123). Similarly, data concerning ECT in youths is scant and its usage is limited. This may be due to restricted knowledge on the topic, caused by scantiness of clinical trials and legal restrictions in the implementation of this treatment (124, 125). Despite this, novel protocols tailored to this age group have been implemented with some positive results concerning efficacy and tolerability (90). Particularly, the use of ECT in youth populations suffering from TRD with suicidal ideation (126) or psychotic symptoms (127) appeared to be particularly effective, with response rates ranging from 50% to 90% depending on the considered report (124, 125, 128). One major issue for the use of physical therapies in adolescents and young adults could be related to possible impairment of cognitive performances, which represent one of the main domains impacting overall functioning in this population, but the tolerability profile appeared to be similar to those evidenced in adults (128).

On the basis of what stated above, the need for novel, tolerable, fast-acting antidepressants represents a crucial need in youth TRD. Several pathophysiological pathways appear to underlie TRD (129). Among the most studied mechanisms, a reduction in glutamate levels in prefrontal areas has been detected (130). This hypothesis has been supported by the antidepressant efficacy of ketamine and esketamine, modulating glutamatergic activity (131–133). At first approved as anesthetic drug in the 1970s, ketamine raised interest among the scientific community also due to its quick and long-lasting antidepressant activity (134–138). This pharmacological agent acts as a modulator of glutamatergic systems by N-methyl-D-aspartate (NMDA) antagonism (136). Other pathophysiological pathways targeted by treatment with ketamine include the modulation of prefrontal GABAergic neurons (132) and the stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (139, 140). These treatments lead to changes in neuroplasticity on mTOR/brain-derived neurotrophic factor (BDNF) signaling (141, 142). To note, the chronic use of ketamine is also associated with increase in blood neurotrophins, such as BDNF (143).

Despite clinical recommendations for TRD have been developed during the last decades (see, e.g (144), widely accepted guidelines have not been implemented yet. Anyway, increasing evidence is being provided for what concerns recently approved treatments for TRD, among which the main one is intranasal esketamine (145). Emerging evidence supports the use of ketamine and esketamine in youths with TRD. As already elucidated, several randomized studies demonstrated that ketamine infusion lead to significant reduction in depressive symptoms compared to placebo in TRD (138, 146–149). Recent evidence also showed that ketamine may act on suicidal ideation with rapid action and minimal side effects (131, 150–157). Since the use of SSRI in adolescents suffering from depression has been associated with increased suicidal risk (158), with a pooled relative risk of 1.28 (95% CI: 1.09–1.51) as detected by a recent meta-analytic study (159), the possible effect of ketamine on this dimension gains even higher importance. Another psychopathological domain on which antidepressants were demonstrated to exert low effectiveness in young populations is anhedonia (87), possibly representing another promising target of treatment with ketamine as demonstrated by previous reports on bipolar depression, demonstrating reductions of anhedonia levels at different times during the 14 days after the infusion, not depending on the effect on other depressive dimensions (160). Despite literature on the topic is still scant, recent studies showed encouraging results concerning the use of intravenous ketamine in youth populations. Indeed, a randomized controlled trial pointed out towards the efficacy of one single dose of intravenous ketamine, compared to active placebo (midazolam), in reducing depressive symptoms in adolescents who did not respond to previous treatments (161). During the 3 days following infusion, the

prevalence of response to ketamine treatment was 76% (p=0.046) compared with 35% of responders in the active placebo group, with a mean difference in the Montgomery-Åsberg Depression Rating Scale (MADRS) of -8.69 ± 15.08 and an effect size of 0.78 (161, 162). Further data from open-label trials and case reports/case series also suggested that low-dose ketamine had a rapidly acting antidepressant effect in adolescents. In particular, an open label trial investigating the efficacy of six ketamine infusions (0.5 mg/kg) over two weeks on adolescent (12-18 years old) TRD demonstrated a reduction of 42.5% (p.<0.01) at the Children's Depression Rating Scale - Revised (CDRS-R) (163, 164). Intravenous ketamine treatment appeared to be safe and well-tolerated in this population, with transitory dissociative and hemodynamic symptoms that resolved after few hours (161, 163, 165). The neural correlates of intravenous ketamine treatment in adolescent TRD may reside in the reduced activation of corticolimbic, corticostriatal, and default mode networks, which underpins an increase in hedonic capacity associated with reduced negativity bias and attitude towards positivity (166). To note, the use of ketamine would appear more appropriate among specific sub-populations of TRD patients, as confirmed by adult studies. Indeed, it has been suggested that the most appropriate use of ketamine would be as a short-term treatment in acute settings, especially in case of suicidal risk, which appears to decrease even before the improvements of depressive symptoms (167). Anyway, the latter were faster than those obtained with other antidepressant drugs, e.g., SSRIs (168). Moreover, studies conducted in adult populations elucidated that efficacy on specific domains, e.g., cognitive symptoms, was obtained only in TRD patients with anxious depression when compared to non-anxious ones (164). Similarly, it can be hypothesized that response to ketamine treatment in youths could depend on specific factors. Most evidence so far showed that response to ketamine in youth populations is associated with a shorter duration and lower severity of the current episode, treatment with SSRIs rather than SNRIs, and ADHD comorbidity (169).

Esketamine, the S-enantiomer of ketamine, was demonstrated to be a precious therapeutic option when combined with serotoninergic drugs in adult TRD (170) and was thus approved by regulatory agencies for the treatment of this condition (171–173). Due to its higher affinity for NMDA receptor and to its intranasal formulation, esketamine offers interesting therapeutic perspectives for outpatient use, and is thus the only treatment approved for TRD in European countries when combined with SSRIs or SNRIs (174). Previous reports showed promising results concerning the use of esketamine in adolescent populations. In a randomized-controlled trial, three intravenous infusions of esketamine (0.25 mg/kg) were associated with higher antidepressant and anti-suicidal effects according to greater reductions in the scoring of depression severity (MADRS total score mean changes: -15.3 ± 11.2 vs -8.8 ± 9.4, p=0.002) and suicide-related measures (Columbia Suicide Severity Rating Scale (CSSRS) ideation score mean changes: -2.6 ± 2 vs -1.7 ± 2.2, p=0.007; CSSRS intensity score mean changes: -10.6 ± 8.4 vs -5 ± 7.4, p=0.002) when compared to active placebo in adolescents aged 13-18 (175). In the esketamine treatment group, a significant improvement in some cognitive domains, particularly processing speed (drug main effect: F=6.607, p=0.013) was also observed, while no impairment of the other domains were reported (176). A double-blind, randomized, midazolam-controlled study of intranasal esketamine for adolescents with MDD at imminent risk of suicide showed that pooled esketamine doses (56 mg, 84 mg) were superior over midazolam in reducing CDRS-R at 24 hours after the initial dose (p=0.037), with relatively low incidence of serious adverse events (28 mg: 13.8%, 56 mg: 22.6%, 84 mg: 4.3%) that did not cause treatment discontinuation in any case (177). Further evidence coming from case report studies (178) confirmed that intranasal esketamine use in youth populations could be tolerable with minimum adverse reactions, despite its efficacy has not been proved yet (175, 176). As for possible issues related to the use of ketamine and esketamine in the long-term, it has been argued that vigilance for possible cognitive effects and the emergence of abuse is essential, despite preliminary data on adult population is encouraging (179). Current evidence for intravenous ketamine treatment in adolescent populations is based on preclinical studies. Despite most of these showed no later cognitive impairment and an overall good tolerability in the long-term with the administration of low-dose ketamine (180, 181), further data underlines a reduction of spatial working memory together with morphological and degenerative brain changes when administering higher doses to adolescent rats (182). This suggests that detrimental effects of ketamine on brain development may depend on the chronicity and dose of administration, but it should also be noted that clinical doses of this medication are significantly lower than those used in these experimental settings (183). As for esketamine, no long-term studies assessed its safety in adolescent populations. To note, encouraging results come from trials conducted in clinical settings evaluating long-term esketamine use in adults, which showed overall good tolerability, with no relevant incidence of serious adverse effects, including abuse (173, 184, 185).

To note, further treatments for TRD are being evaluated, such as psychedelics and cannabidiol, with promising results in adult populations but no preliminary evidence, including preclinical studies, in adolescents (108). Among classical psychedelics, psylocibin is being evaluated for the treatment of affective - and particularly depressive - disorders, with preliminary clinical evidence in adult populations (186). Based on animal models, the antidepressant efficacy of this compound may rely on its effect on 5HT-2A receptors, possibly increasing serotonin and glutamate levels and modulating the excitability of pyramidal neurons and synaptic plasticity processes (187). As for cannabidiol, its possible usefulness in the improvement of affective and stress-induced symptoms has been widely proved by preclinical studies, despite its efficacy may vary on the basis of different biological determinants, e.g., sex (188, 189). Preclinical evidence is also available for the use of the compound in adolescence, confirming its effectiveness at lower doses than those needed in adulthood (190). Contrasting results on cannabidiol length of action in adolescent rodents were provided, suggesting that the fast-acting antidepressant action may not be sustained over time (190, 191), but these data require further validation. Since evidence for novel antidepressant strategies has not been confirmed by clinical studies on adolescent populations and preclinical data is still scant, no

conclusions can be drawn on possible uses of these molecules in youths so far.

Despite some novel agents, particularly ketamine and esketamine, have demonstrated to be rapid and effective treatments, it is crucial to correctly assess the risk-benefit ratio for each subject, to make informed decisions about treatment appropriateness, especially in vulnerable populations. Indeed, together with the already-cited dissociative symptoms, further side effects, such as alterations in blood pressure levels and the risk of developing addiction, should be considered. Moreover, not all subjects with TRD respond positively to this treatment: severity of depression, comorbidities, and previous treatment history should be considered in order to select individuals that are most likely to benefit from the treatment (192). Is should also be noticed that the long-term impact of these drugs on young people's physical, cognitive, and emotional development has not been fully studied yet (193). Further research is thus needed in order to consider these aspects, together with legal and ethical issues that safeguard the well-being of young subjects with TRD (194). Providing psychiatric care to young people, and particularly minors, rises a series of ethical and legal concerns that fully reflect the dynamism of this field, always facing new challenges related to broader changes at societal level. One major issue is the capacity of providing informed consent to treatments, which remains controversial. In case of minors, parents have the power to guide treatment choices, expressing their preference and eventually outweighing children's willingness to undergo specific therapies (195). On the other hand, there are specific jurisdictions that consider the possibility of adolescents with a clear understanding of their condition expressing their informed consent, as well as emancipation following marriage or economic independence (196). Prescribing principles are similar for adult and adolescent populations and are based on beneficence and nonmaleficence, since clinicians should always evaluate the best treatment choice for their patients and avoid short- and long-term harmful effects (197). To note, most prescriptions in adolescent populations may come from psychiatrists working with adults and not receiving specific training. In this context, prescription of specific pharmacological agents, e.g., antidepressants, may result in further criticalities, being burdened by warnings due to possible adverse effects and issues like worsening of depression and the emergence of suicidal ideation. This may be particularly relevant in case of new pharmacological strategies that have not been studied in depth in youth, and particularly adolescent, populations, due to scant knowledge concerning their possible effects on rapidly developing brains. Apart from the already-elucidated possible effects on cognitive function and the development of structural and functional alterations in the central nervous system (198), it should also be noted that depressive symptoms in youths could underpin the later emergence of further conditions, such as schizophrenia-spectrum disorders (178). In this case, the use of ketamine and esketamine should be cautious due to the potential influence on the development of psychosis (199).

Several challenges need to be addressed to ensure adequate treatment for youth populations suffering from TRD, as well as appropriate and safe usage of new pharmacological agents in these patients. Indeed, current literature on the topic of youth TRD lacks a precision approach in the identification of this major health problem, since a univocal definition has not yet been provided and symptom domains that could more clearly characterize the clinical picture have not been examined in depth. Addressing these issues would help a more accurate selection of patients included in clinical trials, helping to establish treatment efficacy and safety of novel pharmacological agents. Studies on fast-acting antidepressants in youths with TRD are scant and are based on small sample sizes, not always following a randomized-controlled design, which limits the generalizability of their findings. This is also a major issue that contributed to the narrative approach of this review, since the possibility of a quantitative and meta-analytic synthesis of the study results was lacking. Despite this, we believe that the promising results obtained by preclinical and clinical studies warrant further investigation. Moreover, we should underline that differential diagnosis, risk assessment, patient selection, long-term monitoring, and ethical concerns are crucial elements to consider even since the diagnostic process and should contribute to treatment choices in youth TRD. A multidisciplinary approach is important for optimizing the usage of ketamine and esketamine in youth populations, and safeguard the well-being of subjects during and after the treatment process, also considering that integrated treatments are expected to be proposed since very early illness stages in order to reduce the overall impact of youth psychopathology on overall well-being (200, 201).

5 Conclusions

Resistance to treatment during a major depressive episode remains a relevant challenge in youth populations, with different possible correlates including an unrecognized bipolar diathesis. The lack a of a univocal definition of this condition suggests that future research on the topic is needed in order to better clarify its clinical correlates. Further characterization of this condition is strongly needed also in order to optimize treatment strategies in a precision psychiatric perspective that goes beyond traditional nosographic descriptions. Moreover, treatments suggested for youth treatment-resistant depression are not population-specific and the current clinical practice advocates the use of strategies that follow those adopted in adults. Despite this, the use of traditional antidepressant agents in adolescents and young adults is burdened by effectiveness and safety concerns. Further research on integrated treatment strategies should clarify the role of non-pharmacological interventions in this population, also considering new psychotherapeutic approaches and psychosocial treatments. Results

from this narrative review also suggest that fast-acting antidepressants are promising in this population and appear to be well-tolerated and effective. Despite this, the scantness of clinical studies, the limitations posed by ethical and legal issues, together with the lack of long-term safety and effectiveness data, advises that further research on the topic would be needed. Future studies are thus expected to provide further evidence concerning this population, where risk-benefit ratio should always be taken into account when addressing treatment choices.

Author contributions

GM: Conceptualization, Writing – review & editing. GCi: Writing – original draft. FS: Writing – original draft. MC: Writing – original draft. GCa: Writing – original draft. PB: Writing – review & editing. FDG: Writing – review & editing. PM: Writing – review & editing. AT: Supervision, Writing – review & editing.

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References

1. Malhi GS, Mann JJ. Depression. *Lancet*. (2018) 392:2299–312. doi: 10.1016/S0140-6736(18)31948-2

2. Luppa M, Sikorski C, Luck T, Ehreke L, Konnopka A, Wiese B, et al. Age- and gender-specific prevalence of depression in latest-life–systematic review and meta-analysis. *J Affect Disord*. (2012) 136:212–21. doi: 10.1016/j.jad.2010.11.033

3. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychol Bull*. (2017) 143:783–822. doi: 10.1037/bul0000102

4. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry*. (2015) 56:345–65. doi: 10.1111/jcpp.12381

5. Sacco R, Camilleri N, Eberhardt J, Umla-Runge K, Newbury-Birch D. A systematic review and meta-analysis on the prevalence of mental disorders among children and adolescents in Europe. *Eur Child Adolesc Psychiatry*. (2022) 1:1–18. doi: 10.1007/S00787-022-02131-2/METRICS

6. Williams SB, O'Connor EA, Eder M, Whitlock EP. Screening for child and adolescent depression in primary care settings: a systematic evidence review for the US Preventive Services Task Force. *Pediatrics*. (2009) 123:e716-35. doi: 10.1542/peds.2008-2415

7. Avenevoli S, Swendsen J, He JP, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. *J Am Acad Child Adolesc Psychiatry*. (2015) 54:37–44.e2. doi: 10.1016/j.jaac.2014.10.010

8. Walter HJ, Abright AR, Bukstein OG, Diamond J, Keable H, Ripperger-Suhler J, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. *J Am Acad Child Adolesc Psychiatry*. (2023) 62:479–502. doi: 10.1016/j.jaac.2022.10.001

9. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: A meta-analysis. *JAMA Pediatr*. (2021) 175:1142–50. doi: 10.1001/jamapediatrics.2021.2482

10. Khalfan AF, Campisi SC, Lo RF, McCrindle BW, Korczak DJ. The association between adolescent depression and dyslipidemia. *J Affect Disord*. (2023) 338:239–45. doi: 10.1016/j.jad.2023.06.017

11. Keyes KM, Platt JM. Annual Research Review: Sex, gender, and internalizing conditions among adolescents in the 21st century - trends, causes, consequences. *J Child Psychol Psychiatry*. (2024) 65:384–407. doi: 10.1111/jcpp.13864

12. Rice F, Riglin L, Lomax T, Souter E, Potter R, Smith DJ, et al. Adolescent and adult differences in major depression symptom profiles. *J Affect Disord*. (2019) 243:175–81. doi: 10.1016/j.jad.2018.09.015

13. Weavers B, Heron J, Thapar AK, Stephens A, Lennon J, Bevan Jones R, et al. The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-based English study. *Lancet Psychiatry*. (2021) 8:1053–61. doi: 10.1016/S2215-0366(21)00281-9

14. Fergusson DM, Woodward LJ. Mental health, educational, and social role outcomes of adolescents with depression. *Arch Gen Psychiatry*. (2002) 59:225–31. doi: 10.1001/archpsyc.59.3.225

15. Centers for disease control and prevention. *Deaths, Percent of Total Deaths, and Death Rates for the 15 Leading Causes of Death in 5-Year Age Groups, by Race and Sex: United States, 1999–2015*. Hyattsville (U.S (2017).

16. Farabaugh A, Bitran S, Nyer M, Holt DJ, Pedrelli P, Shyu I, et al. Depression and suicidal ideation in college students. *Psychopathology*. (2012) 45:228–34. doi: 10.1159/000331598

17. Dunn V, Goodyer IM. Longitudinal investigation into childhood- and adolescence-onset depression: psychiatric outcome in early adulthood. *Br J Psychiatry*. (2006) 188:216–22. doi: 10.1192/bjp.188.3.216

18. Rybak YE, Lai KSP, Ramasubbu R, Vila-Rodriguez F, Blumberger DM, Chan P, et al. Treatment-resistant major depressive disorder: Canadian expert consensus on definition and assessment. *Depress Anxiety*. (2021) 38:456–67. doi: 10.1002/da.23135

19. McLachlan G. Treatment resistant depression: what are the options? *BMJ*. (2018) 363:k5354. doi: 10.1136/bmj.k5354

20. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. *J Clin Psychiatry*. (2021) 82:20m13699. doi: 10.4088/JCP.20m13699

21. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412. doi: 10.1002/wps.21120

22. Bartova L, Dold M, Kautzky A, Fabbri C, Spies M, Serretti A, et al. Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice. *World J Biol Psychiatry*. (2019) 20:427–48. doi: 10.1080/15622975.2019.1635270

23. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, et al. Defining treatment-resistant depression. *Depress Anxiety*. (2020) 37:134–45. doi: 10.1002/da.22968

24. Ng CH, Kato T, Han C, Wang G, Trivedi M, Ramesh V, et al. Definition of treatment-resistant depression - Asia Pacific perspectives. *J Affect Disord*. (2019) 245:626–36. doi: 10.1016/j.jad.2018.11.038

25. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. (2006) 163:28–40. doi: 10.1176/appi.ajp.163.1.28

26. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

27. Vitiello B, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller MB, et al. Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. *J Clin Psychiatry*. (2011) 72:388–96. doi: 10.4088/JCP.09m05885blu

28. Berlim MT, Fleck MP, Turecki G. Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. *Ann Med*. (2008) 40:149–59. doi: 10.1080/07853890701769728

29. McAllister-Williams RH, Christmas DMB, Cleare AJ, Currie A, Gledhill J, Insole L, et al. Multiple-therapy-resistant major depressive disorder: a clinically important concept. *Br J Psychiatry*. (2018) 212:274–8. doi: 10.1192/bjp.2017.33

30. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Res*. (2016) 240:421–30. doi: 10.1016/j.psychres.2016.04.034

31. Kautzky A, Dold M, Bartova L, Spies M, Kranz GS, Souery D, et al. Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. *Acta Psychiatr Scand*. (2019) 139:78–88. doi: 10.1111/acps.12959

32. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. (2005) 62:629–40. doi: 10.1001/archpsyc.62.6.629

33. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*. (2008) 299:901–13. doi: 10.1001/jama.299.8.901

34. Strawn JR, Aaronson ST, Elmaadawi AZ, Schrodt GR, Holbert RC, Verdoliva S, et al. Treatment-resistant depression in adolescents: clinical features and measurement of treatment resistance. *J Child Adolesc Psychopharmacol*. (2020) 30:261–6. doi: 10.1089/cap.2020.0008

35. Ayvaci ER, Croarkin PE. Special populations: treatment-resistant depression in children and adolescents. *Psychiatr Clin North Am*. (2023) 46:359–70. doi: 10.1016/j.psc.2023.02.007

36. Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. *J Child Psychol Psychiatry*. (2020) 61:312–32. doi: 10.1111/jcpp.13202

37. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson R, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. (2007) 46:1503–26. doi: 10.1097/chi.0b013e318145ae1c

38. Hughes CW, Emslie GJ, Crismon ML, Posner K, Birmaher B, Ryan N, et al. Texas children's medication algorithm project: update from Texas consensus conference panel on medication treatment of childhood major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. (2007) 46:667–86. doi: 10.1097/chi.0b013e31804a859b

39. Korczak DJ, WestwellRoper C, Sassi R. Diagnosis and management of depression in adolescents. *CMAJ : Can Med Assoc J*. (2023) 195:E739. doi: 10.1503/cmaj.220966

40. National Institute for Health Care and Excellence. Depression in children and young people: Identification and management. *NICE guidelines*. (2019).

41. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. (2004) 292:807–20. doi: 10.1001/jama.292.7.807

42. Kennard BD, Silva SG, Tonev S, Rohde P, Hughes JL, Vitiello B, et al. Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): acute and long-term outcomes. *J Am Acad Child Adolesc Psychiatry*. (2009) 48:186–95. doi: 10.1097/CHI.0b013e31819176f9

43. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. *Cochrane Database Syst Rev*. (2016) 9:CD006727. doi: 10.1002/14651858.CD006727.PUB3

44. Cuijpers P, Smit F. Excess mortality in depression: A meta-analysis of community studies. *J Affect Disord*. (2002) 72:227–36. doi: 10.1016/S0165-0327(01)00413-X

45. van der Weele GM, Gussekloo J, de Waal MWM, de Craen AJM, van der Mast RC. Co-occurrence of depression and anxiety in elderly subjects aged 90 years and its relationship with functional status, quality of life and mortality. *Int J Geriatr Psychiatry*. (2009) 24:595–601. doi: 10.1002/gps.2162

46. Feng L, Yap KB, Ng TP. Depressive symptoms in older adults with chronic kidney disease: mortality, quality of life outcomes, and correlates. *Am J Geriatr Psychiatry*. (2013) 21:570–9. doi: 10.1016/j.jagp.2012.12.020

47. Bjørkløf GH, Engedal K, Selbæk G, Kouwenhoven SE, Helvik AS. Coping and depression in old age: a literature review. *Dement Geriatr Cognit Disord*. (2013) 35:121–54. doi: 10.1159/000346633

48. Walker J, Holm Hansen C, Martin P, Sawhney A, Thekkumpurath P, Beale C, et al. Prevalence of depression in adults with cancer: a systematic review. *Ann Oncol*. (2013) 24:895–900. doi: 10.1093/annonc/mds575

49. Ho CS, Feng L, Fam J, Mahendran R, Kua EH, Ng TP. Coexisting medical comorbidity and depression: multiplicative effects on health outcomes in older adults. *Int Psychogeriatr*. (2014) 26:1221–9. doi: 10.1017/S1041610214000611

50. Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. *BMC Psychiatry*. (2019) 19:247. doi: 10.1186/s12888-019-2222-4

51. Olfson M, Amos TB, Benson C, McRae J, Marcus SC. Prospective service use and health care costs of medicaid beneficiaries with treatment-resistant depression. *J Manag Care Spec Pharm*. (2018) 24:226–36. doi: 10.18553/jmcp.2018.24.3.226

52. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv*. (2014) 65:977–87. doi: 10.1176/appi.ps.201300059

53. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry*. (2007) 68:1062–70. doi: 10.4088/JCP.v68n0713

54. Halaris A, Sohl E, Whitham EA. Treatment-resistant depression revisited: A glimmer of hope. *J Pers Med*. (2021) 11:1–28. doi: 10.3390/jpm11020155

55. Caraci F, Calabrese F, Molteni R, Bartova L, Dold M, Leggio GM, et al. International union of basic and clinical pharmacology CIV: the neurobiology of treatment-resistant depression: from antidepressant classifications to novel pharmacological targets. *Pharmacol Rev*. (2018) 70:475–504. doi: 10.1124/pr.117.014977

56. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep*. (2007) 9:449–59. doi: 10.1007/s11920-007-0061-3

57. Spielmans GI, Gerwig K. The efficacy of antidepressants on overall well-being and self-reported depression symptom severity in youth: a meta-analysis. *Psychother Psychosom*. (2014) 83:158–64. doi: 10.1159/000356191

58. Blom EH, Forsman M, Yang TT, Serlachius E, Larsson J-O. Latent classes of symptoms related to clinically depressed mood in adolescents. *Scand J Child Adolesc Psychiatr Psychol*. (2014) 2:19–28. doi: 10.21307/sjcapp-2014-004

59. Nardi B, Francesconi G, Dell'Osso MC, Bellantuono C. Adolescent depression: clinical features and therapeutic strategies. *Eur Rev Med Pharmacol Sci*. (2013) 17:1546–51.

60. Warren BJ. The synergistic influence of life experiences and cultural nuances on development of depression: A cognitive behavioral perspective. *Issues Ment Health Nurs*. (2020) 41:3–6. doi: 10.1080/01612840.2019.1675828

61. Hong JS, Peguero AA, Espelage DL. Experiences in bullying and/or peer victimization of vulnerable, marginalized, and oppressed children and adolescents: An introduction to the special issue. *Am J Orthopsy*. (2018) 88:399–401. doi: 10.1037/ort0000330

62. Lachal J, Moro MR, Carretier E, Simon A, Barry C, Falissard B, et al. Assessment of transcultural psychotherapy to treat resistant major depressive disorder in children and adolescents from migrant families: Protocol for a randomized controlled trial using mixed method and Bayesian approaches. *Int J Methods Psychiatr Res*. (2020) 29:1–10. doi: 10.1002/mpr.1847

63. Stewart SM, Simmons A, Habibpour E. Treatment of culturally diverse children and adolescents with depression. *J Child Adolesc Psychopharmacol*. (2012) 22:72–9. doi: 10.1089/cap.2011.0051

64. de Haan AM, Boon AE, de Jong JTVM, Vermeiren RRJM. A review of mental health treatment dropout by ethnic minority youth. *Transcult Psychiatry*. (2018) 55:3–30. doi: 10.1177/1363461517731702

65. Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: Results of a long-term prospective study of hospital admissions. *J Affect Disord*. (2005) 84:149–57. doi: 10.1016/S0165-0327(03)00195-2

66. Barbuti M, Menculini G, Verdolini N, Pacchiarotti I, Kotzalidis GD, Tortorella A, et al. A systematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalistic settings: The role of antidepressant and antipsychotic drugs. *Eur Neuropsychopharmacol*. (2023) 73:1–15. doi: 10.1016/j.euroneuro.2023.04.013

67. Perugi G, Pacchiarotti I, Mainardi C, Verdolini N, Menculini G, Barbuti M, et al. Patterns of response to antidepressants in major depressive disorder: Drug resistance or worsening of depression are associated with a bipolar diathesis. *Eur Neuropsychopharmacol*. (2019) 29:825–34. doi: 10.1016/j.euroneuro.2019.06.001

68. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry*. (2013) 170:1249–62. doi: 10.1176/appi.ajp.2013.13020185

69. Bechdolf A, Ratheesh A, Cotton SM, Nelson B, Chanen AM, Betts J, et al. The predictive validity of bipolar at-risk (prodromal) criteria in help-seeking adolescents and young adults: a prospective study. *Bipolar Disord*. (2014) 16:493–504. doi: 10.1111/bdi.12205

70. Tondo L, Visioli C, Preti A, Baldessarini RJ. Bipolar disorders following initial depression: modeling predictive clinical factors. *J Affect Disord*. (2014) 167:44–9. doi: 10.1016/j.jad.2014.05.043

71. Vöhringer PA, Perlis RH. Discriminating between bipolar disorder and major depressive disorder. *Psychiatr Clinics North America*. (2016) 39:1–10. doi: 10.1016/j.psc.2015.10.001

72. Barbuti M, Mainardi C, Pacchiarotti I, Verdolini N, Maccariello G, Angst J, et al. The role of different patterns of psychomotor symptoms in major depressive episode:

Pooled analysis of the BRIDGE and BRIDGE-II-MIX cohorts. *Bipolar Disord*. (2019) 21 (8):785–793. doi: 10.1111/bdi.12816

73. Yee CS, Hawken ER, Baldessarini RJ, Vázquez GH. Maintenance pharmacological treatment of juvenile bipolar disorder: review and meta-analyses. *Int J Neuropsychopharmacol*. (2019) 22:531–40. doi: 10.1093/ijnp/pyz034

74. Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, et al. Genetic variants associated with response to lithium treatment in bipolar disorder: A genome-wide association study. *Lancet*. (2016) 387:1085–93. doi: 10.1016/S0140-6736(16)00143-4

75. Brent D, Melhem N, Ferrell R, Emslie G, Wagner KD, Ryan N, et al. Association of FKBP5 polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. *Am J Psychiatry*. (2010) 167:190–7. doi: 10.1176/appi.ajp.2009.09040576

76. Kronenberg S, Apter A, Brent D, Schirman S, Melhem N, Pick N, et al. Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/or anxiety disorders. *J Child Adolesc Psychopharmacol*. (2007) 17:741–50. doi: 10.1089/cap.2006.0144

77. Axelson DA, Perel JM, Birmaher B, Rudolph GR, Nuss S, Bridge J, et al. Sertraline pharmacokinetics and dynamics in adolescents. *J Am Acad Child Adolesc Psychiatry*. (2002) 41:1037–44. doi: 10.1097/00004583-200209000-00003

78. Pan L, McKain BW, Madan-Khetarpal S, Mcguire M, Diler RS, Perel JM, et al. GTP-cyclohydrolase deficiency responsive to sapropterin and 5-HTP supplementation: relief of treatment-refractory depression and suicidal behavior. *BMJ Case Rep*. (2011) 2011:bcr0320113927. doi: 10.1136/bcr.03.2011.3927

79. Pan LA, Martin P, Zimmer T, Segreti AM, Kassiff S, McKain BW, et al. Neurometabolic disorders: potentially treatable abnormalities in patients with treatment-refractory depression and suicidal behavior. *Am J Psychiatry*. (2017) 174:42–50. doi: 10.1176/appi.ajp.2016.15111500

80. Emslie GJ, Mayes T, Porta G, Vitiello B, Clarke G, Wagner KD, et al. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. *Am J Psychiatry*. (2010) 167:782–91. doi: 10.1176/appi.ajp.2010.09040552

81. Chen MH, Pan TL, Hsu JW, Huang KL, Su TP, Li CT, et al. Attention-deficit hyperactivity disorder comorbidity and antidepressant resistance among patients with major depression: A nationwide longitudinal study. *Eur Neuropsychopharmacol*. (2016) 26:1760–7. doi: 10.1016/j.euroneuro.2016.09.369

82. White MJ. Treatment-resistant depression: consider autism. *Br J Gen Pract*. (2019) 69:14. doi: 10.3399/bjgp19X700373

83. Joshi G, Petty C, Wozniak J, Henin A, Fried R, Galdo M, et al. The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: a large comparative study of a psychiatrically referred population. *J Autism Dev Disord*. (2010) 40:1361–70. doi: 10.1007/s10803-010-0996-9

84. Maalouf FT, Atwi M, Brent DA. Treatment-resistant depression in adolescents: review and updates on clinical management. *Depress Anxiety*. (2011) 28:946–54. doi: 10.1002/da.v28.11

85. Defilippis M. Depression in children and adolescents with autism spectrum disorder. *Children (Basel)*. (2018) 5:112. doi: 10.3390/children5090112

86. Walkup J, Labellarte M. Complications of SSRI treatment. *J Child Adolesc Psychopharmacol*. (2001) 11:1–4. doi: 10.1089/104454601750143320

87. McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. *J Am Acad Child Adolesc Psychiatry*. (2012) 51:404–11. doi: 10.1016/j.jaac.2012.01.011

88. Maalouf FT, Porta G, Vitiello B, Emslie G, Mayes T, Clarke G, et al. Do sub-syndromal manic symptoms influence outcome in treatment resistant depression in adolescents? A latent class analysis from the TORDIA study. *J Affect Disord*. (2012) 138:86–95. doi: 10.1016/j.jad.2011.12.021

89. Strawn JR, Dobson ET, Giles LL. Primary pediatric care psychopharmacology: focus on medications for ADHD, depression, and anxiety. *Curr Probl Pediatr Adolesc Health Care*. (2017) 47:3–14. doi: 10.1016/j.cppeds.2016.11.008

90. Dwyer JB, Bloch MH. Antidepressants for pediatric patients. *Curr Psychiatr*. (2019) 18:26–42.

91. Harmanci D, Edelman N, Richardson D, Lunt A, Llewellyn C. How are young people's mental health related to their sexual health and substance use? A systematic review of UK literature. *Int J Adolesc Med Health*. (2023) 35:131–58. doi: 10.1515/ijamh-2022-0090

92. Carton L, Pignon B, Baguet A, Benradia I, Roelandt JL, Vaiva G, et al. Influence of comorbid alcohol use disorders on the clinical patterns of major depressive disorder: A general population-based study. *Drug Alcohol Depend*. (2018) 187:40–7. doi: 10.1016/j.drugalcdep.2018.02.009

93. Shamseddeen W, Clarke G, Keller MB, Wagner KD, Birmaher B, Emslie GJ, et al. Adjunctive sleep medications and depression outcome in the treatment of serotonin-selective reuptake inhibitor resistant depression in adolescents study. *J Child Adolesc Psychopharmacol*. (2012) 22:29–36. doi: 10.1089/cap.2011.0027

94. Joffe RT. Refractory depression: Treatment strategies, with particular reference to the thyroid axis. *J Psychiatry Neurosci*. (1997) 22:327–31.

95. Shamseddeen W, Asarnow JR, Clarke G, Vitiello B, Wagner KD, Birmaher B, et al. Impact of physical and sexual abuse on treatment response in the Treatment of Resistant Depression in Adolescent Study (TORDIA). *J Am Acad Child Adolesc Psychiatry*. (2011) 50:293–301. doi: 10.1016/j.jaac.2010.11.019

96. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am J Psychiatry*. (2012) 169:141–51. doi: 10.1176/appi.ajp.2011.11020335

97. Rengasamy M, Mansoor BM, Hilton R, Porta G, He J, Emslie GJ, et al. The bi-directional relationship between parent-child conflict and treatment outcome in treatment-resistant adolescent depression. *J Am Acad Child Adolesc Psychiatry*. (2013) 52:370–7. doi: 10.1016/j.jaac.2013.01.012

98. Swartz HA, Cyranowski JM, Cheng Y, Zuckoff A, Brent DA, Markowitz JC, et al. Brief psychotherapy for maternal depression: impact on mothers and children. *J Am Acad Child Adolesc Psychiatry*. (2016) 55:495–503.e2. doi: 10.1016/j.jaac.2016.04.003

99. Russell ST, Fish JN. Mental health in lesbian, gay, bisexual, and transgender (LGBT) youth. *Annu Rev Clin Psychol*. (2016) 12:465–87. doi: 10.1146/annurev-clinpsy-021815-093153

100. Hazell P, O'connell D, Heathcote D, Robertson J, Henry D. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *BMJ*. (1995) 310:897. doi: 10.1136/bmj.310.6984.897

101. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet*. (2012) 379:1056–67. doi: 10.1016/S0140-6736(11)60871-4

102. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev*. (2013) 2013:CD002317. doi: 10.1002/14651858.CD002317.PUB2

103. Cipriani A, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*. (2016) 388:881–90. doi: 10.1016/S0140-6736(16)30385-3

104. Garland EJ, Kutcher S, Virani A, Elbe D. Update on the use of SSRIS and SNRIS with children and adolescents in clinical practice. *J Can Acad Child Adolesc Psychiatry*. (2015) 25:4–10.

105. Locher C, Koechlin H, Zion SR, Werner C, Pine DS, Kirsch I, et al. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: A systematic review and meta-analysis. *JAMA Psychiatry*. (2017) 74:1011–20. doi: 10.1001/jamapsychiatry.2017.2432

106. Janiaud P, Cornu C, Lajoinie A, Djemli A, Cucherat M, Kassai B. Is the perceived placebo effect comparable between adults and children? A meta-regression analysis. *Pediatr Res*. (2017) 81:11–7. doi: 10.1038/pr.2016.181

107. DeFilippis M, Wagner KD. Management of treatment-resistant depression in children and adolescents. *Paediatr Drugs*. (2014) 16:353–61. doi: 10.1007/s40272-014-0088-y

108. Ledesma-Corvi S, Jornet-Plaza J, Gálvez-Melero L, García-Fuster MJ. Novel rapid treatment options for adolescent depression. *Pharmacol Res*. (2024) 201:107085. doi: 10.1016/j.phrs.2024.107085

109. Voineskos AN, Mulsant BH, Dickie EW, Neufeld NH, Rothschild AJ, Whyte EM, et al. Effects of antipsychotic medication on brain structure in patients with major depressive disorder and psychotic features: neuroimaging findings in the context of a randomized placebo-controlled clinical trial. *JAMA Psychiatry*. (2020) 77:674–83. doi: 10.1001/jamapsychiatry.2020.0036

110. Hayden JD, Horter L, Parsons T, Ruble M, Townsend S, Klein CC, et al. Metabolic monitoring rates of youth treated with second-generation antipsychotics in usual care: results of a large US national commercial health plan. *J Child Adolesc Psychopharmacol*. (2020) 30:119–22. doi: 10.1089/cap.2019.0087

111. Smith KA, Cipriani A. Lithium and suicide in mood disorders: Updated meta-review of the scientific literature. *Bipolar Disord*. (2017) 19:575–86. doi: 10.1111/bdi.12543

112. Stafford MR, Mayo-Wilson E, Loucas CE, James A, Hollis C, Birchwood M, et al. Efficacy and safety of pharmacological and psychological interventions for the treatment of psychosis and schizophrenia in children, adolescents and young adults: a systematic review and meta-analysis. *PloS One*. (2015) 10:e0117166. doi: 10.1371/journal.pone.0117166

113. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry*. (2007) 64:1132–44. doi: 10.1001/archpsyc.64.10.1132

114. Emslie GJ, Kennard BD, Mayes TL, Nakonezny PA, Moore J, Jones JM, et al. Continued effectiveness of relapse prevention cognitive-behavioral therapy following fluoxetine treatment in youth with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. (2015) 54:991–8. doi: 10.1016/j.jaac.2015.09.014

115. Suresh V, Mills JA, Croarkin PE, Strawn JR. What next? A Bayesian hierarchical modeling re-examination of treatments for adolescents with selective serotonin reuptake inhibitor-resistant depression. *Depress Anxiety*. (2020) 37:926–34. doi: 10.1002/da.23064

116. Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. (2006) 45:1427–39. doi: 10.1097/01.chi.0000240838.78984.e2

117. Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, et al. A randomised controlled trial of cognitive behavior therapy in adolescents with major

depression treated by selective serotonin reuptake inhibitors. *ADAPT trial. Health Technol Assess.* (2008) 12:iii–iv, ix–60. doi: 10.3310/hta12140

118. Glass RM. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *J Pediatr*. (2005) 146:145. doi: 10.1016/j.jpeds.2004.10.032

119. Weersing VR, Jeffreys M, Do MCT, Schwartz KTG, Bolano C. Evidence base update of psychosocial treatments for child and adolescent depression. *J Clin Child Adolesc Psychol.* (2017) 46:11–43. doi: 10.1080/15374416.2016.1220310

120. Mufson L, Sills R. Interpersonal Psychotherapy for depressed adolescents (IPT-A): an overview. *Nord J Psychiatry*. (2006) 60:431–7. doi: 10.1080/08039480601022397

121. Goodyer IM, Reynolds S, Barrett B, Byford S, Dubicka B, Hill J, et al. Cognitive behavioral therapy and short-term psychoanalytical psychotherapy versus a brief psychosocial intervention in adolescents with unipolar major depressive disorder (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled superiority trial. *Lancet Psychiatry*. (2017) 4:109–19. doi: 10.1016/S2215-0366(16)30378-9

122. Croarkin PE, Zuckerman S, Middleton VJ, Monira N, Kriske J, Bowman J, et al. Clinical outcomes in adolescents undergoing sequential bilateral 1 Hz/20 Hz transcranial magnetic stimulation for treatment resistant depression. *Brain Stimul.* (2024) 17:431–3. doi: 10.1016/j.brs.2024.03.018

123. Thai M, Nair AU, Klimes-Dougan B, Albott S, Silamongkol T, Corkrum M, et al. Deep transcranial magnetic stimulation for adolescents with treatment-resistant depression: A preliminary dose-finding study exploring safety and clinical effectiveness. *J Affect Disord*. (2024) 354:589–600. doi: 10.1016/j.jad.2024.03.061

124. Karayağmurlu A, Coşkun M, Elboğa G, Ghaziuddin N, Karayağmurlu E, Gökçen C, et al. Efficacy and safety of electroconvulsive therapy in adolescents: A retrospective chart review study from Turkey. *J ECT*. (2020) 36:54–9. doi: 10.1097/YCT.0000000000000602

125. Freeman B. Pathway to electroconvulsive treatment for minors. *Child Adolesc Psychiatr Clin N Am.* (2019) 28:1–19. doi: 10.1016/j.chc.2018.07.001

126. Weiner RD, Reti IM. Key updates in the clinical application of electroconvulsive therapy. *Int Rev Psychiatry*. (2017) 29:54–62. doi: 10.1080/09540261.2017.1309362

127. Consoli A, Benmiloud M, Wachtel L, Dhossche D, Cohen D, Bonnot O. Electroconvulsive therapy in adolescents with the catatonia syndrome: efficacy and ethics. *J ECT*. (2010) 26:259–65. doi: 10.1097/YCT.0b013e3181fb3924

128. Castaneda-Ramirez S, Becker TD, Bruges-Boude A, Kellner C, Rice TR. Systematic review: Electroconvulsive therapy for treatment-resistant mood disorders in children and adolescents. *Eur Child Adolesc Psychiatry*. (2023) 32:1529–60. doi: 10.1007/s00787-022-01942-7

129. Papp M, Cubala WJ, Swiecicki L, Newman-Tancredi A, Willner P. Perspectives for therapy of treatment-resistant depression. *Br J Pharmacol.* (2022) 179:4181–200. doi: 10.1111/bph.15596

130. Kim YK, Na KS. Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. (2016) 70:117–26. doi: 10.1016/j.pnpbp.2016.03.009

131. DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. (2010) 71:1605–11. doi: 10.4088/JCP.09m05327blu

132. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Sci (1979).* (2012) 338:68–72. doi: 10.1126/science.1222939

133. Zarate CA, Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, et al. A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. *Biol Psychiatry*. (2013) 74:257–64. doi: 10.1016/j.biopsych.2012.10.019

134. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Hum Psychopharmacol.* (2015) 30:152–63. doi: 10.1002/hup.2475

135. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med*. (2015) 45:693–704. doi: 10.1017/S0033291714001603

136. Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. (2015) 172:950–66. doi: 10.1176/appi.ajp.2015.15040465

137. Bobo WV, Voort JLV, Croarkin PE, Leung JG, Tye SJ, Frye MA. KETAMINE FOR TREATMENT-RESISTANT UNIPOLAR AND BIPOLAR MAJOR DEPRESSION: CRITICAL REVIEW AND IMPLICATIONS FOR CLINICAL PRACTICE. *Depress Anxiety*. (2016) 33:698–710. doi: 10.1002/da.22505

138. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry*. (2016) 173:816–26. doi: 10.1176/appi.ajp.2016.16010037

139. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron*. (2019) 102:75–90. doi: 10.1016/j.neuron.2019.03.013

140. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*. (2016) 533:481–6. doi: 10.1038/nature17998

141. Ricci V, Martinotti G, Gelfo F, Tonioni F, Caltagirone C, Bria P, et al. Chronic ketamine use increases serum levels of brain-derived neurotrophic factor. *Psychopharmacol (Berl)*. (2011) 215:143–8. doi: 10.1007/s00213-010-2121-3

142. Ardalan M, Elfving B, Rafati AH, Mansouri M, Zarate CA, Mathe AA, et al. Rapid effects of S-ketamine on the morphology of hippocampal astrocytes and BDNF serum levels in a sex-dependent manner. *Eur Neuropsychopharmacol.* (2020) 32:94–103. doi: 10.1016/j.euroneuro.2020.01.001

143. Rossi GN, Hallak JEC, Baker G, Dursun SM, dos Santos RG. The effects of ketamine and classic hallucinogens on neurotrophic and inflammatory markers in unipolar treatment-resistant depression: a systematic review of clinical trials. *Eur Arch Psychiatry Clin Neurosci*. (2023) 273:129–55. doi: 10.1007/s00406-022-01460-2

144. Bennabi D, Charpeaud T, Yrondi A, Genty JB, Destouches S, Lancrenon S, et al. Clinical guidelines for the management of treatment-resistant depression: French recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation FondaMental. *BMC Psychiatry*. (2019) 19:262. doi: 10.1186/s12888-019-2237-x

145. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. *Neuropsychiatr Dis Treat*. (2020) 16:221–34. doi: 10.2147/NDT.S198774

146. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392

147. Diamond PR, Farmery AD, Atkinson S, Haldar J, Williams N, Cowen PJ, et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. *J Psychopharmacol*. (2014) 28:536–44. doi: 10.1177/0269881114527361

148. Cusin C, Ionescu DF, Pavone KJ, Akeju O, Cassano P, Taylor N, et al. Ketamine augmentation for outpatients with treatment-resistant depression: Preliminary evidence for two-step intravenous dose escalation. *Aust N Z J Psychiatry*. (2017) 51:55–64. doi: 10.1177/0004867416631828

149. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856

150. Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry*. (2009) 66:522–6. doi: 10.1016/j.biopsych.2009.04.029

151. Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *J Psychiatr Res.* (2014) 58:161–6. doi: 10.1016/j.jpsychires.2014.07.027

152. Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, et al. Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs*. (2012) 26:189–204. doi: 10.2165/11599770-000000000-00000

153. Reinstatler L, Youssef NA. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. *Drugs R D*. (2015) 15:37–43. doi: 10.1007/s40268-015-0081-0

154. Wilkinson ST, Sanacora G. KETAMINE: A POTENTIAL RAPID-ACTING ANTISUICIDAL AGENT? *Depress Anxiety*. (2016) 33:711–7. doi: 10.1002/da.22498

155. Ionescu DF, Luckenbaugh DA, Niciu MJ, Richards EM, Slonena EE, Vande Voort JL, et al. Effect of baseline anxious depression on initial and sustained antidepressant response to ketamine. *J Clin Psychiatry*. (2014) 75:e932–8. doi: 10.4088/JCP.14m09049

156. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Focus (Am Psychiatr Publ)*. (2019) 17:55–65. doi: 10.1176/appi.focus.17105

157. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. *Am J Psychiatry*. (2018) 175:327–35. doi: 10.1176/appi.ajp.2017.17060647

158. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. (2006) 63:332–9. doi: 10.1001/archpsyc.63.3.332

159. Li K, Zhou G, Xiao Y, Gu J, Chen Q, Xie S, et al. Risk of suicidal behaviors and antidepressant exposure among children and adolescents: A meta-analysis of observational studies. *Front Psychiatry*. (2022) 13:880496/FULL. doi: 10.3389/FPSYT.2022.880496/FULL

160. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry*. (2014) 4:e469. doi: 10.1038/tp.2014.105

161. Dwyer JB, Landeros-Weisenberger A, Johnson JA, Tobon AL, Flores JM, Nasir M, et al. Efficacy of intravenous ketamine in adolescent treatment-resistant depression:

A randomized midazolam-controlled trial. *Am J Psychiatry*. (2021) 178:352–62. doi: 10.1176/appi.ajp.2020.20010018

162. Shin C, Kim YK. Ketamine in major depressive disorder: mechanisms and future perspectives. *Psychiatry Investig*. (2020) 17:181–92. doi: 10.30773/pi.2019.0236

163. Cullen KR, Amatya P, Roback MG, Albott CS, Westlund Schreiner M, Ren Y, et al. Intravenous ketamine for adolescents with treatment-resistant depression: an open-label study. *J Child Adolesc Psychopharmacol*. (2018) 28:437–44. doi: 10.1089/cap.2018.0030

164. Liu W, Zhou Y, Zheng W, Wang C, Zhan Y, Lan X, et al. Repeated intravenous infusions of ketamine: Neurocognition in patients with anxious and nonanxious treatment-resistant depression. *J Affect Disord*. (2019) 259:1–6. doi: 10.1016/j.jad.2019.08.012

165. Di Vincenzo JD, Siegel A, Lipsitz O, Ho R, Teopiz KM, Ng J, et al. The effectiveness, safety and tolerability of ketamine for depression in adolescents and older adults: A systematic review. *J Psychiatr Res*. (2021) 137:232–41. doi: 10.1016/j.jpsychires.2021.02.058

166. Thai M, Başgöze Z, Klimes-Dougan B, Mueller BA, Fiecas M, Lim KO, et al. Neural and behavioral correlates of clinical improvement to ketamine in adolescents with treatment resistant depression. *Front Psychiatry*. (2020) 11:820. doi: 10.3389/fpsyt.2020.00820

167. Marshall R, Valle K, Sheridan D, Kothari J. Ketamine for treatment-resistant depression and suicidality in adolescents: an observational study of 3 cases. *J Clin Psychopharmacol*. (2023) 43:460–2. doi: 10.1097/JCP.0000000000001730

168. Emslie GJ. Editorial: novel approaches to the treatment of suicidality and depression in youth. *J Am Acad Child Adolesc Psychiatry*. (2023) 63(5):500–1. doi: 10.1016/j.jaac.2023.06.019

169. Lineham A, Avila-Quintero VJ, Bloch MH, Dwyer J. Exploring predictors of ketamine response in adolescent treatment-resistant depression. *J Child Adolesc Psychopharmacol*. (2024) 34:63–9. doi: 10.1089/cap.2023.0047

170. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

171. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *Am J Psychiatry*. (2019) 176:428–38. doi: 10.1176/appi.ajp.2019.19020172

172. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*. (2018) 75:139–48. doi: 10.1001/jamapsychiatry.2017.3739

173. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry*. (2020) 81:19m12891. doi: 10.4088/JCP.19m12891

