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Addictive disorders and digital medicine: technology-based solutions for addictive disorders

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Addictive disorders and digital medicine: technology-based solutions for addictive disorders

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Editorial: Addictive disorders and digital medicine: technology-based solutions for addictive disorders

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Editorial on the Research Topic
Addictive disorders and digital medicine: technology-based solutions for addictive disorders

Addictive disorders pose a major global health burden, yet access to effective treatment remains limited (1). This Research Topic brings together twelve original contributions that showcase how digital innovations—ranging from mobile applications and blended interventions to AI-driven tools—are reshaping addiction care (2). The contributions span four main domains: (1) mobile and app-based interventions, (2) blended or hybrid digital therapies, (3) artificial intelligence and immersive technologies, and (4) psychosocial and neurocognitive correlates of digital addiction.

Mobile and app-based solutions highlight the scalability and personalization potential of digital CBT (3). Redeł et al. developed Nałogometr 2.0, a mobile app incorporating CBT and mindfulness elements with real-time ecological assessments. Jeong et al. evaluated a digital self-care device that uses behavioral metrics to assess alcohol-related risk. Lim et al. demonstrated the superiority of digital CBT over face-to-face CBT in improving abstinence rates and engagement.

Several studies explored hybrid models that blend digital and traditional therapies. Tarp et al. examined therapist experiences with Blend-A, showing successful clinical integration despite initial resistance. Schettini et al. analyzed gender differences in iCBT outcomes for alcohol use disorder, suggesting broad applicability. Labrenz et al. targeted adolescents with digital media use disorder through a blended mobile and group therapy model, while Meads et al. assessed a wearable neuromodulation device for opioid recovery, showing feasibility and improved sleep.

AI and virtual platforms are emerging as transformative tools. Joseph et al. discussed the promise of machine learning for real-time, adaptive interventions in underserved

populations. Lee et al. provided a systematic review of chatbot-based interventions, with strong results for smoking cessation. Matthews et al. proposed virtual reality psychedelic simulations (VRP) for alcohol use disorder, positioning VRP as a complementary or standalone therapeutic tool.

Two studies expanded the conversation to include emotional and neurocognitive vulnerabilities underlying digital addiction. Ursoniu et al. linked social media addiction to alexithymia and empathy deficits in medical students. Liu et al. used network analysis to show that autistic traits, communication difficulties, and cyberspace-oriented relationships are key nodes connecting digital addiction and depression among college students. These findings call for more nuanced, trans-diagnostic intervention strategies.

Conclusion and future directions

This Research Topic illustrates the multifaceted potential of digital solutions in addiction care from enhancing access and engagement to tailoring interventions through machine learning. Just-in-time adaptive interventions (JITAI), wearable biosensors for craving detection, and chatter-bot based therapy represent a new frontier. Future research should prioritize real-world implementation, cross-platform integration, and user-centered design, especially for marginalized and high-risk populations. We hope this Research Topic encourages interdisciplinary collaboration and accelerates the integration of digital medicine into mainstream addiction treatment.

Author contributions

S-KL: Conceptualization, Writing – original draft, Writing – review & editing. C-HC: Writing – original draft, Writing – review & editing. DK: Writing – original draft, Writing – review & editing.

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Revolutionising alcohol use disorder treatment in developing countries: integrating artificial intelligence and technology-driven approaches

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The escalating occurrence of alcohol use disorder (AUD) in developing countries, exacerbated by an inadequate strategic reorientation in treatment methodologies, demands a transition to technology-driven solutions like artificial intelligence (AI) and machine learning (ML) (1). The conventional treatment methods that follow a one-size-fits-all approach primarily centred on psychiatric models often disregard the multidimensional nature of AUD, characterised by the scarcity of resources and infrastructure (2, 3). The diverse cultural and socio-economic context of each region magnifies the intensity of this problem by resisting the in-person treatment-seeking behaviour of individuals with AUD, including inadequate support systems like community support groups, long-term psycho-social support, and family involvement in treatment and management (4, 5). This situation calls for a paradigm shift towards integrating more sophisticated, technology-driven methodologies, particularly AI and ML, which can offer holistic, adaptable, personalised, and culturally appropriate treatment approaches to accommodate the distinct requisites of individuals with AUD.

Existing research from developing countries has not yet examined the potential of AI to analyse extensive data repositories to identify problematic patterns and predictors of AUD, including the identification of underlying causes. Therefore, leveraging these technological advancements in AUD treatment and research constitutes a pragmatic shift in cost-effective AUD treatment and management, transcending conventional methodologies. This transition is critical in varied cultural contexts where conventional methods fail to access and reach. Moreover, AI and ML algorithms can sophisticate treatment strategies by customising person-centric treatment models, and continuous monitoring allows real-time adjustment to treatment plans to enhance success rates (6). This shift compels rigorous research to explore: What patterns and predictors of AUD can AI identify and conventional methods cannot? How does the manifestation of AUD range across distinct cultural settings, and how can AI contribute to a nuanced knowledge of these variations? How can

AI and technology-driven knowledge be efficiently utilised to tailor treatment plans for individuals with AUD? What are the comparative outcomes of personalised treatment plans with general treatment protocols that fit all?

Exploring the potential of AI and technology-driven solutions within community-based AUD interventions in developing countries is a crucial academic endeavour. These interventions would include AI-driven social media platforms for local peer support, integration of local healthcare systems, automated text analysis for early prevention to track the digital footprints of children, educational and awareness campaigns using AI analytics, and geospatial data analysis for resource mapping, allocation, and distribution (7). However, rigorous research should also examine how AI can assist in making ethical decisions in community-based interventions, emphasising cultural sensitivity and upholding individual rights such as identifying potential biases in treatment recommendations, predicting treatment outcomes based on cultural and socioeconomic characteristics, and preventing relapse. The sustainability of such interventions might be a concern in resource-constrained developing countries. The ability of AI to enhance the impact of these interventions and cater to the unique needs and characteristics of local communities signifies a vital advancement. Utilising AI in this context has the capacity to substantially enhance community engagement in AUD treatment, proficiently linking the gap between clinical methods and the real-life experiences of individuals across diverse communities. Therefore, integrating AI could strengthen community engagement in AUD treatment by bridging clinical treatment methods and the real-life experiences of individuals in various communities. Thus, investigating the role of AI in community-based AUD interventions opens vital questions: How can AI contribute to the development of powerful, culturally appropriate strategies and ethical decision-making in community-based AUD interventions? How can AI be utilised in complex situations to develop cost-effective evidence-based strategies to ensure the optimum outcomes of AUD interventions?

Moreover, rigorously examining the efficacy of technology-driven interventions, such as telehealth, mental health applications, digital platforms for meditation, gamification strategies to manage mental health, therapies using virtual and augmented reality, AI-based chatbots, and wearable intervention monitoring devices, compared to conventional face-to-face interventions. However, while embracing the capabilities of AI and technically-driven solutions in treating and managing AUD, it is imperative to meticulously examine the feasibility and pragmatic obstacles encountered in developing countries with this paradigm shift. The uncertainty lies in the accessibility of technological resources, digital literacy and insufficient infrastructure and mechanisms for financial support. Therefore, scholarly inquiries should be entitled to develop economically viable and scalable AI and technologically-driven solutions compatible with the existing technological advancements and healthcare system in each context.

Furthermore, there is a need to cultivate technological proficiency among healthcare professionals and patients alike to ensure the efficient utilisation of these sophisticated tools through capacity-building training programmes. Moreover, it is critical to administer the need assessments and resource mapping by utilising stakeholder engagement and partnership. Collaborating with global healthcare organisations is vital for local government bodies to acquire financial backing and policy endorsements. Pilot projects are essential for evaluating the adaptability and gradual implementation of such interventions, fostering local and global applicability and cultural resonance. Thus, examining policy and governance mechanisms for integrating the capabilities of AI and other advanced technologies into the therapeutic arena demands the development and scaling up of policies. This academic pursuit is a nexus of technological innovation, healthcare policy, and cultural adaptability, thereby shaping the trajectory of AUD treatment methodologies globally.

Therefore, this letter advocates for a comprehensive, interdisciplinary research initiative that integrates clinical practices with AI and Technology-driven solutions to manage the nuances of AUD in developing countries. Sustainable interventions might enhance the current rehabilitation methods and reshape the socio-economic impact of AUD, necessitating a paradigm shift. This requires synergic effort from researchers, policymakers, and healthcare professionals to understand the complexities of AUD and develop culturally sensitive, technologically-driven interventions to prevent AUD in developing nations, marking a significant step towards progress.

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Evaluating the effectiveness of a mobile app-based self-guided psychological interventions to reduce relapse in substance use disorder: protocol for a randomized controlled trial

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Background: Substance Use Disorder (SUD) persists as a significant public health challenge worldwide, with an estimated prevalence of approximately 10-15% across the global populace. This condition is characterized by a notably high risk of lapses and relapses, even subsequent to treatment interventions. Mobile health interventions, owing to their widespread accessibility, emerge as a promising approach to diminish the risk of relapse post-treatment and to broaden the scope of care, especially in regions with a scarcity of trained medical professionals.

Method: This study is designed to assess the effectiveness of mobile interventions in mitigating cravings and preventing lapses among individuals diagnosed with SUD. Employing a two-armed, randomized controlled trial framework, the study will evaluate a self-administered psychological intervention delivered through a mobile application, Nałogometr 2.0. Over a period of three months, participants will engage with intervention modules that primarily incorporate mindfulness techniques and Cognitive Behavioral Therapy (CBT) principles. Ecological Momentary Assessment (EMA) will be utilized to gather longitudinal data on a range of variables that are indicative of craving intensity and the risk of lapse. In addition to this, a monthly-administered battery of questionnaires will be

employed to gauge the severity of substance dependence, as well as to measure levels of anxiety, depression, and overall life satisfaction.

Results: Results will be submitted for publication in peer-reviewed journals.

Clinical trial registration: https://clinicaltrials.gov/, identifier [NCT05730504].

KEYWORDS

SUD, addiction, EMA, mHealth, mobile app, cognitive behavioral therapy

Introduction

Substance Use Disorder (SUD) continues to be a grave concern for public health, affecting an estimated 10-15% of the global population (1). The 5-th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) lists 11 criteria for an SUD diagnosis, falling into four categories. Criteria 1-4 are related to the impaired control of substance use (consuming the substance in larger quantities and for longer than intended, continuing usage despite the desire to cut down or regulate use, spending a great deal of time on obtaining, using, and recovering from the substance, and experiencing cravings, defined as a persistent desire to use substance). Criteria 5-7 refer to an impairment of social life due to substance use (like inability to fulfill major social and work obligations due to substance use, continuing usage despite it causing significant interpersonal problems, and reduction or discontinuation of social activities because of substance use). Criteria 8 and 9 describe risky use – using the substance in unsafe environments, and persistent usage despite knowing that it may cause physical or psychological problems. Criteria 10 and 11 are physiological: experiencing the buildup of tolerance (requiring increasingly higher doses to achieve the same level of intoxication) and symptoms of withdrawal (adverse effects occuring when substance levels in the body decrease).

Among European countries, Eastern European region has the highest rates of alcohol consumption. Latvia, with 13.19 litres of pure alcohol consumed per capita yearly, is a country with the highest alcohol consumption in the region. In Poland, the yearly consumption is estimated at 11.89 litres of pure alcohol per capita, which is well above recommended use.

Even though in United States less alcohol is consumed (9.97 litres per capita), alcohol dependence rates are similar. It is estimated that 13.9% of US populations struggles with alcohol dependence, which makes US the 5th most affected country (higher rates of alcohol dependence are found in Hungary, Russia, Belarus and Latvia).

In Poland, the most common forms of addiction are alcohol dependence, impacting roughly 12.8% of population (2), and nicotine dependence, affecting around 21% (3). The prevalence of addiction to other psychoactive substances is more difficult to quantify, largely due to legal constraints; however, based on the percentage of individuals seeking treatment, amphetamine (33%) and cannabis (32.8%) are the leading substances of illicit use, followed by opioids (15%) and cocaine (3.1%) (4). The high global prevalence, coupled with the considerable risk of relapse—approximately 40-80% of individuals in recovery return to substance use following treatment completion (5, 6) underscores the particularly chronic and intractable nature of SUD. Morover, a vast majority of those affected, potentially up to 80%, never engage in any form of therapy (7, 8). Contributing factors include a scarcity of medical professionals skilled in treating addiction disorders and patients' tendency to minimize the severity of their issues. Furthermore, the societal stigma associated with substance use often serves as a barrier, deterring individuals from seeking the help they need (9, 10).

Cognitive Behavioral Therapy (CBT) and mindfulness-based interventions have been established as the most effective methods for treating a range of addictions (11–14). CBT, in particular, demonstrates substantial benefits in addiction treatment as it offers a multifaceted approach by addressing mood disturbances and addiction cravings through the reconstruction of maladaptive beliefs and behaviors, proving its effectiveness in conjunction with pharmacotherapy within clinical settings (15, 16). Additionally, the advent of computer-assisted CBT presents a promising alternative, capitalizing on the ubiquity of computers and internet-enabled mobile devices. Notably, research underscores the utility of a six-module computer-assisted CBT program as a valuable supplement to traditional substance use disorder therapy (17). This innovative solution not only exhibits cost-effectiveness compared to standard CBT but also obviates the necessity for continuous clinician access, marking a significant stride in addiction treatment accessibility.

Mindfulness meditation is recognized for its efficacy in diminishing psychological distress and rumination, as well as reducing symptoms of anxiety and enhancing positive affect (18). Standardized mindfulness interventions have also been shown to significantly alleviate emotional distress and symptoms associated with certain mental disorders (19). Techniques intrinsic to mindfulness, such as focused attention and open monitoring, aim to develop and refine skills in attentional reorientation, metacognition, cognitive reappraisal, and inhibitory control.

These competencies are central in effectively managing cravings and maladaptive addictive behaviors (20). Mindfulness-Based Interventions (MBIs) are structured to promote awareness of one's moment-to-moment experiences, including emotions, thoughts, bodily sensations, and surrounding stimuli. These interventions have demonstrated success in treating SUDs, as they target fundamental mechanisms of addiction by enhancing the recognition and comprehension of triggers, emotions, and thoughts tied to addictive behaviors. MBI programs integrate mindfulness practices to aid in coping with the symptoms of SUD, for instance, by maintaining a mindful presence during experiences of craving in everyday life (21). MBIs have shown greater effectiveness in mitigating withdrawal symptoms and cravings, as well as reducing negative substance use outcomes, in comparison to other psychotherapeutic modalities. However, in terms of substance use frequency and relapse rates, Cognitive Behavioral Therapy (CBT), MBIs, and treatment as usual (*ie, education on substance use, participating in 12-step process-orientated group, or medical management including pharmacotherapy and weekly individual counseling sessions*) did not show significant differences (22).

The emerging sector of mobile health (mHealth) technologies presents a potential strategy to tackle challenges faced by patients with SUD, particularly the heightened risk of relapse following treatment completion. Mobile health encompasses a spectrum of mobile technologies aimed at bolstering health, including mental health (23). Interventions delivered via smartphones are increasingly popular due to their widespread accessibility (24). mHealth interventions have shown promise in augmenting the long-term outcomes of SUD treatments and may play a role in mitigating issues related to social stigma and the insufficient availability of healthcare professionals (25, 26).

Psychological interventions disseminated through mobile technology may offer beneficial therapeutic effects in managing addiction, offering cost-effectiveness and increased accessibility since they do not necessitate continuous contact with a healthcare professional (27, 28). These interventions can be integrated as complementary treatments alongside conventional SUD therapy and pharmacological approaches (17, 29). Additionally, mobile interventions grounded in Cognitive Behavioral Therapy (CBT) can function as supportive measures post-treatment, assisting in the reduction of relapse risk and bolstering therapeutic gains (30).

Mobile technologies facilitate the efficient collection of data via Ecological Momentary Assessment (EMA) (31). EMA entails the real-time and recurrent sampling of participants' current moods, behaviors, and experiences as they occur in the individual's natural environment, throughout their daily life (32). While traditional surveys are employed in addiction research, they are often limited to single-time measurements and may not adequately capture the dynamics and fluctuations in behavior (33). EMA not only serves as a research tool for scientists but also supports participants in developing self-monitoring and self- management skills (34), which are recognized as beneficial for behavioral modification in individuals coping with addiction (35–37).

Although interest in mobile health (mHealth) technologies is surging, with over 300,000 applications available in digital marketplaces (38), only a limited number have undergone clinical evaluation before being released for widespread usage (39). Despite many of these applications employing scientific terminology to substantiate their benefits, the evidence supporting them is frequently of poor quality or altogether absent (40). Nonetheless, those apps that have been subject to scientific scrutiny have demonstrated promising outcomes, with positive effects on health-related behaviors (41). The inherent characteristics of mHealth interventions render them an encouraging support mechanism for patients with Substance use disorder (SUD) — given their remote delivery, they can be utilized on demand, providing immediate assistance and support amid episodes of increased craving. Consequently, mHealth solutions are particularly valuable for relapse prevention among patients who have concluded formal treatment. The persistent and considerable risk of relapse following treatment poses a significant challenge in the management of addictive disorders, and mHealth interventions offer a viable approach due to their convenience, ease of use, and broad accessibility. Moreover, mHealth solutions hold the potential to overcome barriers to accessing therapy, such as social stigma, while remaining cost-effective and widely available.

There are some mobile apps dedicated to reducing substance use already available on the market (e.g. *Quitzilla, Drinker's Helper, Helpic*), but only a few of them have been scientifically tested – examples of such apps include *Drink Less* (42) for alcohol use or *Assess, Plan, Track, Tips (APTT;* 43*)* and *Norwegian Cannabis Cessation app* (44) for cannabis use. Their features include tracking day-to-day substance usage in a form of sobriety calendars, as well as psychoeducational content on substance dependence and psychological components on recognizing and dealing with triggers and craving.

Given these insights, it becomes imperative to provide patients with addictive disorders access to scientifically validated, evidence-based mobile health (mHealth) solutions. This paper introduces a protocol for a two-arm randomized controlled trial (RCT) designed to evaluate the effectiveness of self-guided, mobile-delivered CBT- and mindfulness-based psychological interventions. The goal is to enhance the post-therapy effects of SUD treatment and aid in the prevention of lapses. These interventions will be administered through the Nałogometr 2.0 app, a science-based mHealth application developed to decrease craving intensity and the risk of lapses in individuals experiencing problematic substance use or those diagnosed with SUD.

The Nałogometr 2.0 app incorporates multiple self-guided psychological interventions predominantly rooted in cognitive behavioral therapy and mindfulness. It offers users the autonomy to interact with any module at their convenience without adhering to a predetermined regimen, thereby affording greater flexibility in tailoring psychological interventions to meet their current needs. Beyond delivering psychological intervention modules, the app is also engineered to foster self-monitoring and self-management by enabling users to self-record their behaviors, and mental and physiological states through Ecological Momentary Assessment (EMA). Additionally, users receive personalized feedback in response to their input.

Materials and methods

Aim

The aim of the study is to evaluate the effectiveness of mobile interventions in reducing craving and lapses in patients with substance use disorder.

Study design

The study was pre-registered within the Open Science Framework (OSF) repository: https://osf.io/z4xqd.

A two-arm participant-blinded randomized control trial will be conducted via a mobile app. The study will compare an intervention experimental condition with a waitlist control condition.

Throughout the duration of the study, participants assigned to the experimental group will have access to self-guided psychological interventions.

Participants will be asked to complete daily EMA questions, as well as questionnaire battery assessments at multiple timepoints: 1) at baseline – in the first week, following onboarding questionnaire; 2) after one month; 3) after two months; 4) after three months.

Participants

The research will be conducted in collaboration with MONAR and AKMED, Polish organizations responsible for overseeing numerous addiction treatment clinics and centers, as well as other independent institutions. Recruitment of participants will target clinical patients who are undergoing either in-patient or out-patient treatment for Substance Use Disorder (SUD). For the in-patient cohort, the study will include individuals who are in the final stage of their therapy, specifically those expected to conclude their treatment within a maximum of 4 weeks but not fewer than 5 days. Eligible participants must be adults, aged 18 years or older, and must possess fluency in Polish. Moreover, in light of the study's methodology, enrollment will be limited to users of iOS or Android smartphones.

Participants will be recruited into three groups: 1) Patients with alcohol addiction, 2) Patients with cross-addiction (alcohol and stimulants), 3) Patients with cannabis addiction. We plan on recruiting 150 participants with alcohol addiction, 150 participants with cross-addiction, and ~100 participants with cannabis addiction, due to lower availability of CUD therapeutic programs in Poland – and subsequently, less patients finishing therapy.

Each participant will be assigned to either experimental or control condition upon logging in to the mobile app for the first time.

Sample size calculation

A simulation-based power analysis was performed to determine the sample size, premised on the use of a linear mixed-effects model with subject-level random intercepts and a small effect size of the intervention. This effect size assumption was informed by literature on the efficacy of mobile interventions in mitigating addictive behaviors (for a review, see 25). The simulation indicated that a minimum of 360 participants would be necessary to achieve an 80% power threshold for detecting a significant group effect. The sampling strategy has been devised to capture maximal demographic variance within the sample, with particular attention to characteristics such as gender, age, geographic location, and socioeconomic status.

Data collection

During recruitment to the study, participants will be asked to read and sign a consent form. They will also receive necessary study materials: a smartband, along with instructions on how to connect it to their phones, and their individual study code to enter upon logging in to the app.

The research project is based on the principle of complete anonymity, which means that personal data allowing the identification of users is not obtained. For study participants, detailed information about the anonymity of data and how it is processed and stored can be found in the 'Privacy Policy' contained in the application and in the 'Terms and Conditions of Service'. The only demographic data entered into the application are gender, age, and size of place of residence - data we need to create a lapse risk prediction model. The analysis is entirely anonymous - the user will not be compared with the results of any specific user. We plan to conduct comparisons between large groups of users, but these will never be analyses of individual users. Without the user's explicit consent, we do not share the collected data with entities other than those directly involved in conducting the research and those to which the provision of data will result from a legal obligation. Unless the research participant decides otherwise, the results will be deleted or left in an anonymized form within 30 days from the end of the last phase of the study.

Ecological data will be gathered through a mobile application installed on the participants' smartphones. Upon initial access, participants will encounter a baseline questionnaire designed to collect demographic data and information regarding their patterns of substance use. Throughout the study's duration, participants will respond to daily EMA prompts and complete a series of questionnaires at specific timepoints, as delineated in Figure 1. Throughout the course of the study, the app will be sending daily reminders about EMA prompts, to enhance compliance.

In conjunction with the mobile app data collection, participants will be equipped with smartbands to monitor various physiological parameters, including sleep duration and quality, heart rate, and physical activity levels.

To bolster participant retention rates, an incentive in the form of a contest has been integrated into the study. Participants will be invited to share their experiences with the Nałogometr app, specifically how it aids in modifying their substance use behaviors. The prizes for this contest include a smartwatch and gift cards from the popular polish bookstore, Empik. This

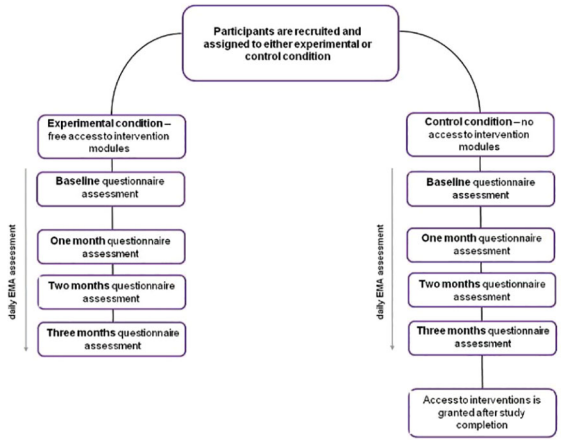

FIGURE 1
Flowchart of the study design.

motivational component is anticipated to enhance participant engagement and adherence to the study protocol.

Randomization

Upon their initial login to the mobile application, participants in each group (alcohol, cross-addiction, and cannabis), will be randomly allocated to either the experimental or control condition based on a code they receive during recruitment. Codes corresponding to experimental and control conditions were generated seperately for each group and then put in a randomized sequence. The randomization was done via an online randomization tool (45. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists). Block sizes were determined using the simulation tool (45. [Online] Available from: https://www.sealedenvelope.com/randomisation/simulation/, taking into account planned sample sizes. Participants assigned to the experimental condition will gain immediate access to all psychological interventions following their initial app login. Those in the control condition will have access only to the daily EMA questions and the sobriety calendar, a tool for tracking their substance use. They will be provided access to the complete version of the app, including the psychological interventions, subsequent to the study's conclusion - which is scheduled for 98 days after the first login.

Procedure

The study will be conducted with the use of *Nałogometr 2.0*, a mobile app designed to reduce craving and lapse risk in SUD and enhance post-treatment effects (available freely on Google Play and App Store). Prior to the first login, participants will be automatically navigated through all the necessary permissions and consents regarding data collection. Following the app installation, participants will be prompted with an onboarding questionnaire to collect demographic data. They will have a one-week window to complete the initial standardized questionnaire battery assessment. The responses from this initial assessment will serve as the baseline for subsequent evaluations throughout the study. The schedule of these assessments is outlined in Figure 1.

During a three-month period, participants will be required to engage in daily EMA assessments and to complete a monthly questionnaire battery. Concurrently, physiological data will be continuously gathered via smartbands.

Mobile application content

The Nałogometr 2.0 app, available at https://nalogometr.pl/, is designed for individuals seeking to decrease or discontinue their problematic substance use or behavioral habits. The app provides features such as Ecological Momentary Assessment (EMA) and self-guided psychological interventions. For the duration of the study, the accessibility of various modules within the app will be contingent upon the participant's assigned condition—the control group will not have access to the app's full capabilities until after the conclusion of the study.

Dashboard. The app features a user-friendly dashboard designed for simplicity and ease of navigation, granting users swift access to psychological interventions, EMA modules, and a sobriety calendar, which allows for tracking participants' substance use.

Intervention modules. The application encompasses a suite of self-guided psychological intervention modules. These interventions include a series of audio-guided sessions that focus on gratitude, thoughts management, motivation, relaxation, along with mindfulness sessions aimed at heightening awareness of emotions and bodily signals, and managing stress. These audio sessions are in line with other empirically evaluated self-guided audio exercises (46–48). Furthermore, the intervention module of the app also incorporates CBT-based written exercises that are rooted in thought management and journaling techniques. These are designed to bolster self-confidence and self-efficacy, as well as to deepen the user's understanding of the interplay between situational triggers, mood, and sobriety. We included longterm

intervention modules based on CBT components, e.g., *My beliefs* which is a thought management technique, *Thinking traps*, another thought management and reframing technique, *Planner*, intended to improve goal achievement and self-efficacy, *Mood Journal*, where users are instructed to better understanding of the relationship between situations, thoughts, mood and sobriety, *Dream diary* and *Success diary* intended to enhance self-observation, self-esteem, self-confidence, and awareness of emotions, and *Gratitude Journal* which improves the positive attitude towards yourself, people and world.

Participants assigned to the intervention group will be granted immediate access to all intervention modules upon logging into the app using their unique code. They will have the autonomy to interact with any of the interventions at their discretion without any mandatory commitment. Adherence to a stringent schedule for engaging with the interventions is not a prerequisite for participants in the intervention condition.

Measures

During the onboarding process—initiated at the first login—participants will be prompted to provide sociodemographic information, including gender, age, place of residence, and details of their addiction profile. They will also respond to questions about their history of substance use, encompassing aspects like the substance involved, duration of use, frequency, treatment history, and periods of abstinence. A series of standardized questionnaires (refer to Table 1 for an overview) will be employed to gather data on a range of psychological variables. These questionnaire batteries will be administered at one, two, and three months into the study, facilitating the collection of longitudinal data.

EMA will be conducted daily to monitor cravings and lapses. The EMA will also record additional variables that are associated with craving intensity, such as current mood, arousal, stress, anxiety, loneliness, fatigue, anger, hunger, and uncertainty.

Primary outcomes

Primary outcomes of interest will include self-reported number of lapses and addiction craving (intensity of the urge to use a substance at a moment of assessment).

Secondary outcomes

During the monthly questionnaire assessment, following measures will be applied:

TABLE 1 Measures used in questionnaire assessment.

	Group 1 (cross-addiction)		Group 2 (alcohol addiction)		Group 3 (cannabis addiction)	
Measures	Baseline	Monthly assessments	Baseline	Monthly assessments	Baseline	Monthly assessments
Socio-demographic questions	x		x		x	
Onboarding questions	x		x		x	
Substance use-related measures						
Dependence severity (Screener)	x	x	x	x	x	x
Substance dependence (SDS)	x	x	x	x	x	x
Alcohol dependence (AUDIT)	x	x	x	x	x	x
Stimulants dependence (DUDIT)	x	x				
Cannabis dependence (CUDIT-R)					x	x
Psychological functioning measures						
Anxiety and depression (HADS)	x	x	x	x	x	x
Coping with stress (mini-COPE)	x	x	x	x	x	x
Sensation seeking (BSSS)	x	x	x	x	x	x
Emotional regulation (DERS)	x	x	x	x	x	x
Impulsivity (SUPPS)	x	x	x	x	x	x
Life satisfaction (SWLS)	x	x	x	x	x	x

Substance use. Self-report psychological measures of substance dependence will be administered across all participant groups. The assessment will include the Severity of Dependence Scale (SDS) (49), which measures dependence on psychoactive substances. Additional questionnaires will be presented depending on the type of addiction. For group A (patients with Alcohol Use Disorder) assessment will include the Alcohol Use Disorders Identification Test (AUDIT) (50). In group B (patients with cross-addiction – alcohol and stimulants) we will administer both AUDIT and the Drug Use Disorders Identification Test (DUDIT) (51). Group C (patients with Cannabis Use Disorder) will complete the Cannabis Use Disorders Identification Test-Revised (CUDIT-R) (52).

Depression and anxiety. Symptoms of depression and anxiety among the participants will be quantified using the Hospital Anxiety and Depression Scale (HADS) (53). This instrument is a 14-item questionnaire divided into two subscales: one for anxiety and one for depression, each comprising 7 items. For both subscales, a score ranging from 8 to 10 suggests mild symptoms of depression or anxiety, while scores between 11 and 21 signify the potential presence of a depressive or anxiety disorder.

*Emotion regulation and coping with stress.*Emotion regulation will be evaluated using the Difficulties in Emotion Regulation Scale (DERS) (54), which is a 36-item questionnaire. Participants will rate items on a scale from 1, indicating 'almost never', to 5, signifying 'almost always'. The DERS is organized into six subscales, each designed to assess different facets of emotion regulation difficulties.

For assessing stress management, the Coping Orientation to Problems Experienced (mini-COPE) questionnaire will be used (55). This instrument includes 28 items referring to various coping strategies individuals employ in response to stress.

Impulsivity and sensation seeking. Impulsivity will be quantified utilizing the short version of the Impulsive Behavior Scale (SUPPS) (56), which is composed of five subscales. Each subscale contains four items. To assess sensation seeking, the study will employ the 8-item Brief Sensation Seeking Scale (BSSS) (57).

Life satisfaction. Life satisfaction will be measured with a 5-item Satisfaction with Life Scale (SWLS) (58).

Engagement metrics

To assess participant engagement with the Nalogometr application and its components, several metrics will be tracked throughout the study period.

Average number of days of app usage during the study: Participants' engagement with the Nalogometr application was measured by recording the average number of days they accessed the app during the study period. This metric provides an overview of participants' overall engagement levels throughout the intervention.

Average number of days of app usage per week: In addition to the total number of days of app usage, we calculated the average frequency of app usage per week for each participant. This allowed us to assess the consistency of participants' engagement with the application over time.

Average number of reminders responded to by the user: The Nalogometr application includes reminder features aimed at promoting engagement with the intervention components. We tracked the average number of reminders responded to by participants throughout the study, both overall and within specific timeframes.

Average number of completed interventions: For participants assigned to the intervention group, the completion of interventions within the Nalogometr application was tracked. We calculated the average number of completed interventions over the study duration and within specific timeframes to evaluate participants' engagement with the intervention components."

Results

Hypotheses

The primary outcomes of this study are centered on the hypothesis that participants receiving the intervention, as opposed to those in the control condition, will exhibit reduced levels of craving and fewer lapses at the one-month follow-up post-app implementation relative to their baseline levels. It is anticipated that this downward trend in craving and lapse incidents will be sustained throughout subsequent evaluations. Additionally, it is conjectured that a single session of self-guided psychological intervention may yield a notable decrement in both craving intensity and the risk of a lapse occurring. Furthermore, the hypothesis extends to posit that participants in the intervention condition will demonstrate lower levels of substance addiction, reduced symptoms of anxiety and depression, and an elevated sense of life satisfaction when compared to those in the control group, as measured by the relevant standardized questionnaires.

Data analysis

Factorial design mixed-effects models will be applied to compare questionnaire battery scores between experimental groups and the control across measurements. In addition, we will perform an interrupted time series analysis to estimate the effects of different types of interventions on longitudinal ecological momentary assessment outcomes.

In the statistical analysis, we will incorporate data from participants who have completed a minimum of 21 Ecological Momentary Assessment (EMA) entries, spread over the one-month period dedicated to evaluating the intervention. For the assessment of the intervention's enduring effects, the analysis will consider participants who have logged at least three EMA entries during the follow-up phase. In addition, within the intervention group, we will include those who have accessed the app and engaged with the self-guided intervention modules on a minimum of four occasions and at least once, respectively; this will represent the minimal therapeutic exposure required for the study. For the analysis of secondary outcomes, we will include participants who

have completed the initial baseline assessment as well as at least one subsequent follow-up assessment.

Data management

Throughout the duration of the research, longitudinal data will be systematically collected via the Nałogometr 2.0 app and securely stored on a protected server. Documentation of this data will comprise codebooks outlining essential information, including data collection protocols, methodological approach, and participant sample characteristics. These codebooks will also detail the types of measures that correspond to each unit of raw data.

The roles of data stewards will be assigned to the Principal Investigators (PIs) and Co-Investigators (CIs), who will oversee the documentation and management of data throughout the processes of collection, analysis, and the eventual dissemination of findings. Team members such as project coordinators, data scientists, and analysts will access the data solely in an anonymized format, adhering to the directives set forth by the PIs and CIs.

After the results have been published, the data will be archived on a server with comparable security measures. Depending on the research phase and the questions being explored, data will be queried and extracted as ASCII files. This anonymized data, including individual participant identifiers, demographic details, and pertinent variable labels and values, will then be made accessible to additional project staff. Subsequently, these team members will undertake any data transformations required to prepare the data for publication-oriented analyses.

Each additional staff member will be obligated to produce documentation describing what data was used and how was it transformed for completing the research task they were involved in. This will include documentation pertaining to the decisions related to any data transformations and coding performed, including variable lists and definitions of the raw data used and how the derived variables were created. Analytical methods and techniques performed for any particular research task will also be documented.

Publications derived from the data collected in this study will strictly utilize anonymized (de-identified) datasets and will focus on presenting results at an aggregate level. Given the anticipated absece of (high) risk to participants, the formation of a data monitoring committee has been deemed unnecessary for this study.

Every additional staff member involved in the research will be required to generate thorough documentation detailing their use and transformation of data in the execution of their assigned research tasks. This documentation will include an explanation of the decisions that guided data transformations and coding, inclusive of comprehensive lists and definitions of the variables derived from raw data, as well as descriptions of the analytical methods and techniques applied in each specific research task. This documentation process ensures transparency and reproducibility of the research findings, and it assists in maintaining the integrity of the data analysis process.

Discussion

In this protocol, we detail the framework for a two-arm randomized controlled trial aimed at evaluating the efficacy of CBT and mindfulness-based mobile intervention modules administered through the Nałogometr 2.0 app. The objective is to ascertain the impact of these mobile interventions in mitigating cravings and lapses associated with SUD. By examining the utility of the interventions across clinical populations with distinct addiction profiles—alcohol, cannabis, and mixed (alcohol and stimulants) addiction—we aim to gauge the effectiveness of the intervention modules for various manifestations of SUD.

Patients with SUD face a high risk of relapse post-treatment, with estimates suggesting that 40-80% of individuals relapse into addiction following the conclusion of therapy. Mobile psychological intervention modules stand as a potentially powerful means of supporting patient recovery and enhancing the long-term outcomes of treatment. Should the interventions prove effective, they could make a significant contribution to the domain of addiction therapy, representing a valuable asset in the ongoing effort to prevent lapses and relapses.

Furthermore, the study will encompass exploratory analyses aimed at discerning whether the efficacy of the interventions correlates with user engagement levels within the app and subsequent alterations in other psychological domains, such as impulsivity, sensation seeking, stress management, and emotion regulation. These analyses will also consider physical functioning indicators collected through physiological metrics, including heart rate, sleep quality, and activity levels. Delving into this ancillary data will provide deeper insights into the recovery mechanisms from SUD and could inform the enhancement of future health interventions for addictive disorders.

The proposed randomized controlled trial (RCT) will focus on a post-therapy clinical patient population—a demographic that is particularly susceptible to relapse. Conducting the study within the naturalistic settings of the patients ensures the ecological validity of the results and the derived conclusions. Through the collection and analysis of longitudinal data over a span of three months, complemented by regular monthly follow-up assessments, the research aims to elucidate the dynamics of post-therapeutic shifts in cravings and behaviors in patients with SUD.

Regarding the limitations of the study, we anticipate the potential for a high dropout rate, a common occurrence in previous studies (42) and a concern intrinsic to trials with a longitudinal design. Nonetheless, the inclusion of a contest as an engagement strategy is expected to enhance participant retention rates. It's crucial to note that the opportunity to win prizes is independent of participants' self-reported levels of craving or instances of lapses, thereby mitigating any potential bias in their responses.

Drop-out rates in mobile application studies on addiction can be high due to various factors, including lack of motivation, technical issues, limited support and guidance, loss of interest, or intervention design. Lack of adequate support, guidance, or encouragement from researchers or healthcare professionals throughout the study can diminish users' motivation and commitment to using the application. Reducing dropout rates in mobile applications designed for addiction

research requires a combination of strategies to increase engagement and enhance the intervention's effectiveness. Behavioral tracking and personalized feedback can help users stay motivated and focused on their goals. We will use push notifications and reminders to prompt users to engage with the application regularly, complete tasks, or provide updates. We also provide educational materials and psychological intervention modules based on CBT and mindfulness techniques, which could increase the retention rate and provide support in coping with substance use disorder. We informed users at the beginning of the study that the application could not replace psychotherapy.

Drawing from existing literature on mobile interventions for substance use reduction, we are prepared for the possibility of observing only small effect sizes (25). The clinical relevance of a therapeutic intervention is contingent upon externally established standards by researchers and other healthcare professionals. There needs to be more consensus concerning the precise criteria for delineating these efficacy standards. Such criteria may encompass a diminished proportion of treated subjects experiencing adverse outcomes or being susceptible to them, resolution of the targeted issue, or achievement of normative levels of functioning post-intervention. Jacobson et al. (59) delineated clinical significance as a transition towards normal functioning attributable to therapy and outlined methodologies for identifying patients manifesting statistically reliable changes considered clinically significant as per their delineation. Providing a definitive recommendation for a specific effect size that clinicians could universally employ to infer clinical significance poses considerable challenges (60). Despite this, any indication of the mobile interventions' effectiveness could still be of significant clinical relevance, contributing valuable knowledge to the field of SUD treatment.

Ethics statement

The study procedures contributing to this work comply with the ethical standards of the Declaration of Helsinki. Ethical approval has been obtained from the Institute of Psychology Polish Academy of Science Ethics Committee (26/XII/2022). The protocol has been registered at a clinical trials database (NCT05730504).

Author contributions

AR: Writing – original draft, Writing – review & editing. AB: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. KO: Conceptualization, Methodology, Writing – review & editing. PM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. KSz: Writing – original draft, Writing – review & editing. KL: Writing – original draft, Writing – review & editing. KSo: Conceptualization, Writing – review & editing. MB: Writing – review & editing. BW: Writing – review & editing. MN: Writing – review & editing. MS: Conceptualization, Funding acquisition, Writing – review & editing. MG: Conceptualization, Funding acquisition, Writing – review & editing. MBi: Writing – original draft, Writing – review & editing.

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Conflict of interest

AR, AB, KO, PM, KSz, KL, KSo, MB, BW, MN, MS, MBi, and MG were employed by the company PredictWatch.

Publisher's note

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A systematic review of chatbot-assisted interventions for substance use

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Objectives: This study systematically reviewed research on the utilization of chatbot-related technologies for the prevention, assessment, and treatment of various substance uses, including alcohol, nicotine, and other drugs.

Methods: Following PRISMA guidelines, 28 articles were selected for final analysis from an initial screening of 998 references. Data were coded for multiple components, including study characteristics, intervention types, intervention contents, sample characteristics, substance use details, measurement tools, and main findings, particularly emphasizing the effectiveness of chatbot-assisted interventions on substance use and the facilitators and barriers affecting program effectiveness.

Results: Half of the studies specifically targeted smoking. Furthermore, over 85% of interventions were designed to treat substance use, with 7.14% focusing on prevention and 3.57% on assessment. Perceptions of effectiveness in quitting substance use varied, ranging from 25% to 50%, while for reduced substance use, percentages ranged from 66.67% to 83.33%. Among the studies assessing statistical effectiveness (46.43%), all experimental studies, including quasi-experiments, demonstrated significant and valid effects. Notably, 30% of studies emphasized personalization and providing relevant tips or information as key facilitators.

Conclusion: This study offers valuable insights into the development and validation of chatbot-assisted interventions, thereby establishing a robust foundation for their efficacy.

KEYWORDS

chatbot, artificial intelligence, substance use, intervention, systematic review

1 Introduction

Chatbots, based on human-computer interaction systems (1, 2), utilize either rule-based systems, which rely on rules defined by expert knowledge (e.g., decision trees), or natural language processing, a branch of artificial intelligence (AI), to emulate a real-time conversation (3). Modern chatbots use a combination of these two approaches (3).

With the development of AI, chatbots are being utilized across diverse sectors such as education, health, entertainment, and business, including e-commerce (2), employing spoken, written, and visual languages (4). In the health care sector, chatbots have been used to educate, prevent, support, treat, and diagnose people with diverse medical needs, including addiction (5–7). Chatbots offer intelligent guidance, enhance productivity through automated engagement, provide on-demand accessibility, mitigate user judgment, and exhibit enduring patience for clients (2, 5, 8).

These characteristics have underscored the utility of emerging technologies like chatbots as a telehealth solution for various mental health challenges, which have become more prevalent amidst the constraints on in-person services since the COVID-19 pandemic (9, 10). Particularly noteworthy is the capacity of chatbot technology to offer emotional support to users in an interactive and empathetic manner, making it appealing for mental health interventions by facilitating the formation of therapeutic relationships (9). Previous studies have provided evidence for the feasibility of utilizing these digital tools to foster "digital therapeutic alliances" (9, 11). Research indicates that some chatbot users find comfort in anonymous interactions, providing a platform for intervention for those averse to traditional counseling settings (9, 12). Furthermore, interventions assisted by chatbots, accessible through smartphones, laptops, and tablets, offer several advantages for addiction management and treatment by providing immediate support without the stigma often associated with seeking help within the community (10).

Individuals grappling with substance use disorders are especially vulnerable to intense negative emotions like guilt, shame, or embarrassment when contemplating seeking help, posing a substantial hurdle to treatment initiation (5, 13). However, interventions facilitated by chatbots can mitigate these obstacles owing to their anonymous and non-face-to-face accessibility (14). Additionally, their capacity for individualized, round-the-clock support without succumbing to fatigue or burnout, even amidst recurring relapses driven by urges and cravings characteristic of addiction (15, 16), positions chatbots as a significant advancement beyond conventional mobile health technologies such as text or instant messaging (14, 17). Chatbot-assist interventions can provide support similar to human interaction and offer customized assistance tailored to individual recovery levels or prevention needs (10).

Hence, within the domain of substance use, encompassing alcohol, smoking, and drugs, an expanding body of literature validates the efficacy of chatbot-assisted approaches for assessment, prevention, and treatment methods (18–20). As a result, systematic reviews have been conducted to identify the effectiveness and research trends of chatbot-based intervention studies for substance use disorders. However, these studies have been limited by their broad scope, which includes not only substance use disorders but also mental health (17) or by excluding nicotine from the category of addictive substances (5). In particular, Ogilvie et al.'s study (5) underscores the uncertain effectiveness of chatbot-assisted intervention for substance use based on a review of only six studies. However, contrasting findings emerge from a scoping review focusing on chatbots for smoking cessation, which predominantly suggests their effectiveness (21). In summary, a more comprehensive investigation is needed, one that encompasses substance use and rigorously compares effectiveness across different types of substances.

This study aims to address this gap by conducting a thorough systematic review, examining the utilization of chatbot-related technologies for prevention, assessment, and treatment across all substance use types, including alcohol, nicotine, and other drugs. We specifically focus our review on digital mental health interventions that encompass diagnosis or screening, symptom management and behavior change, prevention, or therapeutic content delivery (22).

2 Methods

2.1 Search strategy

The systematic review meticulously analyzed records from four databases—PubMed, PsycINFO, Scopus, and CINAHL—up to March 7, 2024, marking the start of the present study. We did not specify a start date for the article inclusion criteria, meaning that all articles, regardless of their publication date, were included from the time the first related article appeared until March 7, 2024. We chose these databases due to their widespread use in systematic reviews covering similar research topics (23). We utilized two sets of distinct topic keywords: 1) chatbot, conversational agent, and conversational artificial intelligence; and 2) substance use, alcohol, smoking, and drug.

2.2 Study selection

Following the PRISMA guideline, the present study progressed through distinct stages—identification, screening (including eligibility assessment), and inclusion (24)—to compile relevant sources. All 998 references from each database were imported into the Covidence program (25), which automatically removed 129 duplicates, leaving 869 records for subsequent title and abstract screening. Three out of four reviewers searched the databases using keywords and imported the results into the Covidence program, with oversight from the fourth reviewer.

The systematic review encompassed studies meeting specific inclusion and exclusion criteria. Inclusion criteria required studies to 1) be peer-reviewed articles published in English regardless of the country where the studies were conducted, 2) contain information on any type of chatbot-assisted intervention (voice, internet, and

messenger platform) for substance use, 3) include experimental, non-experimental, and qualitative studies, 4) provide all necessary data information (e.g., sample size, odds ratio, 95% CI, or other effect size values), and 5) be rated as "fair" or "good" based on the National Institute of Health (NIH) quality assessment tool (26). Conversely, exclusion criteria encompass studies that are 1) master's theses or doctoral dissertations, 2) commentary and editorials, and 3) review papers, including systematic reviews and meta-analyses. Three out of four reviewers independently rated each article as "yes," "no," or "maybe" based on the criteria. In cases of conflicting ratings, the reviewers discussed them together to reach a consensus, with oversight from the fourth reviewer. From the first screening stage, 837 irrelevant records were removed, resulting in 32 articles advancing to full-text review. Four articles were excluded based on these criteria, leaving 28 articles for final analysis (See Figure 1).