174. Mahase E. Esketamine is approved in Europe for treating resistant major depressive disorder. *BMJ*. (2019) 367:l7069. doi: 10.1136/bmj.l7069

175. Zhou Y, Lan X, Wang C, Zhang F, Liu H, Fu L, et al. Effect of repeated intravenous esketamine on adolescents with major depressive disorder and suicidal ideation: A randomized active-placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. (2023) 63(5):507–18. doi: 10.1016/j.jaac.2023.05.031

176. Lan X, Wang C, Zhang F, Liu H, Li W, Ye Y, et al. Short-term cognitive effects of repeated-dose esketamine in adolescents with major depressive disorder and suicidal ideation: a randomized controlled trial. *Child Adolesc Psychiatry Ment Health*. (2023) 17:108. doi: 10.1186/s13034-023-00647-2

177. DelBello MP, Kosik-Gonzalez C, Fu D-J, Chen L, Lane R, Drevets WC, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of depressive symptoms in adolescents with MDD at imminent risk for suicide: results of a double-blind, randomized, psychoactive-controlled study. *J Am Acad Child Adolesc Psychiatry*. (2023) 62:S319–20. doi: 10.1016/j.jaac.2023.09.513

178. Skala K, Doganay K, Eder H, Mairhofer D, Neubacher K, Plener PL. Intranasal esketamine as therapeutic option: a case report of an adolescent with treatment resistant depression. *Front Psychiatry*. (2023) 14:1118737. doi: 10.3389/fpsyt.2023.1118737

179. Hope J, Copolov D, Tiller J, Galbally M, Hopwood M, Newton R, et al. What clinicians need to know about intranasal esketamine for treatment-resistant depression? *Australas Psychiatry*. (2023) 31:841–5. doi: 10.1177/10398562231211171

180. Bates MLS, Trujillo KA. Long-lasting effects of repeated ketamine administration in adult and adolescent rats. *Behav Brain Res*. (2019) 369:111928. doi: 10.1016/j.bbr.2019.111928

181. Jornet-Plaza J, García-Fuster MJ. SEX DIFFERENCES IN THE ANTIDEPRESSANT-LIKE RESPONSE OF KETAMINE IN ADOLESCENT RATS: EVALUATING LONG-TERM SAFETY THROUGH COGNITION. *IBRO Neurosci Rep*. (2023) 15:S586. doi: 10.1016/j.ibneur.2023.08.1161

182. Onaolapo AY, Ayeni OJ, Ogundeji MO, Ajao A, Owolabi AR, Onaolapo OJ. Subchronic ketamine alters behavior, metabolic indices and brain morphology in adolescent rats: Involvement of oxidative stress, glutamate toxicity and caspase-3-mediated apoptosis. *J Chem Neuroanat*. (2019) 96:22–33. doi: 10.1016/j.jchemneu.2018.12.002

183. Kim S, Rush BS, Rice TR. A systematic review of therapeutic ketamine use in children and adolescents with treatment-resistant mood disorders. *Eur Child Adolesc Psychiatry*. (2021) 30:1485–501. doi: 10.1007/s00787-020-01542-3

184. Zaki N, Chen L, Lane R, Doherty T, Drevets WC, Morrison RL, et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. *Neuropsychopharmacology*. (2023) 48:1225–33. doi: 10.1038/s41386-023-01577-5

185. Nikayin S, Murphy E, Krystal JH, Wilkinson ST. Long-term safety of ketamine and esketamine in treatment of depression. *Expert Opin Drug Saf*. (2022) 21:777–87. doi: 10.1080/14740338.2022.2066651

186. Becker AM, Holze F, Grandinetti T, Klaiber A, Toedtli VE, Kolaczynska KE, et al. Acute effects of psilocybin after escitalopram or placebo pretreatment in a randomized, double-blind, placebo-controlled, crossover study in healthy subjects. *Clin Pharmacol Ther*. (2022) 111:886–95. doi: 10.1002/cpt.2487

187. Chen T, Cheng L, Ma J, Yuan J, Pi C, Xiong L, et al. Molecular mechanisms of rapid-acting antidepressants: New perspectives for developing antidepressants. *Pharmacol Res*. (2023) 194:106837. doi: 10.1016/j.phrs.2023.106837

188. Silote GP, Gatto MC, Eskelund A, Guimarães FS, Wegener G, Joca SRL. Strain-, sex-, and time-dependent antidepressant-like effects of cannabidiol. *Pharm (Basel)*. (2021) 14:1269. doi: 10.3390/ph14121269

189. Martín-Sánchez A, González-Pardo H, Alegre-Zurano L, Castro-Zavala A, López-Taboada I, Valverde O, et al. Early-life stress induces emotional and molecular alterations in female mice that are partially reversed by cannabidiol. *Prog Neuropsychopharmacol Biol Psychiatry*. (2022) 115:110508. doi: 10.1016/j.pnpbp.2021.110508

190. Bis-Humbert C, García-Cabrerizo R, García-Fuster MJ. Decreased sensitivity in adolescent versus adult rats to the antidepressant-like effects of cannabidiol. *Psychopharmacol (Berl)*. (2020) 237:1621–31. doi: 10.1007/s00213-020-05481-4

191. Ledesma-Corvi S, Hernández-Hernández E, García-Fuster MJ. Exploring pharmacological options for adolescent depression: a preclinical evaluation with a sex perspective. *Transl Psychiatry*. (2022) 12:220. doi: 10.1038/s41398-022-01994-y

192. Sapkota A, Khurshid H, Qureshi IA, Jahan N, Went TR, Sultan W, et al. Efficacy and safety of intranasal esketamine in treatment-resistant depression in adults: A systematic review. *Cureus*. (2021) 13:e17352. doi: 10.7759/cureus.17352

193. Yavi M, Lee H, Henter ID, Park LT, Zarate CA. Ketamine treatment for depression: a review. *Discover Ment Health*. (2022) 2:9. doi: 10.1007/s44192-022-00012-3

194. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence*. (2012) 6:369–88. doi: 10.2147/PPA.S29716

195. de Jesus VD, Liem A, Borra D, Appel JM. Who's the boss? Ethical dilemmas in the treatment of children and adolescents. *Focus: J Life Long Learn Psychiatry*. (2022) 20:215. doi: 10.1176/APPI.FOCUS.20210037

196. Appel JM. A role for psychiatry in parental override cases. *Int J Adolesc Med Health*. (2015) 27:107. doi: 10.1515/ijamh-2015-5000

197. Dell ML. Child and adolescent depression: psychotherapeutic, ethical, and related nonpharmacologic considerations for general psychiatrists and others who prescribe. *Psychiatr Clin North Am*. (2012) 35:181–201. doi: 10.1016/j.psc.2011.12.002

198. Hung CC, Liu YH, Huang CC, Chou CY, Chen CM, Duann JR, et al. Effects of early ketamine exposure on cerebral gray matter volume and functional connectivity. *Sci Rep*. (2020) 10:15488. doi: 10.1038/s41598-020-72320-z

199. Zimmermann KS, Richardson R, Baker KD. Esketamine as a treatment for paediatric depression: questions of safety and efficacy. *Lancet Psychiatry*. (2020) 7:827–9. doi: 10.1016/S2215-0366(19)30521-8

200. Sarakbi D, Groll D, Tranmer J, Sears K. Achieving quality integrated care for adolescent depression: A scoping review. *J Prim Care Community Health*. (2022) 13:21501319221131684. doi: 10.1177/21501319221131684

201. Hinckley JD, Riggs P. Integrated treatment of adolescents with co-occurring depression and substance use disorder. *Child Adolesc Psychiatr Clin N Am*. (2019) 28:461–72. doi: 10.1016/j.chc.2019.02.006

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Overcoming treatment-resistant depression with machine-learning based tools: a study protocol combining EEG and clinical data to personalize glutamatergic and brain stimulation interventions (SelecTool Project)

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Treatment-Resistant Depression (TRD) poses a substantial health and economic challenge, persisting as a major concern despite decades of extensive research into novel treatment modalities. The considerable heterogeneity in TRD's clinical manifestations and neurobiological bases has complicated efforts toward effective interventions. Recognizing the need for precise biomarkers to guide treatment choices in TRD, herein we introduce the SelecTool Project. This initiative focuses on developing (WorkPlane 1/WP1) and conducting preliminary validation (WorkPlane 2/WP2) of a computational tool (SelecTool) that integrates clinical data, neurophysiological (EEG) and peripheral (blood sample) biomarkers through a machine-learning framework designed to optimize TRD treatment protocols. The SelecTool project aims to enhance clinical decision-making by enabling the selection of personalized interventions. It leverages multi-modal data analysis to navigate treatment choices towards two validated therapeutic options for TRD: esketamine nasal spray (ESK-NS) and accelerated repetitive Transcranial Magnetic

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Stimulation (arTMS). In WP1, 100 subjects with TRD will be randomized to receive either ESK-NS or arTMS, with comprehensive evaluations encompassing neurophysiological (EEG), clinical (psychometric scales), and peripheral (blood samples) assessments both at baseline (T0) and one month post-treatment initiation (T1). WP2 will utilize the data collected in WP1 to train the SelecTool algorithm, followed by its application in a second, out-of-sample cohort of 20 TRD subjects, assigning treatments based on the tool's recommendations. Ultimately, this research seeks to revolutionize the treatment of TRD by employing advanced machine learning strategies and thorough data analysis, aimed at unraveling the complex neurobiological landscape of depression. This effort is expected to provide pivotal insights that will promote the development of more effective and individually tailored treatment strategies, thus addressing a significant void in current TRD management and potentially reducing its profound societal and economic burdens.

KEYWORDS

transcranial magnetic stimulation (rTMS), esketamine nasal spray, machine-learning (ML) algorithms, treatment resistant depression (TRD), endophenotypes

1 Background

It is imperative to improve our therapeutic strategies and provide optimal treatment options for depression. Major Depressive Disorder (MDD) is a substantial contributor to global disability, affecting more than 300 million people (1). Multiple lines of evidence suggest that MDD may stem from various pathophysiological changes (2), including disruptions in glutamatergic function (3). A significant challenge arises as approximately 30-50% of MDD patients exhibit inadequate responses to initial treatment approaches (4). Consequently, these individuals endure distressing symptoms for extended periods, with a significant portion developing treatment-resistant depression (TRD). TRD is operationally defined as the lack of a substantial therapeutic response after two antidepressant trials that are deemed adequate in both duration (specifically, a minimum of 4-6 weeks) and dosage (5). Studies have shown that individuals with TRD have reduced glutamate levels in prefrontal regions (6).

Recently, two rapid-acting interventions gained approval to address TRD: glutamatergic pharmacotherapies, such as esketamine nasal spray (ESK-NS), and non-invasive brain stimulation, specifically repetitive transcranial magnetic stimulation (arTMS), with accelerated protocols being able to exert similar antidepressant effectiveness to standard protocols with a reduced timeframe (7, 8). Both treatments require a significant time investment and are administered in specialized settings, but there is currently insufficient data guiding the choice between them. rTMS can locally modify cortical excitability in specific brain regions, inducing changes in brain circuits typically underactive in MDD (9). In contrast, ESK-NS acts on glutamatergic ionotropic N-methyl-D-aspartate (NMDA) receptors, transiently increasing glutamate release (10). The challenge of identifying personalized interventions for TRD and MDD remains a significant concern, with the absence of tools able to guide treatment selection as a prominent issue. Coupling effective treatments with suitable patients reduces costs, chronicity, and avoidable suffering (4).

Addressing the "treatment-selection" problem requires a deeper understanding of biomarkers in depression: objectively measurable characteristics reflecting underlying biological processes that contribute to heterogeneity of the MDD subtype and predict the therapeutic response (11–13). Resting-state electroencephalography (EEG), a neuroimaging technique known for its high temporal resolution, appears to be a promising approach for response prediction in depressive illness (14). It is a valuable tool to explore neural biomarkers associated with TRD, offering information on neural activity alterations and functional connectivity related to depression. Evidence suggests that EEG-derived biomarkers, such as alpha band asymmetry, altered EEG resting-state B microstate, or EEG functional connectivity patterns, could accurately help predict treatment outcomes (15–17).

Peripheral blood-based biomarkers, such as markers of systemic inflammation (including interleukines: IL-6, IL-8, IL-2p70) and hormone levels (thyroid-stimulating hormone, cortisol, norepinephrine) can also aid in subtyping MDD and predicting treatment response (18).

These biomarkers are easy to measure and have significant potential for practical implementation in routine clinical practice. Additionally, computational phenotyping, which generates research-grade profiles based on clinical presentation and

computer-executable algorithms, contributes to a comprehensive understanding of personalized treatment approaches (19).

Machine learning (ML), a subset of artificial intelligence, encompasses diverse algorithms capable of building predictive models based on specific datasets (20). These algorithmic approaches aim to reveal fundamental principles underlying observations without explicit instructions, extracting structured knowledge from extensive datasets (21). A recent review demonstrates that ML technologies and data analytics can be applied at various stages of the patient journey, including detection and diagnosis, prognosis, treatment selection and optimization, outcome monitoring and tracking, and relapse prevention. Furthermore, data-driven ML approaches can identifying subtypes of symptoms and cognitive deficits, enabling model-based phenotyping (22). In this regard, significant progress has been made in the field of oncology. Specifically, it has become possible to robustly predict treatment responders and non-responders by using network-based biomarker expression levels in patients with melanoma, metastatic gastric cancer, and bladder cancer treated with immune checkpoint inhibitors targeting the programmed cell death 1/programmed cell death ligand 1 axis (23). On the other hand, integrating ML methods with extensive electronic health record databases has the potential to facilitate personalized psychiatry (22).

In this area, to fill the gap between the largely unmet needs of TRD and the enormous potential that has been opened by available innovations (e.g., neuroscience techniques, artificial intelligence methods, and advanced therapeutics), computerized tools can be developed, integrating clinical, neurophysiological, and peripheral data to guide treatment selection. These machine-learning methods could overcome the difficulty of treating TRD and its devastating consequences.

This study aims to develop and preliminarily validate a computational system that integrates clinical, electroencephalographical, and peripheral marker data, thus creating a tool to inform the treatment of Treatment-Resistant Depression (TRD) called "SelecTool". This tool is designed to support clinical decision-making by helping select personalized, tailored interventions. Using a machine-learning analysis of multi-channel data, the SelecTool will guide treatment selection towards ESK-NS or arTMS. This manuscript delineates the study protocol of the SelecTool project, a translational, multicentric investigation encompassing two distinct phases that aim to develop a machine-learning based tool to help guide clinicians in managing TRD.

2 Methods/design

2.1 Study design and settings

The project comprises two phases (Figure 1). The first (WP1; see Figure 1) involves the development of SelecTool for treatment orientation towards ESK-NS and arTMS by creating a machine-learning system. This phase includes:

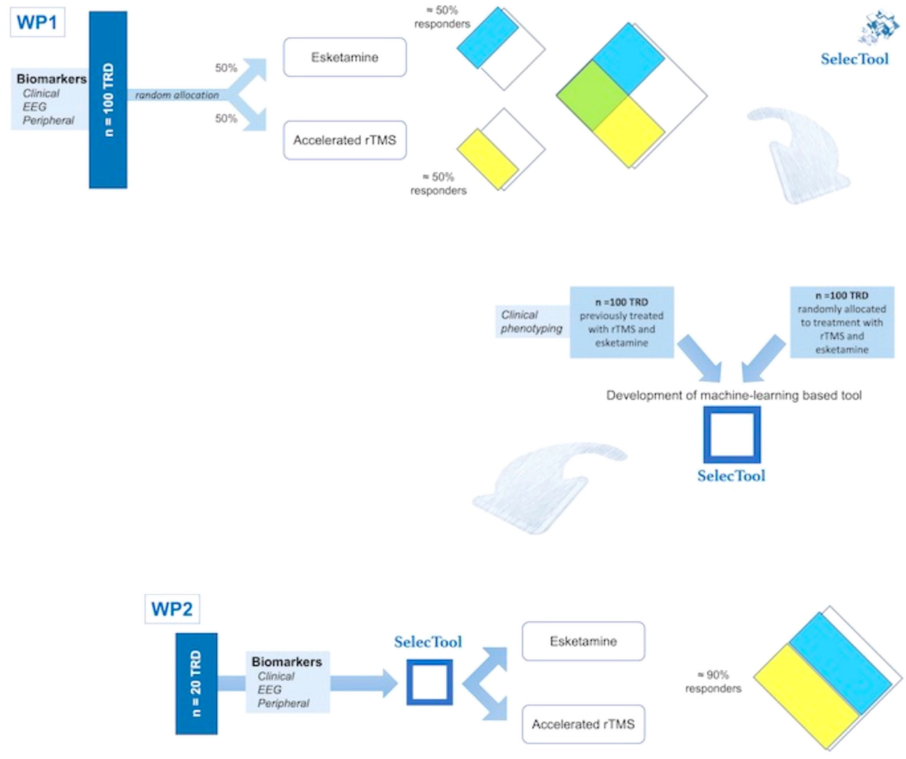

FIGURE 1
Flow chart of the study protocol describing the two different phases.

• Prospective evaluation of clinical, electrophysiological, and peripheral biomarkers to predict the antidepressant response to ESK-NS and arTMS (n = 100).

• Integration of the above data with those previously collected from subjects with TRD treated with ESK-NS (n = 50) and arTMS (n = 50).

• Training a computerized system to develop a machine-learning-based tool that guides the treatment selection.

The subsequent stage (WP2; see Figure 1) focuses on the pilot validation of the ESK-NS and arTMS prescription using SelecTool, including the proof-of-concept estimation of SelecTool's accuracy in an independent cohort (n = 20; out-of-sample validation). In this step, the identified biomarkers guiding treatment will be integrated into the SelecTool model as input data. Using the SelecTool's output, individuals will undergo nonrandomized assignment to ESK-NS or arTMS interventions. Therefore, the accuracy in determining an increase in the number of responders to treatment will be estimated and compared with the response rates observed in random assignment.

2.2 Sample size and eligibility criteria

One-hundred and twenty subjects (WP1: 100 subjects; WP2: 20 subjects) who are diagnosed with major depressive episode (both during the course of MDD or bipolar disorder) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (24), will be recruited by three Research Units: the 'G. d'Annunzio' University of Chieti, the University of Milano, and the Tor Vergata University of Rome.

The inclusion criteria will be the following: age between 18 and 65; current major depressive episode within at least the past month; TRD, defined as the absence of clinical response despite two or more treatments with antidepressants at adequate doses for 4-6 weeks (5); current stable psychopharmacological therapy for at least 1 month.

The exclusion criteria will be the following: presence of severe organic or neurological comorbidities, any substance use disorder (except nicotine dependence) in the past 6 months, intellectual disability or decline (Mini-Mental State Examination, MMSE < 26); uncontrolled systemic hypertension (specific for safety of ESK-NS treatment); presence of a positive history of seizures in the patient's history or a first-degree relative (specific for arTMS safety); pregnant and postpartum women.

To refine the processing precision of the tool, we will consolidate the dataset from participants enrolled in the study with clinical data gathered retrospectively. These supplemental data will be obtained from a dedicated TRD dataset, which includes information from subjects who met identical inclusion and exclusion criteria and underwent prior treatment in our centers with ESK-NS (n = 50) and arTMS (n = 50).

2.3 Study schedule

The enrolled patients will undergo a comprehensive clinical examination as the initial step. Electrophysiological (EEG recordings) and peripheral biomarkers will be collected during this process. The administration of ESK-NS or arTMS will be determined according to the groupings of participants. Specifically, in the first phase, subjects will be randomly assigned to arTMS or ESK-NS. In the second phase, the extracted treatment-orienting biomarkers will be introduced in the SelecTool model as input data. Based on the SelecTool output, subjects will be assigned to the ESK-NS or arTMS interventions.

Baseline and 1-month follow-up assessments will include neuropsychological and psychiatric evaluations, behavioral assessments, neurophysiological data acquisition, and the collection of peripheral biomarkers.

After one month, the clinical response will be measured by a blind rater based on the MADRS score (> 50% reduction).

2.4 Neuropsychological and psychiatric assessment

Subjects will undergo assessments at the screening visit (T0) and one month after initiation of treatment (T1) using a battery of validated psychometric tests (Table 1). At baseline, collection of anamnestic data will include sociodemographic factors, the history of depressive illness, treatment history for the current major depressive episode (MDE), comorbidities, lifetime antidepressant trials, augmentation strategies (such as the combined use of mood stabilizers, benzodiazepines, or antipsychotics), and other therapeutic interventions for treating treatment-resistant depression (TRD). These evaluations will be conducted by qualified psychiatrists, residents in psychiatry or clinical psychologists blinded to the treatment assignment. The primary outcome will be assessed in terms of clinical response, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS; score reduction > 50%) (25). Patients will be evaluated for mood

TABLE 1 Psychometric assessment at T0 and T1.

Psychometric assessment	
Mood	*Hamilton Depression Scale* *Young Mania Rating Scale*
Anhedonia	*Snaith-Hamilton Pleasure Scale*
Temperamental aspects	*Temperament Evaluation of Memphis, Pisa and San Diego Autoquestionnaire version* *Big Five Questionnaire*
Anxiety	*Hamilton Anxiety Scale*
Alexithymia	*Toronto Alexithymia Scale*
General psychiatric symptomatology	*Brief Psychiatric Rating Scale*
Traumatic experiences	*Childhood Trauma Questionnaire*
Suicide risk	*Columbia-Suicide Severity Rating Scale*
Resilience	*Connor-Davidson Resilience Scale*
Health-related assessments	*Clinical Global Impression-Severity scale Health Status Questionnaire*

(Hamilton Depression Scale; Young Mania Rating Scale) (26), anhedonia (Snaith-Hamilton Pleasure Scale) (27), temperamental aspects (Temperament Evaluation of Memphis, Pisa and San Diego Autoquestionnaire version) (28); Barratt Impulsiveness Scale version 11; Big Five Questionnaire) (29, 30), anxiety (Hamilton Anxiety Scale) (31), alexithymia (Toronto Alexithymia Scale) (32), general psychiatric symptoms (Brief Psychiatric Rating Scale) (33), traumatic experiences (Childhood Trauma Questionnaire) (34), suicide risk (Columbia-Suicide Severity Rating Scale, Beck Hopelessness Scale) (35, 36), and resilience (Connor-Davidson Resilience Scale) (37). Health-related assessments will use the Clinical Global Impression-Severity scale (CGI-S) (38).

2.5 Behavioral evaluation

A comprehensive neuropsychological evaluation targeting various cognitive functions will be conducted for all patients. The assessment battery will primarily encompass measures of global cognition (MMSE) (39), attention (sustained spatial attention, Trail Making Test-A [TMT-A]; divided spatial attention, TMT-B; cognitive flexibility, TMT-AB) (40), short- and long-term episodic memory (Babcock Memory test) (41), and executive function (Frontal Assessment Battery) (42).

2.6 Neurophysiological data

At T0 and T1, EEG electrical activity will be acquired utilizing a 64-channel EEG system (eego^{TM}mylab; ANT Neuro, Hengelo, Netherlands). Resting-state EEG will be recorded with eyes open and closed. Electrooculography and electrocardiography will also be acquired using additional electrodes. The data will undergo pre-processing to eliminate sections of poor quality and channels with unreliable data. Independent component analysis will be applied to eliminate periodic, non-brain signals. EEG analysis aims to identify pertinent and effective electro-neurophysiological biomarkers (at the channel/scalp, source, and source connectivity levels) indicative of treatment response in TRD (Table 2).

2.7 Peripheral biomarkers

Blood samples (15 ml) will be collected at T0 and T1 by forearm venipuncture after an overnight fast. These samples will be stored in BD Vacutainer tubes containing ethylenediaminetetraacetic acid. Serum and plasma will be prepared by centrifugation at 1500 rpm for 10 minutes at 4°C. The serum will be stored in 0.5 ml Eppendorf tubes at -80°C until analysis.

Enzyme-linked immunosorbent assays (ELISAs) will be used to assess systemic inflammation and oxidative stress markers, including C-reactive protein, interleukin-1b (IL-1b), IL-5, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-alpha). The levels of cortisol and adrenocorticotropic hormone will be determined using ELISA. Using specific monoclonal antibodies, the levels of TSH, FT3, and FT4 will be determined. Plasma brain-derived neurotrophic factor (BDNF) and proBDNF levels as biomarkers of synaptic integrity and plasticity will be investigated using ultra-sensitive high-performance single-molecule arrays or conventional ELISA.

TABLE 2 EEG biomarkers to predict treatment response.

Alpha asymmetry	Based on the approach-withdraw model (43), this measures relative alpha band activity between brain hemispheres (mainly in frontal regions; higher alpha may reflect lower brain activity). Alpha asymmetry has been proposed as a suitable prognostic biomarker related to anxious subtype and bipolar features (44).
Microstate abnormalities	Using polarity-insensitive k-mean clustering, we will segment resting-state high-density EEG data into microstates (45). The proportion, duration, occurrence, and transition of microstates will be studied as potential biomarkers of state and trait abnormalities and as predictors of treatment outcome.
Rostral anterior cingulate cortex theta activity	This is a robust marker that predicts greater improvement in selective serotonin reuptake inhibitor-induced depressive symptom (46).
Subgenual/ prefrontal connectivity	Based on recent findings that suggest that changes in rTMS-induced within-network connectivity are a mediator of treatment response (47), eLORETA linear-lagged connectivity measures of theta (4-7.5 Hz) and alpha (8-13 Hz) frequency will be obtained between the following regions of interest: right and left DLPFC, dorsomedial prefrontal cortex, and subgenual cingulate cortex (as in Iseger et al, 2017).
Gamma-band power envelope connectivity	Orthogonalized power envelope correlation will measure EEG source connectivity (48). Large-scale connectivity patterns have been proposed as predictors of placebo/ antidepressant outcomes.

2.8 Treatment administration

During the first phase (WP1), subjects will be randomly assigned in a 1:1 ratio to receive arTMS or ESK-NS. A stratified randomization approach with a four-block size will be implemented to minimize inadvertent bias. Stratification factors will include sex (male, female), age (expected cutoff 50 years old), depression severity (mild/moderate depression, MADRS ≤ 34; severe depression, > 34), and treatment site (Chieti, Milan, and Rome). The randomization process will be carried out by an investigator external to the study.

In the pilot validation phase (WP2), the extracted treatment-guiding biomarkers will be incorporated into the SelecTool model as input data. Subsequently, subjects will be allocated to esketamine or arTMS interventions based on the output of the SelecTool.

All subjects will undergo a comprehensive preliminary visit to assess potential contraindications to treatments. Qualified medical personnel, specifically trained to handle potential side effects and emergencies related to treatments, will administer ESK-NS and arTMS treatments.

Subjects in the ESK-NS group will be administered the drug according to the EMA guidelines (49). It will be supplied in a double-use nasal spray device containing 200 µl of vehicle solution (two sprays), each delivering 28 mg (14 mg ESK-NS base per 100 µl

of spray). This dose will be administered twice a week for the first week, followed by 84 mg (three devices) administered twice a week for three weeks, resulting in a total of 1 month of treatment. Before initial administration, patients will be instructed to blow their nose (only before the first device is administered) and then assisted to recline their head 45° (semi-reclined position) during administration to enhance retention of the medication within the nasal cavity. Each ESK-NS session will be conducted by qualified personnel who closely monitor vital parameters (blood pressure, heart rate) before and at 45 and 90 minutes after treatment, following international safety guidelines (50).

Patients in the arTMS group will undergo a 5-day arTMS protocol involving four daily sessions (8). This protocol, developed following the safety guidelines (51) and the principles of accelerated protocols (52), aims to deliver the same number of magnetic pulses as the FDA-approved protocol (53). Stimulation will be performed using a MagPro R30 (MagVenture) system with a B-70 coil targeting the left dorsolateral prefrontal cortex (L-DLPFC), a region approved for TRD treatment (53). The L-DLPFC will be identified using the BEAM F3 method (54), facilitating rapid localization through anthropometric measures. The resting motor threshold will be determined using the evoked potential motor method (55). Each session will adhere to the following parameters, aligning with the FDA-approved standard (53): 10 Hz frequency, 120% resting motor threshold, 40 pulses/train (4 s duration), 26 s inter-train interval, 3000 pulses/session, and a total duration of 35 minutes. This session will be repeated four times within the same day, with a 55-minute interval between sessions (total duration of the cycle session pause: 90 minutes), thus adhering to the accelerated stimulation protocol. The entire protocol will take approximately 5 hours and 5 minutes. Throughout this time, patients will be continuously monitored for side effects. The onset of potential side effects will be evaluated at each stimulation session using a specific and approved scale for rTMS-related side effects (56).

2.9 Statistical analysis

Drawing from the existing literature on the efficacy of arTMS and ESK-NS for Treatment-Resistant Depression (TRD), we anticipate a response rate of approximately 50% for each treatment (52, 57). The sample size was determined using the G*Power 3.1 software, taking into account specific parameters: a substantial effect size of predictors (expected Cohen effect size F = 0.4), power 1-beta = 0.80, one-way, four groups (2x2; treatment: ESK-NS, arTMS; responders and non-responders), and a significance level corrected for multiple comparisons (alpha = 0.001). These calculations resulted in a total sample size of n = 144. Considering a possible imbalance in the allocation of responders (10%) and to mitigate possible dropouts (10%), we increased the total sample size to n = 200.

We will develop a machine-learning model to predict the primary treatment outcome and use it for treatment guidance. This model will leverage both neurophysiological data and clinical scores. We also aim to interpret the model and extract the features that influence it. Given the heterogeneous nature of the collected data, an appropriate solution is to opt for ensemble methods, particularly random forest techniques, which have shown suitability for such tasks (19, p. 202) and are relevant for *post hoc* analysis of results. To provide comprehensive insights, our exploration will not be restricted to random forest techniques; we will also investigate other approaches such as neural networks or support vector classifiers. Dealing with missing values in clinical and psychometric tests is a critical concern, and we will address this using advanced techniques such as multivariate imputation (58, 59). The model parameters and performance will be assessed using nested and shuffle cross-validation, which is recognized as optimal to minimize bias in model error estimations (60). The results' significance will be evaluated using permutation tests, which are acknowledged as the gold standard for statistical assessments of machine-learning algorithms (61).

2.10 Ethical issues

This study has received approval from a local Institutional Review Board (C.Et.R.A., approval number: 6/2023). It will follow the principles and recommendations of Good Clinical Practice and the Declaration of Helsinki (World Medical Association, 2013), which offer guidance to physicians engaged in biomedical research with human subjects. The patient will sign the informed consent form, which will be witnessed, dated, and retained by the investigator responsible for recruiting patients into the study.

3 Discussion

This research proposal is designed to spearhead an innovative methodology for enhancing clinical decision-making processes in the context of TRD. The aim is to develop and preliminarily validate an advanced computational framework that adeptly consolidates clinical assessments, peripheral biomarkers, and EEG data to address the selection of advanced treatment for TRD. This integration aims to predict treatment outcomes precisely (62), thus facilitating the tailored orientation of therapeutic strategies that reduce unnecessary suffering. To construct this pivotal tool for TRD treatment optimization, we plan to utilize a machine learning algorithm capable of processing complex, multi-dimensional data streams (18, 63).

Machine learning has been employed in the medical sector since the late 1990s, notably in oncology – a principal area of application (20). Within this field, a critical challenge involves the identification of markers that can accurately predict drug responses among diverse groups of cancer patients. A recent study introduced a network-based machine-learning framework capable of generating robust predictions across immune checkpoint inhibitor datasets and pinpointing potential biomarkers (23).

In the area of clinical neurosciences, there is significant potential for benefit from these technological advances, especially considering the nuanced presentation of symptoms characteristic of neurological disorders. A study conducted in 2022 focused on the use of machine

learning algorithms to classify subtypes of immune microenvironment and identify unique genes in Alzheimer's disease. This research highlighted five immune microenvironment-related genes that strongly correlate with pathological markers and reliably predict the disease's trajectory (64).

The field of psychiatry has also seen considerable advancements through pioneering research efforts. A recent multicenter study applied multimodal machine learning methods, integrating clinical, neurocognitive, structural magnetic resonance imaging, and polygenic risk scores to predict the onset of psychosis in individuals at high clinical risk or with recent-onset depression (65). Furthermore, a recent narrative review investigated the application of machine learning in diagnosing and forecasting schizophrenia, concluding that various machine learning-based models can potentially help healthcare professionals in diagnosing the condition and predicting its clinical presentations and complications (66).

Concerning TRD, a very recent machine learning study has highlighted that characteristics such as profound anhedonia, anxious distress, mixed symptoms, and bipolarity in patients treated with ESK-NS represent factors that predict a positive response and remission. In contrast, the use of benzodiazepines and the severity of depression were associated with delayed responses (67). The levels of accuracy achieved with data exclusively symptom-based do not allow for incorporation into clinical practice and justify the attempt of the SelecTool Project to refine selection methods by integrating other biomarkers.

Given the substantial global health impact of TRD, which doubles the risk of hospitalization and increases the risk of suicide sevenfold compared to treatment-responsive depressed patients (68) our primary objective is to identify treatment approaches that optimize patients' prospects for recovery. On the one hand, arTMS is a proven intervention for TRD, strongly supported by existing literature, demonstrating response rates of 40–50% and remission rates of 25–30%. (52, 69). On the other hand, in patients treated with ESK-NS, the percentage of remitters has been observed to be less than half (70).

As a result, despite the established antidepressant efficacy of ESK-NS and arTMS, achieving clinical response rates of approximately 50-60% even in real-world studies (8, 71–75), there remains a notable gap in our understanding of their response biomarkers. This proposal is also set to significantly expand our understanding of the complex and heterogeneous nature of the pathophysiology and treatment of MDD. Viewing MDD through the lens of brain connectivity disorders highlights its varied neurobiological foundations, likely related to disparate brain network functionalities (76). Such neurobiological diversity leads to distinct MDD subtypes, each with its unique treatment response profile, particularly to neuromodulation and glutamatergic interventions.

By deepening our understanding of the biomarkers associated with various depression subtypes, including clinical, EEG, and peripheral indicators, we aim to pioneer a patient-centered approach to treatment selection. Given the substantial social, occupational, and physical repercussions associated with TRD, not to mention the increased healthcare costs that make TRD a significant economic burden on healthcare systems (68, p. 201; 77, 78), this research has the potential for considerable social and economic benefits.

In conclusion, this research proposal not only aims to change the approach to treating TRD by leveraging cutting-edge machine learning techniques and comprehensive data analysis, but also aims to shed light on the intricate landscape of the neurobiological underpinnings of depression. Through this endeavor, we anticipate contributing valuable insights that could influence and offer potential advantages for clinical practice, facilitating the development of more effective and personalized treatment regimens. This approach addresses a critical gap in the current management of TRD and potentially alleviating its significant societal and economic impacts.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Comitato Etico Regione Abruzzo (C.Et.R.A.). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MP: Writing – original draft, Writing – review & editing. GD: Writing – original draft, Writing – review & editing. BB: Writing – original draft, Writing – review & editing. Gd: Writing – original draft, Writing – review & editing. CC: Writing – original draft, Writing – review & editing. RC: Writing – original draft, Writing – review & editing. GM(7^{th} author): Writing – original draft, Writing – review & editing. OD: Writing – original draft, Writing – review & editing. GM(9^{th} author): Writing – original draft, Writing – review & editing. AD(10^{th} author): Writing – original draft, Writing – review & editing. EB: Writing – original draft, Writing – review & editing. IR: Writing – original draft, Writing – review & editing. AC: Writing – original draft, Writing – review & editing. LP: Writing – original draft, Writing – review & editing. GB: Writing – original draft, Writing – review & editing. MP: Writing – original draft, Writing – review & editing. RG: Writing – original draft, Writing – review & editing. AD(18^{th} author): Writing – original draft, Writing – review & editing. LM: Writing – original draft, Writing – review & editing. FZ: Writing – original draft, Writing – review & editing. BD: Writing – original draft, Writing – review & editing. GM(22^{nd} author): Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. WHO. (2021). World Health Organization.

2. Papp M, Cubała WJ, Swiecicki L, Newman-Tancredi A, Willner P. Perspectives for therapy of treatment-resistant depression. *Br J Pharmacol*. (2022) 179:4181–200. doi: 10.1111/bph.15596

3. Aleksandrova LR, Phillips AG, Wang YT. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. *J Psychiatry Neurosci*. (2017) 42:222–9. doi: 10.1503/jpn.160175

4. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: Definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. (2023) 22:394–412. doi: 10.1002/wps.21120

5. Sforzini L, Worrell C, Kose M, Anderson IM, Aouizerate B, Arolt V, et al. A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. *Mol Psychiatry*. (2022) 27:1286–99. doi: 10.1038/s41380-021-01381-x

6. Kim Y-K, Na K-S. Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. (2016) 70:117–26. doi: 10.1016/j.pnpbp.2016.03.009

7. Zheng W, Zhang X-Y, Xu R, Huang X, Zheng Y-J, Huang X-B, et al. Adjunctive accelerated repetitive transcranial magnetic stimulation for older patients with depression: A systematic review. *Front Aging Neurosci*. (2022) 14:1036676. doi: 10.3389/fnagi.2022.1036676

8. Pettorruso M, d'Andrea G, Di Carlo F, De Risio L, Zoratto F, Miuli A, et al. Comparing fast-acting interventions for treatment-resistant depression: An explorative study of accelerated HF-rTMS versus intranasal esketamine. *Brain Stimulation: Basic Translational Clin Res Neuromodulation*. (2023) 16:1041–3. doi: 10.1016/j.brs.2023.06.003

9. Chou P-H, Lin Y-F, Lu M-K, Chang H-A, Chu C-S, Chang WH, et al. Personalization of repetitive transcranial magnetic stimulation for the treatment of major depressive disorder according to the existing psychiatric comorbidity. *Clin Psychopharmacol Neuroscience*. (2021) 19:190–205. doi: 10.9758/cpn.2021.19.2.190

10. D'Andrea G, Pettorruso M, Lorenzo GD, Mancusi G, McIntyre RS, Martinotti G. Rethinking ketamine and esketamine action: Are they antidepressants with mood-stabilizing properties? *Eur Neuropsychopharmacol*. (2023) 70:49–55. doi: 10.1016/j.euroneuro.2023.02.010

11. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med*. (2017) 23:28–38. doi: 10.1038/nm.4246

12. Gadad BS, Jha MK, Czysz A, Furman JL, Mayes TL, Emslie MP, et al. Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks. *J Affect Disord*. (2018) 233:3–14. doi: 10.1016/j.jad.2017.07.001

13. D'Onofrio AM, Pizzuto DA, Batir R, Perrone E, Cocciolillo F, Cavallo F, et al. Dopaminergic dysfunction in the left putamen of patients with major depressive disorder. *J Affect Disord*. (2024) 357:107–15. doi: 10.1016/j.jad.2024.04.044

14. Widge AS, Bilge MT, Montana R, Chang W, Rodriguez CI, Deckersbach T, et al. Electroencephalographic biomarkers for treatment response prediction in major depressive illness: A meta-analysis. *Am J Psychiatry*. (2019) 176:44–56. doi: 10.1176/appi.ajp.2018.17121358

15. Arns M, Bruder G, Hegerl U, Spooner C, Palmer DM, Etkin A, et al. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. *Clin Neurophysiol*. (2016) 127:509–19. doi: 10.1016/j.clinph.2015.05.032

16. Vellante F, Ferri F, Baroni G, Croce P, Migliorati D, Pettoruso M, et al. Euthymic bipolar disorder patients and EEG microstates: A neural signature of their abnormal self experience? *J Affect Disord*. (2020) 272:326–34. doi: 10.1016/j.jad.2020.03.175

17. Benschop L, Vanhollebeke G, Li J, Leahy RM, Vanderhasselt M-A, Baeken C. Reduced subgenual cingulate-dorsolateral prefrontal connectivity as an electrophysiological marker for depression. *Sci Rep*. (2022) 12:16903. doi: 10.1038/s41598-022-20274-9

18. Jani BD, McLean G, Nicholl BI, Barry SJE, Sattar N, Mair FS, et al. Risk assessment and predicting outcomes in patients with depressive symptoms: A review of potential role of peripheral blood based biomarkers. *Front Hum Neurosci*. (2015) 9:18. doi: 10.3389/fnhum.2015.00018

19. Dadi K, Varoquaux G, Houenou J, Bzdok D, Thirion B, Engemann D. Population modeling with machine learning can enhance measures of mental health. *GigaScience*. (2021) 10. doi: 10.1093/gigascience/giab071

20. Nichols JA, Herbert Chan HW, Baker MAB. Machine learning: Applications of artificial intelligence to imaging and diagnosis. *Biophys Rev*. (2019) 11:111–8. doi: 10.1007/s12551-018-0449-9

21. Bzdok D, Altman N, Krzywinski M. Statistics versus machine learning. *Nat Methods*. (2018) 15:233–4. doi: 10.1038/nmeth.4642

22. Chen ZS, Kulkarni P, Galatzer-Levy IR, Bigio B, Nasca C, Zhang Y. Modern views of machine learning for precision psychiatry. *Patterns*. (2022) 3:100602. doi: 10.1016/j.patter.2022.100602

23. Kong J, Ha D, Lee J, Kim I, Park M, Im S-H, et al. Network-based machine learning approach to predict immunotherapy response in cancer patients. *Nat Commun*. (2022) 13:3703. doi: 10.1038/s41467-022-31535-6

24. APA. *Diagnostic and Statistical Manual*. Arlington: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596

25. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry : J Ment Sci*. (1979) 134:382–9. doi: 10.1192/bjp.134.4.382

26. Hamilton M. A rating scale for depression. *J Neurology Neurosurgery Psychiatry*. (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

27. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry : J Ment Sci*. (1995) 167:99–103. doi: 10.1192/bjp.167.1.99

28. Elias LR, Köhler CA, Stubbs B, Maciel BR, Cavalcante LM, Vale AMO, et al. Measuring affective temperaments: A systematic review of validation studies of the Temperament Evaluation in Memphis Pisa and San Diego (TEMPS) instruments. *J Affect Disord*. (2017) 212:25–37. doi: 10.1016/j.jad.2017.01.023

29. Reise SP, Moore TM, Sabb FW, Brown AK, London ED. The Barratt Impulsiveness Scale-11: Reassessment of its structure in a community sample. *psychol Assess*. (2013) 25:631–42. doi: 10.1037/a0032161

30. Widiger TA, Crego C. The Five Factor Model of personality structure: An update. *World Psychiatry : Off J World Psychiatr Assoc (WPA)*. (2019) 18:271–2. doi: 10.1002/wps.20658

31. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x

32. Bagby M, Taylor GJ, Ryan D. Toronto alexithymia scale: relationship with personality and psychopathology measures. *Psychother Psychosomatics*. (2010) 45:207–15. doi: 10.1159/000287950

33. Zanello A, Berthoud L, Ventura J, Merlo MCG. The Brief Psychiatric Rating Scale (version 4.0) factorial structure and its sensitivity in the treatment of outpatients with unipolar depression. *Psychiatry Res*. (2013) 210:626–33. doi: 10.1016/j.psychres.2013.07.001

34. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl*. (2003) 27:169–90. doi: 10.1016/S0145-2134(02)00541-0

35. Salvi J. Calculated decisions: columbia-suicide severity rating scale (C-SSRS). *Emergency Med Pract*. (2019) 21:CD3–4.

36. Pettorruso M, D'Andrea G, Martinotti G, Cocciolillo F, Miuli A, Di Muzio I, et al. Hopelessness, dissociative symptoms, and suicide risk in major depressive disorder: clinical and biological correlates. *Brain Sci*. (2020) 10. doi: 10.3390/brainsci10080519

37. Connor KM, Davidson JRT. Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depression Anxiety*. (2003) 18:76–82. doi: 10.1002/(ISSN)1520-6394

38. Busner J, Targum SD. The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry (Edgmont (Pa.: Township))*. (2007) 4:28–37.

39. Measso G, Cavarzeran F, Zappalà G, Lebowitz BD, Crook TH, Pirozzolo FJ, et al. The mini-mental state examination: Normative study of an Italian random sample. *Dev Neuropsychol*. (1993) 9:77–85. doi: 10.1080/87565649109540545

40. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: Normative values from 287 normal adult controls. *Ital J Neurological Sci*. (1996) 17:305–9. doi: 10.1007/BF01997792

41. Carlesimo GA, Caltagirone C, Gainotti G. The Mental Deterioration Battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *Eur Neurol*. (1996) 36:378–84. doi: 10.1159/000117297

42. Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, et al. The Frontal Assessment Battery (FAB): Normative values in an Italian population sample. *Neurological Sci*. (2005) 26:108–16. doi: 10.1007/s10072-005-0443-4

43. Coan JA, Allen JJB. Frontal EEG asymmetry as a moderator and mediator of emotion. *Biol Psychol*. (2004) 67:7–49. doi: 10.1016/j.biopsycho.2004.03.002

44. Nusslock R, Walden K, Harmon-Jones E. Asymmetrical frontal cortical activity associated with differential risk for mood and anxiety disorder symptoms: An RDoC perspective. *Int J Psychophysiology*. (2015) 98:249–61. doi: 10.1016/j.ijpsycho.2015.06.004

45. Murphy M, Whitton AE, Deccy S, Ironside ML, Rutherford A, Beltzer M, et al. Abnormalities in electroencephalographic microstates are state and trait markers of major depressive disorder. *Neuropsychopharmacology*. (2020) 45:2030–7. doi: 10.1038/s41386-020-0749-1

46. Pizzagalli DA, Webb CA, Dillon DG, Tenke CE, Kayser J, Goer F, et al. Pretreatment rostral anterior cingulate cortex theta activity in relation to symptom improvement in depression: A randomized clinical trial. *JAMA Psychiatry*. (2018) 75:547–54. doi: 10.1001/jamapsychiatry.2018.0252

47. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry*. (2012) 72:595–603. doi: 10.1016/j.biopsych.2012.04.028

48. Rolle CE, Fonzo GA, Wu W, Toll R, Jha MK, Cooper C, et al. Cortical connectivity moderators of antidepressant vs placebo treatment response in major depressive disorder: secondary analysis of a randomized clinical trial. *JAMA Psychiatry*. (2020) 77:397–408. doi: 10.1001/jamapsychiatry.2019.3867

49. EMA. *Spravato, Summary of Product Characteristics*. European Medicines Agency, EU. (2019).

50. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *Am J Psychiatry*. (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

51. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. (2021) 132:269–306. doi: 10.1016/j.clinph.2020.10.003

52. Miron J-P, Jodoin VD, Lespérance P, Blumberger DM. Repetitive transcranial magnetic stimulation for major depressive disorder: Basic principles and future directions. *Ther Adv Psychopharmacol*. (2021) 11:20451253211042696. doi: 10.1177/20451253211042696

53. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry*. (2018) 79, Fascicolo 1. doi: 10.4088/JCP.16cs10905

54. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulation*. (2009) 2:50–4. doi: 10.1016/j.brs.2008.09.006

55. Bestmann S, Krakauer JW. The uses and interpretations of the motor-evoked potential for understanding behaviour. *Exp Brain Res*. (2015) 233:679–89. doi: 10.1007/s00221-014-4183-7

56. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. (2009) 120:2008–39. doi: 10.1016/j.clinph.2009.08.016

57. Jones RR, Freeman MP, Kornstein SG, Cooper K, Daly EJ, Canuso CM, et al. Efficacy and safety of esketamine nasal spray by sex in patients with treatment-resistant depression: Findings from short-term randomized, controlled trials. *Arch Women's Ment Health*. (2022) 25:313–26. doi: 10.1007/s00737-021-01185-6

58. Josse J, Prost N, Scornet E, Varoquaux G. *On the consistency of supervised learning with missing values*. (2019). pp. 1–43.

59. Little R, Rubin D. *Statistical Analysis with Missing Data. 3rd ed*. Wiley Online Library (2019). doi: 10.1002/SERIES1345

60. Varoquaux G. Cross-validation failure: Small sample sizes lead to large error bars. *NeuroImage*. (2018) 180:68–77. doi: 10.1016/j.neuroimage.2017.06.061

61. Combrisson E, Jerbi K. Exceeding chance level by chance: The caveat of theoretical chance levels in brain signal classification and statistical assessment of decoding accuracy. *J Neurosci Methods*. (2015) 250:126–36. doi: 10.1016/j.jneumeth.2015.01.010

62. Marzetti L, Basti A, Chella F, D'Andrea A, Syrjälä J, Pizzella V. Brain functional connectivity through phase coupling of neuronal oscillations: A perspective from magnetoencephalography. *Front Neurosci*. (2019) 13:964. doi: 10.3389/fnins.2019.00964

63. Beijers L, Wardenaar KJ, van Loo HM, Schoevers RA. Data-driven biological subtypes of depression: Systematic review of biological approaches to depression subtyping. *Mol Psychiatry*. (2019) 24:888–900. doi: 10.1038/s41380-019-0385-5

64. Lai Y, Lin P, Lin F, Chen M, Lin C, Lin X, et al. Identification of immune microenvironment subtypes and signature genes for Alzheimer's disease diagnosis and risk prediction based on explainable machine learning. *Front Immunol*. (2022) 13:1046410. doi: 10.3389/fimmu.2022.1046410

65. Koutsouleris N, Dwyer DB, Degenhardt F, Maj C, Urquijo-Castro MF, Sanfelici R, et al. Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-Risk syndromes and recent-Onset depression. *JAMA Psychiatry*. (2021) 78:195–209. doi: 10.1001/jamapsychiatry.2020.3604

66. Gashkarimov VR, Sultanova RI, Efremov IS, Asadullin AR. Machine learning techniques in diagnostics and prediction of the clinical features of schizophrenia: A narrative review. *Consortium Psychiatricum*. (2023) 4:43–53. doi: 10.17816/CP.202343

67. Pettorruso M, Guidotti R, d'Andrea G, De Risio L, D'Andrea A, Chiappini S, et al. Predicting outcome with Intranasal Esketamine treatment: A machine-learning, three-month study in Treatment-Resistant Depression (ESK-LEARNING). *Psychiatry Res*. (2023) 327:115378. doi: 10.1016/j.psychres.2023.115378

68. Amos TB, Tandon N, Lefebvre P, Pilon D, Kamstra RL, Pivneva I, et al. Direct and indirect cost burden and change of employment status in treatment-resistant depression: A matched-cohort study using a US commercial claims database. *J Clin Psychiatry*. (2018) 79. doi: 10.4088/JCP.17m11725

69. D'Andrea G, Mancusi G, Santovito MC, Marrangone C, Martino F, Santorelli M, et al. Investigating the role of maintenance TMS protocols for major depression: systematic review and future perspectives for personalized interventions. *J Personalized Med*. (2023) 13. doi: 10.3390/jpm13040697

70. Sapkota A, Khurshid H, Qureshi IA, Jahan N, Went TR, Sultan W, et al. Efficacy and safety of intranasal esketamine in treatment-resistant depression in adults: A systematic review. *Cureus*. (2021) 13. doi: 10.7759/cureus.17352

71. Chiappini S, D'Andrea G, De Filippis S, Di Nicola M, Andriola I, Bassetti R, et al. Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: A viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study. *Eur Neuropsychopharmacol*. (2023) 74:15–21. doi: 10.1016/j.euroneuro.2023.04.011

72. d'Andrea G, Chiappini S, McIntyre RS, Stefanelli G, Carullo R, Andriola I, et al.). Investigating the effectiveness and tolerability of intranasal esketamine among older adults with treatment-resistant depression (TRD): A *post-hoc* analysis from the REAL-ESK study group. *Am J Geriatric Psychiatry*. (2023). doi: 10.1016/j.jagp.2023.06.016

73. d'Andrea G, Pettorruso M, Di Lorenzo G, Rhee TG, Chiappini S, Carullo R, et al. The rapid antidepressant effectiveness of repeated dose of intravenous ketamine and intranasal esketamine: A *post-hoc* analysis of pooled real-world data. *J Affect Disord*. (2024) 348:314–22. doi: 10.1016/j.jad.2023.12.038

74. Martinotti G, Vita A, Fagiolini A, Maina G, Bertolino A, Dell'Osso B, et al. Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. (2022) 319:646–54. doi: 10.1016/j.jad.2022.09.043

75. Martinotti G, Dell'Osso B, Di Lorenzo G, Maina G, Bertolino A, Clerici M, et al. Treating Bipolar Depression with Esketamine: Safety and Effectiveness data from a naturalistic multicentric study on Esketamine in Bipolar versus Unipolar Treatment-Resistant Depression. *Bipolar Disord*. (2023). doi: 10.1111/bdi.13296

76. Li BJ, Friston K, Mody M, Wang HN, Lu HB, Hu DW. A brain network model for depression: From symptom understanding to disease intervention. *CNS Neurosci Ther*. (2018) 24:1004–19. doi: 10.1111/cns.12998

77. Perrone V, Sangiorgi D, Andretta M, Ducci G, Forti B, Francesa Morel PC, et al. Healthcare resource consumption and related costs of patients estimated with treatment-resistant depression in Italy. *ClinicoEconomics Outcomes Res: CEOR*. (2021) 13:629–35. doi: 10.2147/CEOR.S314111

78. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. *J Clin Psychiatry*. (2021) 82. doi: 10.4088/JCP.20m13699

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Multichannel tDCS with advanced targeting for major depressive disorder: a tele-supervised at-home pilot study

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Introduction: Proof-of-principle human studies suggest that transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) may improve depression severity. This open-label multicenter study tested remotely supervised multichannel tDCS delivered at home in patients (N=35) with major depressive disorder (MDD). The primary aim was to assess the feasibility and safety of our protocol. As an exploratory aim, we evaluated therapeutic efficacy: the primary efficacy measure was the median percent change from baseline to the end of the 4-week post-treatment follow-up period in the observer-rated Montgomery-Asberg Depression Mood Rating Scale (MADRS).

Methods: Participants received 37 at-home stimulation sessions (30 minutes each) of specifically designed multichannel tDCS targeting the left DLPFC administered over eight weeks (4 weeks of daily treatments plus 4 weeks of taper), with a follow-up period of 4 weeks following the final stimulation session. The stimulation montage (electrode positions and currents) was optimized by employing computational models of the electric field generated by multichannel tDCS using available structural data from a similar population (group optimization). Conducted entirely remotely, the study employed the MADRS for assessment at baseline, at weeks 4 and 8 during treatment, and at 4-week follow-up visits.

Results: 34 patients (85.3% women) with a mean age of 59 years, a diagnosis of MDD according to DSM-5 criteria, and a MADRS score ≥20 at the time of study enrolment completed all study visits. At baseline, the mean time since MDD diagnosis was 24.0 (SD 19.1) months. Concerning compliance, 85% of the participants (n=29) completed the complete course of 37 stimulation sessions at home, while 97% completed at least 36 sessions. No detrimental effects were observed, including suicidal ideation and/or behavior. The study observed a median MADRS score reduction of 64.5% (48.6, 72.4) 4 weeks post-treatment (Hedge's g = -3.1). We observed a response rate (≥ 50% improvement in MADRS scores) of 72.7% (n=24) from baseline to the last visit 4 weeks post-treatment. Secondary measures reflected similar improvements.

Conclusions: These results suggest that remotely supervised and supported multichannel home-based tDCS is safe and feasible, and antidepressant efficacy motivates further appropriately controlled clinical studies.

Clinical Trial Registration: https://clinicaltrials.gov/study/NCT05205915?tab=results, identifier NCT05205915.

KEYWORDS

tDCS, MDD, tES (transcranial electrical current stimulation), telemedicine, home tDCS, multichannel tDCS, Starstim

1 Introduction

Major depressive disorder (MDD) is a pervasive and debilitating mental health condition that affects millions of individuals worldwide (1). The overall point prevalence of depressive disorders in Europe is estimated to be 6% and higher in women (8%) than in men (5%) (2), possibly due to differences in biopsychosocial, psychological, and environmental factors (3). The one-year and lifetime prevalence of depression has been estimated to be 10.4% and 20.6%, respectively (4). Furthermore, recent evidence indicates a rising incidence in youth (5), with MDD-afflicted adolescents up to thirty times more likely to commit suicide (6). MDD is characterized by a persistent first-person experience of sadness, hopelessness, lack of interest or pleasure in activities, and associated cognitive, behavioral, and autonomic dysfunction, with 30% of patients with treatment-resistant depression attempting suicide at least once in their lives. Beyond the devastating impact on personal well-being, MDD carries substantial economic costs, including healthcare expenses and reduced work productivity (7).

About 20–40% of patients do not benefit sufficiently from conventional antidepressant therapies, including trials of medication and psychotherapy (8). Pharmacological treatments have limited efficacy, side effects are common (9), and one-third of patients are medication-resistant (10) and experience recurrent depressive episodes (11). For patients with treatment-resistant MDD, several neuromodulation strategies offer potential relief, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) (12). While these treatments are safe and effective, they often come with significant costs, potential side effects, and the need for complex equipment and highly trained staff, making them less accessible in regions lacking specialized facilities. Moreover, device neuromodulation therapies require complex logistics, including daily ambulatory visits over several weeks for TMS or the need for a chaperone to transport patients to and from the ECT service thrice or twice a week, given the use of general anesthesia: these logistical requirements associated with clinic-based treatments continue to impose barriers for access to care with device neurotherapeutics. This accessibility issue is particularly problematic for elderly populations who face additional mobility restrictions and require assistance and support to access outpatient clinic services. Indeed, it is estimated that approximately 15% of the elderly (aged > 65) experience clinically significant depressive symptoms (13), which can lead to increased morbidity and early mortality (14). Additionally, older age significantly predicts a more challenging progression of depression (15), including a lower likelihood of treatment response (16, 17), reduced prospects for functional recovery (18) and increased risk of relapse (19). Developing safe and effective home-based neuromodulation therapies can help address access to care and scalability challenges (20).

In an earlier study (21), we investigated the feasibility of an innovative protocol where multichannel tDCS is administered at home for older adults with MDD, supported by a caregiver (N=5). This investigation employed a multichannel electric field-informed montage (22) and a remotely hosted training program to equip caregivers with the necessary knowledge and skills to administer tDCS at home, eliminating lab visits (21). Based on this preliminary work, we conducted the present home tDCS pilot study of subject and subject-administrator device utilization, remotely supervised and supported home-based tDCS for antidepressant treatment of adult patients aged 22 and older with MDD who had failed to get satisfactory improvement from at least one prior antidepressant medication in the current episode. This study includes several innovative elements, including advanced electric field-informed montage design methods and multichannel tDCS home technology.

1.1 tDCS

tDCS is a method for noninvasive brain stimulation based on decades-old observations that neuronal firing is modulated by low-amplitude electrical direct current (DC). When applied to the cerebral cortex, cathodal DC suppresses neuronal firing (23, 24), while anodal DC increases neuronal firing and leads to increased excitability in the targeted cortex. More precisely, our present understanding indicates that the electric field associated with tDCS currents by Ohm's law is responsible for the depolarization or hyperpolarization of the soma membrane of elongated neurons

(pyramidal cells) and possibly, others to a lesser extent (25, 26), depending on the direction of the field relative to the orientation of the cells (22, 27, 28): the electric field component normal (orthogonal) to the cortical surface will depolarize the soma of pyramidal neurons if it is pointing "inward" at that location (from apical dendrite to soma), and vice-versa. With multichannel tDCS, it is possible to choose the position, intensity, and polarity of the electrodes and currents to optimize stimulation at a chosen target map involving one or more regions (a cortical network). Low-intensity, controlled currents (typically ~1 mA and <4 mA) are applied through scalp electrodes in repeated 20-60 min sessions. The resulting subtle but persistent modulation of neuronal activity is believed to lead to plastic effects derived from Hebbian mechanisms. Notably, tDCS-generated electric fields can interact with functional brain networks (28), thus enabling the modulation of neurophysiological dynamics and brain connectivity related to mood disorders and MDD.

A recently emerging technology is model-optimized multichannel tDCS (22). This technology relies on using realistic physical models (derived from finite element models created from anatomical MRI) of current flow to estimate the electric field generated by a particular multichannel montage. New systems such as *Starstim* (*Neuroelectrics*) employ up to 32 electrodes with relatively small contact areas of a few square centimeters to precisely control the electric field delivered to the cortex. If a cortical stimulation scheme is prescribed by a clinician or derived from physiological brain models (28), this technology allows to configure electrode currents to target the desired area.

Hundreds of trials have demonstrated that when appropriate guidelines are followed, tDCS is easy to use, safe and extremely well tolerated (29) both in the clinic and in remotely supervised home tDCS (30, 31).

1.2 tDCS studies in MDD

There has been a large number of studies, including randomized, sham-controlled clinical trials (RCTs) on the effects of tDCS in MDD. Results have been variable and, in part, discrepant. For example, Brunoni et al. (32) found tDCS to have similar efficacy to antidepressant medications, while Loo et al. (33) found no efficacy of real tDCS over sham. Nonetheless, several meta-analyses have concluded that tDCS is effective for MDD (34, 35). Razza et al. (36) provided a systematic review of all studies of tDCS for the treatment of acute major depressive episodes completed up to January 2020. They included all randomized, sham-controlled RCTs enrolling participants with an acute depressive episode, a total of 23 RCTs with 1,092 participants. They found that active tDCS was superior to sham regarding endpoint depression scores, response, and remission rates. Moreover, active tDCS was safe with a side-effect profile comparable to sham. Moffa et al. (37) recently published an individual patient data (IPD) meta-analysis evaluating the efficacy and acceptability of tDCS for the treatment of acute major depressive episodes. Moffa (37) included data from all published placebo-controlled trials on tDCS as the only intervention in MDD conducted until December 2018. This included 9 eligible studies with a total of 572 participants. They found active tDCS to be significantly superior to sham for an antidepressant response (31% vs. 19% respectively; OR = 1.96), remission (20% vs. 12%, OR = 1.94), and depression improvement (effect size $\beta = 0.31$). Moreover, they found a consistent, continuous clinical improvement after the end of the tDCS treatment course. Notably, the clinical efficacy was substantially higher in the studies where the tDCS course was longer (3-4 weeks versus 1-2 weeks). Zhang et al. (38) conducted a comprehensive meta-analysis to evaluate the antidepressant efficacy of tDCS as a nonpharmacological treatment for depression. By reviewing randomized controlled trials up to December 30, 2020, the analysis included 27 studies with a total of 1204 patients, comparing 653 patients receiving active tDCS treatment to 551 receiving sham tDCS. The results indicated that active tDCS significantly improved depressive symptoms over sham treatments, with a moderate effect size ($g = 0.46$). Although active tDCS showed superiority in increasing response and remission rates, these differences were not statistically significant. Dropout rates between active and sham tDCS groups were similar, suggesting comparable tolerability. The findings suggest that tDCS, particularly with specific parameters such as a 2 mA stimulation current for 30-minute sessions and in patients not on antidepressants, holds promise as a treatment modality for depressive episodes.

The variability in the literature on the antidepressant effects of tDCS may reflect differences in patient selection as well as in the tDCS protocol. Longer courses of treatment seem particularly important to ensure sustained, lasting benefits. Consistent with the current understanding of mechanisms of action, tDCS antidepressant effects may involve long-term neuroplastic changes that take time to develop and may, in fact, continue to evolve and mature even after the tDCS treatment course has ended. This makes long treatment courses with maintenance phases important and home-based interventions appealing. Importantly, across all studies, active tDCS has been well tolerated, and there have been no significant adverse or side effects.

1.3 tDCS at home

As a relatively simple and portable technology, tDCS is particularly well suited for remotely supervised, home-based treatment. Several equipment manufacturers have developed systems for remotely supervised, home-based use, where the treatment is administered by the patient or an administrator. Treatment parameters, scheduling, and use can be monitored remotely by clinic or research staff. To date, this has been piloted for the treatment of a number of conditions, including neuropathic pain (39), auditory hallucinations in schizophrenia (40), attention-deficit/hyperactivity disorder (41), multiple sclerosis (42–45), Parkinson's disease (46, 47), trigeminal neuralgia (48), vascular dementia (49), Prader-Willi syndrome (50), and, recently, MDD (31, 51) with promising results.

Palm et al. (52) completed a systematic review of all available evidence on home use of tDCS until May 2017. They identified 22 original research papers, trial protocols, or trial registrations involving home-use tDCS. They showed that treatment adherence

was high and side effects minimal, and thus, they concluded that remotely controlled and supervised home-used tDCS was feasible and promising. The experience with home-use tDCS has continued to grow since then.

In the setting of depression, Clayton et al. (53) reported a case of one patient with comorbid multiple sclerosis and recurrent depressive episodes who received a course of remotely supervised tDCS following ECT treatment. Fatigue and mood ratings improved. More recently, Alonzo et al. (54) completed a proof-of-principle, open-label trial in 34 participants suffering from MDD who were taught to self-administer 20–28 tDCS sessions (2 mA, 30 min, F3-anode and F8-cathode montage according to 10–20 EEG placement) over 4 weeks followed by a taper phase of 4 sessions 1 week apart. Participants were initially monitored *via* video link for a few days and then through the completion of an online treatment diary. One participant withdrew from the study due to too many missed sessions. The remaining 33 participants completed 93% of the scheduled sessions in the initial 4-week phase. Ten of the thirteen participants who qualified for the maintenance phase opted to continue. Mood improved significantly from baseline (mean of 27.5 on MADRS) to 1 month after the end of acute treatment (MADRS 15.5; $p < 0.001$). Side effects reported across 1,149 sessions were minimal, primarily mild to moderate tingling or burning/heat sensation during stimulation and redness at the electrode sites.

Recently (21), we investigated the feasibility of a protocol similar to the one used in the present study, with multichannel tDCS administered within the homes of older adults with MDD with the help of a study companion (i.e., caregiver). The study, designed by us during the COVID crisis, explored the feasibility of a remotely-hosted training program to avoid visiting the lab. We employed a newly developed multi-channel tDCS system and protocol with real-time monitoring designed to guarantee the safety and efficacy of home-based tDCS. We found that the home-based, remotely-supervised, study companion administered, multi-channel tDCS protocol for older adults with MDD was feasible and safe, paving the way for the design of the larger study described here.

In the study by Charvet (51), home tDCS was evaluated as a novel therapeutic approach for MDD through an observational clinical trial. This trial involved 16 participants with moderate-to-severe major depressive episodes who underwent 28 sessions of left anodal DLPFC using a bipolar tDCS montage (using 25 cm^2 sponges on F3/F4) over six weeks, followed by a tapering phase of weekly sessions for an additional four weeks. There were no serious or treatment-limiting adverse events caused by the tDCS intervention, and no participant experienced an increase in depression or suicidality that warranted treatment discontinuation or additional intervention. The findings revealed a significant reduction in depressive symptoms as early as week 2, with continuous improvement noted at each subsequent biweekly assessment. By the end of the acute intervention, responder and remission rates were 75% and 63%, respectively, which increased to 88% and 81% following the tapering period.

In a recent study by Woodham (31), tDCS (using large rubber electrodes with sponges (23 cm^2) with anode over F3 and cathode over F4 in the 10/20 EEG system) was evaluated as a home-based treatment for MDD in a fully remote, multisite, double-blind, placebo-controlled, randomized superiority trial conducted in the UK and USA. The study's protocol included a 10-week blinded phase, consisting of five tDCS sessions per week for the first three weeks, followed by three sessions per week for the subsequent seven weeks. This was followed by a 10-week open-label phase. The tDCS treatment featured 30-minute sessions, where active tDCS was administered at 2 mA and sham tDCS at 0 mA, both with brief ramping up and down phases. A total of 174 participants with MDD were randomized into either the active treatment group (n=87; mean age 37.1 ± 11.1 years) or the sham treatment group (n=87; mean age 38.3 ± 10.9 years). The results revealed a significant improvement in the HDRS scores in the active treatment group, with a mean reduction of 9.4 ± 6.25 points, compared to a mean reduction of 7.1 ± 6.10 points in the sham treatment group (95% CI 0.5 to 4.0, $p = 0.012$). Concerning MADRS ratings, the active tDCS treatment arm significantly improved from baseline to week 10, with a mean improvement of 11.3 ± 8.81 relative to the sham treatment of 7.7 ± 8.47 ($p= 0.006$). The effects were evident at week 10, supporting a recent individual patient data analysis, which found that tDCS effect sizes continue to increase up to 10 weeks compared to sham stimulation (55). Safety was monitored using real-time assessments through video conference and the availability of a dedicated study number with 24-hour access to researchers. There were no significant differences in the rates of discontinuation between the active (n=13) and sham (n=12) groups. There were no serious adverse events related to the device and no incidents of serious suicide risk.

The purpose of the present study was to explore the safety and technical feasibility of a long-duration intervention employing a specifically designed multichannel montage (i.e., electrode locations, current intensity) with the *Starstim* at-home tDCS device in subjects diagnosed with MDD. This pilot aimed at obtaining preliminary data in advance of a larger clinical trial designed to test whether repeated, daily sessions during two months of at-home advanced tDCS can lead to a robust, clinically significant improvement in MDD patients. Our hypothesis was that using a more complex but well-designed tDCS montage, together with an increased dose and number of sessions, can lead to higher efficacy and that, despite its increased complexity, this technology is feasible for home use. Finally, our goal was also to explore the duration of effects one month after the end of treatment.

2 Methods

2.1 Participants

Inclusion criteria for this prospective, single cohort, multicenter clinical investigation included a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as determined *via* a telehealth interview with a study site psychiatrist or study staff physician with experience in the management of MDD, 22 years or older as of the date of study enrolment, experiencing a major depressive episode of at least four weeks

duration, and a MADRS score ≥20 at the time of study enrolment without a pre-specified upper or lower limit of failed antidepressant medications in the current episode or lifetime. Participants also had to be taking at least one medication approved by the FDA for the treatment of depression (except bupropion, which can lower the seizure threshold) whose dose had remained unchanged for four weeks before study enrolment. In addition, participants had to identify and designate one or more adults (persons aged 22 or older) as 'Administrator/s.' These individuals had to be willing, able, and formally agree to administer the home-based tDCS, be accessible to the study staff, reporting any safety concerns, potential protocol violations, and any other study-related matters. Subjects also needed access to a wireless internet (Wi-Fi) connection where the study treatments were administered. An accurate and current accounting of the study treatments for each subject was maintained on an ongoing basis by the device interface within the NE portal.

Exclusion criteria included any DSM-5-defined psychotic disorder in the three months preceding the date of study enrolment, active suicidal ideation assessed on C-SSRS (Columbia-Suicide Severity Rating Scale, history of clinically defined medically significant neurological disorder, skin lesions on the scalp at the proposed electrode sites, any cranial metal implants (excluding ≦1 mm thick epicranial titanium skull plates and dental fillings) or medical devices (i.e., cardiac pacemaker, deep brain stimulator, medication infusion pump, cochlear implant, vagus nerve stimulator), previous surgeries opening the skull leaving skull defects capable of allowing the insertion of a cylinder with a radius greater or equal to 5 mm. Participants on antidepressant medications (except bupropion) were allowed to enter the trial provided that the medication dose remained unchanged for four weeks prior to enrolment in the trial and there was no planned dose change for the duration of the trial.

The study (NCT05205915, clinicaltrials.gov) was approved by the WCG-IRB (Western Institutional Review Board-Copernicus Group), and written informed consent was obtained from each participant before the start of study-specific procedures. Because of the nature of this study, consent was obtained electronically online. Information was provided both verbally and in writing, and subjects (or their legal representatives) had ample opportunity to inquire about the details of the study. The study was conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Safety reporting in clinical investigations of medical devices under Regulation (EU) 2017/745, Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 812), and Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice (ISO 14155:2020). The clinical investigation was approved by the FDA (protocol number: NE-02, version 5 dated January 22nd, 2022 (FDA approval letter RE: G160208/S010 dated March 3, 2022) and WCG- IRB on January 31st, 2022).

Results from other home studies suggested that approximately 30 subjects were appropriate to establish preliminary evidence of the safety, tolerability, and feasibility of home administration. Concerning the exploration of efficacy, robust intervention effects (follow-up vs. baseline) were observed with this sample size in a similar open-label study (54). Formal sample size calculation in this open-label study was not applicable. Participants were recruited from five centers in the United States (three in Florida, one in Oklahoma, and one in Georgia, v. NCT05205915, clinicaltrials.gov, for more information).

2.2 Protocol

This study was conducted on a "virtual" basis with patients recruited at four U.S.-based sites selected for their specialized expertise and infrastructure dedicated to the efficient management and execution of clinical trials. All visits were remote. The treatment course (see Figure 1) consisted of an acute phase of 28 tDCS sessions conducted daily (7 days per week) over four weeks, consistent with the protocol of Alonzo et al. (54) and our prior study (21). This was motivated by the results of Brunoni et al. (34) and the meta-analysis of Moffa et al. (37), which found a positive association between increased tDCS 'dose' and treatment efficacy. After that, participants underwent a taper phase of an additional 9 sessions of tDCS applied in progressively decreasing frequency until day #60 of the study as follows: (i) Three tDCS sessions once every other day, (ii) three tDCS sessions once every third day, (iii) three tDCS sessions once every fourth day. An incomplete session was defined as one that discontinued stimulation before 100% completion and could be repeated within 24 hours if less than 75% of the session was delivered to the subject. A missed session

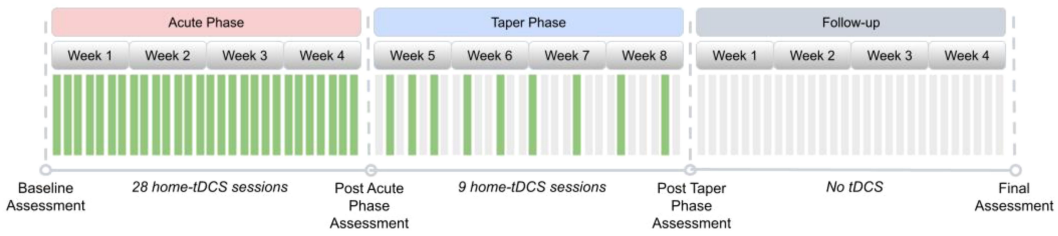

FIGURE 1
Study design. The design included an Acute Phase with 28 home tDCS sessions followed by a Taper Phase during four weeks. Assessments were all remote. Green bars indicate days with a stimulation session, and grey bars indicate days without a stimulation session. Assessments occurred at four time points – baseline, post-acute treatment, post-taper, and at follow-up four weeks after the end of treatment.

(0% stimulation delivered) was defined as an anticipated session that did not occur within 24 hours of the assigned date/time. The Montgomery-Asberg Depression Rating Scale (MADRS) (56) was completed at baseline, approximately at days #28 (end of acute phase) and #56 (end of taper phase) of treatment, and at the end of the 4-week follow-up period.

2.3 Multichannel tDCS montage

Stimulation was applied using the *Starstim* device, with current delivered *via* four *NG Pi* electrodes (circular Ag/AgCl electrodes using gel with a contact area of 3.14 cm^2) embedded in a neoprene cap. All study subjects used the same fixed montage (electrode locations and currents). The left dorsolateral prefrontal cortex (L-DLPFC) has been consistently related to depression symptomatology (57, 58). Specifically, the L-DLPFC is hypoactive in depression, and an increase in activity is associated with antidepressant response. The stimulation target for this study is shown in Figure 2. This target region was selected because it encompasses many clinically validated transcranial magnetic stimulation (TMS) targets for refractory MDD, including those proposed by Fox (59), Mir-Moghtdaei (61), Herbsman (62), Rusjan (63), and Fitzgerald (64). Consequently, we designed the multichannel tDCS montage with the maximal normal (orthogonal to the cortex) component of the electrical field targeting the L-DLPFC (excitatory, with the component pointing from CSF into gray matter) with minimal off-target stimulation and for administration *via* four *NG Pistim* electrodes (3.14 cm^2 Ag/AgCl gel electrodes) using the *Starstim*®*-Home* system (see Figure 3 for montage design and the *Starstim Home* system).

To design a unique (non-personalized) montage appropriate for use across our study subjects, we used the *Stimweaver*® algorithm (22) with *Group Optimization* (GO, 65). The original *Stimweaver*® algorithm explores the space of electrode locations and currents to match the produced electric field with the desired weighted target map, minimizing an Objective Function (OF) that reflects the error of the match for a particular subject. In GO, the objective function is defined as the average OFs of many subjects from an anatomically representative MRI dataset, as shown in Figure 2. In this particular

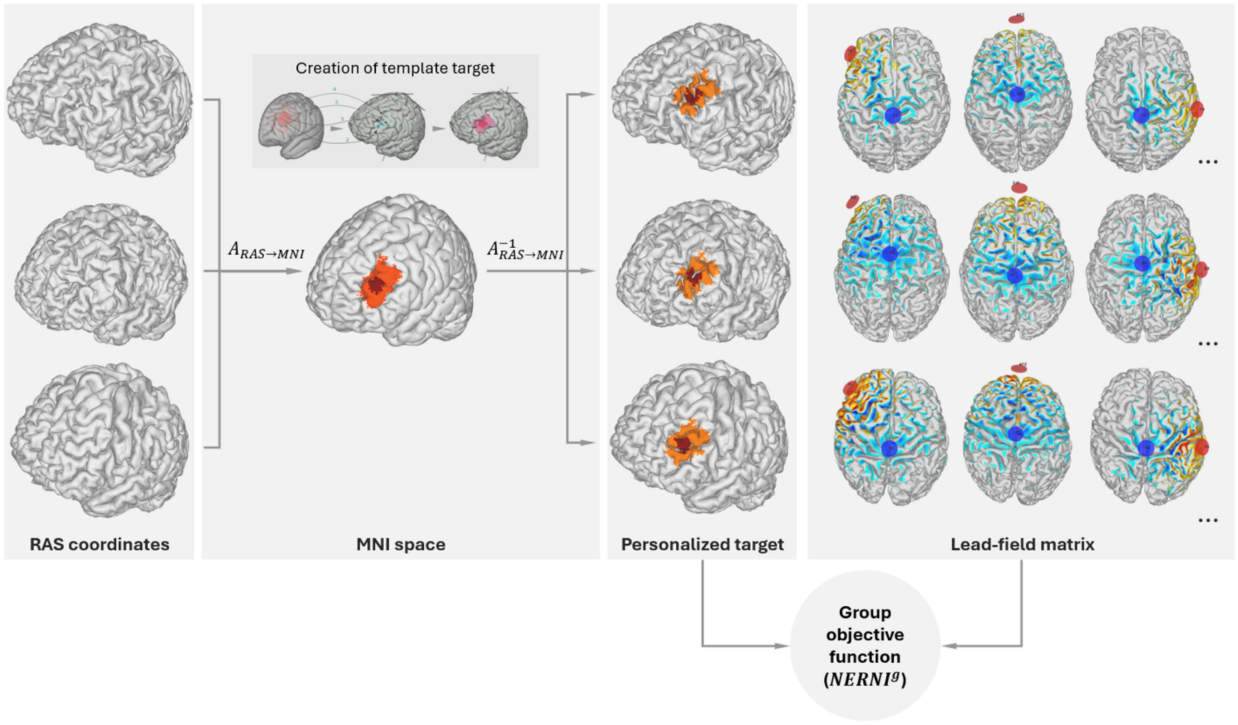

FIGURE 2
Target definition and mapping to the individualized brain model of each subject in the Group Optimization database. The central inset ("Creation of template target") in the MNI space column provides a view of the target specification process. The target consists of a central region (dark red) surrounded by a buffer region of lower weights (in orange). The red rectangle represents the left DLPFC derived from evidence-based TMS targets for depression (59) in combination with the Beam F3 method (60). The MNI coordinates [*x,y,z*] of the TMS hotspots (1: [−40.6, 41.7, 34.3; −41.5, 41.1, 33.4], 2: [39.3, 46.2 27.5; −41.3, 48.9, 27.7], 3:[−50, 30,36], 4: [−33.6, 30.8, 51.11]) were remapped on the cortex of a default brain model. To obtain the target map in the model, we drew an inner hotspot area encompassing all the mapped points and surrounded it by a buffer area. Group Objective function creation: An individualized transformation is derived by mapping the brain model of each subject from RAS (Right, Anterior, Superior) coordinates into MNI (Montreal Neurological Institute) space. The target map in MNI space is then projected into the brain of each of the database subjects using the inverse transformation (from MNI to RAS coordinates), as described in the main text. The group-objective function ($NERNI^g$, a normalized version of the *ERNI* described in 22) takes as inputs a weighted target map for each of the subjects. The calculation of the objective function also requires the *Lead-field matrix*, which is assembled by calculating all possible bipolar calculations with *Cz* as a common cathode (-1 mA) and the other electrode as an anode (+1 mA), as discussed in 22 (right panel).

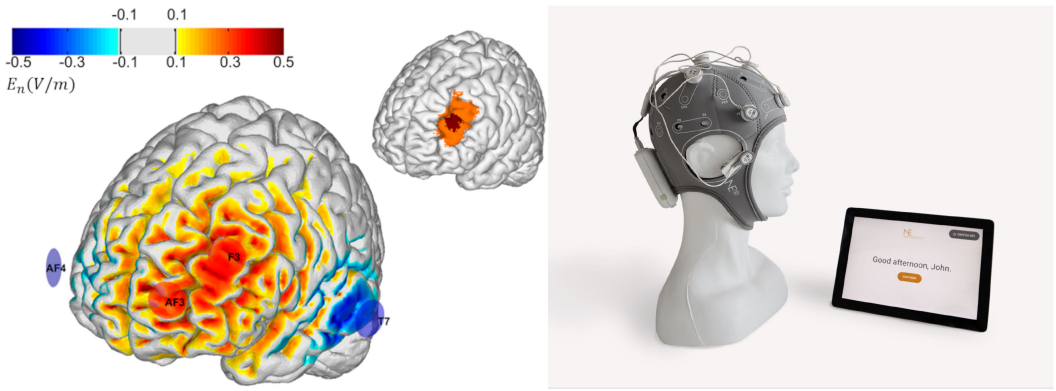

FIGURE 3
Left: Montage design produced by group optimization. The selected group optimized montage consisted of 4 electrodes: two anodes located over the target (AF3 and F3) and cathodes located further away (T7 and AF4). The color scale represents *En*, the normal component (normal to the cortical surface with red/blue denoting inward/outward E-field normal component) of the E-field induced by the optimized montage in the cortical surface (in V/m). Right: Starstim Home system (including tablet).

case, we performed a group optimization over 27 healthy subjects with an age range between 18 and 93 (55±25 years old). The computation of the group OF requires the calculation of the lead-field matrix (see Figure 2) for each subject, calculated from personalized biophysical head models created by using the methods summarized in Mercadal et al. (66). A target map with the weighted target En (the component of the E-field normal to the cortical surface) is also required for each subject. The target map used in this study (left DLPFC) was first defined in the cortical surface of a reference head model in MNI space (Colin27 brain template). This was done by specifying MNI coordinates of regions previously defined using several criteria (also described in 21) (see Figure 2) from areas identified by neuronavigated TMS, areas activated by working memory tasks identified by fMRI, and areas associated with the subgenual cortex based on rs-fMRI data. These MNI coordinates were clustered into a core area, assigned to higher weights in the optimization algorithm, and surrounded by a buffer area with lower weights. This is shown in Figure 2 (inset box: *Creation of template target*). This target was then mapped to the cortical surface of each of the subjects used in the group optimization, as displayed in Figure 2: each cortical surface was mapped to MNI space using an individualized affine transformation calculated by Freesurfer (v6.0.0, https://surfer.nmr.mgh.harvard.edu/); then, in MNI space, the coordinates of the nodes of the target area defined in the template brain were assigned to the closest node in the personalized cortical surface. The desired En-field in the target region was set to 0.75 V/m (with weights set to 8 for the buffer region and 10 for the core area). The rest of the cortical surface was assigned a 0 V/m target En with a lower weight of 2. The montage was constrained to a maximum of four stimulation electrodes for ease of use by participants at home. The currents were limited to 1.7 mA max per electrode (in absolute value) and 4.0 mA for the total injected current (here defined as the sum of current in all the anodes), well below the recommended safety limits (29). The total injected current in the group-optimized montage was 3.1 mA. The electrode positions found were AF3 and F3 (anodes) as well as T7 and AF4 (cathodes), according to the 10-20 EEG system (Figure 3). The average normal En-field on the target produced by this montage ranged from 0.07 V/m to 0.26 V/m (0.13±0.04 V/m), where positive numbers indicate the field direction pointing into the cortex (with excitatory effects according to the first order model of membrane perturbation of pyramidal cells, 22). In the rest of the non-involved cortex, field amplitude remained low: -0.002±0.001 V/m. For all participants, the current intensity was ramped up over 30 s, then sustained at the stimulation intensity for 30 min, and then ramped down over 30 seconds.

2.4 Home tDCS system

This study used the *Starstim Home Kit* (Neuroelectrics, see Figure 3). Neuroelectrics developed this system for home-based tDCS, effectively overcoming previous challenges with other forms of tDCS and used in several studies, e.g., 39 (NCT02346396). The *Starstim Home Kit* uses Neuroelectrics' *Starstim* system with additional features that allow researchers and clinicians to "prescribe" and monitor home-based tDCS to end users. The users could communicate in real time with remote study staff *via* video-conferencing during device training and during the first three use sessions. The *Starstim* system includes an EEG-like neoprene headcap with holes located where small electrodes can be attached and secured in place in the correct position on the scalp. These electrode holes are color- and number-coded so that electrode leads with corresponding colors in the tDCS device are appropriately attached to the corresponding electrodes, eliminating the potential for accidental mismatching of the electrodes and the leads. The *Starstim*®*-Home Kit* further incorporates a smart tablet wirelessly connected to the internet.

In more detail, the system includes 1) *Necbox*, the portable wireless tDCS device that applies brain stimulation; 2) Neoprene headcap: electrode positioner on which the relevant electrode

positions are marked on the headcap with different colors; 3) Color-coded electrode cables: marked with the same colors as the headcap and with numbers visible on the software interface; 4) *Pistim* (3.14 cm^2) Ag/AgCl electrodes; 5) Tablet with *HomeApp*: a user interface that guides patients throughout the session and ensures correct delivery of the treatment. 6) Neuroelectrics Portal: a web interface that allows investigators to schedule treatment sessions and monitor compliance in real time.

The tablet allowed the study companions and patient participants to initiate the tDCS sessions, receive specific step-by-step instructions needed to complete the tDCS administration process, and record any side effects *via* custom-developed questionnaires on the tablet. The table provides simplified instructions and step-by-step touchscreen prompts for the participant. This process has been designed for ease of use, even for individuals who are not computer savvy. The tablet automatically runs an impedance check before and during the delivery of the tDCS current and blocks the stimulation if the electrode impedance reaches above 20 kΩ. Moreover, the tablet has a manual abort function that allows the participant to stop the stimulation if they are experiencing any discomfort or pain. The research staff are notified if this occurs and reach out to the participant to resolve the situation. The tablet further interfaces with another component of the Starstim®-Home Kit called the Neuroelectrics Portal, which the research staff can use to schedule a specific time slot when the execution of the tDCS sessions is allowed. If the stimulation is attempted outside of this time slot, the tablet will inform the participant that the stimulation is currently unavailable and indicate when the next time slot is scheduled. The tablet further allows the study staff to remotely monitor patient participant progression through each session, side effects, and treatment compliance. This portal also ensures that all the stimulation parameters, including stimulation intensity, stimulation duration, and number of sessions, are pre-configured into the system and cannot be adjusted by study companions or patient participants.

Finally, following earlier work described in Cappon et al. (67), we developed a training and supervision program to accompany the Starstim Home Kit. Study staff members used these training materials to train subjects and administrators on the proposed use of the device. Study staff members monitored treatment sessions until the subject-administrator pairs demonstrated proficiency in all treatment-related procedures, typically through the first three sessions. At the end of each treatment period, the study staff continued to stay in touch with the subject-administrator pairs and inquire about their use of treatment sessions.

2.5 Clinical measures

The main purpose of this study was to obtain preliminary data in advance of a larger clinical trial designed to test whether repeated, daily sessions of at-home transcranial direct current stimulation (tDCS) are feasible and safe and explore if this approach can lead to a clinically significant improvement in patients with MDD.

The Neuroelectrics cloud portal provided information related to electrode impedance, tDCS progress, and tDCS session interruption or termination, whether voluntary or due to a technical issue. These metrics were used to assess feasibility (number of interrupted sessions, missed sessions). Adverse Event collection and concomitant medication evaluation occurred at the start of the acute treatment, start of the taper phase, end of treatment and end of the study, and any Serious Adverse Experiences were evaluated as the primary safety endpoint (SAEs, adverse events occurring at any dose that results in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent, permanent or significant disability/incapacity, required intervention to prevent permanent impairment or damage, a congenital anomaly/birth defect, or other important medical events that may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the study subject or require intervention to prevent one of the outcomes listed).

An exploratory aim of the study was to assess the therapeutic antidepressant efficacy of our protocol. The primary efficacy measure for this study was the median percentage change from baseline to the end of the 4-week post-treatment period in the observer-rated Montgomery-Asberg Depression Mood Rating Scale (MADRS, 56). The secondary outcome measures were: a) Response rate, where "clinically significant" response was defined as ≥ 50% improvement in MADRS score from baseline to the 4-week follow-up, b) Median percentage change in MADRS score from baseline to the end of week 4 of treatment (acute treatment), to the end of week 8 of treatment (taper phase), c) Change from baseline in the participant-rated Quick Inventory of Depressive Symptomatology (QIDS-SR) (68) administered at the same time points as the MADRS, d) Change from baseline in the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) (69), administered at the same time points as the MADRS. Finally, a Safety secondary endpoint was the Change from baseline C-SSRS responses ideation and attempt at any time during acute treatment. C-SSRS evaluation was carried out at contacts between the investigator and subject daily during the first 4 weeks of daily stimulation sessions (unless the subject discontinued the protocol during that time).

2.6 Statistical analysis

This open-label pilot feasibility telemedicine study involved a total of 37 at-home stimulation sessions (30 minutes each) of multichannel excitatory tDCS targeting the L-DLPFC administered over eight weeks, with a follow-up period of 4 weeks following the final stimulation session.

No inferential statistical analysis was planned. The following populations of descriptive analysis were used: a) Safety population (SAF): all participants who have undergone transcranial direct current stimulation at least once (including incomplete stimulation sessions); b) Intention-to-treat (ITT): all participants who have signed the Informed Consent form; c) Per protocol (PP): all participants who have completed at least 75% of the 37 tDCS

sessions, have had the final MADRS score recorded and have no major protocol deviations.

For the primary efficacy analysis, the efficacy measure was the median percentage change (MPC) from baseline to the end of the 4-week post-treatment period in the observer-rated MADRS scores. A descriptive analysis of the MADRS at each visit, baseline, week 4, week 8, and at the 4-week post-treatment visit, is also presented. This analysis was performed for both the ITT and the PP sets.

3 Results

3.1 Participants

The total valid sample included 35 patients. Figure 4 provides a flowchart of patients recruited and the number and reasons for the exclusion of each population during the study.

At baseline, the study ITT population participants (n=34) were aged between 24 and 78 years, with a mean (standard deviation) of 58.9 (12.9) years. They were primarily female (85.3%). Twenty-one participants (61.8%) were of Hispanic or Latino ethnicity. The mean (standard deviation) time since MDD diagnosis was 24.2 (19.1) months. Additional demographic and education characteristics at baseline for the ITT population are summarized in Table 1.

Regarding concomitant psychiatric medications, more than one-third of the patients (12, or 35.3%) were on Sertraline, six (17.6%) were on Citalopram. Three patients (8.8%) were on Duloxetine, three (8.8%) on Memantine, 3 (8.8%) on Quetiapine, and three (8.8%) on Trazodone.

3.2 Safety and adverse event monitoring

Concerning safety, no detrimental effects were observed for the patients. Noteworthy, as measured with the C-SSRS, no participants had suicidal ideation and/or behavior, whether at baseline during treatment or at four weeks post-treatment.

Protocol deviations were evaluated for any trends or patterns that would require additional corrective actions or submissions. All of them were minor, and none resulted in an adverse event or required patient discontinuation from the study. Only 5 (15%) patients experienced adverse events during the study. None of them were reported as serious. Two unexpected adverse events were reported in one patient (3%), and eight adverse device events were reported in four patients (12%). Likewise, no serious adverse device events were reported.

3.3 Feasibility and compliance

85% of the patients (n=29) in the ITT group (n=34) completed all 37 stimulation sessions at home during the acute and taper phases, and 97% (n=33) completed at least 36 sessions (one subject was excluded, see Figure 4).

3.4 Efficacy

The mean (SD) difference between the final visit and baseline for the MADRS score was -19.8 (8.6) for both ITT and the PP population datasets. The primary endpoint (median percentage change in the MADRS score) was 64.5% (48.6%, 72.4%) in both populations.

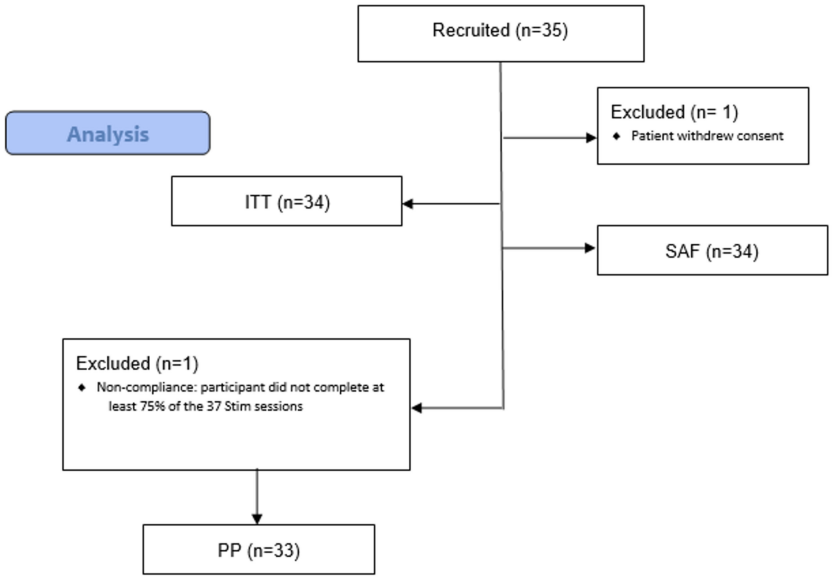

FIGURE 4
CONSORT flow diagram.

TABLE 1 Baseline demographic data (ITT).

	ITT population (n=34)
Variable	
Age, mean (SD), y	58.9 (12.9)
Sex at birth	
Female, n (%)	29 (85.3%)
Male, n (%)	5 (14.7%)
Ethnicity	
Hispanic or Latino, n (%)	21 (61.8%)
Not Hispanic or Latino, n (%)	13 (38.2%)
Race	
American Indian or Alaska native, n (%)	1 (2.9%)
Black or African American, n (%)	3 (8.8%)
White, n (%)	30 (88.2%)
Head Circumference, mean (SD), (cm)	56.0 (1.6)
Education level	
High School Diploma or GED, n (%)	17 (50.0%)
Bachelor's Degree, n (%)	8 (23.5%)
Some college, no degree, n (%)	5 (14.7%)
Did not graduate High School or obtain a GED, n (%)	2 (5.9%)
Academic Associate Degree, n (%)	1 (2.9%)
Master's Degree, n (%)	1 (2.9%)

In assessing the effect size between baseline and week 12 conditions, the pooled standard deviation of MADRS scores was calculated to be approximately 5.8. Cohen's *d* was 3.1, suggesting a large and statistically significant difference between the group means (to account for the small sample size bias, Hedges' *g* was also computed, resulting in a value of approximately 3.1). On the other hand, Cohen's d_z was 2.0. These statistics reflect the pronounced difference between the baseline and final-visit conditions under study.

The response rate analysis showed that in 73% of patients (n=24), an improvement ≥ 50% was observed in the MADRS score from baseline to the last visit (4 weeks post-treatment, see Figure 5). Finally, improvement was observed from baseline to the end of the study (4 weeks post-treatment) for the QIDS-SR and the Q-LES-Q-SF scores. The mean (SD) and the median (IQR) difference between the final visit and baseline for the Q-LES-Q-SF score were 27.9 (13.8) and 26.8 (17.9, 35.7), respectively.

4 Discussion

This exploratory study has demonstrated the feasibility, safety, and potential efficacy of a multichannel home-based, remotely-supervised tDCS intervention with the *Starstim* device in persons with MDD and generated valuable data for planning the next step, i.e., a randomized, sham-controlled, more extensive clinical trial. A single-arm prospective multicenter study with 35 MDD patients was carried out. The population who completed all study visits consisted of 34 patients (85% women and 15% men) with a mean age of 60 years and a MADRS score ≥20 at the time of study enrolment. One patient did not complete at least 75% of all the stimulation sessions. The sample was a representative subset of the MDD population and reflects some of the characteristics of a larger group that could benefit from home-based tDCS.

Regarding primary feasibility objectives, for feasibility, 85% of the subjects completed all the programmed home stimulation sessions throughout the acute and taper phases, and 97% (n=33) completed at least 36 (out of 37) sessions. These positive results confirm the feasibility of the *Starstim* home device and provide crucial information that should be considered for further pivotal studies.

Concerning safety, no detrimental effects were observed for the patients, and all adverse events were minor (see Table 2). Noteworthy, as measured with the C-SSRS, no participants had suicidal ideation and/or behavior, whether at baseline during treatment or at four weeks post-treatment.

The treatment effects were evident at the end of the acute and taper phases and robust four weeks after treatment. The median percentage reduction of the MADRS score was 64.5% (48.6, 72.4), and the mean (SD) difference between the final visit and baseline for the MADRS score was -19.8 (8.6) for both the ITT and the PP population datasets. These results are comparable or superior to those in earlier studies (70), as well as the results in Woodham (31), where the active tDCS treatment arm showed a significant improvement from baseline to week 10, with a change of the MADRS mean score of -11.3 ± 8.8 relative to sham treatment (-7.7 ± 8.5). The results in this study are similar to those in the active arm in the recent placebo-controlled study by Salehinejad et al. (71). They contrast with earlier recent studies that failed to show efficacy with respect to sham (72, 73). An important difference in our study is the dose and the use of a specifically designed multichannel montage to target the region of interest (these other studies use a standard bifrontal montage with two large sponge electrodes).

Likewise, concerning secondary objectives, in more than 70% of patients (n=24), an improvement of ≥ 50% was observed in the MADRS score from baseline to the last visit (4 weeks post-treatment). The calculated response rate (RR) was 73%. The remission rate in the PP group, evaluated as the percent of participants with a MADRS score equal to or below 10 at the end of acute treatment, taper phase, and four-week follow-up time points, were 30%, 30%, and 52%, respectively. Along the same lines, improvement was observed from baseline to the end of the study (4 weeks post-treatment) for the QIDS-SR and the Q-LES-Q-SF scores. The mean (SD) and the median (IQR) difference between the final visit and baseline for the Q-LES-Q-SF score were 27.9 (13.8) and 26.8 (17.9, 35.7), respectively.

Protocol deviations were evaluated for any trends or patterns requiring additional corrective actions or submissions. All of them were minor, and none resulted in an adverse event or required patient discontinuation from the study.

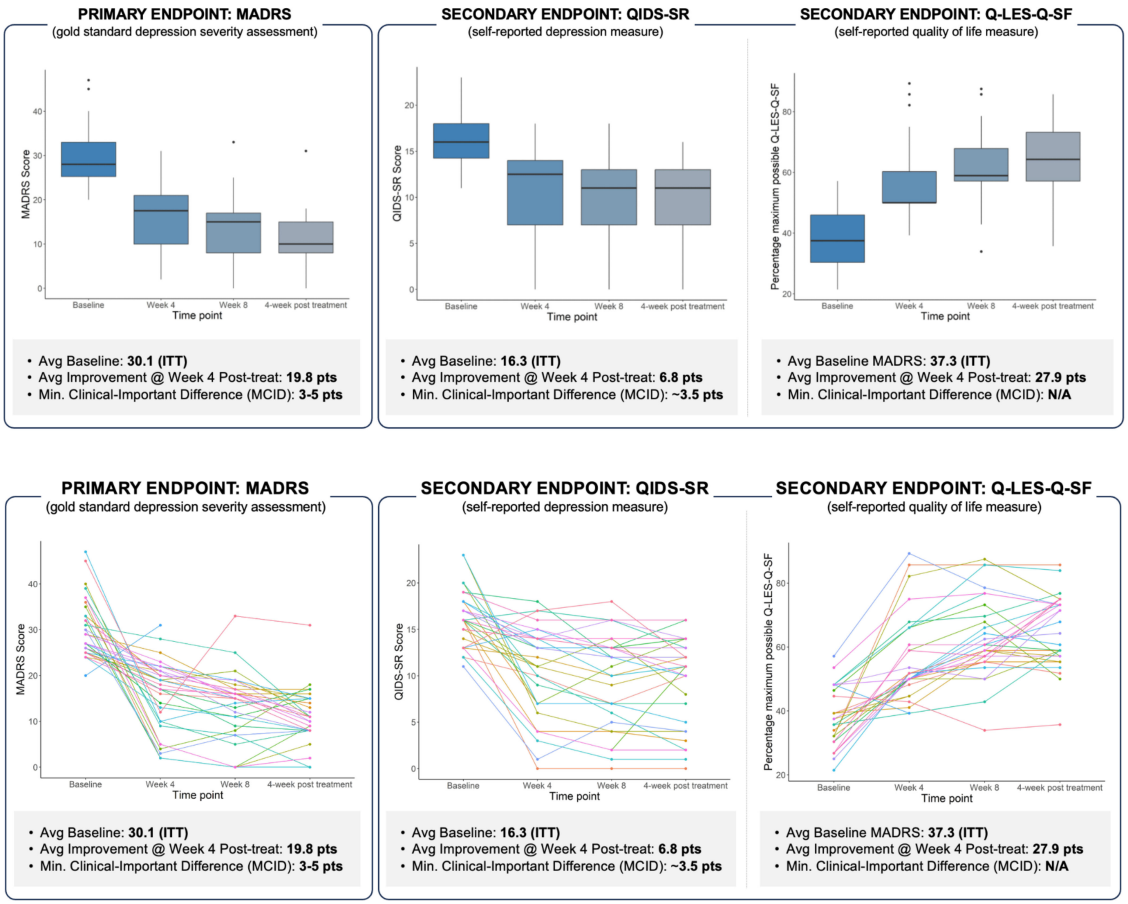

FIGURE 5
Exploratory aims: comprehensive depiction of treatment response over time in patients with Major Depressive Disorder (MDD). Top panel: Boxplots illustrating the distribution of scores (with outliers) at baseline and at weeks 4, 8, and 12. MADRS mean/median scores (STD) at baseline, weeks 4, 8, and 12 post-randomization were 29.8/27 (6.2), 16.7/19 (6.5), 14.4/15 (6.6), and 11.8/11 (5.3). Bottom panel: Longitudinal trajectories of individual patient scores, indicating varied response patterns over the treatment course. The data collectively underscore the heterogeneity in treatment response and the progressive nature of symptom reduction over time.