2.3 Data extraction and analysis

Prior to the coding process, approximately 10% of the final sample was randomly selected by the authors for double screening to ensure consistency among raters (27, 28). Three reviewers conducted individual rating and coding of articles in the Excel spreadsheet matrix. The authors collectively discussed and resolved any differences in wording choice. The coding encompassed various details, including author and year, study type, data source, sampling methods, sample characteristics (e.g., size, age range, mean age, gender distribution, racial demographics), type of chatbot-assisted intervention (e.g., assessment, prevention, treatment), contents of the intervention (e.g., theoretical framework, duration, session), type of substance use, measurement tools for substance use, and main findings/outcomes, which include the effectiveness of chatbot-assisted interventions on substance use and the facilitators and barriers impacting their effectiveness.

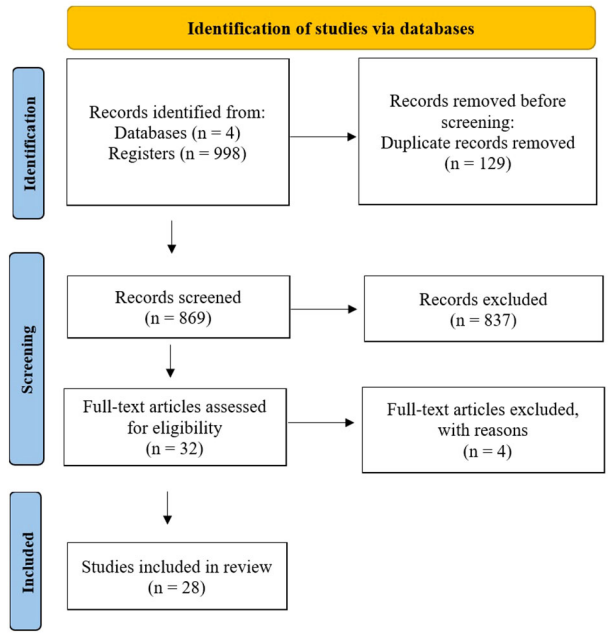

FIGURE 1
PRISMA Flow Chart.

3 Results

3.1 Study characteristics (date of publication, study type, data source, and research methods)

A total of 28 studies met our inclusion criteria. All studies included in this analysis were conducted between 2018 and 2024. Most studies (57.14%; 16 out of 28) were published in 2022 and 2023 (See Figure 2).

Reviewed studies collected primary data from diverse channels, with 64.29% (18 out of 28) using online platforms (such as web-based platforms, social media, and telephone) and 35.71% (10 out of 28) using offline sources, encompassing open advertisement, clinical, community-based settings, and school.

In our analysis of 28 studies, we identified three primary study types. Quantitative studies constituted 60.71% (n = 17), followed by mixed methods studies at 28.57% (n = 8), and qualitative studies at 10.71% (n = 3). Most (52.94%, 9 out of 17) quantitative studies employed experimental designs, whereas 35.29% (6 out of 17) utilized quasi-experimental designs, and 11.76% (2 out of 17) adopted non-experimental designs. Various statistical analyses (e.g., frequency analysis, t-test, correlation, logistic regression model, generalized linear mixed model, chi-square test, ANOVA, etc.) were conducted across the studies, with the t-test being the most frequently utilized method (32.14%, 9 out of 28). This choice was primarily motivated by the need to discern differences between groups within the dataset. In mixed methods studies, researchers employed a range of data collection methods, such as interviews (29), surveys (30–33), transcript analysis (3), literature reviews (30), and observations (34). The most common combination entailed open-ended questions for qualitative data and rating on a scale such as a Likert scale for quantitative data (37.5%, 3 out of 8). The qualitative data were gathered through semi-structured telephone interviews (19, 35), in-depth, one-on-one semi-structured interviews (36), and focus group discussions (19). Thematic analysis is applied to all three qualitative studies, which aim to obtain users' experiences, feedback, and opinions.

In this study, we categorized the study stage into two distinct stages: planning and testing of the chatbot program. The planning stage, which encompasses research protocol, accounted for 25% (7 out of 28) of the studies. This stage involved protocol studies (29, 31, 37, 38) and design and development, such as a methodological framework for the emulation of human-conversational agent interactions that build on social media sequencing (39). The testing stage, comprising 75% (21 out of 28) of the studies, was conducted to investigate the feasibility and preliminary efficacy outcomes of chatbot interventions. Specifically, nine out of the 28 studies (32.14%) analyzed program effectiveness through descriptive analysis (frequency), three (10.71%) examined program effectiveness through descriptive analysis (mean),

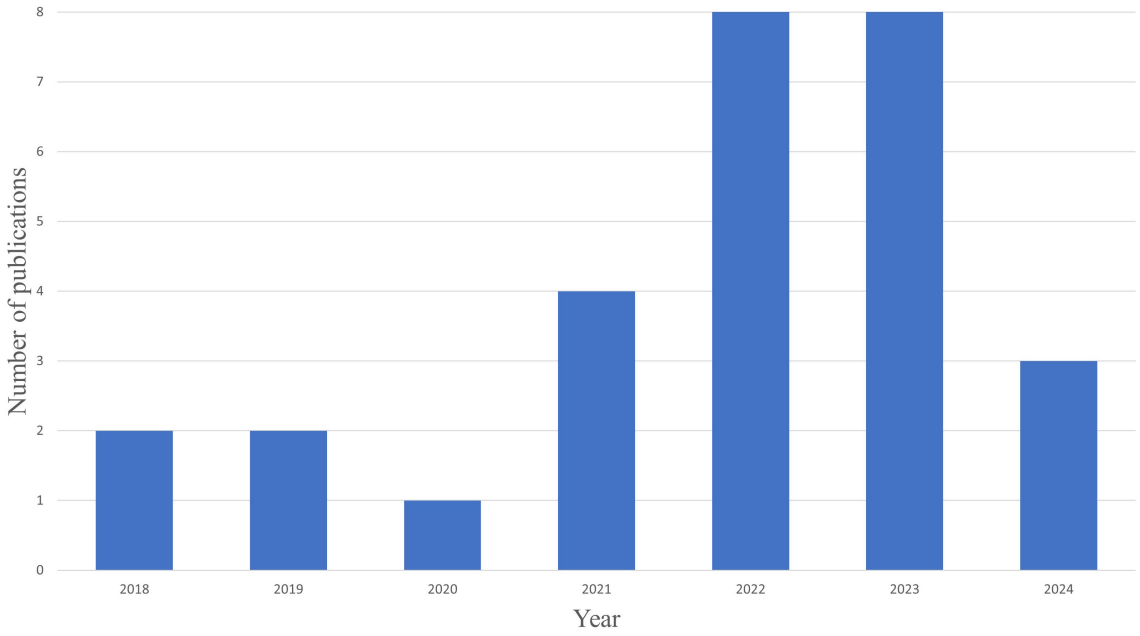

FIGURE 2
Date of Publication.

while 14 (50%) assessed the effectiveness of chatbot-based interventions for substance use through experimental and quasi-experimental designs (not exclusively).

3.2 Types and contents of chatbot-assisted interventions

Of the 28 papers reviewed, 18 (64.29%) present theories or therapies that form the basis of chatbot program content. Among these 18, the most frequent approach (9 papers, 50%) was the fusion of various theories, such as dialectical behavior therapy, mindfulness, problem-solving, and person-centered therapy, primarily based on cognitive behavioral therapy and motivational interviewing (MI). Next, three studies (16.66%) applied only MI, and another three studies (16.66%) presented evidence based on the World Health Organization (WHO) or the country's standardized intervention manual. Acceptance and commitment therapy (5.55%), mindfulness-based relapse prevention (5.55%), and behavioral theory (5.55%) were each confirmed in one study, respectively.

A total of 22 studies (78.57%) presented specific program content. The content varied substantially depending on the underlying theory or therapy and the intervention period. Programs often included motivation-boosting messages or feedback (40, 41), psychoeducation, and emotion management related to craving and stress (29, 42). Additionally, daily notifications, craving tracking, goal setting for substance use cessation, and daily feedback or guidance were provided (29, 35). Six articles (27.27%) provided session-type content, which organizes content sequentially as users access it. Three articles (13.63%) provided module-type content, which bundles content by specific topics, allowing users to select topics based on their interests. The remaining 13 articles (59.09%) did not disclose specific methods. The number of sessions ranged from 1 to 14, while the number of modules ranged from 6 to 8.

Among the chatbot-assisted programs, 24 out of 28 (85.72%) were designed to treat substance use by changing the user's behavior or cognition, followed by two programs (7.14%) focused on prevention and one (3.57%) on assessment. Sixteen out of 28 studies (57.14%) reported the intervention period of the chatbot programs. The intervention periods varied widely, ranging from a single session to a maximum of six months. The most common duration was an 8-week intervention, reported in 4 out of 16 studies (25.0%), followed by 2-week interventions (18.75%), 10-week interventions (12.50%), 12-week interventions (12.50%), and 6-month interventions (12.50%), with each of these durations reported in two studies. Additionally, one study each reported interventions lasting 1 day (6.25%), 16 weeks (6.25%), and 14 weeks (6.25%).

3.3 Sample characteristics (sampling method)

Among the 28 studies reviewed, 23 (82.14%) involved sampling human participants. Only three studies (10.71%) explicitly stated the sampling methods used, encompassing purposive sampling (3, 35) and convenience sampling (43). In contrast, the remaining studies briefly described the recruitment process, utilizing web-based platforms, social media, Facebook, hospitals, clinical and community-based settings, flyers, universities, and psychiatric centers, without specifying the sampling methods employed. The mean sample size across the studies was 2,739 (Standard deviation; *SD* = 11,618.34), with a considerable range from 6 (44) to 57,214

participants (45). Of the 23 studies, 15 (21.74%) reported the mean age of participants, with an average of 36.76 (*SD* = 10.35), ranging from 15 to 76 years old.

Regarding gender representation, 18 out of 28 studies (64.29%) disclosed the percentage of male and female participants included in their studies. On average, the percentage of male participants was 42.62% (*SD* = 20.17), while the percentage of female participants was 45.06% (*SD* = 21.07). The mean percentage of participants identifying as other genders was 3.03% (*SD* = 2.11).

Additionally, 7 out of 28 studies (25%) reported participants' race/ethnicity. On average, the percentage of White, Black, Hispanic, Asian, and other participants was 66.87% (*SD* = 15.73), 17.67% (*SD* = 15.87), 23.78% (*SD* = 35.12), 5.14% (*SD* = 1.36), and 9.62% (*SD* = 9.29), respectively.

Three out of the 28 studies (10.71%) employed text sampling methods, which included the following: a "sample of recorded telephone-counseling sessions" focusing on various aspects of smoking cessation (3), "QuitNet Peer Interactions" comprising 2.23 million labeled peer interactions with 2,005 manually annotated messages (39), and an analysis of "236,000 sessions in Pahola's page" accessed by 188,000 users (34).

3.4 Target and measurement tools used to assess

Out of 28 studies, 50% (*n* = 14) focused specifically on smoking (i.e., tobacco, nicotine), while 21.43% (*n* = 6) adopted a comprehensive approach to substance use that included alcohol, tobacco, cannabis, methamphetamine, cocaine, and pharmaceutical medications. Furthermore, 17.86% (*n* = 5) of the studies focused on alcohol use, 7.14% (*n* = 2) targeted methamphetamine use, and 3.57% (*n* = 1) addressed both alcohol and tobacco concurrently.

Out of 28 studies, 16 (57.14%) reported measurement tools for substance use. Nine out of 16 studies (56.25%) utilized standardized measurement tools to measure substance use, such as the Heaviness of Smoking Index (40), CAGE Adapted to Include Drugs, Drug Abuse Screening Test (DAST-10), Brief Situational Confidence Questionnaire (38, 42, 46), Short Inventory of Problems—Alcohol and Drugs (38, 42), Alcohol Use Disorders Identification Test (AUDIT-C) (46), US AUDIT, Readiness to Change Questionnaire, Short Inventory of Problems – Revised, and Timeline Followback (47), Cigarette Dependence Scale-5 (CDS-5), CAGE (48), Fagerstrom Test of Nicotine Dependence (FTND) and Smoking Abstinence Self-Efficacy Questionnaire (31), FTND (49), Stages of Change Readiness and Treatment Eagerness Scale, and Visual Analogue Scale (50).

Three studies (18.75%) used medical tests, including the Drug Urine Test in conjunction with DSM-5 criteria (10) and the Co-oximetry Test, which measured exhaled air in parts per million (37, 51). Three studies (18.75%) solely relied on non-standardized tools such as "smoke at least 1 cigarette daily" (44), "time to first cigarette," "cigarettes per day" (45), "at risk-drinking in the preceding 30 days," "total number of alcoholic drinks consumed in the preceding 30 days," "tobacco/e-cigarette smoking, preceding 30 days," "quantity of cigarettes smoked preceding 30 days," "cannabis use, preceding 30 days," "cannabis use days, preceding 30 days" (43). One study (6.25%) (52) utilized both standardized (Drinking Refusal Self-Efficacy Questionnaire) and non-standardized measurement tools ("binge drinking in past 30 days," "maximum number of alcoholic standard drinks consumed in past 30 days," "total number of alcoholic standard drinks consumed in past 30 days").

3.5 Main findings

3.5.1 Effectiveness of program – Descriptive analysis

Nine out of the 28 studies (32.14%) analyzed program effectiveness through descriptive analysis (frequency), categorizing responses into seven themes: 1) Helpful for substance use, 2) Quit/cut substance use, 3) Reduced/cut down substance use, 4) Positive feelings, 5) Willingness to recommend or participate again, 6) Easiness/comprehensibility, and 7) Lifelike/related to their situation.

The percentage of respondents indicating programs as 1) Helpful for substance use varied from 8.3% (smoking) (53) to 84.6% (alcohol) (52), 85% (methamphetamine) (10), and 100% (smoking) (44). The percentage of respondents indicating they 2) Quit/cut substance use ranged from 25%-40% (attempt to quit) (40), 33.33% (quit smoking) (36), 50% (setting a quit smoking date within 14 days) (44), to 50% (choosing to cut back on drinking; 75% of Spanish, 60% of English users, and 50% of Portuguese users) (34). The percentages of respondents who 3) Reduced/cut down substance use were 66.67% (cut down smoking) (36), 70.5% (made some kind of smoking reduction attempt) (40), and 83.33% (reduced smoking) (44). Regarding the measurement of sustained time for stopping/reducing substance use, 12 out of 28 studies (42.9%) reported the duration measured. The most common period was one month (*n* = 5), followed by six months (*n* = 3), one year (*n* = 2), one week (*n* = 1), and two weeks (*n* = 1).

Regarding 4) Positive feelings, "rate positively" ranged from 94% (46) to 96% (42). "Pleasant" was reported at 34.7% (53), "enjoyed" at 87.9% (52), "impressive" at 100% (44), and "feeling cared" at 67% (10). "Satisfaction" ranged from 84% (10) to 100% (44). Regarding 5) Willingness to recommend or participate again, "would Recommend" ranged from 67% (10) to 76.2% (52) and 86% (42). Additionally, 89.1% answered that they would participate again (52). For 6) Easiness/comprehensibility, the rate of easy interaction was reported at 83.3% (44), and the rate of comprehensibility was 100.0% (52). Finally, regarding 7) Lifelike/related to their situation, 70.8% indicated they felt it was relevant to their individual situations (52), and 66.67% felt it was lifelike (44).

Three out of the 28 studies (10.71%) examined program effectiveness through descriptive analysis (mean). Boustani et al. (33) found that participants reported high acceptability and utility of the technology (Mean (M); *M* = 2.31, *SD* = 1.05, out of 7), high engagement (*M*= 2.86, *SD* = 0.96, out of 7), and a high number of human-like traits (*M* = 2.07, *SD* = 0.89, out of 7) of a chatbot-based intervention for alcohol. Auriacombe et al. (48) also reported high Acceptability E-Scale scores (24.8; out of 30, *SD* = 4.2) of a chatbot-based intervention for alcohol and tobacco use. Loveys et al. (32)

revealed that users reported a positive overall experience with a chatbot-based intervention for tobacco use (M = 3.17, SD = 0.82, out of 4) and found the chatbot to provide useful information and advice (M = 3.21, SD = 0.92, out of 4).

3.5.2 Program effectiveness—Experimental and quasi-experimental designs

In 13 out of 28 studies (46.43%), the effectiveness of chatbot-based interventions for substance use was examined through experimental and quasi-experimental designs. Among these 13 studies, 100% reported significant effectiveness. For smoking, intention to quit (M change 0.8, standard error (SE); SE = 0.1, p <.001, respectively) (49), motivation to quit (F (1,151) = 32.67, p < .001) (41), quit success (79.55% in the intervention group vs. 73.35% in the control group, OR for the adjusted model; OR_{adj} = 1.36, 95% confidence interval (CI); CI = 1.16-1.61, p < .001) (45), quitting confidence (M change 0.1, SD = 2.0-2.3, p <.001), quitting importance (M change = 0.7, SD = 2.0, p < .001), and quitting readiness (M change 0.4, SD = 1.7, p <.01) (40); biochemically validated abstinence rate of smoking (26% for the intervention group vs. 18.8% in the control group, odds ratio (OR); OR = 1.52, 95% CI = 1.00-2.31, p = .05) (20) increased after exposure compared to baseline or were higher in the intervention group compared to the control group. In addition, significant group effects were observed for the 30-day point prevalence for tobacco/e-cigarette smoking (OR for the intervention group; OR_{ITT} = 0.74, 95% CI = -0.55-1.01, OR for the control group; OR_{CC} = 0.62, 95% CI = 0.40-0.96) (43).

For alcohol, binge drinking (OR = 0.32, 95% CI = 0.18-0.57, p <.001), maximum alcohol consumption (incidence rate ratio (IRR); IRR = 0.75, 95% CI = 0.68-0.82, p <.01), and number of standard drinks per month (IRR = 0.62, 95% CI = 0.58-0.67, p < .01) significantly decreased, while drinking refusal self-efficacy significantly increased (β = 0.24, 95% CI = 0.06-0.42, p = .01) (52). Use of any interventions (chatbot or non-bot app) was shown to predict reduced drinking (β= 0.25, 95% CI = 0.00-0.01, p = .04) (47). Scores on the AUDIT-C (M change -1.3, SD = 2.6, p <.001) significantly decreased (46). Significant group effects were observed for at-risk drinking in the past 30 days (*Cohen's d* for the intervention group; *Cohen's* d_{ITT} = 0.68, 95% CI = 0.52-0.89, *Cohen's d* for the control group; *Cohen's* d_{CC} = 0.61, 95% CI = 0.43-0.84), and total number of alcoholic drinks consumed in the past 30 days (*Cohen's* d_{ITT} = 0.07, *Cohen's* d_{CC} = 0.11) (43).

For methamphetamine, the experimental group had fewer methamphetamine-positive urine samples than the control group (19.5% in the experimental group vs. 29.6% in the control group, F = 9.116, p = .003) (10). For substance or drug use, treatment motivation for substance use (p < .001, *Cohen's d* = -0.60) (50), motivation for abstaining from drugs (p = .045, *Cohen's d* = -0.30) (50), confidence (p < .01, *Cohen's d* = -0.45) (46, 50), and importance (p < .001, *Cohen's d* = -0.50) (50) significantly increased, while craving (p = .01, *Cohen's d* = 0.038 in Chen et al.'s (50) study and M change -0.38, $B(SE)$ = −.38(0.16), OR = 0.69, 95% CI = 0.50-0.90 in Prochaska et al.'s (46) study, past-month substance use occasions (M change -9.1, SE = 2.0 in intervention group vs. M change = -3.3, SE = 1.8 in control group; p = .039, Eta^2 = .029 in Prochaska et al.'s (42) study and M change -9.3, SD = 14.1, p <.001 in Prochaska et al.'s (46) study), scores on the DAST-10 (M change -1.2, SD = 2.0, p <.001) (46), number of cannabis use days in the past month (*Cohen's* d_{ITT} = 0.06, *Cohen's* d_{CC} = 0.14) (43) significantly decreased.

One study (48) examined chatbot-based assessment for tobacco or alcohol use disorder and found that the chatbot named Embodied Conversational Agent (ECA) was acceptable and valid to screen tobacco or alcohol use disorder among patients not requesting treatment for addiction, as the correlation between the ECA, CDS-5, and CAGE interviews and the paper version questionnaires scores were high [r(139) = .944, p < .0001 for CDS-5 and r(139) = .893, p < .0001 for CAGE] (48).

3.5.3 Facilitator or barriers affecting program effectiveness

Ten out of the 28 studies (35.71%) reported facilitators influencing the effectiveness of chatbot interventions. Among these, three (30%) (3, 35, 43) identified personalization (e.g., individualized, personal agency, personalized, etc.) as a key facilitator, while three (30%) (35, 41, 44) emphasized the importance of providing relevant tips or information. Additionally, factors such as younger age, lower severity of substance use (40), reinforcement and positive feedback, friendly and knowledgeable interactions, repetition of key messages, supportive interpersonal relationships (44), immediate access to responses (10), and the perception of conversing with a human (47) were mentioned as facilitators. Moreover, Chen et al. (50) found that patients' scores on the Generalized Anxiety Disorder-7 assessment (b = 3.57, p <.001, 95% CI 0.80-2.89) and Barratt Impulsiveness Scale-Motor Impulsiveness (b = -2.10, p = .04, 95% CI = -0.094-0.02) were predictors of changes in treatment motivation during treatment.

Six out of the 28 studies (21.43%) reported barriers affecting program effectiveness, including technical problems (e.g., login difficulties, heavy tablets, technical errors) (44, 47), short session durations (41, 44), inappropriate responses (e.g., inappropriate reflections in conversation, repetitiveness of bot conversations, excessive pressure to set a quit date, poor response sequencing, lack of liveliness compared to human interaction) (35, 40, 44), lack of personalization (e.g., receipt of non-tailored daily tips) (35), higher severity of substance use (10), low readiness to change (10), and text-centric chatbots that are perceived as simpler and less engaging compared to those incorporating visual graphs and pictures (47).

3.5.4 Qualitative results

Of the 11 studies employing qualitative methods (eight mixed methods and three qualitative), eight studies presented qualitative results (72.72%). Among these, five (62.5%) utilized a mixed research design, while three (37.5%) employed a purely qualitative research design. The purely qualitative studies included those aimed at identifying users' needs for program development (3, 30, 39) and assessing usability through experiences with chatbot program users. This variable was investigated via qualitative interviews or open-ended surveys (32, 33, 35, 36).

Research on users' needs for program development emphasized the presence of individual differences in the situations and characteristics in which substance users feel cravings, highlighting the necessity for chatbot responses to consider this context (39). Studies on the user experience of chatbot programs revealed that users appreciated friendliness and showed interest in interacting with chatbots that had more human-like features (voice, appearance, communication), reporting sufficient acceptability (32, 33, 36). Additionally, users positively evaluated personalized interventions, improved insight into addiction, appropriate ventilation for cravings, and daily tips (35, 36). However, some studies indicated that while chatbot-assisted interventions can provide efficient care, they have limitations in achieving deep, open, empathetic communication, as reported through interviews with users and field counselors (19).

4 Discussion

This study aimed to identify and summarize gaps in the published literature on chatbot-assisted interventions for substance use through a systematic review. Half of the studies reviewed specifically targeted smoking, while 21.43% took a comprehensive approach covering various substances; additionally, 17.86% focused solely on alcohol, 7.14% on methamphetamine use, and 3.57% addressed both alcohol and tobacco simultaneously. The fact that most studies focus only on smoking suggests the necessity for future studies to encompass a broader range of substances. In addition, over 85% of chatbot-assisted programs were designed for therapeutic purposes, highlighting the need for the development and validation of more assessment and prevention programs as well. The percentage of respondents reporting chatbot-assisted interventions as helpful for substance use varied widely, ranging from 8.3% to 100%. Similarly, perceptions of effectiveness in quitting substance use ranged from 25% to 50% and from 66.67% to 83.33% for reducing substance use.

Furthermore, a minority of the studies assessed the statistical effectiveness of chatbot-based interventions for substance use using experimental and quasi-experimental designs, emphasizing the need for future research to actively confirm the statistical effectiveness of evidence-based interventions for clients. Among the 46.43% (n =13) of studies that assessed statistical effectiveness, all (100%) studies demonstrated significant and valid effects. Focusing specifically on smoking cessation, the interventions led to heightened intention to quit, motivation, success rates, confidence, importance, and readiness to quit among smokers, with post-exposure biochemically validated abstinence rates significantly higher compared to baseline or control groups. Alcohol-related interventions resulted in significant reductions in binge drinking, maximum alcohol consumption, AUDIT-C scores, and monthly standard drink consumption, alongside a noteworthy increase in drinking refusal self-efficacy. For methamphetamine, the experimental group had fewer methamphetamine-positive urine samples than the control group. In the context of substance or drug use, significant increases were found in treatment motivation for substance use, motivation for abstaining from drugs, confidence, and perceived importance, alongside notable decreases in craving, past-month substance use occasions, DAST-10 scores, and the number of cannabis use days in the past month.

All experimental and quasi-experimental studies confirmed that chatbot-assisted programs are effective in promoting awareness and behavior change among substance users. This suggests that chatbot-assisted programs facilitate the delivery of relevant information by providing interventions in an internet environment without physical barriers such as geography and time. Furthermore, the results suggest that frequent exposure and stimulation can be effective. While the theories underlying the content provided by each chatbot program varied, all showed significant effects. That is, some studies compared the effectiveness of chatbots with and without reflection feedback (40) or tested differences based on applied MI and confrontational counseling (49), but these studies found no differences between groups, suggesting that chatbot-based interventions for substance users should focus on stimulating users to inquire about their substance use, engage in feedback conversations, and provide appropriate information daily rather than adhering to specific theories or therapies.

In 35.71% and 21.43% of the studies, facilitators and barriers affecting the effectiveness of chatbot-assisted interventions were identified, respectively. Among the highlighted facilitators, 30% of studies noted personalization and the provision of relevant tips or information, respectively. Additionally, factors such as younger age, lower severity of substance use, reinforcement, positive feedback, friendly and knowledgeable interactions, repetition of key messages, supportive relationships, immediate responses, and the perception of conversing with a human were also cited as facilitators. Conversely, reported barriers to program effectiveness included technical issues, short session durations, inappropriate responses, lack of personalization, higher severity of substance use, low readiness to change, and text-centric chatbots. However, few studies explored the statistical association between these facilitators and barriers and the program's effectiveness. Therefore, future studies should examine this association more deeply. Nevertheless, comprehensively considering the aforementioned facilitators and barriers is crucial when developing chatbot-assisted interventions for substance use.

Recognizing the importance of chatbots resembling humans is especially crucial. This implication is evident in the use of human-like virtual agents that mimic human responses and converse with a human voice (32, 33). Regarding appearance, voice, race, and gender, the design of these chatbot avatars must avoid perpetuating biases towards specific genders, generations, races, or vulnerable populations (54). Chatbots, like humans, can acquire incorrect information or misuse it, potentially reinforcing societal biases (54).

Moreover, current chatbot-assisted programs are more useful for individuals with lower substance use severity and may be limited for those with higher levels of severity. Some studies have reported that younger users (40) and those with lower severity of substance use are more likely to actively use the applications (10, 40). Additionally, in the case of chatbot counseling, the capacity for extended, in-depth counseling and intervention is limited (19). In

summary, interventions for individuals with moderate or severe substance use problems should prioritize active intervention by a professional, with chatbot-assisted programs serving as adjunctive tools until the subsequent appointment or consultation. For those with less severe substance use, chatbot programs may be more effective for prevention and early intervention. Considering this, current chatbot intervention types for prevention (7.14%) and assessment (3.57%) are very limited and need to be expanded. Furthermore, only one study (48) examined chatbot-based assessment for tobacco or alcohol use disorder. This study found the chatbot was acceptable and valid to screen for tobacco or alcohol use disorder. Therefore, developing more chatbots for prevention and assessment is necessary to enhance prevention and early intervention, particularly for young adults and youth.

Furthermore, while some studies have identified hotlines as effective responses to emergencies, including suicide (38, 42, 46), a clear protocol for detecting such crises during chatbot interactions and the post-detection process was not identified. Because substance use, such as alcohol and methamphetamine, is strongly associated with violence, suicide, and self-harm (10, 29), chatbots targeting this population must reflect intervention protocols for users in crisis.

We also suggest considering the following ethical aspects when developing chatbot-assisted programs for substance use. First, thorough security management of emotional state information, including substance use data provided by users, must be ensured. Social and moral criticism of substance use brings stigma to substance users, creating a significant barrier to their entry into treatment (5, 13). Mental health information has been cited as a sensitive area requiring special attention in AI applications (54). Thus, transparent disclosure of the retention period and disposal of such personal information may reduce user anxiety and increase trust in chatbots among substance users over the long term. Furthermore, the high usability and accessibility of chatbot services should not limit them to specific groups, such as young people and the highly educated, who are familiar with IT devices (54). Therefore, the use of these programs must be evaluated for various generations to make them accessible and comfortable for the elderly. As large-scale language models are imperfect and can be manipulated or misused based on misinformation, ongoing monitoring of the feedback and guidance provided by chatbots to users should be supervised (54) to ensure the safe delivery of interventions.

Consequently, our findings suggest that chatbot technology can facilitate ongoing interventions as an adjunctive tool without the constraints of time or place. Additionally, future research on chatbot-assisted technology for substance users requires not only more sophisticated experimental studies but also technical improvements to address ethical concerns.

This systematic review has several limitations. First, the four databases (PubMed, PsycINFO, Scopus, and CINAHL) and the keywords used to screen relevant studies may not have been exhaustive. Furthermore, because we did not conduct technical evaluations for chatbot-assisted interventions, future studies need to delve deeper into technical issues in these interventions. Additionally, due to the diverse study types (e.g., research designs) and limited number of studies with varying target variables, conducting a meta-analysis was challenging. However, as more studies accumulate, meta-analyses will become necessary. Nevertheless, our systematic review of trends in chatbot-assisted interventions (i.e., assessment, prevention, and treatment) for substance use (i.e., alcohol, smoking, and drugs) provides a valuable foundation for leveraging chatbot technology to address substance use issues. Integrating these insights into future research endeavors holds promise for advancing interventions and strategies in tackling substance use effectively.

5 Conclusion

This study has filled critical gaps in the literature by systematically reviewing 28 studies relevant to chatbot-assisted interventions for substance users. The results showed that the studies primarily focused on smoking and therapeutic applications, with the identified experimental studies demonstrating valid effects regardless of the theoretical approach. Chatbot programs were found to be actively used by individuals with low severity of substance use, suggesting their potential as an adjunct to interventions for substance users and as a preventive tool for adolescents and young adults. Additionally, we recommend future consideration of the ethical aspects of AI-based chatbots, particularly as they handle sensitive mental health information.

Data availability statement

The original contributions presented in this study are included in this article, further inquiries can be directed to the authors.

Author contributions

SL: Conceptualization, Data curation, Methodology, Project administration, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. JY: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. YC: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. JC: Writing – review & editing, Supervision, Resources, 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.

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Supplementary material

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The interconnection between social media addiction, alexithymia and empathy in medical students

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Introduction: This study explores whether high alexithymia values correlate with low levels of empathy, while also trying to identify potential connections with social media addiction.

Methods: We hypothesized that alexithymia mediates the relationship between social media addiction and empathy levels in a sample of undergraduate students. The study population consisted of 649 medical students in the 4th/5th/6th University year, recruited between March and May 2021. For this assessment, we employed three psychometric instruments: the Toronto Empathy Questionnaire (TEQ), the Social Media Addiction Scale-Student Form (SMAS-SF), and the Toronto Alexithymia Scale (TAS-20). A pathway analysis investigated alexithymia as a mediator between social media addiction and the degree of empathy in medical undergraduates. Sobel's test and the Baron and Kenny approach were used for testing mediation.

Results: The TEQ total mean score was 48.76 $\pm$ 5.65, while the TAS-20 total mean score was 47.71 $\pm$ 11.49. Further analysis of the TAS-20 scale scores showed that 21.42% of students had possible alexithymia, while 14.02% had clear alexithymia. The SMAS-SF total mean score was 73.20 $\pm$ 14.59. None of the students reported levels consistent with major social media addiction. The mediated effect of the TAS-20 is about 1.3 times larger than the direct effect of the SMAS-SF on TEQ.

Discussion: We found a significant negative correlation between empathy and alexithymia in medical students. Alexithymia was a mediator between social media addiction and empathy. Therefore, we recommend further efforts to identify potential levels of alexithymia in medical students, in order to successfully develop tailored interventions aimed at increasing their emotional awareness.

KEYWORDS

social media addiction, medical students, empathy, smartphone addiction, alexithymia

1 Introduction

Alexithymia represents an inability to describe one's emotional states. Several studies point out that alexithymia disrupts the ability to identify feelings of others (1). From an etymological point of view, the word comes from Greek: a = lack, lexis = word, and thymos = mood or emotion. Thus, it can be translated as the inability to read and express emotions. The term was coined during the 1970s by two psycho-therapists (Peter E. Sifneos and John C. Nemiah), looking to summarize symptoms they had noticed in their patients suffering from psychosomatic illnesses (2–4). More recently, there has been a growing scientific interest in the way alexithymia affects interpersonal relationships, with some authors hypothesizing that alexithymic individuals have difficulty interacting with others, since alexithymia correlates with emotional skills-related problems, such as difficulties in building and maintaining interpersonal relationships, smaller social networks, and reduced social skills (5, 6).

Since alexithymia is frequently linked to depressive and anxious states of mind, it is likely that people with alexithymia have trouble controlling their negative emotions (1, 7). Alexithymia along with high impulsivity, has been correlated with problematic internet use, consequently raising the theory that people who struggle to identify and communicate their emotions are more inclined to use online video games to escape negative feelings (8). Social media has increased over the past years and has been proven to be used as a maladaptative coping mechanism (9). The use of emotion- and avoidance-oriented coping strategies is favorably correlated with alexithymia, as assessed by the TAS-20 in teenage samples, and negatively correlated with task-oriented coping strategies (10). Di Blasi et al. view the emotional challenges associated with impulsivity and alexithymic features as specific elements that constitute an emotion dysregulation process (11). In alexithymic individuals, restricted and intolerant attitudes toward their own shortcomings and limitations, as well as a failure to recognize themselves as a part of the larger human condition, go alongside a constricted awareness of emotions in self and others (12). Therefore, maladaptive coping mechanisms, such as drinking and negative emotional states, like despair, anxiety, and stress can be frequently linked to alexithymia (13).

The prevalence of alexithymia in the general population is estimated to be around 10% (14–16). Some researchers established that this deficiency exists in both healthy and unhealthy individuals (17), characterized by difficulties in identifying, analyzing, and ex-pressing emotions, as well as involving certain restrictions, in terms of externally oriented thinking and imagination. A 5-year follow-up study in the general population has indicated that alexithymia can essentially be considered a stable personality trait (18). There are different theories regarding the emergence of alexithymia, with some studies showing that childhood trauma is a substantial contributing element (19). Some authors suggest that childhood trauma, including emotional abuse and severe emotional and physical neglect, can predict the emergence of alexithymia in later life (20).

According to the research examining the relationship between alexithymia, social media use, and smartphone addiction, there was a strong correlation between alexithymia and the severity of smartphone use (21).

The ability to identify and control one's own emotions as well as those of others is known as emotional intelligence (EI). On the other hand, empathy is the capacity to comprehend the feelings of others, and alexithymia is the inability to feel and communicate emotions verbally. Emotional intelligence is a crucial prerequisite for success in the medical field (22).

Empathy has a multidimensional character, comprising cognitive and emotional dimensions. It includes the ability to perceive the perspective of others, correctly identify their subjective reality, and have appropriate affective responses that follow the perception of the emotional states of those around us (23).

Empathy has two components: affective, which comprises the individuals' capacity to feel what others feel; cognitive, which is the ability to identify, interpret and understand the mental states of others, which involves perspective-taking (24, 25). Empathy helps create and maintain these social connections, allowing people to understand, share and respond accordingly to other people emotional states (26).

In healthcare, the professional-patient relationship is primarily based on empathy, as this can help build trust and improve communication, thus creating a safe environment to explore existing possibilities and make the best medical decisions (27, 28). Alternatively, a healthcare professional showing high levels of empathy has been shown to help reduce patients' stress levels, as well as their anxiety and depression, as well as improve their prognosis (29, 30).

As medical professionals on the frontline of dealing and acting immediately and without fail for the most vulnerable, doctors must be highly specialized. On the path to-ward developing their medical career, medical students must spend significantly more time acquiring the required professional knowledge. Research suggests that this particular area of expertise involves significantly higher academic pressure than other disciplines (31). Keeping this in mind, it becomes somewhat inevitable to logically infer that, as a direct cause of these inherent and long-term pressures, medical students are at a high risk of developing mental health issues, such as burnout, anxiety or depression (32), as alexithymia is a recognized risk factor for these mental health difficulties, particularly in health science students (33). These facts indicate that alexithymia may negatively impact the health professional-patient relationship, starting early on and notable in medical students' personal and professional lives (34).

In recent years, socializing via the Internet has become an increasingly integral part of young adults' lives. Social networking sites are online communication tools that allow users to create a public or private profile to interact with others. Although they have helped people connect in new and innovative ways, several researchers have pointed out that excessive use of social networks has negative health consequences, including structural and functional changes in brain regions involved in emotional processing, attention, decision-making, and cognitive control.

Pertaining to our subject at hand, there are differing views regarding the correlation between social media use and empathy. Various studies have noted that empathy is negatively correlated to social media addiction (35), as, according to Dailey (36), empathetic individuals are less likely to develop a social media addiction.

However, certain studies have suggested that this is an indirect connection (37, 38), some authors have demonstrated the opposite (39, 40), while others have highlighted mostly a neutral relationship between the two (41).

This study aimed to explore if high values of alexithymia in medical students correlate with low values of empathy, and to identify any potential connections with social media addiction. We hypothesized that alexithymia mediates the relationship between social media addiction and the degree of empathy in undergraduate medical students, all of which are elements that may influence future medical careers, since these factors influence how we relate to those around us.

2 Materials and methods

The study population consisted of 649 medical students in their 4th, 5th, or 6th year of studies, recruited between March and May 2021. The sample is part of one designed for a survey with larger scope, aiming to identify the relationship between the use of social networking and individual Theory of Mind (ToM), empathy and alexithymia levels in undergraduate students.

2.1 Socio-demographic features of participants

The mean age of participating students was 23.45 ± 1.30 years. Of all the participants, 79.66% were female, 38.83% were fourth-year students, 26.35% were fifth-year students, and 34.82% were sixth-year students. The socio-demographic characteristics of the sample are shown in Table 1

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee of the "Victor Babes" University of Medicine and Pharmacy of Timisoara, Romania (protocol No. 15/20.03.2020).

TABLE 1 Socio-demographic features of the student sample (N = 649).

Features		n	%
Gender	Female	517	79.66
	Male	132	20.34
Age category	21–22 years old	173	26.66
	23-24 years old	357	55.01
	25+ years old	119	18.33
Year of Study	4th	252	38.83
	5th	171	26.35
	6th	226	34.82

Informed consent was obtained from all subjects involved in the study.

2.2 Instruments

We used several instruments for this assessment. The Toronto Empathy Questionnaire (TEQ) was priorly validated in Romanian (42) and measures the empathy level as a uni-dimensional instrument, consisting of 16 items, with a 5-point Likert scale-type answer: never, rarely, sometimes, often, always, and with scores ranging from 0 to 4. Total scores range from a minimum of 16 to 64 points. The validation study for TEQ in Romanian (42) reported a Cronbach's alpha of 0.727 and an ICC of 0.776. The validation of TEQ was conducted using the same sample as in the current study.

The Social Media Addiction Scale-Student Form (SMAS-SF) was developed by Sahin et al. (43) and was previously validated in Romanian (44). The questionnaire consists of 29 items with a 5-point Likert scale, from "totally disagree" (1 point), "disagree" (2 points), "neither agree nor disagree" (3 points), "agree" (4 points), "totally agree" (5 points). The total score ranges from a minimum of 29 to a maximum of 145. The total score can be interpreted as: no addiction (≤ 58 points), mild addiction (59-87 points), moderate addiction (88-116 points), and severe addiction (≥ 117 points). The validation of the SMAS-SF in Romanian (44) demonstrated a Cronbach's alpha of 0.817 and an ICC of 0.829 and used the same sample as in the current study.

The Toronto Alexithymia Scale (TAS-20) was developed by Bagby et al. (45) and consists of 20 items measuring the difficulty in identifying and describing emotions. Alexithymia, as measured by this instrument, is characterized by three factors. The first, entitled "difficulties in identifying feelings" (DIF), and the second factor, entitled "difficulties in describing feelings" (DDF), refer to emotional awareness and expression. They might, therefore, be considered as "affect-related". The third factor, entitled "externally-oriented thinking" (EOT), refers to a specific tendency to deal with simple themes and to avoid affective thinking. Possible answers are quantified on a 5-point Likert scale, from "strongly disagree" (1 point), "disagree" (2 points), "neither agree nor disagree" (3 points), "agree" (4 points), "strongly agree" (5 points). We employed the recently validated Romanian version (46) for this study. Total scores ranged from 20 points, as a minimum, to 100 points as a maximum. Scores were classified as non-alexithymia (≤51 points), possible alexithymia (52-60 points), and alexithymia (≥61 points) (47). The validation study in Romanian (Morariu, 2013) reported a Cronbach's alpha of 0.83. For the TAS-20, the Cronbach's alpha in the current sample was 0.749.

Besides the specific questionnaires mentioned above, the survey also included demographic questions, such as gender, age, year of study, and final average grade in the previous academic year.

The survey was hosted on a platform and could be accessed using a Google Play application (android and iOS) or a desktop version (https://timsonet.ro). Students could access the survey using a series of alphanumeric codes, randomly generated to assure anonymity.

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The final database was imported to the Stata program version 16.1 (StataCorp, College Station, Texas, USA). The categorical variables are represented as absolute and relative frequencies, and continuous variables are presented as mean and standard deviation (SD). A p-value < 0.05 was considered statistically significant. Since the data were not normally distributed, we used the Mann-Whitney test to test for differences between males and females for total scores. The degree of correlation between different questionnaires was test-ed with the Pearson point product correlation. Using structural equation modeling, we created a pathway analysis investigating alexithymia as a mediator between social media addiction and the degree of empathy in medical undergraduates.

The mediation model was analyzed using sgmediation2 command in Stata. For the best test of mediation effect, the bootstrapping procedure to measure indirect effect was carried out and 95% confidence intervals were estimated. The number of bootstrap samples was 5000.

3 Results

3.1 The participants' scales' mean scores

The study's findings showed that the TEQ total mean score was 48.76 ± 5.65, with scores ranging from 18 to 63. The TAS total mean score was 47.71 ± 11.49, with scores ranging from 23 to 83 (Table 2). Further analysis of the TAS scale scores showed that 21.42% of the students had possible alexithymia, and 14.02% had clear alexithymia. The SMAS-SF total mean score was 73.20 ± 14.59, with scores ranging from 31 to 115. A detailed analysis of the SMAS-SF scale scores indicated that as much as 67.18% of the students had a mild addiction, and 15.72% had a moderate addiction. None of the students presented levels consistent with major social media addiction. The use of the SMAS-SF scale allowed the study group to be divided. Those who fell into the no addiction group were considered to be social media users.

TABLE 2 The participants' Toronto Empathy Questionnaire, Toronto Alexithymia Scale, and SMAS-SF scores (N = 649).

Instruments	Mean ± SD	Min	Max
The Toronto Empathy Questionnaire	48.76 ± 5.65	18	63
The Toronto Alexithymia Scale	47.71 ± 11.49	23	83
	n	%	
Nonalexithymia (≤51 points)	419	64.56	
Possible alexithymia (52-60 points)	139	21.42	
Alexithymia (≥61 points)	91	14.02	
SMAS-SF	73.20 ± 14.59	31	115
	n	%	
no addiction (≤ 58 points)	111	17.10	
mild addiction (59-87 points)	426	67.18	
moderate addiction (88-116 points)	102	15.72	
severe addiction (≥ 117 points)	0	0	

3.2 Distribution of the scale mean scores according to gender

The students' TEQ total mean score was higher in females (P<0.001). The difference between mean scores for the TAS total was statistically insignificant between males and females. However, the DIF and EOT factors recorded statistically significant differences between the genders. The SMAS-SF total mean score was also higher in females (P=0.001). All data are presented in Table 3.

3.3 Correlations

The DDF and EOT were negatively correlated with the TEQ; the DIF presented a much lower significant negative correlation with the TEQ. The DIF and DDF scores were positively correlated with the SMAS-SF scores, and there was no significant correlation between the TEQ and the SMAS-SF. All correlations are presented in Table 4.

3.4 Path analysis model

Following the correlation analyses results, we performed mediation analyses to further examine the association between social media addiction, alexithymia and the degree of empathy in undergraduate medical students.

In Model 1, social media addiction was not significantly associated with empathy (path c)(β= -0.0068, P =0.652). In Model 2, social media addiction had a significant relationship

TABLE 3 Distribution of the scales mean scores according to the gender of the participants.

	All Mean (SD)	Range	Women Mean (SD)	Men Mean (SD)	The P-value for gender difference*
TEQ	48.76 (5.65)	18-63	49.74 (4.99)	44.97 (6.46)	<0.001
TAS total	47.71 (11.49)	23-83	47.97 (11.72)	46.68 (10.56)	0.171
DIF	17.30 (6.43)	7-34	17.75 (6.44)	15.56 (6.14)	<0.001
DDF	13.74 (4.52)	5-25	13.81(4.69)	13.47 (3.79)	0.377
EOT	16.67 (3.79)	8-28	16.41 (3.72)	17.65 (3.91)	0.001
SMAS-SF	73.20 (14.59)	31-115	74.16 (14.28)	69.45 (15.23)	0.001

*Based on the Mann–Whitney test.

TABLE 4 Pearson-moment product correlations between alexithymia, empathy, and social media addiction scores.

Factors	TEQ	DIF	DDF	EOT	TAS total
DIF	-0.098*	–			
DDF	-0.215**	0.624**	–		
EOT	-0.339**	0.221**	0.261**	–	
TAS total	-0.251**	0.878**	0.829**	0.555**	–
SMAS-SF	-0.0178	0.351**	0.239**	0.099*	0.323**

*P<0.05.
**P<0.001.

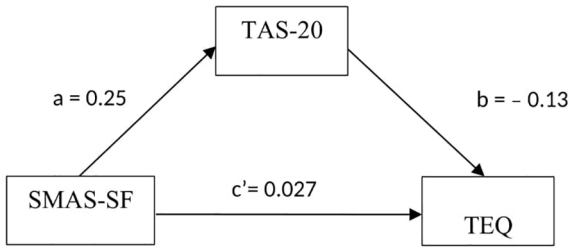

FIGURE 1
Path diagram showing alexithymia as a mediator between social media addiction and the degree of empathy in undergraduate medical students. Numbers on the single-headed arrows represent standardized regression coefficients (Beta).

with alexithymia (path a)(β=0.254, P < 0.001). In Model 3, both social media addiction and alexithymia were included in the mediation model and showed a significant relationship with empathy. Simultaneously, the standardized regression coefficient (β) for social media addiction decreased from -0.007 to 0.027. Moreover, the results of the non-parametric bootstrapping method confirmed the significance of the indirect effect of social media addiction through alexithymia (95% bootstrap CI=-0.047, -0.021). A bootstrapped 95% confidence interval (CI) confirmed that the indirect effect of social media addiction had an impact of -0.034 which was produced by alexithymia as a mediator on empathy (Table 5). These findings corroborate our hypothesis that alexithymia may play a mediator role in the association between social media addiction and empathy. Figure 1 illustrates the mediation model, along with standardized path coefficients.