Considering the good performance of the home-based device plus the overall improvement in depression rating scales (MADRS), symptomatology, and satisfaction questionnaires, it can be said that the developed solution deployed using the Starstim home system was well-accepted and useful for the patients and that it presumably fulfills an unmet need. The Starstim portable multichannel technology proved relatively simple to use and exhibited outstanding performance with a good safety profile. Pending larger controlled trials, this study provides early substantial evidence that home-based, remotely supervised, and supported tDCS treatment with model-designed multichannel montages is feasible for depressed patients and offers a potentially effective intervention. The improved targeting and larger injected current (up to 4 mA) afforded by multichannel *Starstim Home* technology employing multiple electrodes, coupled with its ease of use for repeated, safe stimulation at home, has the potential to deliver more effective solutions. Therefore, this tool may play a significant and outstanding role in applying knowledge to improve the health and healthcare of MDD patients.

Some recent studies with tDCS have produced negative results. In Borrione et al. (73), a randomized clinical trial assessing the effectiveness of unsupervised home tDCS for major depression, no significant treatment benefits were observed. The study included 210 participants who were administered tDCS with or without a digital psychological intervention versus a sham control. The study protocol involved twenty-one sessions delivered at 2 mA for 30 minutes each day, five days a week for the first three weeks, followed by twice a week for the remaining three weeks. tDCS was administered using large sponge electrodes positioned over the F3 and F4 locations according to the international 10-20 EEG system, with a fixed distance of 10.5 cm from the midline. Participants ensured correct placement of the device with the help of an augmented-reality tool *via* a smartphone camera. Stimulation was halted if the impedance exceeded 9 kOhm, indicating displacement or removal of the device. For sham stimulation, the setup was identical, but the current was only active for the first and last 45 seconds of each session, peaking at 1 mA. Results indicated no substantial differences in depression severity changes among the

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TABLE 2 Summary of Mild Adverse Events. No Serious Adverse Experiences were reported, and all Adverse Events were Mild.

Mild Adverse Events				Relationship to the study device			
	N° pat. (%)	N° AE	Duration (days)*	Definitely	Probably	Possibly	Unrelated
Total (n=34)	5 (14.7%)	9	10.3 (20.4)	5	2	1	1
Skin and subcutaneous tissue disorders	3 (8.8%)	4	21.7 (33.2)	3	1		
Erythema	1 (2.9%)	1	4.0 (.)		1		
Paraesthesia	1 (2.9%)	2	1.0 (.)	2			
Skin burning sensation	1 (2.9%)	1	60.0 (.)	1			
Nervous system disorders	2 (5.9%)	2	1.5 (0.7)		1	1	
Headache	2 (5.9%)	2	1.5 (0.7)		1	1	
Infections and infestations	1 (2.9%)	1	11.0 (.)				1
Sinusitis	1 (2.9%)	1	11.0 (.)				1
Musculoskeletal and connective tissue disorders	1 (2.9%)	2	1.5 (0.7)	2			
Myalgia	1 (2.9%)	2	1.5 (0.7)	2			

groups. Notably, adverse effects such as skin redness and heat sensations were more prevalent in active tDCS groups. In a related study, Burkhardt et al. (72) carried out an in-clinic multicenter, triple-blind, randomized, sham-controlled study conducted across eight sites in Germany of the efficacy of tDCS as an adjunct to stable SSRI treatment in adults with MDD was evaluated. Participants aged 18 to 65 who met DSM-5 criteria for MDD and had been on a stable SSRI dose were randomly assigned to receive either active tDCS or sham stimulation. The treatment consisted of 30-minute, 2-mA bifrontal tDCS sessions for 20 consecutive weekdays, followed by two weekly sessions for an additional two weeks. No significant differences were observed in the mean improvement on MADRS after six weeks between the active tDCS and sham groups. The study concluded that tDCS, when used as an add-on treatment to SSRIs, does not demonstrate superiority over sham stimulation in improving depressive symptoms. Mild adverse events were more frequent with active tDCS. The main differences between these negative studies, others discussed above, and the study presented in this paper include target and montage design (large bifrontal sponge electrode vs. single target multichannel using small Ag/AgCl electrodes), current intensity (smaller total injected current) or a reduced number of sessions. All these factors are likely important in achieving clinical efficacy.

4.1 Limitations

Probably the most important shortcoming of this study is the absence of a sham treatment arm. As the effect-sizes to inert "placebo" treatments have gained prominence for psychiatric conditions, especially MDD, the importance of a control condition cannot be underscored enough. The purpose of this investigation, however, was to examine the feasibility of tDCS delivered entirely at home using the *Starstim* portable device with supervision provided remotely, and the study demonstrated that not only was it possible for users to self-administer the intervention but to also derive benefit with improvement in symptoms of major depression. The lack of a control group makes it difficult to argue potential time-dependent changes or to relate changes just to the investigational medical device intervention. However, in comparison with similar studies, the effect size results are very promising. The absence of a control arm also meant that the raters evaluating participants were not blind to the intervention. This was overcome by performing not just objective (MADRS) and subjective (QIDS-SR) assessments of depression severity but also participant reported changes on measures of wellbeing, like the Q-LES-Q-SF. It is also important to note that 21 (of 33 [or 34]) participants were on antidepressant medications and 30 (of 34) participants were on psychotropic medication. Hence, the improvement in MADRS (and other) scores was observed, at least in part, in persons who had been treated for major depression.

The study was conducted remotely and investigators did not assess whether participants had placed the Neuroelectrics Starstim Neoprene cap correctly. While it is possible that some study subjects might not applied the tDCS correctly on the DLPFC, there were a number of safeguards to such errors from happening. The electrode positions on the head-cap and electrode cables were color-coded, and the HomeKit ® tablet provided step-by-step instructions regarding setup, which were specially developed to be simple and easy even for those not familiar with computers. Above all, a web portal allowed study personnel to monitor and assist participants with sessions at any time, allowing proper treatment delivery.

However, this study is one of few of its kind in which a home intervention is being assessed for its impact on MDD well-being.

The incremental development of innovative/breakthrough health technologies takes a long time, during which innovation will have to successfully go through testing and evidence generation before it can be launched. As part of this process, early feasibility studies provide the opportunity to capture relevant additional information for the intended use from a real-world setting that would not be possible in non-clinical studies (i.e., bench testing and animal studies) at a very early stage.

Further studies are needed to assess the impact of a digital intervention on MDD, with a longer follow-up period, including a control group and a larger sample size. However, our proof of concept was planned to verify whether the *Starstim* portable technology was feasible and could achieve the desired outcome, and this has been convincingly shown in a real-world setting.

5 Conclusions

This pilot study aimed to demonstrate the feasibility of an innovative home-based, remotely supervised, study companion-led, modeling-designed multi-channel tDCS intervention for older adults suffering from MDD in an open-label manner, and available data demonstrates that this was accomplished successfully. The investigation also provided useful safety and preliminary efficacy data for the design of a larger, randomized, controlled at-home trial that will be essential for the broad adoption of tDCS for the treatment of MDD. Since a substantial proportion of patients with major depression show only partial or no improvement after treatment with antidepressants, the availability of additional treatment options would be key to improving the treatment response.

Data availability statement

The data is available upon reasonable request. Requests to access the datasets should be directed to giulio.ruffini@neuroelectrics.com.

Ethics statement

The studies involving humans were approved by the clinical investigation was approved by the FDA: Protocol number: NE-02, version 5 dated January 22nd, 2022 (FDA approval letter RE: G160208/S010 dated March 3, 2022) and WCG- IRB on January, 31st, 2022. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GR: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing, Formal Analysis. RS: Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. FC: Project administration, Visualization, Writing – original draft, Writing – review & editing. TB: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing. JC: Writing – review & editing. MC: Writing – review & editing. DC: Writing – review & editing. AP-L: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

TB, FC, and RS work for Neuroelectrics, a company dedicated to creating brain stimulation solutions. GR works for and is a co-founder of Neuroelectrics and holds several patents in model-driven non-invasive brain stimulation. AP-L is partly supported by grants from the National Institutes of Health R01AG076708, R01AG059089, R03AG072233, and P01 AG031720, and BrightFocus Foundation. AP-L serves as a paid member of the scientific advisory boards for Neuroelectrics, Magstim Inc., TetraNeuron, Skin2Neuron, MedRhythms, and Hearts Radiant. He is co-founder of TI solutions and co-founder and chief medical officer of Linus Health. AP-L is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging, and applications of noninvasive brain stimulation in various neurological disorders, as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia. JC is partly supported by grants from the Gerstner Foundation and the NIH R61 MH132869, R01 MH112737, R21 MH131878, R21 AG078692, is a member of the scientific advisory boards of Hyka and Flow Neuroscience, a consultant for Mifu Technologies, Neuroelectrics, and LivaNova, and an inventor of patents and patent applications on neuromodulation targeting methods held by Massachusetts General Hospital. DC was partly supported by the National Institutes of Health (R01AG076708), the NARSAD-Brain and Behavior Research Foundation (30772), and the Bright Focus Foundation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer PL declared a shared affiliation with the authors DC, AP-L, JC to the handling editor at the time of review.

Publisher's note

References

1. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. *Lancet*. (2012) 379:1045–55. doi: 10.1016/S0140-6736(11)60602-8

2. Arias de la Torre J, Vilagut G, Ronaldson A, Serrano-Blanco A, Martín V, Peters M, et al. Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. *Lancet Public Health*. (2021) 6:e729–38. doi: 10.1016/S2468-2667(21)00047-5

3. Kuehner C. Why is depression more common among women than among men? *Lancet Psychiatry*. (2017) 4:146–58. doi: 10.1016/S2215-0366(16)30263-2

4. Hasin DS, Sarvet AL, Meyers JL, Tulshi D, Saha W, June Ruan MA, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. (2018) 75:336–46. doi: 10.1001/jamapsychiatry.2017.4602

5. Liu CH, Zhang E, Wong GTF, Hyun S, Hahm HC. Factors associated with depression, anxiety, and PTSD symptomatology during the COVID-19 pandemic: Clinical implications for U.S. *young adult Ment Health Psychiatry Res*. (2020) 290:113172. doi: 10.1016/j.psychres.2020.113172

6. Stringaris A. Editorial: what is depression? *J Child Psychol Psychiatr*. (2017) 58:1287–9. doi: 10.1111/jcpp.12844

7. Adorjan K, Falkai P. Premature mortality, causes of death, and mental disorders. *Lancet*. (2019) 394:1784–6. doi: 10.1016/S0140-6736(19)32521-8

8. Greden JF. The burden of disease for treatment-resistant depression. *J Clin Psychiatry*. (2001) 62 Suppl 16:26–31.

9. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychother Psychosom*. (2016) 85:270–88. doi: 10.1159/000447034

10. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D Report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

11. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry*. (2007) 68 Suppl 8:17–25.

12. Hyde J, Carr H, Kelley N, Seneviratne R, Reed C, Parlatini V, et al. Efficacy of neurostimulation across mental disorders: systematic review and meta-analysis of 208 randomized controlled trials. *Mol Psychiatry*. (2022) 27:2709–19. doi: 10.1038/s41380-022-01524-8

13. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci*. (2003) 58:249–65. doi: 10.1093/gerona/58.3.M249

14. Schulz R, Drayer RA, Rollman BL. Depression as a risk factor for non-suicide mortality in the elderly. *Biol Psychiatry*. (2002) 52:205–25. doi: 10.1016/S0006-3223(02)01423-3

15. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry*. (2005) 162:1588–601. doi: 10.1176/appi.ajp.162.9.1588

16. Licht-Strunk E, van der Windt DA, van Marwijk HW, de Haan M, Beekman AT. The prognosis of depression in older patients in general practice and the community. A systematic review. *Fam Pract*. (2007) 24:168–80. doi: 10.1093/fampra/cml071

17. Tedeschini E, Levkovitz Y, Iovieno N, Ameral VE, Nelson JC, Papakostas GI. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *J Clin Psychiatry*. (2011) 72:1660–8. doi: 10.4088/JCP.10r06531

18. Little JT, Reynolds CF, Dew MA, Frank E, Begley AE, Miller MD, et al. How common is resistance to treatment in recurrent, nonpsychotic geriatric depression? *Am J Psychiatry*. (1998) 155(8):1035–8. doi: 10.1176/ajp.155.8.1035

19. Beekman AT, Geerlings SW, Deeg DJ, Smit JH, Schoevers RS, de Beurs E, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry*. (2002) 59:605–11. doi: 10.1001/archpsyc.59.7.605

20. Gersten M, Jamil A, Cassano P, Camprodon Joan A. Transcranial direct current stimulation (tDCS) for major depressive disorder. *Psychiatr Annals*. (2022) 52:451–5. doi: 10.3928/00485713-20221025-01

21. Cappon Davide dBT, Caleb J, Yu W, Lo A, Nicole L, Chiara BM, et al. Safety and feasibility of tele-supervised home-based transcranial direct current stimulation for major depressive disorder, frontiers in aging neuroscience. (2022) 13:. doi: 10.3389/fnagi.2021.765370

22. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. *Neuroimage*. (2014) 89:216–25. doi: 10.1016/j.neuroimage.2013.12.002

23. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical DC currents on cortical neuronal activity. *Exp Neurol*. (1962) 5:436–52. doi: 10.1016/0014-4886(62)90056-0

24. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. (2000) 527:633–9. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

25. Molaee-Ardekani B, Márquez-Ruiz J, Merlet I, Leal-Campanario R, Gruart A, Sánchez-Campusano R, et al. Effects of transcranial Direct Current Stimulation (tDCS) on cortical activity: a computational modeling study. *Brain Stimul*. (2013) 6:25–39. doi: 10.1016/j.brs.2011.12.006

26. Galan-Gadea A, Salvador R, Bartolomei F, Wendling F, Ruffini G. Spherical harmonics representation of the steady-state membrane potential shift induced by tDCS in realistic neuron models. *J Neural Eng*. (2023) 20. doi: 10.1088/1741-2552/acbabd

27. Ruffini G, Wendling F, Merlet I, Molaee-Ardekani B, Mekonnen A, Salvador R, et al. Transcranial current brain stimulation (tCS): models and technologies. *IEEE Trans Neural Syst Rehabil Eng*. (2013) 21:333–45. doi: 10.1109/TNSRE.7333

28. Ruffini G. Fabrice Wendling, Roser Sanchez-Todo, Emiliano Santarnecchi, Targeting brain networks with multichannel transcranial current stimulation (tCS). *Curr Opin Biomed Eng*. (2018) 8:70–7. doi: 10.1016/j.cobme.2018.11.001

29. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol*. (2017) 128(9):1774–809. doi: 10.1016/j.clinph.2017.06.001

30. Pilloni G, Vogel-Eyny A, Lustberg M, Best P, Malik M, Walton-Masters L, et al. Tolerability and feasibility of at-home remotely supervised transcranial direct current stimulation (RS-tDCS): Single-center evidence from 6,779 sessions. *Brain Stimul*. (2022) 15(3):707–16. doi: 10.1016/j.brs.2022.04.014

31. Woodham RD, Selvaraj S, Lajmi N, Hobday H, Sheehan G, Ghazi-Noori A-R, et al. Home-based transcranial direct current stimulation RCT in major depression. *medRxiv*. (2023) 11:27.23299059. doi: 10.1101/2023.11.27.23299059

32. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. *N Engl J Med*. (2017) 376:2523–33. doi: 10.1056/NEJMoa1612999

33. Loo CK, Husain MM, McDonald WM, Aaronson S, O'Reardon JP, Alonzo A, et al. International randomized-controlled trial of transcranial Direct Current Stimulation in depression. *Brain Stimul*. (2018) 11:125–33. doi: 10.1016/j.brs.2017.10.011

34. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br J Psychiatry*. (2016) 208:522–31. doi: 10.1192/bjp.bp.115.164715

35. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. *Neurosci Biobehav Rev*. (2018) 92:291–303. doi: 10.1016/j.neubiorev.2018.05.015

36. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. *Depress Anxiety*. (2020) 37(7):594–608. doi: 10.1002/da.23004

37. Moffa AH, Martin D, Alonzo A, Bennabi D, Blumberger DM, Benseñor IM, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. (2020) 99:109836. doi: 10.1016/j.pnpbp.2019.109836

38. Zhang R, Lam CLM, Peng X, Zhang D, Zhang C, Huang R, et al. Efficacy and acceptability of transcranial direct current stimulation for treating depression: A meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev*. (2021) 126:481–90. doi: 10.1016/j.neubiorev.2021.03.026

39. Garcia-Larrea L, Perchet C, Hagiwara K, André-Obadia N. At-home cortical stimulation for neuropathic pain: a feasibility study with initial clinical results. *Neurotherapeutics*. (2019) 16:1198–209. doi: 10.1007/s13311-019-00734-3

40. Andrade C. Once- to twice-daily, 3-year domiciliary maintenance transcranial direct current stimulation for severe, disabling, clozapine-refractory continuous auditory hallucinations in schizophrenia. *J ECT*. (2013) 29:239–42. doi: 10.1097/YCT.0b013e3182843866

41. Leffa DT, Grevet EH, Bau CHD, Schneider M, Ferrazza CP, da Silva RF, et al. Transcranial direct current stimulation vs sham for the treatment of inattention in adults with attention-deficit/hyperactivity disorder: the TUNED randomized clinical trial. *JAMA Psychiatry*. (2022) 79(9):847–56. doi: 10.1001/jamapsychiatry.2022.2055

42. Kasschau M, Sherman K, Haider L, Frontario A, Shaw M, Datta A, et al. A protocol for the use of remotely-supervised transcranial direct current stimulation (tDCS) in multiple sclerosis (MS). *J Vis Exp*. (2015) (106):e53542. doi: 10.3791/53542

43. Charvet LE, Dobbs B, Shaw MT, Bikson M, Datta A, Krupp LB. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. *Mult Scler J*. (2017) 24:1760–9. doi: 10.1177/1352458517732842

44. Charvet LE, Shaw MT, Dobbs B, Frontario A, Sherman K, Bikson M, et al. Remotely supervised transcranial direct current stimulation increases the benefit of at-home cognitive training in multiple sclerosis. *Neuromodulation*. (2018) 21:383–9. doi: 10.1111/ner.12583

45. Kasschau M, Reisner J, Sherman K, Bikson M, Datta A, Charvet L. Transcranial direct current stimulation is feasible for remotely supervised home delivery in multiple sclerosis. *Neuromodulation*. (2016) 19:824–31. doi: 10.1111/ner.12430

46. Agarwal S, Pawlak N, Cucca A, Sharma K, Dobbs B, Shaw M, et al. Remotely-supervised transcranial direct current stimulation paired with cognitive training in Parkinson's disease: an open-label study. *Clin Neurosci*. (2018) 57:51–7. doi: 10.1016/j.jocn.2018.08.037

47. Dobbs B, Pawlak N, Biagioni M, Agarwal S, Shaw M, Pilloni G, et al. Generalizing remotely supervised transcranial direct current stimulation (tDCS): feasibility and benefit in Parkinson's disease. *J Neuroeng Rehabil*. (2018) 15:114. doi: 10.1186/s12984-018-0457-9

48. Hagenacker T, Bude V, Naegel S, Holle D, Katsarava Z, Diener HC, et al. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. *J Headache Pain*. (2014) 15:78. doi: 10.1186/1129-2377-15-78

49. André S, Heinrich S, Kayser F, Menzler K, Kesselring J, Khader PH, et al. At-home tDCS of the left dorsolateral prefrontal cortex improves visual short-term memory in mild vascular dementia. *J Neurol Sci*. (2016) 369:185–90. doi: 10.1016/j.jns.2016.07.065

50. Azevedo C, Gomes JS, Trevizol AP, Dias AM, Cordeiro Q. At-home transcranial direct current stimulation in Prader-Willi syndrome with severe intellectual disability: a case study. *J ECT*. (2017) 33:e29–30. doi: 10.1097/YCT.0000000000000409

51. Charvet L, George A, Charlson E, Lustberg M, Vogel-Eyny A, Eilam-Stock T, et al. Home-administered transcranial direct current stimulation is a feasible intervention for depression: an observational cohort study. *Front Psychiatry*. (2023) 14:1199773. doi: 10.3389/fpsyt.2023.1199773

52. Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Woürsching J, et al. Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. *Neuromodulation*. (2018) 21:323–33. doi: 10.1111/ner.12686

53. Clayton AM, Howard J, Dobbs B, Shaw MT, Charvet LE. Remotely supervised transcranial direct current stimulation after ECT improves mood and cognition in a patient with multiple sclerosis: a case study. *J Ect*. (2018) 34:e15. doi: 10.1097/YCT.0000000000000474

54. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *J Affect Disord*. (2019) 252:475–83. doi: 10.1016/j.jad.2019.04.041

55. Nikolin S, Moffa A, Razza L, Martin D, Brunoni A, Palm U, et al. Time-course of the tDCS antidepressant effect: An individual participant data meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. (2023) 125:110752. doi: 10.1016/j.pnpbp.2023.110752

56. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. (1979) 134:382–9. doi: 10.1192/bjp.134.4.382

57. Mayberg H. "Depression and frontal-subcortical circuits: focus on prefrontal-limbic interactions". In: Lichter DG, Cummings JL, editors. *Frontal-subcortical circuits in psychiatric and neurological disorders*. Guilford Press, New York, NY (2001). p. 177–206.

58. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology*. (2011) 36:183–206. doi: 10.1038/npp.2010.166

59. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry*. (2012) 72:595–603. doi: 10.1016/j.biopsych.2012.04.028

60. Trapp NT, Bruss J, Johnson MK, Uitermarkt BD, Garrett L, Heinzerling A, et al. Reliability of targeting methods in TMS for depression: beam F3 vs. 5.5 cm. *Brain Stimul*. (2020) 13:578–81. doi: 10.1016/j.brs.2020.01.010

61. Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, et al. Concordance between beamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. *Brain Stimul*. (2015) 8:965–73. doi: 10.1016/j.brs.2015.05.008

62. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, et al. More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. *Biol Psychiatry*. (2009) 66:509–15. doi: 10.1016/j.biopsych.2009.04.034

63. Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, et al. Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. *Hum Brain Mapp*. (2010) 31:1643–52. doi: 10.1002/hbm.20964

64. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology*. (2009) 34:1255–62. doi: 10.1038/npp.2008.233

65. Salvador R, Biagi MC, Manor B, Ruffini G. Group level montage optimization in transcranial electrical stimulation. *Brain Stimulation*. (2021) 14:1646. doi: 10.1016/j.brs.2021.10.185

66. Mercadal B, Salvador R, Biagi MC, Bartolomei F, Wendling F, Ruffini G. Modeling implanted metals in electrical stimulation applications. *J Neural Eng*. (2022) 19(2). doi: 10.1088/1741-2552/ac55ae

67. Cappon D, den Boer T, Yu W, LaGanke N, Fox R, Brozgol M, et al. An educational program for remote training and supervision of home-based transcranial electrical stimulation: feasibility and preliminary effectiveness. *Neuromodulation: Technol at Neural Interface*. (2023) 27(4):636–44. doi: 10.1016/j.neurom.2023.04.477

68. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. (2003) 54:573–83. doi: 10.1016/S0006-3223(02)01866-8

69. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of life enjoyment and satisfaction questionnaire: a new measure. *Psychopharmacol Bull*. (1993) 29(2):321–6.

70. Wang Y. Transcranial direct current stimulation for the treatment of major depressive disorder: A meta-analysis of randomized controlled trials. *Psychiatry Res*. (2019) 276:186–90. doi: 10.1016/j.psychres.2019.05.012

71. Salehinejad M, Abdi M, Dadashi M, Zolghadriha A, Salvador R, Ruffini G, et al. Optimized multichannel tDCS protocol for clinical use in patients with major depressive disorder: A randomized, controlled trial. (2024). doi: 10.31219/osf.io/tms4h

72. Burkhardt G, Kumpf U, Crispin A, Goerigk S, Andre E, Plewnia C, et al. Transcranial direct current stimulation as an additional treatment to selective serotonin reuptake inhibitors in adults with major depressive disorder in Germany (DepressionDC): a triple-blind, randomised, sham-controlled, multicentre trial. *Lancet*. (2023) 402:545–54. doi: 10.1016/S0140-6736(23)00640-2

73. Borrione L, Cavendish BA, Aparicio LVM, Luethi MS, Goerigk S, Ramos MRF, et al. Home-use transcranial direct current stimulation for the treatment of a major depressive episode: A randomized clinical trial. *JAMA Psychiatry*. (2024) 81:329–37. doi: 10.1001/jamapsychiatry.2023.4948

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Prediction of pharmacological treatment efficacy using electroencephalography-based salience network in patients with major depressive disorder

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Introduction: Recent resting-state electroencephalogram (EEG) studies have consistently reported an association between aberrant functional brain networks (FBNs) and treatment-resistant traits in patients with major depressive disorder (MDD). However, little is known about the changes in FBNs in response to external stimuli in these patients. This study investigates whether changes in the salience network (SN) could predict responsiveness to pharmacological treatment in resting-state and external stimuli conditions.

Methods: Thirty-one drug-naïve patients with MDD (aged 46.61 ± 10.05, female 28) and twenty-one healthy controls (aged 43.86 ± 14.14, female 19) participated in the study. After 8 weeks of pharmacological treatment, the patients were divided into non-remitted MDD (nrMDD, n = 14) and remitted-MDD (rMDD, n = 17) groups. EEG data under three conditions (resting-state, standard, and deviant) were analyzed. The SN was constructed with three cortical regions as nodes and weighted phase-lag index as edges, across alpha, low-beta, high-beta, and gamma bands. A repeated measures analysis of the variance model was used to examine the group-by-condition interaction. Machine learning-based classification analyses were also conducted between the nrMDD and rMDD groups.

Results: A notable group-by-condition interaction was observed in the high-beta band between nrMDD and rMDD. Specifically, patients with nrMDD exhibited hypoconnectivity between the dorsal anterior cingulate cortex and right insula ($p = 0.030$). The classification analysis yielded a maximum classification accuracy of 80.65%.

Conclusion: Our study suggests that abnormal condition-dependent changes in the SN could serve as potential predictors of pharmacological treatment efficacy in patients with MDD.

KEYWORDS

electroencephalography, major depressive disorder, salience network, prediction of antidepressant responsiveness, condition-dependent functional network

1 Introduction

Major depressive disorder (MDD) is a prevalent yet heterogeneous mental disorder. It is widely known that about 30% of patients do not respond to antidepressant treatment even though it is one of the most popular and neurobiologically validated therapies for MDD (1–3). Predicting the efficacy of antidepressant treatment is a crucial issue for personalized therapy, aiming to avoid ineffective treatment so that minimize unwarranted side effects resulting from ineffective medications (3, 4).

For the prediction of the treatment response in patients with MDD, a variety of neuroimaging studies have focused on the identification of reliable biomarkers. Recently, numerous studies have consistently reported that patients who exhibit similar functional brain network (FBN) patterns to healthy controls (HCs) tend to show a strong response to antidepressant treatment (5, 6). Specifically, several studies have suggested that aberrant resting-state functional connectivity (FC) patterns could serve as effective predictors of treatment outcomes in patients with MDD. In recent years, these FC patterns have been utilized as features to train machine-learning models, enhancing the performance in predicting treatment response.

Among various neuroimaging modalities, electroencephalography (EEG) is advantageous for studying FBN due to its great temporal resolution and cost-effectiveness (4, 7, 8). Some studies found distinct resting-state FBN patterns in patients with medication treatment-resistant MDD. For example, Whitton et al. (9) revealed that resting-state theta-band functional connectivity between the rostral anterior cingulate cortex and right anterior insula was associated with the efficacy of the antidepressant. Using an unsupervised machine learning (ML) model, Zhang et al. (6) successfully divided patients with MDD and post-traumatic stress disorder (PTSD) into two subtypes: drug responders and resistors. Relatively fewer EEG studies identified distinct FBN patterns in these patients under conditions involving external stimulation. For example, Sumner et al. (10) reported that rapid antidepressant efficacy was associated with dynamic forward connectivity in response to the unexpected auditory stimuli between the right primary auditory cortex and the right inferior temporal cortex. Overall, most EEG studies have primarily concentrated on investigating a single paradigm FBN pattern, particularly in the context of the resting-state condition.

Several up-to-date neuroimaging studies have investigated various condition-dependent brain activities to explore dysfunctional pathophysiological pathways (11–17). Among them, recent studies have consistently suggested that our understanding of neurobiology and various mental disorders could be broadened by investigating condition-dependent FBN patterns, including stimuli-based FBN patterns themselves and comparison of FBN patterns for various conditions (e.g., resting vs. stimuli, target vs. non-target) (11–14). However, it is yet to be investigated whether the condition-dependent changes in EEG-FBN could predict the treatment response in patients with MDD, despite their significant potential. For example, several EEG studies found that patients with drug-resistant MDD exhibited malfunctioning salience network (SN) connectivity patterns in the resting state, known for involvement of the selective attention control by processing salient events (18–22). Considering the role of SN, it is reasonable to hypothesize that those patients would also show abnormal FBN patterns under the condition with external salient stimulation. The malfunctioning changes in stimuli-induced SN have been observed in patients with treatment-resistant MDD in functional magnetic resonance imaging (fMRI) studies (12, 14, 20, 23).

In this study, we investigated condition-dependent changes in EEG-derived FBN in patients with MDD, using a dual-paradigm consisting of resting state and passive auditory oddball paradigm, generally known as the mismatch negativity (MMN) paradigms. Specifically, the SN was explored between patients with non-remitted MDD (nrMDD) and those with remitted MDD (rMDD) after an 8-week pharmaceutical therapy. The study is based on the hypothesis that the condition-dependent SN would show distinct patterns between groups; particularly, patients with nrMDD would exhibit more divergent patterns compared to demographically-matched healthy controls (HCs), consistent with existing resting-state FBN studies. To demonstrate the potential of the condition-dependent changes in SN as predictors of antidepressant responsiveness, we performed statistical analysis and ML-based classification analysis.

2 Methods and materials

2.1 Participants

A total of 33 patients with MDD (aged 46.00 ± 10.04, male: 3) and 22 HCs (aged 44.36 ± 14.00, male: 3) participated in the study. Due to

poor data quality, the data of two patients with MDD and one HC were discarded in the subsequent analysis; hence, data analysis was performed with 31 patients with MDD (aged 46.61 ± 10.05, male: 3) and 21 healthy controls (aged 43.86 ± 14.14, male: 2).

Patients with MDD were recruited from the Department of Psychiatry at the Inje University Ilsan Paik Hospital. The MDD was diagnosed by board-certified psychiatrists, based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (APA). The patients had no history of neurological illness, intellectual disability, substance abuse, head injury, or impaired hearing ability. Patients did not take any medication for at least one month before the study. After data acquisition, they received vortioxetine 10 mg po for the first week, followed by 20 mg po for the second week. Subsequently, the dosage was maintained flexibly ranging from 10 to 20 mg po, until the conclusion of the treatment period (i.e., 8^{th} week). Concerning the depressive symptom severity at the conclusion, namely, Hamilton Depression (Ham-D) Rating Scale score for the 8th week (Ham-D_8) (details in the following section) patients were finally divided into two groups: (i) non-remitted MDD (nrMDD; Ham-$D_8 \geq 8$, $n = 14$), and (ii) remitted MDD (rMDD; Ham-$D_8 < 8$, $n = 17$).

HCs were recruited from the community using flyers and posters. They also had no history of head injury or medications with psychiatric disorders, and also have no family history of psychiatric disorders. All the participants signed an informed consent form approved by the Institutional Review Board at Inje University Ilsan Paik Hospital before participation in the experiment (IRB No. 2016-08-017).

2.2 Symptomatic and psychological measures

The symptom severity of depression and anxiety were assessed by the Hamilton Depression Rating Scale (Ham-D) (24), and Hamilton Anxiety (Ham-A) (25) rating scales, respectively. The Ham-D and Ham-A consisted of 17 and 14 items, respectively. After 8 weeks of treatment, patients with a Ham-D score lower than 8 were classified as remitted MDD (rMDD), while the others were categorized as non-remitted MDD (nrMDD). The Ham-D and Ham-A were acquired at the 0th, 2nd, 4th, and 8th weeks (Supplementary Table S1). Only Ham-D and Ham-A were utilized from our previous study, as other measures were not of interest in the current study.

2.3 Experimental conditions

All participants engaged in two experimental paradigms: (i) resting-state (RS), and (ii) MMN paradigms. In the RS paradigm, participants closed their eyes for 5 min without any stimulation. Then, a duration-variant auditory oddball paradigm was conducted. The probability of deviant stimulus occurrence was set to 10% in a total of 750 trials. Participants were required to watch a silent movie during the auditory stimulus presentation and instructed not to focus on the auditory stimuli.

In the passive oddball experiment, the auditory stimuli were delivered binaurally with noise-canceling MDR-D777 headphones (Sony, Tokyo, Japan). The loudness and the pitch of all stimuli were set to 85 dB and 1000 Hz, respectively. The duration of the stimulation was set to 50 ms for the standard stimuli (Std) but 100 ms for the deviant stimuli (Dev), with 10 ms of rising and falling edges. The interstimulus interval was fixed at 600 ms.

2.4 Signal acquisition and pre-processing

The participants were asked to sit comfortably in a chair. Biosignal data were acquired using Neuroscan SynAmps2 (Compumedics USA, El Paso, TX, USA). For the EEG, a total of 64 Ag-AgCl electrodes mounted on a Quik-Cap were placed following the extended 10-20 system. For the electrooculogram (EOG), four electrodes were placed above and below the left eye and on the outer canthi of both eyes. Throughout signal acquisition, the impedance of all the electrodes was below 5 kΩ. The signals were recorded at 1,000 Hz of sampling rate and then bandpass filtered between 0.1 - 100 Hz.

The acquired signals were pre-processed using the EEGLAB toolbox (26) implemented in MATLAB R2019b (MathWorks, Natick, MA, USA). For the elimination of physiological artifacts, independent component analysis was performed. The components containing artifacts including EOG, electromyogram, and electrocardiogram were manually rejected. The EEG signals were then band-pass filtered between 0.1 – 50 Hz using a 6th-order Butterworth filter. After manual inspection, the EEG signals were segmented into 700 ms. For the auditory oddball data, the epochs ranged from 100 ms of a pre-stimulus interval to 600 ms of a post-stimulus interval (i.e., -100 – 600 ms). The segmented data were detrended and then baseline corrected using the pre-stimulus interval data. For the resting-state data, the epochs were segmented using the same length of time window (i.e., 700 ms) without any overlap. Regardless of experimental paradigms, all epochs with absolute maximum values exceeding 75 μV were excluded from the analysis. Among the noise-free segments, 250, 300, and 45 epochs were randomly selected for the RS, Std, and Dev conditions, respectively, from each participant.

2.5 Construction of salience network

For the construction of the SN, source localization was performed using the Brainstorm toolbox (27). The source activities were calculated with a depth-weighted L2-norm estimator from the randomly segmented EEG signals. Excluding mastoid electrodes, we selected all 62 EEG electrodes for source localization. The Colin27 MRI brain template with 15,002 voxels was employed for the estimation of the cortical activities. For the construction of the lead field matrix, a three-layer boundary element model was implemented from the OpenMEEG project software (28).

Three regions of interest (ROIs) were selected as the representative nodes of the SN according to the previous fMRI studies: (i) dorsal anterior cingulate cortex (dACC); (ii) left insula

(lIns); (iii) right insula (rIns) (Supplementary Materials). The Montreal Neurological Institute (MNI) coordinates of the ROI seeds were determined as centers of gravity of the provided coordinates (Supplementary Table S2), with manual verification of the coordinates. From the seed coordinates, the voxels within a 5 mm Euclidean distance were selected as representative ones. Finally, the representative source signal of the ROIs was obtained by the first component of the principal component analysis, using source signals acquired from the neighboring voxels.

The weighted phase-lag index (wPLI) (29) was calculated for evaluation of the edge between a pair of nodes (i.e., FC) for 4 frequency bands: (i) alpha (8 – 12 Hz); (ii) low beta (12 – 18 Hz); (iii) high beta (18 – 30 Hz); (iv) gamma (30 – 50 Hz). For each 0.7 s epoch, a pair of the representative source signals from the ROIs were bandpass filtered according to the frequency band. Subsequently, the Hilbert transform-based instantaneous phase was calculated. Finally, the absolute value of the temporal expectation of the instantaneous phase difference between the ROIs was divided by the temporal expectation of the absolute phase difference, as follows (30):

$$wPLI = \frac{|E(\sin \Delta\phi(t))|}{E(|\sin \Delta\phi(t)|)}$$

where the $\Delta\phi(t)$ denotes the difference in instantaneous phase as a function of time, t, |.| denotes the absolute operator, and the E(.) denotes the expectation operator across the time. Herein, the phase differences of the intervals for the initial and end 0.1 s were excluded from the calculation of the expectation values to eliminate edge effects caused by the filtering and Hilbert transform, as well as discard the baseline interval data in the oddball paradigm. The wPLI values can vary from 0 (entirely out-of-phase) to 1 (entirely phase-locked). It should be noted that the wPLI values were calculated for each band (i.e., $n = 4$), pair of nodes ($n = 3$), and epoch (n = 250, 300, and 45 for RS, Std, and Dev, respectively), and subsequently averaged across epochs. Finally, the FCs were defined as these averaged wPLI values. In addition, the global strength of the SN was evaluated as the sum of all pairs of the wPLI values (i.e., 3 wPLI values).

2.6 Statistical analysis

For verification of the assumption of data normality, skewness and kurtosis of the data distribution were examined. All absolute values of the skewness and kurtosis were less than 2 and 7, respectively (31); hence, all the data distributions were assumed to follow a normal distribution. For comparison of the demographic differences between 3 groups (i.e., nrMDD, rMDD, and HC), an analysis of variance (ANOVA) was used for age and education, while the chi-squared test was used for the sex ratio.

For evaluation of the group-by-condition interaction in the MDD groups, repeated-measures ANOVA (rmANOVA) was performed for three experimental conditions (i.e., RS, Std, Dev) as within-subject factors and the group (nrMDD vs. rMDD) as the between-subject factors, for each frequency band. We initially tested global strength and subsequently tested the three pairs of wPLIs if notable group-related effects were observed. Regarding rmANOVA, Mauchly's sphericity assumption was used given that the data distribution met the condition; otherwise, Greenhouse-Geisser correction was alternatively used. When significant group-related interaction was observed, *post-hoc* analyses were performed as follows. First, rmANOVA was performed for each group. Second, an independent t-test was performed. To avoid multiple correction issues, the bootstrap resampling technique (n = 5,000) was performed (32).

2.7 Feature ext

To demonstrate the potential of condition-dependent changes in SN patterns to predict pharmacological treatment response in patients with MDD, a further ML-based classification analysis was conducted. Consequently, classification between the MDD groups (nrMDD vs. rMDD) was performed using EEG features.

2.7.1 Feature extraction

From the SN-related measures, two types of condition-dependent FCs were determined as feature candidates. First, three pairs of FCs in the Dev-condition were selected. Second, three pairs of FC differences were selected, by subtracting FC values in the Std condition from FC values in the Dev condition, similar to the traditional MMN amplitude.

Some conventional measures were also included as feature candidates to enhance the classification performance. From the RS condition, absolute band power was calculated over the six cortical regions: bilateral frontal, central, and parieto-occipital areas. In addition, MMN amplitude was obtained from the frontocentral cortical regions. To obtain the MMN amplitude for each participant, the difference ERP curve was acquired by subtracting the Std-ERP curve from the Dev-ERP curve. Both ERP curves were obtained by averaging epochs for each condition, with bandpass filtered at 0.1 – 30 Hz using the 6th-order Butterworth filter. The potential values lasting from 130 ms to 280 ms were averaged and then defined as MMN amplitude. For more detail, please refer to our previous study (33).

2.7.2 Cross-validation and feature selection

To assess the performance of the classifiers, leave-one-out cross-validation (LOOCV) was conducted. Subsequently, the optimal feature subset was determined from the training dataset using the Fisher score (34). The number of selected features ranged from 1 to 15, the Fisher scores of which were the highest, to prevent the dimensionality-related overfitting issue. The selected features were then normalized to z-score to eliminate the inter-feature biases. It is noted that the statistics used for normalization (i.e., mean and standard deviation) were extracted from the training datasets to prevent information leakage.

2.7.3 Classification analysis

For the classification analysis, four ML-based classifiers were utilized to differentiate between nrMDD and rMDD: linear discriminant analysis (LDA), support vector machine (SVM), k-nearest neighbors (KNN), and naive-Bayes (NB). To evaluate the classification performance, three indices were computed: (i) classification accuracy, (ii) sensitivity, and (iii) specificity. Specifically, sensitivity and specificity were determined using nrMDD as the reference group. For instance, sensitivity was defined as the proportion of patients with nrMDD who were correctly classified. Finally, the receiver operating characteristic (ROC) curve was generated by using various decision thresholds, for the best-performing classifier. From the ROC curve, the area under the curve (AUC) was calculated for the evaluation of the performance of the classifier.

TABLE 1 Demography, symptom severity, and socio-cognitive function.

	nrMDD (n = 14)	rMDD (n = 17)	HC (n = 21)	*p-value*
Age	43.14 ± 11.07	48.35 ± 9.00	43.86 ± 14.14	*0.159*
Sex (M/F)	1/13	2/15	2/19	*0.764*
Education	13.86 ± 2.98	13.53 ± 3.43	13.24 ± 4.16	*0.778*
Ham-D				
Week 0	30.00 ± 5.57	26.24 ± 6.81		*0.108*
Week 8	17.14 ± 8.05	4.41± 1.77		*< 0.001*
Ham-A				
Week 0	27.07 ± 6.73	24.76 ± 6.57		*0.344*
Week 8	16.43 ± 7.36	4.06 ± 2.73		*< 0.001*

3 Results

3.1 Demographic and psychological measures

No significant demographic differences between the nrMDD, rMDD, and HC groups (p > 0.1 for all variables; Table 1). Furthermore, no significant differences were found in terms of baseline symptom severity (i.e., Ham-D and Ham-A; p > 0.1).

3.2 Comparison of the condition-dependent changes in SN patterns

In qualitative terms, patients with nrMDD exhibited aberrant patterns of condition-dependent changes in the high-beta band SN, demonstrating an opposite trend compared to HC. More specifically, while transitioning from RS- to Std- and Dev-condition, HC showed an increasing tendency in SN strength, whereas patients with nrMDD showed a decreasing tendency (Figure 1). Unlike patients with nrMDD, those with rMDD showed relatively similar condition-dependent changing patterns compared to HC.

In terms of SN strength, there was a notable group-by-condition interaction between nrMDD and rMDD in the high-beta band; however, it did not reach the significant level (p = 0.066; Figure 1). However, there was no other significant group-related effect.

In the FC analysis, there was a significant group-by-condition interaction between nrMDD and rMDD in the high-beta band (p = 0.026; Figure 2). A *post-hoc* analysis revealed that nrMDD showed lower FC than rMDD under the Dev-condition (p = 0.030; 95%CI -0.055 ~ -0.005). However, there was no other significant group-related effect.

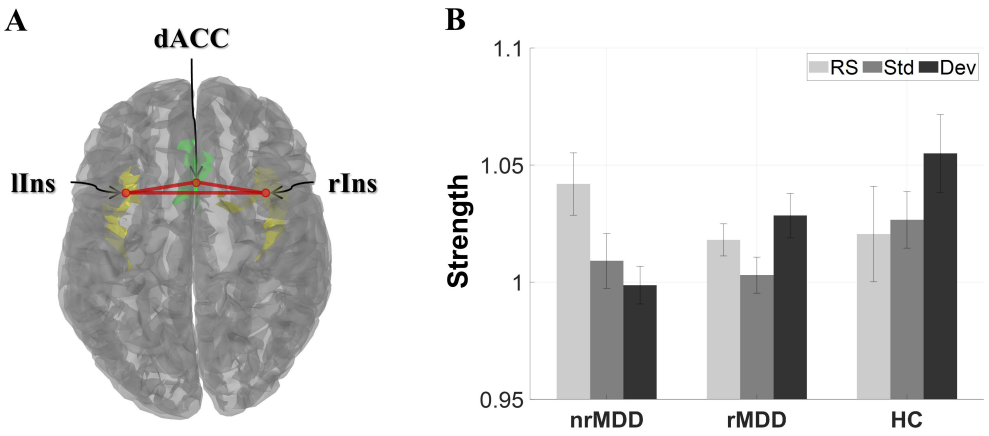

FIGURE 1
The global strength of the high-beta band salience network for each group under three different conditions. **(A)** Structure of the salience network, consisting of 3 regions of interest. **(B)** Global strength. The error-bars indicate the standard errors. dACC, dorsal anterior cingulate cortex; lIns, left insula; rIns, right insula; nrMDD (n = 14), non-remitted MDD; rMDD (n = 17), remitted MDD; HC (n = 21), healthy control. The brain image was obtained from the Brainstorm toolbox.

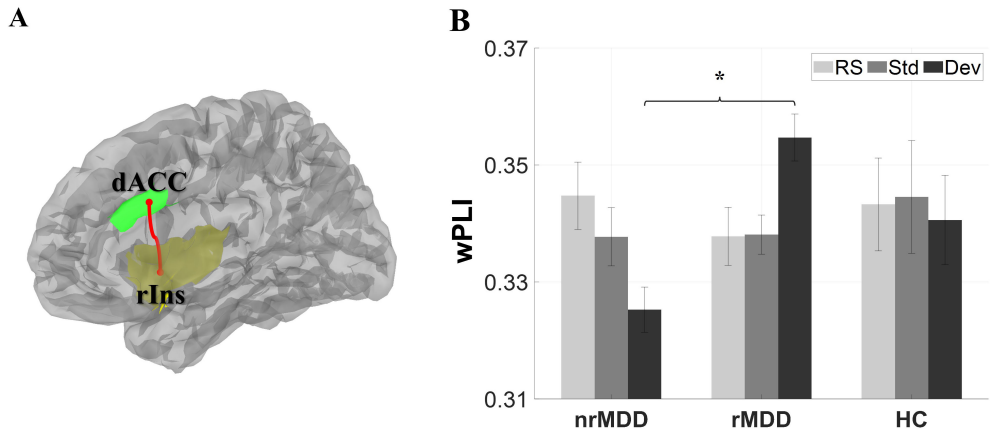

FIGURE 2
Functional connectivity (FC) between the dorsal anterior cingulate cortex (dACC) and right insula (rIns). **(A)** Structure of the dACC and rIns. **(B)** FC. The error-bars indicate the standard errors. *$p < 0.05$. dACC, dorsal anterior cingulate cortex; rIns, right insula; nrMDD (n = 14), non-remitted MDD; rMDD (n = 17), remitted MDD; HC (n = 21), healthy control. The brain image was obtained from the Brainstorm toolbox.

3.3 Classification analysis

In the ML-based classification analysis, the best performance was yielded using an LDA classifier with 13 selected features (Table 2). The classification accuracy, sensitivity, and specificity values of the model were 80.65%, 78.57%, and 82.35%, respectively (Figure 3A). In addition, the AUC of the model was 0.8277 (Figure 3B). The model incorporated a variety of features, including FC under Dev-condition and conventional features (i.e., MMN and resting-state band power).

TABLE 2 The feature subset with the best performance (i.e., n = 13).

Feature	Frequency
MMN	31
FCdiff_rIns_dACC	31
FCdev_rIns_dACC	31
BPb2_LF	31
BPg_LC	31
BPg_LPO	31
FCdiff_lIns_dACC	30
BPg_RPO	30
BPb2_RF	28
BPg_RF	28
BPb2_RPO	27
BPg_LF	22
FCdev_lIns_rIns	14

MMN, mismatch negativity; FC, functional connectivity; FCdev, FC under the deviant condition; FCdiff, the difference between FCdev and FCstd; BP, band power; BPb2, high-beta BP; BPg, gamma BP; lIns, left insula; rIns, right insula; dACC, dorsal anterior cingulate cortex; L, left; R, right; F, frontal; C, central; PO, parieto-occipital.

4 Discussion

In this study, we investigated the condition-dependent changes in SN in patients with drug-naive nrMDD and rMDD using EEG. Our findings point to the high-beta band SN as a key condition-dependent network for predicting the efficacy of pharmacological treatments in patients with MDD. Specifically, the strength of SN displayed a contrasting condition-dependent tendency in patients with nrMDD compared to that of the HC group. In the deviant-stimulus condition, high-beta band FC between dACC and rIns exhibited an abnormal decrease in patients with nrMDD compared to those with rMDD. The ability of these condition-dependent SN-related features to serve as potential biomarkers for predicting responsiveness to antidepressants was further demonstrated through a machine learning (ML)-based classification analysis.

Our findings indicate that EEG-derived condition-dependent changes in FBN patterns could be reliable measures to predict the efficacy of pharmacological treatment. To the best of our knowledge, this is the first study to explore the pharmacological treatment response in patients with MDD using condition-dependent changes in FBN. To date, most EEG-derived FBN studies aiming for the prediction of treatment effects have been interested in resting-state FBN. It appears that patients with MDD showing similar resting-state FBN patterns to HC are more receptive to the pharmacological treatment effect (5, 6), than other neuroimaging modality-derived FBN studies (20, 35). However, despite their potential, little is known about the association between stimuli-related FBN patterns and treatment responsiveness. Recent neuroimaging studies have shown that the integration of stimuli-related and resting-state neural activity could facilitate a more comprehensive understanding of various psychiatric disorders (11–14). Specifically, our findings show that stimuli-related FBN patterns in patients with rMDD are relatively similar to those in HC, consistent with the resting-state FBN patterns. Therefore, stimuli-related FBN patterns might be interpreted as similar to the resting-state FBN patterns, underpinning their reliability.

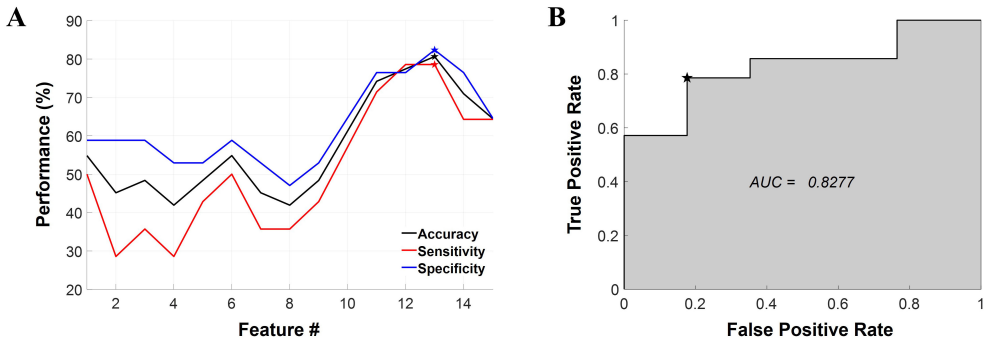

FIGURE 3
Results of the machine learning-based classification analysis. **(A)** The classification performance represented as a function of the number of features. The LDA model achieved optimal performance when 13 features were selected, as denoted by the pentagonal star symbol in the graph. Classification accuracy, sensitivity, and specificity are represented in black, red, and blue respectively. **(B)** The ROC curve for the best-performing classifier. The AUC is also provided within the graph. The chosen threshold on the ROC curve is marked by a pentagonal star symbol. LDA, linear discriminant analysis; ROC, receiver operating characteristic; AUC, area under the curve, Feature #, the number of features.

Our results indicate that high-beta band SN is a key FBN exhibiting different condition-dependent FBN patterns between nrMDD and rMDD under the resting state and MMN paradigms. This is consistent with the previous MDD studies. Several FBN studies reported hyperconnectivity in the resting-state high-beta band for MDD (36, 37). Furthermore, several studies revealed that magnetic seizure therapy could help the hyperactive beta band be reduced to become normalized in patients with MDD (38, 39). Our findings indicate that the observed phenomena are more likely attributable to patients with treatment-resistant MDD. We also found significant group (nrMDD and rMDD)-by-interaction in the total-beta band (12 – 30 Hz; Supplementary Material), underpinning the suggestion. Furthermore, our findings bolster the view that a hyperactive resting-state SN in the high-beta band could lead to inefficient condition-dependent reconfiguration. It is worth mentioning that, despite its potential significance, theta band was excluded in the current study (9). This decision was made due to the limited time window resulting from the short inter-stimulus interval (0.6 s), which allows for at most 2.4 cycles of the 4-Hz oscillation, generally the lower limit of the theta band. Therefore, further studies are needed to investigate whether the theta-band SN could serve as a biomarker to predict antidepressant responsiveness in patients with MDD.

Our study suggests that patients with nrMDD are characterized by more dysfunctioning condition-dependent changes in SN. This finding is in line with the previous neuroimaging studies. Recent fMRI studies have consistently reported inefficient information transfer within the SN among patients with treatment-refractory MDD (20, 21). Such patients may experience a reduced quality of life due to diminished affective functions (40, 41), a key role of the SN. It is worth noting that our study also suggests that SN is readily reconfigured by the neutral-valence stimuli, demonstrated by condition-dependent changes in SN for HCs: strength of the high-beta band increased but that of the alpha band decreased under the stimulus condition, particularly for the deviant stimulation (Supplementary Figure S1). Beta-band phase synchronization is generally believed to be associated with attentional control and short-term working memory, by interacting with relatively distant regions (42, 43), providing support for our hypothesis.

Within the high-beta band SN, patients with nrMDD showed decreased FC between the dACC and rIns, compared to those with rMDD, which serves as a potential biomarker for predicting antidepressant response. Furthermore, sensitive condition-dependent change in FC between them was associated with the early period antidepressant responsiveness (Supplementary Figure S2). Both regions are well known to play essential roles in condition-dependent FBN reconfiguration. The rIns plays a role in selective attention by switching the attentional focus between the default mode network and the central executive network, according to the salient external stimulation (19, 44). dACC is a crucial hub for flexible FBN reconfiguration, the malfunctioning of which has been repetitively reported in MDD studies (45, 46). In conclusion, the hypoconnectivity between the dACC and rIns under the Dev condition in patients with nrMDD could be linked to the dysfunctions of the dynamic FBN flexibility, hindering efficient selective attention.

Based on the machine learning models, we showed the potential that the condition-dependent FBN characteristics identified in our study could serve as informative biomarkers to predict pharmacological treatment responsiveness. The optimal feature subset included various condition-dependent FBN patterns (i.e., strength and FCs) as well as various conventional measures (i.e., MMN and band powers). Our findings suggest that neurobiologically meaningful measures, derived from conventional experimental paradigms, can reflect condition-dependent changes in SN and have the potential to enhance the performance of machine learning classifiers as predictors. Notably, we acquired similar levels of sensitivity and specificity across various classifiers (Supplementary Table S2), including the best-performing classifier (Figure 3), rendering our results more reliable.

Our study has several limitations. Firstly, more replications are needed for our results to be generalizable, due to our small sample size and the lack of performance evaluation with an external dataset. Secondly, this study only considered an 8-week remission period for patients, without addressing other prognostic factors such as potential relapse. Thirdly, our study design did not include a placebo control group. Fourth, the majority of participants in the

study were female, which may limit generalizability. This gender imbalance could be attributed to the higher prevalence of MDD in females and the lower participation rate of male patients in research studies. Finally, as individual brain MRI scans were not available in this study, a common template was used for estimating source estimation, which may have reduced the accuracy of estimating cortical electrophysiological activity. Future research will benefit from replicating these findings with a larger sample size and an external cohort to enhance generalizability. Additionally, examining an effective brain network or constructing a whole-brain network could provide meaningful insights into the underlying brain mechanisms in patients with non-remitted MDD.

Our study investigated the potential of condition-dependent changes in the EEG-derived salience network to predict antidepressant responsiveness in patients with MDD, assessed through both resting state and MMN paradigms. Patients with non-remitted MDD exhibited hyperconnectivity in the resting state but hypoconnectivity in response to salient stimuli (i.e., deviant condition) in the high-beta band SN, particularly for the FC between the dACC and rIns. In conclusion, understanding these condition-dependent connectivity patterns may contribute to the development of more targeted and effective treatments for MDD patients. It is hoped that our study pioneers research into condition-dependent changes in FBN.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: data are not publicly open because our dataset includes personal information. Requests to access these datasets should be directed to Seung-Hwan Lee, lshpss@paik.ac.kr.

Ethics statement

The studies involving humans were approved by Institutional Review Board at Inje University Ilsan Paik Hospital (IRB No. 2016-08-017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KC: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. TL: Writing – review & editing, Methodology, Formal analysis. CI: Writing – review & editing, Supervision, Funding acquisition. SL: Writing – review & editing, Supervision, Project administration, Funding acquisition.

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The authors declare that ChatGPT 4.0 and Grammarly were used for grammar checking in the creation of this manuscript.

Conflict of interest

Author S-HL was employed by the company Bwave Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1469645/full#supplementary-material

References

1. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence*. (2012) 6:369–88. doi: 10.2147/PPA.S29716

2. Iseger TA, Korgaonkar MS, Kenemans JL, Grieve SM, Baeken C, Fitzgerald PB, et al. EEG connectivity between the subgenual anterior cingulate and prefrontal cortices in response to antidepressant medication. *Eur Neuropsychopharmacol*. (2017) 27:301–12. doi: 10.1016/j.euroneuro.2017.02.002

3. Wu H, Liu R, Zhou J, Feng L, Wang Y, Chen X, et al. Prediction of remission among patients with a major depressive disorder based on the resting-state functional connectivity of emotion regulation networks. *Transl Psychiatry*. (2022) 12:391. doi: 10.1038/s41398-022-02152-0

4. Wade EC, Iosifescu DV. Using electroencephalography for treatment guidance in major depressive disorder. *Biol Psychiatry Cognit Neurosci Neuroimaging*. (2016) 1:411–22. doi: 10.1016/j.bpsc.2016.06.002

5. Rolle CE, Fonzo GA, Wu W, Toll R, Jha MK, Cooper C, et al. Cortical connectivity moderators of antidepressant vs placebo treatment response in major depressive disorder: secondary analysis of a randomized clinical trial. *JAMA Psychiatry*. (2020) 77:397–408. doi: 10.1001/jamapsychiatry.2019.3867

6. Zhang Y, Wu W, Toll RT, Naparstek S, Maron-Katz A, Watts M, et al. Identification of psychiatric disorder subtypes from functional connectivity patterns in resting-state electroencephalography. *Nat BioMed Eng*. (2021) 5:309–23. doi: 10.1038/s41551-020-00614-8

7. Toll RT, Wu W, Naparstek S, Zhang Y, Narayan M, Patenaude B, et al. An electroencephalography connectomic profile of posttraumatic stress disorder. *Am J Psychiatry*. (2020) 177:233–43. doi: 10.1176/appi.ajp.2019.18080911

8. Olbrich S, Arns M. EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. *Int Rev Psychiatry*. (2013) 25:604–18. doi: 10.3109/09540261.2013.816269

9. Whitton AE, Webb CA, Dillon DG, Kayser J, Rutherford A, Goer F, et al. Pretreatment rostral anterior cingulate cortex connectivity with salience network predicts depression recovery: findings from the EMBARC randomized clinical trial. *Biol Psychiatry*. (2019) 85:872–80. doi: 10.1016/j.biopsych.2018.12.007

10. Sumner RL, McMillan R, Spriggs MJ, Campbell D, Malpas G, Maxwell E, et al. Ketamine improves short-term plasticity in depression by enhancing sensitivity to prediction errors. *Eur Neuropsychopharmacol*. (2020) 38:73–85. doi: 10.1016/j.euroneuro.2020.07.009

11. Gupta A, Wolff A, Northoff DG. Extending the "resting state hypothesis of depression" - dynamics and topography of abnormal rest-task modulation. *Psychiatry Res Neuroimaging*. (2021) 317:111367. doi: 10.1016/j.pscychresns.2021.111367

12. Northoff G, Gomez-Pilar J. Overcoming rest-task divide-abnormal temporospatial dynamics and its cognition in schizophrenia. *Schizophr Bull*. (2021) 47:751–65. doi: 10.1093/schbul/sbaa178

13. Wu G, Palaniyappan L, Zhang M, Yang J, Xi C, Liu Z, et al. Imbalance between prefronto-thalamic and sensorimotor-thalamic circuitries associated with working memory deficit in schizophrenia. *Schizophr Bull*. (2022) 48:251–61. doi: 10.1093/schbul/sbab086

14. Yang Y, Zhong N, Imamura K, Lu S, Li M, Zhou H, et al. Task and resting-state fMRI reveal altered salience responses to positive stimuli in patients with major depressive disorder. *PloS One*. (2016) 11:e0155092. doi: 10.1371/journal.pone.0155092

15. Cea-Canas B, Gomez-Pilar J, Nunez P, Rodriguez-Vazquez E, de Uribe N, Diez A, et al. Connectivity strength of the EEG functional network in schizophrenia and bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. (2020) 98:109801. doi: 10.1016/j.pnpbp.2019.109801

16. Iglesias-Tejedor M, Diez A, Llorca-Bofi V, Nunez P, Castano-Diaz C, Bote B, et al. Relation between EEG resting-state power and modulation of P300 task-related activity in theta band in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. (2022) 116:110541. doi: 10.1016/j.pnpbp.2022.110541

17. Ma S, Calhoun VD, Eichele T, Du W, Adali T. Modulations of functional connectivity in the healthy and schizophrenia groups during task and rest. *Neuroimage*. (2012) 62:1694–704. doi: 10.1016/j.neuroimage.2012.05.048

18. Wolff A, de la Salle S, Sorgini A, Lynn E, Blier P, Knott V, et al. Atypical temporal dynamics of resting state shapes stimulus-evoked activity in depression-an EEG study on rest-stimulus interaction. *Front Psychiatry*. (2019) 10:719. doi: 10.3389/fpsyt.2019.00719

19. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Front Hum Neurosci*. (2013) 7:930. doi: 10.3389/fnhum.2013.00930

20. He Z, Cui Q, Zheng J, Duan X, Pang Y, Gao Q, et al. Frequency-specific alterations in functional connectivity in treatment-resistant and -sensitive major depressive disorder. *J Psychiatr Res*. (2016) 82:30–9. doi: 10.1016/j.jpsychires.2016.07.011

21. Su H, Zuo C, Zhang H, Jiao F, Zhang B, Tang W, et al. Regional cerebral metabolism alterations affect resting-state functional connectivity in major depressive disorder. *Quant Imaging Med Surg*. (2018) 8:910–24. doi: 10.21037/qims.2018.10.05

22. Han S, Cui Q, Wang X, Li L, Li D, He Z, et al. Resting state functional network switching rate is differently altered in bipolar disorder and major depressive disorder. *Hum Brain Mapp*. (2020) 41:3295–304. doi: 10.1002/hbm.v41.12

23. Piani MC, Maggioni E, Delvecchio G, Brambilla P. Sustained attention alterations in major depressive disorder: A review of fMRI studies employing Go/No-Go and CPT tasks. *J Affect Disord*. (2022) 303:98–113. doi: 10.1016/j.jad.2022.02.003

24. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. (1988) 45:742–7. doi: 10.1001/archpsyc.1988.01800320058007

25. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depress Anxiety*. (2001) 13:166–78. doi: 10.1002/(ISSN)1520-6394

26. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*. (2004) 134:9–21. doi: 10.1016/j.jneumeth.2003.10.009

27. Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci*. (2011) 2011:879716. doi: 10.1155/2011/879716

28. Gramfort A, Papadopoulo T, Olivi E, Clerc M. OpenMEEG: opensource software for quasistatic bioelectromagnetics. *BioMed Eng*. (2010) 9:45. doi: 10.1186/1475-925X-9-45

29. Vinck M, Oostenveld R, van Wingerden M, Battaglia F, Pennartz CM. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage*. (2011) 55:1548–65. doi: 10.1016/j.neuroimage.2011.01.055

30. Yu M. Benchmarking metrics for inferring functional connectivity from multi-channel EEG and MEG: A simulation study. *Chaos*. (2020) 30:123124. doi: 10.1063/5.0018826

31. Curran PJ, West SG, Finch JF. The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *psychol Methods*. (1996) 1:16–29. doi: 10.1037/1082-989X.1.1.16

32. Dudoit S, van der Laan MJ, Pollard KS. Multiple testing. Part I. Single-step procedures for control of general type I error rates. *Stat Appl Genet Mol Biol*. (2004) 3:13. doi: 10.2202/1544-6115.1040

33. Kim H, Baik SY, Kim YW, Lee SH. Improved cognitive function in patients with major depressive disorder after treatment with vortioxetine: A EEG study. *Neuropsychopharmacol Rep*. (2022) 42:21–31. doi: 10.1002/npr2.12220

34. Quanquan Gu ZL, Han J. Generalized fisher score for feature selection. *arXiv preprint arXiv:1202.3725*. (2012). doi: 10.48550/arXiv.1202.3725

35. Sun J, Ma Y, Guo C, Du Z, Chen L, Wang Z, et al. Distinct patterns of functional brain network integration between treatment-resistant depression and non treatment-resistant depression: A resting-state functional magnetic resonance imaging study. *Prog Neuropsychopharmacol Biol Psychiatry*. (2023) 120:110621. doi: 10.1016/j.pnpbp.2022.110621

36. Choi KM, Kim JY, Kim YW, Han JW, Im CH, Lee SH. Comparative analysis of default mode networks in major psychiatric disorders using resting-state EEG. *Sci Rep*. (2021) 11:22007. doi: 10.1038/s41598-021-00975-3

37. Kim S, Baek JH, Shim SH, Kwon YJ, Lee HY, Yoo JH, et al. Alteration of cortical functional networks in mood disorders with resting-state electroencephalography. *Sci Rep*. (2022) 12:5920. doi: 10.1038/s41598-022-10038-w

38. Deng ZD, McClinctock SM, Lisanby SH. Brain network properties in depressed patients receiving seizure therapy: A graph theoretical analysis of peri-treatment resting EEG. *Annu Int Conf IEEE Eng Med Biol Soc*. (2015) 2015:2203–6. doi: 10.1109/EMBC.2015.7318828

39. Hill AT, Zomorrodi R, Hadas I, Farzan F, Voineskos D, Throop A, et al. Resting-state electroencephalographic functional network alterations in major depressive disorder following magnetic seizure therapy. *Prog Neuropsychopharmacol Biol Psychiatry*. (2021) 108:110082. doi: 10.1016/j.pnpbp.2020.110082

40. Xue S, Wang S, Kong X, Qiu J. Abnormal neural basis of emotional conflict control in treatment-resistant depression. *Clin EEG Neurosci*. (2017) 48:103–10. doi: 10.1177/1550059416631658

41. Heerlein K, Young AH, Otte C, Frodl T, Degraeve G, Hagedoorn W, et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: Baseline patient characteristics. *J Affect Disord*. (2021) 283:115–22. doi: 10.1016/j.jad.2020.11.124

42. Mizuhara H, Yamaguchi Y. Human cortical circuits for central executive function emerge by theta phase synchronization. *Neuroimage*. (2007) 36:232–44. doi: 10.1016/j.neuroimage.2007.02.026

43. Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, et al. Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *Proc Natl Acad Sci U S A*. (2004) 101:13050–5. doi: 10.1073/pnas.0404944101

44. Eckert MA, Menon V, Walczak A, Ahlstrom J, Denslow S, Horwitz A, et al. At the heart of the ventral attention system: the right anterior insula. *Hum Brain Mapp*. (2009) 30:2530–41. doi: 10.1002/hbm.20688

45. Wu X, Lin P, Yang J, Song H, Yang R, Yang J. Dysfunction of the cingulo-opercular network in first-episode medication-naive patients with major depressive disorder. *J Affect Disord*. (2016) 200:275–83. doi: 10.1016/j.jad.2016.04.046

46. Ho TC, Sacchet MD, Connolly CG, Margulies DS, Tymofiyeva O, Paulus MP, et al. Inflexible functional connectivity of the dorsal anterior cingulate cortex in adolescent major depressive disorder. *Neuropsychopharmacology*. (2017) 42:2434–45. doi: 10.1038/npp.2017.103

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MADRS single items differential changes among patients with melancholic and unspecified depression treated with ECT: an exploratory study

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Introduction: Major depressive disorder (MDD) exhibits heterogeneity in treatment response.

Objective: This exploratory analysis aims to evaluate the differential changes in individual items of the MADRS between melancholic MDD (M-MDD) and unspecified MDD (U-MDD) following electroconvulsive therapy (ECT).

Methods: The study included 23 patients with unipolar MDD who received ECT. Patients were classified as M-MDD or U-MDD according to DSM-5 criteria. MADRS scores were assessed at baseline and one-month post-ECT. Differences between subtypes were analyzed using the Wilcoxon test and multiple linear regression.

Results: Among 23 participants receiving ECT for MDD, 10 had M-MDD and 13 had U-MDD. Baseline MADRS items showed significantly higher scores in the M-MDD group, except for reported sadness, suicidal ideation, and concentration difficulties. Total MADRS score reduction was significantly greater in the M-MDD group. This decline was especially pronounced in M-MDD patients for specific items, including apparent sadness, inability to feel, pessimistic thoughts, sleep disturbances, reduced appetite, and concentration difficulties, after adjusting for age and sex.

Conclusion: MADRS score reductions were more substantial for M-MDD than U-MDD in both total and specific items following one month of ECT. Further research with larger samples is needed to clarify MADRS response differences after ECT between melancholic and unspecified depressive subtypes.

KEYWORDS

major depressive disorder, melancholic depression, unspecified depression, ECT, MADRS

1 Introduction

Major depressive disorder (MDD) has a lifetime prevalence of 15-18% (1) and exhibits diverse manifestations, clinical courses, and treatment responses, with numerous potential underlying and interconnected etiologies (2). For instance, the melancholic major depressive disorder (M-MDD) subtype is primarily characterized by anhedonia, lack of reactivity, empty mood, early morning awaking, psychomotor agitation or retardation, anorexia, and excessive guilt, and it may be associated with hypothalamic-pituitary-adrenal axis dysfunction (3–6). In addition to the interconnected etiologies underlying MDD (4, 5), temperamental traits have also been implicated in influencing the clinical presentation and treatment response of its subtypes (7).

A European multicenter study involving 1,410 individuals diagnosed with MDD, of whom 60.71% exhibited melancholic features, examined the impact of these features on the socio-demographic and clinical profiles in patients with depression. People with melancholic features had a higher body weight and exhibited higher rates of severe depressive symptoms, psychotic symptoms, suicide risk, inpatient treatment, and unemployment (8). The pharmacological profile for the M-MDD subtype appears distinct, demonstrating a lower placebo response and a more rapid response to pharmacological treatment compared to non-melancholic depression (9–13). Common treatment strategies for M-MDD patients include augmentation or combination therapies, with a preference for adjunctive treatments such as antidepressants, antipsychotics, benzodiazepines, and pregabalin (8). The unique comorbidities and prognostic characteristics of the M-MDD subtype underscore the need for tailored treatment approaches.

Electroconvulsive therapy (ECT) is a widely utilized treatment in modern psychiatry that induces a generalized convulsive seizure under general anesthesia. ECT is currently regarded as the most effective treatment for acute severe major depression (14, 15). The primary side effects are those related to general anesthesia and temporary cognitive effects, with occasional side effects including cardiac arrhythmias, confusion, increased drowsiness, urinary retention, and headache (14). There is no absolute medical contraindication for ECT (16).

MDD (both unipolar and bipolar) remains the main indication for ECT, with remission rates frequently exceeding 60% (17). Given the heterogeneity of MDD's clinical presentation, it is appropriate to consider how different subtypes respond to ECT (18). In the case of melancholic features, a meta-analysis and systematic review examining predictive factors of response to ECT in depression analyzed seven trials reporting remission data and five trials reporting response data (19). No significant differences in response or remission were found between melancholic and non-melancholic groups (19).

While ECT is widely used and generally effective for treatment-resistant depression, there is limited evidence on the varied responses of depression subtypes (according to the DSM-5) to ECT. This gap in research is important because understanding these variations could enhance personalized treatment approaches (20).

Most of the studies assessing the specificity of MDD compare M-MDD with non-melancholic depression. However, considering the heterogeneity within depression and the presence of different subtypes (e.g., with mixed, anxious, or atypical features) (21), in this study, limited to patients who had received ECT, i.e. with M-MDD and unspecified MDD (U-MDD), rather than comparing M-MDD with all other depression types, we compare M-MDD with participants with depression who do not have characteristics of atypical or M-MDD. We believe this comparison between M-MDD and U-MDD may provide clearer insights into the specific characteristics of these two more homogenous depression subtypes.

The Montgomery-Asberg Depression Rating Scale (MADRS) (22) is a 10-item rating scale that measures the severity of depressive symptoms. MADRS is widely used in clinical and research settings as an overall measure of depressive symptoms. The traditional approach of summing symptom scores and treating depression as a single, uniform construct has been increasingly challenged by evidence highlighting the multidimensional and variable nature of major depressive disorder (23). Findings suggest that individual depressive symptoms are distinct phenomena with unique biological, functional, and risk profiles, rather than interchangeable indicators of a single underlying disorder (23). Although various factorial models have been proposed to evaluate ECT's impact on depression, results have varied between samples, leaving implications inconclusive (24–26).

There are very few studies in the literature that examine the response to ECT on the individual items of the MADRS (27, 28). Carstens et al. analyzed the predictive value of individual MADRS items and their changes throughout ECT treatment, providing a nuanced view of ECT's impact on specific depression symptoms (27). According to Carstens et al., each MADRS item may capture different dimensions of depression that vary among patients (27). Their findings concluded that individual MADRS items are strong predictors of ECT response, remission, and overall symptom reduction, with "apparent sadness," "reported sadness," and "inability to feel" items being especially predictive (27).

Identifying relevant depression subtypes and their response to ECT in treatment-resistant depression could facilitate more personalized treatment interventions. Additionally, ECT may differentially affect specific symptoms, and certain items, such as suicidal ideation, may hold greater clinical importance (29, 30). Therefore, when comparing M-MDD and U-MDD patients, we chose to use single-item scoring to examine changes in each MADRS item individually, as this approach may reveal subtle shifts otherwise obscured by aggregate scores.

In this study, we expect that the global change of MADRS scores following ECT will differ between unipolar M-MDD and U-MDD subtypes. Since each MADRS item represents a distinct symptom of depression, we also expect item-specific differences between the two subtypes after ECT. The aim of this exploratory analysis is to assess differences on the global score and individual MADRS items between M-MDD and U-MDD subtypes after one month of ECT treatment in a group of patients with unipolar depression.

Abbreviations: M-MDD, melancholic major depressive disorder; U-MDD, unspecified major depressive disorder; ECT, electroconvulsive therapy; MDD, major depressive disorder; MADRS, Montgomery-Asberg Depression Rating Scale.

2 Material and methods

2.1 Sample

Our exploratory study included a sample of 23 subjects with unipolar depression and treated with ECT. This exploratory analysis was conducted at the Interventional Unit of the Old-Age Psychiatry Service of the Lausanne University Hospital.

We reviewed medical records of patients who received ECT for M-MDD or U-MDD between January 2020 and December 2024. Baseline MADRS scores (collected prior to ECT) and 1-month MADRS scores (collected one month after initiating ECT) were obtained for analysis. Inclusion criteria required patients to be aged 18 or older, receiving ECT for their current depressive episode, diagnosed with unipolar affective disorder according to DSM-5 criteria, and having signed the general consent form for CHUV. Exclusion criteria included diagnoses of schizoaffective or bipolar disorder and any missing data essential to the study variables.

The study received approval from the Medical Ethics Committee of the Canton of Vaud (CER-VD).

2.2 Assessment of clinical characteristics

Demographic data, including age, sex, duration from onset of unipolar depressive disorder to ECT initiation, history of suicide attempts, presence of comorbid psychiatric disorders, and other medical conditions, were collected. MDD subtypes were determined based on DSM-5 criteria, which includes specifiers for melancholic features during the depressive episode, i.e., loss of pleasure or anhedonia and three of the following criteria: marked quality of depressed mood, depression worse in the morning, early morning awakening, psychomotor agitation or retardation, weight loss, or feelings of guilt. According to these criteria, each MDD case was classified as either M-MDD or U-MDD, meaning it did not meet criteria for atypical or melancholic features.

Depression severity at baseline and 1 month follow-up after ECT was assessed using the MADRS. The MADRS was systematically administered during the initial consultation to determine ECT indication. Baseline melancholic or unspecified features were documented from the comprehensive psychiatric evaluation conducted during this consultation. At the 1-month follow-up, the MADRS scores were either obtained from a routine consultation conducted one month after ECT initiation or reconstructed from the comprehensive psychiatric assessment conducted during the follow-up evaluation.

We also extracted a list of pharmacological treatments from medical records, documenting medications patients were receiving at the time ECT was initiated.

2.3 ECT procedure

ECT sessions were administered twice weekly using a Mecta machine. The initial seizure threshold was determined using the stimulus dose titration method outlined by Weiner and colleagues (31). For subsequent sessions, the dose was set at 1.5 to 2 times the seizure threshold for bilateral (BL) electrode placement and 5 times the threshold for right unilateral (RUL) electrode placement. Electrodes were positioned either right fronto-temporally for RUL or bilaterally fronto-temporally for BL. ECT was performed under general anesthesia, using etomidate and succinylcholine for muscle relaxation, with continuous monitoring of ECG, blood pressure, and pulse oximetry.

An adequate seizure was defined as one lasting at least 20 seconds by the cuff method or 25 seconds on the EEG. Dosages were adjusted throughout the treatment to ensure adequate seizure activity. All procedures were conducted by a highly trained and experienced team of psychiatrists and anesthetists.

The protocol included an initial frequency of twice-weekly sessions for a total of 12 sessions, followed by weekly sessions, with further treatment frequency and duration adjusted according to symptom progression. Participants received approximately eight ECT sessions over the first month, with the MADRS follow-up conducted at the one-month mark.

Time from the onset of depressive disorder to ECT treatment was defined as the duration from the first depressive episode to the initial ECT session, which could include multiple depressive episodes within this timeframe.

2.4 Statistical analysis

Descriptive statistics, including mean (SD) for continuous variables and count (percentage) for categorical variables, were used to summarize the baseline characteristics of the sample. Baseline characteristics were compared between the two MDD subtypes, M-MDD and U-MDD, using the Wilcoxon rank-sum test and Fisher's exact test, as appropriate.

The differences in MADRS total score and its 10 individual items at baseline and 1 month after ECT treatment were compared between M-MDD and U-MDD group using Wilcoxon rank sum test as the sample size is small.

For each patient, changes in MADRS scores and its 10 individual items were calculated from baseline to the one-month follow-up after ECT treatment. Boxplots of these changes were generated for each MDD subtype group. The Wilcoxon rank-sum test was applied to assess differences in these changes between the M-MDD and U-MDD groups.

Separate multiple linear regression analyses were conducted to evaluate the differences in changes for the MADRS total score and each of its 10 subscales between the M-MDD and U-MDD groups, controlling for sex and age as covariates.

All statistical analyses were performed using the R software environment (Version 4.1.0). The significance level was set at $p \leq 0.05$.

3 Results

A total of 23 participants met the inclusion criteria and received an acute course of ECT for MDD. The mean age of the sample was 60 years. 48% were women and 43% had a M-MDD (vs. 57% U-MDD). The mean estimated time from the onset of depressive

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disorder to the start of ECT treatment was 177 months; however, data on prior depressive episodes was not available in this dataset. Most patients received ECT in the BL electrode position (Table 1).

At the initiation of ECT treatment, 19 out of 23 patients were on antidepressant medication, with 3 patients taking two antidepressants from different pharmacological classes simultaneously (Supplementary Table 1).

Patients in the M-MDD group primarily received SSRIs or SSNIs, sometimes in combination with a second antidepressant (such as trazodone or mirtazapine). In contrast, antidepressant use in the U-MDD group was more varied. At the start of ECT, 69.5% of patients were also taking a benzodiazepine, most of whom had melancholic features. The proportions of M-MDD and U-MDD patients on atypical antipsychotics were similar (Supplementary Table 1).

The mean baseline MADRS score was significantly higher in M-MDD patients (48) compared to U-MDD patients (35) ($p < 0.001$), whereas this difference is no more significant after 1 month of treatment with ECT, M-MDD patients (18) and U-MDD (21) ($p=0.7$) (Supplementary Table 2). Baseline MADRS subscores showed significantly higher scores across most items for M-MDD patients compared to U-MDD, with the exceptions of reported sadness, suicidal ideation, and concentration difficulties. However, no significant differences were found in specific item scores between M-MDD and U-MDD at the 1-month follow-up MADRS assessment (Supplementary Table 2).

The change in overall MADRS scores from baseline to the 1-month follow-up differed significantly ($p = 0.034$) between M-MDD (mean = -30, SD = 17) and U-MDD (mean = -14, SD = 13) (Supplementary Table 3; Figure 1). In the analysis of specific items, changes in pessimistic thoughts, reduced sleep, reduced appetite, and difficulty concentrating were significantly more pronounced in the M-MDD group than in the U-MDD group (Figure 1).

After adjusting for age and sex, the global difference in MADRS scores between baseline and 1-month follow-up for M-MDD and U-MDD groups remained significant (Table 2). In the specific MADRS item analysis, significant differences were observed for

TABLE 1 Descriptive statistics.

Characteristics	Overall sample N = 23 n(%),mean(sd)[a]	M-MDD N = 10 n(%),mean(sd)	U-MDD N = 13 n(%),mean(sd)	p-value[b]
Sex				0.2
Male	12 (52%)	7 (70%)	5 (38%)	
Female	11 (48%)	3 (30%)	8 (62%)	
Age	60 (19)	65 (14)	57 (23)	0.6
Time onset to ECT (month)	177 (170)	198 (182)	159 (165)	0.6
Suicide attempts	3 (13%)	1 (10%)	2 (15%)	>0.9
Age onset (year)	45 (20)	50 (18)	42 (22)	0.3
Comorbidities:				
Hypertension	7 (30%)	5 (50%)	2 (15%)	0.2
Diabetes	3 (13%)	2 (20%)	1 (7.7%)	0.6
Obesity	2 (8.7%)	1 (10%)	1 (7.7%)	>0.9
Dyslipidaemia	4 (17%)	2 (20%)	2 (15%)	>0.9
History of stroke	2 (8.7%)	1 (10%)	1 (7.7%)	>0.9
History of migraine	1 (4.3%)	1 (10%)	0 (0%)	0.4
Active substance use disorder	3 (13%)	1 (10%)	2 (15%)	>0.9
Historyof substance use disorder	4 (17%)	1 (10%)	3 (23%)	0.6
History of anxiety disorder	5 (22%)	4 (40%)	1 (7.7%)	0.13
History of psychotic disorder	3 (13%)	2 (20%)	1 (7.7%)	0.6
Electrodes position				>0.9
BL	19 (83%)	8 (80%)	11 (85%)	
RUL	4 (17%)	2 (20%)	2 (15%)	

(a) Number of observation, n, and percentages (%) mean, and standard deviation(sd) are reported for categorical and continuous variables accordingly.
(b) Wilcoxon rank sum test and Fisher's exact test were performed for continuous and categorical variables, respectively.
M-MDD, melancholic major depressive disorder; U-MDD, unspecified major depressive disorder.

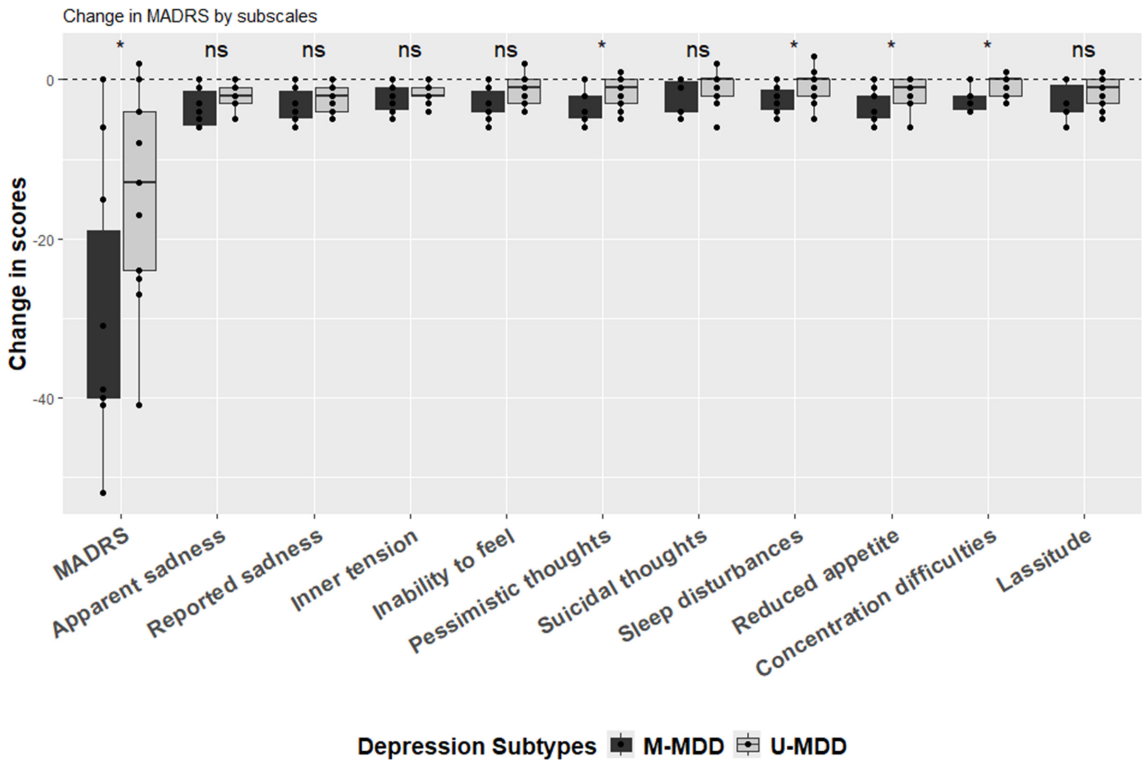

FIGURE 1
Change in MADRS (1 month after ECT-before ECT). (*) statistically significant (i.e. p<0.05) and (ns) statistically non-significant based on the unpaired two-samples Wilcoxon test.

TABLE 2 Multiple linear regression (a) for Change in Overall MADRS between baseline and 1 month after ECT treatment and change in each sub-scale item.

Outcome	Estimates(β) [(b)]	LCI	UCI	Effect-size[(c)]	P_value
MADRS_change	**17.45**	**5.42**	**29.48**	**1.07**	**0.007**
Apparent sadness_change	**1.72**	**0.05**	**3.4**	**0.83**	**0.044**
Reported sadness_change	1.38	-0.31	3.06	0.71	0.104
Inner tension_change	1.04	-0.05	2.13	0.69	0.059
Inability to feel_change	**1.76**	**0.28**	**3.25**	**0.89**	**0.023**
Pessimistic thoughts_change	**2.15**	**0.39**	**3.91**	**1.00**	**0.019**
Suicidal thoughts_change	1.81	-0.18	3.81	0.82	0.073
Sleep disturbance_change	**2.17**	**0.44**	**3.9**	**1.04**	**0.016**
Reduced appetite_change	**2.17**	**0.49**	**3.85**	**1.04**	**0.014**
Concentration difficulties_change	**1.61**	**0.45**	**2.76**	**1.05**	**0.009**
Lassitude_change	1.5	-0.16	2.76	0.71	0.075

(a) All Models are controlled for age and sex.
(b) β represents the coefficient for M-MMD vs U-MDD, where MD is taken as reference group.
(c) effect-size is calculated as standardized coefficient (standardized beta) from the multiple linear regression.
Bold values mean statistically significant.

apparent sadness, inability to feel, pessimistic thoughts, reduced sleep, reduced appetite, and difficulty concentrating, with M-MDD patients showing a greater reduction in these symptoms (Table 2).

4 Discussion

This is the first study to compare changes in M-MDD and U-MDD following ECT using a MADRS single-item model. We observed a significantly greater reduction in overall MADRS scores among participants with M-MDD compared to those with U-MDD. Specifically, focusing on individual MADRS items, we found that reductions in apparent sadness, inability to feel, pessimistic thoughts, reduced appetite, sleep disturbances, and difficulty concentrating were statistically significantly more pronounced in the M-MDD group than in the U-MDD group, after adjusting for age and sex.

Given the novel perspective of our study, direct comparisons with previous research are challenging. Previous studies assessing the effect of ECT on MDD have yielded inconclusive results regarding specific responses in depression with melancholic features, primarily due to inconsistencies in the definition of melancholia and variations in reported response and remission outcomes (32–36). The aim of this exploratory study is mainly to generate hypotheses for future prospective research.

In terms of analysis and interpretation of results, we could have opted to use a factorial model similar to that proposed by Tominaga et al. (26). Their model defines three MADRS factors: Factor 1 includes three items representing dysphoria (reported sadness, pessimistic thoughts, and suicidal thoughts); Factor 2 includes four items representing retardation (fatigue, inability to feel, apparent sadness, and difficulty concentrating); and Factor 3 includes three items representing vegetative symptoms (reduced sleep, reduced appetite, and inner tension) (26). In our study, however, we chose to analyze each item individually to capture more detailed, item-specific differences. We considered each item as potentially making an independent contribution to the overall depressive symptomatology. This approach is well supported by our findings, which show that the MADRS items demonstrating greater reductions after ECT in participants with M-MDD versus those with U-MDD span across the three factors identified by Tominaga et al. (26). It is also worth noting that certain MADRS items (e.g., difficulty concentrating) could be directly influenced by ECT-related side effects, potentially impacting the overall factor score.

Other findings are noteworthy, such as the estimated mean interval of 14.7 years between the onset of the first depressive episode and initiation of ECT in our unipolar depression population. A meta-analysis found no predictive effect of age at onset on ECT response in participants with depression (37), but we found no literature addressing the specific predictive value of this interval (time from the first depressive episode onset to ECT) on ECT outcomes.

The results focusing on the differences between M-MDD and U-MDD on the specific items of the MADRS are particularly important for several reasons. First, certain depressive symptoms are associated with increased mortality. For instance, in depressed patients, low energy, poor appetite or overeating, and lack of interest in activities have been independently linked to higher mortality from all causes and cardiovascular disease (38). Thus, based on our findings, it could be suggested that patients with M-MDD who exhibit symptoms of inability to feel, and reduced appetite might be prioritized for ECT. Clearly, this should be verified with further evidence, ideally through a prospective study with a larger sample size.

Secondly, the greater reduction in the aforementioned items in the M-MDD group following ECT suggests that for patients with severe or resistant MDD with melancholic features who experience these symptoms, ECT may be a beneficial alternative to polypharmacy. Treatment strategies for M-MDD often implies polypharmacy (8); however, pharmacotherapy alone has limited efficacy in these patients, with a response rate of approximately 40% in those with melancholic depression (10) and is associated with notable side effects (39). Introducing ECT earlier in the treatment algorithm for these patients could potentially reduce response time and minimize the side effects associated with polypharmacy.

Thirdly, residual symptoms following acute ECT treatment may predict the risk of relapse. For instance, Lambrichts et al. examined the association between individual MADRS items at the end of acute ECT and relapse at six-month follow-up in patients with late life depression (28). Their findings indicated that residual symptoms such as sleep disturbances and lassitude were significantly associated with a higher risk of relapse. This suggests that addressing these symptoms could help reduce post-ECT relapse rates in late-life depression. Although studies with larger sample sizes are needed to confirm these associations, based on the limited scientific evidence currently available, it can be hypothesized that identifying and treating M-MDD patients with ECT as a priority may be beneficial, as they could experience fewer residual symptoms after acute ECT treatment.

One possible explanation for our findings may lie in the neuroendocrine-diencephalic theory of ECT, which suggests that ECT works by correcting the neuroendocrine dysfunctions associated with M-MDD (40). M-MDD is indeed linked to hypothalamic-pituitary-adrenal (HPA) axis dysfunction, resulting in altered hormone secretion, particularly of cortisol (3–5, 40). Dysregulated cortisol levels are associated with sleep disturbances, as the HPA axis plays a key role in regulating the sleep-wake cycle, and may also contribute to appetite control issues, thereby exacerbating appetite disturbances in mood disorders. Chronic elevation of cortisol has been connected to cognitive deficits and impairments in brain function. Additionally, prolonged HPA axis activation and elevated cortisol levels may help sustain negative emotions and thoughts in individuals with mood disorders (41).

Another possible explanation could be related to the age difference between the subgroups, as the M-MDD group is on average 8 years older than the U-MDD group. Some studies suggest that age may be positively associated with ECT efficacy (19). However, after adjusting for age, the difference in MADRS score changes between the M-MDD and U-MDD groups remained significant.

Furthermore, the severity of depressive symptoms is also positively associated with response to ECT (19), and patients with

melancholic features typically present with higher baseline MADRS scores (42). This was evident in our M-MDD group, which had higher baseline MADRS scores and showed a greater overall reduction in MADRS scores after ECT compared to the U-MDD group. This may help explain the observed differential response in the M-MDD group in clinical practice.

This exploratory study lays the groundwork for a prospective study to further investigate differences in MADRS outcomes following ECT in patients with late-life depression, specifically comparing those with melancholic versus unspecified features. Future prospective studies should investigate whether the differential effects of ECT on depressive symptoms in patients with M-MDD and U-MDD persist beyond the one-month treatment period used in this exploratory study, particularly as ECT session frequency decreases. Investigating specific response factors and examining the relationships between various biomarkers or temperamental traits and reductions in depressive symptoms across different depressive subtypes could yield valuable insights.

Adjusting for a list of potential confounding factors will be essential in future analyses, as these may influence the observed differences in response between subtypes; however, this will require a larger sample size. Additionally, applying a correction method, such as Bonferroni adjustment, to account for multiple comparisons will enhance the validity of the results and reduce the risk of Type I errors in the future studies where the aim extends beyond exploration.

A key hypothesis derived from the current analysis is that patients with symptoms such as apparent sadness, inability to feel, pessimistic thoughts, reduced appetite, sleep disturbances, and concentration difficulties may experience a more substantial reduction in MADRS scores following ECT. Testing this hypothesis in a larger sample and over a longer treatment period will be crucial to validate these findings and to refine personalized treatment strategies for melancholic and unspecified depression.

Moreover, future research should compare ECT with other neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and other electromagnetic therapies, as these also may show variability in response and remission rates for MDD. Using a single-item approach to MADRS in these studies could uncover subtle changes in individual symptoms that might be masked by aggregate scores, thereby allowing for a more detailed interpretation of treatment effects across neuromodulation interventions for depression.

4.1 Limits

One limitation in this study is that some patients received unilateral ECT, while the majority received bilateral treatment, which may impact treatment efficacy. However, the proportion of patients receiving unilateral treatment is low (17%).

Another limitation relates to the sample size, which may limit the generalizability of our findings and the ability to include all confounding factors in adjusted model, including baseline depression severity. As previously mentioned, these analyses are exploratory and intended to provide a basis for future prospective studies with a larger number of participants.

Additionally, our dataset does not include information on the history of depressive episodes between the first episode and the first ECT treatment for each participant. Although the number of previous depressive episodes is not known to be a predictor of ECT response in the general population with depression (37), investigating this association across different subtypes could yield interesting insights.

Baseline depression severity also presents a potential limitation, as patients with melancholic features often have higher initial MADRS scores, which may influence the differential response observed between subtypes. Future studies with larger samples that have overlap with respect to depression severity at baseline between M-MDD and U-MDD groups will be necessary to confirm these effects while controlling for baseline severity.

Finally, this study does not include patients with atypical features. While the original study design aimed to include melancholic, atypical, and unspecified subtypes, we did not find any patients with atypical depression who received ECT in our population according to DSM-5 criteria. This finding aligns with Husain et al. (43), which assessed remission probabilities following ECT in 453 depressed participants, of whom only 36 had atypical features (43). Interestingly, the atypical group was 2.6 times more likely to remit than the majority group with more typical features (95% CI=1.1-6.2). The reason why patients with atypical depression are rarely referred for ECT remains unclear, although this is a significant issue given that patients with atypical depression represent a substantial subgroup of MDD patients.

4.2 Strengths

This exploratory analysis is the first study to examine the response to each MADRS item specifically between M-MDD and U-MDD, in contrast to previous research that compared melancholic with non-melancholic patients (32–36). Another strength of this study is its naturalistic population analysis, which provides insights into how this type of intervention performs in real-world interventional psychiatry clinical practice.

5 Conclusion

In this exploratory study, we found a greater reduction in MADRS scores for items such as apparent sadness, inability to feel, pessimistic thoughts, reduced appetite and sleep, and difficulty concentrating in M-MDD patients compared to U-MDD patients. Although our findings should be interpreted with consideration of several limitations, they may contribute to defining a more personalized psychiatric treatment approach for severely depressed patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Commission Cantonale d'éthique de la recherche sur l'être humain. CER-VD. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. SR: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. KS: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. JS: Conceptualization, Writing – review & editing. LZ: Conceptualization, Writing – review & editing. Av: Conceptualization, Methodology, Validation, Visualization, Writing – review & editing. PV: Conceptualization, Methodology, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1491451/full#supplementary-material

References

1. Mathers C. *The global burden of disease: 2004 update*. Geneva, Switzerland: World Health Organization (2008).

2. Antonijevic IA. Depressive disorders—is it time to endorse different pathophysiologies? *Psychoneuroendocrinology*. (2006) 31:1–15. doi: 10.1016/j.psyneuen.2005.04.004

3. Ghaemi SN, Vöhringer PA. The heterogeneity of depression: an old debate renewed. *Acta Psychiatr Scand*. (2011) 124:497. doi: 10.1111/j.1600-0447.2011.01746.x

4. Kaestner F, Hettich M, Peters M, Sibrowski W, Hetzel G, Ponath G, et al. Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity. *J Affect Disord*. (2005) 87:305–11. doi: 10.1016/j.jad.2005.03.012

5. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry*. (2013) 18:692–9. doi: 10.1038/mp.2012.144

6. Moyano BP, Strippoli MF, Ranjbar S, Vandeleur CL, Vaucher J, Preisig M, et al. Stability of the subtypes of major depressive disorder in older adults and the influence of mild cognitive impairment on the stability. *Am J Geriatr Psychiatry*. (2023) 31:503–13. doi: 10.1016/j.jagp.2023.02.041

7. Favaretto E, Bedani F, Brancati GE, De Berardis D, Giovannini S, Scarcella L, et al. Synthesising 30 years of clinical experience and scientific insight on affective temperaments in psychiatric disorders: State of the art. *J Affect Disord*. (2024) 362:406–15. doi: 10.1016/j.jad.2024.07.011

8. Dold M, Bartova L, Fugger G, Kautzky A, Mitschek MM, Fabbri C, et al. Melancholic features in major depression–a European multicenter study. *Prog Neuropsychopharmacol Biol Psychiatry*. (2021) 110:110285. doi: 10.1016/j.pnpbp.2021.110285

9. Brown WA. Treatment response in melancholia. *Acta Psychiatr Scand Suppl*. (2007) 2007(433):125–9. doi: 10.1111/j.1600-0447.2007.00970.x

10. Undurraga J, Vázquez GH, Tondo L, Baldessarini RJ. Antidepressant responses in direct comparisons of melancholic and non-melancholic depression. *J Psychopharmacol*. (2020) 34:1335–41. doi: 10.1177/0269881120953983

11. Lin CH, Huang CJ, Liu SK. Melancholic features in inpatients with major depressive disorder associate with differential clinical characteristics and treatment outcomes. *Psychiatry Res*. (2016) 238:368–73. doi: 10.1016/j.psychres.2015.11.009

12. Musil R, Seemüller F, Meyer S, Spellmann I, Adli M, Bauer M, et al. Subtypes of depression and their overlap in a naturalistic inpatient sample of major depressive disorder. *Int J Methods Psychiatr Res*. (2018) 27. doi: 10.1002/mpr.v27.1

13. Parker G, Bassett D, Outhred T, Morris G, Hamilton A, Das P, et al. Defining melancholia: A core mood disorder. *Bipolar Disord*. (2017) 19:235–7. doi: 10.1111/bdi.2017.19.issue-3

14. Swierkosz-Lenart K, Mall JF, von Gunten A. Interventional psychiatry in the management of behavioural and psychological symptoms of dementia: a qualitative review. *Swiss Med Wkly*. (2019) 149:w20140. doi: 10.4414/smw.2019.20140

15. Pozuelo Moyano B, Swierkosz Lenart K, Rosselet Amoussou J, von Gunten A, Schuster J-P. Prediction of electroconvulsive therapy response and remission in late-life depression: a review. *Swiss Med Weekly*. (2024) 154:3684. doi: 10.57187/s.3684

16. Rasmussen K. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (second edition). *J Ect*. (2002) 18:58–9. doi: 10.1097/00124509-200203000-00015

17. Kellner CH, Knapp R, Husain MM, Rasmussen K, Sampson S, Cullum M, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry*. (2010) 196:226–34. doi: 10.1192/bjp.bp.109.066183

18. Loef D, Hoogendoorn AW, Somers M, Mocking RJT, Scheepens DS, Scheepstra KWF, et al. A prediction model for electroconvulsive therapy effectiveness in patients with major depressive disorder from the Dutch ECT Consortium (DEC). *Mol Psychiatry*. (2024). doi: 10.1038/s41380-024-02803-2

19. van Diermen L, van den Ameele S, Kamperman AM, Sabbe BCG, Vermeulen T, Schrijvers D, et al. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *Br J Psychiatry*. (2018) 212:71–80. doi: 10.1192/bjp.2017.28

20. Cappon DB, Pascual-Leone A. Toward precision noninvasive brain stimulation. *Am J Psychiatry*. (2024) 181:795–805. doi: 10.1176/appi.ajp.20240643

21. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*. Washington, DC: American Psychiatric Association (2013).

22. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. (1979) 134:382–9. doi: 10.1192/bjp.134.4.382

23. Fried EI, Nesse RM. Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. *BMC Med*. (2015) 13:1–11. doi: 10.1186/s12916-015-0325-4

24. Okazaki M, Tominaga K, Higuchi H, Utagawa I, Nakamura E, Noguchi M, et al. Predictors of response to electroconvulsive therapy obtained using the three-factor structure of the Montgomery and Asberg Depression Rating Scale for treatment-resistant depressed patients. *J Ect*. (2010) 26:87–90. doi: 10.1097/YCT.0b013e3181b00f32

25. Spashett R, Fernie G, Reid IC, Cameron IM. MADRS symptom subtypes in ECT-treated depressed patients: relationship to response and subsequent ECT. *J Ect*. (2014) 30:227–31. doi: 10.1097/YCT.0000000000000091

26. Tominaga K, Okazaki M, Higuchi H, Utagawa I, Nakamura E, Yamaguchi N. Symptom predictors of response to electroconvulsive therapy in older patients with treatment-resistant depression. *Int J Gen Med*. (2011) 4:515–9. doi: 10.2147/IJGM.S21029

27. Carstens L, Hartling C, Stippl A, Domke AK, Herrera-Mendelez AL, Aust S, et al. A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. *Eur Arch Psychiatry Clin Neurosci*. (2021) 271:1275–84. doi: 10.1007/s00406-021-01301-8

28. Lambrichts S, Vansteelandt K, Hebbrecht K, Wagenmakers MJ, Oudega ML, Obbels J, et al. Which residual symptoms predict relapse after successful electroconvulsive therapy for late-life depression? *J Psychiatr Res*. (2022) 154:111–6. doi: 10.1016/j.jpsychires.2022.07.056

29. Floden L, Hudgens S, Jamieson C, Popova V, Drevets WC, Cooper K, et al. Evaluation of individual items of the patient health questionnaire (PHQ-9) and Montgomery-Asberg depression rating scale (MADRS) in adults with treatment-resistant depression treated with esketamine nasal spray combined with a new oral antidepressant. *CNS Drugs*. (2022) 36:649–58. doi: 10.1007/s40263-022-00916-2

30. Hudgens S, Floden L, Symonds T, Slagle A. PRM9-a longitudinal, item-level analysis methodology to support the interpretability of multi-item patient-reported outcomes. *Value Health*. (2018) 21:S357. doi: 10.1016/j.jval.2018.09.2134

31. Mankad MV, Beyer JL, Weiner RD, Krystal A. *Clinical manual of electroconvulsive therapy*. USA: American Psychiatric Pub (010).

32. Fink M, Rush AJ, Knapp R, Rasmussen K, Mueller M, Rummans TA, et al. DSM melancholic features are unreliable predictors of ECT response: a CORE publication. *J Ect*. (2007) 23:139–46. doi: 10.1097/yct.0b013e3180337344

33. Veltman EM, de Boer A, Dols A, van Exel E, Stek ML, Sienaert P, et al. Melancholia as predictor of electroconvulsive therapy outcome in later life. *J Ect*. (2019) 35:231–7. doi: 10.1097/YCT.0000000000000579

34. Alves LP, Freire TF, Fleck MP, Rocha NS. A naturalistic study of high-dose unilateral ECT among severely depressed inpatients: how does it work in the clinical practice? *BMC Psychiatry*. (2016) 16:396. doi: 10.1186/s12888-016-1095-z

35. Birkenhäger TK, Pluijms EM, Ju MR, Mulder PG, den Broek WW. Influence of age on the efficacy of electroconvulsive therapy in major depression: a retrospective study. *J Affect Disord*. (2010) 126:257–61. doi: 10.1016/j.jad.2010.02.131

36. Bjølseth TM, Engedal K, Benth J, Dybedal GS, Gaarden TL, Tanum L. Clinical efficacy of formula-based bifrontal versus right unilateral electroconvulsive therapy (ECT) in the treatment of major depression among elderly patients: a pragmatic, randomized, assessor-blinded, controlled trial. *J Affect Disord*. (2015) 175:8–17. doi: 10.1016/j.jad.2014.12.054

37. Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *J Clin Psychiatry*. (2015) 76:18164. doi: 10.4088/JCP.14r09528

38. Zhang Z, Jackson SL, Gillespie C, Merritt R, Yang Q. Depressive symptoms and mortality among US adults. *JAMA Netw Open*. (2023) 6:e2337011–e. doi: 10.1001/jamanetworkopen.2023.37011

39. Trindade E, Menon D, Topfer L-A, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *Cmaj*. (1998) 159:1245–52.

40. Bolwig TG. How does electroconvulsive therapy work? Theories on its mechanism. *Can J Psychiatry*. (2011) 56:13–8. doi: 10.1177/070674371105600104

41. Bao AM, Swaab DF. The human hypothalamus in mood disorders: The HPA axis in the center. *IBRO Rep*. (2019) 6:45–53. doi: 10.1016/j.ibror.2018.11.008

42. Musil R, Seemüller F, Meyer S, Spellmann I, Adli M, Bauer M, et al. Subtypes of depression and their overlap in a naturalistic inpatient sample of major depressive disorder. *Int J Methods Psychiatr Res*. (2018) 27:e1569. doi: 10.1002/mpr.v27.1

43. Husain MM, McClintock SM, Rush AJ, Knapp RG, Fink M, Rummans TA, et al. The efficacy of acute electroconvulsive therapy in atypical depression. *J Clin Psychiatry*. (2008) 69:406–11. doi: 10.4088/JCP.v69n0310

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A meta-analysis comparing the effectiveness and safety of repetitive transcranial magnetic stimulation versus theta burst stimulation for treatment-resistant depression

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Objective: This study compares the safety and effectiveness of theta-burst stimulation (TBS) and repetitive transcranial magnetic stimulation (rTMS) for treating treatment-resistant depression (TRD).

Methods: We reviewed randomized controlled trials (RCTs) that evaluated rTMS and TBS in managing TRD. Searches were conducted in PubMed, Embase, the Cochrane Library, and Web of Science for studies published up to July 31, 2024. Data from these studies were analyzed using statistical software.

Results: Five RCTs involving 1,196 patients were included, with 553 receiving rTMS and 663 receiving TBS. The analysis found no significant differences between rTMS and TBS in reducing depression [SMD = -0.07, 95% CI (-0.19, 0.04)] or anxiety [SMD = -0.02, 95% CI (-0.15, 0.11)], nor in side effects like headaches [OR = 1.00, 95% CI (0.72, 1.40)], nausea [OR = 1.42, 95% CI (0.79, 2.54)], or fatigue [OR = 0.87, 95% CI (0.46, 1.64)].

Conclusions: Both rTMS and TBS are similarly effective in reducing depression and anxiety symptoms, with comparable side effect profiles. However, TBS is more time-efficient, with sessions lasting only 192 seconds, making it a cost-effective option for patients. These findings support TBS as a practical treatment choice for TRD.

KEYWORDS

transcranial magnetic stimulation, theta burst stimulation, treatment-resistant depression, meta-analysis, depression

1 Introduction

Major depressive disorder (MDD) is a significant global public health concern, characterized by high morbidity, a high incidence of suicide, and a high recurrence rate (1, 2). Selective serotonin reuptake inhibitors (SSRIs) are the cornerstone of current MDD therapy. However, studies show that approximately 44% of patients who complete a full course of antidepressant treatment fail to achieve remission, leading to a prolonged depressive state (3) and ultimately resulting in treatment-resistant depression (TRD). Research indicates that about one-third of patients with TRD attempt suicide at least once in their lifetime (4, 5), severely impairing social functioning, increasing societal burdens, and posing a significant challenge in clinical practice (6–8).

TRD is typically defined as depression that does not respond to a full course of treatment with two or more antidepressants (9). Conventional pharmacological treatments often show limited efficacy in TRD, with delayed onset of therapeutic effects, significant cognitive side effects, and low remission rates, all of which contribute to poor medication adherence (10, 11). In light of these limitations, recent research has emphasized the importance of exploring alternative and multimodal strategies to address the complexity of TRD. Approaches such as augmentation with atypical antipsychotics, mood stabilizers, and agents targeting non-monoaminergic systems have demonstrated potential benefits (12, 13). For instance, cariprazine, an atypical antipsychotic, has shown efficacy as an augmentation agent in TRD, particularly in patients who failed previous augmentation trials. Additionally, treatments like esketamine nasal spray provide rapid-acting options by targeting the glutamate pathway, further underscoring the need for innovative interventions in TRD management.One promising alternative for the treatment of TRD is rTMS (14). rTMS is a relatively new brain stimulation method that has shown potential in several studies (6, 15). Its use for the treatment of TRD has been approved by Health Canada (2002), the US Food and Drug Administration (2008), and regulatory bodies in the EU, Australia, Israel (16), and other regions.

A more recent form of rTMS is TBS, a sophisticated non-invasive neuromodulation technique with a distinct stimulation pattern. Compared to traditional rTMS, TBS offers several advantages, including lower stimulation intensity, shorter session duration, better tolerability, and a closer approximation to natural neuronal activity. TBS can induce stronger and more sustained cortical excitability, thereby reducing the overall treatment duration and producing faster antidepressant effects (17). Despite these advantages, the relative effectiveness of rTMS versus TBS in treating TRD remains a topic of ongoing debate (18). This study aims to address this issue through a meta-analysis, providing professionals with clearer recommendations and offering patients more effective treatment options.

Abbreviations: TBS, theta-burst stimulation; iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; RCTs, randomized controlled trials; MDD, major depressive disorder; TRD, treatment-resistant depression; FEM, fixed effects model; FEM, random-effects model; ACC, anterior cingulate cortex; lDLPFC, left dorsolateral prefrontal cortex.

2 Methods

2.1 Systematic review registration

This systematic review has been officially registered in the PROSPERO database, an international registry of prospective systematic reviews of health-related interventions produced by the National Institute for Health Research (19).

2.2 Inclusion and exclusion criteria

The study population consisted of individuals diagnosed with treatment-resistant depression (TRD). The experimental group received repetitive transcranial magnetic stimulation (rTMS), while the control group was treated with theta-burst stimulation (TBS). The primary outcomes measured were anxiety and depression levels, with adverse event rates as secondary outcomes. Only randomized controlled trials (RCTs) were included. Exclusion criteria applied to meeting abstracts, meta-analyses, systematic reviews, animal studies, studies with inaccessible full text, case reports, and research involving participants who had previously undergone other treatments.

2.3 Literature search

A comprehensive search was conducted across the PubMed, Embase, Cochrane Library, and Web of Science databases. Keywords such as “TBS,” “rTMS,” and “TRD” were used both as free-text terms and indexed phrases. The final search update occurred on July 31, 2024. The complete search strategy is outlined in Supplementary Table S1 in the Supplementary Material.

2.4 Data extraction

Two authors independently screened the literature based on predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion, and if necessary, a third reviewer was consulted to reach a consensus. Key information extracted from the eligible studies included study characteristics, average age, sex distribution, sample size, publication year, intervention methods, and outcomes.

2.5 Bias risk assessment

The bias in the included studies was assessed independently by two reviewers using the Cochrane Collaboration’s methods (20). A third reviewer was consulted to resolve any disagreements. The assessment covered seven domains: completeness of outcome data (attrition bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), selective reporting (reporting bias), and

other potential sources of bias. Among these, the most common biases identified were performance bias, due to inadequate blinding of participants and personnel, and detection bias, arising from the lack of blinding of outcome assessors. These biases could potentially lead to overestimation or underestimation of treatment effects, influencing the reliability and validity of the study outcomes. In particular, performance bias may result in differences in care or treatment between groups, while detection bias can affect the accuracy of outcome measurements, leading to biased conclusions about the effectiveness of interventions.

Each study was evaluated based on these criteria. Studies that met all the requirements were classified as having "low risk of bias," indicating high quality and minimal risk. Studies that did not meet the criteria were labeled as having "high risk," suggesting significant bias and lower quality. Those that partially met the criteria were categorized as having "unclear risk," indicating a moderate risk of bias.

2.6 Data analysis

Data were statistically analyzed using Stata 15.0 (Stata Corp., College Station, TX, USA). Heterogeneity among the included studies was assessed using the Q-statistic and the I^2-statistic. I^2 values were interpreted as follows: 25% indicated low heterogeneity, 50% indicated moderate heterogeneity, and 75% indicated high heterogeneity. If the I^2 value was 50% or higher, sensitivity analysis was performed to explore potential sources of heterogeneity. For I^2 values below 50%, a fixed effects model (FEM) was applied. For continuous variables, SMDs and 95% CIs were calculated, while ORs and 95% CIs were used for dichotomous variables. Additionally, Egger's test and a random-effects model (REM) were applied to assess publication bias.

3 Results

3.1 Literature search

Figure 1 illustrates the methods used for the literature search. A total of 703 articles were identified from PubMed (n = 115), Embase (n = 162), the Cochrane Library (n = 158), and Web of Science (n = 268). After removing 300 duplicates and excluding 396 articles based on titles and abstracts, two additional articles were eliminated after full-text review. Ultimately, five randomized controlled trials (RCTs) (21–25) were included in the study.

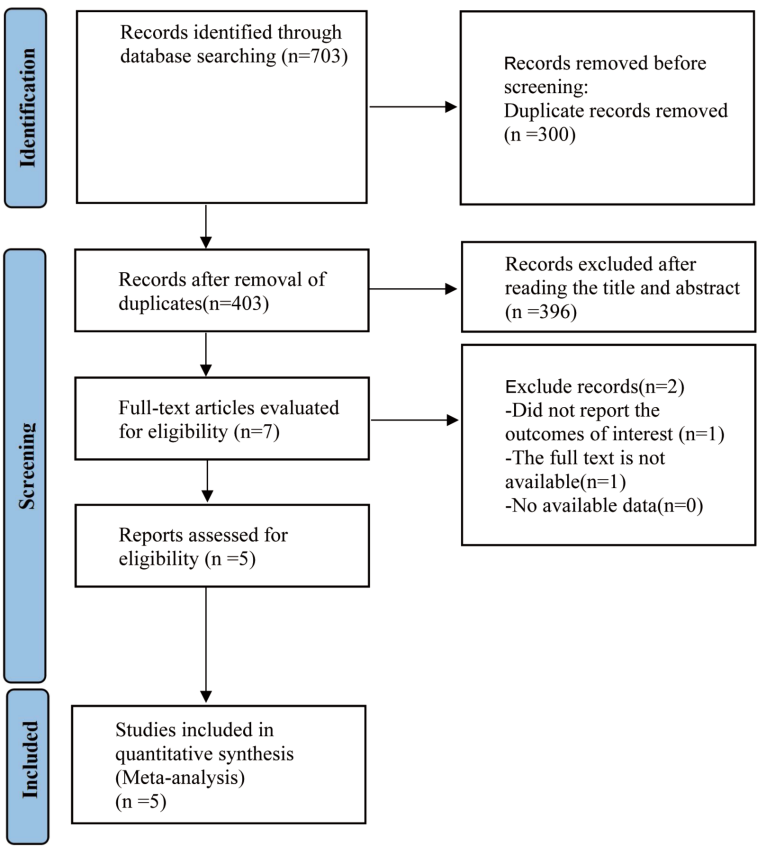

FIGURE 1
RISMA diagram of research procedure. PRISMA, preferred reporting items for systemic review and meta-analysis.

3.2 Baseline features and bias risk in associated research

A total of 1,196 participants, aged 41.6 to 61.7 years, were involved in the five investigations. The TBS group included 663 participants, while the rTMS group had 553. TBS was administered at a frequency of 50 Hz, and rTMS at 10 Hz. Table 1 provides information on the baseline characteristics of the included studies. All studies described the randomization procedures used, although some did not fully detail the blinding strategies. Figures 2 and 3 present the risk of bias for each study.

3.3 Meta-analysis results

3.3.1 Depression scores

All five studies reported depression scores. Since the test for heterogeneity (I^2 = 46.3%, p = 0.097) indicated moderate heterogeneity, a fixed-effects model was utilized. The analysis (Figure 4) showed no significant difference between rTMS and TBS in terms of depression scores [SMD = -0.07, 95% CI (-0.19, 0.04)].

3.3.2 Anxiety score

Anxiety scores were reported in four studies. With no heterogeneity detected (I^2 = 0%, p = 0.870), a fixed-effects model was used. The data (Figure 5) revealed no statistically significant difference in anxiety levels between rTMS and TBS [SMD = -0.02, 95% CI (-0.15, 0.11)].

3.3.3 Headache

Headache incidence was reported in three trials. With no evidence of heterogeneity (I^2 = 0%, p = 0.735), a fixed-effects model was applied. According to Figure 6, there was no significant difference in the occurrence of headaches between rTMS and TBS [OR = 1.00, 95% CI (0.72, 1.40)].

3.3.4 Nausea

Three studies reported nausea incidence. Since there was no heterogeneity (I^2 = 0%, p = 0.518), a fixed-effects model was used. The analysis (Figure 7) showed no significant difference in the occurrence of nausea between rTMS and TBS [OR = 1.42, 95% CI (0.79, 2.54)].

3.3.5 Fatigue

Three studies reported on fatigue. Based on the heterogeneity test results (I^2 = 0%, p = 0.831), a fixed-effects model was applied. The analysis found no significant difference in fatigue between rTMS and TBS (Figure 8; OR = 0.87, 95% CI (0.46, 1.64)).

3.4 Publication bias

Egger's test was used to assess publication bias. The results indicated no significant publication bias across the following categories: depression (p = 0.680), anxiety (p = 0.635), headache (p = 0.125), nausea (p = 0.991), and fatigue (p = 0.436).

4 Discussions

This meta-analysis is the first to evaluate both the safety and efficacy of rTMS compared to TBS in the treatment of TRD. Our results revealed no significant differences in the incidence of headaches, nausea, and fatigue, nor in the depression and anxiety scores between rTMS and TBS. These findings suggest that the 37.5-minute, 10 Hz rTMS protocol may not be as effective as the 3-minute intermittent TBS (iTBS) strategy for treating TRD.

rTMS is a treatment method that uses focused magnetic field pulses to directly stimulate the left dorsolateral prefrontal cortex (DLPFC) with a 10 Hz frequency. It has been shown to be a well-tolerated, evidence-based treatment widely used for TRD (26). Theta burst stimulation (TBS) is a non-invasive brain stimulation technique aimed at modulating the underlying neural networks in psychiatric and neurological disorders. TBS can be applied in either intermittent or continuous forms (27). TBS utilizes patterned burst stimulation, requiring only a fraction of the time compared to traditional protocols (28). Compared to standard transcranial magnetic stimulation, TBS may offer a more effective form of physiological stimulation, as it is based on the coupling of brain γ and θ frequency rhythms (20).Additionally, patient-specific factors, such as affective temperament traits, have been shown to influence treatment outcomes in psychiatric disorders, including TRD. Recent studies highlight the role of temperaments as stable, genetically determined predispositions that can modulate clinical dimensions such as disease course, treatment adherence, and therapeutic response (29). For instance, cyclothymic and

TABLE 1 Baseline Characteristics and Methodological Quality of Included Studies.

Study	Year	Country	Sample size		Gender (M/F)	Mean age		Intervention		Outcome
			rTMS	TBS		rTMS	TBS	rTMS	TBS	
Blumberger	2022	Canada	87	85	80/92	67.1	66.3	10HZ	50HZ	F1; F2; F3
Blumberger	2018	Canada	205	209	168/246	43.2	41.6	10HZ	50HZ	F1; F2; F3
Bulteau	2022	France	30	30	19/41	48.5	56.1	10HZ	50HZ	F1;
Chen	2021	Australia	84	211	103/192	48.5	48.67	10HZ	50HZ	F1; F3
Morriss	2024	UK	127	128	123/132	43.8	43.7	10HZ	50HZ	F1; F2; F3

rTMS, repetitive transcranial magnetic stimulation; TBS, Theta burst stimulation; M/F, Male/female; F1, depression; F2, adverse events; F3, anxiety.

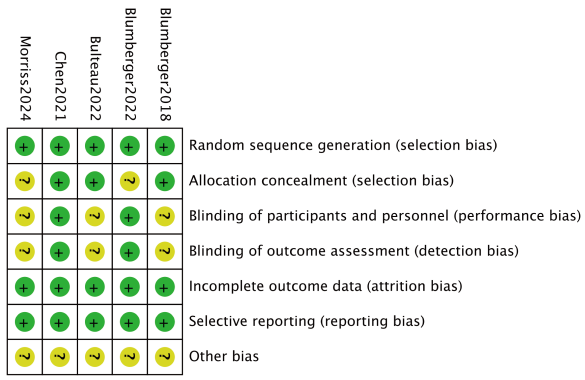

FIGURE 2
Bias risk summary.

depressive temperaments are associated with poorer adherence and less favorable outcomes in mood disorders, whereas hyperthymic temperament may confer resilience and predict better responses to certain interventions. Understanding the temperamental profiles of TRD patients could help refine treatment strategies and improve personalized care approaches.The conventional 10 Hz rTMS protocol requires longer sessions and typically takes 4–6 weeks to produce significant antidepressant effects. In contrast, TBS is a more time-efficient form of rTMS, offering comparable antidepressant efficacy in a shorter treatment duration (30). Studies have demonstrated that multiple daily sessions of TBS, either accelerated or intensified, can result in clinically meaningful antidepressant effects in fewer treatment days (31). While many studies on accelerated or intensified TBS have focused on patients with TRD, the subjects in this trial were experiencing their first

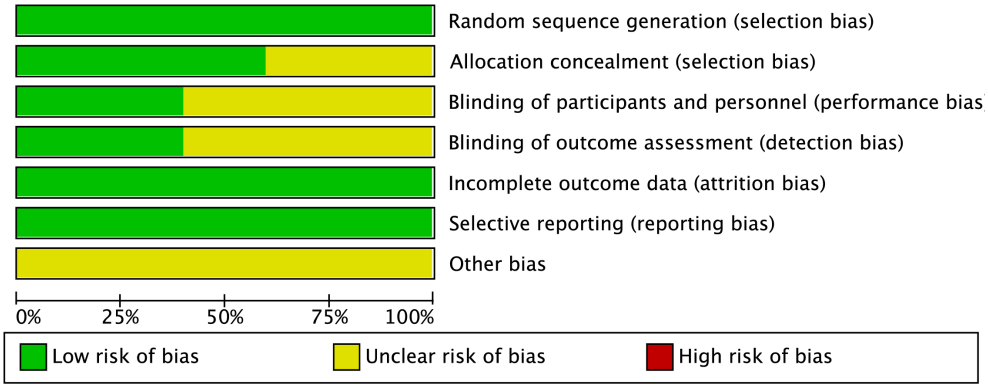

FIGURE 3
Bias risk graph.

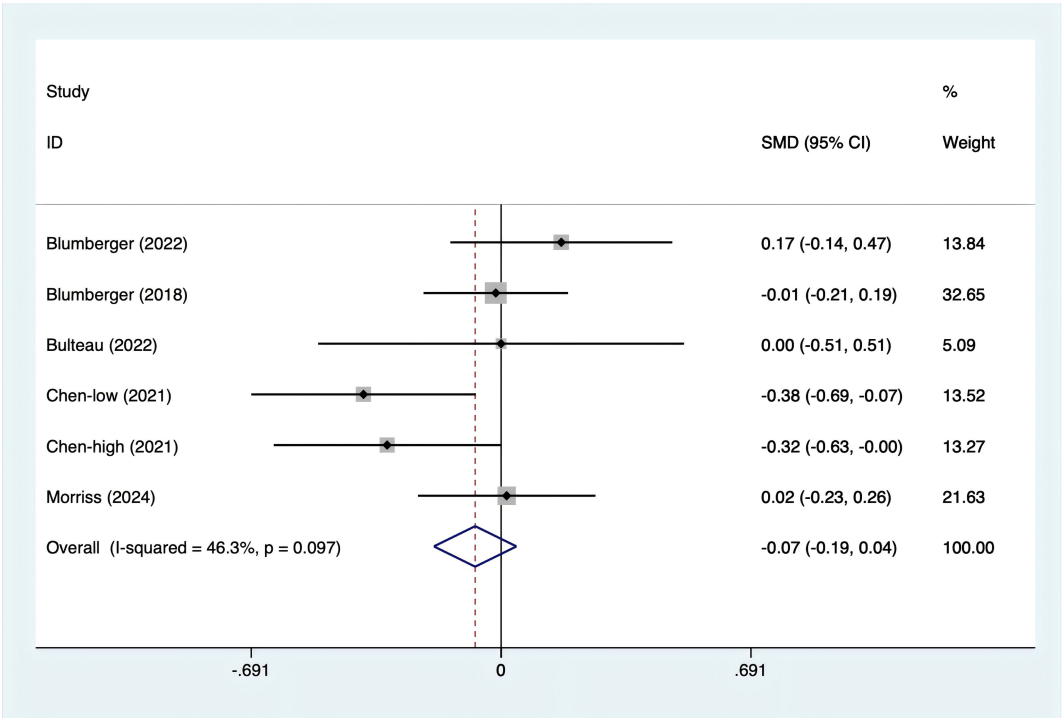

FIGURE 4
Forest plot of rTMS and TBS in depression scores.

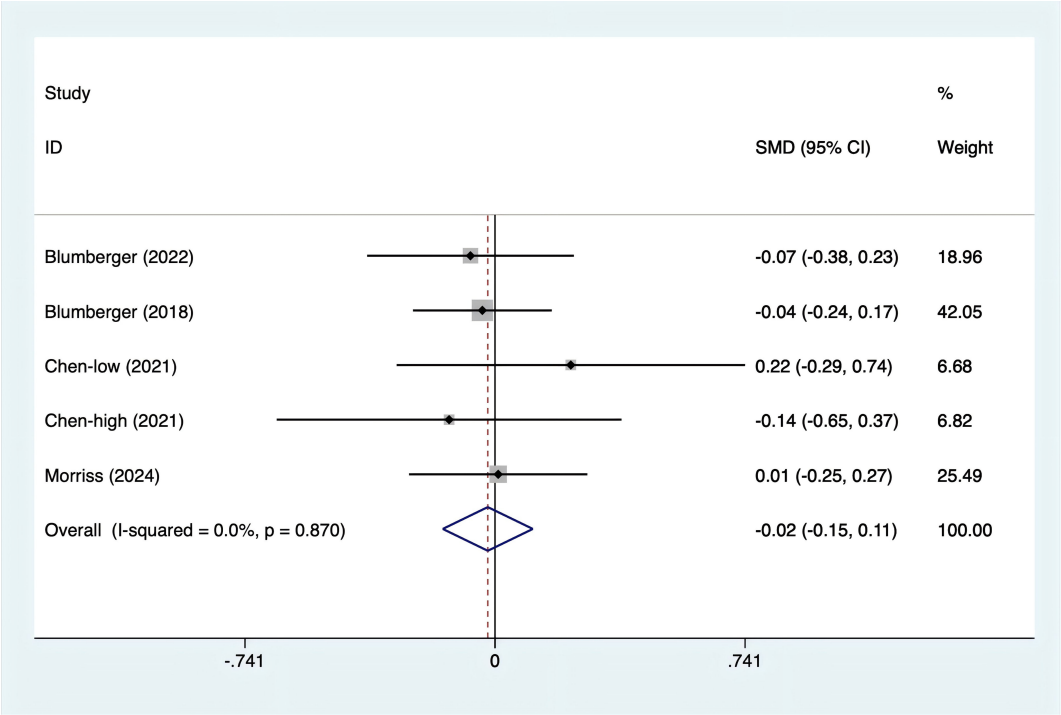

FIGURE 5
Forest plot of rTMS and TBS in depression scores.

episode of depression. Early and rapid improvement of clinical symptoms in these patients may improve treatment adherence, reduce suicide risk, lower relapse rates, and aid in the recovery of social functioning (32). In this study, different TMS modalities, combined with sertraline, were used to treat first-episode depression. The results demonstrated that both intensive TBS and 10 Hz rTMS provided similar clinical efficacy, improving depressive and anxiety symptoms, sleep quality, and cognitive function.

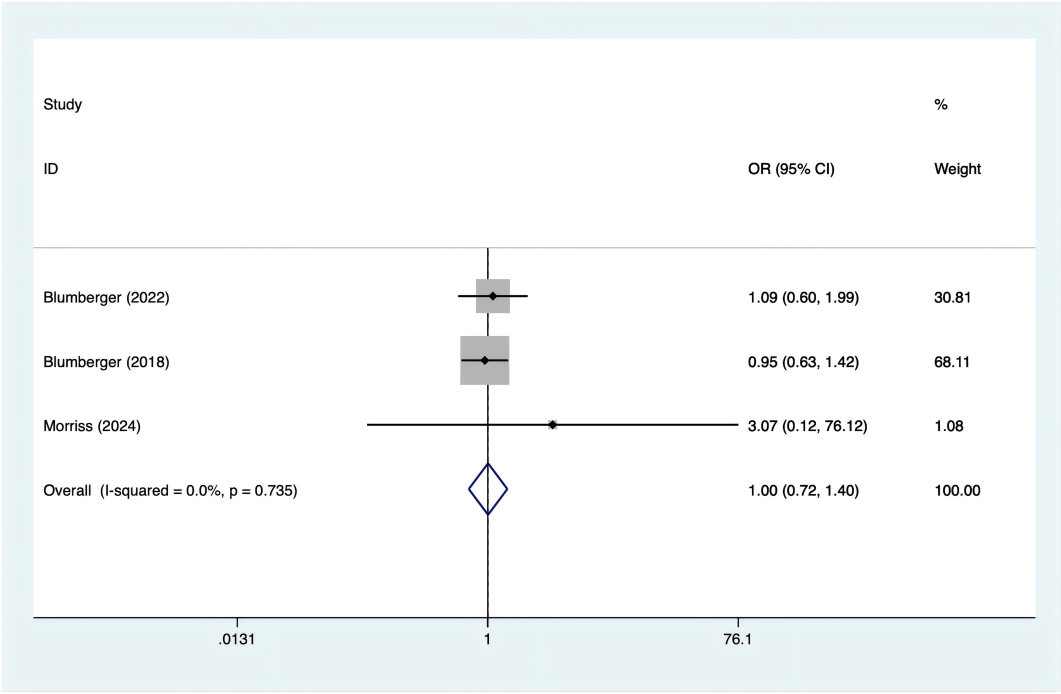

FIGURE 6
Forest plot of rTMS and TBS in anxiety scores.

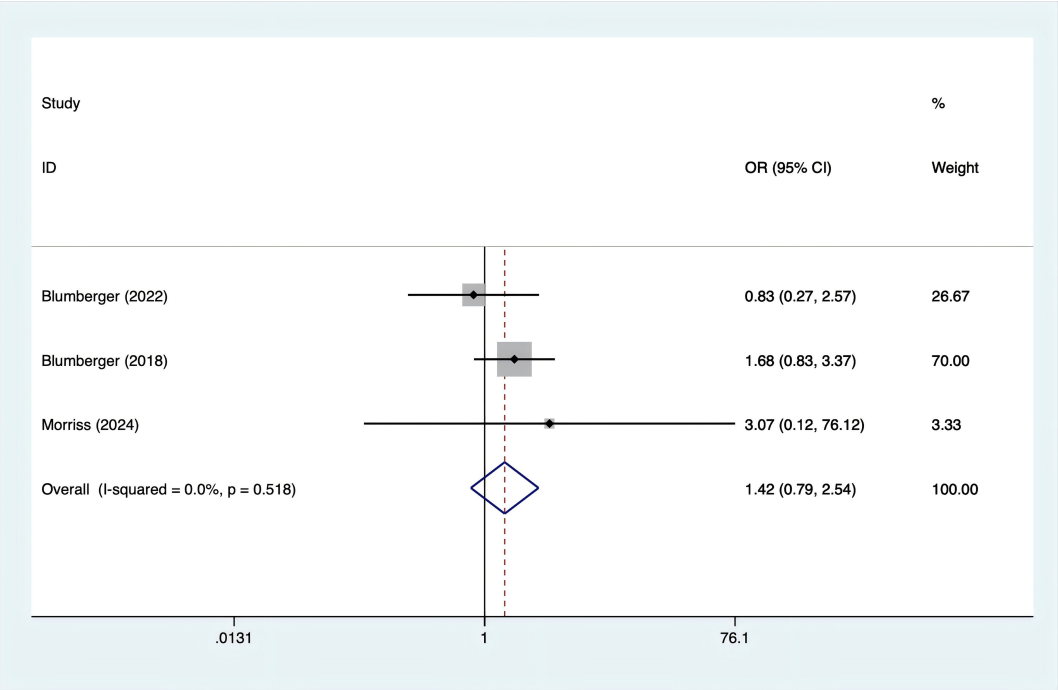

FIGURE 7
Forest plot of rTMS and TBS in the incidence of nausea.

Notably, intensive TBS showed greater improvement in executive function. Additionally, both treatments were found to be safe and well-tolerated.

Several studies (33, 34) have reported that iTBS offers similar antidepressant efficacy to 10 Hz rTMS, and our findings are consistent with these results. Additionally, two RCTs that tailored and expedited either rTMS or iTBS based on the functional connectivity between the subgenual anterior cingulate cortex (ACC) and the left dorsolateral prefrontal cortex (lDLPFC) demonstrated more substantial reductions in depressive symptoms over a 3–4 week period compared to

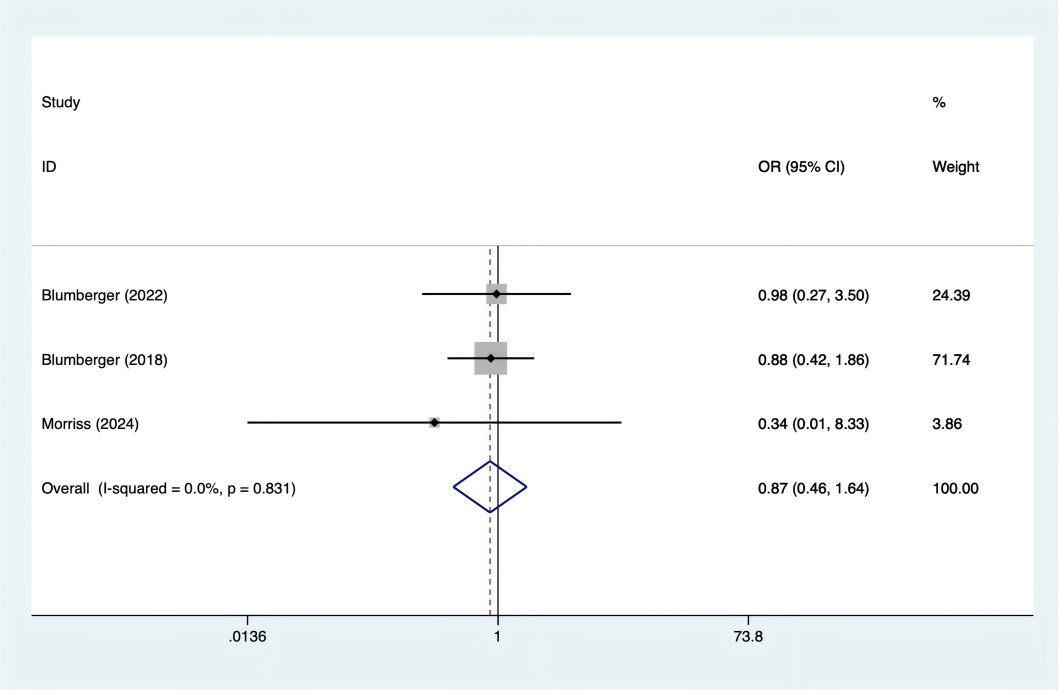

FIGURE 8
Forest plot of rTMS and TBS in the occurrence of fatigue.

conventional or sham TBS (35, 36). This suggests that targeting the lDLPFC may be critical for the effectiveness of TMS in treating depression (37). Another study (38) comparing twice-daily TBS with once-daily TBS found no significant difference in antidepressant efficacy after one week of treatment. However, by the end of the 12-week observation period, twice-daily TBS showed superior antidepressant effects, indicating that increasing the frequency of treatments may not result in immediate improvement, but the benefits of intensive TBS may emerge over time.

Previous research has shown that high-frequency rTMS has anxiolytic effects in patients with depression and co-occurring anxiety symptoms (39). We also observed that intensive TBS can alleviate anxiety symptoms. Some studies suggest that rTMS targeting the medial prefrontal cortex and dorsal ACC may help manage anxiety (40). Further research using neuroimaging and electrophysiological techniques is needed to clarify the precise mechanisms by which rTMS targeting the dorsolateral prefrontal cortex improves both anxiety and depression in individuals with concurrent anxiety symptoms.

This study has several limitations. First, the inclusion of only five RCTs limits the generalizability of the findings, reducing statistical power and increasing the risk of errors. Future research should aim to include more studies with larger sample sizes to strengthen the evidence. Second, heterogeneity may have arisen from differences in intervention sites, timings, protocols (e.g., dosages, frequencies), and patient populations. The variability in intervention protocols, such as differences in stimulation frequency and treatment duration, is a significant limitation that warrants more detailed discussion in future studies. Such heterogeneity could impact the interpretation of the results, as different treatment parameters may lead to varying outcomes. To address this, future studies should standardize these factors and conduct sensitivity analyses to assess their impact. Third, subgroup analyses were not feasible due to the limited number of studies. Larger, multicenter RCTs with adequate power are needed to enable meaningful subgroup analyses and gain a deeper understanding of treatment effects in specific patient groups. Additionally, the study did not evaluate the potential protective role of routine psychotherapy and counseling interventions, which are commonly used by patients with depression to prevent or alleviate symptoms. In conclusion, while this study provides valuable insights, addressing the limitations of small sample size, intervention protocol heterogeneity, and the lack of assessment of protective factors in future high-quality, multicenter RCTs will be crucial to confirm these findings and provide stronger clinical evidence.

5 Conclusions

While our study did not identify significant differences between rTMS and TBS in terms of depression, anxiety levels, or side effects, TBS offers advantages in terms of shorter session duration and efficiency. With each TBS treatment lasting only 192 seconds, it may be a more affordable option for patients. Therefore, we recommend TBS as a potential therapeutic approach for depression that does not respond to conventional treatments. However, due to the limitations of our research, further high-quality, multicenter randomized controlled trials are necessary to strengthen the evidence supporting this recommendation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

XT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. ZJ: Data curation, Investigation, Writing – review & editing. WY: Data curation, Formal analysis, Writing – original draft. GY: Investigation, Methodology, Project administration, Writing – original draft. XF: Data curation, Project administration, Validation, Writing – original draft. LS: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1504727/full#supplementary-material

References

1. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduct Target Ther*. (2024) 9:30. doi: 10.1038/s41392-024-01738-y

2. Marx W, Penninx B, Solmi M, Furukawa TA, Firth J, Carvalho AF, et al. Major depressive disorder. *Nat Rev Dis Primers*. (2023) 9:44. doi: 10.1038/s41572-023-00454-1

3. Njenga C, Ramanuj PP, de Magalhães FJC, Pincus HA. New and emerging treatments for major depressive disorder. *Bmj*. (2024) 386:e073823. doi: 10.1136/bmj-2022-073823

4. Chakrabarti S, Jolly AJ, Singh P, Yadhav N. Role of adjunctive nonpharmacological strategies for treatment of rapid-cycling bipolar disorder. *World J Psychiatry*. (2023) 13:495–510. doi: 10.5498/wjp.v13.i8.495

5. Gaddey HL, Mason B, Naik A. Depression: managing resistance and partial response to treatment. *Am Fam Physician*. (2024) 109:410–6.

6. Gogulski J, Ross JM, Talbot A, Cline CC, Donati FL, Munot S, et al. Personalized repetitive transcranial magnetic stimulation for depression. *Biol Psychiatry Cognit Neurosci Neuroimaging*. (2023) 8:351–60. doi: 10.1016/j.bpsc.2022.10.006

7. Havlik JL, Wahid S, Teopiz KM, McIntyre RS, Krystal JH, Rhee TG. Recent advances in the treatment of treatment-resistant depression: A narrative review of literature published from 2018 to 2023. *Curr Psychiatry Rep*. (2024) 26:176–213. doi: 10.1007/s11920-024-01494-4

8. Hsu TW, Yeh TC, Kao YC, Thompson T, Brunoni AR, Carvalho AF, et al. The dose-effect relationship of six stimulation parameters with rTMS over left DLPFC on treatment-resistant depression: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. (2024) 162:105704. doi: 10.1016/j.neubiorev.2024.105704

9. Jha MK, Mathew SJ. Pharmacotherapies for treatment-resistant depression: how antipsychotics fit in the rapidly evolving therapeutic landscape. *Am J Psychiatry*. (2023) 180:190–9. doi: 10.1176/appi.ajp.20230025

10. Ledesma-Corvi S, Jornet-Plaza J, Gálvez-Melero L, García-Fuster MJ. Novel rapid treatment options for adolescent depression. *Pharmacol Res*. (2024) 201:107085. doi: 10.1016/j.phrs.2024.107085

11. Patrick RE, Dickinson RA, Gentry MT, Kim JU, Oberlin LE, Park S, et al. Treatment resistant late-life depression: A narrative review of psychosocial risk factors, non-pharmacological interventions, and the role of clinical phenotyping. *J Affect Disord*. (2024) 356:145–54. doi: 10.1016/j.jad.2024.04.017

12. Pessina E, Martini A, Raffone F, Martiadis V. Cariprazine augmentation in patients with treatment resistant unipolar depression who failed to respond to previous atypical antipsychotic add-on. *A case-series. Front Psychiatry*. (2023) 14:1299368. doi: 10.3389/fpsyt.2023.1299368

13. Maina G, Adami M, Ascione G, Bondi E, De Berardis D, Delmonte D, et al. Nationwide consensus on the clinical management of treatment-resistant depression in Italy: a Delphi panel. *Ann Gen Psychiatry*. (2023) 22:48. doi: 10.1186/s12991-023-00478-7

14. Cappon D, den Boer T, Jordan C, Yu W, Metzger E, Pascual-Leone A. Transcranial magnetic stimulation (TMS) for geriatric depression. *Ageing Res Rev*. (2022) 74:101531. doi: 10.1016/j.arr.2021.101531

15. Massé-Leblanc C, Desbeaumes Jodoin V, Nguyen DK, Fournier-Gosselin MP, Stip E, Lespérance P, et al. Evaluating real-world effectiveness of accelerated transcranial magnetic stimulation for treatment-resistant depression in a tertiary referral center based in Quebec, Canada. *Psychiatry Res*. (2024) 332:115685. doi: 10.1016/j.psychres.2023.115685

16. Tsai YC, Li CT, Juan CH. A review of critical brain oscillations in depression and the efficacy of transcranial magnetic stimulation treatment. *Front Psychiatry*. (2023) 14:1073984. doi: 10.3389/fpsyt.2023.1073984

17. Adu MK, Shalaby R, Chue P, Agyapong VIO. Repetitive transcranial magnetic stimulation for the treatment of resistant depression: A scoping review. *Behav Sci (Basel)*. (2022) 12:195. doi: 10.3390/bs12060195

18. Elsayed OH, Ercis M, Pahwa M, Singh B. Treatment-resistant bipolar depression: therapeutic trends, challenges and future directions. *Neuropsychiatr Dis Treat*. (2022) 18:2927–43. doi: 10.2147/NDT.S273503

19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

20. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. (2011) 343:d5928. doi: 10.1136/bmj.d5928

21. Blumberger DM, Mulsant BH, Thorpe KE, McClintock SM, Konstantinou GN, Lee HH, et al. Effectiveness of standard sequential bilateral repetitive transcranial magnetic stimulation vs bilateral theta burst stimulation in older adults with depression: the FOUR-D randomized noninferiority clinical trial. *JAMA Psychiatry*. (2022) 79:1065–73. doi: 10.1001/jamapsychiatry.2022.2862

22. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet (london england)*. (2018) 391:1683–92. doi: 10.1016/S0140-6736(18)30295-2

23. Bulteau S, Laurin A, Pere M, Fayet G, Thomas-Ollivier V, Deschamps T, et al. Intermittent theta burst stimulation (iTBS) versus 10 Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) to alleviate treatment-resistant unipolar depression: a randomized controlled trial (THETA-DEP). *Brain stimulation*. (2022) 15:870–80. doi: 10.1016/j.brs.2022.05.011

24. Chen L, Thomas EHX, Kaewpijit P, Miljevic A, Hughes R, Hahn L, et al. Accelerated theta burst stimulation for the treatment of depression: A randomised controlled trial. *Brain Stimul*. (2021) 14:1095–105. doi: 10.1016/j.brs.2021.07.018

25. Morriss R, Briley PM, Webster L, Abdelghani M, Barber S, Bates P, et al. Connectivity-guided intermittent theta burst versus repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled trial. *Nat Med*. (2024) 30:403–13. doi: 10.1038/s41591-023-02764-z

26. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry*. (2018) 79:16cs10905 [pii]. doi: 10.4088/JCP.16cs10905

27. Cole E, O'Sullivan SJ, Tik M, Williams NR. Accelerated theta burst stimulation: safety, efficacy, and future advancements. *Biol Psychiatry*. (2024) 95:523–35. doi: 10.1016/j.biopsych.2023.12.004

28. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. (2005) 45:201–6. doi: 10.1016/j.neuron.2004.12.033

29. Favaretto E, Bedani F, Brancati GE, De Berardis D, Giovannini S, Scarcella L, et al. Synthesising 30 years of clinical experience and scientific insight on affective temperaments in psychiatric disorders: State of the art. *J Affect Disord*. (2024) 362:406–15. doi: 10.1016/j.jad.2024.07.011

30. Wathra RA, Mulsant BH, Daskalakis ZJ, Downar J, McClintock SM, Nestor SM, et al. Effect of prior pharmacotherapy on remission with sequential bilateral theta-burst versus standard bilateral repetitive transcranial magnetic stimulation in treatment-resistant late-life depression. *Br J Psychiatry*. (2023) 223:504–6. doi: 10.1192/bjp.2023.81

31. Saez I, Lin J, Stolk A, Chang E, Parvizi J, Schalk G, et al. Encoding of multiple reward-related computations in transient and sustained high-frequency activity in human OFC. *Curr Biol*. (2018) 28:2889–99.e3. doi: 10.1016/j.cub.2018.07.045

32. Parker G, Tavella G, Spoelma MJ, Sazhin V. Does theta burst stimulation have differential benefit for those with melancholic or non-melancholic depression? *J Affect Disord*. (2024) 350:847–53. doi: 10.1016/j.jad.2024.01.190

33. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. *JAMA Psychiatry*. (2017) 74:143–52. doi: 10.1001/jamapsychiatry.2016.3644

34. Fitzgerald PB, Chen L, Richardson K, Daskalakis ZJ, Hoy KE. A pilot investigation of an intensive theta burst stimulation protocol for patients with treatment resistant depression. *Brain Stimul*. (2020) 13:137–44. doi: 10.1016/j.brs.2019.08.013

35. Cash R, Cocchi L, Lv J, Fitzgerald PB, Zalesky A. Functional magnetic resonance imaging-guided personalization of transcranial magnetic stimulation treatment for depression. *JAMA Psychiatry*. (2021) 78:337–9. doi: 10.1001/jamapsychiatry.2020.3794

36. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford Neuromodulation Therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry*. (2022) 179:132–41. doi: 10.1176/appi.ajp.2021.20101429

37. Anderson RJ, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for treatment resistant depression: re-establishing connections. *Clin Neurophysiol*. (2016) 127:3394–405. doi: 10.1016/j.clinph.2016.08.015

38. Blumberger DM, Vila-Rodriguez F, Wang W, Knyahnytska Y, Butterfield M, Noda Y, et al. A randomized sham controlled comparison of once vs twice-daily intermittent theta burst stimulation in depression: A Canadian rTMS treatment and biomarker network in depression (CARTBIND) study. *Brain Stimul*. (2021) 14:1447–55. doi: 10.1016/j.brs.2021.09.003

39. Chen L, Hudaib AR, Hoy KE, Fitzgerald PB. Is rTMS effective for anxiety symptoms in major depressive disorder? An efficacy analysis comparing left-sided high-frequency, right-sided low-frequency, and sequential bilateral rTMS protocols. *Depress Anxiety*. (2019) 36:723–31. doi: 10.1002/da.2019.36.issue-8

40. Etkin A, Schatzberg AF. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. *Am J Psychiatry*. (2011) 168:968–78. doi: 10.1176/appi.ajp.2011.10091290

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Effect of TMS laterality on clinical outcomes in treatment resistant depression patients with comorbid anxiety - a retrospective study

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Objectives: High-frequency repetitive transcranial magnetic stimulation (rTMS) of the left-hemisphere dorsolateral prefrontal cortex (DLPFC) is FDA cleared for the treatment of adult treatment-resistant major depressive disorder (MDD). Though off-label, sequential bilateral stimulation (SBS), which combines high-frequency left-hemisphere and low-frequency right-hemisphere DLPFC stimulation, is offered in various clinics to treat depression with comorbid anxiety. Few systematic studies investigate the comparative efficacy of the SBS protocol versus the FDA-label protocol for the clinical management of depression with comorbid anxiety. The objective of the current study was to compare the efficacy of HF-LUS to that of SBS within a clinical setting where both are offered to patients with anxious depression. Based on both theories of the pathophysiology of anxious depression as well as clinical practice, we hypothesized that SBS would result in greater symptom reduction as compared to HF-LUS.