4 Discussions

In our daily life, and to function optimally as medical professionals, we employ instinct and intuition, alongside reasoning and logical deductions. In this complex inter-play, empathy plays an essential role, found at the core of the therapeutic relationship, and the essence of the doctor-patient relationship. Being able to place oneself in someone else's place can be challenging, especially when the other is suffering. However, instrumental, as it is the only way to more precisely try to understand what that the other is going through.

The present study examined the relationships between alexithymia, social media addiction, and empathy using validated self-administered questionnaires for medical students. People with alexithymia experience difficulties understanding their feelings, as well as those of others, which could result in limitations in the empathic abilities of alexithymia individuals. On the other hand, in the workplace, they also experience difficulties in being able to socialize with colleagues, as they seem inexpressive, aloof, which, in turn, leads to a high probability of becoming unemployed (48).

There are several studies that suggest alexithymia plays an important role in the etiology of addictive behaviors (49–51). Social media is what facilitates interpersonal relationships, which can lead to addiction in people with a high level of alexithymia.

Both empathy and alexithymia are necessary qualities for someone looking to pursue a future medical career. When considering the question of the reasoning behind that, the most likely answer is that empathy allows the building of relationships, and facilitates understanding what patients think, thus making it easier for healthcare workers to respond appropriately. Empathy allows us to manage what we feel, even when faced with stressful situations, without being overwhelmed (52). Moreover, empathy is what allows us to offer unconditional and disinterested help to another.

In our study, the total TEQ score was 48.76 ± 5.65, which is slightly higher than those reported in the literature. Differences between women and men were also significant, favoring the former. A recent study carried out in 57 countries, in 2022, reached the same conclusions, namely that women, regardless of their age and country of origin, scored higher than men in the "Reading the Mind in the Eyes" test, used on a broad scale, to measure the degree of "cognitive empathy" (53).

In this study, the prevalence of medical students with alexithymia was of 14.01%, slightly higher than that reported in the general population (13, 53), but lower than those reported in other student populations (54, 55). For someone with alexithymia, understanding one's own emotional issues is problematic, which is even more difficult when dealing with someone else. An alexithymic health professional will struggle in their interactions, ultimately negatively impact the therapeutic alliance and treatment they offer others (56). Therefore, we suggest that medical students and health professionals in general should be familiar with the concept of alexithymia and its significance in their own personal and professional lives (57, 58).

Among other results, we also found a negative, and significant correlation between the TEQ Scale and the mean TAS-20 scores. Current research supports a cerebral connection between alexithymia and empathy, with the connection established at the level of the insular cortex, where the processing of internal affective states is carried out. The anterior cingulate cortex is associated with emotion processing and social rewards, and a reduced activity in this cerebral area may be

TABLE 5 Mediating model examination by bootstrap.

	Social media addiction → Empathy			
	Effect	SE	LL 95%CI	UL 95%CI
Indirect effect	-0.034	0.006	-0.047	-0.021
Direct effect	0.027	0.015	-0.003	0.057

associated with alexithymia (59). In this view, those with alexithymic traits will tend to have less empathy. Consequently, young people undergoing healthcare education should determine their own capacity for empathy, and those who struggle in this area should receive specific psycho-education on empathy (60).

In our study, we chose to position the personality trait as a mediator rather than a predictor due to specific theoretical considerations. While personality traits are generally considered stable and develop early in life, recent research suggests that they can also be influenced and shaped by environmental factors and behaviors acquired later in life, such as social media use. For instance, there is evidence that frequent engagement in certain behaviors can reinforce or even modify certain personality traits over time, suggesting a bidirectional relationship (61, 62). Valdespino et al. (63) have explored the temporal relationship between alexithymia and empathy, demonstrating that alexithymia serves as a precursor to empathy abnormalities. Therefore, in our theoretical model, social media use is posited as an influential factor that could shape personality traits, thereby justifying its role as a predictor.

Our path analysis model showed that alexithymia is an essential mediator between social media addiction and empathy. Empathy implies one's capacity to adopt and understand another's experiences and emotions. Secondary to their difficulty in identifying and describing emotions, people with alexithymia might find it strenuous to imagine and perceive the emotional experiences of others. In terms of virtual communication, social media rarely offers non-verbal clues, such as facial expressions, body language and tone of voice, essential elements on which communication skills are built and how we, as a species, have learned to understand emotional states in others. Also, social media usually offers curated, unrealistic portrayals of life, as well as acts of aggression, which some-times surmount current constrains and policies, subsequently being responsible for traumatic effects on their consumers. Thus, this confirms studies showing that maltreatment and trauma may be a contributing factor in alexithymia (64–66).

For people with alexithymia, who struggle on a daily-basis to accurately interpret said clues, the interposition of social media raises their inaccurate interpretation of other people's emotions, and lowers their empathy. Increasing the overall time spent on social media might impair empathic responses and reduce the quality of social interactions. According to certain clinical studies, people suffering from social media addiction also have lower empathy levels (67, 68), adding to the well-established theory that empathy correlates with social relationships (69).

Although the present study shows that alexithymia can mediate the relationship between social media use and empathy, it is not the major determining factor, since there are specific individual coping mechanisms, and characteristic personality traits, which can also influence the dynamics of this relationship.

The present research has several limitations, the main one being that it was con-ducted in a single location, on a population with shared cultural traits. Although alexithymia is a mediator of empathy, only about 11% of the variability in empathy is explained by this model. Since the SRMR was zero, other factors should be considered in the future. The study was performed on medical students, so conclusions cannot be extended to the general population. However, the number of participants in our study was large enough to consider the results as reliable. For future studies, objective measures and investigator ratings should be added to the assessment of the connections between alexithymia and empathy.

A significant limitation of this study is the use of cross-sectional data for mediation analysis. While we identified a potential mediating role of alexithymia in the relationship between social media addiction and empathy, it is important to acknowledge that cross-sectional designs limit our ability to infer causality or the temporal order of these relationships. Longitudinal data would be necessary to confirm these mediation effects over time and to establish a clearer causal pathway.

5 Conclusions

According to our best knowledge, this is the first paper that analyzes alexithymia as a mediating factor between social media addiction and empathy. Our results indicated a significant negative correlation between empathy and alexithymia in medical students. Alexithymia was a mediator between social media addiction and empathy. Therefore, we recommend timely and specific efforts to identify levels of alexithymia in more medical students, which can lead to the design of tailored interventions aimed at increasing emotional awareness and aptitudes.

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.

Ethics statement

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

SU: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. A-CB: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. CS: Formal analysis, Investigation, Methodology, Writing – original draft. IR: Investigation, Writing – original draft. AB: Investigation, Methodology, Writing – original draft. IP: Investigation, Writing – original draft. CG-O: Investigation, Writing – original draft.

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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.

Correction note

This article has been corrected with minor changes. These changes do not impact the scientific content of the article.

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Feasibility and acceptability of wearing a neuromodulation device at night in individuals in recovery from opioid use disorder

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Introduction: Opioid use disorder (OUD) is a serious and persistent problem in the United States with limited non-pharmacological treatment options, especially for the concomitant sleep disorders experienced by most individuals with addiction. While new, non-invasive interventions such as low-intensity focused ultrasound (LIFU) have shown promise in targeting the brain regions impacted throughout addiction and recovery, the devices used are not amenable to outpatient treatment in their current form factor and cannot be used at night during sleep. To bridge this gap and provide a much-needed treatment option for repeated, at-home use, we developed a wearable LIFU device out-of-clinic use.

Methods: This study evaluated the feasibility and acceptability of the portable treatment device among individuals recovering from OUD in an unsupervised, at-home setting. 31 subjects were recruited from a Baltimore, Maryland (USA) outpatient treatment facility and, along with a separate group of 14 healthy controls (HC), were asked to wear a prototype EEG-only (non-LIFU) device for 7 consecutive nights to assess their willingness and adherence to nightly use. Participants used a smartphone application, TrialKit (ePRO), to self-report nightly sleep data (e.g. duration, quality, possible disturbances, and device comfort).

Results: Of the 31 OUD participants recruited, 30 (97%) successfully completed the at-home study, and the majority responded that they would participate in future studies using the head wearable device (OUD, 87%; HC, 71%). OUD participants were statistically more likely than HCs to respond that they would consider using the device in the future to help them sleep (OUD, 70%; HC, 29%). Despite some participants facing technological issues (e.g. lack of reliable phone access or cellular data plans), the OUD group demonstrated high study compliance on par with the healthy control group.

Discussion: Participant's daily ePRO and exit interview results established that at-home use of advanced treatment technology is feasible in a population group challenged with recovering from OUD. Even more so, numerous participants noted strong willingness to participate in future LIFU-enabled intervention studies to address their persistent sleep issues during recovery.

KEYWORDS

addiction, sleep, insomnia, human factors, focused ultrasound, sex differences, methadone, ePro

1 Introduction

The Centers for Disease Control and Prevention (CDC) National Center for Health Statistics reports that over 80,000 people died each year from an opioid overdose in 2021, 2022, and 2023 (1). As undergoing opioid agonist treatment (OAT) decreases the risk of overdose for individuals with opioid use disorder (OUD) by nearly 50% (2), encouraging adherence to OUD treatment is imperative in the fight against the opioid epidemic. Unfortunately, relapse is a defining feature of OUD due to the difficulty of opioid withdrawal symptoms (3, 4), and poor sleep health can persist for years following treatment initiation. Not surprisingly, poor sleep is a primary driver of relapse (5–7). Numerous reports confirm that more than 70% of OUD patients undergoing OAT self-report sleep disturbances or disorders (5, 8–10), underscoring its prevalence.

Sleep disturbances persist across the addiction, withdrawal, and recovery process, with inability to sleep serving as a feed-forward stressor that can contribute to relapse. Reports have found inhibition of rapid eye movement (REM) and non-REM (NREM) deep sleep (11–13), decreased total sleep time, and increased wakefulness after sleep onset in those using opioids (14, 15). Longitudinal evaluations indicate that sleep does not naturally improve over the course of OAT with either methadone or buprenorphine use (9, 10, 16). These data suggest that alleviating sleep disturbances in OUD requires targeted and synergistic interventions that are distinct from standard OAT.

Unfortunately, historically prescribed pharmacological interventions for mitigating sleep disturbances can further perpetuate addictive behavior among people recovering from OUD (17–19). The combined use of opioids and sleep aids increases the risk of overdose (20) and non-pharmacological treatments like cognitive behavioral therapy for insomnia (CBTi) may be ineffective as stand-alone treatments for sleep disturbances in OUD, especially for individuals with comorbid pain disorders (21, 22). These findings indicate a need for new non-pharmacological interventions that directly modify sleep physiology with the goal of improving sleep quality, reducing relapse, and promoting abstinence from drug misuse in individuals undergoing outpatient OAT.

To date, non-invasive brain stimulation therapies like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been explored (23–25) for their ability to reduce opioid cravings, while auricular vagus nerve stimulation (aVNS) (26) has been utilized to improve opioid withdrawal symptoms. Encouragingly, these neuromodulatory interventions have shown some efficacy in improving recovery outcomes but are not ideal for targeting the deep brain structures necessary to directly augment sleep.

Low-intensity focused ultrasound (LIFU) has emerged as a promising new non-invasive tool for stimulating or suppressing intact brain circuits with great potential for treating a range of psychiatric disorders and sleep issues (27–30). The differentiating feature of LIFU is that ultrasound (US) beams can be focused onto specific deep regions of the brain without impacting surrounding tissue (31–33), unlike with electrical or magnetic stimulation. Unfortunately, until now, the technology has been limited to in-hospital use and, as a result, could not readily translate to routine addiction intervention. To overcome this barrier to treatment, Attune Neurosciences developed a portable, offline MRI-guided head-worn LIFU device for in-clinic or at-home use to manage addiction and treat sleep disturbances. The device is designed to be comfortably worn while real-time electroencephalography (EEG) is analyzed for sleep stage and cortical phase determination, allowing for personalized LIFU stimulation treatment based on a person's real-time physiological data.

Here, we conducted a 7-night at-home sleep EEG study (*no therapy was administered*) to evaluate nightly device usability and gauge acceptance and adherence of use in the target population, individuals in recovery from OUD. We also examined nightly device usability and adherence in a smaller cohort of healthy controls (HCs) to compare the results and determine if differences exist between the populations. Given the high incidence of sleep disturbances in people with OUD, and the challenge of pharmaceutically treating them, we hypothesized that this group would be amenable to alternative neuromodulation approaches and demonstrate use of the technology on par with the HC group.

2 Methods

2.1 Study design

This study was designed to evaluate the feasibility and acceptability of nightly wear of a head-worn neuromodulation device among individuals recovering from OUD, as compared to HCs. While no therapy was delivered, participants wore the prototype EEG-only device for 7 consecutive nights in an unsupervised, at-home setting. Nightly sleep EEG data was collected to ensure proper device wear. Survey data was collected daily via a smartphone electronic patient-reported outcomes (ePRO) application (TrialKit; Crucial Data Solutions) to monitor, in real-time, participant perceptions of the device and any issues encountered.

The TrialKit ePRO platform developed by Crucial Data Solutions is purpose-built as a data capture system for clinical trials and medical research. Its functionality extends into electronic health record integration and data collection for regulatory submission. User acceptance testing was performed by Attune prior to study initiation to verify that the application's functionality met the needs of the study, and captured data accurately for future analysis.

2.2 Participant recruitment

All study procedures were approved by Advarra, an independent institutional review board. The addiction arm of the study was conducted in partnership with REACH IBR (Recovery Enhanced by Access to Comprehensive Healthcare, Institute for Behavioral Resources) in Baltimore, Maryland (USA), to recruit and enroll individuals who are in recovery from OUD. The REACH IBR

treatment center provides behavioral counseling in addition to daily pharmacological support (e.g. methadone). Study participants were referred for recruitment by councilors or responded to flyers posted throughout the facility. Healthy control participants were recruited via college students through network referral. An index patient was recruited, and subsequent referrals were made via snowball sampling. Participants were compensated $25 per day for their time and effort to wear the device overnight, charge it, and answer daily survey questions. To encourage study adherence and device return, participants received a $100 bonus at their exit interview for wearing the device and completing daily surveys for all 7 nights (34). Visa gift cards were utilized for participant payment, consistent with best practices in populations with addiction (35).

2.2.1 Inclusion and exclusion criteria

Participant recruitment was open to either sex, 18 - 65 years old (inclusive). Criteria included: English speaking, no illegal drug use in the prior 30 days, a working smartphone and data plan for daily survey application use, no use of a continuous positive airway pressure (CPAP) device that could interfere with the head wearable tested in this study, and residing at the same address for the past 30 days (stable sleeping environment). Participants in the addiction arm of the study additionally must have been diagnosed with OUD and be undergoing outpatient OAT with either methadone or buprenorphine. In contrast, HC subjects were free from a substance use diagnosis and were not dependent on other substances except nicotine.

2.2.2 Participant retention

A flow diagram of participant retention is presented in Figure 1. Participants were screened for study inclusion based on the criteria previously described. Five individuals in the OUD group were excluded from further participation due to recent drug use (n = 2) or lack of working smartphone (n = 3). In the OUD and HC groups, 31 (17 females) and 14 (4 females) participants were consented, respectively. A single male participant in the OUD group dropped out due to device discomfort on the first night of wear. During the exit interview, it was determined that the participant was sleeping on a friend's recliner and should have been excluded from study participation based on lack of stable sleeping environment. Of the 30 remaining OUD participants, 4 either did not answer daily survey questions or had issues with the ePRO application, while 1 HC participant did not answer survey data. Nightly EEG data was available for 30 OUD participants and 14 healthy controls, while 26 and 13 participants also completed the ePRO surveys, respectively.

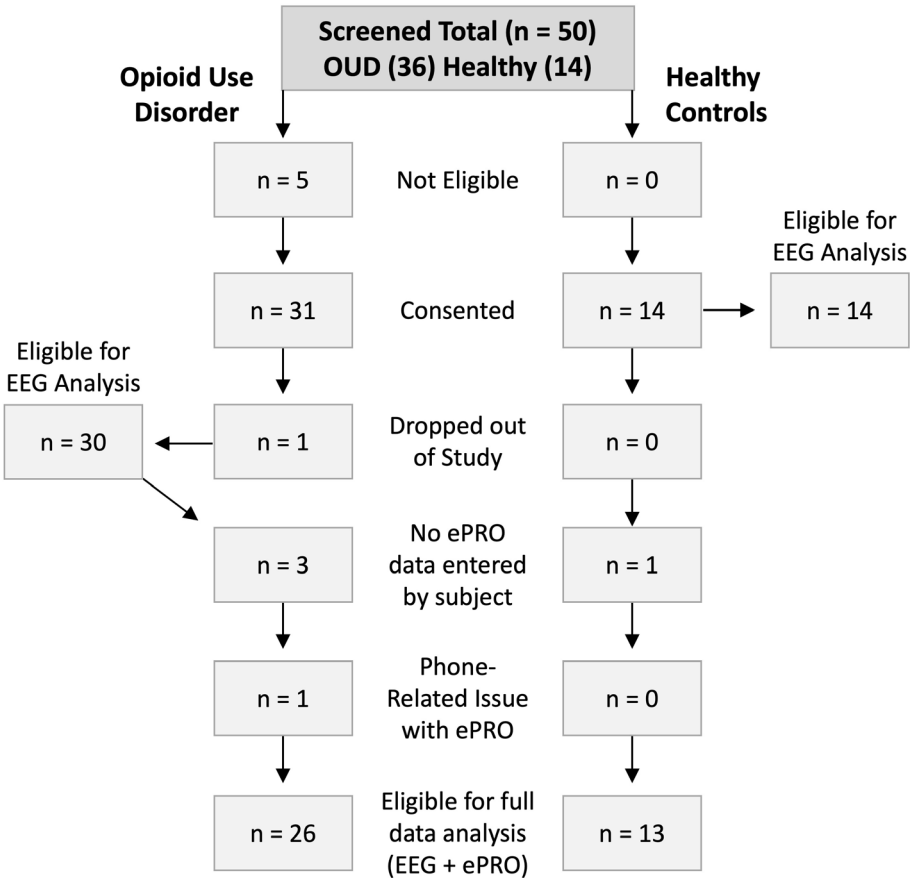

FIGURE 1
Flow diagram of participant recruitment and retention for both OUD and HC groups.

2.3 Study procedure

Participants were electronically screened to determine eligibility. Those eligible for participation were automatically redirected to an electronic consent form. Once consented, participants provided information on age, drug treatment history, traumatic brain injury (TBI) history, skin sensitivities, difficulty sleeping, relationship status, and smoking history. After enrolling participants in the TrialKit ePRO survey platform, the study coordinator assisted them in downloading and logging into the TrialKit phone application and completing a practice questionnaire. Participants were then fitted with the Attune head-wearable prototype device and provided verbal and written instructions for use, as well as a device charger and necessary EEG electrode and device cleaning consumables. Participants were scheduled for an exit interview seven days later to return the device and answer follow-up questions. Each morning upon waking, participants were expected to complete a survey questionnaire via TrialKit and charge their wearable device. Participants were responsible for replacing or re-wetting hydrogel EEG electrode pads nightly before wear. Upon study completion, participants underwent an exit interview to assess overall acceptance, feasibility and willingness of using the device in a future clinical study. All participants were incentivized to complete the week-long study with a prepaid debit card provided at the completion of their exit interview.

2.3.1 Survey collection

During the initial study consent, participants were asked what time to be contacted in the morning regarding daily survey completion. Text messages were sent through the TrailKit phone application reminding participants to answer the daily survey if they had not already done so prior to their agreed upon time. Those who did not complete the survey within an hour were sent one follow-on reminder text by the study coordinator. Complete versions of each survey can be found in the Supplementary Materials (Supplementary Tables S1–S4).

2.3.2 Head-worn device

The clinical head-worn LIFU device includes bilateral ultrasound transducers that interface with the "temporal window," a thin portion of skull bone posterior to the eyes that allows access to centralized deep brain structures. A silicone pad overlaid on the US transducer offers contouring and comfort. The front band of the clinical device has integrated 2-channel EEG to measure cortical brain activity, 3-axis accelerometry for capturing head movement, and temperature and photoplethysmography sensors. Custom padding maximizes comfort, and a detachable nose bridge-centered fit-tool allows the user to repeat positioning of the US transducers across use sessions.

Here, we tested a non-clinical human factors version of the device (Figure 2) that was geometrically identical to the clinical device but was powered by an integrated rechargeable battery. The device was stripped of all LIFU components (*no therapy delivery*) and replaced with 3D-printed resin surrogates to match the fit and feel of the clinical version. The housing was made from a 3D-printed thermoplastic polyamide elastomer (TPA) material that was free of dyes and secured to the head via an elastic and Velcro rear band. A pair of active EEG sensors (ConMed Softrace Small ECG hydrogel electrodes) were included in the front band approximately at FP1 and FCZ (Figure 2C), both referenced to the mastoid (Kendall H124SG ECG electrode), with data streamed and stored at 250 Hz on a local micro-SD memory card for offline analysis. An embedded 3-axis accelerometer (250 Hz) captured head motion throughout use. Applying pressure to a central power button on the front of the device allowed users to turn it on and off.

The human factors device utilized mini-light emitting diodes (LEDs) embedded into the circuit board, and light pipes channeled the diffuse light to the front of the wearable to signal device functionality. When plugged in, an orange or red LED on the right side of the device indicated charging still in progress while a green light indicated charging is complete. The left LED indicator light would glow blue when powered on if the device was adequately charged and a memory card was properly inserted (Figure 2B). If the left light was red or orange after powering on, the memory card was likely not inserted correctly or had malfunctioned. Participants were instructed to only use the device if it was properly charged, and the left light indicator was blue during operation.

FIGURE 2
Wearable device worn by participants for each night of the study. **(A)** Side profile 3D rendering of a head model wearing the device. The mastoid EEG reference is shown in green behind the right ear. The circle over the right temple is the ultrasound transducer found in the clinical device. **(B)** Frontal photograph of the wearable human factors device with the SD card inserted, and blue LED power light demonstrating proper device function. **(C)** Rear photograph of the wearable with EEG and mastoid electrodes installed. The rear elastic band is pulled over the top of the device as it is done when donning the device.

2.4 Data analysis

Statistical analysis was performed using GraphPad Prism Version 10.2.3. Discrete data was summarized using median and median absolute deviation (MAD), while continuous data was summarized using mean and standard deviation (SD). A two-sided $p < 0.05$ was used to determine statistical significance and adjusted for multiple comparisons, as needed.

2.4.1 Nightly EEG recordings

After each participant completed the study, the micro-SD cards were removed from the wearable devices for analysis. A custom Python script was generated to batch-process each nightly EEG file. The data processing pipeline began with extracting raw EEG and accelerometer signals from the binary data files, followed by the EEG signals being de-medianed to ensure accurate amplitude representation and to remove very low frequency oscillations. The EEG signals then underwent band-power extraction, including Fourier transformation, to assess frequency content over time (10 second bins, 0.1 Hz resolution). Two graphs were generated, one displaying the 3-axis accelerometry and a spectrogram showing the EEG time frequency signal of the entire night recording. The EEG graph and raw data were manually reviewed for regions of electrical noise contamination, which can be seen as high power across multiple frequency bands, or disconnected electrodes which present as horizontal banding in the spectrogram. Regions of data deemed noisy were manually reviewed for confirmation. Each night of EEG recording was then categorized into "5 - Very Good", "4 - Good", "3 - Moderate", "2 - Poor", and "1 - Very Poor" based on the length and quality of EEG signal (Supplementary Figure S1). Recordings considered "Very Good" displayed clean readable data (>80%) and had both EEG channels recording properly without noise contamination or electrode disconnection. Data considered "Good" displayed clean EEG data (70-80%) but may have only one EEG channel with properly recorded data. Data categorized as "Moderate" showed identifiable EEG signal patterns (50-70%) and contained only one properly recorded EEG channel. "Poor" or "Very Poor" data had little to no identifiable EEG signal patterns (<50%) across the two EEG channels. Files with insufficient duration (< 60 minutes) were also classified as "Very Poor". Due to firmware issues with the EEG acquisition circuit, timestamps were not included with the signal data. This precluded a more in-depth analysis and comparison of sleep/wake cycles between the OUD and HC groups, as originally intended.

2.4.2 TrialKit ePRO daily surveys and exit Interview

Survey data was compiled for each question across all 7 nights of the study and analyzed using descriptive statistics, which was also used to describe demographic and participant histories. Prevalence of smoking and sleep issues were analyzed across study groups and biological sex using a Chi-square (Fisher's exact) test.

3 Results

3.1 Demographics

Participant demographics were obtained during consent and are included in Table 1. For the OUD group, the mean age was 45.1 ± 13.0 years, while the HCs were younger at 22.6 ± 10.0 years. The OUD group was comprised of 56.7% females (OUD-F), while the HCs were 28.6% female (HC-F). No participants in either group reported skin or scalp sensitivities. A statistically greater proportion of responding OUD participants reported difficulty sleeping (OUD, 67.9%; HC, 21.4%; P = 0.0080), with no difference between males and females in either group (OUD, P = 0.23; HC, P = 0.99; Supplementary Table S5). The OUD participants were statistically more likely to smoke cigarettes compared to healthy controls (OUD, 78.6%; HC, 14.3%, P = 0.0001), with no difference between males and females (OUD, P = 0.65; HC, P = 0.066; Supplementary Table S5).

3.2 ePRO responses

Upon waking each morning, participants were required to login to the ePRO application (TrialKit) and respond to a series of questions regarding their nightly sleep and their experience using the wearable device. Additional questions focused on lifestyle factors that could influence their sleep and perceptions of device use. Nearly all participants in both groups completed the required seven days of ePRO surveys (Table 2). There was one HC and four OUD participants who did not use the ePRO system because of technology issues related to phone and text reminders; hence, no self-reported data were available for these participants (Figure 1).

3.2.1 Sleep

From the available ePRO data, participants across groups and biological sexes self-reported similar nightly total sleep time (TST) durations (ANOVA, P = 0.28) that were greater than the associated TST duration of acquired EEG data (mean difference ± sd; OUD-M, 2.96 ± 3.74 hrs; OUD-F, 2.18 ± 3.12 hrs; HC-M, 1.71 ± 3.12 hrs; HC-F, 0.38 ± 1.98 hrs). Nightly EEG data were analyzed for signal quality and continuity of recording throughout each night to confirm device wear by the participants. Most of the device-recorded EEG data from both participant groups received a qualitative score of 3 or higher (Moderate quality; Supplementary Figure S1) (OUD-M, 59.4%; OUD-F, 52.5%; HC-M, 61.0%; HC-F, 60.7%).

From the available ePRO data, participants reported similar median sleep quality ratings (Median, IQR [25th, 75th Percentile]; OUD-M, 3 [2.5, 4]; OUD-F, 3 [2, 4]; HC-M, 3 [3, 4]; HC-F, 4 [3, 4]; Table 3), with the only statistical difference being between OUD-M and HC-M (Kruskal-Wallis, P = 0.024). In addition to self-reported sleep ratings, participants also commented on the disruption of sleep, and other possible sleep factors such as the wearable's blue LED power light, exercise, caffeine, and/or alcohol use within four

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TABLE 1 Participant demographics.

	OUD Participants (N = 30)	Healthy Controls (N = 14)
Age		
Mean [SD]	45.1 [13.0]	22.6 [10.0]
Median	42	20
Sex		
Male	13	10
Female	17	4
Marital status		
Single	15	9
In a relationship	5	3
Married	2	0
Living with partner	4	1
Widowed	1	0
Separated	1	0
Divorced	0	1
NR	2	0
Drug treatment		
Yes	24	0
No	4	14
NR	2	0
Number of times in drug treatment		
Average	2.1	–
Median	2	–
Traumatic brain injury		
Yes	1	0
No	19	14
NR	10	0
Skin sensitivity (head or scalp)		
Yes	0	0
No	20	14
NR	10	0
Sleep difficulties		
Yes	19	3
No	9	11
NR	2	0
Nicotine consumption		
Yes	22	2
No	6	12
NR	2	0

hours of bedtime. Regarding the blue light, the majority of participant's nightly responses were reported as either "No" or "N/A" on the disruption of their personal (OUD-M, 88%; OUD-F, 79%; HC-M, 91%; HC-F, 88%) or their partner's (OUD-M, 91%; OUD-F, 79%; HC-M, 90%; HC-F, 91%; Table 3) sleep. A majority of responses in both groups also indicated "No" to exercising (OUD-M, 96%; OUD-F, 98%; HC-M, 86%; HC-F, 92%; Table 4) and caffeine/energy drink use within four hours of wearing the device and going to sleep (OUD-M, 85%; OUD-F, 96%; HC-M, 89%; HC-F, 83%; Table 4).

Concerning alcohol use between the broader groups, the HC participants (which mostly consisted of college students) were statistically more likely to drink alcohol within four hours of going to sleep than the OUD participants (Fisher's Exact Test, $P < 0.0001$). Within the OUD group, OUD-M participants were statistically more likely to drink alcohol as compared to OUD-F (Fisher's Exact Test, $P = 0.046$); no statistical difference was found between HC-M and HC-F (Fisher's Exact Test, $P = 0.612$). When we examined nightly responses to alcohol use, OUD participants consistently responded with "No" to alcohol use within four hours of going to sleep (OUD-M, 92%; OUD-F, 97%). This is in contrast to the HC participants who were less likely to respond with "No" to nightly alcohol use (HC-M, 64%; HC-F, 54%; Table 4).

3.2.2 Medication use

Based on ePRO self-reported data on nightly medication use (Table 5), a higher percentage of females with OUD took prescribed medication at least once during the study (OUD-M, 8%; OUD-F, 41%), although this was not statistically different from males ($P = 0.09$). Similarly, there was no statistical difference in unprescribed (over-the-counter, OTC) medication use before bed between males and females with OUD ($P = 0.11$). Examples of reported prescribed medications include Ambien, Clonidine, Gabapentin, Strattera, Propanol, Prazosin, and Seroquil; while reported OTC medications included Ibuprofen, Tylenol, Benadryl, Advil, and Allegra. In contrast, none of the HC participants (HC-M, 0%; HC-F, 0%) reported taking any prescribed medications. In both groups, only the females reported taking OTC medications (OUD-F, 24%; HC-F, 25%). Across the total study nights, OUD-F were statistically more likely to take prescribed (Fischer's Exact, $P < 0.0001$) and OTC (Fischer's Exact, $P = 0.035$) medications, as compared to OUD-M (Table 5).

3.2.3 Wearable device comfort

Figure 3A was used to determine potential areas of discomfort caused by the head wearable device during sleep. Based on the total nightly reports of any pain occurrence (Table 6), most responses across all groups reported "0 or (No Pain)" from the wearable device (OUD-M, 79%; OUD-F, 73%; HC-M, 84%; HC-F, 58%). Only a few responses indicated participants experiencing pain at multiple (at least 3) different locations while wearing the device (OUD-M, 1%; OUD-F, 4%; HC-M, 0%; HC-F, 8%). From the total nightly pain location reports (Table 7), there was no statistical difference between OUD-M and OUD-F participants who reported

TABLE 2 ePRO and EEG data yield.

Participant group		Participants (N)	ePRO responses [median, MAD]	Avg nightly ePRO recorded sleep duration (hrs) [mean, SD]	Avg total nightly EEG recordings (hrs) [mean, SD]	Avg nightly usable EEG recordings (hrs) [mean, SD]	Avg nightly non-usable EEG recordings (hrs) [mean, SD]
OUD	Male	13	7, 0	8.14, 1.81	10.26, 5.41	5.62, 2.61	4.64, 4.02
	Female	17	6, 1	8.05, 1.33	11.33, 6.50	5.26, 3.76	6.07, 4.81
Healthy Controls	Male	10	7, 0	7.34, 0.91	12.34, 4.36	5.66, 3.24	6.68, 4.99
	Female	4	7, 1	8.16, 2.08	15.40, 4.52	7.78, 1.29	7.62, 5.63

TABLE 3 Participant sleep quality rating and reported nighty sleep disruption from the blue power LED indicator.

Participant group		N	Median sleep rating - 99% CI (upper, lower)	Did the blue light disrupt your sleep last night?			Did the blue light disrupt the sleep of anyone who slept by you last night?			
				Yes	No	N/R	Yes	No	N/A	N/R
OUD	Male	13	3 (3, 3)	3 (4%)	64 (88%)	6 (8%)	1 (1%)	59 (81%)	7 (10%)	6 (8%)
	Female	17	3 (3, 4)	3 (3%)	73 (79%)	16 (17%)	4 (4%)	64 (70%)	8 (9%)	16 (17%)
Healthy Controls	Male	10	3 (3, 4)	1 (2%)	51 (91%)	4 (7%)	2 (4%)	20 (36%)	30 (54%)	4 (7%)
	Female	4	4 (3, 4)	1 (4%)	21 (88%)	2 (8%)	0 (0%)	14 (58%)	8 (33%)	2 (8%)

TABLE 4 Reported nightly alcohol and caffeine use and exercise within 4 hours of going to sleep.

Participant group		N	Did you drink alcohol yesterday within 4 hrs of going to sleep?			Did you consume any caffeine or energy drinks yesterday within 4 hrs of going to sleep?			Did you exercise yesterday within 4 hrs of going to sleep?		
			Yes	No	N/R	Yes	No	N/R	Yes	No	N/R
OUD	Male	13	6 (8%)	67 (92%)	0 (0%)	11 (15%)	62 (85%)	0 (0%)	3 (4%)	70 (96%)	0 (0%)
	Female	17	1 (1%)	89 (97%)	2 (2%)	3 (3%)	88 (96%)	1 (1%)	2 (2%)	90 (98%)	0 (0%)
Healthy Controls	Male	10	20 (36%)	36 (64%)	0 (0%)	6 (11%)	50 (89%)	0 (0%)	8 (14%)	48 (86%)	0 (0%)
	Female	4	10 (42%)	13 (54%)	1 (4%)	4 (17%)	20 (83%)	0 (0%)	2 (8%)	22 (92%)	0 (0%)

pain across the different regions of the head ($P_A = 0.14$; $P_B = 0.13$; $P_C > 0.99$; $P_D = 0.55$; $P_E = 0.79$). This was similar in the HC group except at the forehead location, where females were statistically more likely to report discomfort ($P_A = 0.0025$) compared to other locations ($P_B > 0.99$; $P_C > 0.99$; $P_D = 0.17$; $P_E = 0.06$).

The total nightly percentage of OUD and HC participants who reported any head pain from the wearable is shown in Figure 3B. The highest percentage of participants who reported pain occurred at night four (OUD, 27%; HC, 29%). There was an initial increase in the percentage of OUD participants who reported pain from night one through four (17% - 27%), then a steady decrease through night seven (27% - 7%). In contrast, there was no generalizable trend of reported pain for the HC group. Figure 3C shows that most participants did not experience discomfort across multiple nights of device use. For instance, in the OUD group only 7% of participants reported pain for four, 0% for five, 3% for six and 0% for seven nights of wearing the device; while, no HC participant (0%) reported experiencing discomfort from the device on more than four nights of the study (Figure 3C).

3.3 Exit interviews

After completing the seven-night study, participants answered exit interviews where they reported on their overall experience with the wearable device, ePRO system, and other aspects of the study. From the verbal exit interview, nearly all participants reported that the device was "Easy" or "Very Easy" to don at night (OUD-M, 100%; OUD-F, 100%; HC-M, 100%; HC-F, 75%; Supplementary Table S6); there was a single female participant who reported having a "Very Difficult" time donning the device. Similarly, nearly all participants also reported that nightly replacement of the EEG electrodes was "Easy" or "Very

TABLE 5 Reported medication use across participant groups.

Participant group		Participants (N) [# of ePRO responses]	Prescribed medication		Unprescribed (OTC) medication	
			# of participants who took at least 1 prescribed medication	Total # of nights where participants took prescribed medication before going to sleep	# of participants who took at least 1 unprescribed medication	Total # of nights where participants took unprescribed medication before going to sleep
OUD	Male	13 [73]	1 (8%)	1 (1%)	0 (0%)	0 (0%)
	Female	17 [92]	7 (41%)	29 (32%)	4 (24%)	6 (7%)
Healthy Controls	Male	10 [56]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Female	4 [24]	0 (0%)	0 (0%)	1 (25%)	1 (2%)

Easy" (OUD-M, 100%; OUD-F, 94%; HC-M, 90%; HC-F, 100%; Supplementary Table S6). The remaining two participants (one from each group) reported having "Moderate" difficulty in the nightly task. Open ended responses to the verbal exit interviews were categorized based on response characteristics. When asked about challenges with the ePRO system, participants in both groups experienced various technical issues (OUD, 40%; HC, 29%; Fisher's Exact Test, P = 0.52) with using the application (Supplementary Table S6). These issues varied from complete inability to respond daily, initial setup challenges with cellular data plans and lack of phone memory storage, or challenges after night one that required study coordinator intervention.

In terms of device comfort, participants reported it as being "Moderate" to "Very Comfortable" to wear (OUD-M, 70%; OUD-F, 95%; HC-M, 70%; HC-F, 50%; Supplementary Table S6). From the Likert responses, all participants in both groups (100%) either "Agree" or "Strongly Agree" that overall, the device was easy to use (Supplementary Table S7) and the majority of participants would participate in future studies using the head wearable device (OUD, 87%; HC, 71%). When participants were asked if they would consider using the device in the future to help them sleep, the OUD group was statistically more likely to respond positively than the HC group (OUD, 70%; HC, 29%; Fisher's Exact Test, P = 0.02; Supplementary Table S7).

3.4 User feedback

During the exit interview, we inquired about overall device comfort and usability (Supplementary Table S3). Notable feedback focused on the participants desire to improve sleep without the use of pharmacology. For instance, one OUD participant who has been drug-free for 10 months, the longest continuous period in 30 years, stated that his only lingering issue is his inability to sleep. He described how this negatively impacts his employment and creates issues with his marriage. This individual was very enthusiastic about new technology and responded that "If I could use [the] device for sleep, without using drugs, Hell yah!". Similarly, another OUD participant responded that the device "was comfortable to wear at night and liked the idea of not having to take medications [to improve sleep]". Another participant noted that the device "was comfortable, and was able to sleep with it" and it was "something you could get used to wearing every night", while another participant noted "I didn't even know I was wearing it". Two female OUD participants reported "sleeping better with the device" due to the "cooling effect of the silicone pads" on their temples. Similarly in the HC group, participants noted the device "was comfortable, didn't realize I was wearing it" and "comfort was good, forehead felt fine".

Participants who slept on their side and/or moved a lot during sleep reported mild discomfort. For instance, participants "felt a slight pressure" and "side discomfort" when sleeping on their side. As a result, the same participant "slept fine only on some nights" and "other nights I had to adjust it", while another participant "felt more comfortable sleeping on [their] back" despite normally being a side sleeper. Regarding hair types, participants with longer and smoother hair had issues keeping the elastic rear band in place and had to "adjust the band several time at night". Nightly wear also presented a challenge for a participant with dreadlocks.

Critical responses around the study requirements focused on use and connectivity issues associated with the TrialKit (ePRO) application. It took some participants a few days to become familiar with the interface, as several had "problems with app", "was confused about pin # [number]", "issue with time stamp(ing) on [the] first two days", and "kept hitting save but wouldn't go through". While others felt the interface was easy to use and had no issues with daily login and reporting. In terms of connectivity, several participants noted temporarily losing internet access for a day and as result failed to complete the previous night's report. Similarly, OUD participants who had limited cellular data plans were unable to receive daily SMS text reminders and failed to complete their daily report.

4 Discussion

This project represents the first step towards developing a functional, non-pharmacological therapeutic device specifically designed to target sleep issues in an OUD population. The current study focused on the comfort of participants while wearing the device, a key component to treatment success that is frequently underappreciated; comfort is integral to treatment adherence and routine use. CPAP machines serve as an example

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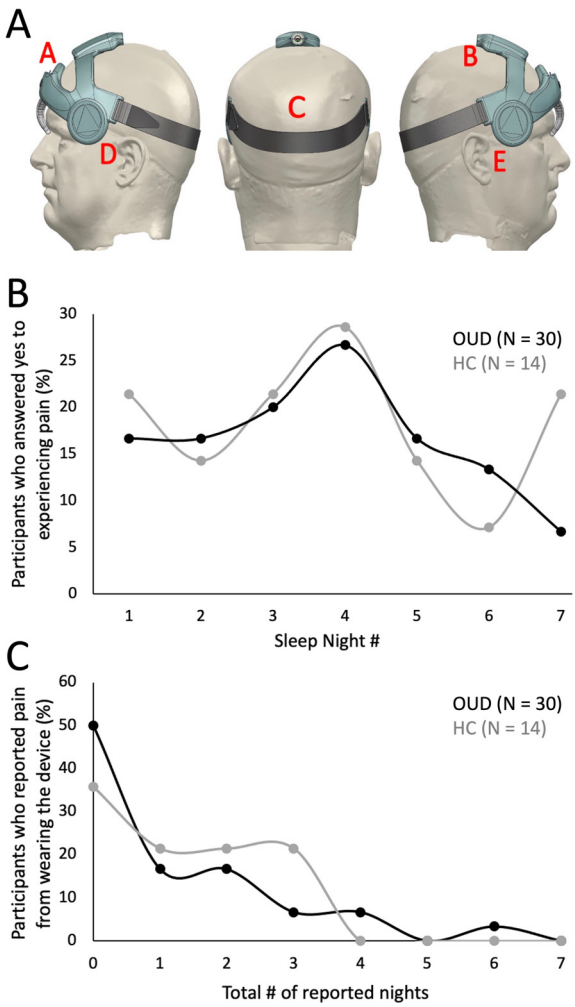

FIGURE 3
Assessment of device comfort. **(A)** Illustration depicting possible areas of discomfort as shown in the participant's daily ePRO surveys (A: Forehead, B: Top of head, C: Back of head, D: Left side of ear, E: Right side of ear). **(B)** Percentage of participants who answered "Yes" to experiencing discomfort across each study night. **(C)** Percentage of participants who reported experiencing device discomfort. Each participant's daily response (No, 0; Yes, 1) was summed to determine the cumulative number of nights where they reported discomfort.

of an effective, non-pharmacological treatment for disordered sleep (obstructive sleep apnea; OSA) in which treatment success suffers due to patient non-adherence. Issues related to patients' discomfort are consistently found to predict non-adherence (36), while improving patient comfort has been found to increase adherence rates in CPAP users (37). In 2023, ResMed, a pioneer in the CPAP field, spent approximately $288 million on its research and development efforts (38). The newly released AirFit F40 CPAP mask highlights the company's focus on creating ultra compact, adjustable, and comfortable devices that fit a broad population range and is critical to improving compliance. Drawing from CPAP user experience, it is imperative to study the degree of comfort that target populations have when wearing a treatment device, which can determine future adherence and therapeutic success.

Here, we tested device comfort and usability in a target population of individuals in recovery from OUD. Results demonstrated a near perfect adherence rate to wearing the device for seven consecutive nights (median = 7 nights), and a high completion rate where 30/31 (97%) consented participants finished the full study. This suggests that the head wearable device was comfortable to sleep with and any discomfort experienced was not sufficient to discontinue nightly use, or warranted dropping out of the study. We also had 100% of the test devices returned during the exit interview and in fully operational condition. This is key to future clinical implementation in a home setting, as it suggests that the participants followed device use and daily care instructions provided to them at the onset of the study.

Our results parallel and extend a pilot study of 8 male participants who underwent nightly EEG monitoring during supervised opioid withdrawal in a residential unit. The participants wore a forehead mounted, battery operated wireless EEG device (Sleep Profiler; Advanced Brain Monitoring, Carlsbad, CA) for 85.6% of the scheduled nights, but compliance varied based on the stage of withdrawal (39). Another study used the same EEG device during a 7 night at-home assessment of sleep in individuals with OUD, with an observed 75% compliance across a larger cohort of 55 participants (15). Our device compliance was higher than both studies, possibly due to our participant section of only individuals who have been free from drug use for over 30 days and having a stable home sleeping environment. Like our results, these studies observed discrepancies between subjective sleep diaries and objective EEG data such that sleep diaries tended to over-estimate TST versus objective EEG measures. However, our results should be interpreted cautiously, as our numbers are particularly discrepant and likely influenced by issues with the EEG recording hardware that precluded a more in-depth signal processing analysis (see Limitations).

From the daily ePRO responses, females reported more OTC and prescribed medication use than males. This is in line with prior research indicating that females are more likely to take medication for sleep, prescribed or OTC, than males (40). Females are also more likely to report pain and are known to have more pain sensitivity (41) that can lead to higher rates of medication use. Females are statistically more likely to develop conditions resulting in excessive pain, such as osteoarthritis, inflammatory arthropathy, and fibromyalgia (42) that can lead to chronic use of pain medications. This mirrors what we found in this study, with females using Tylenol, Advil, Ibuprofen, while males did not report use of any of these OTC medications. Severe pain conditions can result in the need to treat pain with opioids, which females are 1.5 times more likely to fill prescriptions for than males (43), which use can lead to addiction.

The study design required participants to use a cell phone-based application (TrialKit) to answer daily survey questions about device comfort. This approach has been successfully used in prior studies by us, and others, with similar subject populations (44). Further, prior research has shown that individuals who have a history of drug injection have high cell phone usage and are

TABLE 6 Occurrence of reported head pain across number of locations and participant groups.

Participant group		Participants (N) [# of ePRO responses]	# of nights where pain was reported at (X) number of location(s)					
			0 (No Pain)	1	2	3	4	5
OUD	Male	13 [73]	58 (79%)	12 (16%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
	Female	17 [92]	67 (73%)	8 (9%)	9 (10%)	4 (4%)	0 (0%)	0 (0%)
Healthy Controls	Male	10 [56]	47 (84%)	5 (9%)	4 (7%)	0 (0%)	0 (0%)	0 (0%)
	Female	4 [24]	14 (58%)	2 (8%)	5 (21%)	2 (8%)	0 (0%)	0 (0%)

comfortable using technology (45). Here, following consent, the research coordinator assisted participants in loading TrialKit onto their phones, which allowed them to answer questions each morning upon awakening (46). Data was used to track, in real-time, their perceptions of the wearable device and any issues encountered. Study participants unanimously expressed a willingness to use TrialKit, but it did pose a challenge for a minority of individuals, particularly those reliant on government sponsored phones and data plans that have limited storage space that restricts application download options. The research coordinator, on many occasions, worked with study participants to remove unwanted or unused applications to free up storage space to install TrialKit (47). This should be taken into consideration in future research that involves smartphone-based technology and applicants should be screened accordingly.