Methods: This open label, retrospective cohort study included 86 patients with MDD and comorbid anxiety who received either high frequency left unilateral stimulation (HF-LUS) (n=44) or SBS (n=42). Patient Health Questionnaire 9 (PHQ9), General Anxiety Disorder 7 (GAD7) questionnaire, a self-reported depression (SRD) Likert scale, and a self-reported anxiety (SRA) Likert scale were used to quantify changes in depressive and anxiety symptoms.

Results: Inconsistent with our hypothesis, both groups saw a significant improvement in depression and anxiety symptoms with no difference in course nor degree of improvement. Improvements in depression and anxiety were significantly positively correlated in both bilateral and unilateral cohorts.

Conclusions: Bilateral rTMS may not provide any additional therapeutic advantages over the standard FDA-cleared left unilateral rTMS protocol for anxious depressive patients.

KEYWORDS

repetitive transcranial magnetic stimulation, anxious depression, dorsolateral prefrontal cortex, unilateral, bilateral

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technology that applies fluctuating magnetic fields over the scalp and generates targeted electrical currents in the brain, leading to neuronal depolarization (1). The non-invasive nature of this modality along with its rare occurrence of side effects (2) has since rendered it an attractive tool in both research and clinical domains. As repetitive application of TMS (rTMS) has plastic effects on the brain with clinically meaningful durability (3, 4), it has also gained popularity as a treatment in the emerging field of interventional psychiatry.

Following several large-scale clinical trials supporting the antidepressant efficacy and safety of rTMS (5, 6), the FDA cleared high frequency (HF - 10Hz) stimulation of the left dorsolateral prefrontal cortex (DLPFC) for the treatment of adult treatment-resistant major depressive disorder (MDD) in 2008 and more recently the same protocol was cleared for reduction of comorbid anxiety symptoms in adult patients with depression, otherwise known as anxious depression, in 2022. In addition to MDD, studies indicate the potential efficacy of rTMS in treating a number of other psychiatric disorders, such as posttraumatic stress disorder (7), obsessive compulsive disorder (8), bipolar disorder (9, 10), and anxiety disorders (7, 11, 12). Anxiety disorders frequently co-occur with major depressive disorder (MDD), with a substantial proportion of individuals with MDD also experiencing significant anxiety symptoms (13). This comorbidity has been associated with poorer treatment response across multiple modalities, including pharmacotherapy and psychotherapy (14). However, the impact of rTMS on this subgroup remains an area of active investigation, with limited data directly comparing different stimulation protocols for anxious depression. In this study, we focus specifically on patients with comorbid anxious depression treated either with the standard unilateral protocol or the bilateral protocol. All patients in the study endorsed both depressive and anxiety symptoms that significantly impaired their quality of life.

Hemispheric lateralization

Electroencephalography (EEG) recordings have shown that negative mood and depression are associated with relatively greater activity in the right hemisphere's (RH) frontal cortex as compared to the analogous region in the left hemisphere (LH) (15, 16). Consistent with this, neuroimaging studies report that in uni-polar depressed patients the LH is characterized by hypometabolism and by hypermetabolism in the RH (17, 18). Studies also find that the severity of depression correlates positively with RH hyperactivity (17, 19). Studies on unilateral brain lesions, which offer an opportunity to study hemispheric balance with one healthy hemisphere operating predominantly without contra hemispheric influence, find that tumors and ischemia in the left hemisphere are frequently accompanied by depressed mood, while similar lesions in the right hemisphere cause euphoria (20–22). Also noteworthy is that the frequency and severity of post-stroke depression is higher in patients with left hemispheric lesions compared with right hemispheric patients (23–25). Within the same vein, inactivation of the left hemisphere via sedative injection into the left carotid artery (effectively isolating the RH), produces crying, pessimistic statements, guilt, complaints, and worries about the future, whereas sedation of the right hemisphere results in smiling, laughing, mimicry, euphoria, and lack of apprehension (26, 27).

The symptoms of anxious depression may be understood in the context of an imbalance in hemispheric activity. Pessimism, negative thinking patterns, unconstructive attribution style, as well as guilt and self-blame thoughts have all been associated with RH hyperactivity (28–31). Difficulties in initiating and maintaining a healthy sleep pattern may also be related to the RH hyperactivity when considering its role in maintaining alertness and vigilance (19) and its role in modulating physiological symptoms of anxiety, such as sweating and increased heart rate (32). Conversely, the relative hypoactivity of the LH may account for the lack of motivation and inability to experience pleasure – anhedonia, as well as the indecisiveness that is associated with depression, as these functions are primarily thought to be processed by the LH (19). Studies on unilateral brain lesions also find that tumors and ischemia in the left hemisphere are frequently accompanied by depressed mood, while similar lesions in the right hemisphere cause euphoria (20–22).

rTMS parameters

Typically, high-frequency (~10 Hz) rTMS is thought to increase local cortical activity, while low-frequency (~1 Hz) rTMS is thought to result in local cortical suppression (33, 34). In accordance with this assumption, studies have found clinical improvements in depression when administering high-frequency left unilateral stimulation (HF-LUS) (5, 35–37), low frequency right unilateral stimulation (35), and Sequential Bilateral Stimulation (SBS), which combines high frequency, left DLPFC stimulation and low frequency, right DLPFC stimulation (36). While all three protocols result in symptom improvements compared to sham (placebo) controls, there is contradictory data in the literature leading to a need for head-to-head comparisons of various protocols superiority (38, 39). Even the most recently pooled data in systematic reviews and meta-analyses, including a review by Aaronson and colleagues (40) which collected data from 111 practice sites in 2022, concluded that there was no significant difference in efficacy between unilateral and bilateral protocols. While their study was retrospective, it provides valuable insight that aligns with our findings.

In spite of approximately half of patients with MDD seeking treatment in the clinic also endorsing significant anxiety (41), patients with comorbid anxiety disorders are often excluded from rTMS studies focused exclusively on MDD. Consequently, while a growing body of findings show promise in patients with anxiety disorders and anxiety symptoms comorbid to other psychiatric

pathologies (11, 12, 42), few studies have investigated which treatment parameters best remediate comorbid anxiety symptoms in those with depression in a clinical setting. Our study aims to investigate whether the SBS protocol, which is commonly offered clinically to depressive patients with significant anxiety, provides significant clinical benefit over the FDA cleared HF-LUS. We hypothesized that, by tackling the inter-hemispheric imbalance from both sides simultaneously, SBS treatment may be more effective than unilateral stimulation for this subpopulation of patients.

Methods

Patients who sought treatment signed a consent form to have their information utilized for research purposes as part of their intake. Patients, TMS technicians, and those analyzing the data were unblinded to treatment protocol. This study was determined to be exempt from IRB review under category # 4(ii), as detailed in 45 CFR 46.104(d) by BRANY IRB Services.

Participants

Patients were assigned to a treatment protocol (cohort) based upon their qualitative report of symptoms obtained by clinic staff during intake. Patients who reported that depressive symptoms alone were the primary cause of impairment were assigned to the unilateral protocol, while those who endorsed both depressive and anxiety symptoms as equally debilitating were assigned to the bilateral protocol. Cohort assignment was not randomized but was based on these patient-reported symptoms during intake interviews. While quantitative symptom severity metrics were also collected as part of intake, these values were used as baseline values prior to treatment and not factored in cohort assignment. Inclusion criteria involved patients with longstanding treatment resistant depression with comorbid anxiety symptoms or anxiety disorder who underwent between 30 and 36 treatments of either unilateral or bilateral TMS stimulation. Patients were classified as having anxious depression if they had a GAD-7 score of at least 10 and a PHQ-9 score of at least 10. Patients were allowed to remain on psychotropic medication and psychotherapy regimens, but those receiving other treatments such as concurrent intranasal ketamine or other neuro-stimulatory treatments were excluded from this analysis. Data for this study was pooled from patients treated at the Neuro Wellness center for Depression in Coral Springs, FL between the years 2020-2022. The groups were not significantly different demographically or clinically and received comparable intensities of stimulation ($p > 0.05$ for all categories) (Table 1).

Measures

As part of the intake protocol, patients completed the Patient Health Questionnaire 9 (PHQ9) and General Anxiety Disorder 7 (GAD7) questionnaire, along with two self-report Likert scales of anxiety and depression symptom severity (i.e. the self-reported anxiety (SRA) scale and the self-reported depression (SRD) scale). The SRA and SRD scales are self-report Likert scales developed by our clinic to provide real-time assessments of patients' subjective experiences of anxiety and depression symptoms throughout the treatment course. These scales range from 0 to 10, with higher scores indicating greater symptom severity. While not standardized or validated like the PHQ-9 and GAD-7, they offer practical utility in tracking symptom changes on a session-by-session basis, complementing the more comprehensive assessments. Patients also documented past and current medications at intake. During treatment, patients completed the SRA and SRD scales prior to every session and the PHQ9 and GAD7 at the end of every treatment week. Finally, patients completed the PHQ9, GAD7, SRA, and SRD as part of the discharge protocol once their treatment course had concluded.

The PHQ9 is a questionnaire utilized by clinicians as a screening and severity assessment tool for depression based upon the DSM-V diagnostic criteria for depressive disorders (43). The threshold score of '4' or less (below 5) was used to define remission for our study, at or below which patients' symptoms do not meet clinical criteria for mild depression/anxiety. The GAD7 is a questionnaire utilized by clinicians as a screening and severity assessment tool for anxiety disorders based upon the DSM-V diagnostic criteria for generalized anxiety disorder (44). Similar to the PHQ9, a score of '4' or less was used to define remission for anxiety symptoms. Response was defined as a $\geq$ 50% improvement from baseline to post-treatment scores on the PHQ-9 and GAD-7. The SRA and SRD are Likert scales which assess a patient's experience of anxiety and depression symptoms. The scales range from 0 to 10, 0 indicating no anxiety/depression and 10 indicating the worst and most debilitating anxiety/depression symptoms imaginable.

Procedures

All patients received magnetic resonance imaging (MRI)-guided rTMS with the Nexstim Navigated Brain Stimulation (NBS) System 5. Prior to their first session, patients received a series of structural MRI scans including a T1-weighted MP-RAGE scan, a three-dimensional T1-weighted scan, and a gradient-echo scan.

On the first day of treatment, a trained TMS technician and the attending psychiatrist confirmed the relevant anatomical landmarks identified on the patient's MRI by the interpreting radiologists (including the left- and right-hand knobs (in the primary motor cortex) and the left and right DLPFC). The individualized location of the M1 hand knobs are defined by anatomical criteria proposed by Ahdab and colleagues (45) and Yousry and colleagues (46) The NBS system employs an algorithm developed by Mylius and colleagues (47) to define the optimal DLPFC target locations. After these anatomical landmarks are identified and marked in the Nexstim interface program, the attending psychiatrist/privileged provider then determined the patient's Motor Threshold (MT) and calculated treatment intensity prior to starting treatment.

TABLE 1 Population Demographics.

Characteritics	Categories	HF-LUS	SBS	Total
Demographics	N	44	42	86
	Male	13 (29.5%)	18 (42.9)	32 (37.2)
	Female	31 (70.5)	24 (57.1)	55 (62.8)
	Mean Age (s.d.)	53 (18.4)	47 (17.4)	50 (17.9)
	Min/Max Age	13/88	20/79	13/88
Treatment	* Mean Motor	L - 30.25	L - 29.5	L - 30.0
	Threshold (MT)		R - 34.3	R - 34.3
	Mean Treatment	L 36.3	L - 35.4	L - 36.0
	Intensity (1.2 x MT)		R - 41.2	R - 41.2
	Mean MT Change	L- 10.16%	L - 5.21%	L - 7.76%
	in Remapping		R - 1.6%	R 1.6%
Medications	SSRI	10 (22.7%)	9 (21.4%)	19 (22.1%)
	SNRI	10 (22.7)	6 (14.3)	16 (18.6)
	Atypical	10 (22.7)	7 (16.7)	17 (19.8)
	Antidepressants			
	Seratonin	7 (16.0)	7 (16.7)	14 (16.3)
	Modulators			
	Benzodiazepine	10 (22.7)	8 (19.0)	18 (20.9)
	Antipsychotic	8 (18.2)	6 (14.3)	14 (16.3)
	Mood Stabilizer	0	1 (2.4)	1 (1.2)
	Stimulants	2 (4.5)	5 (11.9)	7 (8.1)
	Anti-Convulsant	6 (13.6)	6 (14.3)	12 (14.0)
	Non-Benzo	1 (2.3)	4 (9.5)	5 (5.8)
	Anxiolytic			
	Z Drug	0	2 (4.8)	2 (2.3)

Demographics of study subjects, treatment doses, and psychotropic medications taken during study period.
*Reported motor thresholds are an average between patient starting motor threshold and corrected motor threshold around week 3. Percent change of adjustment was not significantly different between the two cohorts.

Motor mapping and MT estimation

Motor mapping was performed by the attending physician to determine the patient's MT and contingent stimulation intensity according to standard procedures. MT is defined within the Nexstim manual as the minimum intensity that elicits an EMG motor evoked potential of 100-500 μV with a latency in the 12-25 ms range 50% of the time. Treatment intensity is then defined as 120% of the MT. Recent findings suggest that MT varies significantly across an rTMS treatment course (48). Thus, MT is reevaluated around week 3 (between treatments 10-15) for all patients to account for any changes in neuronal excitability and to ensure that stimulation target(s) are optimal. While both cohorts receive motor mapping of the left hemisphere, the SBS group additionally undergoes the same process for the right hemisphere. Once a patient's MRI is uploaded, MT(s) are determined, and cortical targets are all tagged, technicians calibrate these targets with landmarks on patient's head to begin MRI guided rTMS.

All patients received the FDA cleared treatment for depression that takes roughly 19 minutes and delivers 3000 pulses in total at a frequency of 10 HZ to the LH DLPFC. These pulses are spaced out in 75 trains, each lasting 4 seconds, delivering 40 pulses each, and spaced out by an 11 second intertrain interval. Once the left side protocol is complete, patients in the bilateral cohort are recalibrated in the machine for right-sided DLPFC stimulation. The right-sided protocol lasts 20 minutes and delivers 1200 pulses at 1 HZ in one single train spaced out by a 1 second interval. Right-sided stimulation was delivered at 120% of the Motor Threshold (MT), consistent with the stimulation parameters for the left-sided treatment.

The average participant received 36 treatments, allotted as 5 times a week for the first 30 sessions, and tapered off to 3 times a week for the final 6.

Data analysis

Data was analyzed using SPSS version 26, with the exception of Fisher's r to z transformation, which was performed using an online calculator (49) as transformation is not available on SPSS 26. A handful of patients went on to receive over thirty-six sessions, but only data up to treatment thirty-six was considered. This was done to standardize the treatment timeline.

Our primary outcome measure was the effect of protocol on improvements in anxiety, thus we used a factorial (2x2) ANOVA to determine if patients reported greater or lesser improvement when comparing their initial quantitative measurement of symptoms to their final value post treatment. We then derived Pearson's correlation coefficients with net treatment proportional improvements ((Intake Score – Final score)/Intake score) by comparing SRA against SRD scores and GAD7 against PHQ9 in a two tailed analysis. Correlation coefficients were then compared via Fisher's r to z transformation. We subsequently calculated patient response (≥ 50% improvement) and remission rates (final scores below 5, for both PHQ9 & GAD7) for all cohorts using PHQ9 and GAD7 and analyzed the means via chi-square. Finally, we used an ANCOVA to determine if treatment trajectories differed between protocols. Due to inconsistent reporting, several patients were missing mid-treatment GAD7 and PHQ9 entries. In order to replace this data without compromising the accuracy of the ANCOVA, we replaced missing data points by using the mean of nearby points in patients with 3 or fewer missing entries and excluded patients with more than 3 missing entries. As a result, 7 participants were excluded for PHQ9 analysis, leaving us with n=79 (unilateral n = 42, bilateral n = 37) and excluded 9 from the GAD7 analysis, leaving us with n=77 (unilateral n= 41, bilateral n= 36).

Results

All participants tolerated the TMS treatment without any adverse medical events.

Metrics of depression – PHQ9 & SRD

For both the Unilateral and Bilateral Group depression symptom severity significantly improved from pre-post treatment as measured both on the PHQ9 (F (1,84) = 210.65, $p < .001$) and SRD (F (1,84) = 85.05, $p < .001$). The mean baseline PHQ9 score for the unilateral cohort was 19.55 (SD = 5.48), and for the bilateral cohort was 19.99 (SD = 4.72). Post-treatment, the mean PHQ9 scores decreased to 9.15 (SD = 6.36) and 10.19 (SD = 6.18), respectively, indicating mean improvements of 53.20% and 49.02% (Figures 1A, B). There was also a significant effect of time such that the trajectory of scores consistently went down for PHQ9 (F (1,628) = 156.73, $p < .001$) and SRD (F (1,684) = 80.57, $p < .001$) (Figures 2A, B). Consistent with prior findings (39), HF-LUS and

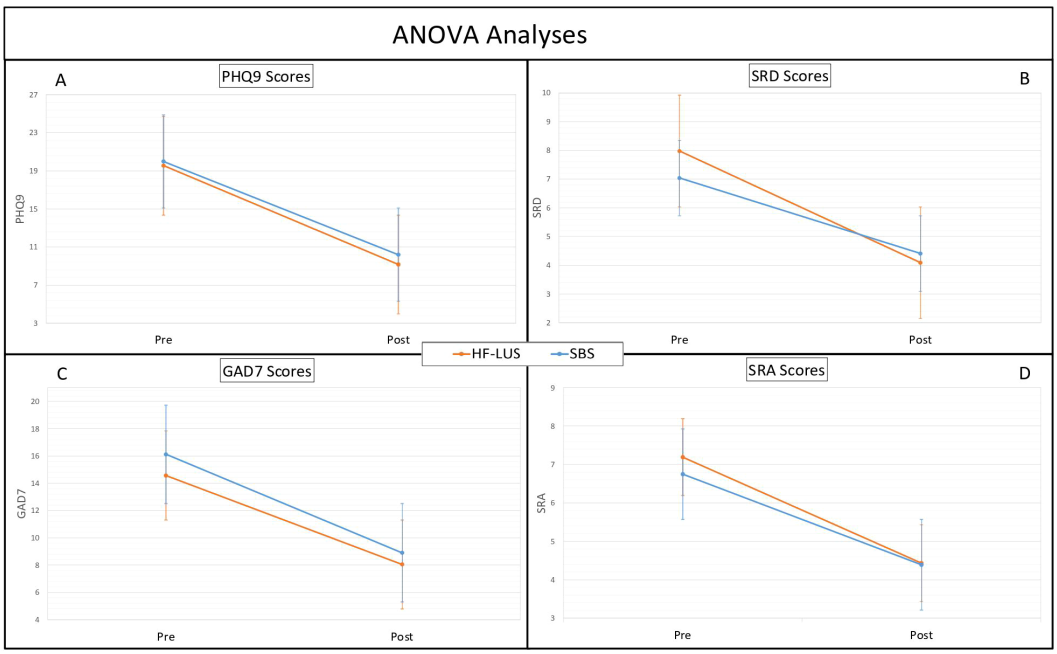

FIGURE 1
ANOVA analyses. Analysis of Variance (ANOVA) between High-Frequency Left Unilateral Stimulation (HF-LUS) and Sequential Bilateral Stimulation (SBS) cohorts in reported metrics of depression and anxiety. Measures of depression, PHQ9 **(A)** and SRD **(B)**, did not vary significantly between cohorts. Likewise measures of anxiety, GAD7 **(C)** and SRA **(D)**, did not vary significant. Patient Health Questionnaire (PHQ9); Self Reported Depression (SRD); Generalized Anxiety Disorder (GAD7); Self Reported Anxiety (SRA).

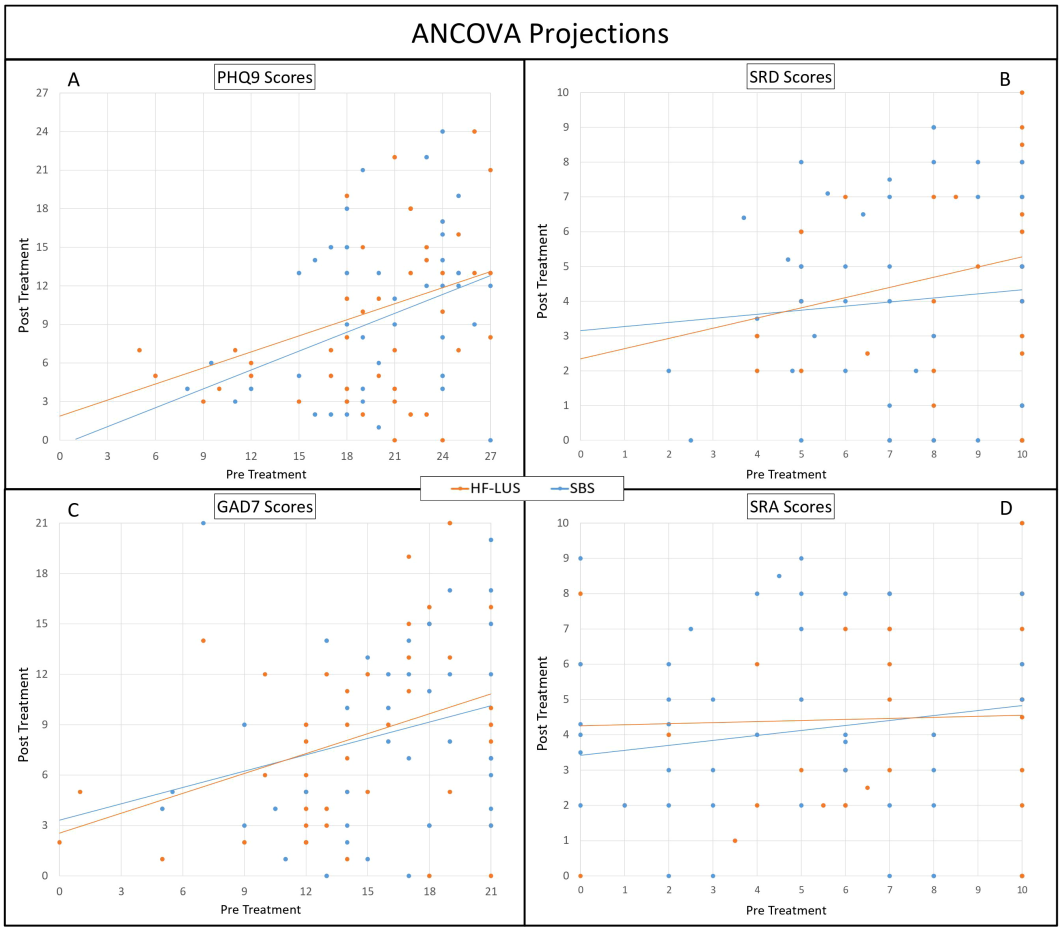

FIGURE 2
AOVA Projections. Analysis of Covariance (ANCOVA) between High-Frequency Left Unilateral Stimulation (HF-LUS) and Sequential Bilateral Stimulation (SBS) cohorts in reported metrics of depression and anxiety. Trajectories of depression, PHQ9 **(A)** and SRD **(B)**, did not vary significantly between cohorts. Likewise, trajectories of anxiety, GAD7 **(C)** and SRA **(D)**, did not vary significantly. Patient Health Questionnaire (PHQ9); Self Reported Depression (SRD); Generalized Anxiety Disorder (GAD7); Self Reported Anxiety (SRA) 2.

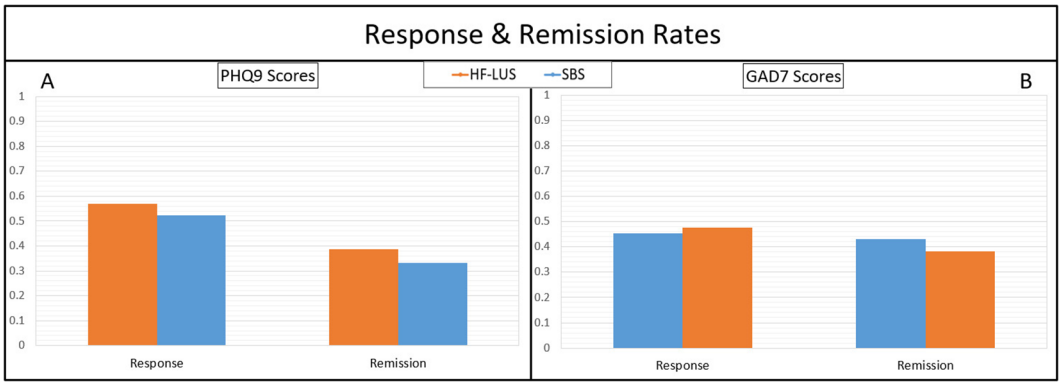

FIGURE 3
Response rates (≥ 50% improvement with treatment) and remission rates (Post-treatment score ≥5) for measures of depression with PHQ9 **(A)**, and anxiety with GAD7 **(B)**. No significant differences between cohorts were found. Health Questionnaire (PHQ9); Generatlized Anxiety Disorder (GAD7).

SBS did not differ significantly for either the factorial ANOVA nor the ANCOVA analysis indicating that neither the improvement in depression symptoms nor trajectory differed between cohorts.

Patient responses to treatment with measure of PHQ9 were 56.82% and 52.38%, for the unilateral and bilateral cohorts, respectively. These two percentages were not significantly different. Remission rates of depression were 38.64% and 33.33% for the unilateral and bilateral cohorts, respectively. These two percentages were not significantly different (Figure 3A).

Metrics of anxiety – GAD7 & SRA

For both the Unilateral and Bilateral Group anxiety symptom severity significantly improved from pre-post treatment as measured both on the GAD7 (F (1,84) = 94.21, p < .001) and SRA (F (1,84) = 48.43, p < .001). The mean baseline GAD7 score for the unilateral cohort was 14.57 (SD = 5.19), and for the bilateral cohort was 16.12 (SD = 4.57). Post-treatment, the mean GAD7 scores decreased to 8.05 (SD = 5.79) and 8.91 (SD = 6.22), respectively, indicating mean improvements of 44.75% and 44.56% (Figures 1C, D). There was also a significant effect of time such that the trajectory of scores consistently went down for GAD7 (F (1,612) = 92.55, p < .001) and SRA (F (1,684) = 282.91, p < .001) (Figures 2C, D). There was not a significant main effect of cohort nor a cohort by time interaction effect for either the factorial ANOVA nor the ANCOVA analysis indicating that neither the improvement in anxiety symptoms nor trajectory differed between cohorts.

Patient responses to treatment with measure of GAD7 were 45.45% and 47.62%, for the unilateral and bilateral cohorts, respectively. These two percentages were not significantly different. Remission rates of anxiety were 43.18% and 38.10% for the unilateral and bilateral cohorts, respectively. These two percentages were not significantly different (Figure 3B).

Correlation of self-reported anxiety and self-reported depression

There was a significant positive correlation in the improvements in self-reported anxiety and self-reported depression in both the unilateral and bilateral cohort (Unilateral: r = .397, p <.05; Bilateral: r = .721, p <.001). Fisher's transformation (z = 2.19, p <.05) confirmed that the correlation was stronger for the SBS cohort as compared to the HF-LUS cohort (Figure 4A).

Correlation of GAD7 and PHQ9

There was a significant positive correlation in the improvements in GAD7 and PHQ9 in both the unilateral and bilateral cohort (Unilateral: r = .768, p <.05; Bilateral: r = .738, p <.001). Fisher's transformation confirmed that the correlations were not statistically different (Figure 4B).

Discussion

Following the logic that many traits of anxiety are associated with hyperactivity of the right frontal lobe (19, 32), it is reasonable to consider direct suppression of the right DLPFC with 1 Hz rTMS as a possible adjunctive treatment to HF-LUS for anxious depression, but this is simply not reflected in the data. It may be that the underlying mechanisms leading to anxiety and depression overlap in such a way

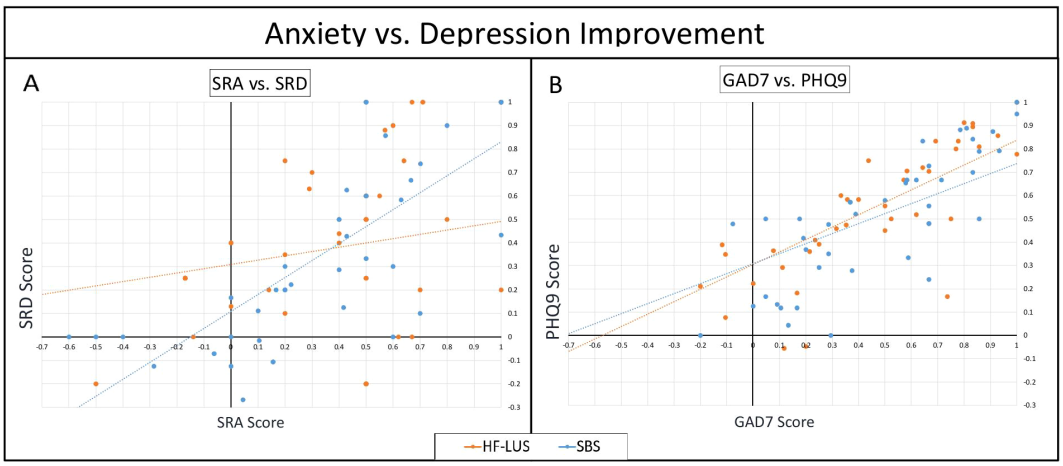

FIGURE 4
Anxiety vs. Depression Improvement. Scatter plots comparing improvement coefficients (Intake Score - Final score) / Intake score) between measures of anxiety vs. depression. In comparing SRA against SRD scores. **(A)**, while both cohorts had a positive correlation, SBS was significantly higher than HF-LUS. In GAD7 against PHQ9 **(B)** both cohorts had significant positive correlations which were not significantly different. Patient Health Questionnaire (PHQ9); Self Reported Depression (SRD); Generalized Anxiety Disorder (GAD7); Self Reported Anxiety (SRA).

that HF-LUS is the optimal treatment protocol to address both pathologies simultaneously, leaving stimulation of the right DLPFC of no additional value. If this is the case, our findings have important implications for healthcare systems and resource allocation, as forgoing the redundant right sided stimulation would save time and resources for both patients and clinicians. The SBS protocol requires additional time and resources due to the inclusion of right-sided stimulation, which our data suggest does not confer additional clinical benefit over the unilateral protocol. By adopting the unilateral HF-LUS protocol for patients with anxious depression, clinics and physicians can enhance treatment efficiency, lower costs, and optimize resource utilization without compromising patient outcomes. This approach could lead to increased accessibility of rTMS treatments for a larger patient population. Despite the growing body of evidence supporting rTMS for treatment-resistant depression, its widespread adoption in clinical practice is influenced by factors such as cost, accessibility, and provider training. While the FDA has approved rTMS for anxious depression, its clinical use specifically for anxiety disorders remains off-label. The broader implementation of rTMS for comorbid anxiety conditions may depend on further research, standardization of protocols, and increased insurance coverage to facilitate accessibility. In any case, the lack of appreciable difference in remediation of depressive or anxiety symptoms between these two protocols, which aligns with prior findings (39), leads us to reject our hypothesis. Our results nonetheless serve as reinforcement to the current literature on rTMS. Both treatment protocols had a significant effect on measures of depression and anxiety, further supporting rTMS as an effective modality for treatment resistant MDD, even in the context of anxious comorbidities, as demonstrated by Clark and colleagues (12).

One noteworthy exception to the absence of significant difference was the strong positive correlation in improvement of self-reported scores in the bilateral cohort compared to the relatively weaker positive correlation in the unilateral. While this correlation seems to indicate that self-reported anxiety and depression are improving more uniformly with the SBS protocol, this observation is of little clinical value as improvements in this cohort were not discernably superior to those observed in its counterpart and this pattern was not seen in the standardized PHQ9 and GAD7 scales. Regardless of protocol, our results showed that as depression got better, so did anxiety, or vice versa. While this correlation in anxious depression has already been observed by prior studies (11), further study is warranted to determine the exact mechanism.

Limitations

This study has several important limitations that need to be acknowledged. First, this is a retrospective, non-randomized study, which inherently introduces biases and confounding factors. One of the major limitations is the lack of random assignment, as patients essentially self-selected their treatment cohorts based on subjective symptom reporting during intake, which could lead to selection bias. Moreover, the open-label nature of the study means both patients and clinicians were unblinded to the treatment protocol, increasing the potential for expectancy effects and bias.

Additionally, the study did not control for medication use, as patients were allowed to continue their psychotropic medication regimens throughout the treatment course. Although no significant differences in medication use between cohorts were observed, this factor could still confound the results. Another limitation is the use of non-validated self-report scales (SRA and SRD) in conjunction with standardized measures like the PHQ-9 and GAD-7. While these scales provided practical real-time assessments, their lack of validation means the accuracy and reliability of these measures may be less robust compared to standardized instruments.

Finally, although we mention the impact of COVID-19, other methodological limitations, such as the lack of control for environmental and situational variables related to the pandemic, may have influenced the results. Future studies should prioritize randomization, blinding, and the use of fully validated measurement tools to reduce potential biases and improve the reliability of findings.

Conclusion

In conclusion, SBS rTMS for anxious depressive patients may not provide any additional clinical advantages than the FDA cleared HF-LUS rTMS. While both protocols were effective in reducing symptoms of depression and anxiety, forgoing the redundant right sided stimulation would save time and resources for both patients and clinicians.

Data availability statement

The datasets presented in this article are not readily available because the analyses presented in this manuscript are based on a preexisting data set owned by Neuro Wellness TMS Centers Of America. This dataset includes private patient information and is not publicly accessible to maintain confidentiality and adhere to data protection regulations. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by BRANY | IRB and Clinical Trial Solutions. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

TC: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. BB: Writing – original draft, Writing – review & editing. LO: Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature*. (2000) 406:147–50. doi: 10.1038/35018000

2. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. (2021) 132:269–306. doi: 10.1016/j.clinph.2020.10.003

3. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. *J Clin Psychiatry*. (2014) 75:1394–401. doi: 10.4088/JCP.13m08977

4. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimulation: Basic Translational Clin Res Neuromodulation*. (2010) 3:187–99. doi: 10.1016/j.brs.2010.07.003

5. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biol Psychiatry*. (2007) 62:1208–16. doi: 10.1016/j.biopsych.2007.01.018

6. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. (2009) 34:522–34. doi: 10.1038/npp.2008.118

7. Cirillo P, Gold AK, Nardi AE, Ornelas AC, Nascimento JD, Machado S, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis. *Brain Behav*. (2019) 9:e01284. doi: 10.1002/brb3.2019.9.issue-6

8. Thatikonda NS, Mehta UM, Thirthalli J, Kishore KR, Sathyaprabha TN, Gangadhar BN, et al. Efficacy of repetitive transcranial magnetic stimulation on comorbid anxiety and depression symptoms in obsessive-compulsive disorder: A meta-analysis of randomized sham-controlled trials. *Can J Psychiatry*. (2022) 68 (6):407–17. doi: 10.1177/07067437221121112?

9. McGirr A, Vöhringer PA, Ghaemi SN, Lam RW, Yatham LN. Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. In: *World Psychiatry*. Italy: Wiley-Blackwell on behalf of the World Psychiatric Association (2016). p. 85–6. Available online at: https://en.wikipedia.org.

10. Tavares DF, Myczkowski ML, Alberto RL, Valiengo L, Rios RM, Gordon P, et al. Treatment of bipolar depression with deep TMS: results from a double-blind, randomized, parallel group, sham-controlled clinical trial. *Neuropsychopharmacology*. (2017) 42:2593–601. doi: 10.1038/npp.2017.26

11. Badawi A, Rushdi MN, Abdelrahman AI. Repetitive transcranial magnetic stimulation: influence on stress and early responsiveness outcomes for depression, anxiety, and stress. *Psychiatr Q*. (2022) 93:385–91. doi: 10.1007/s11126-021-09953-4

12. Clarke E, Adams M, Heaney D. Efficacy of repetitive transcranial magnetic stimulation in the treatment of depression with comorbid anxiety disorders. *J Affect Disord*. (2019) 252:435–9. doi: 10.1016/j.jad.2019.03.085

13. Saha S, Lim CCW, Cannon DL, Burton L, Bremner M, Cosgrove P, et al. Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis. *Depress Anxiety*. (2020) 38:286. doi: 10.1002/DA.23113

14. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: A STAR*D report. *Am J Psychiatry*. (2008) 165:342–51. doi: 10.1176/APPI.AJP.2007.06111868/ASSET/IMAGES/S814F0.JPEG

15. Henriques JB, Davidson RJ. Left frontal hypoactivation in depression. *J Abnorm Psychol*. (1991) 100:535–45. doi: 10.1037/0021-843X.100.4.535

16. Flor-Henry P, Lind JC, Koles ZJ. A source-imaging (low-resolution electromagnetic tomography) study of the EEGs from unmedicated males with depression. *Psychiatry Research: Neuroimaging*. (2004) 130:191–207. doi: 10.1016/j.pscychresns.2003.08.006

17. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol Psychiatry*. (2008) 63:369–76. doi: 10.1016/j.biopsych.2007.05.033

18. Janocha A, Pilecki W, Bolanowski M, Małyszczak K, Salomon E, Laszki-Szczachor K, et al. Interhemispheric cerebral asymmetry detected by VEPS in diabetic patients with recognized depression. *Neuro Endocrinol Lett*. (2009) 30:119–24. doi: 10.1016/j.comppsych.2008.03.007?

19. Hecht D. Depression and the hyperactive right-hemisphere. *Neurosci Res*. (2010) 68:77–87. doi: 10.1016/j.neures.2010.06.013

20. Braun CMJ, Daigneault R, Champagne D, Larocque C, Stip E. Diagnostic and Statistical Manual of Mental Disorders, symptoms of mania: which one (s) result (s) more often from right than left hemisphere lesions? *Compr Psychiatry*. (2008) 49:441–59. doi: 10.1001/archpsyc.58.10.925

21. Carran MA, Kohler CG, O'Connor MJ, Bilker WB, Sperling MR. Mania following temporal lobectomy. *Neurology*. (2003) 61:770–4. doi: 10.1212/01.WNL.0000086378.74539.85

22. Vataja R, Pohjasvaara T, Leppävuori A, Mäntylä R, Aronen HJ, Salonen O, et al. Magnetic resonance imaging correlates of depression after ischemic stroke. *Arch Gen Psychiatry*. (2001) 58:925–31. doi: 10.1001/archpsyc.58.10.925

23. Nishiyama Y, Ueda M, Okubo T, Hayashida K, Terada H, Katayama Y. Early depressive symptoms after ischemic stroke are associated with a left lenticulocapsular area lesion. *J Stroke Cerebrovascular Dis*. (2010) 19:184–9. doi: 10.1016/j.jstrokecerebrovasdis.2009.04.002

24. Hama S, Yamashita H, Shigenobu M, Watanabe A, Kurisu K, Yamawaki S. Post-stroke affective or apathetic depression and lesion location: left frontal lobe and bilateral basal ganglia. *Eur Arch Psychiatry Clin Neurosci*. (2007) 257:149–52. doi: 10.1007/s00406-006-0698-7

25. Barker-Collo SL. Depression and anxiety 3 months post stroke: prevalence and correlates. *Arch Clin Neuropsychol*. (2007) 22:519–31. doi: 10.1016/j.acn.2007.03.002

26. Ahern GL, Schwartz GE, Pasternak RE. Affective self-report during the intracarotid sodium amobarbital test. *J Clin Exp Neuropsychol*. (1994) 16:372–6. doi: 10.1080/01688639408402647

27. Lee GP, Loring DW, Meador KJ. Influence of premorbid personality and location of lesion on emotional expression. *Int J Neurosci*. (1993) 72:157–65. doi: 10.3109/00207459309024104

28. Mohr C, Porter G, Benton CP. Psychophysics reveals a right hemispheric contribution to body image distortions in women but not men. *Neuropsychologia*. (2007) 45:2942–50. doi: 10.1016/j.neuropsychologia.2007.06.001

29. Vickery CD, Evans CC, Lee JE, Sepehri A, Jabeen LN. Multilevel modeling of self-esteem change during acute inpatient stroke rehabilitation. *Rehabil Psychol*. (2009) 54:372. doi: 10.1037/a0017854

30. Williams LM, Gatt JM, Schofield PR, Olivieri G, Peduto A, Gordon E. 'Negativity bias' in risk for depression and anxiety: Brain–body fear circuitry correlates, 5-HTT-LPR and early life stress. *Neuroimage*. (2009) 47:804–14. doi: 10.1016/j.neuroimage.2009.05.009

31. Leyman L, De Raedt R, Vanderhasselt MA, Baeken C. Influence of high-frequency repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex on the inhibition of emotional information in healthy volunteers. *psychol Med*. (2009) 39:1019–28. doi: 10.1017/S0033291708004431

32. Balderston NL, Roberts C, Beydler EM, Deng ZD, Radman T, Luber B, et al. Mechanistic link between right prefrontal cortical activity and anxious arousal revealed using transcranial magnetic stimulation in healthy subjects. *Neuropsychopharmacology*. (2020) 45:694–702. doi: 10.1038/s41386-019-0583-5

33. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*. (1997) 48:1398–403. doi: 10.1212/WNL.48.5.1398

34. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*. (1998) 15:333–43. doi: 10.1097/00004691-199807000-00005

35. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, et al. Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. *Biol Psychiatry*. (1999) 46:1451–4. doi: 10.1016/S0006-3223(99)00182-1

36. Fitzgerald PB, Brown TL, Daskalakis ZJ, Chen R, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry*. (2006) 163:88–94. doi: 10.1176/appi.ajp.163.1.88

37. Herwig U, Fallgatter AJ, Höppner J, Eschweiler GW, Kron M. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *Br J Psychiatry*. (2007) 191:441–8. doi: 10.1192/bjp.bp.106.034371

38. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. *JAMA Psychiatry*. (2017) 74:143–52. doi: 10.1001/jamapsychiatry.2016.3644

39. Fitzgerald PB, Hoy KE, Elliot D, McQueen S, Wambeek LE. A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. *Psychol Med*. (2011) 41:1187–96. doi: 10.1017/S0033291710001923

40. Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, et al. Comparison of clinical outcomes with left unilateral and sequential bilateral Transcranial Magnetic Stimulation (TMS) treatment of major depressive disorder in a large patient registry. *Brain Stimul*. (2022) 15:326–36. doi: 10.1016/j.brs.2022.01.006

41. Hirschfeld RMA. The comorbidity of major depression and anxiety disorders: recognition and management in primary care. *Prim Care Companion J Clin Psychiatry*. (2001) 3:244–54. doi: 10.4088/PCC.v03n0609

42. Sehatzadeh S, Daskalakis ZJ, Yap B, Tu HA, Palimaka S, Bowen JM, et al. Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over two decades. *J Psychiatry Neurosci*. (2019) 44(3):151–63. doi: 10.1503/jpn.180056

43. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x

44. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Internal Med*. (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092

45. Ahdab R, Ayache SS, Brugières P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiologie Clinique/Clinical Neurophysiol*. (2010) 40:27–36. doi: 10.1016/j.neucli.2010.01.001

46. Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, et al. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain: J Neurol*. (1997) 120:141–57. doi: 10.1093/brain/120.1.141

47. Mylius V, Ayache SS, Ahdab R, Farhat WH, Zouari HG, Belke M, et al. Definition of DLPFC and M1 according to anatomical landmarks for navigated brain stimulation: inter-rater reliability, accuracy, and influence of gender and age. *Neuroimage*. (2013) 78:224–32. doi: 10.1016/j.neuroimage.2013.03.061

48. Cotovio G, Oliveira-Maia AJ, Paul C, Afonso P, Castelo-Branco M. Day-to-day variability in motor threshold during rTMS treatment for depression: Clinical implications. *Brain Stimul*. (2021) 14:1118–25. doi: 10.1016/j.brs.2021.07.013

49. Lowry R. Significance of the difference between two correlation coefficients (2001-2023). Available online at: http://vassarstats.net/rdiff.html (Accessed March 02, 2025).

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Transcranial focused ultrasound targeting the default mode network for the treatment of depression

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Introduction: Up to 50% of individuals fail to respond to current depression treatments. Repetitive negative thought and default mode network hyperconnectivity are central in depression and can potentially be targeted using novel neuromodulation techniques. This community-based study assessed whether a treatment using non-invasive transcranial focused ultrasound targeting the default mode network can decrease depression symptoms and repetitive negative thought, and improve quality of life.

Methods: Study recruitment began in August 2023 and ended in February 2024. Twenty individuals aged 18 – 50 were enrolled from among 247 screened. Exclusion criteria included history of psychosis/mania, acute suicidality, MRI contraindications, pregnancy, and medical and neurological factors that may complicate diagnosis or brain function. Participants completed up to three weeks of transcranial ultrasound (11 sessions) targeting the anterior medial prefrontal cortex; ten minutes per session. Depression severity (Beck Depression Inventory – II and the Hamilton Depression Rating Scale), repetitive negative thought (Perseverative Thinking Questionnaire), and quality of life (World Health Organization Quality of Life Scale) were outcomes.

Results: This sample was young (mean 30.4 years ± 10.0), predominantly female (75%), with moderate to severe depression and high comorbidity. Fifty percent of participants endorsed current psychiatric medication use. Ten percent of subjects dropped out of the study due to time constraints. Significant decreases in depression were observed over the course of treatment on self-report, 10.9 ($p < 0.001$, CI = -13.55, -7.92) and interview depression ratings, 4.2 ($p < 0.001$, CI = -5.85, -2.62), as well as significant decreases in repetitive negative thought, 8.4 ($p < 0.001$, CI = -10.55, -6.03). Improvements in physical and psychological well-being were also observed over the course of treatment, 7.2 ($p < 0.001$, CI = 3.64, 10.63) and 11.2 ($p < 0.001$, CI = 7.79, 14.49), respectively, as well as improvements in environment satisfaction, 5.0 ($p = 0.001$, CI = 2.24, 7.56).

Discussion: Non-invasive transcranial focused ultrasound holds promise as a treatment for depression holds promise as a treatment for depression, however,

future work including control arms is required to ascertain its causal role in depression.

Clinical trial registration: https://clinicaltrials.gov/study/NCT06320028intr=Ultrasound&cond=depression&locStr=Arizona&country=United%20States&state=Arizona&rank=1, identifier NCT06320028.

KEYWORDS

mood disorder, transcranial ultrasonic neuromodulation, repetitive negative thinking (RNT), depression, default mode network

Introduction

Depression is a leading cause of disability (1), affecting 21 million adults and significantly diminishing quality of life (2). Major Depressive Disorder (MDD) is typically recurrent (3–5), and impairment is compounded with subsequent episodes (6). Critically, current interventions are not effective for certain profiles of depression (7, 8).

In conjunction with depressed mood and related symptoms, Repetitive Negative Thought (RNT) has been identified as a maintaining factor in depression (9), as well as a predictor of depression improvements (8). The brain's Default Mode Network (DMN), which has greater connectivity during self-referential processing [e.g., mind-wandering (10, 11)] and, in particular, *negative* self-referential processing [e.g., RNT (12)], is also shown to play an important role in depression. Studies have identified that greater DMN connectivity (e.g., hyperconnectivity) has been associated with greater depression severity and RNT (13, 14). Together, these findings highlight the mechanistic roles that RNT and DMN hyperconnectivity play in the development and maintenance of depression.

Because roughly 50% of depressed individuals are treatment-resistant to traditional treatments (7, 15), more effective interventions are needed, ideally those deriving from a better mechanistic understanding of depression. DMN connectivity has been altered (e.g., using transcranial magnetic stimulation (TMS), psychedelics, meditation) in various clinical populations (16, 17), with the goal of improving treatment approaches. A novel neuromodulation technique, non-invasive Transcranial Focused Ultrasound Stimulation (tFUS), holds promise in the treatment of depression (18, 19).

Unlike other noninvasive methods (TMS and transcranial electrical stimulation (TES) using direct (tDCS) or alternating (tACS) current), tFUS uses low-intensity ultrasound involving a focused nonthermal ultrasound beam, which safely passes through the skull (20) to exert electro-mechanical effects on target neurons, including the ability to induce excitatory and inhibitory effects depending on the ultrasound parameters used (21, 22). tFUS also presents advantages beyond other non-invasive neuromodulation techniques (e.g., TMS) due to its ability to target deeper brain regions with greater precision (22), without side effects (e.g., skin irritation, local pain) that can accompany techniques like TMS (23).

Limited research supports tFUS as a treatment for depression. Resnik and colleagues examined tFUS targeting the right inferior frontal gyrus, a component of the executive control network, on symptoms of depression; those engaging in a five-day treatment regime experienced a decrease in worry (18) compared to those receiving sham. Additionally, Sanguinetti and colleagues also found that tFUS decreased negatively-valanced emotions and altered DMN connectivity (19). These findings provide the foundation for further exploring the use of tFUS as a treatment for depression.

The present study aimed to assess whether treatment using tFUS delivered to the anterior medial prefrontal cortex (amPFC), a hub of the DMN (11), can decrease depression symptoms and RNT, improve quality of life, and whether changes in depression severity are mirrored by changes in RNT.

Methods

The Institutional Review Board of the University of Arizona approved the experimental protocol (IRB approval number: STUDY00002019). All participants signed an informed consent document before participation. Participants were recruited from August 2023 to February 2024.

Clinical Trial Registration number: 019782-00001, https://clinicaltrials.gov/study/NCT06320028intr=Ultrasound&cond=depression&locStr=Arizona&country=United%20States&state=Arizona&rank=1 identifier, NCT06320028.

Participants

Individuals with a current major depressive episode, assessed using the Structured Clinical Interview for the DSM-5 (SCID-5) (24) were enrolled. They also experienced clinically significant RNT, characterized by a total score on the Perseverative Thinking Questionnaire (PTQ) (25) above the 75% percentile (≥37).

The SCID-5 is a gold-standard, semi-structured clinical interview tool used to assess psychiatric disorders recognized by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (26), including modules assessing current episode and history of depression, mania and psychosis, substance-use, anxiety-related disorders, and posttraumatic stress (24). The interrater reliability of the SCID-5 has been extensively validated, with published kappa coefficients ranging from 0.66 to 0.83 across various diagnostic modules (24), indicating good agreement on categorical judgements between raters. The PTQ is a self-report measure consisting of 15-items measuring the degree of negative thinking patterns (e.g., The same thought keeps going through my mind, Thoughts intrude into my mind) using a Likert scale of 0 (never) to 4 (almost always) for each question (25). Validation studies indicate that PTQ is a highly reliable measure of RNT (α =0.95) (25).

Participants were ages 18 – 50, right-handed, English-speaking, and without any neurological symptoms or symptoms of mania/psychosis. Additional exclusion criteria included: history of head injury with loss of consciousness; uncorrected vision and/or hearing impairment that would interfere with study participation; current or history of brain or mental illness judged likely to interfere with testing, including drug and/or alcohol dependence; a diagnosed sleep disorder (e.g., Insomnia); current drug, alcohol or prescription drug intoxication; history of epilepsy; history of diagnosed migraines; metal implants in head or face, including permanent dental retainers; history of cardiac problems that could impact brain function (e.g., atrial fibrillation); and current active suicidal ideation necessitating immediate treatment. During the consent process, participants were instructed to maintain their current medication and psychotherapy regimens and not make any changes for the duration of their study participation.

Overview of ultrasound treatment protocol

Eligible participants completed up to three weeks of ultrasound treatment. Before treatment, they completed an MRI session, a clinical interview, and self-report surveys. The first week of ultrasound involved five sessions within a seven-day period. Participants completed the same baseline assessments after completing week 1, and if they did not meet early remission criteria (defined below), they continued tFUS treatment for for two more weeks, three sessions per week, each within a seven-day period. Participants completed the same series of assessments after week 3. Participants completed a subset of the symptom outcome measures after completing week 1 and week 3 (weekly), and some after each tFUS session (daily).

Symptom outcome measures and adverse event tracking

Before any ultrasound intervention sessions, participants completed baseline surveys: Beck Depression Inventory-II (BDI-II) (27), PTQ (25), Hamilton Depression Rating Scale (HDRS) (28), the World Health Organization Quality of Life Scale (WHOQOL-BREF) (29), and the Columbia Suicide Severity Rating Scale (CSSRS) (30).

The BDI-II is a self-report measure consisting of 21 items measuring current, key symptoms of depression (e.g., sadness, loss of interest, suicidality) using a Likert response scale from 0 to 4 (e.g., 0 – I do not feel sad; 4 – I am so unhappy I cannot stand it) (27). The Hamilton Depression Rating Scale (HDRS) is a 17-item interview administered by a clinician to assess current key depression symptoms (e.g., depressed mood, pathological guilt, Suicide) on a Likert scale of 0 to 4 (e.g., 0 – absent; 4 – severe: Patient reports virtually only these feeling states in verbal and non-verbal communication, *or* depressed almost every day and missed three or more days of work *or* reports suicidal ideation for three or more days) (28). Both the BDI-II and HDRS have excellent published reliability [BDI-II α = 0.93 (27) and HDRS interrater reliability = 0.90 (28)]. As previously mentioned, the PTQ is a highly reliable measure of RNT (α =0.95) (25).

The WHOQOL-BREF is a 26-item self-report measure assessing four aspects of quality of life (QOL): physical well-being, psychological well-being, social satisfaction, and environment satisfaction (29). This measure uses a Likert scale of 1 to 5 for each question (e.g., How would you rate your quality of life? 1 – very poor; 5 – very good). The WHOQOL-BREF is a reliable measure of QOL with published alpha coefficients ranging from 0.66 – 0.8 across the four domains of QOL (29).

The CSSRS is an assessment tool for evaluating the severity of suicidal ideation and behaviors, measuring key aspects such as the intensity and frequency of suicidal thoughts, associated intent, and types of behaviors (e.g., actual, aborted, or interrupted attempts) (30). It includes both "yes or no" questions (e.g., "Have you wished you were dead or wished you could go to sleep and not wake up?") and scaled questions (e.g., "When you have the thoughts how long do they last?": 1 - easily able to control thoughts; 5 - more than 8 hours/persistent or continuous). In prior work, the CSSRS demonstrates 100% sensitivity and specificity for identifying actual and interrupted attempts, and 99.4% specificity and 100% sensitivity for identifying aborted attempts, demonstrating high accuracy in identification while minimizing false positives (30). This measure was used in the present study to track changes in suicidal ideation throughout treatment.

These measures were re-administered following the conclusion of treatment after 1 week and 3 weeks (if applicable) of ultrasound sessions to assess weekly changes in symptoms. In addition to being administered before and after treatment, the BDI-II and PTQ were administered after each ultrasound session to assess daily symptom progression.

Before each ultrasound session, subjects were asked whether they experienced adverse events that may be due to the ultrasound. For reported events, the onset and duration of the event were noted, the severity was rated, and the relationship to study procedure was assessed. After each ultrasound session, participants completed a sensation questionnaire to assess sensations subjects may have experienced from the ultrasound, including: itching, heat/burning,

tingling, vibrating/pulsing, sound, tension, and pain. Before beginning each subsequent ultrasound session (e.g., at the beginning of the next session) and acutely after completion of the sensation questionnaire, subjects were asked whether they experienced any sensations or other issues during the ultrasound session. For reported events, further probing would determine whether an adverse event related to the study occurred. If related to the study, the onset and duration of the event were noted, the severity rated, and the relationship to study procedure assessed. Additionally, SWI MRI images were collected at baseline and after treatment conclusion to provide an objective index of whether ultrasound may have created any damage to neurons or vasculature (see MRI scans section for more detail).

Early remission, remission, and response criteria

To meet early remission criteria following week 1, participants must have a BDI-II score of < 13 and a HDRS score of < 8, and a PTQ score of < 18. If any of these criteria were not met, the participant continued treatment for two additional weeks.

After completion of the treatment protocol (i.e., after week 1 or week 3), remission (defined above) and response were assessed, with a decrease of scores below 50% of baseline considered a response as commonly used in previous treatment literature (15, 31).

MRI scans

Scanning sessions included a T1 weighted structural scan, PETRA short TE scan (skull density), twelve-minute BOLD functional resting-state scan, and Susceptibility Weighted Image (SWI) before beginning ultrasound treatment, after one week of treatment, and after three weeks of treatment (if applicable). The PETRA scans were used for localization and targeting and the SWI images were assessed by board-certified neurologists to assess micro-hemorrhaging. Other MRI acquisitions are not analyzed here and will be reported in a separate paper.

Ultrasound session procedures, device specifications, and targeting precision

After localization and placement of the ultrasound device, each ultrasound session took ten minutes to complete. Participants were instructed to sit quietly, keeping their eyes open. After the ultrasound treatment was complete, the participant sat quietly for another 20 minutes, with eyes open or closed and letting their thoughts come and go.

tFUS was delivered using a custom Neuromodulation device (32) consisting of 128 element ultrasound array (Openwater) with the steerable ultrasound beam having the following parameters: acoustic frequency = 400 kHz, pulse duration = 5 ms, pulse repetition rate (PRR) = 10 Hz, a maximal spatial peak/temporal average acoustic intensity = 670 mW/cm^2, peak negative pressure 820 kPa. The ultrasound probe was secured by a custom-designed headset created by Openwater. Localite Neuronavigation Software (TMS Navigator 3.3 adapted for ultrasound device) and hardware registered the position of the probe with respect to the patient's structural MRI, providing information to develop a novel electronically-steered, stereotactic tFUS treatment plan to the personalized target for each participant's left anterior-medial prefrontal cortex [amPFC; MNI Coordinates -5, 45, -3 (10, 33, 34)]. This target was selected because this region was defined by resting-state connectivity, showing high between-node centrality as a DMN hub and showing a large main effect of self-relevancy in task-related paradigms (10).

The ultrasound array in the custom headset was affixed at the general location of the amPFC target (MNI coordinates: -5, 45, -3) with precise targeting achieved by electronic steering within limits that meet safety parameters for ultrasound exposure (32) (Figure 1). A multi-foci, radial pattern approach was used that distributed the delivered energy in five sub-foci within 5mm from each other (which is the width of the focus in the nominal place, as defined by the -6dB pressure region). The K-Wave modeled peak energy delivery relative to the target location was highly accurate, with the -3dB centroid location of the focus falling within 1.0 +/- 1.1mm of the data measured with a hydrophone in a water tank (.02 +/-.276 mm in the lateral-axial plane, and.87 +/- 1.2mm in the axial direction). The actual pressure values estimated in K-wave and measured in the water tank agreed within 3.6 +- 1.2% within the -6dB contours. For a detailed description of translating MNI coordinates of our target into participant native space, as well as more information about the modeling approach, please see Bawiec et al. (2024) (32).

Statistical analysis

For all statistical analyses, an alpha of 0.05 was employed and significance tests were two-tailed. Analyses were conducted in R studio (version: 2023.09.1 + 494) (35).

Seven Multi-level Models (MLM), which can account for missing data and within-subject variability, were used to assess change in the main outcomes of interest: depression symptoms (BDI-II and HDRS), RNT (PTQ), and four subscales reflecting QOL (WHOQOL-BREF physical well-being, psychological well-being, social satisfaction, and environment satisfaction subscales).

In each model, "time" was specified as the independent variable, modeling the average change in symptoms across timepoints. A random intercept was specified to account for within-subject variation in baseline symptoms.

Full information maximum likelihood estimation was applied to each model to handle missing data from three subjects who did not complete post 3 assessments. A Satterthwaite degrees of freedom adjustment was applied to each model to account for the small sample size.

Given that "time" was already scaled from 0 to 2 (baseline = 0; week 1 = 1; week 3 = 2) centering was not required. This scaling represents the progression of assessment timepoints. Bootstrap confidence intervals (CIs), a non-parametric approach that resamples the data to estimate the distribution of the model

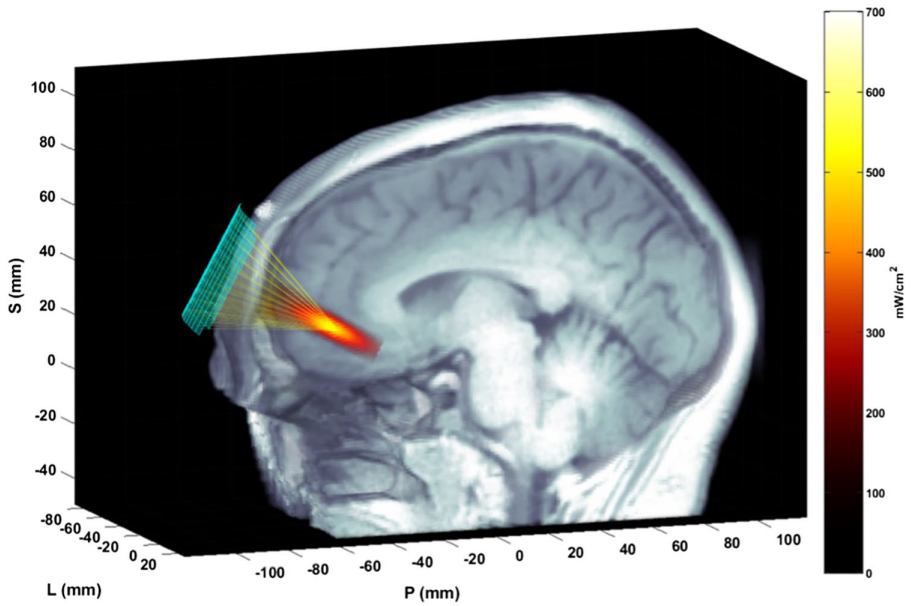

FIGURE 1
Ultrasound focusing to the amPFC. The matrix array transducer is positioned on the forehead and focuses sound through the skull and to the target. The transducer position is measured with the Localite TMSNavigator Neuronavigation system (Localite GmbH, Bonn, Germany). A focal spot, modeled based on the computed time delays using the ultrasound simulation package K-Wave, is overlain on the MRI image, representing the pulse-averaged spatial distribution of applied acoustic intensity.

parameters, were used to assess the robustness of the results. Bootstrapping is ideal for small sample sizes and data with considerable variability.

Two linear regression models assessed the relationship between change in depression symptoms and change in RNT. Model one assessed the relationship between change in self-report depression symptoms (BDI-II) and change in RNT (PTQ) and model two assessed the relationship between change in clinical interview depression ratings (HDRS) and change in RNT (PTQ). Change scores for the BDI-II, HDRS, and PTQ were calculated as baseline minus post, with greater change values indicating a greater decrease in depression symptoms and RNT.

Results

Sample characteristics

From among 386 individuals initially contacted, 247 completed the initial pre-screen web-based survey. Eighty-six potential participants completed a phone screen to confirm responses on the pre-screen survey related to eligibility, and 35 completed the SCID for DSM-5 to confirm a diagnosis of current depression and an absence of mania/psychosis. Twenty participants were enrolled in the study (CONSORT diagram in Figure 2). Participant demographics are presented in Table 1. This relatively young (mean 30.4 years ± 10.0) and predominantly female (75%) sample had moderate to severe depression (BDI-II = 38.9 ± 9.3, HDRS = 19.9 ± 6.3, PTQ = 144.4 ± 6.2). The sample was also highly comorbid, and more than half had early onset depression (before the age of 13). Fifty percent of participants were currently taking medication related to their anxiety and/or depression during the intervention.

Thirty percent of participants did not provide race and ethnicity information. For the 70% of participants that did complete demographic information, 45% of participants identified as White, 10% Black, 5% Chinese, 5% Middle Eastern, and 5% Indian. Seventy percent of participants identified as non-Hispanic. Additionally, 45% of participants were employed part-time and 15% employed part-time, 15% were students, and 25% of participants were unemployed at the time of study enrollment.

Adverse events

Dropout rate, as one index of the acceptability of tFUS treatment, was low: 10% (2/10) did not complete treatment, discontinuing after week 1 of treatment due to lack of symptom improvement. Dropout was not due to adverse events.

No serious adverse events were reported. Reported sensations (itching, heat/burning, tingling, vibrating/pulsing, sound, tension, and pain) are presented in Table 2; for aversive sensations, the modal and median endorsement was 0 (no sensation). All means were below 2.2 on the 10-point scale. For pain and tension specifically, individual reports attributed the pain and tension to the tightness of the headset, not the ultrasound itself. Additionally, none of the participants endorsed suicidal ideation posing imminent risk to self. One subject reported a transient increase, compared to baseline, in suicidal ideation during the post 3 assessment due to a "relationship breakup" unrelated to study procedures.

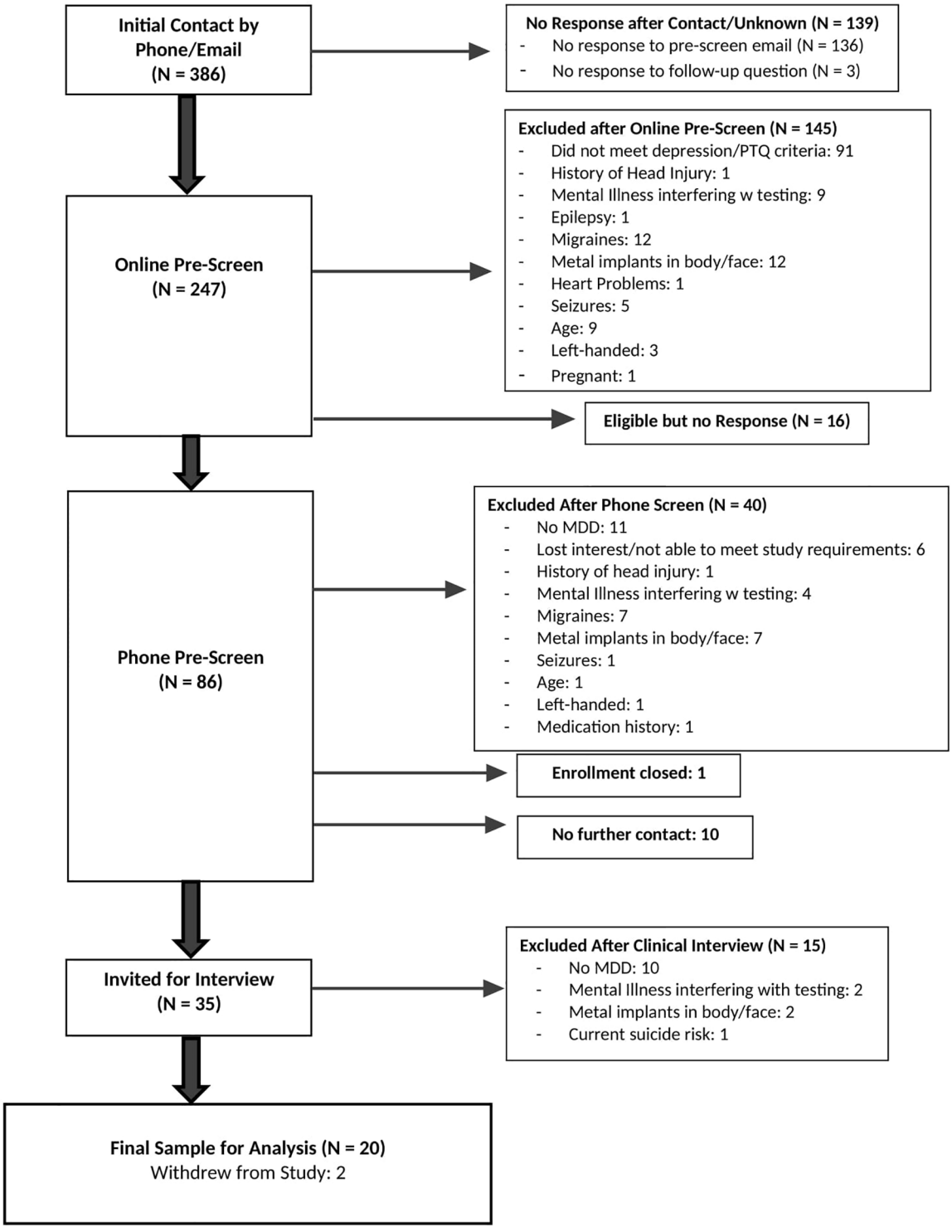

FIGURE 2
CONSORT diagram. Diagram showing participant flow through the study procedures.

SWI images acquired at baseline before tFUS sessions and again after week 1 and week 3 were read by two board-certified neuroradiologists. SWI images are sensitive to vascular micro-hemorrhages. All 20 scans per timepoint were determined to be normal with no findings on SWI, indicating that there were no microhemorrhages resulting from tFUS delivery. Three participants' baseline SWI readings revealed nonspecific white matter hyperintensities which may be seen with chronic microangiopathic ischemic changes and decreased susceptibility which may be related to microhemorrhages. With no change in the pre and post treatment MRI scans of these presumed microhemorrhages, they were deemed chronic.

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TABLE 1 Participant demographics.

Demographics		N = 20
Age, Mean (SD)		30.35 (10.04)
Gender (F/M/Other), No. %		75/20/5
Years of education, Mean (SD)		13.83 (1.93)
Race, No. %		
	White	45
	Black	10
	Chinese	5
	Middle Eastern	5
	Indian	5
	Unknown	30
Ethnicity, No. %		
	Hispanic	0
	Non-Hispanic	70
	Unknown	30
Employment, No. %		
	Full-time	15
	Student	15
	Part-time	45
	Unemployed	25
Baseline BDI-II, Mean (SD)		38.85 (9.34)
Baseline PTQ, Mean (SD)		44.35 (6.24)
Baseline HDRS, Mean (SD)		19.90 (6.34)
Depression onset (Early/Teen/Adult), No. %		55/25/20
Comorbidities, No. %		
	Anxiety and Stress-related Disorder	85
	Trauma-related Disorder	15
	Attention Deficit Hyperactivity Disorder	35
	Eating Disorder	5
	Persistent Depressive Disorder	55
History of Suicidal Ideation (Passive/Active/None), No. %		30/60/10
Hospitalization History (Any), No. %		35
History of Suicide Attempts (None/One/Multiple), No. %		70/15/15
Current Treatment (Medication/Psychotherapy/None), No. %		50/20/10
Past Treatment (Medication/Psychotherapy/None), No. %		75/60/10
Current Medication Type, No. %		
	SSRI (Luxov, Prozac, Sertraline)	15
	SARI (Trazadone)	5
	NDRI (Wellbutrin)	10
	Anti-convulsant (Gabapentin, Lamotrigine)	15
	Beta-Blockers (Propranolol)	5
	CNS stimulant (Adderall, Vyvanse)	10
	Sedative (propofol)	5
	Anti-hypertensives (Clonidine)	10

TABLE 2 Sensation intensities reported on the sensation questionnaire.

Sensation	Mode	Median	Mean	Std Dev	Min	Max
Pain	0	0	0.91	1.76	0	7
Itching	0	0	0.28	0.82	0	7
Heat/Burning	0	0	0.65	1.14	0	5
Tingling	0	1	0.87	1.62	0	8
Vibrating/Pulsing	0	0	1.20	1.64	0	8
Sound	0	0	1.36	1.92	0	10
Tension	0	0	1.63	2.16	0	8

Depression symptoms and RNT

For the BDI-II and HDRS, respectively, 60% and 45% of all 20 participants met response criteria. Thirty-five percent (7/20) met remission criteria for both the BDI-II and HDRS. Significant decreases in depression severity and RNT were observed (Figure 3). Depression symptoms, characterized by the BDI-II and HDRS total scores, significantly decreased by 10.9 ($p < 0.001$, CI = -13.55, -7.92) and 4.2 ($p < 0.001$, CI = -5.85, -2.62), respectively, across time. RNT, characterized by PTQ total scores, also significantly decreased by 8.4 ($p < 0.001$, CI = -10.55, -6.03), across time.

There was a significant positive relationship between change in depression and change in RNT (Figure 4), for both the BDI-II self-report ($R^2 = 0.67$, $F = 36.84$ (1, 18), $p < 0.001$, CI = 0.76, 1.57) and

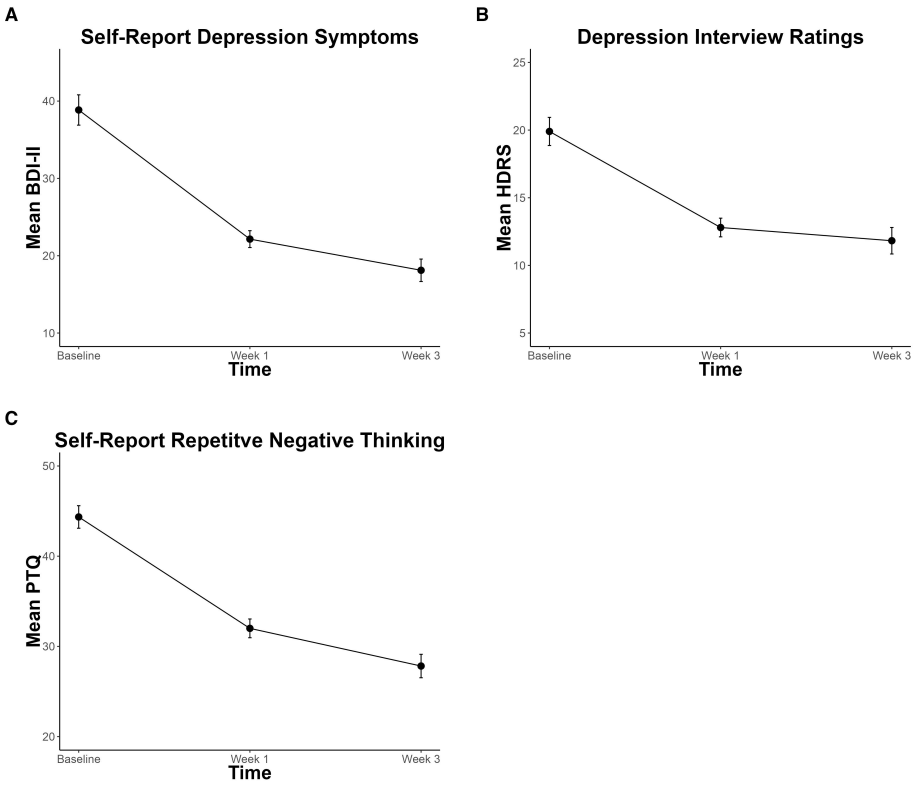

FIGURE 3
Significant decreases in depression symptoms and repetitive negative thought over the course of non-invasive Transcranial Focused Ultrasound Treatment, assessed by **(A)** Beck-Depression Inventory – II (BDI-II), **(B)** Hamilton Depression Rating Scale (HDRS), and **(C)** Perseverative Thinking Questionnaire (PTQ). Error bars represent within-participant standard error.

HDRS interview ratings (R^2 = 0.37, F =10.59 (1, 18), p = 0.004, CI = 0.17, 0.79).

Quality of life

Physical and psychological well-being significantly improved by 7.2 (p < 0.001, CI = 3.64, 10.63) and 11.2 (p < 0.001, CI = 7.79, 14.49) and environment satisfaction improved by 5.0 (p < 0.001, CI = 2.24, 7.56), across time (Figure 5). No significant improvements in social satisfaction were observed (p = 0.15, CI = -0.87, 6.61).

Discussion

Adverse events

Transcranial focused ultrasound treatment for depression using a novel, electronically-steered, stereotactic approach was successfully delivered without serious adverse events. Participants only reported transient, mild to moderate discomfort (e.g., tension and pain) which is similar to sensations experienced in many neuromodulation treatments for depression, such as rTMS (36). Unlike TMS or tDCS, where the source of the pain and discomfort is largely due to the delivery of the magnetic stimulation itself (e.g., skin irritation, local pain) (23), several participants identified the source of the pain and tension to be from the headset. Unlike other neuromodulation techniques, such as TMS, where up to 22.6% of participants experienced headaches from the active treatment (37), there were no reports of headaches related to tFUS delivery.

On average, previous neuromodulation techniques experience a 4.5% dropout rate due to stimulation-related adverse events (38, 39). In the present study, zero percent of participants dropped out due to tFUS-related adverse events and only 10% of participants dropped out due to lack of positive effects of the treatment, which is also significantly better than dropout rates in traditional clinical depression trials, such as individual psychotherapy and pharmaceuticals with up to one-third drop out prior to treatment completion (40–42). Overall, these findings support the notion that not only is tFUS comparably safe to novel interventions such as TMS and tDCS, it may also have fewer side effects and lower dropout compared to other neuromodulation techniques.

Decreases in depression symptoms and RNT

There was a significant, observed decrease in depressed mood and RNT in individuals with current major depression over the course of treatment in just three weeks. For the BDI-II and HDRS,

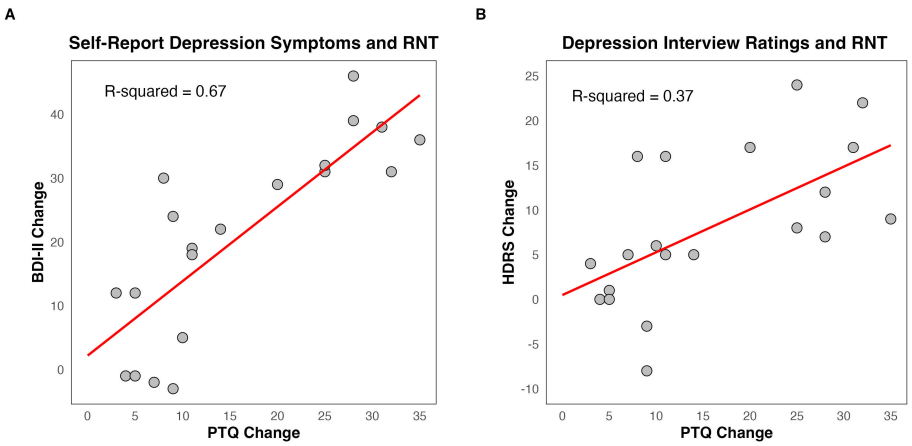

FIGURE 4
Relationship between change in depression symptoms and change in repetitive negative thought (RNT). **(A)** Change in Beck Depression Inventory – II (BDI-II) and change in Perseverative Thinking Questionnaire (PTQ). **(B)** Change in Hamilton Depression Rating Scale (HDRS) and change in PTQ. The scatter plot represents a linear regression containing the R-squared value to assess the strength of the relationship and the red line to visualize the linear fit. Change scores for BDI-II, HDRS, and PTQ were computed as baseline minus post scores, meaning greater positive numbers reflect a greater decrease in depression symptoms and RNT.

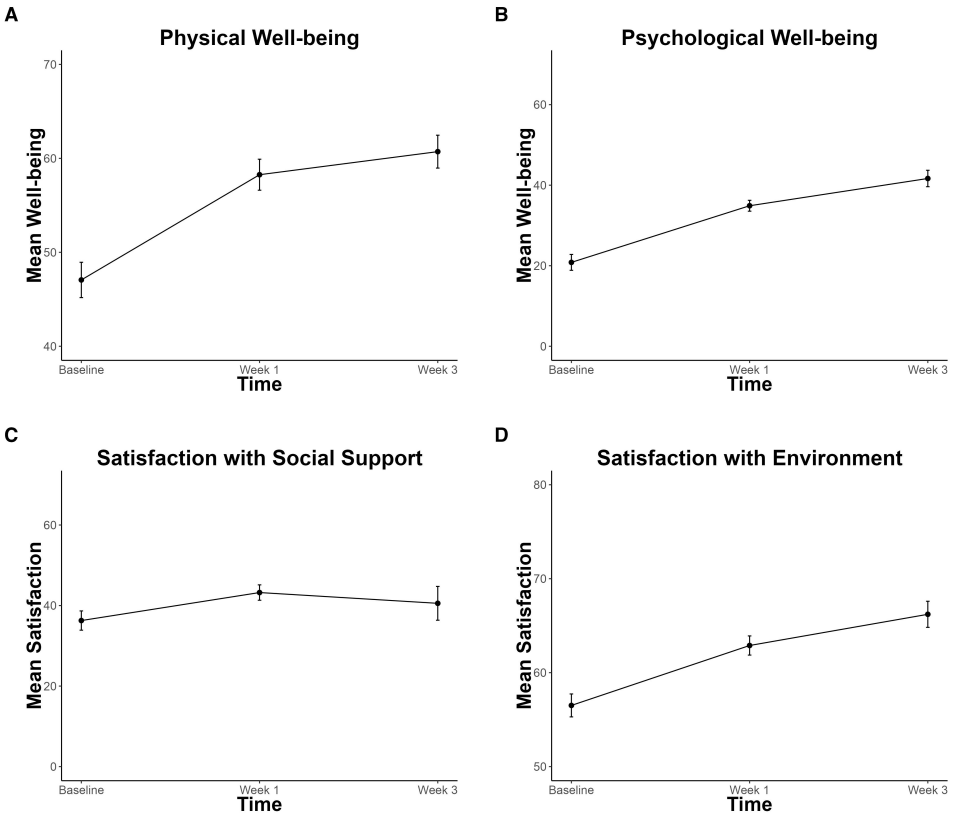

FIGURE 5
Improvements in Quality of Life. **(A)** Physical Well-being **(B)** Psychological Well-being **(C)** Social Satisfaction **(D)** Environment Satisfaction subscales of the World Health Organization Quality of Life Scale (WHOQOL-BREF). Significant improvement is found for panels **(A, B, D)**. Error bars represent within-participant standard error.

respectively, 60% and 45% of participants met response criteria. These percentages are comparable to traditional treatments for depression, such as antidepressants and psychotherapy (45 – 55%) in samples without substantial comorbidity; (43). The rates in the current study were achieved despite substantial comorbidity, a known poor prognostic sign (44).

A potential advantage of tFUS compared to traditional interventions is the rapidity of response: the response rate of 45-60% and remission rate of 35% occurred after just three weeks of treatment, which exceeds what has been found in rTMS interventions for depression with remission rates of as little as 18.6% and up to 30% after up to six weeks of treatment involving more sessions (36, 45). The response from tFUS also occurred with fewer sessions (11) than traditional cognitive behavioral therapy (46) [~12 – 20 sessions, once or twice per week (47)]. Given the open-label design without a control group, it is not possible to infer that tFUS is the causal reason participants experienced decreases in depression symptoms and RNT at this time. This study, however, shows initial promise for the application of tFUS for treating MDD with the potential to offer a more rapid response than traditional treatments.

Improvements in quality of life

Physical and psychological functioning, as well as satisfaction with one's environment, significantly increased over the course of treatment. This extends previous clinical intervention work where quality of life is not commonly considered a main outcome in treatments for depression (48, 49). Additionally, certain treatments (e.g., antidepressants) fail to lead to greater improvements in quality of life compared to controls (50), which prompts an important re-evaluation of what "improvement" means when developing and validating treatment protocols. It will be critical in future work to assess sustained changes in quality of life resulting from tFUS for depression, as well as treatments for depression generally.

The lack of improvement in social satisfaction after tFUS suggests the potential for future tFUS studies to augment tFUS with interventions that are known to improve social relationships and support, such as interpersonal psychotherapy and cognitive behavioral therapy (51), as a multimodal package that addresses the full dimensionality of improving QOL. Despite the promise of tFUS on quality of life in depressed individuals based on these findings, future work with control arms is needed to ascertain the causal role of tFUS in depression.

Impact of tFUS on the DMN

tFUS is a novel neuromodulation technique that holds promise as a tool that can directly modulate brain function with precision (22). Although the direct immediate impact of tFUS on functional connectivity was not assessed in the present study, it is hypothesized that the tFUS parameters used in this open-label case series (pulse repetition rate = 10Hz, acoustic frequency = 400kHz) promoted an inhibitory effect on brain connectivity. Low pulse repetition frequency of tFUS coupled with lower acoustic frequency have been shown to have an inhibitory effect on brain activity by weakening neural firing patterns (52–55). Lord and colleagues demonstrated that targeting the other major hub of the DMN, the posterior cingulate cortex (PCC), using similar inhibitory tFUS parameters (pulse repetition frequency = 10.526Hz, acoustic frequency = 500kHz) in a healthy sample had an inhibitory effect on DMN connectivity, where there was observed decrease in connectivity between the amPFC and PCC (56). The precise mechanism of how the delivery of ultrasound energy translates to changes in neural activity, however, remains a matter of some debate (21), and more research is needed to confirm its inhibitory effects on neural function.

Role of RNT and the DMN in depression

There was a significant, positive relationship between the change in depression symptoms and change in RNT, wherein those with greater decreases in RNT experienced greater decreases in depression symptoms. These findings support previous literature identifying the relationship between RNT and depression (8, 9), however, future work requiring larger sample sizes and a control group should aim to apply more sophisticated models coupled with longitudinal datasets to assess a predictive relationship between RNT and depression.

Our results also provide preliminary support regarding the DMN's role in depression and RNT, as we were successfully able to decrease symptoms while directly targeting a major hub of the DMN. Although the casual relationship between DMN connectivity, depression symptoms, and RNT was not assessed in the present study, it is hypothesized that through directly inhibiting DMN function, resulting in a decrease in functional connectivity within the DMN, participants are experiencing decreases in RNT and depression symptoms. It is critical that future research, namely randomized clinical trials, aim to assess the causal relationship between changes in DMN connectivity, RNT, and depression symptoms, as well as the temporal relationship between change in RNT and change in DMN connectivity throughout the course of tFUS treatment. Further evidence will include resting-state functional connectivity MRI analysis to assess whether changes in DMN connectivity track changes in depression symptoms and RNT.

Limitations and future directions

The present study provides important, preliminary evidence for the potential use of tFUS as a novel, targeted intervention for depression. A critical limitation is that this study was an open-label unblinded trial with a relatively small sample size and, as such, the present study was not able to assess the causal role of tFUS targeting

the amPFC in depression treatment. To assess whether there is a causal relationship between tFUS delivery and a decrease in depression symptoms and RNT, a randomized controlled trial with active and sham ultrasound is needed to control for nonspecific factors and minimize the impact of a placebo effect.

Limitations related to the delivery of tFUS include choosing a target (amPFC) that requires traversing a region with thicker skull density compared to other potential DMN targets (e.g., PCC) and, as a result, delivering less energy to the target due to dispersion of the tFUS signal. However, we are confident that some energy was delivered, and although we cannot infer causality without a control group, we also observed decreases in depression symptoms in the present study. It is, therefore, unclear whether targeting the amPFC is the most potent approach for modulating DMN connectivity in relation to decreasing depression symptoms, and future work incorporating control arms is needed to dissect the differential impact of targeting different hubs of the DMN (56). An empirical question that also still remains is whether engaging in tasks or activities acutely after ultrasound delivery amplify or attenuate effects (57). Future work should aim to understand the optimal protocol for neuromodulation delivery (TMS, TDCS, tFUS). Finally, future work should employ cognitive measures that may relate to symptom improvement and DMN targeting (58–60). Despite these limitations, the present findings provide a strong foundation for the implementation of tFUS as a treatment for depression with pronounced and rapid observed anti-depressant effects over the course of treatment, suggesting the promise of a randomized clinical trial.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Human Subjects Protection Program (HSPP). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. JD-F: Data curation, Methodology, Supervision, Writing – review & editing. KA: Project administration, Writing – review & editing. CB: Conceptualization, Investigation, Methodology, Resources, Software, Supervision, Writing – review & editing. PH: Investigation, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. SO: Investigation, Resources, Software, Writing – review & editing. SK: Resources, Writing – review & editing. AA: Conceptualization, Resources, Supervision, Writing – review & editing. JA: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing, Investigation, Software, Visualization.

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Conflict of interest

JA received an investigator-initiated grant from Openwater. SK and PH are full-time employees of Openwater. AA, CB, & SO were full-time employees of Openwater during parts of the study. The Openwater team supported the success of the study by ensuring the ultrasound equipment was functioning properly. The Openwater team was involved in the review of the manuscript, providing their expertise in describing the ultrasound technology and providing Figure 1. The remaining authors affiliated with the University of Arizona, JS, JF, KA, and JA declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. World Health Organization. Depression (2024). Available online at: https://www.who.int/health-topics/depression (Accessed April 17, 2024).

2. Depression - National Institute of Mental Health (NIMH) (2024). Available online at: https://www.nimh.nih.gov/health/topics/depression (Accessed April 17, 2024).

3. Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clin Psychol Rev*. (2007) 27:959–85. doi: 10.1016/j.cpr.2007.02.005

4. Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry*. (2000) 157(9):1501–4. doi: 10.1176/appi.ajp.157.9.1501

5. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, et al. Multiple recurrences of major depressive disorder. *Am J Psychiatry*. (2000) 157:229–33. doi: 10.1176/appi.ajp.157.2.229

6. Kessler RC, Avenevoli S, Ries Merikangas K. Mood disorders in children and adolescents: an epidemiologic perspective. *Biol Psychiatry*. (2001) 49:1002–14. doi: 10.1016/S0006-3223(01)01129-5

7. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, et al. Defining treatment-resistant depression. *Depress Anxiety*. (2020) 37:134–45. doi: 10.1002/da.22968

8. Kertz SJ, Koran J, Stevens KT, Björgvinsson T. Repetitive negative thinking predicts depression and anxiety symptom improvement during brief cognitive behavioral therapy. *Behav Res Ther*. (2015) 68:54–63. doi: 10.1016/j.brat.2015.03.006

9. Taylor MM, Snyder HR. Repetitive negative thinking shared across rumination and worry predicts symptoms of depression and anxiety. *J Psychopathol Behav Assess*. (2021) 43:904–15. doi: 10.1007/s10862-021-09898-9

10. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron*. (2010) 65:550–62. doi: 10.1016/j.neuron.2010.02.005

11. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network. *Ann N Y Acad Sci*. (2008) 1124:1–38. doi: 10.1196/nyas.2008.1124.issue-1

12. Nejad AB, Fossati P, Lemogne C. Self-referential processing, rumination, and cortical midline structures in major depression. *Front Hum Neurosci*. (2013) 7:666. doi: 10.3389/fnhum.2013.00666

13. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A*. (2010) 107:11020–5. doi: 10.1073/pnas.1000446107

14. Shi H, Wang X, Yi J, Zhu X, Zhang X, Yang J, et al. Default mode network alterations during implicit emotional faces processing in first-episode, treatment-naive major depression patients. *Front Psychol*. (2015) 6:1198. doi: 10.3389/fpsyg.2015.01198

15. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

16. Gattuso JJ, Perkins D, Ruffell S, Lawrence AJ, Hoyer D, Jacobson LH, et al. Default mode network modulation by psychedelics: A systematic review. *Int J Neuropsychopharmacol*. (2023) 26:155–88. doi: 10.1093/ijnp/pyac074

17. Marchetti I, Koster EHW, Sonuga-Barke EJ, De Raedt R. The default mode network and recurrent depression: A neurobiological model of cognitive risk factors. *Neuropsychol Rev*. (2012) 22:229–51. doi: 10.1007/s11065-012-9199-9

18. Reznik SJ, Sanguinetti JL, Tyler WJ, Daft C, Allen JJB. A double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention: TUS mitigates worry among depressed participants. *Neurol Psychiatry Brain Res*. (2020) :37:60–6. doi: 10.1016/j.npbr.2020.06.004

19. Sanguinetti JL, Hameroff S, Smith EE, Sato T, Daft CMW, Tyler WJ, et al. Transcranial focused ultrasound to the right prefrontal cortex improves mood and alters functional connectivity in humans. *Front Hum Neurosci*. (2020) 14:52. doi: 10.3389/fnhum.2020.00052

20. Kubanek J. Neuromodulation with transcranial focused ultrasound. *Neurosurg Focus*. (2018) 44:E14. doi: 10.3171/2017.11.FOCUS17621

21. Dell'Italia J, Sanguinetti JL, Monti MM, Bystritsky A, Reggente N. Current state of potential mechanisms supporting low intensity focused ultrasound for neuromodulation. *Front Hum Neurosci*. (2022) 16:872639. doi: 10.3389/fnhum.2022.872639

22. Fini M, Tyler WJ. Transcranial focused ultrasound: a new tool for non-invasive neuromodulation. *Int Rev Psychiatry Abingdon Engl*. (2017) 29:168–77. doi: 10.1080/09540261.2017.1302924

23. Taylor R, Galvez V, Loo C. Transcranial magnetic stimulation (TMS) safety: a practical guide for psychiatrists. *Australas Psychiatry*. (2018) 26:189–92. doi: 10.1177/1039856217748249

24. First MB, Williams JBW, Karg RS, Spitzer RL. Structured clinical Interview for DSM-5 Disorders-Clinician Version SCID-5-CV. Arlington, VA: American Psychiatric Association (2016). Available at: https://www.appi.org/Products/Interviewing/Structured-Clinical-Interview-for-DSM-5-Disorders (Accessed February 18, 2024).

25. Ehring T, Zetsche U, Weidacker K, Wahl K, Schönfeld S, Ehlers A. The Perseverative Thinking Questionnaire (PTQ): Validation of a content-independent measure of repetitive negative thinking. *J Behav Ther Exp Psychiatry*. (2011) 42:225–32. doi: 10.1016/j.jbtep.2010.12.003

26. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th ed*. (2022) American Psychiatric Association. Maine. doi: 10.1176/appi.books.9780890425787

27. Dozois DJA, Dobson KS, Ahnberg JL. A psychometric evaluation of the Beck Depression Inventory–II. *Psychol Assess*. (1998) 10:83–9. doi: 10.1037/1040-3590.10.2.83

28. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

29. The World Health Organization quality of life assessment (WHOQOL). World Health Organization Group. *Soc Sci Med*. (1995) 41:1403–9. doi: 10.1016/0277-9536(95)00112-K

30. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The columbia–suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. (2011) 168:1266–77. doi: 10.1176/appi.ajp.2011.10111704

31. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the ACNP task force on response and remission in major depressive disorder. *Neuropsychopharmacology*. (2006) 31:1841–53. doi: 10.1038/sj.npp.1301131

32. Bawiec CR, Hollender PJ, Ornellas SB, Schachtner JN, Dahill-Fuchel JF, Konecky SD, et al. A wearable, steerable, transcranial low-intensity focused ultrasound system. *J Ultrasound Med*. (2024) 44(2):239–61. doi: 10.1002/jum.16600

33. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci*. (2005) 102:9673–8. doi: 10.1073/pnas.0504136102

34. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*. (2015) 72:603–11. doi: 10.1001/jamapsychiatry.2015.0071

35. RStudio Team. RStudio: Integrated Development for R. Boston, MA: RStudio (2020). Available at: http://www.rstudio.com/ (Accessed February 18, 2024).

36. Miron JP, Jodoin VD, Lespérance P, Blumberger DM. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. *Ther Adv Psychopharmacol*. (2021) 11:20451253211042696. doi: 10.1177/20451253211042696

37. Wang WL, Wang SY, Hung HY, Chen MH, Juan CH, Li CT. Safety of transcranial magnetic stimulation in unipolar depression: A systematic review and meta-analysis of randomized-controlled trials. *J Affect Disord*. (2022) 301:400–25. doi: 10.1016/j.jad.2022.01.047

38. Moffa AH, Brunoni AR, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: Analysis of individual patient data. *J Affect Disord*. (2017) 221:1–5. doi: 10.1016/j.jad.2017.06.021

39. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biol Psychiatry*. (2007) 62:1208–16. doi: 10.1016/j.biopsych.2007.01.018

40. Cooper AA, Conklin LR. Dropout from individual psychotherapy for major depression: A meta-analysis of randomized clinical trials. *Clin Psychol Rev*. (2015) 40:57–65. doi: 10.1016/j.cpr.2015.05.001

41. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, et al. National institute of mental health treatment of depression collaborative research program: general effectiveness of treatments. *Arch Gen Psychiatry*. (1989) 46:971–82. doi: 10.1001/archpsyc.1989.01810110013002

42. MaChado M, Iskedjian M, Ruiz I, Einarson TR. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. *Curr Med Res Opin*. (2006) 22:1825–37. doi: 10.1185/030079906X132415

43. Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA. A systematic review of comparative efficacy of treatments and controls for depression. *PloS One*. (2012) 7:e41778. doi: 10.1371/journal.pone.0041778

44. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr., Kasper S. Prognosis and improved outcomes in major depression: a review. *Transl Psychiatry*. (2019) 9:1–17. doi: 10.1038/s41398-019-0460-3

45. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med*. (2014) 44:225–39. doi: 10.1017/S0033291713000512

46. Bruijniks SJE, Lemmens LHJM, Hollon SD, Peeters FPML, Cuijpers P, Arntz A, et al. The effects of once- versus twice-weekly sessions on psychotherapy outcomes in depressed patients. *Br J Psychiatry*. (2020) 216:222–30. doi: 10.1192/bjp.2019.265

47. Beck AT. *Cognitive Therapy of Depression*. New York: Guilford Press (1979). 442 p.

48. Hofmann SG, Curtiss J, Carpenter JK, Kind S. Effect of treatments for depression on quality of life: a meta-analysis*. *Cognit Behav Ther*. (2017) 46:265–86. doi: 10.1080/16506073.2017.1304445

49. Kolovos S, Kleiboer A, Cuijpers P. Effect of psychotherapy for depression on quality of life: meta-analysis. *Br J Psychiatry*. (2016) 209:460–8. doi: 10.1192/bjp.bp.115.175059

50. Almohammed OA, Alsalem AA, Almangour AA, Alotaibi LH, Yami MSA, Lai L. Antidepressants and health-related quality of life (HRQoL) for patients with depression: Analysis of the medical expenditure panel survey from the United States. *PloS One*. (2022) 17:e0265928. doi: 10.1371/journal.pone.0265928

51. Gaines AN, Constantino MJ, Coyne AE, Atkinson LR, Bagby RM, Ravitz P, et al. Change in satisfaction with social support as a common outcome in interpersonal psychotherapy and cognitive behavioral therapy for depression. *J Psychother Integr*. (2023) 33:457–64. doi: 10.1037/int0000303

52. Fomenko A, Neudorfer C, Dallapiazza RF, Kalia SK, Lozano AM. Low-intensity ultrasound neuromodulation: An overview of mechanisms and emerging human applications. *Brain Stimulat*. (2018) 11:1209–17. doi: 10.1016/j.brs.2018.08.013

53. Dalecki D. Mechanical bioeffects of ultrasound. *Annu Rev BioMed Eng*. (2004) 6:229–48. doi: 10.1146/annurev.bioeng.6.040803.140126

54. Blackmore J, Shrivastava S, Sallet J, Butler CR, Cleveland RO. Ultrasound neuromodulation: A review of results, mechanisms and safety. *Ultrasound Med Biol*. (2019) 45:1509–36. doi: 10.1016/j.ultrasmedbio.2018.12.015

55. Kuhn T, Spivak NM, Dang BH, Becerra S, Halavi SE, Rotstein N, et al. Transcranial focused ultrasound selectively increases perfusion and modulates functional connectivity of deep brain regions in humans. *Front Neural Circuits*. (2023) 17:1120410. doi: 10.3389/fncir.2023.1120410

56. Lord B, Sanguinetti JL, Ruiz L, Miskovic V, Segre J, Young S, et al. Transcranial focused ultrasound to the posterior cingulate cortex modulates default mode network and subjective experience: an fMRI pilot study. *Front Hum Neurosci*. (2024) 18:1392199. doi: 10.3389/fnhum.2024.1392199

57. Ziebell P, Rodrigues J, Forster A, Sanguinetti JL, Allen JJ, Hewig J. Inhibition of midfrontal theta with transcranial ultrasound explains greater approach versus withdrawal behavior in humans. *Brain Stimul Basic Transl Clin Res Neuromodulation*. (2023) 16:1278–88. doi: 10.1016/j.brs.2023.08.011

58. Vatansever D, Menon DK, Manktelow AE, Sahakian BJ, Stamatakis EA. Default mode network connectivity during task execution. *NeuroImage*. (2015) 122:96–104. doi: 10.1016/j.neuroimage.2015.07.053

59. Sambataro F, Visintin E, Doerig N, Brakowski J, Holtforth MG, Seifritz E, et al. Altered dynamics of brain connectivity in major depressive disorder at-rest and during task performance. *Psychiatry Res Neuroimaging*. (2017) 259:1–9. doi: 10.1016/j.pscychresns.2016.11.001

60. LeMoult J, Gotlib IH. Depression: A cognitive perspective. *Clin Psychol Rev*. (2019) 69:51–66. doi: 10.1016/j.cpr.2018.06.008

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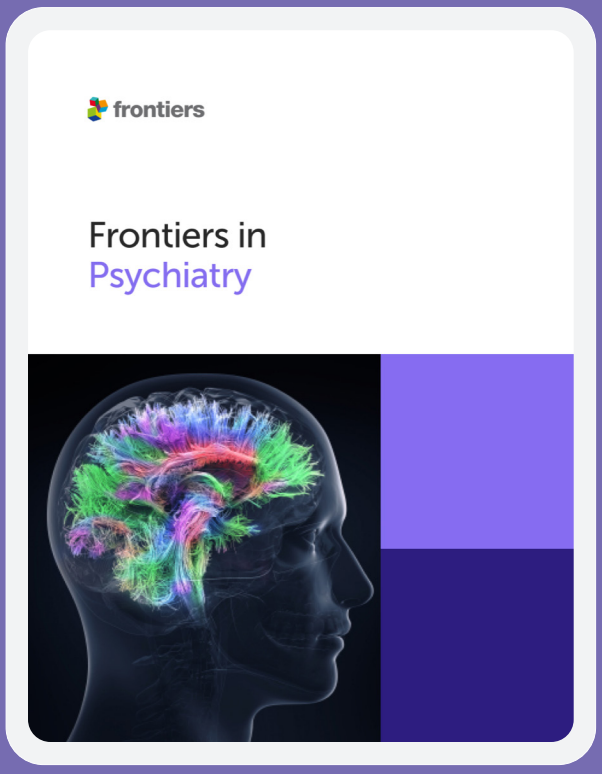

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