During the exit interview, we asked participants if they would like to be contacted about future clinical research studies that involve delivery of LIFU to potentially help them sleep. The OUD participants were statistically more likely to positively respond versus HC participants (OUD, 70%; HC 29%), which is in line with the percent of each population that reported trouble sleeping during initial study consent (OUD, 68%; HC, 21%). These numbers also approximate published numbers on sleep disorders in individuals with OUD and who are undergoing OAT (70%) (5, 8–10). Encouragingly, it demonstrates the desire of these individuals to embrace non-pharmacological treatment options. As technology advances, options to treat sleep disorders and other components of addiction will continue to grow.

LIFU represents one such technology and which underlies the clinical version of the wearable device tested here. In contrast to other approaches, LIFU allows precise neuromodulation of centralized deep brain structures such as the thalamus (48), hypothalamus, amygdala (49), nucleus accumbens (NAc) (50), and hippocampus. These, and additional brain regions, serve as tractable targets for addressing components of addiction, the sleep/wake system, and for treating psychiatric disorders (51), demonstrating the highly versatile nature of the technology. Indeed, recent published evidence suggests that targeting LIFU to the NAc, a critical core region of addiction, can dramatically reduce cue-induced drug craving for a range of substances that includes cocaine, alcohol, nicotine, and opioids (52, 53). Remarkably, these results persist for many weeks post-treatment, suggesting that LIFU could be a promising new therapeutic approach with outcomes that rival that of pharmaceuticals while avoiding side effects. While encouraging, the technology used in those studies is limited to in-hospital use and does not readily translate to routine addiction treatment. Further advances in wearable devices that broaden treatment options to community addiction centers such as REACH IBR, and at-home use, offer tremendous potential for addressing the persistent opioid epidemic.

4.1 Next steps

Based on current results of intermittent EEG connectivity in some participants, we aim to improve conformal fit of the device by reducing the form-factor of our current EEG components and

TABLE 7 Reported number of instances of pain at each identified location on the head.

Pain Location			A	B	C	D	E
Participant group		Participants (N) [# of ePRO responses]	Forehead	Top of head	Back of head	center side of ear	Right side of ear
OUD	Male	13 [73]	5 (7%)	1 (1%)	1 (1%)	4 (5%)	8 (11%)
	Female	17 [92]	14 (15%)	6 (7%)	2 (2%)	8 (9%)	8 (9%)
Healthy Controls	Male	10 [56]	1 (2%)	0 (0%)	2 (4%)	6 (11%)	4 (7%)
	Female	4 [24]	6 (25%)	0 (0%)	0 (0%)	6 (25%)	6 (25%)

transitioning to a flexible circuit design with interchangeable front band. A follow-on study utilizing the current design could be performed to evaluate engineering improvements on nightly data collection for statistical comparison to the current dataset. Due to the demonstrated success of working directly with an OUD population for feasibility and acceptability testing, future clinical trials will focus on treating multiple aspects of addiction (e.g., drug craving and underlying sleep disorders) to reduce rates of relapse. The ATTN201 is particularly amenable to this, as it can be used in an at-home, out-of-clinic, setting in contrast to the LIFU system used in prior addiction treatment studies that requires an active MRI for neuronavigation (52, 53).

4.2 Limitations

Study limitations include only testing one device form factor; thus, it is unknown how these results translate to other head wearable devices. We experienced firmware issues with EEG record timing and a sensitive power button precluded a comparative analysis of EEG and sleep features between OUD and HC participants. In TrialKit, participants should not have been allowed to leave daily survey questions unanswered; thus, resulting in non-responses (NR) to some questions. This feature was tested prior to implementation, and it remains unknown how this materialized during study use. OUD participants were recruited from a single recovery clinic in Baltimore, MD (USA), although our participant sample included a broad range of demographics and number of times in drug treatment.

To simulate real-world device usage, participants were allowed to continue their medications, including sleep aids, and consume alcohol, which may have impacted overnight perceptions of wearing the device. There was a notable age discrepancy between the OUD and HC groups, where the mean age of the OUD group was >20 years older than the HC, which could influence their perception and usage of the device. Future clinical studies using LIFU therapy will more tightly age match across groups. Participants were compensated for nightly device wear and daily survey responses, and provided a bonus for completing all 7 nights and returning the device upon study conclusion. This payment schedule was based on our study coordinators history in working with similar populations with addiction in Baltimore, MD, and common practices with this population (34, 35).

5 Conclusions

This study demonstrated that Attune's head-worn medical device is feasible for at-home, nightly use among individuals with OUD, opening the door to future addiction treatment options with LIFU. Strong study adherence (e.g., daily survey completion, device wear and maintenance, and return of the research device to the study coordinator) also indicates that with proper study design and support, the recovering OUD population can effectively participate in longer-duration, outpatient studies.

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.

Ethics statement

The studies involving humans were approved by Advarra - Independent 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. 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

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Conflict of interest

KLM, DA, SW, KRM, and CG are employed by Attune Neurosciences, who developed the wearable device that was tested. SH and HJ are contract consultants for Attune Neurosciences.

The remaining author declares 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.2024.1481795/full#supplementary-material

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Is internet-based cognitive behavioral therapy for alcohol use disorder equally effective for men and women? Implications of a secondary analysis of a clinical trial

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Introduction: Excessive alcohol use is a major public health concern, for which internet interventions have shown to be effective. Group-average effects may however mask substantial inter-individual variations in changes; identifying predictors of this variation remains an important research question. Biological sex is associated with pharmacokinetic differences in alcohol tolerance, which is reflected in many national guidelines recommending sex-specific thresholds for excessive drinking. Whether effects of internet interventions are moderated by sex, and whether any moderation is due to confounders, remains largely unexplored.

Aim: To examine sex-differences in outcomes (both response and remission) after an internet intervention for alcohol use disorder, and to identify any confounders.

Method: The current study is a secondary analysis of a randomized controlled trial. After identifying factors in which men and women differed at baseline, mixed effects models were re-run using a subsampling matching strategy.

Results: Men and women differed in baseline sum of drinks and self-rated anxiety. Sex was found to moderate (absolute) response but not remission, neither when using sex-specific or common thresholds for risky drinking. However, after controlling for baseline drinking through subsampling, the difference in response was no longer significant.

Conclusion: Our findings suggest that the apparent sex-difference in treatment response was confounded by intercept-slope correlation – i.e. since men on average drank more at baseline, this offered larger room for decreasing. When conducting studies on internet interventions for addictive disorders, it is crucial to consider which outcomes to use, and how these are operationalized.

KEYWORDS

addiction, gender-difference, sex-difference, alcohol, digital interaction, cofounders

Introduction

Globally, alcohol is one of the greatest risk factors for deaths and causes substantial health loss among the world's population (1, 2). Even though there are several efficient ways to prevent and treat problematic alcohol use (3–5), only approximately 15% of individuals with alcohol use disorder seek and receive help (6). This constitutes one of the largest treatment gaps among mental disorders (7). Internet-based interventions for problematic alcohol use have emerged as an alternative to traditional face to face treatments (8–10). Availability and anonymity appear to make this option attractive to sufferers (11–14), creating a potential to attract those who would not otherwise seek help (15–17). Meta-analyses have revealed these interventions to be efficacious (8, 18), even comparable in effects to traditional face-to-face treatments (19).

However, as in traditional alcohol interventions (3–5), significant group-average decreases in drinking and symptom scores can mask substantial inter-individual variations in change (17). Past research has shown that the population of individuals with alcohol problems shows substantial heterogeneity with regards to many key characteristics (1, 20), which could reasonably be expected to moderate outcomes of an internet intervention. Indeed, matching individuals to different alcohol interventions has been a topic of some past research, dating back over twenty years (21–23).

One dimension well-known to moderate the presentation of many psychiatric disorders (24, 25), preferences for treatment (26) and even treatment outcomes (27), is sex. We recognize that it is often unclear whether studies within these field use sex (what sex one is assigned to at birth), or gender (which can be the same as what one is assigned to at birth, but also differ from it). Since this distinction is not made in most of the extant literature, we have opted to use sex consistently where the distinction is not clearly stated, since sex-specific guidelines on drinking are grounded in biological, pharmacokinetic sex-difference (28), but also recognize that this is a simplification. There is robust evidence that men, on average, drink more than women, and are over-represented in addiction care (1, 20), but whether sex is also a moderator of the effects of treatment intervention has received little attention in the extant literature. There are some studies suggesting that women with problematic alcohol use benefit from interventions that encompass recognition of gender expectations and the stigma of not living up to the results (29). A meta-analysis that investigated moderators of outcomes of internet-based alcohol interventions (30), concluded that data on sex were limited, particularly women, but that five studies that did investigate this failed to find that gender modified the difference in alcohol consumption between the trial arms. A later, individual-patient meta-analysis instead found that gender was a moderating factor, where females decreased their mean weekly standard units less than men (18). These results did not remain significant when imputing missing values, yet to what degree the imputation technique took gender into account, was not reported.

An often-overlooked dimension when examining sex-moderated outcomes of alcohol interventions, is that the outcome measure may *in-itself* be sex-moderated. As per clinical trial methodology, one needs to distinguish between *change* and *final state*. The former is captured by continuous measures such as *reduction* and *response* (typically denoting numeric decreases in symptom ratings, either absolute or relative, respectively), while the latter is captured by ratios of participants above or below a prespecified threshold, as in the case of *remission*. Importantly, the fact that men on average drink more than women, has important, but often neglected consequences for both types of outcomes. Many studies (31–33), including our own, have for example relied on national guidelines to threshold drinking into risk- and non-risky. In many countries, these guidelines are sex-specific (34), with the previous Swedish guidelines for example allowing men to drink 55% more standard units per week than women. Whether the average sex-difference in baseline drinking between men and women is equal, either in absolute or relative magnitude, to the sex-difference in remission thresholds, is not typically reported. Even if so, this assumes equidistance of change scores, i.e. that a 7-drink reduction from 22 drinks to 15, is the same as from 15 to 8. Importantly, it is mathematically impossible to match equidistance in both relative and absolute terms at the same time, assuming there is a baseline difference. This means that a baseline sex-difference may also confound numeric outcome measure such as reduction and response (henceforth used synonymously).

A baseline sex-difference in drinking may thus be a confounder in examining moderating effects of sex on treatment outcomes. Third-variable confounding (e.g. in psychiatric comorbidity) complicate the issue further. This highlights a potential concern: if studies investigate whether a treatment's effectiveness differs by gender but rely solely on the number of drinks consumed as an outcome measure, they may mistakenly interpret a difference as treatment-related. However, this apparent difference might actually stem from baseline values or cofounders rather than the treatment itself. Therefore, the hypothesis of this study is that there will be a significant difference between genders, but this difference may be explained by baseline variations and/or other confounding factors.

In sum, there are inconsistent findings in the extant literature as to whether internet-based interventions for alcohol use disorder have different effects for men and women and to our knowledge, no previous study examining sex-moderation of outcomes in interventions for a problematic alcohol use has systematically examined confounding. It remains unknown whether previous positive findings were due to confounding. To examine this important question, we performed secondary analyses of a randomized controlled trial.

Methods

Ethics

The RCT from which data was used, was approved by the Swedish Ethical Review Authority (no. 2014/1758-31/2) and all participants provided digital informed consent. Additional, secondary analyses for the purpose of the current study were also approved by the Swedish Ethical Review Authority (2022-01019-02).

Data

This study is a secondary analysis of data from a three-arm randomized controlled trial (35) which investigated the effects of a web-based alcohol program with or without therapist guidance among anonymous adult help-seekers. The participants (n=1169) were individuals with a harmful use of alcohol [defined as >15 total score in AUDIT (36), the gold standard screening test for problematic alcohol use, with good psychometric properties (37)] or alcohol dependence (defined as 3 or more ICD-10 criteria). The participants were randomly assigned to an internet-delivered CBT program as self-help (i.e. texts and videos based on motivational interviewing (38), relapse prevention (39), and behavioral self-control (40) followed by checklists and open questions), an internet-delivered CBT program with therapist guidance (the same program as the self-help iCBT group, with a therapist giving feedback on what the participants wrote and registered), or information control in a ratio of 1:1:1. Baseline data, including birth sex and gender, drinking pattern, depression, anxiety, and quality of life, were collected before the participants were randomly assigned (the full demographic variables are shown in Appendix 1). Follow-ups were conducted 3 and 6 months after allocation, with the primary outcome being self-reported standard drinks per week, with AUDIT scores serving as secondary outcome. The results showed that the therapist-guided program significantly reduced both weekly drinking and AUDIT scores more than the information control, that the self-help program significantly reduced AUDIT scores more than the information control but not weekly drinking, and that there were no significant differences in either weekly drinking or AUDIT score between the therapist-guided and self-help programs. The attrition was 49% at 3-month follow-up. For more details on participant recruitment, procedure, interventions and full outcomes, see the primary trial reporting (35).

At baseline, participants provided data on both their assigned sex at birth (man or woman), and their gender identity (several options). Concordance rate was calculated to 97.4%. Since national drinking guidelines are exclusively based on biological sex, in turn grounded in pharmacokinetic differences (28), the assigned sex at birth was used for the moderation analyses herein described.

Measures

In the current study, the primary measure used was weekly self-reported alcohol consumption, using the timeline follow-back (TLFB) method (41) with the Swedish definition of standard drinks (where one standard drink contains 12 grams pure alcohol). The TLFB data was used to calculate both (absolute) response (continuous), as well as remission, defined as low-risk drinking (categorical). Here, we used both the previous, sex-moderated Swedish guidelines (<10 for women and <15 for men), as well as the current, common Swedish guidelines (<10 for both men and women). In examining potential confounders, we examined both raw scores of the 10-item AUDIT (36) as well an adapted version omitting the three consumption items. The number of self-endorsed ICD-10 criteria for alcohol dependence (42) was also analyzed, as was self-rated anxiety using the GAD7 (43), depression measured using the MADRS-S (44), and health related quality of life, measured using the EQ5D (45).

Statistical analyses

Since our goal was to examine whether men and women had different outcomes, the current study only includes the two arms that received treatment (n=777); these arms were collapsed into one since the primary outcome study revealed no difference in outcomes between the two. Importantly, preliminary analyses revealed no three-way interactions between time, gender, and whether therapist-support was provided or not, when the two treatment arms were directly contrasted. Moreover, since the primary outcome study found that the treatment effect was observable at the three-month assessment, only two timepoints (pre- and post-

treatment) were included in the secondary analyses to simplify modeling and interpretation of parameters.

First, we used t-tests to examine which potential baseline confounders (including baseline drinking) were associated both with sex and decrease in drinking after treatment. Using a subsampling matching strategy that involved dropping either the top or bottom 10% from each sex for each respective confounder, we then re-ran our random-intercept, time × sex linear mixed effect model, using the matched subsample and compared findings. For linear mixed effects models, bootstrapped confidence intervals were calculated to account for non-normal distribution of residuals due to excess zeros post-treatment.

Next, since the association between baseline drinking and subsequent decrease in drinking was of *a priori* interest, we performed quantile regression (46), with the former as predictor and the latter as outcome, with quantiles 0.2-0.8 in steps of 0.2, and compared intercept and beta estimate quantile curves across sex. This was first done using the whole sample with sex as an additional predictor, including the interaction term. Next, analyses were repeated for each sex separately. These supplementary analyses were performed on complete data only (n=383), as not to risk neither introducing nor neglecting sex-specific associations in any imputation.

Results

Potential baseline confounders

Analyses revealed that at baseline, men and women differed significantly in mean weekly drinks and mean GAD-7 scores (see Table 1). No significant differences in mean MADRS scores, EQ5-D scores, self-endorsed dependency symptoms, or AUDIT scores (either raw, or consumption items omitted), were found.

Remission outcomes

Logistic mixed effects modeling revealed no significant time × sex effects on remission outcomes, either when using sex-specific thresholds for low-risk drinking (95% CI: -0.65—0.88) or the common threshold (95% CI: -0.37—0.944). Hence, there was no effect for which to consider confounding.

Response outcome

In the raw mixed effect model, there was a significant time × sex effect such that men decreased their drinking more than women (B=5.85, 95% CI: 2.35—9.62), departing from a greater baseline level (B=6.42, 95% CI:-8.61—4.32). Posthoc testing using estimated marginal means revealed no between-group difference at post (p=0.727). When re-running this analysis using the matched subsample, neither the baseline difference in drinking (B=0.92, 95% CI: -1.00—2.99) nor the time × sex effect (B=-0.49, 95% CI: -3.75—2.58) remained significant, suggesting that the apparent sex-difference in decreased drinking was not driven by sex per se, but by an omnibus slope-intercept correlation.

Further analyses with quantile regression using the full sample revealed a significant baseline drinking × sex effect on decreased drinking only on the 0.8 quantile (B=-0.021, 95% CI: -0.089—0.011), but this was likely due to a convergence error. Congruently, examining sex-specific intercept and estimate curves across quantiles. See Figure 1.

In examining the possible confounding effect of baseline anxiety on sex-differences in decreased drinking, we transformed the (numeric) baseline GAD-7 scores into a binary (time-invariant) predictor of high baseline anxiety using a median-split approach; this was done in order to avoid assuming linear two-way interaction effects. Although subsequent mixed effects modeling did reveal that there was indeed a significant time × anxiety effect (95% CI: 4.28–15.13), those with high baseline anxiety also had higher baseline drinking (95% CI: 2.83–9.45) and there was no significant time × anxiety × sex effect (95% CI: -11.05–3.25) that would have revealed differential treatment effects between the sexes in cases of comorbid high anxiety.

Discussion

The current study replicated past research in showing differential treatment outcomes between men and women when

TABLE 1 Baseline descriptives for women and men.

	Women (n=448)		Men (n=329)		T statistics (df=777)	
Measure	M	SD	M	SD	t	p
AUDIT	21.96	5.87	22.43	5.17	1.158	0.247
AUDIT item 4–10*	13.84	4.82	13.90	4.30	0.196	0.844
Dependence	4.23	1.31	4.31	1.36	0.861	0.389
EQ5index	1.53	11.06	1.10	5.30	-0.644	0.520
GAD7	8.97	5.50	7.77	5.15	-3.083	0.002
MADRS	18.76	8.95	18.04	9.24	-1.104	0.270
Weekly drinks	22.67	14.25	29.09	19.59	5.292	<.001

*AUDIT item 4–10 refers to the adapted AUDIT score without the three consumption items.

examining response (32), but not remission (33). However, after taking a baseline difference in drinking into account through a subsampling strategy, the difference in response was no longer significant, suggesting that this apparent sex-difference was confounded by intercept-slope correlation – i.e. since men on average drank more at baseline, this offered larger room for decreases.

Our findings stress the importance of carefully considering which outcome that best captures the desired change after treatment, as well as how other study characteristics impact outcome modeling. First, the definitions of both low-risk drinking and hazardous drinking differ greatly between countries – and in most countries, the definition of low-risk drinking also differs by sex (34). A direct consequence of this sex-based target differentiation is that women must reduce their drinking more to achieve low-risk drinking, assuming they start from the same baseline level. This, in turn, is however seldom the case (including in the current study). In several studies similar to ours, sex-specific definitions are also used as outcome, with inconsistent results. For instance, some studies on predictors of change in internet interventions have not found any significant difference among women (47) or somewhat better results among women (48). But in a study that investigated predictors of change in a similar intervention as the current study, women were found to be less likely to have low-risk consumption at follow-up compared to men when previous Swedish sex-specific guidelines were used as outcome (32). These results were replicated a few years later (49). A more recent study, exploring the effects of a web-based intervention for alcohol and PTSD symptoms among veterans, also showed that significantly fewer women achieved low-risk drinking after one-month, but also that women did not reduce their weekly drinking as much as men after six months (33). These results on continuous drinking outcome are similar to the findings in our study and the findings from the previously mentioned individual data meta-analysis by Riper et al. (18). In a British study investigating the predictors of outcomes of a mobile app targeting harmful alcohol use, the only predictor associated with the extent of alcohol reduction was how much the participant drank at baseline (50), similar to the findings in the current study.

Multiple studies have revealed that both the sensitivity and specificity of the sex-specific definitions have had large variation (51, 52). Also, there are ethical aspects in using assigned sex rather than individuals identified gender. Gender is not necessarily binary, and using uniform measures could result in more inclusive standards (53). Further, there has also been an ongoing discussion about using categorical outcomes for alcohol interventions, such as cut-off scores for heavy, or hazardous drinking (54). Unless the explicit target of an intervention is to decrease drinking to a specific, sex-indifferent level [e.g. before planned surgery (55)], capturing change after treatment with an absolute or relative response metric will circumvent this issue; should sex-differences in outcomes be of special interest, analyses should then preferably be adjusted similar as to in the current study. Of note, this applies only when considering any change in drinking as clinically meaningful: if total abstinence (i.e. a naturally occurring zero) is the only intended outcome, the entire issue of sex-specific outcomes is largely rendered irrelevant.

Strengths of the current study are that the sample is both large and inclusive. Another strength is that a multitude of confounders were considered. There are also several limitations to the study. First, we opted to focus on total number of standard units per week, since this is the most common outcome in the field of digital interventions for alcohol problems, and also the main metric (along with daily drinks) on which national drinking guidelines are based. Similar analyses could also be performed for other TLFB-derived metrics like drinking days, average number of drinks per drinking day, days with binge drinking, maximum drinks on any given day, and other clinically pertinent metrics. Second, it was deemed out of scope in the current study to examine whether popular imputation

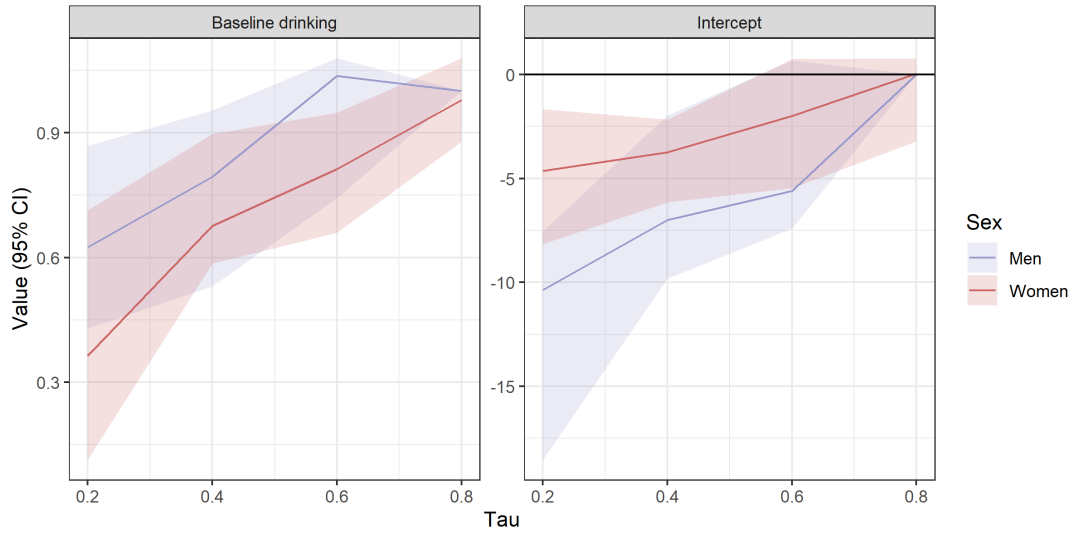

FIGURE 1
Quantile regression plots by sex. One upper bound value replaced with lower bound equivalence due to convergence error. Note that the dependent variable (decrease in drinking) was calculated by T0 scores minus T1 scores, entailing that a true decrease corresponds to a positive value.

techniques for missing data should be performed separately by sex. Third, the current study did not attempt to associate change in drinking to treatment adherence; such analyses would however need to account for the non-randomized nature of this variable, which has shown to be associated with baseline severity in at least one other study on internet interventions for addictive disorders (56).

Considering the magnitude of the alcohol problem, and that iCBT already has a proven track record of reaching and attracting large samples, there are excellent reasons to continue developing and evaluating the effects such similar interventions not only on a group-level, but also subgroup-level. In choosing which potential moderators to examine, it is important that these are anchored in evidence and proper deductions that show why these may indeed moderate outcomes, as to avoid Type 1 errors through involuntary *hypothesizing after the results are known* (57). Findings of the current study highlight the importance of carefully consider which outcomes to specify when conducting studies on internet interventions for addictive disorders which accept both sexes.

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 study was approved by Swedish Ethical Review Authority (no. 2022-01019-02). This study is secondary analysis on data from a previous study, which was also approved by Swedish Ethical Review Authority (no. 2014/1758-31/2). The participants provided their written informed consent to participate in this study. Both studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

GS: Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Visualization. MJ: Conceptualization, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. SA: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. DR: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. AB: Supervision, Writing – original draft, Writing – review & editing. PL: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, 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.

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Appendix 1

Demographics of the participants.

		Women (n=448, 57.66%)		Men (n=329, 42.34%)	Total (n=777)
Education					
	University or college	254 (56.7%0)		152 (46.20%)	406 (52.25%)
	Upper secondary school, high school or equivalent	159(35.49%)		147 (44.68%)	306 (39.38%)
	Primary school or folk school	25 (5.58%)		27 (0.20%)	52 (6.69%)
	Other	10 (2.23%)		3 (0.91%)	13 (1.67%)
Residence					
	Villa or townhouse	180 (40.18%)		140 (42.55%)	320 (41.18%)
	Rental apartment/room	159 (35.49%)		109 (33.13%)	268 (34.49%)
	Condominium	101 (22.54%)		76 (23.10%)	177 (22.78%)
	Other	8 (1.79%)		4 (1.22%)	12 (1.54%)
Living circumstances					
	With partner and child(ren)	156 (34.82%)		121 (36.78%)	277 (35.65%)
	With partner only	110 (24.55%)		99 (30.09%)	209 (26.90%)
	With child(ren) only	44 (9.82%)		11 (3.34%)	55 (7.08%)
	Alone	75 (16.74%)		63 (19.15%)	138 (17.76%)
	Other	63 (14.06%)		35 (10.64%)	98 (12.61%)
Civil status					
	Married	158 (35.27%)		127 (38.60%)	285 (36.70%)
	Cohabiting	111 (24.78%)		84 (23.53%)	195 (25.10%)
	Single	111 (24.78%)		87 (26.44%)	198 (25.48%)
	Separated/divorced	64 (14.29%)		30 (9.12%)	94 (12.10%)
	Widow/widower	4 (0.89%)		1 (0.30%)	5 (0.64%)
Source of income					
	Employment	347 (77.46%)		265 (80.55%)	612 (78.76%)
	Study allowance	29 (6.47%)		12 (3.65%%)	41 (5.28%)
	Pension	15 (3.35%)		22 (6.69%)	37 (4.76%)
	Other	57 (12.72%)		30 (9.12%)	87 (11.20%)
Country of birth					
	Sweden	413 (92.19%)		310 (94.22%)	723 (93.05%)
	Other Nordic country	18 (4.02%)		7 (2.13%)	25 (3.22%)
	Rest of Europe	11 (2.46%)		6 (1.82%)	17 (2.19%)
	Outside Europe	6 (1.34%)		6 (1.82%)	12 (1.54%)

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Network analysis of autism traits and problematic mobile phone use and their associations with depression among Chinese college students

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The current study employed network analysis to examine the relationship between symptoms from factor level about autism traits and problematic mobile phone use (PMPU) and to explore their associations with depression. We measured the above three variables in 949 college students in China with Autism Spectrum Quotient (AQ), Smartphone Addiction Scale (SAS), Center for Epidemiological Studies Depression Scale (CES-D). Central and bridge symptoms were pinpointed through the examination of centrality index. In the AQ and PMPU network, results revealed that WD ("Withdrawal"), COR ("Cyberspace-oriented relationship") and OU ("Overuse") emerged as the core symptoms. AS ("Attention switching"), CO ("Communication") and COR ("Cyberspace-oriented relationship") were the most symptoms bridging the AQ and PMPU communities, suggesting that these symptoms could serve as focal points for interventions aimed at college students with concurrent autism traits and PMPU. SK ("Social skills"), COR ("Cyberspace-oriented relationship"), CO ("Communication"), and DLD ("Daily-life disturbance") were most strongly associated with depression. In addition, future research should consider various measurement tools and methods to investigate the location of AD ("Attention to detail"), because AD was an isolated symptom in the flow network of depression.

KEYWORDS

autism traits, problematic mobile phone use, depression, network analysis, college students

1 Introduction

In individuals with autism spectrum disorder (ASD), deficiencies in social interaction, interpersonal communication, repetitive and restrictive behaviors and interests are characteristic features (1). These traits span from clinical to subclinical manifestations, initially identified in the immediate family members indicating genetic susceptibility (2).

However, nowadays, personal and subclinical traits linked with autism have been demonstrated to be prevalent in the general population (3). Meanwhile, with further studies, researchers have found co-morbidity between clinical and sub-clinical symptoms and other disorder (4). Depression, anxiety, attention deficit hyperactivity disorder (ADHD), and substance-related addictive are typically the most common comorbidities, followed by several other disorders (5).

Addiction behaviors, especially problematic internet use, commonly occur in individuals with autism spectrum (6). Until now, there is strong evidence linking autistic symptoms with problematic internet use. For instance, individuals with ASD often show more severe symptoms of problematic internet use compared to those without ASD (7–9). Furthermore, college students or adults with higher autism traits are also at increased risk of developing problematic internet use (10, 11). On the one hand, this association could be attributed to rigid and limited behaviors, interests of the ASD phenotype (12). On the other hand, while the internet offers opportunities that assist individuals with ASD in overcoming offline challenges, their preoccupation with it may originate from limited interpersonal skills in face-to-face interactions (13, 14).

The link between autism traits and problematic mobile phone use (PMPU) has not received as much attention as problematic internet use. Here, we use the term "PMPU" because it is not formally classified in DSM-5 or ICD-11. PMPU involves excessive mobile phone use with addiction symptoms like tolerance, withdrawal, and continued use despite negative effects (15, 16). Despite mobile phones being common tools for internet access, PMPU is rising globally (17), with China notably affected (18). To date, few studies have explored the relationship between autism traits and PMPU. Research by Lu (19) suggested that elevated autism traits may increase the risk of PMPU among college students. Our research aims to investigate which aspects of autism traits are most associated with PMPU, paralleling previous research on problematic internet use.

Recent studies have shown that both autism traits and PMPU are associated with mental health issues, such as depression (20, 21). Higher levels of autism traits are linked to difficulties in face-to-face interactions, leading to challenges in interpersonal relationships and overall well-being, including increased depression (22). Similarly, PMPU has been consistently associated with psychological distress (e.g., depression) in various cross-sectional (23, 24) and longitudinal studies (25, 26). While some researchers proposed a unidirectional causal relationship between PMPU and depression (26, 27), others argued for a bidirectional association (28, 29). In summary, limited research has examined the concurrent impact of autism traits and PMPU, necessitating further exploration of their interaction with depression and underlying mechanisms.

Recent advances in methods allow us to use network analysis to understand mental disorders. In network modeling, mental syndromes and disorders are seen as intricate networks of symptoms that reinforce each other (30, 31). By measuring connections between symptoms, network models can identify key symptoms driving a disorder, thus pinpointing intervention targets (32). This approach overcomes the limitations of traditional psychopathology, which viewed symptoms as static constructs and potentially obscured important associations and distinctions. In network analysis, symptoms are nodes and their relationships are edges. Strength and expected influence (EI) are key centrality measures to identify pivotal symptoms (33). Bridge symptoms, those most linked with other conditions, offer insights into comorbid psychiatric mechanisms (34). Identifying these symptoms can uncover the underlying mechanisms of disorders and propose potential strategies for treatment. Network analysis has been applied to various concurrent psychiatric conditions, including autism spectrum disorder and internet addiction (35).

In this study, we aimed to: (1) analyze the network structure of autism traits and PMPU from factor level among Chinese college students in the general population; (2) identify central and bridge symptoms within the AQ and PMPU networks in non-ASD Chinese college students; (3) compare gender differences in AQ and PMPU network characteristics in the general population; and (4) identify symptoms directly and indirectly related to depression in the AQ and PMPU networks using the "flow" function. Given the exploratory nature of our study, specific hypotheses were not formulated. Our goal is to better understand the complex relationship between autism traits and PMPU, then offering insights that could inform interventions and support strategies for individuals with autism traits vulnerable to PMPU.

2 Methods

2.1 Participants

The study, conducted from September to October 2023 at a university in southwest China, aimed to investigate specific issues among university students. A total of 1029 questionnaires were distributed, resulting in 949 valid responses (436 males and 513 females), with a high effective response rate of 92.23%. The participants were from a general population of university students, spanning the ages of 19 to 23 (M = 19.12). Strict ethical principles were followed to protect participant privacy and rights throughout the data collection process.

2.2 Measures

Autism traits were measured using Chinese version of the Autism-Spectrum Quotient (AQ) tool (36), originally proposed by Baron-Cohen (37). The AQ included five factors, each factor with 10 questions, comprising social skills (e. g., "I find social situations easy"), attention switching (e. g., "New situations make me anxious"), attention to detail (e. g., "I often notice small sounds when others do not"), communication (e. g., "I am good at social chit-chat"), and imagination (e. g., "I find making up stories easy"). Each question was assessed ranging from 1 (definitely agree) to 4 (definitely disagree). A higher score on the AQ indicates a greater severity of autism traits. In this study, the Cronbach's alpha was calculated to be 0.73.

The Smartphone Addiction Scale (SAS), introduced by Kwon (38), was utilized to measure the degree of problematic mobile phone use. With 33 items, the SAS encompassed six factors, comprising daily-life disturbance (e. g., "Missing planned works due to smartphone usage"), positive anticipation (e. g., "Feeling calm or cozy while using a smartphone"), withdrawal (e. g., "Won't be able to stand not having a smartphone"), cyberspace-oriented relationship (e. g., "Feeling great meeting more people via smartphone use"), overuse (e. g., "Using my smartphone longer than I had intended"), and tolerance (e. g., "Always thinking that I should shorten my smartphone use time"). Each item was rated from 1 ("strongly disagree") to 6 ("strongly agree"), with higher scores indicating greater severity. The Cronbach's alpha was 0.93 in present study.

The subjects' depression symptoms were surveyed by using the Center for Epidemiological Studies Depression Scale (CES-D), developed by Radloff (39). The scale comprised 20 items, rated on a scale between 1 ("rarely or none of the time") and 4 ("most or all of the time"). Elevated total scores suggested greater severity of depression symptoms. In our study, the scale demonstrated strong internal consistency, with a Cronbach's alpha of 0.91.

2.3 Data analysis

Before network estimation, Pearson's correlation between factors was estimated using SPSS 27.0.

2.3.1 Network estimation

The analysis was conducted using R-studio software. The study employed the Graphical Gaussian Model (GGM) to construct the network of autism traits and PMPU based on polychoric correlations (40). Each node in the network represents a specific symptom, connected by edges that indicate positive (blue) or negative (red) associations. Edge thickness (i.e. the edge weight) reflects the strength of the partial correlation coefficient. The network was refined using Lasso regularization (EBICglasso method) to optimize explanatory power by systematically reducing non-significant edges to zero. Visualization utilized the "qgraph" package, and node predictability was assessed using the "mgm" package (41). Additionally, the flow network exploring depression with autism traits and PMPU was estimated (42).

2.3.2 Network centrality and stability

To evaluate node significance in the AQ and PMPU network, we used the "qgraph" package to analyze centrality indices: expected influence (EI; The sum of edge weights from the node to all other nodes including both positive and negative connections) (43); and bridge expected influence (bEI; The summed edge weights that a node to all other symptoms connecting two clusters of psychiatric symptoms) (34). Higher values of these indices indicate greater importance within the network. Subsequently, the accuracy and stability of network edges and centrality indices were assessed using the bootstrap method from the "bootnet" package (40).

2.3.3 Network comparison

In line with earlier research suggestions, we explored variations in network attributes related to gender using the "NetworkComparisonTest" package. The Network Comparison Test (NCT) was employed to evaluate disparities, such as edge weight distributions, overall strength, and individual edges between networks based on gender, applying the Holm-Bonferroni correction for multiple test p-values (43).

3 Results

3.1 Correlation analyses

Specific values of correlation analyses for the study variables are shown, accompanied by a correlation heat map (Figure 1) through the utilization of ChiPlot (https://www.chiplot.online/). Within the PMPU network, every symptom demonstrates a positive correlation with one another. Meanwhile, it is worth noting, one symptom ("Attention to detail") and the other four symptoms have a negative correlation within the AQ network. In the whole network, contrary to correlation between three symptoms ("Attention switching", "Communication", "Social skills") of AQ and each symptom of PMPU, two symptoms ("Attention to detail", "Imagination") of AQ and each symptom of PMPU have more negative edge.

3.2 Network structure

Figure 2 illustrates the network of AQ and PMPU symptoms among Chinese college students. The ring-shaped chart visually represents the predictability of individual symptoms, revealing an average predictability of 0.372. This suggests that neighboring nodes often explain approximately 37.2% of the variation in each node. Concrete predictability value of each node is shown in Table 1. In the symptoms of the AQ community, the strongest positive edge was between SK ("Social skills") and AS ("Attention switching"), followed by the edges between SK ("Social skills") and CO ("Communication"). In the PMPU community, the edge between COR ("Cyberspace-oriented relationship") and WD ("Withdrawal") was the strongest positive one, followed by the edges between nodes DLD ("Daily-life disturbance") and TR ("Tolerance"). In the symptoms of the AQ and PMPU network, the strongest edge was CO ("Communication") and COR ("Cyberspace-oriented relationship"), followed by the edges between AS ("Attention switching") and WD ("Withdrawal"). The edge weights for the AQ and PMPU network can be found in Supplementary Table S1.

Figure 3 shows the EI and bEI metrics of symptoms in the AQ and PMPU network. The most central symptom was WD ("Withdrawal"), followed by COR ("Cyberspace-oriented relationship") and OU ("Overuse") (Figure 3, left), implying these three symptoms are pivotal and exert significant influence in unraveling the framework of the AQ and PMPU network. The most core symptoms bridging the AQ and PMPU communities

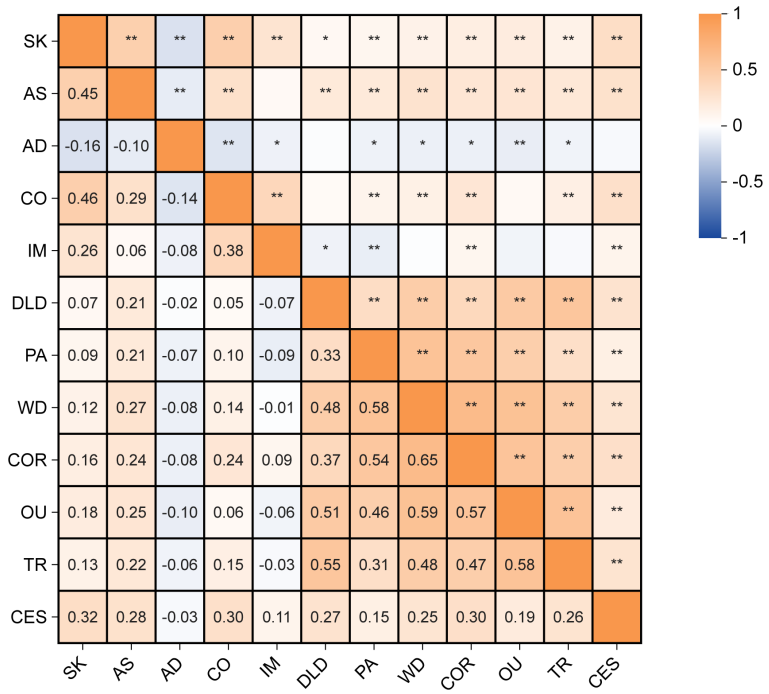

FIGURE 1
The correlation heat map of autism traits, problematic mobile phone use and depression. *p <.05, **p <.01. SK, Social skills; AS, Attention switching; AD, Attention to detail; CO, Communication; IM, Imagination; DLD, Daily-life disturbance; PA, Positive anticipation; WD, Withdrawal; COR, Cyberspace-oriented relationship; OU, Overuse; TR, Tolerance; CES, Depression.

were AS ("Attention switching"), CO ("Communication") and COR ("Cyberspace-oriented relationship") (Figure 3, right part).

3.3 Network accuracy and stability

At CS coefficients of 0.75 for EI and 0.672 for bEI, it indicates that when 75% or 67.2% of the sample are discarded, the EI and bEI networks will not change significantly (Figure 4). The outcomes of the bootstrap 95% CIs for edge weights by bootstrapped stability test are depicted in Supplementary Figure S1, and the findings of estimation of edge weight difference by bootstrapped difference test are illustrated in Supplementary Figure S2. According to the bootstrapped difference test for EI and bEI, the most influential nodes exhibited significant differences from the remaining symptoms (Supplementary Figures S3, S4).

3.4 Network comparisons based on gender

Previous findings indicated that the autism traits and PMPU levels had significant differences in gender among the general population, thus we compared network model between gender (3, 17). The network structure diagram of males and females is shown in Supplementary Figure S5. Analysis of network structures in male (n = 436) and female (n = 513) college students did not yield significant differences in network global strength (3.78 for males; 3.97 for females; S = 0.18, p = 0.655) or edge weights (M = 0.12, p = 0.570; Supplementary Figure S6).

3.5 Flow network of depression

The flow network diagrams about depression with autism traits and PMPU symptoms were created to explore which of their symptoms were related to depression (Figure 5). Because AD ("Attention to detail") was identified as an isolated node, lacking connections to other nodes within these two networks, our study excluded it from the estimation of other symptoms. In the flow network of depression, the node SK ("Social skills") emerged with the most robust positive correlation to depression, followed by the COR ("Cyberspace-oriented relationship"), CO ("Communication"), and DLD ("Daily-life disturbance").

4 Discussion

To the best of our understanding, this investigation represents the initial exploration that probed into the network of AQ and PMPU symptoms from a factor structure level, and their association with depression in Chinese college students. In the AQ and PMPU network, the most central symptom was WD ("Withdrawal"), followed by COR ("Cyberspace-oriented relationship") and OU ("Overuse"). These symptoms are very crucial for understanding

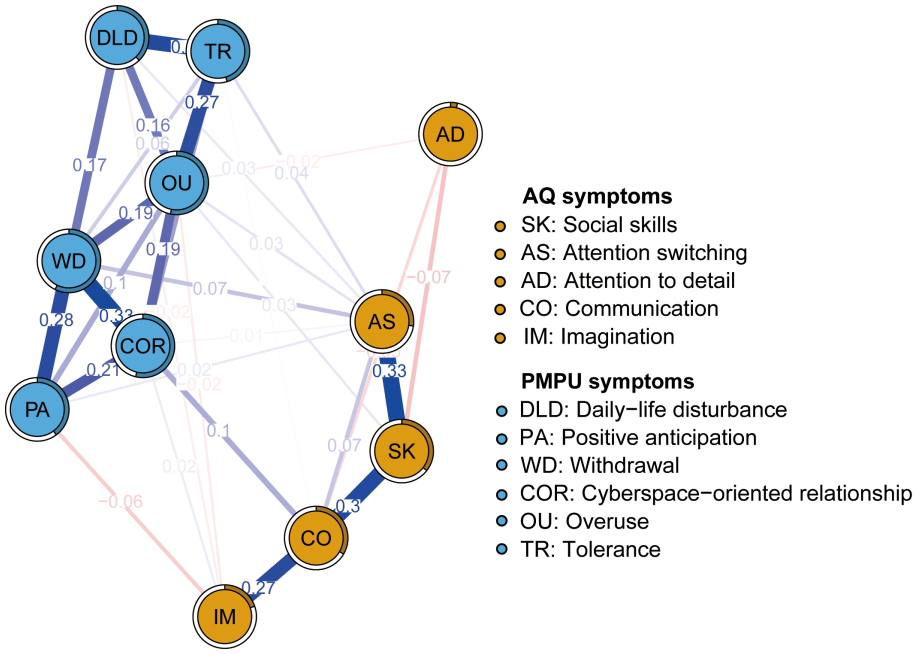

FIGURE 2
Network structure of autism traits and problematic mobile phone use.

the network structure of AQ and PMPU in the sample. Furthermore, the core ridge symptoms linking AQ and PMPU communities were AS ("Attention switching"), CO ("Communication") and COR ("Cyberspace-oriented relationship"). We also noted that SK ("Social skills"), COR ("Cyberspace-oriented relationship"), CO ("Communication"), and DLD ("Daily-life disturbance") were the most associated with depression. Notably, AD ("Attention to detail") did not exhibit connections with other symptoms in the flow network of depression.

This was the first report to highlight its centrality in the AQ and PMPU network model. WD ("Withdrawal") and OU ("Overuse") were two of the central symptoms in this study. This finding aligns with the outcomes of an earlier investigation carried out among adolescents in Japan (35). They also found "Failure to cut down the time spent online" and "Staying online longer than you intend" were the central symptoms in the internet addiction network among a clinical and non-clinical sample with ASD. Extensive literature has reported excessive time use in both ASD and non-ASD individuals (9, 10, 44). These outcomes are consistent with addiction's neurological pathways, often understood as a cycle of binging, withdrawal/negative affect, and preoccupation/anticipation (45). WD ("Withdrawal") and OU ("Overuse") correspond to the first two stages.

COR ("Cyberspace-oriented relationship") was another central symptom indicating that individuals with higher autism traits prefer interaction through mobile phones over real-life situations. Social interaction's significance in the relationship between PMPU and autistic traits could explain outcomes (19). Individuals with higher autism traits often face challenges in interpersonal interactions due to inhibitions and perceived incompetence, making them vulnerable. Despite their aversion to direct social interactions, there is no clear association with a desire for social exclusion. As such, they may gravitate towards the safer realm of online communication, which offers them opportunities to address these challenges (13, 14). This preference for online interactions could strain traditional social bonds over time, possibly contributing to addiction to online games as a means of avoiding real-life interaction.

The bridge symptoms, AS ("Attention switching"), CO ("Communication") and COR ("Cyberspace-oriented relationship"), should be central targets for therapeutic interventions addressing PMPU in individuals with higher autism traits. AS ("Attention switching") was the most core bridge symptom, suggesting that attention deficiency is a key factor in PMPU symptoms among these individuals. One possible explanation is that ADHD and autism traits have strong comorbidities in genes, neurobiology, and behaviors (46), with related symptoms extending into adulthood (47). While not confirmed across the broader population, individuals with ASD exhibit a higher risk for problematic internet use and ADHD symptoms (44). Additionally, cognitive deficits like inhibition control may cause difficulty in controlling internet use once engaged.

Another two key bridge symptoms were CO ("Communication") and COR ("Cyberspace-oriented relationship"). Difficulties in communication and social interaction in individuals with higher autism traits interact with problematic internet use (10, 11). However, the modes of communication and interaction among individuals with higher autism traits are not entirely clear. A recent study found individuals with ASD using electronics for fewer social activities than general population while they engage in face-to-face communication

TABLE 1 Descriptive statistics of measurement factors.

Factor abbreviation	Factor content	Mean (SD)	Expected Influence	Predictability
SK	Social skills	2.45 (0.46)	1.754	0.355
AS	Attention switching	2.62 (0.30)	2.089	0.273
AD	Attention to detail	2.53 (0.38)	-0.903	0.035
CO	Communication	2.13 (0.36)	1.729	0.334
IM	Imagination	2.12 (0.33)	0.438	0.197
DLD	Daily-life disturbance	3.80 (1.02)	2.467	0.391
PA	Positive anticipation	3.47 (0.85)	2.441	0.407
WD	Withdrawal	3.37 (1.07)	3.221	0.572
COR	Cyberspace-oriented relationship	3.03 (0.90)	3.244	0.540
OU	Overuse	3.99 (1.01)	3.030	0.532
TR	Tolerance	3.56 (1.11)	2.787	0.454

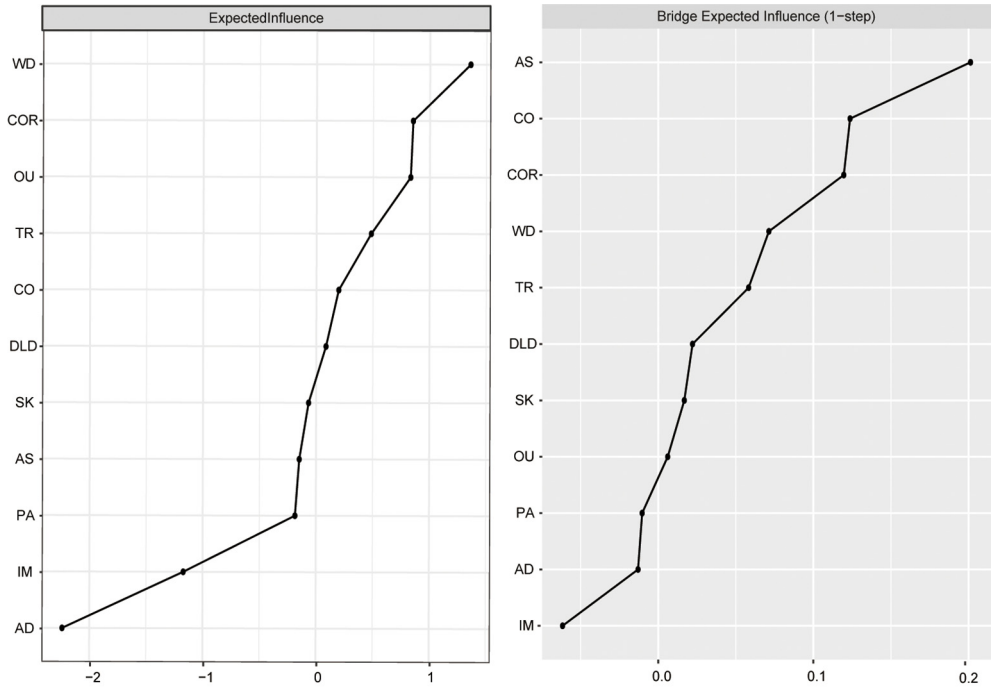

FIGURE 3
Centrality indices: EI and bEI values.

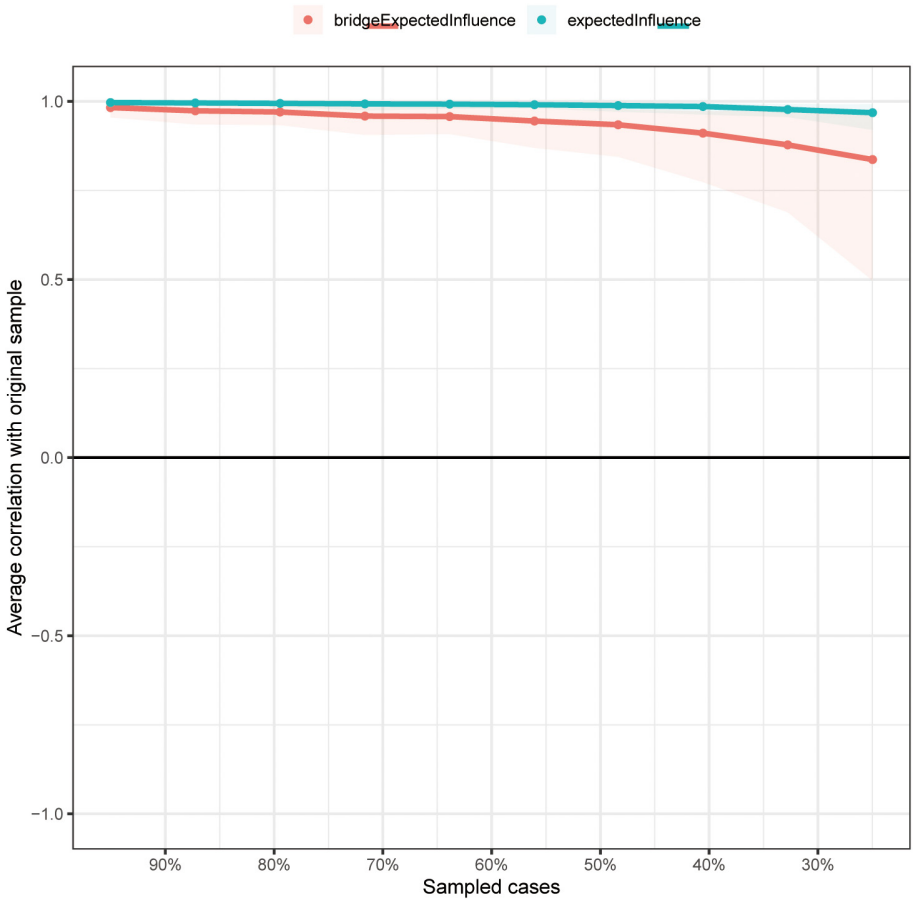

FIGURE 4
The stability of EI and bEI indices using case-dropping bootstrap.

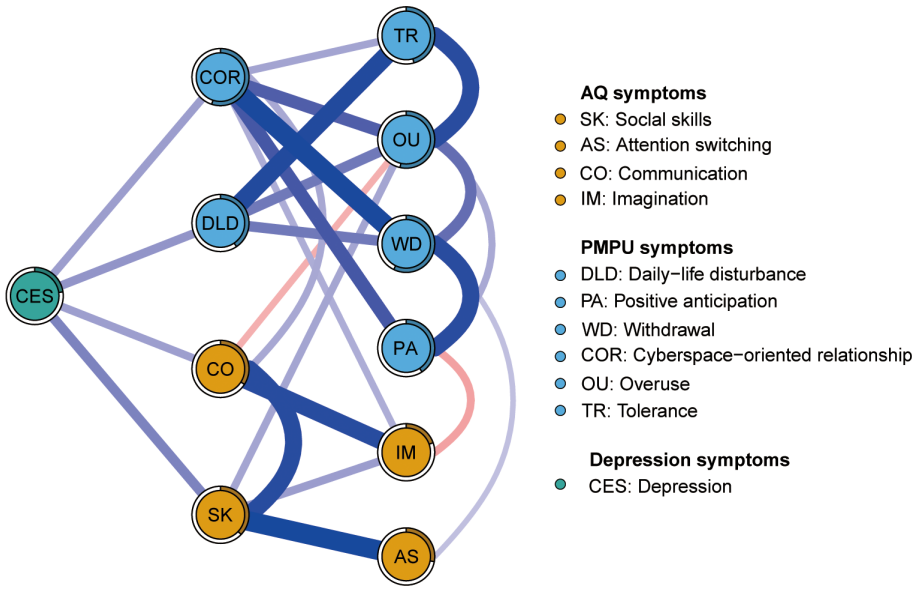

FIGURE 5
Flow network of depression.

under protest (7). The result may seem counterintuitive. Yet, interestingly, the preference for communication for individuals with ASD is dependent upon how close and accepting the relationship is (48). In consideration of complex modes of communication, future studies should compare communication styles between individuals with higher autism traits and those with ASD to improve communication levels (49).

In the flow network, SK ("Social skills"), COR ("Cyberspace-oriented relationship"), CO ("Communication"), and DLD ("Daily-life disturbance") showed the strongest associations with depression compared to other symptoms. SK ("Social skills") was found to have the strongest association with depression, consistent with recent research linking social ability to increased depression (22). Individuals with social deficit showed reduced risk avoidance, heightening susceptibility to frustration and depression. COR ("Cyberspace-oriented relationship") and CO ("Communication") showed the second strongest association with depression, highlighting that while smartphones can compensate for offline communication deficits, excessive use may exacerbate negative emotions (26, 28). DLD ("Daily-life disturbance") ranked third in association with depression. Previous studies indicated that depression negatively impacts sleep quality, leading to heightened stress and affecting overall life satisfaction (26, 28).

Notably, AD ("Attention to detail") emerged as an independent symptom in the flow network, showing no significant associations with other symptoms. Correlation analyses across the AQ and PMPU network similarly revealed a negative or zero correlation with other symptoms. This aligns with autism diagnostic criteria, which distinguish between social and non-social domains. AD ("Attention to detail") represents a non-social dimension within the AQ scale used in general population studies (50). However, our findings diverge from previous research indicating no positive association between internet preoccupation and repetitive behaviors in college students (12). This discrepancy suggests a need for careful interpretation, possibly influenced by measurement limitations in assessing Autism-Spectrum Quotient traits.

Our findings underscore the importance of targeting bridge symptoms such as AS ("Attention Switching"), CO ("Communication"), and COR ("Cyberspace-oriented relationship") in designing therapeutic interventions for individuals with higher autism traits experiencing PMPU. Interventions that enhance attention regulation, such as mindfulness training or cognitive-behavioral therapy (CBT) focused on improving executive functioning, could be particularly effective in mitigating PMPU symptoms related to attention deficits (14). Similarly, social skills training programs could address CO ("Communication") challenges by equipping individuals with practical strategies for face-to-face interactions, reducing reliance on cyberspace relationships (35). For COR ("Cyberspace-oriented relationship"), interventions might include psychoeducation on balanced technology use and guided exposure to real-life social interactions to build confidence and resilience (19). These approaches could reduce the negative emotional impacts associated with PMPU, such as depression, while also promoting healthier social and behavioral patterns. Future research should evaluate the efficacy of such interventions to further refine these strategies and ensure their applicability.

This study involves several limitations. Firstly, it does not clarify the similarities and differences in PMPU between individuals with ASD and those without ASD, as it primarily focuses on the general population. Future studies should aim to include samples from both groups. Secondly, symptoms are not entirely specific at the factor level due to the inclusion of multiple items within a single factor. Finally, our findings provide only a preliminary exploration of the overlapping symptoms between autism traits and PMPU. Given the varied motivations for smartphone use, these overlapping symptoms may differ significantly. Therefore, further research should consider specific aspects of problematic mobile phone use, such as video consumption, gaming, or social media engagement, to provide a more comprehensive understanding.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

GL: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. YL: Conceptualization, Project administration, Writing – review & editing. ZC: Investigation, Data curation, Writing – review & editing. SZ: Investigation, Writing – review & editing. LM: 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.2024.1521453/full#supplementary-material

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Blended digital health intervention for adolescents at high risk with digital media use disorders: protocol for a randomised controlled trial within the Res@t-Consortium

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Background: Digital media use disorder (DMUD) is a prevalent problem among young people, which can result in adverse consequences and functional impairments across multiple domains of life due to a persistent inability to regulate one's use, which can lead to the development of psychological problems. In particular, children and adolescents who live in families that are part of the child and youth welfare system and receive support services are considered to be at high risk of developing mental disorders. It is less likely that these families will choose a therapeutic setting for the treatment of DMUD. The objective is to reduce DMUD-related symptoms and improve media use behaviour through the implementation of an app-based training programme.

Methods: The efficacy of Res@t digital, initially conceived as an adjunct to child and adolescent psychiatric treatment, is to be evaluated for n= 32 children and adolescents with a media use disorder or at risk of developing this disorder, and their families enrolled in child and youth welfare services. The efficacy of the app will be evaluated in a randomised controlled trial with a waitlist control group. The primary outcome is the reduction of DMUD symptoms over a 20-week period following the onset of app training. Secondary outcomes include EEG measurements and changes in standardised psychopathological variables.

Discussion: Should the Res@t app prove efficacious when compared to a waitlist control group, it would constitute an evidence-based intervention for the

treatment of DMUD in children and adolescents. For high-risk families, the app could serve as a motivational tool to prompt action regarding potential DMUD and facilitates access to therapeutic facilities.

Clinical trial registration: https://drks.de, identifier DRKS00033379.

KEYWORDS

digital media use disorders, digital health intervention, youth at high risk, adolescents, child and youth welfare services

1 Introduction

1.1 Background and rationale

As time progresses, the public healthcare system is confronted with ever new phenomena of cultural and technological progress. Such advances have been seen in the recent past in the digital media sector, where availability and attractiveness of digital media use are increasing worldwide, apparently not without harbouring health risks. So-called "Digital media use disorders" (DMUDs) refer to behavioural addictions in which the use of digital media leads to a dependency and persistent impairment of psychosocial functioning over a certain period of time (1–3). This is an umbrella term that can be used to summarise different types of media (e.g. computer, smartphone, television), usage patterns (e.g. playing video games or gaming, watching video streams, social networking) and connectivity (online on the internet or offline). Global prevalence rates (with considerable regional differences) from an international meta-analysis by Meng et al. (4) show that 17.4% of the population have a social media addiction and 6.0% a game addiction. Furthermore, 27.0% have a smartphone addiction and 14.2% have an internet addiction. As a result, the first specifically described DMUD, "Gaming Disorder" has been included in the 11th version of the International Classification of Diseases (ICD-11; icd.who.int/browse/2024-01/mms/en) with the code 6C51 and the extension predominantly online (.0) or offline (.1). 6C51 is met with all of the following criteria related to gaming behaviour: impaired control over temporal or situational aspects, neglect of other interests or activities in favour of the behaviour, persistent behaviour despite evidence of harmful consequences, manifested over a considerable period of time (continuously or in recurring episodes for e. g. 12 months), and significant impairment in areas of psychosocial functioning (e.g. family, friends or education). Other DMUDs such as social media use disorder and streaming disorder are listed under the code 6C5Y with the generic term "Other specified disorders due to addictive behaviours". If the criteria for a DMUD are not met, but risky user behaviour is present, this can be coded with QE22 for "Hazardous Gaming" or QE2Y "Problems with other specified health-related behaviours".

With maturing brains, adolescents are a particularly vulnerable group for DMUD due to their still developing cognitive control and responsiveness to reinforcing systems, which are widely used in digital media today (5). Especially impulsivity and depressive rumination facilitate Internet addiction in adolescents (6). The younger generation growing up with information and communication technology is also frequently exposed to digital media, which leads to multidimensional interactions, particularly with regard to the causes of and attempts to cope with psychiatric disorders (7–11). Digital media presents a number of advantages: lower barriers when it comes to difficulties in social communication and interaction, immersion allows the "escape" from stressful events into an alternative reality and compensates for the lack of reinforcement in everyday life (12, 13). In particularly severe cases, DMUD gives rise to the phenomenon of "hikikomori", initially documented in Japan. Hikikomori individuals isolate themselves in their homes, only venturing out on rare occasions. This represents a severe form of social withdrawal in which digital media play a significant role (14).

Social factors, including poverty, social exclusion, a lack of parental competence and supervision, and inconsistent parental behaviour, have been identified as playing a role in the development of Internet Gaming Disorder (IGD) (15). In particular, in school-aged children, family factors such as family violence and poor parental care have been identified as major risk factors for IGD (16). It is often the case that children growing up in environments more susceptible to the aforementioned risk factors are referred to child and youth services for care. The provision of child and youth welfare services plays a crucial role in the well-being of children. Children placed in child welfare systems are often characterised by a high prevalence of behavioural problems that are often associated with multiple family problems, such as parental mental health issues or substance use disorders (17, 18). It is recommended that young people be provided with more accessible psychological support services that offer measures to promote healthy coping mechanisms (19). In light of the recent coronavirus pandemic, the development of appropriate programmes to prevent and reduce behavioural addictions such as DMUDs is of particular importance (20–22).

In order to meet the specific needs of adolescents with emotional disabilities and youth at special risk, the incorporation of multimedia elements and electronic performance support systems in prevention and intervention for these subgroups has proven to be more effective than traditional interventions (23, 24). In particular, for the treatment of

depression and anxiety, internet-guided and unguided digital E-mental health interventions have been demonstrated to be an effective form of treatment for adolescents, with the potential to reduce symptoms and promote well-being (25–27). A blended approach, which combines online intervention with guided contact during digital training, offers multiple advantages. This is particularly relevant from the perspective of young people and their families in the context of gaming disorder (28, 29). As part of the Res@t-Consortium (www.uke.de/projekte/resat), an app was developed that is tailored to the specific needs of young people with DMUD, serving as a digital counterpart to the CBT-based Res@t offline therapy program. The goal of this study is to demonstrate feasibility and effectiveness of the intervention for adolescents at high risk with DMUD or hazardous use pattern, who are to be reached in a blended approach and motivated to participate and train with the app. Adolescents at high risk was defined as 1) family was approached by the youth welfare service because of family-related problems (e.g. long-standing conflicts, family violence, parents or youth seeking help, school absenteeism), or 2) the family had received a recommendation for contacting the youth welfare service (from school, child and adolescent psychiatry, police), or 3) the adolescent had special needs for schooling (e.g. attention problems, hyperactivity or learning difficulties). The theoretical embedding and assessment of the effectiveness of the treatment is based on Prochaska's Transtheoretical Model of Change in Behaviour (29, 30), which is one of the most frequently used models in this field. It describes an experience of different phases of change, which begins with the stage of Precontemplation (lack of intention to change behaviour) and leads through Contemplation (intention to change behaviour in the future) to the stage of Preparation (first steps towards behaviour change), Action (performing the behavioural change) and Maintenance (maintaining the behaviour) stages. The respective individual stage is an important factor to consider when evaluating the impact of interventions.

Moreover, for a more comprehensive understanding of DMUD, its neurobiological underpinnings of these behavioural addictions should be investigated, in addition to measures of experience and behaviour. This kind of multidimensional approach is not only in line with the Research Domain Criteria (RDoC) approach, which considers psychiatric disorders through various constructs on several units of analysis (31), but also offers a chance to detect neurobiological predictors of effective treatment. In order to follow the transdiagnostic approach of the RDoC, not only DMUD diagnoses, but also hazardous use patterns that do not yet justify a DMUD diagnosis, as well as a wide range of comorbidities are included in this study. Especially in the view of DMUD as dysfunctional coping with e.g. emotional stress, "pure" DMUD diagnoses (no comorbidities or precursors of the diagnosis) would exclude parts of the target group in need of support and distort the therapeutic effect of the intervention in real practice. For this reason, no comorbidities are excluded, with the exception of those that make participation in the study impossible. The domains investigated are addiction-related, such as positive valence (reward responsiveness, learning, and valuation) and cognition (cognitive control). In order to take the neurobiological basis into account and investigate fundamental mechanisms, the analysis levels circuits and physiology are examined by means of electroencephalography (EEG) in addition to self-reports, behaviours and paradigms.

1.2 Objectives and trial design

In accordance with the Res@t consortium's plan, the efficacy and effectiveness of the digital health intervention "Resource-Strengthening Training for Adolescents with Problematic Digital-Media Use and their Parents" (Res@t digital) will be examined. The aim of this training is to reduce the mental health problems associated with DMUD in adolescents and to strengthen parental self-efficacy. In order to shed light on various aspects of such a novel care programme, high-risk groups within child and youth welfare services are being investigated in this additional study alongside a main study (31). As an addition, this study supplements the main study by recording potential neurophysiological changes using EEG.

Participants will be randomised-controlled with a 1:1 allocation ratio into two arms of parallel groups, consisting of an intervention group (IG) and a waitlist control group (CG). Both groups receive the treatment as usual (TAU), meaning the standard child and youth welfare programme, while the IG additionally receives the Res@t digital intervention during the study period. Each subject in the CG will be given the opportunity to receive the training after full participation following the last data collection.

Our trial aims to test the hypothesis of the superiority of Res@t digital combined with child and youth welfare service through a greater reduction in the symptoms of the most prominent DMUD or hazardous use pattern in the individual adolescent, compared to child and youth welfare service alone. Primary hypothesis: Res@t +TAU reduces symptoms of specific DMUD in adolescents compared with TAU alone, measured as a group-by-time interaction over 5 measurement points from screening to a 10-week follow-up. Secondary hypotheses: a) Res@t+TAU reduces symptoms of specific DMUD in adolescents as assessed by their parents compared with TAU alone, measured as a group-by-time interaction over 5 measurement points from screening to a 10-week follow-up. b) Res@t+TAU reduces symptoms of specific DMUD in adolescents assessed by authorised personnel compared with TAU alone, measured as change from screening to post-intervention. c) Res@t+TAU will have a beneficial influence on several observation-based constructs related to DMUD in adolescents (improved readiness to change and sleep quality), in parents (improved life satisfaction and family self-efficacy) and in both adolescents and parents (reduced stress levels and improved family functioning and mindfulness) compared with TAU alone, measured as change from baseline to post-intervention. d) Res@t+TAU reduces DMUD typical or potential markers in the EEG compared with TAU alone, measured as change from baseline to post-intervention.

2 Methods

2.1 Study setting

The study presented here is one of two additional studies accompanying the main Res@t study (32). It is carried out by the

University Medical Centre Rostock and will be conducted in the urban area of Rostock and the district of Rostock (approx. 200 and 220 thousand inhabitants) in the German state of Mecklenburg-Western Pomerania. We are planning recruitment for the period from May 2024 (first participant in) to March 2025 (last participant in). The study presented here takes an approach, where child and youth welfare providers identify adolescents who are at particularly high risk for DMUD. We expect this group to be low on motivation, calling for a more blended approach wherein extended face to face contacts are necessary to maintain compliance.

2.2 Eligibility criteria

Inclusion criteria for participants:

- Recipients of or the recommendation to receive child or youth welfare or have special needs for schooling.
- 10 to 19 years of age (WHO definition of adolescence).
- Cut-off for disordered or hazardous media use in the Gaming Disorder Scale for Adolescents/for Parents (GADIS-A/-P), Social Media Disorder Scale for Adolescents/for Parents (SOMEDIS-A/-P) and Streaming Disorder Scale for Adolescents/for Parents (STREDIS-A/-P) is reached (see primary outcome).
- Fulfilled criteria for disordered or hazardous media use according to ICD-11 criteria (6C51, 6C5Y, QE22, QE2Y).
- Written informed consent is given (for adolescents under the age of 16, the informed consent of the legal guardian is also necessary).

Or

- Are a parent/legal guardian of a participant fulfilling the criteria above.

Exclusion criteria for participants:

- Acute severe psychiatric disorders with a symptom burden that prevents participation in the study (i. e. psychotic disorders or disorders due to substance use).
- Pervasive developmental disorders (i. e. autism spectrum disorder).
- Acute suicidality.
- Inability to understand the study instructions (i. e. severe disorders of speech or language, diminished intelligence or lack of german language skills).

2.3 Recruitment

Access to the sample is mainly via the employees of child and youth welfare services and facilities. They establish contact between potential participants and our study team. As soon as contact has been established, the study team takes on all tasks relevant to the study and the employees of the child and youth welfare services have no further obligations. Furthermore, recruitment takes place in the district and meeting centres of the city of Rostock, as these are places that are frequented by adolescents from problematic backgrounds on the one hand and are accompanied by child and youth welfare staff in these facilities on the other. Finally, the work groups on child and adolescent psychiatry and addiction disorders in the city and district of Rostock are also included by the corresponding psychiatry coordinators and potential participants who are in child and youth welfare services are recruited. Once the study team has received the contact details of willing participants from the youth and social services, the participants and legal guardians provide informed consent to the study team. The study team then administers questionnaires at all-time points (screening, baseline, interim, post-intervention, follow-up 1 and 2) and conducts the clinical interviews (baseline and post-intervention).

2.4 Intervention

The IG receives the app-based resource-strengthening adolescent and parent training programme (Res@t digital) after completing baseline assessment. The training consists of 10 modules: a first week training start following two weeks of psychoeducation, five weeks of specific contents, a one week relapse prevention and finally a booster session. A new module is activated every week, whereby the booster module is only activated 5 weeks after module 9 in week 15 of the training. The specific contents differ for adolescents (Res@t-A) and parents (Res@t-P), with the exception of the module on communication. Adolescents receive modules with specific contents on health and sleep hygiene, self-care, dealing with emotions and social relationships, while parents receive modules on developmental tasks and parenting styles, implementing rules, applying rules and family health. Depending on the type of dominant DMUD or hazardous use pattern, the content of the app is adapted to it. In addition, participants can use a diary in which they can enter daily times of media use, mood, activities, daily structure and sleeping times. For a detailed description of the training and the app contents, see Paschke et al. (32). Participation by parents is encouraged but not mandatory. Participants in the CG are assessed in the same way as in the IG using questionnaires and EEG (see outcomes below), but receive Res@t-A/P only after completing the last assessment and on an optional basis.

2.5 Outcomes

2.5.1 Primary outcome

The primary outcome is the difference in the severity of specific DMUD or hazardous use pattern between IG and CG within 20

weeks of enrolment, measured at 5 time points (screening, interim, post-intervention, follow-up 1 and 2) at 5-week intervals. It is assumed that the group using the app (IG) shows bigger decreases in DMUD or hazardous use pattern compared to the group without (CG). In the event that an individual shows more than one DMUD or hazardous use pattern, the severity is operationalised by the supervising study team with the most severe type of DMUD or hazardous use pattern (gaming, social media or streaming). In order to assess gaming, social media and streaming as key areas of digital media consumption, the GADIS-A/-P, SOMEDIS-A/-P and STREDIS-A/-P are used to identify disordered or hazardous media use (33–38). All three questionnaires are based on the ICD-11 criteria for gaming disorder and other specified disorders due to addictive behaviours, which are specified here as social media use disorder and streaming disorder. The questionnaires consist of 4 items cognitive-behavioural symptoms (CBS) of problematic media use, 5 items negative consequences (NC) and one item on the frequency of these difficulties, with the exception of STREDIS-A/-P, in which CBS and NC account for 3 and 6 items respectively. If the cut-offs for CBS and NC are reached and the time criterion is met, disordered media use is indicated. If only the cut-off for CBS is reached, but not for NC, hazardous media use is assumed. If only NC but no CBS is present, another mental disorder may be present. In addition, a clinical interview to diagnose the presence of disordered or hazardous media use according to ICD-11 is assessed (at Screening and Post-Intervention) by authorised personnel. In order to take the high-risk sample into account, the assessment times were set more closely compared to the main study (32) and the baseline, post-intervention and follow-up assessments were supplemented by a measurement with GADIS-A/P, SOMEDIS-A/P and STREDIS-A/P interim (5 weeks after baseline in the middle of training) and an additional follow-up (5 weeks after the end of training and 5 weeks before the original follow-up). The interval of the DMUD questionnaires is therefore shortened from every 10 weeks to every 5 weeks (see participant timeline).

2.5.2 Secondary outcomes

As for secondary outcomes we assume that the use of the app will have a beneficial influence on several observation-based constructs related to DMUD. For psychopathological symptoms of the adolescents and perceived stress by adolescents and parents we assume a bigger decrease for the IG. The Strengths and Difficulties Questionnaire (SDQ) measures the psychopathological symptom burden of adolescents using five items on each of five subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationships problems and prosocial behaviour (39–41). The self-assessment exists from 11 years of age and a parallel external assessment by parents from 4 years of age. A slightly age-adapted version is available for 18 year olds and older. Adolescents are asked about the last six months in the screening and about the last month in the post-intervention. Parents only complete the SDQ-f at screening and were also asked about the last six months. The perceived stress of adolescents and parents within the past month is assessed using the 10 items of the Perceived Stress Scale (PSS-10) (42, 43). Analogous to the Transactional Theory of Stress and Coping, the scales Perceived Helplessness (primary appraisal; assessment of the situation and its stressors) and Perceived Self-Efficacy (secondary appraisal; assessment of resources and coping strategies) are formed (44). The phrasing was slightly adapted for adolescents in this study. The PSS-10 is measured at pre- and post-intervention.

On the other hand, we expect a greater increase in the IG for family functioning, family communication and mindfulness in adolescents and parents as well as an increase in family self-efficacy and quality of life of the parents. Family functioning is assessed using the five items giving the questionnaire its name: Adaptability, Partnership, Growth, Affection and Resolve, referred to as Family APGAR (45, 46). The family communication scale (FCS) measures "the act of sharing ideas, participating in decision making, and expressing feelings among members as a family unit" through ten items by self-assessment (47–49). Family functioning and communication are self-assessed by adolescents and parents. Family self-efficacy in parenting is measured by parents in the questionnaire with the same name (Familiäre Selbstwirksamkeit [FSW]) using nine items (50). The Mindful Attention Awareness Scale (MAAS-5) measures mindfulness (a state of mind characterised by receptivity, in which the subject is able to observe their thoughts, feelings and surroundings non-judgementally, thereby being present in the moment) in five items in adolescents and parents (51, 52). The Ulm Quality of Life Inventory for Parents (ULQIE) is used to assess parents' life satisfaction over the last seven days (53). The 29 items of the ULQIE are partially incorporated into the subscales of physical and daily functioning, satisfaction with family support, emotional strain due to the child's illness, self-development and well-being. All of the above mentioned questionnaires are collected at baseline and post-intervention.

With regard to the stages of change, we expect that adolescents in both groups will initially be in the stages of precontemplation or contemplation. After the intervention, more adolescents in the intervention group should be in the action stage than in the control group. Moreover, the influence of adolescent motivation should be explored as these variables should be modelled as covariates of change in DMUD or hazardous use pattern. Based on Prochaska's Transtheoretical Model of Change in Behaviour (29, 30), we identify the stage of behaviour change in adolescents by means of the questionnaire for the assessment of readiness to change (Fragebogen zur Erfassung der Veränderungsbereitschaf [FEVER]) (54). The scales Precontemplation, Contemplation, and Action, each with eight items, are collected through self-assessment at baseline and post-intervention by the adolescents. The Preparation and Maintenance stages are not included in the questionnaire, as these are practically less informative.

Further, we expect an increase in sleep quality and a decrease in sleepiness and severity of insomnia among adolescents. Adolescents self-assess their sleep quality through the nineteen items of the Pittsburgh Sleep Quality Index (PSQI), their sleepiness in eight

items of the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), and their severity of insomnia in seven items of the Insomnia Severity Index (ISI) (55–59). The sleep quality assessed by the PSQI can be determined from a combination of 7 components: subjective quality, latency (time required to fall asleep), duration of sleep, efficiency (ratio between time in bed and actual sleep), disturbance, use of sleep medication, and daytime dysfunction (e.g. due to fatigue or low activity level). The PSQI and ESS-CHAD reflect assessments over the last four weeks, while the ISI reflects assessments within the last two weeks.

To measure neurophysiological characteristics of brain activity, an EEG is used. For this purpose, a resting-state EEG (rsEEG) with 5 minutes of eyes open and 5 minutes of eyes closed is recorded at the beginning, followed by approx. 6 minutes of an oddball paradigm. A 30-minute sequence of a favoured media related activity (e.g. gaming) follows. The EEG is therefore carried out in the participants' homes using a mobile EEG. The EEG ends with another rsEEG identical to the one at the beginning of the recording (see Figure 1). 45 minutes are planned for the preparation of a 32-channel montage. The oddball task is active visual and administered as described in Kappenman et al. (60). Participants are presented with the letters A, B, C, D and E in random order in a trial. In each block, one of these letters is defined as a target, which must be distinguished from the nontargets by pressing the up and down arrow keys using the dominant hand. There are a total of 5 blocks, each with 40 trials, in which each letter is presented 8 times. Each stimulus is presented for 200 ms and the inter-stimulus interval is 1,200 to 1,400 ms. The first EEG is carried out in the period from screening to the start of training and a further EEG after the end of training.

There is already a modest number of EEG studies that investigate neurophysiological measures of DMUD in the EEG and qualify as potential biomarkers of DMUD and its therapy response (61, 62). As these studies showed, people with IGD exhibit reduced power in the beta frequency band and increased power in the lower frequency bands of delta and theta in the rsEEG. In addition, a hyperconnectivity of the default mode network (DMN) and reward/salience network (RSN) appeared in the rsEEG of IGD subjects (63). In the domain of ERPs, the components of N2 and P3 showed increased negativity and positivity as markers of IGD (64, 65). Therefore we assume several EEG parameters to be associated to the intervention:

- Decreasing theta/beta-ratio in Power Spectral Density of the rsEEG.
- Decreasing connectivity within the DMN and RSN.
- Decreasing negativity N2 in the oddball task.
- Decreasing positivity P3 in the oddball task.

2.5.3 Additional variables

Additional variables collected concern socio-demographic information, media rules, adolescent and parental media use, parental symptom burden and parenting style (66). Parental symptom burden is assessed at baseline by self-assessment of the nine items in the Patient Health Questionnaire (PHQ-9) for depressiveness and the seven items in the Generalizied Anxiety Disorder Scale (GAD-7) for anxiety within the last two weeks (67–70). Parents assess their parenting style in the Parenting Style Inventory (Eltern-Erziehungsstil-Inventar [EEI]) on the ten-item scales love, discipline, autonomy and on the seven-item additional scales cooperation with partners and cooperation with school, teachers and carers also at baseline (71). The religiosity scale is not surveyed. In addition, data on app usage behaviour is collected in regard to the number of app usage sessions, days, weeks, quests started, quests completed, mindfulness exercises observed, calendar entries, the relative completion of modules and the complete training.

2.6 Sample size

Calculating the sample size for the primary outcome of the change in the severity of DMUD or hazardous use pattern between the intervention and control group over 5 measurement points is based on a mixed ANOVA with repeated measures and a within-between interaction. Assuming an effect size of 0.20, alpha error

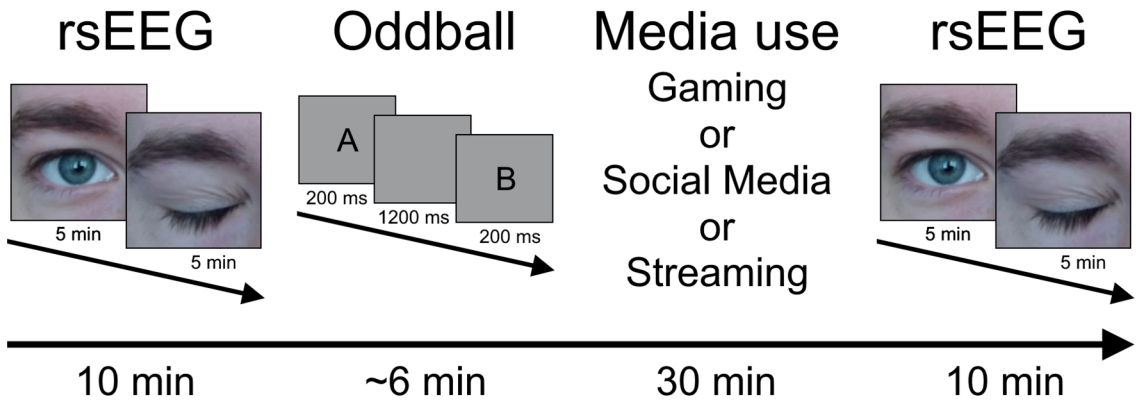

FIGURE 1
Procedure for the EEG assessment. rsEEG, resting-state EEG.

probability.05 and power.8, GPower 3.1.9.7 calculated a total sample size of 32 subjects with 16 per group. Due to the high-risk conditions of the target group, we assume a drop-out rate of 50%, which results in a total of 64 subjects to be recruited.

2.7 Incentives

We expect the adolescents in our target sample of child and youth welfare programme to be less motivated than the participants from the clinical setting of the main study and are therefore pursuing a stronger and more consistent incentive strategy. Potential adolescent study participants already receive a €5 voucher for the screening, regardless of whether they will take part in the study or not. Adolescents receive €10 each for the complete baseline and post-intervention questionnaires and €5 each for the shorter GADIS/SOMEDIS/STREDIS-A questionnaires at interim, follow-up 1 and 2. The closer timing of the assessments results in a higher reward frequency.

2.8 Assignment of interventions and blinding

Allocation to IG or CG is carried out by our consortium partner at the University Hospital Schleswig-Holstein Kiel, whose participants are randomised by ourselves in return. A computer-generated central randomisation list with variable block lengths, will be created by a project-independent employee of the Institute of Medical Biometry and Epidemiology at the University Medical Center Hamburg-Eppendorf. Since the CG does not receive any sham treatment and the randomisation as well as the installation and implementation of the app is coordinated by the study team, there is no blinding.

2.9 Data collection, management, and analysis

The data is collected continuously using the Res@t app with the ISO-certified Embloom platform as the backend. Furthermore, the PsychoEQ programme, which facilitates the collection of questionnaire data via mobile phones, tablets and personal computers, is employed. All data pertaining to participants will be pseudonymized.

Descriptive statistics are presented separately for each group and for the total sample. The data will be analysed using IBM SPSS 28 Statistics. A complete-case analysis will be conducted on the main outcome variable, the specific DMUD score, which will be evaluated at five points in time: baseline, interim, post-intervention, follow-up 1, and follow-up 2 (see Table 1 and Figure 2). In order to determine whether there are notable differences in the impact of the treatment, a mixed ANOVA will be used, with the specific DMUD scores serving as the dependent variable and time and group serving as the within-subject factors and between-subject factors, respectively.

In the event of missing values, a sensitivity analysis will be conducted in accordance with intention-to-treat principles. Missing values will be assumed to be missing at random and handled using the multiple imputation method. A baseline-adjusted linear mixed model will be calculated with random intercept for patient, group and timepoint as well as their interaction as main effects and respective baseline value as covariate. The threshold for statistical significance of the primary outcome is set at $p < 0.05$. Further outcomes are analysed in an exploratory manner.

3 Discussion

The Res@t digital intervention aims to close a gap in the treatment and care of adolescents with DMUD and their parents. The aim of this study is to test the effectiveness and efficacy of an evidence-based training programme for high-risk groups such as adolescents in child and youth services. In this kind of setting, the DMUD or hazardous use pattern is embedded in highly stressed adolescents and family members, whereby awareness of the problem and motivation for treatment as well as family support regarding the DMUD are likely to differ from adolescents who are undergoing primarily treatment. It is possible that the highly individual circumstances and conditions in which children and young people supported by youth and social services live may limit the generalisability of the findings on the usability and efficacy of Res@t digital. The same applies to the subsample concerning school-related difficulties. Nevertheless, the efficacy of Res@t digital will be further examined in the main study (32) of outpatients diagnosed with DMUD, recruited from psychotherapeutic and psychiatric practices and hospitals. To address the presumably harder-to-reach high-risk target group, we use a high dose of reinforcement in the form of gift cards every five weeks. It is hypothesised that this reinforcement system will be effective when used in conjunction with a blended approach, in which personal contact is intended to ensure the successful implementation of the intervention. Study staff will then support adolescents and parents with motivational barriers, technical issues, or organising app implementation. Combining digital and face-to-face components to address the various challenges of participation may be innovative, but not universally effective. For example, adolescents with high levels of stress or low motivation may benefit less from the digital component, or face-to-face contact may be a barrier for those who are socially averse. Furthermore, the lack of blinding in a waitlist design could lead to participants in the IG being influenced by expectations of their group allocation, leading to placebo effects and biased results. Participants in the CG could feel disadvantaged, which could change their perception and response to the use of digital media. In addition, the lack of intervention could lead to reduced adherence if participants feel inappropriately treated. Another limitation is the acquisition of neurophysiological parameters

TABLE 1 Measurement time points.

Time point/Content	t_0	t_1	t_2	t_3	t_4	t_5
Enrollment						
Informed Consent	X					
Eligibility Screen	X					
Interventions						
Res@t digital app intervention		◆	—	◆		
Standard child and youth welfare	◆	—	—	—	—	◆
Assessment						
Adolescents						
Sociodemographics	X	X				
Media use	X					
GADIS-A, SOMEDIS-A, STREDIS-A	X		X	X	X	X
SDQ		X		X		
PSQI		X		X		
ISI		X		X		
ESS-CHAD		X		X		
PSS-10		X		X		
Family APGAR		X		X		
FCS		X		X		
MAAS-5		X		X		
FEVER		X		X		
Clinical interview	X			X		
EEG		X		X		
Parents						
Sociodemographics		X				
Parental media use		X				
Media rules		X		X		
GADIS-P, SOMEDIS-P, STREDIS-P	X		X	X	X	X
SDQ-f	X					
PSS-10		X		X		
Family APGAR		X		X		
FCS		X		X		
PHQ-9		X				
GAD-7		X				
EEI-R		X				
FSW		X		X		
ULQIE		X		X		
MAAS-5		X		X		

Time points: t_0 = Screening (< week 0), t_1 = Baseline (week 0), t_2 = Interim (week 5), t_3 = Post-intervention (week 10), t_4 = Follow-up 1 (week 15), t_5 = Follow-up 2 (week 20). GADIS-A, Gaming Disorder Scale for Adolescents; SOMEDIS-A, Social Media Disorder Scale for Adolescents; STREDIS-A, Streaming Disorder Scale for Adolescents; SDQ, Strength and Difficulties Questionnaire; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; ESS-CHAD, Epworth Sleepiness Scale - Children and Adolescents; PSS-10, Perceived Stress Scale; Family APRGAR, Family Functionality; FCS, Family Communcation Scale; MAAS-5, Mindfulness Attention Awareness Scale; FEVER, Questionnaire for the Assessment of Readiness to Change; EEG, Electroencephalography; GADIS-P, Gaming Disorder Scale for Parents; SOMEDIS-P, Social Media Disorder Scale for Parents; STREDIS-P, Streaming Disorder Scale for Parents; SDQ-f, Strength and Difficulties Questionnaire – External Assessment; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder Questionnaire; EEI-R, Parenting Inventory - Revised; FSW, Parental Self-Efficacy; ULQIE, Ulm Quality of Life Inventory for Parents of Chronically Ill Children.

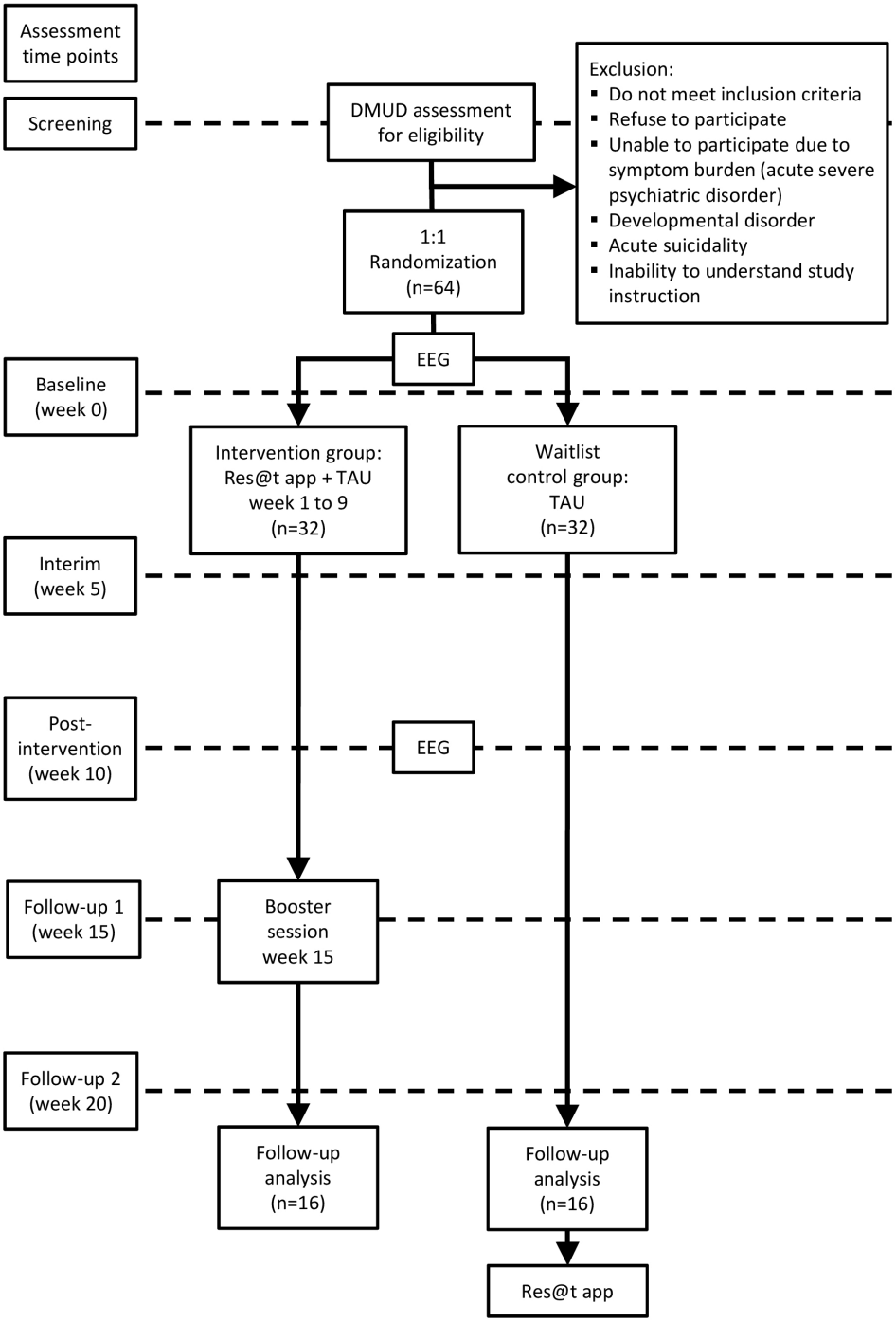

FIGURE 2
Study flowchart of participants. DMUD, digital media use disorder; EEG, Electroencephalography; TAU, treatment as usual.

using EEG in the participants' homes rather than under laboratory conditions. This results in a higher validity of the media use measures, but may lead to an overall lower reliability caused by environmental factors. Despite the limitations mentioned, a positively evaluated Res@t app can represent a low-threshold treatment option compared to outpatient and inpatient treatment and serve as a motivational tool to facilitate entry into further treatment in a therapeutic setting. The evaluation will also show whether the combination of Res@t digital with the blended approach and reinforcement strategies has the potential to be an effective treatment option for hard-to-reach adolescents at high-risk, underscoring the need for real people to accompany the digital.

Ethics statement

The studies involving humans were approved by Ethikkommission an der Medizinischen Fakultät der Universität Rostock, St.-Georg-Str. 108, 18055 Rostock Deutschland. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

OL: Visualization, Writing – original draft, Writing – review & editing, Investigation. LW: Writing – original draft, Writing – review & editing, Investigation, Visualization. MK: Writing – review & editing, Resources. SL: Writing – review & editing, Methodology. CW: Writing – review & editing, Resources. AF: Writing – review & editing. KP: Writing – review & editing, Conceptualization, Funding acquisition, Software. RT: Writing – review & editing, Conceptualization, Funding acquisition, Software. OR: Conceptualization, Funding acquisition, Methodology, Project administration, 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

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Effectiveness of digital self-care device for at risk drinking problems: focus on individuals at risk for alcohol-related issues

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Aims: This study was conducted to verify the effectiveness of using digital self-care devices in reducing alcohol-related problems among high-risk alcohol users in community addiction-related institutions.

Methods: Data were collected from 257 adults in Korea aged 18 and over (157 men and 60 women), examining their level of alcohol use disorder and the usage of digital self-care devices (such as the number of days alcohol consumption was logged, continuous days of sobriety, feeling, alcohol cravings, alcohol probability, etc.).

Results: The results confirmed that the severity of alcohol use disorder significantly decreased before and after the use of digital self-care devices, as analyzed by a t-test (M = 5.239, SD = 10.121, t = 6.945, df = 179, P = .000***). Additionally, a machine learning analysis (random forest) was conducted to explore the factors that most influence the reduction in alcohol risk levels among participants. The analysis revealed that the factor "continuous days of sobriety" had the most significant impact on the reduction of alcohol risk levels. The predictive accuracy of this factor was demonstrated using an ROC curve (AUC = 0.724). Subsequently, a multiple regression analysis was conducted to explore the factors influencing continuous days of sobriety. The results indicated that age and the logging of sobriety days had a significant impact, with the logging of sobriety days emerging as the most influential factor.

Conclusion: These results suggest that in reducing alcohol consumption and achieving successful sobriety, it may be more important to maintain continuous sobriety rather than the total number of sober days. Additionally, it is necessary to identify the key factors that help maintain continuous sobriety. Understanding

which elements need to be fulfilled through digital self-care devices to sustain continuous sobriety is also essential.

Clinical trial registration: https://cris.nih.go.kr/cris/search/detailSearch.do?search_lang=EM&focus=reset_12&search_page=M&pageSize=10M&page=undefinedM&seq=16267M&status=5M&seq_group=16267, identifier, KCT0005135.

KEYWORDS

alcohol use disorder, digital self-care device, continuous days of sobriety, machine learning, ROC curve, multiple regression

1 Introduction

The mental health care system underwent significant changes due to COVID-19, and the effectiveness of telemedicine services had already been actively studied for a decade before the pandemic (1–3). The primary function of early telemedicine services was remote consultations and prescriptions. Regarding the anticipated concerns about patients' attitudes toward receiving remote care, it was found that over 80% of participants who received consultations via video or phone had excellent or good attitudes toward the service (2). Based on these findings, as of 2021, 98% of psychiatrists in the United States were providing remote consultations to their patients (4). In addition to remote medical services, technologies such as digital therapeutic devices or self-management apps, which involve more active patient participation through web or app-based platforms, have been continuously developed. These advancements have further validated the necessity of telemedicine services (5, 6).

Most of the self-directed therapeutic devices developed are based on Cognitive Behavioral Therapy (CBT) as the primary treatment concept and offer services such as worksheets, self-assessment and monitoring, daily check-ins, and feedback on assessment results (7, 8). Additionally, recent studies have shown that structured psychological self-care using digital therapeutic devices for individuals with Alcohol Use Disorder (AUD) involved 8 weeks of patient-driven digital interventions, which demonstrated effectiveness in most participants (9).

According to a meta-analysis by Sliedrecht et al. (10), which reviewed literature from 2000 to 2019 on various relapse factors in patients with Alcohol Use Disorder (AUD), several key factors were identified as contributors to relapse. These include psychiatric comorbidities, addiction severity, alcohol cravings, negative emotions, use of other substances, and health and social factors. Notably, recent research has established a link between cravings and reduced alcohol consumption levels (11). Additionally, demographic factors have also been studied in relation to relapse and treatment outcomes, with job stability or marital stability being suggested as factors that contribute to successful treatment (12–14). Most studies focus on exploring the factors that lead to alcohol relapse or the development of Alcohol Use Disorder rather than therapeutic factors (15–18).

According to De Witte et al. (19), recent developments in the field of healthcare and welfare categorize remote healthcare services into three forms: (1) online management technologies, (2) user-driven expert interventions, and (3) new technology formats (e.g., VR, AR, wearables). Gan et al. (20) found that when comparing individuals who undergo digital therapy entirely in a self-directed manner to those who receive some level of intervention, the latter group showed slightly higher treatment efficacy. The device used in this study can be seen as a hybrid of (1) online management technologies and (2) user-driven expert interventions, primarily employed by patients visiting community centers but also including monthly in-person consultations. Specifically, the approach uses approximately 80% of (1) online management technologies and about 20% of (2) expert interventions, minimizing expert involvement while allowing users to self-direct most of the services.

Therefore, the purpose of this study is to verify the effectiveness of a pre-developed digital self-care device by recommending its use to patients who are at high risk for alcohol abuse, or who were previously patients, and who visit community centers. Additionally, assuming the effectiveness is validated, the study aims to identify the characteristics of factors that influence the reduction of alcohol use disorder risk, thereby deriving therapeutic factors for alcohol use disorders. The research questions of this study can be summarized as follows:

1. Verification of the effectiveness of the pre-developed digital self-care device.
2. Exploration of the characteristics of factors that influence the reduction of alcohol use disorder risk, assuming the effectiveness is validated.

2 Methods

2.1 Participant

This study utilized data obtained from the clinical validation of a project requested by the National Center for Mental Health under the Ministry of Health and Welfare in Korea. The study aimed to verify the effectiveness of a digital self-care device and to explore

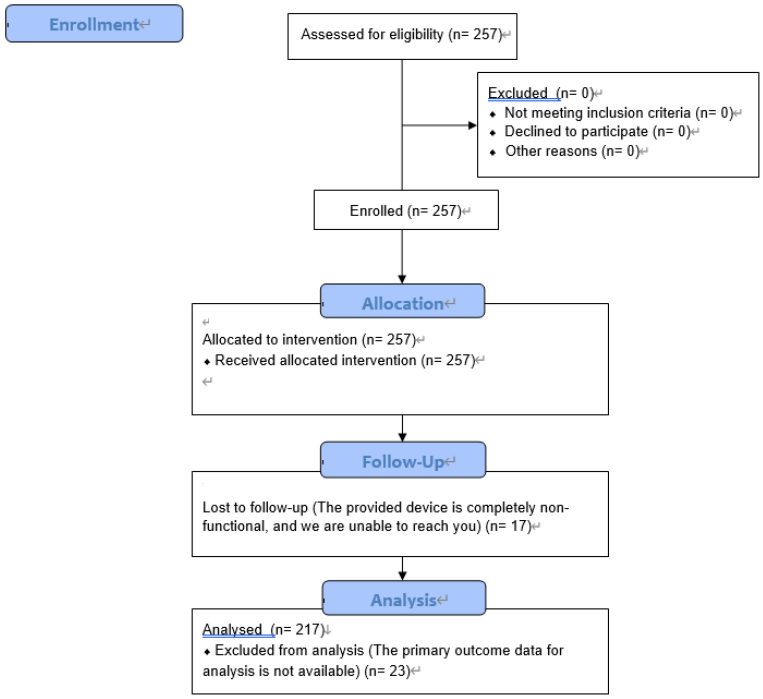

FIGURE 1
The clinical trial enrollment, assignment, tracking, and analysis process.

predictive factors that could effectively reduce alcohol-related risks, leading to sobriety. A total of 257 participants were involved in the clinical validation, recruited from approximately 20 community addiction-related institutions across Korea. Participants were compensated with an in-kind reward equivalent to 100,000 KRW. The compensation was provided via direct bank transfer, with 50,000 KRW paid prior to the clinical trial and the remaining 50,000 KRW paid upon its completion. The majority of participants were aged between 40 and 60, and consent was obtained from them regarding participation in the clinical trial and the use of their information. After the validation process, participants were provided with a nominal incentive, and data from 40 individuals who dropped out during the study were excluded Figure 1. Consequently, the final sample consisted of 217 participants with demographic information as follows: the average age was 50 years (M = 50.51, SD = 12.63), with 157 males (72.4%) and 60 females (27.6%). The AUDIT-K was used as the measurement tool to identify the drinking status of participants, with the overall alcohol consumption levels categorized as follows: 38 participants (19%) were in the low-risk drinking group, 58 participants (25.3%) were in the high-risk drinking group, and 121 participants (55.8%) were in the alcohol use disorder group Table 1. Among the 40 dropouts, the demographic breakdown by gender showed 27 males and 13 females, with an average age of 63 years (M = 63.17, SD = 4.73). No significant differences were observed in other characteristics, but the average age was approximately 12.66 years higher than that of the 217 participants who completed the study.

This study was approved by the Institutional Review Board (IRB) of the hospital to protect the rights, safety, and welfare of human subjects (IRB no. CHUNCHEON 2022-08-012). In addition, informed consent was obtained from participants to participate in the study and to use their information. Furthermore, this study utilized secondary analysis based on data collected from a clinical trial conducted in 2020, and the clinical trial registration number is as follows (Clinical Trial Registration Number (CRIS No.): KCT0005135).

2.2 Procedures

2.2.1 Digital self-care application

The digital self-care device app used in this study is provided to individuals identified as high-risk for alcohol use by the Community Addiction Management Integrated Support Center. The app includes features such as a sobriety diary, self-assessment (for risk group classification based on the SBIRT stages), treatment schedule (to check the schedules of treatment programs registered in community centers), communication forums (recovery journal, sobriety communication meetings, and request-for-help communication), and support materials (card news, information about treatment facilities, and educational videos).

Upon the first launch, the app utilizes SBIRT and PPC to accurately assess the user's condition and facilitate appropriate intervention. SBIRT (Screening, Brief Intervention, and Referral

TABLE 1 Demographic and clinical characteristics of participants (N = 217).

Characteristic	N (%) or Mean ± SD
Gender	
Male	154 (70.0%)
Female	60 (27.6%)
Missing value	3 (1.4%)
Age (years)	50.51 ± 12.63
Marital Status	
Single	65 (30.0%)
Married	82 (37.8%)
Other	66 (30.4%)
Missing value	4 (1.8%)
Education Level	
High school or below	138 (63.5%)
Bachelor's degree	61 (28.1%)
Graduate degree	14 (6.4%)
Missing value	4 (1.8%)
Primary Diagnosis	
Low-risk drinking	38 (19%)
High-risk drinking	58 (25.3%)
Alcohol use disorder	121 (55.8%)

to Treatment) is an early intervention method designed to prevent issues in high-risk individuals from worsening by intervening early. PPC (Patient Placement Criteria) assesses six domains to determine the appropriate level of treatment based on the patient's condition. Additionally, users can self-report and manage their condition through the sobriety diary feature, as shown in Table 2, and are required to use it consistently over a four-week period. The app also provides useful information through "online sobriety communication meetings" and resources like "card news and educational videos" to support sobriety efforts.

As a condition for using this device, the individual must first register for alcohol treatment at a community center. Once registered, the individual will receive an ID and password from their treatment provider to access the device. The user then progresses through the SBIRT stages within the device. If the user is classified as high-risk or above through the AUDIT-K within the SBIRT and consents to receive brief intervention, the PPC process will be initiated. The results of the PPC are then communicated to the user's treatment provider, who uses this information to assist in creating an Individualized Service Plan (ISP) when the user visits the center.

In this study, only the results from the AUDIT-K within the SBIRT process and the measurements obtained through the sobriety diary were used for analysis, excluding the PPC results.

TABLE 2 Digital self-care measurement factors.

Factors	Measurement Method	Unit of Measure
Sobriety Status, Days of Sobriety	Yes/No	Yes = 1 No = 0
Continuous Sobriety Days	From the first Sober day to the next	
Feeling	Likert 1-7	1 = Very Bad 7 = Very Good
Craving Level		1 = Very High 7 = Very Low
Probability of Drinking		
Days of Sobriety Journaling	Sobriety Status, Today's Feeling, Today's Alcohol Carving, Likelihood of Drinking Today, Medication Status Completed sobriety diary at time of writing	

2.3 Measures

2.3.1 Alcohol use disorder screening test

The Korean version of the Alcohol Use Disorders Identification Test (AUDIT-K) was used to determine the presence and severity of alcohol use among the participants in this study (21, 22). The AUDIT-K is a self-report measurement tool consisting of 10 items that assess an individual's level of alcohol consumption (e.g., "How often do you have a drink containing alcohol?"). Each item evaluates factors such as the frequency and quantity of alcohol intake, as well as experiences within the past year. Higher total scores indicate a greater likelihood of alcohol use disorder. The Cronbach's alpha for AUDIT-K is 0.92 (21), demonstrating high reliability.

2.3.2 Digital self-care measurement factors

In this study, the digital self-care device allows for the monitoring of participants' sobriety status. Participants can manage their condition by self-reporting their status through the sobriety diary feature within the device. The self-reporting measurement factors are composed of Yes/No questions and a 1-7 point Likert scale, as outlined in Table 2.

2.4 Data analysis

2.4.1 Analysis method

In this study, SPSS Statistics version 27.0 was used to primarily analyze the effectiveness of the digital self-care device through t-tests. The analysis involved comparing the mean scores of the Alcohol Use Disorders Identification Test (AUDIT) administered before and after using the digital self-care device to determine the effect size. Additionally, to identify the main effects of the digital self-care device, the mean AUDIT scores of participants who fully engaged with the device's content during the participation period were compared with those who did not engage at all.

TABLE 3 List of variables used in statistical analysis.

Analysis Methods	Variables Used	Variables Type
t-test	AUDIT-K Score (pre-post)	Continuous
	Overall Device Performance Rate(pre-post)	Categorical
Random Forest	Decreased AUDIT-K Score	Categorical
	Sex	Categorical
	Age	Continuous
	Marriage	Categorical
	Craving Level	Continuous
	Probability of Drinking	Continuous
	Feeling	Continuous
	Days of Sobriety Journaling	Continuous
	Rate of Sobriety Journaling	Categorical
	Total Sobriety Days	Continuous
	Total Sobriety Rate	Categorical
	Continuous Sobriety Days	Continuous
	Continuous Sobriety Rate	Categorical
Multi-Regression	Continuous Sobriety Days	Continuous
	Age	Continuous
	Sex	Categorical
	Today's Feeling	Continuous
	Today's Alcohol Carving	Continuous
	Likelihood of Drinking Today	Continuous
	Days of Sobriety Journaling	Continuous

To explore the factors that reduce the risk of alcohol use disorder, the R programming language was used with a machine learning technique, specifically the random forest algorithm. Finally, multiple regression analysis was conducted to analyze the characteristics that influence factors reducing the risk of alcohol use disorder. A total of 13 variables, including the dependent variable, the variables used in the analysis showed differences in scores due to differing reference points. By normalizing these scores into percentages, we standardized the contributions of the variables, allowing us to identify which variables had a greater influence on the dependent variable. The relevant variables are Sobriety Journaling, Total Sobriety, and Continuous Sobriety, with detailed information provided in Table 3. To demonstrate the predictive power of the identified factors through random forest analysis, a confusion matrix was used, with accuracy metrics serving as the validation measure. Precision and sensitivity were also presented to provide more specific values. Furthermore, to visually represent the predictive factors, feature importance was employed to indicate which factors had the greatest influence. To statistically express the precise predictive power of the explored factors, an ROC analysis was conducted to derive the AUC value. For the multiple regression analysis, the significance of the identified characteristics was defined using F, R-Square, B, β, and p-values.

2.4.2 Missing value

When it comes to data analysis, there are various methods for handling missing values. In this study, it was determined that even after removing missing values, there would still be a sufficient sample size for conducting the analysis. Therefore, missing values were removed. As a result, the final sample size used for analysis was 175 participants, and this sample size was consistently applied across both the t-test and random forest analyses.

The 42 dropouts only participated in the pre-assessment during the 4-week clinical process and did not participate in the post-assessment, making accurate data analysis impossible. However, they were compensated for their participation in the study. Since there were no post-assessment results, they were excluded from the statistical analysis.

2.4.3 Random forest

Random forest analysis is a method that improves predictive performance by combining multiple decision trees, a technique known as ensemble learning. It is primarily used for classification and regression tasks and enhances predictive accuracy by addressing the weaknesses of single models like decision trees. One key method random forest use to overcome the limitations of single models is "bagging" (Bootstrap Aggregating). In bagging, random subsets of training data are generated to create diverse models, thereby mitigating the weaknesses inherent in any single model. To reduce the correlation between variables, instead of considering all features as in a typical decision tree analysis, random forests consider only a randomly selected subset of features. This approach helps to reduce the risk of overfitting by limiting the model's complexity and thus decreasing variance, which ultimately improves the generalization performance of the resulting model (23–25).

3 Results

3.1 Data analysis result

3.1.1 The progression of alcohol use disorder severity

To analyze the results of this study, a paired-sample t-test was conducted. The results showed that the mean score of alcohol dependence severity (AUDIT-K) in the pre-intervention group was

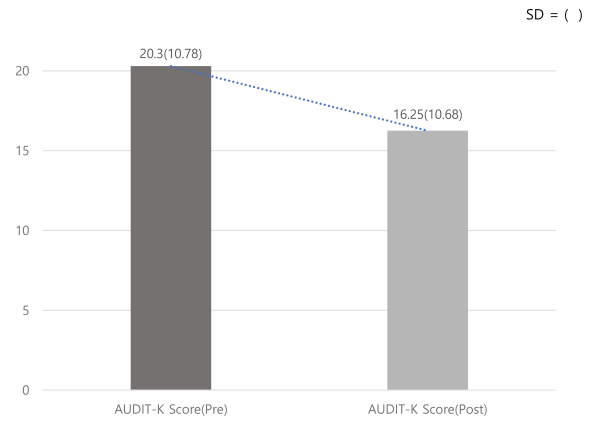

FIGURE 2
Comparing AUDIT-K Score pre-post Use of Digital Self-Care Devices. SD = ().

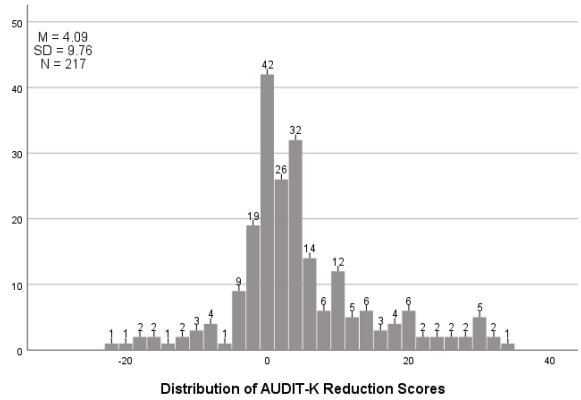

FIGURE 3
AUDIT-K score reduction distribution table.

(M = 20.3), while the mean score in the post-intervention group was (M = 16.25) Figure 2. The mean difference between the pre- and post-intervention groups was (M = 5.239), (SD = 10.121), (t = 6.945), (P = .000***), indicating that the difference was statistically significant at the (p <.001***) level Table 4.

The group used in the analysis was a single group, with the AUDIT-K scores measured before and after the intervention being used for comparison. A frequency analysis was conducted to compare the improvement scores based on the AUDIT-K scores, and the distribution of the overall scores was represented in a histogram. As a result, the AUDIT-K reduction score for all 217 participants was (M = 4.09), with a standard deviation (SD = 9.76) Figure 3. To provide more clarity, a frequency analysis was conducted by distinguishing between patients who experienced a reduction in their alcohol use disorder scores and those who did not. Among the 217 participants, N = 128 (59.0%) showed a reduction in their alcohol use disorder scores, while N = 86 (39.6%) did not. Missing data accounted for N = 3 (1.4%). As a result, the percentage of patients who experienced a reduction in their alcohol use disorder scores was 19.4% higher compared to those who did not Table 5.

Subsequently, based on the measured activity rate within the app over the study period, the 175 participants were divided into two groups: those who used the self-care device extensively (100% activity = 52 participants) and those who used it minimally (0% activity = 62 participants). Additional activity groups included 25% (28 participants), 50% (14 participants), and 75% (14 participants); however, due to extreme sample size differences, these groups were not included in the analysis. Given the short study duration of 4 weeks and the expectation that AUDIT-K scores might not show dramatic changes, we adopted a more conservative 99% significance level instead of the standard 95%. The results showed that the pre- and post-intervention mean scores for the 0% activity group were (M = 21.37) and (M = 18.71), respectively, while those for the 100% activity group were (M = 19.94) and (M = 13.87), respectively. When examining the significance of the mean differences, the 0% activity group showed (M = 2.651), (SD = 10.052), (t = 2.093), (P = .040), indicating that the p-value was not statistically significant. In contrast, the 100% activity group showed (M = 6.075), (SD = 10.181), (t = 4.344), (P = .001***), revealing a statistically significant difference at the (p <.001***) level Table 6, Figure 4.

To gain a more detailed understanding of the observed results, a frequency analysis was conducted to examine the characteristics of each group. Differences were found in variables such as 'age,' 'marital status,' 'mood,' 'alcohol craving,' and 'likelihood of drinking.' In terms of age, the 100% activity group had a relatively lower average age compared to the 0% activity group, with a significant difference in standard deviation as well Table 7. Additionally, the 0% activity group scored lower on mood, craving, and likelihood of drinking compared to the 100% activity group. These scales were measured using a 1–7 point Likert scale, with reverse scoring applied to the craving and likelihood of drinking variables, meaning that a score closer to 7 indicated a better state for all variables. Finally, regarding marital status, the 0% activity group had a higher proportion of married individuals compared to the 100% activity group.

TABLE 4 AUDIT-K Score pre-post group t-test results.

AUDIT-K Score (pre-post)	Mean	SD	T	DF	P-value
	5.239	10.121	6.945	179	.000***

p-value < 0.001***.

TABLE 5 Reduction or non-reduction of AUDIT-K score(pre-post).

Reduction of AUDIT-K score (pre-post)	N (%) or Mean ± SD
Reduction	128 (59.0%)
Non-reduction	86 (39.6%)
Missing value	3 (1.4%)

TABLE 6 Frequency analysis results by performance rate.

Type	Group(N)	Mean (SD)	Group(N)	Mean(SD)
Age	Performance Rate 0% (62)	52.5(1.169)	Performance Rate 100% (52)	46.5(12.871)
Feel		4.81(1.37)		5.31(1.16)
Craving		5.21(1.49)		6.11(1.02)
Probability		5.34(1.70)		6.34(.88)
Type	**Group(N)**	**Mode(N)**	**Group(N)**	**Mode(N)**
Marital Status	Performance Rate 0% (62)	1 = marriage(27)	Performance Rate 100% (52)	2 = unmarried(23)

After conducting a frequency analysis, a chi-square test was performed to determine whether there were mean differences between the characteristics of the 0% and 100% activity groups. However, no significant differences were found between the characteristics.

3.1.2 Exploration of predictive factors

Earlier, the effectiveness of the digital self-care tool was verified through a paired-sample t-test. Following this, factors and characteristics collected through the digital self-care tool and questionnaires were organized, and a representative machine learning technique, random forest, was used to analyze which variables actually influence the "reduction in alcohol dependence severity". The analysis revealed that "consecutive days of sobriety" had the most significant impact on the "reduction in alcohol risk." Additionally, according to the feature importance in the random forest analysis, apart from "consecutive days of sobriety" and "participation rate in consecutive sobriety," no other variables significantly influenced the level of alcohol risk reduction Figure 5. Interestingly, the result that "consecutive days of sobriety" had a greater impact on reducing alcohol risk than "total days of sobriety" is somewhat unusual and will be discussed in more detail in the conclusion and discussion sections.

Furthermore, the prediction accuracy was found to be 0.7317, which is a highly significant value. For a prediction model to be considered accurate and reliable, the confusion matrix should show high TP (True Positive) and TN (True Negative) values, with low FP (False Positive) and FN (False Negative) (Table 8). In this analysis, the confusion matrix showed TP = 11, TN = 19, FP = 6, and FN = 5, indicating very good predictive results. Additionally, the precision and sensitivity of the model were also strong, with precision at 0.7600 and sensitivity at 0.6875, suggesting that the model is stable. To visually assess the model's performance, an ROC Curve was utilized, and the results indicated that the AUC (Area Under the Curve) value was 0.724. This confirms that the model has quite good predictive performance Figure 6.

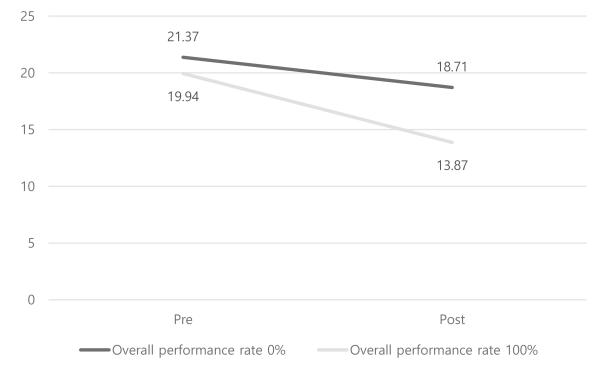

FIGURE 4
Compare average AUDIT-K score(pre-post) by overall performance rate.

3.1.3 Predictive factors for continuous days of sobriety

As previously identified through random forest analysis, consecutive days of sobriety were found to be a key factor in reducing alcohol risk levels. To explore which factors collected through the digital self-care device influence consecutive days of sobriety, a multiple regression analysis was conducted. The stepwise selection method was chosen for this analysis.

The analysis results demonstrated that the regression model was appropriate, with F = 68.319, ($p < .001$). The adjusted R-squared value was ($R^2 = .699$), indicating that the model explained 69.9% of the variance in consecutive days of sobriety. Among the predictor variables used in the analysis, age was found to have a significant effect on consecutive days of sobriety, with B = -.135, ($p < .05$). Since the coefficient B is negative, it indicates that for every one-year increase in age, consecutive days of sobriety decrease by 0.135 days. Additionally, the number of days the sobriety diary was completed (Create Diary) was shown to have a significant positive effect on consecutive days of sobriety, with B = .822, ($p < .001$). This means that for every additional day the sobriety diary was completed, consecutive days of sobriety increased by 0.822 days. Other variables did not have a significant impact on consecutive days of sobriety Table 9.

When comparing which variable had a greater influence on consecutive days of sobriety between age and the number of days the sobriety diary was completed, the standardized coefficients (β) were examined. The results showed that age had a (β = -.088), while the number of days the sobriety diary was completed had a (β = .750), indicating that the completion of the sobriety diary had a relatively higher influence on consecutive days of sobriety compared to age.

TABLE 7 Compare average AUDIT-K score(pre-post) by overall activity rate.

	Mean	SD	T	DF	P-value	95%CI	
						Lower	Upper
Overall Activity Rate 0%	2.651	10.052	2.093	62	.040	1.119	5.182
Overall Activity Rate 100%	6.075	10.181	4.344	52	.001***	3.269	8.882

p-value < 0.001***.

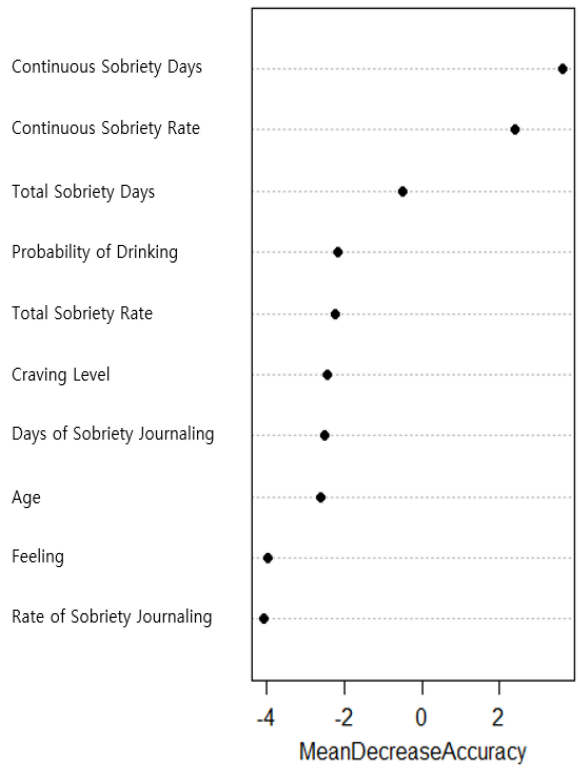

FIGURE 5
Predictor feature importance results.

4 Discussion

4.1 Discussion

This study was conducted to verify the effectiveness of self-care among individuals at high risk for alcohol use and to identify factors that reduce alcohol risk levels. While research related to remote digital medical devices and self-care is actively ongoing worldwide (7–9), there appears to be a lack of studies, like this one, that utilize self-care devices through nationwide institutional collaboration within a country. Additionally, while many previous studies have focused on identifying factors that contribute to the onset or relapse of alcohol use disorder (15–18), this study aimed to explore whether factors that reduce alcohol risk levels could be identified through self-care and to determine which specific characteristics could contribute to this reduction.

As numerous remote digital therapeutic devices and self-care tools are being developed, proving their effectiveness has often been challenging. However, in this study, participants who regularly visited community institutions (e.g., addiction centers, mental health welfare centers) for alcohol treatment monitoring (using the SBIRT framework) and simultaneously used a remote digital self-care device demonstrated significant effectiveness. This aligns with previous research findings, which suggest that self-care approaches are more effective when combined with some level of expert intervention rather than relying solely on a fully self-directed digital therapeutic process (20). Moreover, unlike other self-care devices used in different studies, the self-care tool in this research emphasized helping users manage their schedules and providing indicators to assess their own condition. It also indirectly indicated that their case managers were overseeing their progress. Given this approach, the study found that for individuals at a high risk of alcohol use disorder—not necessarily those already suffering from it—basic monitoring combined with self-care can effectively reduce alcohol risk levels and maintain longer periods of sobriety. This approach marks a departure from previous studies, which often focused more on therapeutic interventions. In conclusion, the results of this study provide significant clinical implications for the reliability, validity, and effectiveness of remote digital self-care devices. The study not only highlights differences from previous research but also offers substantial insights for future studies in this area.

Additionally, while many studies have focused on identifying the factors that contribute to the onset of alcohol use disorder, the significance of this study lies in its exploration of key factors that can reduce alcohol use disorder. The results indicate that consecutive days of sobriety had the most substantial impact on reducing alcohol risk levels, which is quite a unique finding when compared to the total number of sober days. This is particularly noteworthy because, among participants using the device, those with a high total number of sober days did not necessarily experience significant reductions in alcohol risk levels compared to those with high consecutive days of sobriety. In some cases, despite having a high total number of sober days, participants did not see substantial changes in their risk levels, or their risk levels remained unchanged. Therefore, the only independent predictor that effectively reduces alcohol risk levels can be considered as "consecutive days of sobriety." This finding aligns with previous research (26), which suggests that the effectiveness of alcohol treatment increases when sobriety is maintained consecutively.

TABLE 8 Confusion matrix.

Reference(Real World)			
Prediction		Yes	No
	Yes	True Positive(TP)	False Positive(FP)
	No	False Negative(FN)	True Negative(TN)
Accuracy: $\frac{TP + TN}{TP + FP + FN + TN}$			
Reference(Real World)			
Prediction		Alcohol Risk Reduction (Yes)	Alcohol Risk Reduction(No)
	Alcohol Risk Reduction (Yes)	11	6
	Alcohol Risk Reduction (No)	5	19
Accuracy: 0.7317			
Specificity: 0.7600			
Sensitivity: 0.6875			

Future studies should consider utilizing the LASSO method instead of regression analysis to evaluate more accurate predictive variables. Additionally, extending the clinical period and increasing the number of evaluations should be considered to improve the assessment outcomes.

In this study, participants with a 100% activity rate showed lower cravings and a reduced likelihood of drinking compared to those with a 0% activity rate. Simultaneously, their alcohol risk levels also decreased more than those in the 0% activity group. This suggests that as the consecutive period of sobriety increases, it likely has a greater impact on reducing cravings and the probability of drinking. Furthermore, the total number of sober days simply represents the cumulative days of sobriety over four weeks, meaning it might not reflect continuous sobriety. This raises the possibility that some participants may have relapsed during the period. For instance, a participant who had a total of 20 sober days over four weeks but drank during the first two weeks and then remained sober for the last two weeks might still exhibit higher levels of craving, a greater likelihood of drinking, and higher alcohol risk levels compared to someone who maintained continuous sobriety throughout the period.

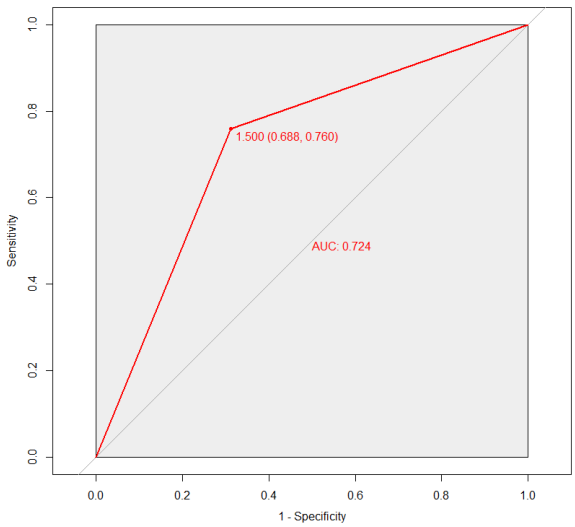

FIGURE 6
Result of ROC curve for random forest model performance.

4.2 Limitations

Despite the conclusions and discussions drawn from this study, there are three significant limitations to consider. The first limitation concerns the measurement tools used. Specifically, the tools within the digital self-care device relied on a 1-7 point Likert scale in a self-report format, rather than using established psychological measurement instruments. This approach has inherent limitations, as it depends heavily on the honesty of the participants due to the single-item nature of the questions. The use of only one item per measure makes it challenging to fully establish the reliability and validity of the participants' reported states. However, to mitigate these limitations, the study instructed social workers and mental health professionals at each community institution to conduct weekly monitoring. Additionally, participants were required to visit the centers weekly to review their status with professionals. Even though the more comprehensive measurement tools were included in the device, the high number of items may have caused participants to feel burdened by the assessment process. This is a chronic issue with digital therapeutic and self-care devices, and finding solutions to this problem will require further research in future studies.

The second limitation is the clinical duration. Although over 20 official public institutions operated by the Korean government

TABLE 9 Factors influencing continuous sobriety days.

Variables	Non-Standardized Coefficients		Standardized Coefficients	t(p)	*TOL*	*VIF*
	B	SE	β			
(Constant)	-8.963	5.361		-1.672		
Age	-.135	.066	-.088	-2.060*	.937	1.067
Sex	-1.015	1.832	-.023	-.554	.924	1.082
Feel	-1.365	.844	-.088	-1.617	.984	1.016
Carving	2.150	1.255	.148	1.714	.581	1.722
Failure	1.873	1.058	.141	1.770	.233	4.283
Create Dairy	.822	.047	.750	17.339***	.272	3.674
F(p)	68.319***					
adj.R^2	.699					
Durbin Watson	2.101					

*p<.05, **p<.01, ***p<.001.

participated in this study, the clinical period was limited to just four weeks. This short duration made it impossible to follow up on the participants' conditions after the clinical trial, preventing an assessment of the long-term effectiveness of the self-care device. Despite this limitation, the satisfaction levels of the patients who used the device during the four-week period were high, and the study demonstrated actual effectiveness. This suggests that the self-care device used in this study may play an important role in helping participants maintain sobriety and prevent relapse, even within a relatively short time frame.

The final limitation lies in the insufficient exploration of key variables related to treating alcohol use disorder. For instance, if the study had delved deeper into major variables such as the reasons for patients seeking treatment for alcohol use disorder—namely, "treatment motivation"—it might have identified additional key predictors that contribute to reducing alcohol risk scores. While this study focused on evaluating the effectiveness of the self-care device, future research should aim to identify various factors to explore the key variables most influential in treating alcohol use disorder. This shift in focus could provide deeper insights and enhance the understanding of impactful factors in treatment.

4.3 Conclusion

In conclusion, the findings of this study suggest that conducting a satisfaction survey for the digital self-care device developed in this research could be beneficial. By identifying any discomforts or areas in need of improvement and then updating the device accordingly, it could be re-released with enhanced functionality. Such improvements would enable individuals at risk of alcohol use disorders to manage themselves more effectively, potentially alleviating socio-economic issues in South Korea and reducing social costs.

Lastly, this study holds significant importance as the first to utilize a digital self-care device across community institutions nationwide in South Korea. It marks a crucial step forward in the development and advancement of research on digital healthcare and self-care devices in the country. The study involved approximately 40% of addiction-related community institutions in South Korea, with more than 70 addiction and mental health experts collaborating. Additionally, with a minimum of 10 participants recruited from each region, the results of this study are considered to be generalizable within the South Korean context.

As a follow-up to this study, two approaches can be considered to examine the sustainability of the effects. First, tracking the participants of this clinical trial to assess how long the effects persist. Another approach would be to extend the duration of the clinical trial to 8 or 12 weeks to evaluate the sustainability of the effects.

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.

Ethics statement

The studies involving humans were approved by Chuncheon Sacred Heart Hospital Institutional Review Board/Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants\' legal guardians/next of kin. This study utilized secondary analysis based on data collected from a clinical trial conducted in 2020, and the clinical

trial registration number is as follows (Clinical Trial Registration Number (CRIS No.): KCT0005135).

Author contributions

YJ: Writing – original draft. YK: Writing – review & editing. SR: Writing – review & editing. ES: Writing – review & editing. HO: Writing – review & editing. IL: Writing – review & editing. EL: Writing – review & editing. HC: Writing – review & editing. SL: 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.

Correction note

A correction has been made to this article. Details can be found at: 10.3389/fpsyt.2025.1644316.

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The effects of cognitive behavioral therapy-based digital therapeutic intervention on patients with alcohol use disorder

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Introduction: This study investigated the effectiveness of a digital therapeutic intervention for individuals with alcohol use problems. Digital interventions are increasingly considered viable alternatives or complements to traditional face-to-face treatments, especially in improving accessibility and adherence.

Methods: A total of 30 outpatients were recruited and randomly assigned to either a digital intervention group or a face-to-face cognitive behavioral therapy (CBT) control group. After excluding two dropouts, data from 28 participants were analyzed. The digital intervention group received a 12-week mobile application-based CBT program, which included 84 video-based CBT sessions. The control group received an 8-session standardized face-to-face CBT program over the same period. Both groups were also provided with a mobile application that included a diary feature for tracking alcohol consumption, cravings, and mood. Assessments were conducted at baseline, mid-treatment (week 4), and post-treatment (week 12) to evaluate risky drinking, craving, readiness for change, depression, anxiety, and alcohol-related symptoms.

Results: The primary outcome, abstinence rate during weeks 9–12, was significantly higher in the digital intervention group (73.3%) compared to the control group (30.8%). Regarding secondary outcomes, the digital group showed significantly greater reductions in risky drinking, craving, and anxiety levels compared to the control group. However, no significant group differences were found for other outcome variables.

Discussion: These findings suggest that digital CBT-based interventions can be an effective alternative to face-to-face CBT for reducing alcohol use and related symptoms. The study highlights the potential of digital therapeutics in addiction treatment, while acknowledging limitations such as small sample size and short follow-up period. Future research should explore long-term effects and broader clinical applicability.

Clinical trial registration: https://cris.nih.go.kr/cris/search/detailSearch.do?seq=29717&status=5&seq_group=29562&search_page=M, identifier KCT0010289.

KEYWORDS

digital therapeutic intervention, alcohol use disorder, cognitive behavioral therapy (CBT), digital therapeutic CBT, addiction treatment

Introduction

Alcohol use disorder (AUD) refers to the continued consumption of alcohol despite persistent physical, psychological, and interpersonal problems caused by alcohol use. Alcohol dependence is characterized by clinically significant behavioral and psychological changes that occur during or shortly after alcohol consumption. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (1), it is essential to approach alcohol-related issues along a continuum. The DSM-5 emphasizes the need to integrate alcohol dependence and alcohol abuse into a single dimension known as alcohol use disorder, based on research findings that indicate these conditions are part of a single spectrum.

AUD is a chronic and highly recurrent condition, recognized not just as an individual problem but as a severe social issue. Studies indicate that over 280 million people worldwide are affected by AUD, which accounts for approximately 4.1% of the global adult population (2). Furthermore, alcohol-related mortality is a significant public health concern globally, According to reports from WHO in 2016 about 3 million people dying annually due to alcohol-related causes, representing around 5.3% of all deaths worldwide (3). These statistics may vary depending on cultural, economic, and social factors in different countries.

As of 2016, the prevalence of AUD in South Korea was 6.2%, which is approximately 1.7 times higher than the Southeast Asian average of 3.9% (4). Specifically, according to the 2021 Korean National Mental Health Survey, the lifetime prevalence of AUD in South Korea was 11.6%, the highest among major mental disorders (5). This high prevalence is closely linked to the permissive drinking culture in Korea.

In a 2016 United Nations survey on annual per capita alcohol consumption, South Korea ranked 17th out of 124 countries, placing it in the top 15% of alcohol consumption globally. Among major countries, it ranked just below Russia (13.9 liters) and the United Kingdom (12.3 liters). Furthermore, over five years, South Korea showed the highest alcohol consumption among four Asian countries in the Organisation for Economic Co-operation and Development (OECD), surpassing major OECD countries such as the United States, Japan, and the United Kingdom, excluding key European nations like Germany and France (6).

Korea's drinking culture is characterized by easy access to alcohol, a permissive attitude towards drinking, and a widespread tendency to encourage excessive drinking or tolerate heavy drinking behaviors (7). However, there is a rare tendency to view alcohol-related disorders as psychiatric problems or diseases, leading to a high incidence of alcohol disorders and a vulnerability in addressing them.

Alcohol-related issues are particularly challenging due to their high prevalence and relapse rates. Among those with alcohol dependence, 71.5% to 82.1% relapse within 3 to 4 months, and 65% to 90% resume drinking within one year after treatment (8). In South Korea, the relapse rate for alcohol dependence within six months ranges from 44.5% to 80.3% (9).

To address the severe and long-term problems caused by alcohol dependence, treatment efforts involve the application of multiple treatment programs to enhance recovery rates. These include combining biological vulnerability treatments with psychosocial interventions such as cognitive-behavioral therapy (CBT), stages of change therapy, relapse prevention, motivational interviewing, exposure-response prevention techniques, and social support network therapy (10–14).

The paradigm in mental health has shifted from post-treatment to recovery-oriented approaches, leading to changes in the clinical field of alcohol dependence treatment. In the Korean version of the 2011 clinical guidelines for AUD published by the Korean Society for Addiction Psychiatry, various psychosocial treatment techniques, including Motivational Enhancement Therapy (MET) and CBT, are strongly recommended with the highest grade of recommendation (Grade A). CBT, in particular, is known to produce the best treatment outcomes when combined with medication (15).

CBT is based on cognitive theory, which posits that emotions and behaviors are influenced by one's thoughts. It involves identifying automatic thoughts, restructuring cognitive distortions that trigger negative emotions into more rational and adaptive thinking, and promoting positive changes. Key components commonly used in CBT include collaboration, case conceptualization, structured therapy sessions, cognitive and motivational strategies, continuity of care, cue exposure, psychoeducation, and coping skills training (16).

While traditional treatment methods are effective, the advancement of digital technology opens new possibilities for complementing and enhancing these approaches. In mental health, digital therapeutic interventions combined with traditional therapies like CBT can play a significant role in improving patients' treatment experiences.

Digital therapeutic interventions are innovative approaches that use digital technology to address various health issues. Digital addiction treatment allows patients to receive treatment via web or mobile applications without needing to visit a hospital, helping to reduce substance use. Because therapeutic training in daily life is effective in addiction treatment, digital interventions can enhance accessibility, reduce spatial and temporal constraints, and improve treatment effectiveness (17).

Moreover, digital addiction treatment allows for the development of personalized treatment plans based on continuously monitored data. Digital therapy is actively applied in clinical settings, with recent studies exploring digital treatments for opioid and alcohol addiction.

For example, a clinical trial was conducted to verify the effectiveness of the digital therapeutic device reSET-O for opioid addiction. In this study, 170 patients were randomly assigned to a single-blind trial (18). The control group received standard treatment, while the experimental group used a digital therapeutic device containing 67 modules alongside standard treatment. Over 12 weeks, the experimental group showed significantly higher treatment retention and abstinence rates between weeks 9 and 12 compared to the control group.

In alcohol addiction treatment, the "Drink Less" program, developed based on Medical Research Council (MRC) guidelines and the Multiphase Optimization Strategy (MOST), showed promising results (19). An exploratory clinical trial conducted

over four weeks found that an enhanced version of the normative feedback and cognitive bias retraining modules significantly affected alcohol consumption changes. Additionally, an enhanced version of the self-monitoring and feedback and action planning modules significantly impacted the total score of the Alcohol Use Disorders Identification Test (AUDIT). While these modules are important for optimizing alcohol addiction treatment, additional confirmatory clinical trials are needed to compare their effectiveness with standard treatment.

Another preliminary study on digital alcohol addiction treatment involved "Vorvida," an internet-based treatment program (20). In this study, the experimental group received treatment through the Vorvida app for three months, while the control group received standard treatment or was placed on a waiting list. Over time, the experimental group showed significant reductions in monthly alcohol consumption (QFI) and Timeline Followback (TLFB) indicators compared to the control group.

Although research on digital addiction treatment is increasing, some controversy remains regarding its effectiveness. Considering various limitations, more research is needed to verify the effectiveness of digital addiction treatment, with a number of studies comparable to those validating the effectiveness of standard treatment. However, the number of studies verifying the effectiveness of digital addiction treatment remains limited.

Building on this background, the present study aims to investigate the effects of digital therapeutic intervention on alcohol addiction by comparing a group that received digital intervention therapy with a control group that received traditional face-to-face cognitive behavioral therapy.

Methods

Study design

Participants

Participants for this study were recruited from outpatient clinics. The inclusion criteria mandated that all participants were adults aged 19 years or older who had a pre-existing clinical diagnosis of either: (1) Alcohol Use Disorder (AUD) according to the DSM-5 criteria, or (2) mental and behavioral disorders due to alcohol use (F10) as defined by the ICD-10.

Specifically, these diagnoses were established by a qualified psychiatrist through a comprehensive clinical evaluation, adhering strictly to the diagnostic criteria outlined in the DSM-5 and ICD-10.

Participants were required to be proficient in reading and writing in Korean and to be able to use mobile applications on common devices such as smartphones or tablet PCs. They needed to provide written informed consent after receiving a thorough explanation of the clinical trial, understanding its purpose, and agreeing to comply with the study procedures. Additionally, participants were excluded if they were diagnosed with dementia as determined by a clinical physician.

The study excluded participants who met the following criteria. Individuals with severe or progressive diseases that could pose a risk to their health were not included. Additionally, those with medical or neurological conditions that may lead to cognitive impairment, such as cerebral palsy, encephalitis, or meningitis, as well as individuals diagnosed with psychotic disorders like schizophrenia, were also excluded.

Furthermore, individuals who had experienced a traumatic brain injury within the past three years, resulting in a loss of consciousness for more than one hour or requiring hospitalization, were not eligible. Those with significant hearing or vision impairments that could interfere with clinical trial procedures were also excluded. Lastly, individuals deemed unsuitable for the study based on the researcher's assessment were not included.

A total of 30 participants met the inclusion criteria and were enrolled in the study. During the study, 1 male and 1 female participant dropped out, resulting in a final analysis that included 20 males and 8 females. The reason for dropout was voluntary withdrawal from the study. Among the 28 participants included in the final analysis, 20 were male (67.86%) and 8 were female (32.14%). The mean age of the participants was 47.43 years (SD = 9.27), and the age range was 23 to 65 years. The mean age by gender was 46.47 years (SD = 10.28) for males and 49.44 years (SD = 6.73) for females, with age ranges of 23 to 65 years for males and 37 to 58 years for females.

Study procedures

Participants provided informed consent after a detailed explanation of the study, and were then evaluated for eligibility based on selection and exclusion criteria.

Random assignment was conducted for participants who met all selection and exclusion criteria, assigning them to either the experimental group or the control group.

Prior to receiving treatment, participants completed self-report questionnaires to assess risky drinking, cravings, readiness for change, depression, anxiety, and alcohol-related symptoms.

Participants installed and logged into the application using an access code provided through a web program. The investigator explained to the participants in the experimental group how to use the application and to the subjects in the control group, the procedures related to daily check.

The experimental group participated in digital cognitive behavioral therapy (CBT) program for alcohol use disorder treatment daily for 84 days, and the results were automatically provided through a web program accessible to healthcare providers. Participants used the diary and notification functions to record their daily abstinence status, craving levels, and mood.

The control group installed an application that did not include CBT-based treatment content and was provided only with diary and notification functions to record their daily abstinence status, craving levels, and mood for the same period. In addition, the control group underwent 40–50 minute CBT sessions every two weeks, with a total of seven in-person sessions.

Both groups received treatment for the same 12-week period and completed self-report questionnaires at the start of treatment, at the 4-week mark, and at the end of the 12-week period.

The self-report questionnaires administered at baseline, 4 weeks later, and at the end of the intervention included not only the AUQ-K to measure alcohol cravings but also the AUDIT-K, RCQ, CIWA-Ar, HADS, CRQ, BADS, MAAS, SOCRATES-K, and HAIS. After the baseline measurement, AUDIT-K, AUQ-K, HADS, and HAIS were administered at both the 4-week and post-intervention time points.

Figure 1 shows the flow of participant allocation and treatment procedures throughout the study.

Randomization procedure

An access code is generated in the clinician's web program for patients who meet all the inclusion and exclusion criteria. Then, patients are randomly assigned using the Interactive Web Response System (IWRS) into either the experimental group, which receives the CBT-based digital therapeutic intervention, or the control group, which receives traditional cognitive-behavioral therapy.

Blinding procedure

A single-blind design is implemented, where the control group, receiving face-to-face cognitive-behavioral therapy, is also provided with an app that does not include digital CBT content but only contains a diary feature (for tracking abstinence status, craving levels, mood, etc.) and notification functions.

Intervention

Cognitive behavioral therapy-based digital therapeutic intervention

The cognitive-behavioral therapy based digital therapeutic intervention for patients with alcohol use disorder is designed to treat symptoms of alcohol use disorder in patients suffering from mental and behavioral disorders caused by alcohol use, utilizing a cognitive-behavioral approach. This intervention consists of a web-based program called the "Clinician

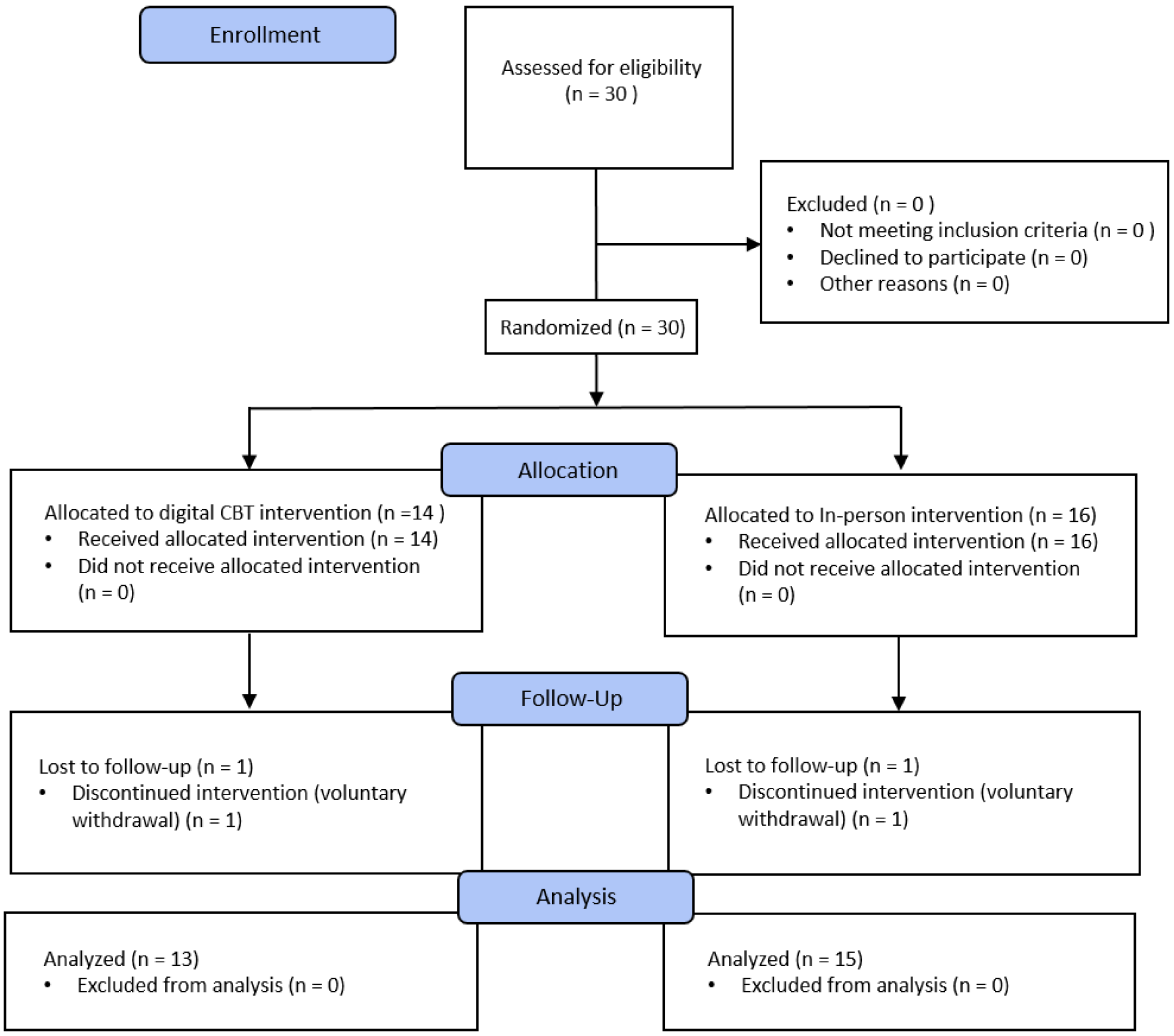

FIGURE 1
Flowchart of participant enrollment, randomization, and treatment.

Dashboard," which helps healthcare providers effectively monitor and manage patients' treatment progress, and a patient application software that supports patients in actively participating in their own treatment.

Patients receiving the digital therapeutic intervention are provided with a total of 84 treatment modules over a 12-week period and are encouraged to complete one module each day. Each treatment module consists of a pair, including a video and a worksheet, designed so that patients can complete the worksheet after watching the video. Additionally, patients are allowed to revisit and complete any missed modules without limitation, but they are restricted from accessing future modules in advance.

The video component of each treatment module is specifically designed to correct maladaptive thoughts and cognitive errors that perpetuate alcohol use disorder, and to prevent the chronic progression of alcohol use disorder. The other component of the treatment module, the worksheet, is a tool designed to help modify maladaptive thoughts and behaviors related to alcohol use. It includes activities such as thought recording, behavior planning, and goal setting. This design enables patients to systematically record and analyze their thoughts, emotions, and behaviors. In addition to CBT techniques, the treatment modules incorporate various therapeutic elements aimed at reducing resistance to treatment and helping patients discover their own motivation for recovery. These elements include motivational enhancement therapy, psychoeducational interventions, mindfulness for managing cravings, and relapse prevention strategies.

The digital therapeutic intervention group is provided with the following features, identical to those offered to the control group. First, participants can use a simple checkbox to record whether or not they consumed alcohol each day. This sobriety tracking feature helps users monitor their progress and see how long they have remained alcohol-free. Additionally, healthcare providers can monitor these records through the web-based program. Secondly, participants have access to a craving tracking feature, which allows them to record the intensity of their alcohol cravings. Alongside this, they can also record their daily emotions, their motivation to remain sober, and the perceived likelihood of drinking, all measured on a 5-point Likert scale, except for the sobriety tracking. Participants are also supported with a step-tracking feature that allows them to monitor their physical activity. Lastly, the system calculates a comprehensive health index based on all these data points and displays it as a graph on the home screen, enabling participants to visually understand their overall health status. Additionally, the system graphs the changes in cravings, mood, and sobriety over time, helping users identify correlations between their emotional state and cravings.

Cognitive behavioral therapy for alcohol use disorder (control group)

The control group received face-to-face cognitive behavioral therapy (CBT) intervention without digital therapeutic intervention for a duration of 12 weeks. This face-to-face CBT consisted of a total of 7 sessions, each lasting 40 to 50 minutes. The content of the sessions included preparation before therapy, exploration of drinking episodes, completion of drinking outcome records, managing negative emotions, coping with alcohol cravings and urges, problem-solving and goal setting, techniques for refusing alcohol, and relapse prevention.

The control group was also provided with an application that included only a sobriety diary feature (tracking sobriety status, cravings, and mood) and notification functions, without the digital CBT modules. Through this application, the control group was able to record and monitor their sobriety status throughout the treatment process.

The therapist who provided CBT at the hospital was one person, and this therapist was a clinical psychology resident who had completed a master's degree in clinical psychology. The therapist received training and supervision from Clinical Psychologist and a psychiatrist, and adhered to the therapist manual while conducting the therapy.

Outcome measurement

Cognitive behavioral therapy-based digital therapeutic intervention

Mobile application

During the treatment period, participants recorded their alcohol use using the application. The application feature allows patients to record their alcohol use through a button, which helps measure their abstinence status and duration. Evaluators can check the abstinence status and the length of abstinence in real-time using data collected from participants through a web program designed for healthcare providers. This enables the assessment of whether participants maintained abstinence throughout the total 84-day treatment period and during the assessment period between weeks 9 and 12.

Self-report measures

Korean version of Alcohol Use Disorder Identification Test

The AUDIT-K used in this study is the Korean version of the Alcohol Use Disorder Identification Test (AUDIT), developed by the WHO. The AUDIT-K is a tool designed to measure alcohol consumption levels, frequency, quantity, symptoms of dependence, and alcohol-related problems. It consists of 10 items, with each item being rated on a scale of 3 to 5 points. Originally, the assessment period was set for one year, but for this study, it was applied with a two-week interval.

The outcome measure is calculated based on the responses provided by the participants to the AUDIT-K items, with each item scored individually to compute a total score. This score is treated as a continuous variable and is used to evaluate the level of alcohol-related risk. The results for each item are coded as continuous variables, with individual item scores ranging from 3 to 5 points. The total score is calculated as a continuous variable, ranging from a minimum of 0 to a maximum of 40 points.

Readiness To Change Questionnaire

The Readiness to Change Questionnaire (RCQ) is a tool developed to measure the treatment motivation of individuals with alcohol dependence (21). This assessment helps determine which stage of change—Precontemplation (P), Contemplation (C), or Action (A) a person is in during their recovery process. The RCQ consists of 12 items, with 4 items for each subscale, and the stage with the highest score is identified as the individual's current stage of readiness for change. In Korea, Yoo adapted this tool (22), and subsequent reliability testing was conducted by Taekyung Lee and colleagues to ensure its applicability in the Korean context..

Korean version of Alcohol Urge Questionnaire

The Alcohol Urge Questionnaire (AUQ) was developed as a self-report tool to measure a single factor of alcohol craving, specifically designed for research on alcohol-related urges (23). The questionnaire consists of 8 items, each rated on a 7-point Likert scale ranging from 0 to 6, with a higher score indicating a greater craving for alcohol. In Korea, Kim et al. (24) validated the reliability of this tool. The total score of this questionnaire, as a continuous variable, was used to measure the level of alcohol craving.

Clinical Institute Withdrawal Assessment for Alcohol Scale

The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) is a scale developed by Sullivan et al. to measure the severity of withdrawal symptoms. It consists of 10 items, including nausea and vomiting, tremor, sweating, anxiety, auditory disturbances, visual disturbances, tactile disturbances, headache, agitation, and orientation and clouding of sensorium. All items, except for disorientation (rated 0-4), are rated on a scale of 0-7, with a total score range of 0–67 to assess the severity of withdrawal symptoms.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item assessment tool developed by Zigmond and Snaith (25) to measure the levels of anxiety and depression specifically in hospital settings. The scale is structured such that the 7 odd-numbered items assess anxiety, while the 7 even-numbered items evaluate depression. In Korea, Min and colleagues translated and standardized the HADS in 1999, ensuring its applicability and cultural relevance for Korean patients (26). The total score of the odd-numbered items of this questionnaire was used to assess the level of anxiety. Additionally, the total score of the even-numbered items was used to assess the level of depression.

Cognitive Reappraisal Questionnaire

To measure the level of cognitive reappraisal, the Cognitive Reappraisal Questionnaire (CRQ), developed and validated by Kim Yoon-kyung in 2019, was used. This tool is designed to assess two subtypes of cognitive reappraisal. First, the objective reappraisal measures the ability to view situations neutrally and objectively, maintaining emotional distance during the evaluation of emotional experiences. The positive reappraisal, on the other hand, assesses the ability to shift focus towards the positive aspects of a situation and the potential benefits that can be gained by overcoming it. The CRQ consists of 20 items, and in Kim Yoon-kyung's study, the internal consistency, as measured by Cronbach's α, was found to be high. Specifically, the reliability of the CRQ was reported with a Cronbach's α of.88 for the objective reappraisal items and.94 for the positive reappraisal items, indicating strong reliability and consistency (27).

Korean version of the Behavioral Activation for Depression Scale

The Behavioral Activation for Depression Scale (BADS) was developed by Kanter, Mulick, Busch, Berlin, and Martell to more accurately assess the level of patient activation and treatment response (28). In this study, the BADS was used to measure the level of behavioral activation. This scale consists of 25 self-report items and is effective in evaluating the outcomes of therapeutic interventions throughout the behavioral activation treatment process. The BADS is composed of four subscales: Activation, Work/School Impairment, Social Impairment, and Avoidance/Rumination. In Korea, the Korean version of the BADS was standardized by Oh Ji-hye and colleagues in 2017 (29).

Korean version of Mindfulness Attention Awareness Scale

To measure mindfulness attention and awareness, the Mindfulness Attention Awareness Scale (MAAS) developed by Brown and Ryan (30) was used. This scale primarily assesses inattentiveness or lack of awareness experienced in everyday life. It consists of 15 items, with participants rating the frequency of experiencing situations related to each item on a 6-point scale ranging from 1 (Almost Always) to 6 (Almost Never). The Korean version of MAAS, a Korean translation of the MAAS developed by Brown and Ryan, was used in this study. The reliability and validity of the K-MAAS were verified by Kwon and Kim (31).

Korean version of Stages of Change Readiness and Treatment Eagerness Scale

The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) was developed to assess the motivation for change in problem drinkers (32). The scale is designed with four subscales: Precontemplation, Contemplation, Determination, and Action stages. It consists of 19 items, each rated on a 5-point Likert scale. Chun Young-min (33) validated the reliability and validity of this scale and developed the Korean version, SOCRATES-K.

Hanil Alcohol Insight Scale

To measure the level of insight in patients with alcoholism, the Insight Evaluation Scale developed by Kim et al. (34) was used in a clinical setting. This scale consists of 20 items, including both positive and negative questions, and utilizes a 3-point scale. It assesses awareness of one's own drinking, recognition of loss of

control over drinking and dependence, acknowledgment of the need for abstinence, understanding that one's drinking contributes to current problems and causes distress to others, and the necessity of treatment. Higher scores indicate a greater level of insight into one's condition. The total score of this questionnaire was used to measure the overall illness.

Statistical analysis

Repeated measures ANOVA was conducted to analyze the differences in change amounts between groups. The analysis was performed by setting the groups (experimental group, control group) as between-subject factors and the measurement times (pre, post) as within-subject factors. To evaluate the differences between groups in terms of abstinence performance, the differences in total days of abstinence between groups were examined using an independent-sample t-test. Abstinence success was defined as not drinking even once between weeks 9 and 12, and the success rates between groups were analyzed using Pearson's chi-square test. Moreover, to examine the interaction effects of groups and measurement times on each dependent variable, a repeated measures ANOVA was performed by setting the groups (experimental group, control group) as between-subject factors and the measurement times (pre, post) as within-subject factors. Log data analysis was conducted to examine the differences between groups in total number of accesses, total access days, total usage time (minutes), average daily app launches, and app usage time (minutes). Additionally, a regression analysis based on log data was conducted to explore the differences between groups in greater detail. Given the small sample size, effect sizes (Cohen's d) were also calculated to assess the magnitude of differences between groups in the relevant measures.

Results

Comparison of digital therapy usage between experimental and control groups

The usage comparison between the groups is summarized as follows. First, we assessed the extent to which patients in the experimental group utilized the cognitive-behavioral therapy-based digital alcohol treatment device.

In the experimental group, the average login frequency was 110.33, the average number of days of access was 40.67, and the average total usage time was 1084.80 minutes. Additionally, the average viewing time of the digital CBT modules was 195.20 minutes, the average number of completed worksheets was 34, and the average number of completed modules was 36.26.

In the control group, the average number of logins was 136.23, the average number of days of access was 45.54 days, and the average total usage time was 230.62 minutes. Additionally, the average number of completed CBT sessions was 36.26 (Table 1).

TABLE 1 Summary of user engagement and completion rates for digital intervention group and control groups.

Characteristic	Digital Intervention Group	Control Group
login frequency	110.33	136.23
Days of access(days)	40.67	45.54
Usage Time (min)	1084.80	230.62
Viewing Time (min)	195.20	N/A
Worksheet Completions(sessions)	34	N/A
Viewing Count(sessions)	36.26	N/A
Face-to-Face CBT Sessions	N/A	4.23

Pretest equivalence test

To ensure that the treatment and control groups were comparable at baseline, a pretest equivalence test was conducted. The pretest scores for both groups were compared using an independent samples t-test. The results revealed no significant differences for any of the variables (see Table 2), indicating that the two groups were statistically equivalent before the intervention.

Analysis of differences in change amounts between groups

To examine the effects of group (digital intervention group, control group) and measurement time (pre-test, post-test) on each dependent variable, a repeated measures ANOVA was conducted with group as the between-subjects variable and measurement time as the within-subjects variable (see Table 3).

First, the interaction effect between group (experimental vs. control) and time (pre-test vs. post-test) was significant [F (1, 14) = 10.146, p <.01]. As shown in Figure 2, the experimental group exhibited a larger decrease in risky drinking levels compared to the control group over the same period. This indicates that the experimental group experienced a more substantial reduction in alcohol use as measured by the AUDIT-K, suggesting that the intervention was effective in decreasing risky drinking behaviors.

Second, the interaction effect between group and time was significant for alcohol craving [F (1, 14) = 9.904, p <.01]. As shown in Figure 3, the magnitude of change from pre-test to post-test was greater in the experimental group compared to the control group. This indicates that the experimental group experienced a faster reduction in alcohol craving over the same period.

Third, the interaction effect between group and time was also significant for anxiety [F (1, 14) = 6.720, p <.05]. As shown in Figure 4, the magnitude of change from pre-test to post-test was greater in the experimental group compared to the control group. This suggests that the experimental group experienced a faster reduction in anxiety over the same period. However, no significant

TABLE 2 Independent samples t-test for mean differences between the intervention and control groups.

Variable	Digital Intervention Group (n=13)		Control Group (n=15)		t-value
	Mean	SD	Mean	SD	
AUDIT-K	24.00	8.86	29.07	6.39	-1.712
RCQ	1.69	4.77	1.8	4.48	-0.061
AUQ-K	24.15	6.01	25.73	4.4	-0.783
CIWA-Ar	12.54	4.63	12.4	4.29	0.082
HADS -Anxiety	14.38	4.59	14.33	3.75	0.032
HADS -Depression	66.15	13.04	63.47	18.02	0.456
CRQ	67.77	24.79	68.4	20.59	-0.073
BADS	17.85	3.85	17.67	2.53	0.144
MAAS	62.85	6.9	62.33	7.76	0.185
SOCRATES-K	1.15	5.64	4.93	5.71	-1.758
HAIS	2.23	4.32	1.27	2.05	0.735

group differences were observed for the remaining variables (Insight: $F = 0.030$; Depression: $F = 2.146$).

Based on the results of the repeated measures ANOVA, significant changes were observed in Risky drinking levels, Alcohol Craving, and Anxiety.

For Risky drinking levels, the digital intervention group showed a substantial decrease from 29.63 (5.34) at pre-test to 3.63 (3.07) at post-test, with a very large effect size of Cohen's d = -5.97. In contrast, the control group showed a change from 23.00 (4.66) at pre-test to 8.63 (7.17) at post-test, with a moderate effect size of Cohen's d = -2.38.

Significant changes were also observed in Alcohol Craving. The digital intervention group experienced a large decrease from 26.25 (2.82) at pre-test to 5.00 (3.30) at post-test, with a very large effect size of Cohen's d = -9.93. The control group showed a change from 24.13 (3.80) at pre-test to 12.63 (6.16) at post-test, with a moderate effect size of Cohen's d = -2.44.

Similarly, in Anxiety, the digital intervention group showed a significant decrease from 14.13 (2.53) at pre-test to 3.13 (3.68) at post-test, with a very large effect size of Cohen's d = -3.48. The control group showed a change from 11.75 (3.85) at pre-test to 7.00 (4.99) at post-test, with a moderate effect size of Cohen's d = -1.07.

Differences between groups in terms of abstinence performance

Comparison of total abstinence days

An independent samples t-test was conducted to compare the total number of abstinence days between the groups. The control group had a mean of 73.15 days (SD = 10.915), while the experimental group had a mean of 79.20 days (SD = 8.495). The difference between the groups was not statistically significant (t = -1.617, p >.05).

TABLE 3 Repeated measures ANOVA results: interaction effect of group and time.

Dependent Variable	Group	Pre-Test (M(SD))	Post-Test (M(SD))	F
Risky drinking level (AUDIT-K Score)	Digital Intervention	29.63 (5.34)	3.63 (3.07)	10.146**
	Control	23.00 (4.66)	8.63 (7.17)	
Alcohol Craving (AUQ-K Score)	Digital Intervention	26.25 (2.82)	5.00 (3.30)	9.904**
	Control	24.13 (3.80)	12.63 (6.16)	
Anxiety (HADS-anxiety Score)	Digital Intervention	14.13 (2.53)	3.13 (3.68)	6.720*
	Control	11.75 (3.85)	7.00 (4.99)	
Depression (HADS-depression Score)	Digital Intervention	15.63 (3.07)	6.00 (5.71)	2.146
	Control	12.88 (4.70)	8.00 (2.73)	
Insight (HAIS Score)	Digital Intervention	5.50 (4.96)	10.63 (7.89)	0.030
	Control	0.88 (5.54)	5.25 (5.95)	

*p <.05, **p <.01.

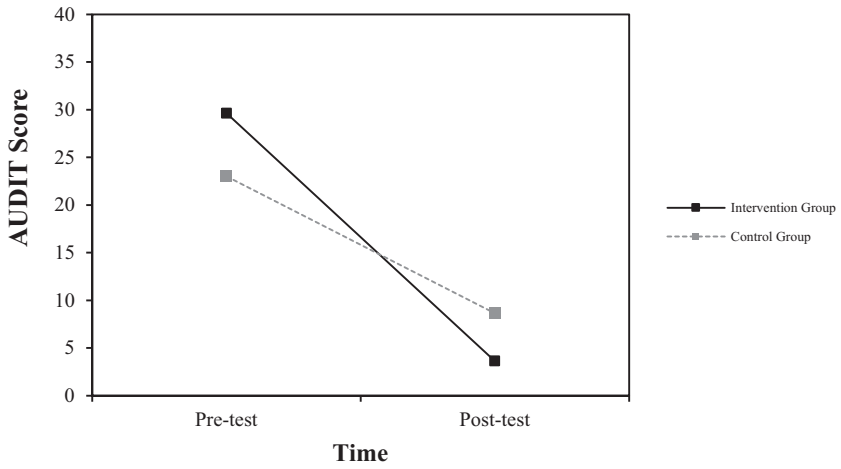

FIGURE 2
Interaction effect of group and time on changes in risky drinking levels as measured by AUDIT-K score.

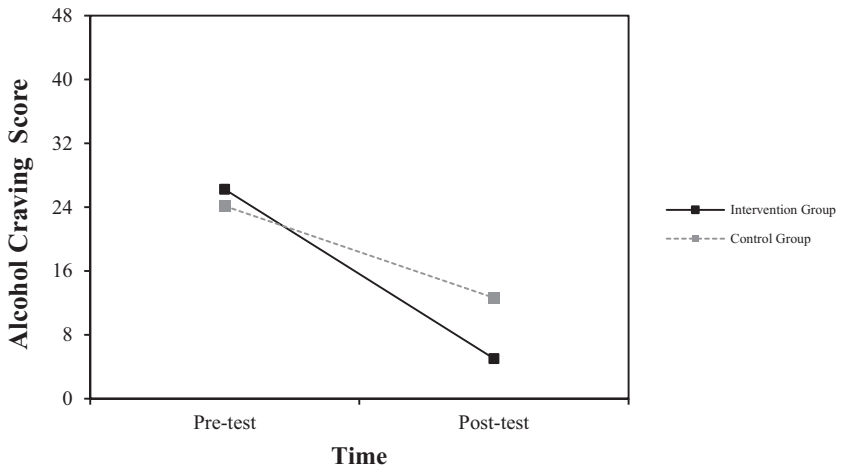

FIGURE 3
Interaction effect of group and time on changes in alcohol craving score.

Comparison of abstinence success rates

Pearson's chi-square test was conducted to evaluate the abstinence success rates between the groups (see Table 4). The analysis revealed a significant difference in abstinence success rates between the groups (χ^2 = 5.073, p <.05). Specifically, the experimental group had a significantly higher abstinence success rate compared to the control group.

Impact of log data metrics on post-intervention outcomes: a hierarchical multiple regression analysis

A hierarchical multiple regression analysis was conducted within the intervention group to investigate the predictive relationships between various log data metrics and post-intervention outcomes, including depression, anxiety, craving for alcohol, insight, and risky drinking levels. The analysis was structured as follows:

Step 1: A baseline model was established incorporating pre-measurement values as independent variables to provide a reference for evaluating the impact of subsequent variables.

Step 2: The model was then expanded by including additional predictors: total number of visits, total number of days visited, total usage time, and total viewing duration of intervention content. This allowed for the assessment of changes in explanatory power, highlighting the incremental value of these log data metrics in predicting post-intervention outcomes.

The results of the hierarchical multiple regression analysis, detailed in Table 5, showed that the total number of visits had a

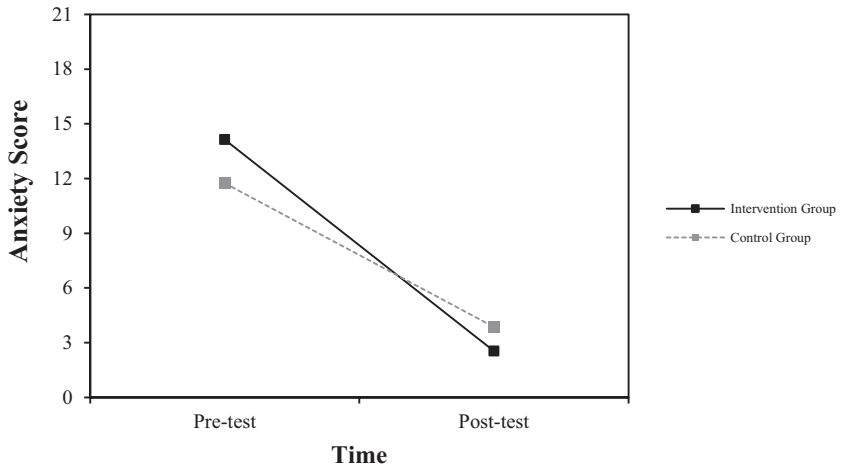

FIGURE 4
Interaction effect of group and time on changes in anxiety score.

significant impact on the reduction of alcohol craving (β = -0.237, p = .029). Specifically, a higher number of visits was associated with a greater decrease in alcohol craving. In contrast, the total number of days visited did not significantly impact the reduction of alcohol craving and showed a tendency towards an increase (β = 0.313, p = .040). Other variables, including total usage time and total viewing duration of intervention content, did not have a significant impact on alcohol craving reduction. These findings suggest that the total number of visits plays a more crucial role in reducing alcohol craving compared to the total number of days visited.

Discussion

The role of digital therapeutic devices in the treatment of alcohol use disorder is becoming increasingly significant. These devices are evolving from a supplementary role—where they were used as adjuncts to traditional treatments—into a primary role within the treatment process. However, to fully evaluate the efficacy and effectiveness of these digital therapeutic devices, rigorous clinical trials and field validations are necessary.

This study aimed to determine whether the newly developed digital therapeutic approach provides therapeutic effects comparable to those of established face-to-face cognitive-behavioral therapy. To achieve this, we compared changes in alcohol use disorder-related symptoms between an experimental group receiving digital therapeutic interventions and a control group undergoing face-to-face cognitive-behavioral therapy.

TABLE 4 Results of the abstinence success rate comparison between groups.

Group	Success	Failure	Success Rate (%)	χ^2	*P*-value
Intervention	11	4	73.3	5.073	<.05
Control	4	9	30.8		

The results of the pre-test equivalence evaluation for this pre-measurement showed no significant differences between the experimental and control groups, confirming the successful implementation of random assignment and indicating no statistically significant difference between the two groups.

The interaction effects of group and measurement time on each dependent variable were examined, and significant interaction effects were found for risky drinking levels, alcohol craving, and anxiety. This means that over the 12-week period from pre- to post-intervention, the changes in these three variables were significantly greater in the experimental group compared to the control group. Specifically, during the same period, the experimental group experienced a more rapid decrease in risky drinking levels, alcohol craving, and anxiety than the control group. The findings of this study suggest that digital intervention is not inferior to the cognitive-behavioral therapy, which has previously been proven effective.

To examine in detail, first, the experimental group experienced a faster reduction in risky drinking levels over the same period. These results suggest that digital therapeutic interventions may have a positive impact on effectively reducing risky drinking behaviors. The interactive elements and real-time feedback provided by the digital therapy could have contributed to the reduction in risky drinking, and the effectiveness of these digital interventions appears to be promising compared to traditional treatment methods.

Connecting these results to prior research, this study provides additional evidence supporting the effectiveness of digital interventions for alcohol use disorders. Previous studies have also demonstrated that digital interventions can effectively reduce various symptoms associated with alcohol use disorders. For example, a clinical study on the digital therapeutic device reSET-O for opioid use disorder involved 170 patients who were randomly assigned to either a control group receiving standard treatment or

TABLE 5 Hierarchical multiple regression analysis predicting reduction in alcohol craving based on log data metrics.

Model	Predictor Variables	*B*	*SE*	*β*	*t*	*p*
1	(Constant)	17.297	11.549			
	Pre-Measurement [AUQ-K Total Score]	-0.468	0.438	-0.400	-1.070	0.326
2	(Constant)	38.966	4.522		8.616	0.013
	Pre-Measurement [AUQ-K Total Score]	-0.896	0.136	-0.766	-6.587	0.022
	Total Number of Visits	-0.237	0.042	-2.273	-5.708	0.029
	Total Number of Days Visited	0.313	0.064	2.067	4.855	0.040
	Total Usage Time	0.008	0.002	2.020	3.299	0.081
	Total Viewing Duration of Intervention Content	-0.044	0.012	-2.516	-3.833	0.062

The unit for "Total Usage Time" and "Total Viewing Duration of Intervention Content" is minutes.

an experimental group receiving standard treatment plus a digital therapeutic device. Over a 12-week period, the experimental group showed significantly higher treatment retention and abstinence rates compared to the control group (35). These findings support the potential of digital interventions to effectively address substance use disorders. Additionally, a study utilizing the internet-based treatment Vorvida demonstrated that digital interventions significantly reduce alcohol consumption (20). This study compared a group of 608 adults with alcohol consumption issues who used the Vorvida app for 3 months with a control group that either received standard treatment or was on a waiting list. The results showed that the experimental group using Vorvida had a significantly greater reduction in alcohol consumption compared to the control group. These findings suggest that digital interventions can be an effective treatment option for alcohol use disorders.

Second, the Digital Intervention Group showed a faster reduction in alcohol cravings compared to the control group over the same period. Additionally, anxiety levels were also significantly reduced. This result suggests that digital therapeutic interventions may be more effective in reducing alcohol cravings and anxiety compared to standard treatment. Additionally, this finding supports the effectiveness of digital therapies as demonstrated by previous research. Prochaska et al. (36) reported that digital therapeutic interventions, such as the Woebot app, which utilizes artificial intelligence, led to significant improvements in alleviating and treating alcohol addiction symptoms. An 8-week preliminary clinical trial was conducted with 101 adults aged 18 to 65. The analysis of changes before and after treatment revealed that 86.1% of participants experienced approximately a 50% reduction in cravings for substances. Furthermore, confidence in overcoming substance urges significantly increased, and mental health indicators such as depression and anxiety also showed significant improvement.

To delve deeper into these significant findings, a thorough analysis of the log data from the experimental group was conducted. This analysis demonstrated that the frequency of visits positively impacted the reduction of alcohol cravings. Specifically, it was observed that more frequent participation in the intervention was associated with a greater decrease in cravings. This suggests that higher levels of user engagement are essential for maximizing the effectiveness of digital therapeutic interventions.

In digital therapy, the frequency of participation can play a crucial role in achieving effective outcomes. While consistent participation is also considered important in traditional face-to-face cognitive behavioral therapy (CBT), in digital therapy, how often a user participates can significantly influence the treatment's effectiveness. In particular, because digital therapy involves user-driven participation, the frequency of participation is likely to be closely linked to the treatment outcomes. Such participation patterns act as an important variable in maximizing the effectiveness of digital therapy, highlighting a distinctive difference from traditional treatment methods.

Additionally, to prior research, user engagement appears to be a crucial factor in determining the success of digital therapies. A systematic review examining the impact of adherence and engagement on the effectiveness of e-therapy has emphasized the critical role of user engagement in the success of digital therapies (37). Similarly, research on internet-based interventions for anxiety and depression has highlighted that user engagement and adherence are key factors in achieving successful treatment outcomes (38).

However, it is important to note that not all studies agree on the direct correlation between user engagement and positive treatment outcomes. Mohr et al. (39) argue that high levels of user engagement do not necessarily guarantee better treatment results. They suggest that other factors, such as the content of the intervention, the user's initial motivation, and the presence of external support, can significantly influence the effectiveness of the treatment.

Additionally, there is a notable gap in research specifically examining the impact of login frequency—how often patients access digital therapy programs—on treatment outcomes. This gap highlights the need for further research that considers these variables to better understand their influence on the success of digital therapies.

In addiction treatment, the frequency of addressing cravings is emphasized as being highly important. According to the study by Tiffany et al. (40), conducting treatment sessions frequently and continuously managing cravings helps to maximize the effectiveness of the treatment. Similarly, the research by Marlatt and Gordon (41) also highlights the importance of frequent treatment sessions and repeated interventions.

Based on these findings, the fact that the number of logins in this study affected the reduction of cravings suggests that understanding and utilizing login frequency metrics has significant implications for the development and improvement of

effective digital therapeutic interventions. In particular, this study found that when separating the total number of logins and the number of days logged into the digital therapeutic app over a specific period, the number of logins had a more significant impact on reducing cravings.

Therefore, this study suggests that how often a user participates, rather than how consistently they participate, is a more critical factor in digital therapeutic interventions targeting alcohol use disorder. This finding underscores the importance of promoting regular and consistent use of digital therapeutic programs to achieve optimal treatment outcomes and provides crucial direction for setting participation metrics and adherence standards as digital health continues to evolve.

This study has several important limitations. First, instances where abstinence status was not confirmed were considered as abstinence. This approach reflects the concern that assuming unreported drinking as drinking could damage the trust between the patient and the therapist. However, assuming abstinence when drinking is not reported introduces a limitation in the accuracy of interpreting treatment outcomes.

Second, personalized modules were not provided. While digital-based addiction treatment allows for the development of detailed and tailored treatment plans based on continuously monitored data, and personalized treatment is generally more effective, this study applied the same intervention to all participants, which is a limitation.

Third, the sample size in this study was limited. The sample size was determined to assess whether the effects of CBT which has established efficacy, were comparable to those of CBT supplemented with digital interventions such as digital devices. However, due to the limited sample size, caution is required when interpreting and generalizing the results. Although there was a difference in AUDIT scores between the two groups at baseline, this difference may have been statistically significant if the sample size were larger. Future research should employ a larger sample size to strengthen the reliability of the results and allow for more robust statistical analysis. More importantly, efforts should be made to ensure the homogeneity of the two groups by applying rigorous randomization methods.

Fourth, a significant limitation of this study is that the actual use of the digital intervention tools by patients could not be directly verified. While digital interventions can contribute to improving treatment adherence and engagement, they cannot fully replace clinical treatment. This limitation may influence the interpretation of treatment outcomes. Furthermore, patients with depression were not excluded from this study, and there is a possibility that participants taking anxiolytics, antidepressants, or other medications were included. Therefore, the potential impact of medication use as a clinical variable affecting the efficacy of the digital intervention cannot be completely ruled out. Future studies should more precisely control for these variables and further enhance the validity of the results through analyses that consider various patient characteristics.

Fifth, in this study, all face-to-face CBT sessions in this study were conducted by a single therapist. While this approach enhanced the consistency of the intervention and allowed for close monitoring of treatment fidelity, it also introduces a potential limitation regarding therapist-specific effects. The use of a single therapist may limit the generalizability of the findings, as treatment outcomes could be influenced by the specific characteristics or clinical competence of that individual. In larger-scale studies, Including multiple therapists is a common practice to minimize such confounding effects. Future research should consider including more than one therapist or statistically controlling for therapist effects in order to increase the external validity of the results.

In summary, digital therapeutic interventions for alcohol use disorder, conducted with random assignments to ensure baseline equivalence, demonstrated superior effectiveness in abstinence success rates compared to face-to-face cognitive behavioral therapy (CBT). Additionally, reductions in hazardous drinking levels, craving, and anxiety were more pronounced in the experimental group than in the control group. However, most other variables did not show significant differences between the two groups. Given the small sample size and the single-institution nature of this study, these results require further validation through more rigorous methodologies. Nonetheless, the findings, which showed comparable results across most aspects and superior therapeutic efficacy in key variables such as abstinence success, craving, and hazardous drinking levels compared to face-to-face CBT, suggest that digital therapeutic approaches could be a promising intervention for patients with alcohol use disorder.

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.

Ethics statement

This study involving human participants was reviewed and approved by the Institutional Review Board (IRB) of Chuncheon Sacred Heart Hospital (Approval Number: [CHUNCHEON 2022-01-014-003]). All procedures were conducted in accordance with the Declaration of Helsinki and local regulations. Written informed consent was obtained from all participants prior to their inclusion in the study.

Author contributions

S-HL: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. J-KS: Software, Validation, Writing – original draft, Writing – review & editing. MA: Methodology, Project administration, Writing – original draft, Writing – review & editing. C-hL: Supervision, Validation, Writing – original draft, Writing – review & editing. S-KL:

Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, 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.

Correction note

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Therapist experiences with implementation of blended (iCBT and face-to-face) treatment of alcohol use disorder (Blend-A): mixed methods study

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Introduction: Though therapists' experiences of offering internet-based treatment for alcohol use disorder have been examined in previous studies, the process of implementing blended internet-based and face-to-face treatment has so far not been studied. This study aims to investigate therapist experiences during implementation of blended face-to-face and internet-based treatment for alcohol use disorder.

Methods: The study employed a mixed methods design, more specifically a triangulation design with a convergence model. Quantitative data using NoMAD were collected in two waves, involving 48 therapists at the 1st wave and 18 at the 2nd wave. Qualitative interviews were conducted six months after the 2nd wave. Eleven therapists participated in focus group interviews for qualitative data collection, and an additional three semi-structured interviews were recorded, transcribed, and subsequently analyzed using the Normalization Process Theory.

Results: We found that the therapists generally had a positive experience with implementing blended face-to-face and internet-based treatment for alcohol use disorder and that their motivation to implement increased. The therapists found it challenging to find coherence between digital and face-to-face treatment in the beginning of the implementation process; however, later in the process, they experienced sense-making. Furthermore, the therapists reflected on their own practice regarding the intervention, both in terms of the amount of time spent on the platform and how it was received by the patients. Moreover, the therapists perceived that if they had all been engaged in the intervention to begin with, it would have led to a shared understanding of the platform and collective ownership. Finally, through each of their individual experiences, the therapists had gained adequate knowledge of the digital intervention; thus, had come to each of their individual perceptions of the best way to incorporate the digital technology in their workday.

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Discussion: Familiarity and perceived normalcy of using Blend-A did not change significantly over time, but the cognitive attitude to Blend-A did. The therapists were optimistic about the possible use of a blended treatment format, and that this had a positive effect on the implementation process. Over time, the therapists developed confidence in benefits and disadvantages of a blended format.

KEYWORDS

internet-based, alcohol use disorder treatment, mixed methods, blended treatment, therapist perspective, implementation, normalization process theory

Introduction

Background

Offering treatment for Alcohol Use Disorders (AUD), for example cognitive behavioral therapy (CBT), via the internet (iCBT) can be an effective way to overcome barriers towards treatment seeking, such as stigma (1). Research has shown that iCBT can be effective in reducing alcohol intake and improving outcomes for both physical and mental health conditions (2–4). iCBT can be delivered in various forms; from pure self-help interventions consisting of self-guided programs, to therapist-guided online programs comprising components with reading materials, assignments, feedback moments, and digital communication with the therapist, and to blended treatment programs, which combine online therapist-guided sessions with in-person sessions (5).

Therapist-guided internet-based interventions are found to rely heavily on the client's intrinsic motivation, and in-person treatment, and guided internet-based treatment is found to appeal to different groups of patients and therapists (6). Ekström & Johansson (4) found that, from the therapist's perspective, being a good therapist in an online setting requires specific considerations and skills. The therapists in their study considered it harder to establish an alliance with patients who only used digital solutions, with communication in writing with the therapist. According to the therapists, it thus became important to communicate in person with the client between homework assignments to create a more personal contact. While the significance of the therapeutic alliance between practitioner and client in the success of iCBT is well acknowledged, the objective of this study is to examine how the implementation of iCBT manifests in practice.

Implementation

Though therapists' experiences of offering iCBT for AUD have been examined in previous studies, the process of implementing blended iCBT and face-to-face (FtF) treatment has not so far. Normalization Process Theory (NPT) (7) is frequently used in qualitative research aiming to understand and evaluate the processes that shape the implementation and delivery of healthcare innovations within organizations. The theory is particularly well-fitted in terms of introducing new and complex digital tools in the healthcare system when it comes to the designing of complex interventions and understanding the dynamics of implementation processes and their outcomes.

NPT is a translational framework, based on empirical studies and evidence syntheses. NPT outlines three context-mechanism-outcome (CMO) domains that have the potential to impact implementation: implementation contexts, implementation mechanisms, and implementation outcomes. All three domains build on primary constructs; and in addition, the second domain, implementation mechanisms, also comprises sub-themes. In present study, we focus on the four primary constructs within the domain implementation mechanisms. May et al. (7) define mechanisms as the work people do when they participate in implementation processes. The domain includes the constructs coherence building, cognitive participation, collective action, and reflexive monitoring, elaborated on below. All constructs can be measured by the means of quantitative data. However, while the constructs all are of importance, the therapists may have additional or alternative views and reflections that questionnaires and quantitative measures may not bring to light. Uncovering this information needs alternative qualitative research methods.

The construct coherence building refers to people's sense-making of an intervention by means of the way they work together in everyday settings to understand and plan the activities, which need to be accomplished to put the intervention and its components into practice. Coherence building comprises four sub-themes, namely differentiation, communal specification, individual specification, and internalization. The sub-themes each respectively represents modes of sense-making internal and external to the involved individuals in terms of understanding various components of the intervention and overcome difficulties associated with the implementation. E.g., the sub-theme differentiation concerns people's ability to understand a set of practices and their objects, which may be understood differently.

The construct cognitive participation comprises the sub-themes initiation, enrolment, legitimation, and activation. These sub-themes cover aspects of practices, which are new or perhaps need to be modified, where a core challenge may be whether key participants are able or willing to drive the practices forward. In the present context, the therapists must organize or reorganize themselves and others to collectively contribute to the work involved in the new practice. This is a complex working process that may involve rethinking individual and group relationships between people and things.

The construct collective action concerns the ability to work together to endorse an intervention and its components. This

may, e.g., refer to the allocation of work, which underpins the division of labor that is built around a set of practices as they are operationalized in the real world.

The construct of reflexive monitoring comprises systematization, individual appraisal, reconfiguration, and communal appraisal, which refers to collecting information, expressions of personal relationship to new technologies, redefinition of procedures, modifying practices, or evaluating the worth of a set of practices. Participants in any set of practices may seek to determine how effective and useful it is for them and others, and this involves the work of collecting information in multiple ways.

A series of phenomena are in play during implementation processes, when therapists are about to adopt a new treatment offer, embedding and routinizing new ways of working. When examining these phenomena, the NPT is a relevant theoretical framework to use, since it involves identifying, differentiating, and codifying the qualities and characteristics of such phenomena. Thus, NPT provides the mechanisms to examine how and why cognitive and social processes are critical for implementation and explains how changes occur in the way employees use and consider an innovation (8).

Aim

Using mixed methods, the present study examines how therapists engage into the process of implementing the *Blending Internet treatment into conventional face-to-face treatment for alcohol use disorder* (Blend-A) (9) treatment platform. The implementation process is viewed through the lens of quantitative and qualitative data material. The quantitative data are extracted from The Normalization MeAsure Development questionnaire (NoMAD) (10–12). The therapists' clinical experiences of transitioning from FtF to blended treatment are uncovered through qualitative interviews and later analyzed by the means of NPT mechanisms.

Materials and methods

Design

This study is conducted in a mixed methods design, using triangulation and the convergence model (13). Survey data using NoMAD were collected in two waves. Qualitative interviews were conducted six months after the 2nd wave. By using this model, quantitative and qualitative data were collected and analyzed separately and subsequently the results were compared. The purpose of using this model was to formulate valid and well-substantiated conclusions about the therapists' perspective of implementation of Blend-A. The consolidated criteria for reporting qualitative studies (COREQ) (14) were used as a checklist for reporting.

Setting

In Denmark, treatment for alcohol use disorder (AUD) is provided by municipalities and is free of charge for the patients. Patients have the option to choose which municipality they wish to receive treatment in and are guaranteed treatment within 14 days. Treatment typically consists of conversational therapy, including Motivational Interviewing (MI), Cognitive Behavioral Therapy (CBT), supportive conversations, family therapy, and network-reinforcing initiatives, and may also include pharmacological treatment. The most common forms of treatment for AUD are MI and CBT (15, 16). Treatment duration is typically four to six months, depending on the patient's needs, and is provided by therapists with professional backgrounds as nurses, psychologists, pedagogues, and social workers.

Context

This study is a sub-study of the larger trial Blend-A (9) and investigates the implementation process of Blend-A in alcohol treatment institutions, located in various municipalities. Blend-A is a treatment program aimed at treating AUD by combining the use of an online digital treatment platform with FtF-sessions at municipal alcohol treatment institutions. This mode of treatment originated in the Netherlands and has been found successful in the implementation of AUD treatment programs (17). The online treatment platform is flexible, the patient can choose to not store personally attributably data on the platform and thus stay anonymous to the system except to the therapist. The platform consists of 21 modules, which patients can choose from in collaboration with the therapists, and the patients can review previous answers and receive feedback from therapists on current issues (18).

All Danish Municipal treatment institutions for AUD were offered participation in the overall Blend-A trial. The trial was designed as a pragmatic stepped wedge cluster randomized controlled study of outcome of Blend-A (9), and 18 institutions accepted the invitation. The implementation of Blend-A was facilitated by members of the author group (RB, KT, and ASN) in the treatment institutions in random sequences between June 2020 and December 2022. Four institutions dropped out during the study period. During the process of implementation, RB, KT, and ASN offered training and supervision aimed at supporting the therapists' ability to use the Blend-A treatment form and had therefore to some extend established some kind of professional relationships with the therapists prior to study commencement.

Data collection

Quantitative data consisted of data collected through a survey in two waves. The survey was sent to all employees at the 14 remaining alcohol treatment institutions via their work e-mail. The survey comprised questions covering demographic information and the implementation process, including the NoMAD questionnaire. NoMAD is based on NPT and was used to study the implementation process. NoMAD operationalizes the implementation process through the four primary NPT-constructs within the CMO-domain "implementation mechanisms": *coherence, cognitive participation, collective action, and reflexive monitoring* (see

TABLE 1 NPT CMO-domains, primary constructs and sub-themes.

CMO-domains	Primary constructs	Sub-themes
Implementation contexts	Strategic intentions *How do contexts shape the formulation and planning of interventions and their components?*	
	Adaptive execution *How do contexts affect the ways in which users can find and enact workarounds that make an intervention and its components a workable proposition in practice?*	
	Negotiations capacity *How do contexts affect the extent that an intervention and its components can fit, or be integrated, into existing ways of working by their users?*	
	Reframing organizational logics *How do existing social structural and social cognitive resources shape the implementation environment?*	
Implementation mechanisms	Coherence building *How do people work together in everyday setting to understand and plan the activities that need to be accomplished to put an intervention and its components into practice?*	Differentiation Communal specification Individual specification Internalization
	Cognitive participation *How do people work together to create networks of participation and communities of practice around interventions and their components?*	Initiation Enrolment Legitimation Activation
	Collective action *How do people work together to enact interventions and their components?*	Interactional workability Relational Integration Skill-set workability Contextual Integration
	Reflexive monitoring *How do people work together to appraise interventions and their components?*	Systematization Communal appraisal Individual appraisal Reconfiguration
Implementation outcomes	Intervention performance *What practices have changed as the result of interventions and their components being operationalized, enacted, and reproduced, over time and across settings?*	
	Relational restructuring *How have working with interventions and their components changed the ways people are organized and relate to each other?*	
	Normative restructuring *How have working with interventions and their components changed the norms, rules and resources that govern action?*	
	Sustainment (normalization) *How have interventions and their components become incorporated in practice?*	

Table 1). The questionnaire consisted of three general questions and is followed by 20 questions on a Likert scale to measure the employees' familiarity with the implementation process. Prior to answering, the participants were informed of the purpose of the study. Data was collected in two waves with five months in between. The questionnaires were filled out through the system Research Electronic Data Capture (REDCap) in Open Patient data Exploratory Network, OPEN.

The qualitative data for analyzing the implementation process of Blend-A was collected through three semi-structured focus group interviews and one individual interview using an NPT-based interview guide (Supplementary file). The interview guide asked open-ended questions to the therapists about their workday with Blend-A, how they used Blend-A in their institutions, and how they used Blend-A in their treatment courses. The four interviews were conducted by RB, RC, and KT via videoconferencing in Cisco Webex. The interviews lasted between 34 min and 76 min and were all audio recorded and transcribed by author SB. No observers were present during the interviews and no field notes were taken.

Data analysis

Data from the questionnaires was analyzed using descriptive statistics. To assess differences in NoMAD questionnaire responses between the 1st and the 2nd wave, a Wilcoxon rank-sum test was employed since the data did not follow a normal distribution. All statistical analyses were conducted using STATA Software Package 17.0 (StataCorp., 2022).

The transcribed interviews were analyzed in NVivo using the General Inductive Approach (GIA) (14). This specific approach is often used when analyzing qualitative evaluation data. The main purposes of the approach is to (a) condense raw data into summary format (b) establish a clear link between the research objective and the findings from the raw data and, (c) create a process-oriented framework on the basis of the structure of experiences/perceptions from the raw data. GIA allows the inductive data analysis to be guided by the aforementioned constructs.

Two coders, authors RC and KT (both female postdocs, who holds MA degrees within anthropology and philosophy, PhD degrees within health sciences, and approximately ten years of experience within qualitative research) independently coded all interview transcripts according to the four primary constructs within the CMO-domain "implementation mechanisms": coherence building, cognitive participation, collective action, and reflexive monitoring. They then collaboratively compared and discussed their coding. In instances of disagreement or ambiguity concerning the alignment between constructs and data, a third researcher ANS was consulted to facilitate consensus. In the final stage of this process, the remaining co-authors reviewed the constructs alongside the corresponding quotations. Essential quotations were translated from Danish

to English by author CHD and included. The final coding decisions regarding the placement of quotations were then made jointly by KT and RC.

Results

Participant sample description

In the middle of the study period for the overall Blend-A study, a survey questionnaire was sent to all staff ($N = 82$) in the 14 alcohol treatment facilities to assess the implementation of the Blend-A platform. Forty-eight participants responded, equivalent to a response rate of 58.5% (see Table 2). The response group had a mean age of 51 (SD 10) years and 17% of them were men. The three largest professional groups were social workers (38%), pedagogues (27%), and nurses (25%). The response group had worked an average of 8 (SD 6) years in their current institutions, and they had an average experience of 9 (SD 7) years treating people with alcohol problems. Of those who answered the questionnaire, it was mainly employees (94%) rather than managers, and 81% of the employees used Blend-A in their daily work (See Table 2).

In addition to filling in the questionnaire, all therapists from the participating treatment centers were invited to participate in a focus group interview. In the invitations, the therapists were informed of the purpose of the study. Of these, 11 therapists agreed to participate in four group interviews; however, one interview ended up being individual. We did not ask for reasons from those who did not opt in. The therapists were from seven different municipalities in Denmark. The therapist interview group consisted of nine women and two men. The therapists had a mean age of 40 years (SD 6, range 31–55). The therapists had different educations: five were social workers, three were nurses, one a psychologist, one a pedagogue, and one had put "other" under education. All therapists had used the internet-based alcohol treatment program with patients, except for one, who was an implementation project manager.

TABLE 2 Information about the participants ($N = 48$).

Categorical variables	%
Sex	
Men	17.0%
Professional groups	
Social worker	37.5%
Nurse	25.0%
Psychologist	2.0%
Pedagogue	27.0%
Other	8.5%
Use of Blend-A in daily work	
No	17.0%
Yes	81.0%
Do not know	2.0%
Function/job description	
Employee	94.0%
Manager	2.0%
Project manager	4.0%
Numeric variables	Mean (SD)
Number of years in the current institution	7.6 (6.3)
Age	50.6 (10.1)
Years of experience with alcohol treatment	9.2 (6.9)

Survey

The results of the scores on the NoMAD instrument from both 1st and 2nd wave as well as the sub-scores are presented in Table 3. It should be noted that the first three questions were rated on a 1–10 scale and were not included in the total score. A positive trend from 1st to 2nd wave is seen; however, not significant.

Questions four to 23 received an average score of more than two, except for question 13, which concerned the interference of Blend-A with the employees' everyday lives, at both waves. In terms of the sub-scores, there was a significant increase in *cognitive participation* from a score of 12.9 (SD 2.7) at 1st wave to 13.4 (SD 2.8) at 2nd wave ($p = 0.012$). There was a positive trend from 1st to 2nd wave, but no significant changes in the other three scores or in the total NoMAD-score.

Therapist experiences with implementation mechanisms

In the present section, the qualitative data is used to uncover the therapists' thoughts and experiences involving the mechanisms influencing the implementation process. The results are grouped along the four primary constructs: *coherence building*, *cognitive participation*, *collective action*, and *reflexive monitoring*, thus allowing for an expanded understanding.

Coherence building

The therapists described how they struggled to find coherence between the new digital intervention and their well-established experiences with the ordinary treatment form of FtF. More specifically, in the early days of the implementation process, the therapists were concerned about how written communication with and feedback to the patient would function, as it was perceived an opposite to their normal way of communicating verbal and FtF feedback to the patient. Not being able to directly experience the patient's facial expression when communicating was considered a real obstacle to having a meaningful communication and thus for the therapist to deliver an appropriate intervention, adjusted to the patient's needs. This worry was central to the therapist, since being able to be adjusting to patients' needs was considered as being central for creating a solid working alliance with the patients.

However, over time and getting familiar with the program, the therapists slowly underwent a process of sense-making, referred to under the sub-theme communal specification. When allowed time to engage in and explore the intervention, the therapists came to rethink the possible benefits of using the blended format. To the extent that the therapists engaged themselves into the intervention, they expressed how they found the intervention a

TABLE 3 1st wave ($n = 48$) and 2nd wave ($n = 18$) answers to the NoMAD instrument (10–12), total score and subcategories.

NoMAD questions	1st wave Mean (SD)	2nd wave Mean (SD)	*p*-values*
(1) When you use Blend-A, how familiar does it feel? (score 0–10)	4.4 (3.5)	6.6 (2.3)	0.164
(2) Do you feel Blend-A is currently a normal part of your work? (score 0–10)	3.6 (3.2)	5.4 (2.6)	0.151
(3) Do you feel Blend-A will become a normal part of your work? (score 0–10)	5.6 (2.9)	6.1 (2.7)	0.558
(4) I can see how Blend-A differs from usual ways of working (score 0–4)	2.7 (0.9)	2.8 (0.9)	0.301
(5) Staff in this organization have a shared understanding of the purpose of Blend-A (score 0–4)	2.8 (1.1)	2.9 (0.9)	0.730
(6) I understand how Blend-A affects the nature of my own work (score 0–4)	2.4 (1.1)	2.5 (1.0)	0.809
(7) I can see the potential value of Blend-A for my work (score 0–4)	3.2 (0.9)	3.2 (1.1)	0.219
(8) There are key people who drive Blend-A forward and get others involved (score 0–4)	2.8 (1.3)	2.9 (1.4)	0.156
(9) I believe that participating in Blend-A is a legitimate part of my role (score 0–4)	3.1 (0.9)	3.3 (1.0)	0.563
(10) I'm open to working with colleagues in new ways to use Blend-A (score 0–4)	3.5 (0.8)	3.8 (0.9)	0.999
(11) I will continue to support Blend-A (score 0–4)	3.5 (0.8)	3.5 (0.9)	0.250
(12) I can easily integrate Blend-A into my existing work (score 0–4)	2.6 (1.0)	2.7 (1.4)	0.480
(13) Blend-A disrupts working relationships (score 0–4)	1.2 (1.1)	1.1 (1.2)	0.488
(14) I have confidence in other people's ability to use Blend-A (score 0–4)	3.4 (0.9)	3.7 (0.7)	0.500
(15) Work is assigned to those with skills appropriate to Blend-A (score 0–4)	3.4 (0.9)	2.1 (1.6)	0.371
(16) Sufficient training is provided to enable staff to implement Blend-A (score 0–4)	2.0 (1.5)	3.3 (1.0)	0.808
(17) Sufficient resources are available to support Blend-A (score 0–4)	2.8 (1.1)	3.2 (1.0)	0.500
(18) Management adequately supports Blend-A (score 0–4)	3.3 (1.1)	3.1 (1.0)	0.529
(19) I am aware of reports about the effects of Blend-A (score 0–4)	2.1 (1.1)	1.9 (1.4)	0.501
(20) The staff agree that Blend-A is worthwhile (score 0–4)	2.4 (0.9)	2.1 (1.3)	0.918
(21) I value the effects that Blend-A has had on my work (score 0–4)	2.3 (1.0)	2.5 (1.2)	0.999
(22) Feedback about Blend-A can be used to improve it in the future (score 0–4)	3.2 (0.8)	3.6 (0.6)	0.625
(23) I can modify how I work with Blend-A (score 0–4)	3.2 (0.7)	3.3 (0.8)	0.531
Total NoMAD-score and sub-scores			
NoMAD-score (score 0–80) (questions 4–23)	55.1 (9.3)	57.6 (8.8)	0.240
Sub-score, *coherence building* (score 0–16) (questions 4–7)	11.1 (2.5)	11.5 (2.6)	0.524
Sub-score, *cognitive participation* (Score 0–16) (questions 8–11)	12.9 (2.7)	13.4 (2.8)	0.012*
Sub-score, *collective action* (score 0–28) (questions 12–18)	18.0 (3.6)	19.2 (3.2)	0.267
Sub-score, *reflexive monitoring* (score 0–20) (questions 19–23)	13.0 (2.8)	13.4 (3.1)	0.982

*Tested via the Wilcoxon rank sum test.
Scored from 0 to 4, where 0 = disagree and 4 = agree.
We have replaced [the intervention] with "Blend-A".

usable tool in their everyday practice. By this recognition, they came to understand and point to differences between online treatment and FtF treatment. A therapist described how there were multiple modes of using the blended format, and pointed to one specific benefit of the blended format that added to her sense-making of the intervention by reference to collaborating with the patient when shifting between FtF conversations and written digital feedback to the patient on his/her work with the modules:

> ".. they shouldn't think of the conversation as just another module, but maybe think that the conversation is.. well, more like, is there something to pick up on from what you've already been through? Or if you feel, 'Hey, there's actually a theme here that you mentioned in that session, where I didn't provide feedback. Would it make sense to you if you come in, and we could work on that a bit?' And then you can proceed with the remaining modules." (Therapist 1)

Here we find sense-making internalized through each patient's individual need for feedback. In coherence with the patients, the therapists sought to work more thoroughly with the intervention by keeping an eye on alternative ways to interact with the patient during the treatment. By the blended intervention the therapist gained new understandings about treatment and responsibilities to engage with the patient.

One therapist mentioned how recognizing the use of the platform as an instrument for solving immediate questions that may arise, changed his/her perceptions of the possibilities inherited in the digital platform—possibilities, which differentiated from the more familiar therapeutic FtF sessions. By the therapists becoming increasingly aware of the difference of the two therapeutical options, they came to gain more visibility about own resources available for working with the digital intervention on a long-term perspective. A therapist explained how the digital intervention could be integrated in or change already existing routines:

> "Yes, and the patient also gets the experience of 'well, if there's something I'm in doubt about, then I'll just write', 'well go ahead and do that' and I could also see when messages ticked in: 'Now there's actually something on the platform'. And I could see, it's a conversation 'Well, I'll just take this right here between two sessions' because it's like an SMS, you don't have to spend a lot of effort on that. But as the patient also experiences, it sparks a connection." (Therapist 1)

Sense-making also involves internalization, which concerns the therapist's ability to understand the value, benefits, and importance of a set of practices. It is about being able to attribute worth to a new way of working. According to the therapists, the work of providing feedback was not only considered to be of benefit to the patient but also something, which offered the therapist a room for providing more in-depth therapy. When the therapists had to provide written feedback, they realized that they became more concerned about weighing up his/her feedback based on their best body of knowledge of the specific patient on the one hand and how the patient would receive the feedback on the other hand.

The therapists also realized that the contact to the patient was more dynamic in structure as there might occur communication between therapist and patient through the platform in between FtF-sessions. A therapist explained how the intervention had not really changed the normal workflow, the feedback module had rather added to the therapist's ability to comprehend the patients' unwritten thoughts and perspectives. In that sense, it offered the therapist, unlike in the FtF-sessions, a space for thinking more thoroughly about the patients' reflections during the treatment course.

Cognitive participation

When the therapists were asked about their experiences on implementing blended care into their daily practices, they placed emphasis on the importance of planning their weekly schedule as to having time for working with the new online platform. A therapist stressed that using the digital platform required following a structure and integrating the working procedures of the platform into the therapists' calendar and workflow, especially if the therapist is to communicate with several patients. The therapist described:

> "… Well, I found it nice that I had a day reserved for it, it gave some peacetime. However, I could also see that if I had gaps here and there, I have never adhered to it so strictly, because I also know that I get cancellations during the week, or some might cancel, and then I naturally use that time to provide feedback. It's more for the patients' sake, so that they know that they had something to relate to. That uncertainty, which we all know is a plague 'when will I get feedback on this?', 'Oh, I know I will at least always get it on Tuesdays.'" (Therapist 1)

In making sense of a blended format of treatment, the therapists in general acknowledged ways to overcome the risk of placing unnecessary scruples to oneself. In partnership the therapists build a shared understanding of the best way to overcome such risk, for example as explained by one of the therapists:

> "…we quickly agreed that it would make a lot of sense to structure the feedback. So, telling the patients, 'Well, we provide feedback once a week', and then you simply allocated an hour. At that time, each of us allocated an hour each week, telling people, 'Here, you can expect to receive feedback'. Personally, I set aside Tuesday mornings from 8 to 9, informing people that 'even if you may want to proceed quickly and are very eager, well, you can't expect to get feedback the day after you've sent it. I aim for it, but if I'm busy, you might not get it, but you can at least expect that you'll always get feedback on a Tuesday.'" (Therapist 1)

As to ensure that the platform successfully became a beneficial element in the treatment, the therapists were aware of the importance of securing the right information and encouragement of the patients through profound relational work. This was best done by ensuring that the patients know what the intervention applied to and how the intervention could be of benefit to the individual patient.

By getting to know the digital intervention and its possibilities and limitations, the therapists became enabled to reflect on their own practice regarding the intervention, both in terms of the amount of time spent on the platform and how the platform was received by the patients. By acknowledging various aspects of difficulties or limitations connected to the use of the platform, it was considered necessary to adjust the intervention to make it more accurately fit the patient's needs and capabilities in using the treatment program. In one treatment center, the therapist had the following way to overcome hurdles associated with the intervention performance:

> "Well, we've had a facilitator, who has been responsible for conveying information regarding you (the provider of Blend-A) and has participated in those meetings until we decided that we wouldn't invest more effort in it. And then all the therapists in the team, the six therapists, have had access to it, and everyone has had the opportunity to offer it to their patients. Occasionally, we've had some theme days where we've considered how we could use it more creatively and in a way that suits our people. And then I recognize that when you've just brainstormed on it, it comes up more than when you haven't." (Therapist 2)

Collective action

The therapists in general considered that if they had all been engaged in the intervention to begin with, it would have led to a shared understanding of the platform and collective ownership. Primarily because had all therapist's been involved in the intervention, there wouldn't have been a division between those working with the platform and those not working with the platform, which may have led to negative relational integration. In the present context, the relational integration refers to the knowledge work, which the therapists build together to maintain confidence in the digital platform and in the way they use the platform, something that is difficult to succeed with when a shared understanding is not present from the onset. Especially the module of providing the patient feedback occupied the minds of the therapists. Providing the patients with feedback was circumscribed with feelings of being insecure about the therapist's role and skills to perform this task. To both patients

and therapists providing online feedback was not part of their usual interaction and communication form, and in addition, they worried about not being able to adjust their communication according to facial expressions. The therapists mentioned various ways they applied to skill set workability:

> "Yes, because I can feel that my feedback—now that I know that it is spot on—then I know that I can write in the feedback what they need to think about. And then you can say, you start to get into a routine, so you don't have to think deeply every time. But then you can say, I feel, sometimes Blend-A might be deprioritized if they haven't done something themselves on the day when I give feedback. Then I'm not always that pro at them, because then, 'oh', I can feel that I have something else for next week, and then I hope it was a better week where I got, um… And sometimes, a month can actually go by where I think, 'damn, I should have addressed them earlier', but yeah, because it becomes theirs. And if they're not quite on it, I can end up stretching it a bit.. It requires some ownership, and they need to know and commit to that, yeah." (Therapist 3)

One way to uphold interactional workability was for the therapists to ensure that they aligned their uses of the digital intervention. A therapist mentioned how regular meetings were important in the process of interactional workability:

> "…And otherwise, we've have used the meetings, for those of us involved in it and dealing with the feedback in Blend-A, also to align it a bit, how one did it, how one thought, how long a thread do we give people when they are inactive before we say, 'Now you need to come in for a conversation, and maybe we'll stop it because it doesn't work when you're not doing anything." (Therapist 4)

Another therapist mentioned how they would have preferred all therapists in the treatment center to be familiar with the digital platform to maintain confidence and build accountability in a set of practices and in each other as they use them:

> "Initially, there were only three of us, who were selected to participate [in the Blend-A project] and had learned how to use the platform. We should have included all nine because it has done something for ownership, even though we've tried to bring it up and incorporate it into our treatment conference and such. It hasn't come naturally to the other therapists. So, it's definitely something we take with us that if we're going to participate in such a project again, everyone accessing the platform and being involved in it should be included." (Therapist 5)

To make the intervention a part of already established procedures, which are well-known to the therapists requires great focus on the contextual integration, which refers to the resource work related to the new intervention. At one treatment center, they decided to implement in-house workshops focusing on finding alternative ways to use the platform as to make it work more in accordance with the workflow at their treatment center. By allowing themselves to meet and evaluate the platform, they acknowledged that further aspects came to light. Aspects that showed the benefits of rearranging the treatment sessions in the case a session was irrelevant to one specific patient or chancing something in accordance with the patient's individual difficulties.

Being aware of the allocation of resources or procedures, would provide the therapist with confidence in the intervention. It was highlighted by one of the therapists that in general the therapists were positive and engaged towards the intervention.

Further, the therapists were aware of the required amount of structure and systematization in the process of integration of the intervention to keep the new platform in view. The therapists also pointed to how, in one treatment center, having internal meetings and assuring that there is a structure to follow in the daily work was perceived helpful. They recognized the process in connecting the therapists to the platform, which was something that required focus on continuity in information as well as supplementing the initial introduction to the platform with a follow-up session.

Reflexive monitoring

The therapists found themselves in a new set of practices, and therefore they also had to work experientially as individuals to appraise the digital interventions effects and the contexts in which they already are a part of. From this experiencing work stem actions through which the therapists expressed their personal relationships to the new digital intervention:

> "We are two therapists who are committed to this in my department. Now we are expanding to three therapists. And you can say that the fact that there are only three of us who can drive it also means that we have a lot of experience with it now, and it might not be as challenging to have a Blend-A client because you gain some routine and experience with it. And feedback might not take as long either. But I think it's nice that we become one more, because sometimes I think it's been a bit 'phew', there have been many. Those who have really been well-assessed, they have truly benefited from it and really gained a lot from the treatment, so there I think it has been really good." (Therapist 3)

The therapists' engagement led to attempts to redefine some already established procedures or modifying their practices. A therapist explained that after being presented to Blend-A, she/he realized that home assignments were something he/she should initiate more often than she/he had done previously, here expressed:

> "I think for us, it has also made us consider that there are alternatives. I may not have been very good at making use of homework myself and perhaps have a respect for what it can do, so I've definitely started thinking about that, even with patients I don't have in Blend-A. I've been focused on giving them homework assignments and saying, 'There's also some responsibility at home', meaning saying, 'You need to complete this before we meet next time." (Therapist 6)

Through the therapists' individual experiences, they gained more adequate knowledge encompassing the digital intervention. The therapists might have come to each of their individual perceptions of the best way to not only incorporate the digital technology in their workday, but also on how the FtF treatment can be inspired by tools and strategies, originating from the digital platform.

Discussion

The aim of present study was to investigate the process of implementation of Blend-A by the means of both quantitative and qualitative data, collected from health- and social professionals. In the following section, the results of the analysis of the quantitative and qualitative data, respectively, will be compared, and discussed.

Coherence building

When looking at the survey results for the therapists' experienced coherence building both individual and in collaboration, there is a high overall score with no remarkable change between the 1st and the 2nd wave. However, delving into the subgroup questions provides valuable insights, particularly in question four, where therapists at the 2nd wave scored 2.8 (SD 0.9). This score suggests a partial agreement among employees that the implementation of Blend-A differs from their usual work processes. When asked about this in the interview a therapist explained that the intervention had minimal impact on their workflow, which could indicate a positive adaptation to the intervention.

Furthermore, in question seven, therapists scored 3.2 regarding their perception of the potential value in Blend-A. This sentiment aligns with the interview findings, showing consensus on Blend-A being a beneficial tool for patients. The interviews also highlighted unanimous agreement that it was easy for therapists to utilize the time between two sessions to respond to messages from patients.

During the interviews, the therapists described how the digital platform might serve as a path to solving immediate or urgent questions from the patient, which potentially could offer both the patient and the therapist a more natural flow in communications and treatment. This finding is in accordance with the conclusions of Månsson and colleagues (19), who found that digital platforms provided therapists with a greater overview of the treatment and the processes involved in the treatment.

We found this supported in our data by means of the therapists' ability to strengthen the transition between written feedback through the digital platform and the therapeutical sessions. This finding is also supported by Ekström and Johansson (4), who found that therapists expressed advantages of having time to prepare, i.e., think for a while, asking someone for a piece of advice, and not having to deliver an answer immediately. Such findings are part of the construct related to *coherence building*, where we found that at early stages of the implementation, the therapists had difficulties in differentiating iCBT from FtF treatment, making it challenging for them to find coherence between the two modes of intervention. In a similar study, Bengtsson and colleagues found that therapists had expressed that this had made them feel as working all the time (6).

Cognitive participation

In the four sub-questions for the category *cognitive participation*, the therapists scored 3.5 points (SD 0.8) in 1st wave that they were open to working with Blend-A and that they would continue to support Blend-A. The employees thereby expressed that they partially agreed or totally agreed that they were motivated for Blend-A, expressed that they would continue to support the use of Blend-A and were open to using Blend-A. The employees answered the lowest score in 1st wave about whether there were key people in the workplace who drove the implementation of Blend-A [2.8 points (SD 1.3)]. This may indicate that at the beginning of an implementation process it is important that there is somebody who shows the way for the other employees.

In general, we found that, over time, the benefits of the blended format were apparent to the therapists and added to their perceived quality of working online in partnership with the patient. Békés and colleagues (20) consider that such change may be closely tied to professional self-doubt which is a contributor to therapists' acceptance level and positivity regarding online treatment. We believe that aspects of self-doubt as presented by Békés and colleagues (20) may be an important and even overlooked factor for discussing cognitive participation because self-doubt may be what drives forward the therapists involvement in the implementation process and the finding of alternative paths to engage with the new platform that is more in consonance with each of their individual approaches to treatment. This is also supported by Bengtsson and colleagues, who found that following a program adds to the feeling of safety to the therapist as the treatment follows what the patient has agreed upon and that the therapist does not get stuck in small things not relevant to treatment (6).

Collective action

The therapists scored low on whether the use of Blend-A interfered with collaborative relationships (question 13). On the one hand, this may indicate that the therapists did not consider Blend-A in their collaborative relationship with patients and colleagues, but on the other hand, it may also indicate that Blend-A was successfully implemented and that they did not consider Blend-A as a disturbance of their relationship with patients and colleagues. To figure out whether it is one or the other, it is relevant to examine the other answers in collective action. Question 16 examines whether the employees felt that everyone involved in Blend-A had received sufficient training in the use of Blend-A, with the therapists scoring 2.0 (SD 1.5). This indicates that there was disagreement about this. A comparison

between the scores in question 16 and 13 suggests that employees may not have implemented Blend-A sufficiently, as they have not received adequate training. This lack of training may be a factor in not perceiving Blend-A as a disruptive element in collaboration with patients, as insufficient education appears to be an unresolved issue in their response.

This is also illustrated in the interviews, where a therapist mentioned how they would have preferred that all therapists in the treatment center from the onset were familiarized with the digital platform to maintain confidence and build accountability in a set of practices.

During the interviews, we found that to overcome struggles and work overload to each individual therapist, aspects comprising the construct collective action pointed to great collegial interest in finding solutions for the intervention to benefit them in the implementation process. The therapists arranged collective meetings and workshops where they had the opportunity to discuss work to be done to enable the intervention. Furthermore, we believe that findings related to the construct collective action such as joint meetings, collaboration, and sense of community are important aspects for successful digital intervention implementation processes.

Reflexive monitoring

In the NoMAD questionnaire, the overall score for *reflexive monitoring* was 13.0 at the 1st wave and 13.4 at the 2nd wave. For the questions for this domain, the therapists scored 2.1 at 1st wave and 1.9 at 2nd wave in question 19 regarding their awareness of the effects of Blend-A. This is a rather low score, which may indicate that the therapists were not aware of or perhaps not truly convinced about the benefits of the use of Blend-A. This outcome was somewhat expected, as there was no initial assumption that therapists would possess detailed knowledge on this matter, as this responsibility was delegated to the authors, facilitating the implementation process. However, lack of knowledge regarding an implementation of a new project can result in bad implementation results (21). Thus, half a year later, when the qualitative interviews were performed, the therapists felt increasingly aware of the effects, which might be due to their own experiences by using Blend-A. Regarding question 22 and 23 concerning how feedback from Blend-A could be used to improve the future and the capability to modify how to work with Blend-A, the therapists scored higher.

During the interviews, the therapists also expressed how they increasingly used knowledge, benefits, and experiences from Blend-A in other settings. Furthermore, the feeling of safety in the treatment form as mentioned above is also considered a part of the construct reflexive monitoring, where we as an example found this to be expressed through increased uses of home assignments in relation to FtF-treatments. We considered if a possible positive outcome of increased use of home assignments could add to levels of increased working alliances with the patient, which furthermore would affect and ease the implementation of iCBT because the therapist would find their effort worthwhile. This would be an important finding since Békés and colleagues found that poor working alliance were equal to less positive attitudes towards online treatment (20). We do not think, however, that our data indicate neither of these two outcomes but instead we found that for the therapist to have the time for working with both in parallel and by time getting to feel that the two modes of treatment complement each rather than exclude one another is of importance when implementing new practices.

Strengths and limitations

Regarding the survey, we saw a low response rate at the 2nd wave with only 37.5% out of those who responded at the 1st wave. This may explain the lack of significant change from autumn 2021 to spring 2022, and the findings should be interpreted with caution.

The NoMAD tool is a useful tool for assessing implementation processes at both the individual and collective levels, and for identifying inhibitors and promotors of the process. However, it was translated into Danish for use in the present study, and we cannot be completely sure that the meaning of the survey questions is preserved in the translation. Additionally, there are no instructions for how to analyze the results, why different studies analyze the data differently. This can make it difficult to compare results across studies, which have used the NoMAD instrument. Despite these limitations, the NoMAD tool is easy to apply and may provide valuable insights into implementation processes. It is a strength of the study that the implementation process was systematically measured.

Regarding the qualitative interviews, we do not assess the relatively small sample size ($n = 11$) to be a limitation, since Guest et al. (22) argue that the first six interviews are crucial for constructing meaningful themes during an inductive analysis. Their recommendation is based on an experiment they conducted with data saturation and variability. With regard to the facilitation of an interviewer-interviewee alliance and thereby the interview validity, Crouch and McKenzie (23) also argue that a small number of participants can be feasible. Since we used independent parallel coding and codes check, the study was strengthened according to the internal validity and reliability (24), enhancing the credibility of the analysis (25, 26). It may be limitations that the interview guide was not pilot tested, no repeat interviews were conducted, and that we did not return transcripts to the participants for comments and/or corrections nor used stakeholder check (26). Other potential limitations may include a lack of explicit triangulation of the findings through assessing other perspectives (for example service users) for knowing the implementation of Blend-A as well as the level of transferability of findings to other places in Europe and outside Europe.

Conclusion

In conclusion, Blend-A was successful in its implementation process, but there were areas for improvement in the implementation process and in future projects as well. Familiarity

and perceived normalcy of using Blend-A did not change significantly over time, but the cognitive attitude to Blend-A did. These findings may have important implications for the successful implementation and sustainability of Blend-A in the workplace. Overall, the therapists were optimistic about the possible use of a blended treatment format, and that this had a positive effect on the implementation process. Over time, the therapists developed confidence in benefits and disadvantages of a blended format.

While previous studies have not prioritized scrutinizing implementation processes; the present study shows that there is much to learn for management and implementers about improving and optimizing implementation processes for clinical studies.

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 Regional Committees on Health Research Ethics for Southern Denmark. 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

KT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. RC: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. CD: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. SB: Writing – original draft. MF: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. AN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, 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/fdgth.2025.1429582/full#supplementary-material

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Virtual reality and psychedelics: new perspectives and new possibilities in the treatment of alcohol use disorder

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Psychedelic-assisted therapy is a remarkably promising treatment for substance use disorders and for alcohol use disorder (AUD) in particular. Research supporting psychedelics as a safe and effective pharmacotherapy for AUD and its comorbid psychiatric conditions dates from the late1940s and includes over 2,000 published studies. There are, however, challenges to the clinical implementation of psychedelics on a scale appropriate to a highly prevalent disease. Virtual reality applications can aid in meeting these challenges. Studies have shown that virtual reality simulations of psychedelic phenomenology (VRP) can replicate neurophysiological and behavioral markers of classic serotonergic psychedelics when viewed by healthy subjects. The results of these studies suggest VRP may have utility as an adjunct to or replacement for aspects of psychedelic-assisted therapy. Here, we introduce four potential clinical applications for VRP in psychedelic-assisted therapy: to prepare for psychedelics, to extend and enhance their efficacy, to facilitate integration following psychedelic dosing, and to standardize the set and setting. VRP may also have application to clinical research in psychedelics as a placebo and as a tool for interrogating the subjective experience of psychedelics in the therapeutic setting. Integrating virtual reality into psychedelic therapy and research holds the promise of new possibilities for psychedelic treatment and new pathways to their implementation.

KEYWORDS

virtual reality, psychedelic assisted therapy (PAT), alcohol use disorder (AUD), psychedelic placebo, psychedelic phenomenology, *DeepDream*

Background

Excessive alcohol consumption is a public health crisis in the United States. As of 2022, 29.5 million people in the United States (10.5% of the population over 12 years old) were estimated to have alcohol use disorder (1). Alarmingly, the situation appears to be getting worse. An analysis of death certificates from 2019 and 2020 showed that deaths involving alcohol rose from approximately 79,000 to more than 99,000, a 25.5% increase (2). In a longer view, a 2023 study showed alcohol-induced mortality in the US increased by 50% from 1999 to 2022 (3). Compounding the problem, only 7.6% of Americans with past-year alcohol use disorder (AUD) received treatment (4). While medication-assisted treatment is considered state of the art, only three medications (Naltrexone, Acamprosate, and Disulfiram) have been approved by the FDA, and an estimated 70% of individuals engaged in treatment relapse within 12 months (1). There is an urgent need for more effective and accessible treatment, including an increased number of pharmacological options. This need has motivated a search for novel or underutilized therapies.

A brief history of psychedelics and AUD

The peculiar history of psychedelics qualifies them as both novel and underutilized. Early research supports their efficacy in the treatment of AUD and its comorbid psychiatric disorders. Between 1948 and 1976, the treatment of an estimated 40,000 subjects was documented in over 1,000 published studies (5, 6). The subjects in these studies were diagnosed with addiction and psychiatric disorders and treated with classic serotonergic hallucinogens, primarily lysergic acid diethylamide (LSD). In a 2012 meta-analysis, Krebs and Johansen looked at six randomized controlled trials with 636 subjects conducted during this period. Subjects in these trials were treated for AUD with LSD. The authors found a significant reduction in alcohol misuse versus placebo, with a 1.96 odds ratio (OR), superior to that of naltrexone (0.69) and all other currently available pharmacotherapies for AUD (7).

So why weren't psychedelics incorporated into the armamentarium of addiction medicine? The reasons for this had everything to do with politics and nothing to do with science. When President Richard Nixon prevailed upon Congress to pass the Controlled Substances Act of 1970, it became illegal to possess classic serotonergic hallucinogens like LSD and psilocybin, and they were classified as Schedule I drugs. This effectively ended academic psychedelic research in the United States (6, 8). It would be nearly a quarter-century before studies of intravenous DMT in healthy volunteers by Strassman et al. in the mid-1990s paved the way for a "second golden age" of psychedelic research beginning in the early 2000s (6, 9–11). Since 2004, over 2000 articles have been published in peer-reviewed journals investigating psychedelics as a treatment for substance use disorders and other psychiatric disorders such as depression (5).

However, nearly all these studies had small sample sizes or did not include a placebo arm. The recently published randomized controlled trial of psilocybin as a treatment for AUD by Bogenshutz, Ross et al. (12) is notable both for its results and its protocol. All participants had a diagnosis of alcohol dependence and engaged in twelve psychotherapy sessions with providers who included a psychiatrist and trained psychotherapists. Participants were dosed with psilocybin during weeks four and eight of the protocol. A significant reduction in the number of heavy drinking days was reported in the psilocybin group between weeks 5 and 36 of the study. These results were consistent with an earlier study (2015) by Bogenshutz et al. and with other studies of psychedelics as a treatment for AUD (8, 13). Like the previous study, this one identified the quality of participant experience, as indicated by scores on the Mystical Experience Questionnaire, as a predictor of clinical efficacy.

Challenges to clinical translation: placebos, implementation, and study design

The placebo problem

Bogenschutz, Ross, et al. demonstrated the difficulty of maintaining blinding in psychedelic research. Participants in this randomized, double-blind clinical trial correctly guessed their treatment assignment at the rate of 93.6% for the first session and 94.7% for the second session. As Van Elk and Fried (2023) observed, most PAT trials are not effectively blinded, and "breaking blind is the rule rather than the exception in psychedelic trials." They noted the absence of tenable placebos and highlighted a finding from a recent systematic review noting that while most psychedelic trials are presented as blinded, blinding was evaluated in only 8 of 81 peer-reviewed studies (14).

Feasibility of implementation

The results of Bogenshutz, Ross, et al. argue for the efficacy of psychedelics as a treatment for AUD. The study also presents some challenges to implementing PAT on a scale appropriate to a highly prevalent illness. Foremost among these is the resource-intensive nature of the treatment. Participants received 12 weeks of sequenced manualized therapy in addition to two eight-hour monitored dosing sessions. It is difficult to imagine this protocol adopted as an outpatient treatment regimen due to its expense and the critical role played by providers with specialized training (15).

Study design limitations

The resource-intensive nature of the study protocol is related to a second challenge: establishing a fund of knowledge sufficient to inform evidence-based clinical practice. To date, the study by

Bogenshutz et al. has been the only recent larger-scale, randomized, controlled trial of PAT for AUD. While there are a considerable number of small-group peer-reviewed studies, they usually have protocols that vary widely and present challenges to evaluation for clinical translation, including the difficulty of maintaining blinding noted above.

It should also be noted that exclusion and inclusion criteria for studies evaluating PAT for AUD would benefit from standardization. An example of this might use of an alcohol breath test to determine exposure prior to beginning a trial of PAT.

A role for virtual reality in psychedelic research and treatment

Here, we propose that virtual reality (VR) applications may contribute to meeting the challenges described above. Below, we introduce some of the modalities through which these contributions might be made.

VR as a treatment modality

VR simulations of psychedelic phenomenology (VRP) modeled on functional aspects of the mammalian visual cortex are an especially promising area of research. *DeepDream* (DD), an algorithm that enables biologically plausible simulation of psychedelic phenomenology, was developed in 2015 by Google engineer Alexander Mordvintsev (16, 17). DD uses pre-trained deep convolutional neural networks (DCNN) to alter images. DCNN image processing parallels that of the mammalian visual cortex, with each layer detecting specific features in an image (18, 19) As information flows through the network, deeper layers combine these features to identify objects and patterns. This identification is possible because DCNN are trained using large-scale image datasets to perform object recognition (20).

Although the DCNN training objective is to forward pass the input image to predict the correct identification, DD instead uses the DCNN to invert the biological image processing model by altering the input image itself. DD provides users the option of clamping processing activity at a user-defined layer in the DCNN and then inverts the information flow so that an input image is changed until the network settles into a stable state (Mordvintsev et al., 2015; Nguyen et al., 2016). This involves changing the image rather than changing the network to match the features of the image with what is represented in the target layer. This results in an image shaped by what the network "expects" to see at the level of detail determined by the clamped layer. Clamping at lower levels will produce images altered in geometric patterns while clamping at higher levels imposes object-like features on the input resembling complex hallucinations (21).

A 2017 paper by Suzuki et al. described using DD to create what the authors called a "Hallucination Machine" to produce biologically realistic visual hallucinations. The Hallucination Machine applied the DD algorithm to each frame of a prerecorded panoramic video presented using a head-mounted device (Oculus Rift 2). Subjects viewed either a control video of nature scenes or the DD panoramic video. After viewing the videos, participants completed a modified version of the Altered States of Consciousness questionnaire (ASC) (22). For participants exposed to DD video, responses on the ASC were similar to subjects in another study who had taken psilocybin for the items assessing the intensity, patterns, feeling of profound inner peace, strangeness, vividness, and spiritual or mystical quality experienced while viewing (23).

This was followed by a 2021 study by Greco et al., providing neurophysiological evidence of the similarity of DD exposure and psychedelic experience following dosing with a hallucinogen. The authors took EEG readings of participants while viewing unaltered video footage and the same footage altered by DD on a computer screen. DD viewing produced increased functional connectivity in the gamma band and increased global entropy. These findings were comparable to those of Roseman, Leech et al. and Carhart-Harris, Leech et al. for subjects under the influence of psilocybin (24–26).

In 2022, a paper by Rastelli et al. provided further evidence of the capacity of DD to simulate psychedelic phenomenology and reproduce its effects (27). One of the central therapeutic markers of psychedelic-assisted therapy is an increase in cognitive flexibility (CF) (28, 29). CF is a central aspect of cognition, permitting adaptation to changing environmental demands, and is markedly decreased in both depression and addiction (30, 31). In Rastelli et al., the authors measured participants' cognitive flexibility through task performance after exposure to virtual reality panoramic videos generated by the DD algorithm. They found that exposure to simulated visual hallucinations increased cognitive flexibility compared to naturalistic (control) videos. This gain in cognitive flexibility was similar to that measured following dosing with psilocybin (32) and was recently replicated in another study using immersive simulated hallucinations (40). Furthermore, another recent study found that perturbing perceptual phenomenology with simulated visual hallucinations modulated high level cognition in human subjects (41, 42).

Taken together, these two studies suggest that virtual reality simulations of psychedelics (VRP) can replicate some of the neurophysiological outcomes of psychedelics in healthy subjects. This argues that VR-simulated hallucinations may be worth investigating as treatments for the same conditions – including alcohol use disorder, nicotine use disorder, and depression – for which psychedelic-assisted therapy has shown efficacy. To date, no study has tested the efficacy of VRP using DD as a treatment for these and other conditions, and no study has trialed VRP against a classic serotonergic psychedelic for any indicated condition.

VR as preparation for psychedelic therapy

Apart from promise as a stand-alone treatment, virtual reality applications may have utility as part of a psychedelic-assisted therapy protocol. With ketamine infusions, providers report that patients naïve to the drug are anxious about starting treatment, regarding the experience as novel and potentially discomforting

(33). It is reasonable to expect that this anxiety may extend to psychedelic therapies as a whole for some individuals. Providing such patients with a virtual reality simulation of the therapy prior to dosing may reduce anxiety and allow the patient to benefit from the treatment. In the event the simulation provokes anxiety or another deleterious response, VRP viewing can be stopped at will, unlike the effects of a psychedelic.

Exposure to nature-based videos that do not attempt to simulate psychedelic experience has been investigated as an option for enhancing set and setting for participants in PAT with AUD. Heinzerling et al. (2023) used "Visual Healing", a nature-themed video, and explained their choice this way: "We chose a nature theme for the video as use of psychedelics in traditional healing rituals and outside of clinical trials often occurred in natural and outdoor settings and a greater feeling of connectedness to oneself, others, and the natural world is consistently reported following psychedelic experiences." Study participants watched a three minute introductory video during a preparation session and forty-two minute and fifteen minute videos at the opening and closing of the psilocybin dosing session. Primary outcomes in this randomized controlled trial were increases in heart rate and blood pressure pre- and post-psilocybin dosing. Exploratory outcomes included alcohol use, psychedelic effects, stress, and anxiety. The investigators found that participants viewing nature themed video, Visual Healing, had a peak increase in post-psilocybin blood pressure significantly lower than participants viewing a control video. There were no statistically significant differences in exploratory outcomes between the control and experimental groups.

While this review focuses on virtual reality simulations of psychedelics experience for a targeted therapeutic intervention (AUD), there have been more general and theoretical explorations of psychedelic simulations. Some of these fall under the heading of "Cyberdelics", conceived as a union of digital technology and psychedelics. Cyberdelics are designed to produce altered states of consciousness distinguished by the experience of awe and transcendence associated with classic serotonergic psychedelics. Cyberdelic pioneers characterized immersive virtual reality applications as the nearest analogue to dosing with psychedelics and promoted cyberdelics as a utopian project with the potential to produce "such beauty, fascination and depth that mankind will be seduced away from mass suicide" (Lanier 2017). To date, there have been no documented attempts to harness applications identified as cyberdelic for social change or therapeutic applications.

While cyberdelics have not been evaluated as a means of promoting pro-social change at population scale, researchers have attempted to replicate aspects of psychedelic experience using VR in group therapy. Glowacki et al. (2022) implemented a VR application called "Is-Ness distributed"in a group setting. The study used healthy volunteers at multiple sites simultaneously using the application. The application depicted the bodies of participants merging in a shared "virtual space", with the primary outcome of the study being induction of a "self-transcendent experience". The authors used the Mystical Experience Questionnaire (MEQ 30), the Ego Dissolution Index (EDI), the Communitas Questionnaire, written reflection, and semi-structured group discussion to assess such experiences. They reported responses for self-transcendent experiences comparable to low doses of psilocybin (18–20 mg) on these assessments.

Although VRP applications are the only ones rigorously evaluated for simulation of psychedelic phenomenology, there are other commercially available virtual reality applications attempting to replicate beneficial or pleasant aspects of the subjective experience of psychedelics. Some of these were designed as psychotherapeutic interventions. They include Liminal VR, Cosmic Flow, and Deep States. These applications are primarily focused on relieving stress, promoting mindfulness, and inducing states of relaxation (Casu et al, 2024).

Using VR to extend and enhance the effects of psychedelics

VRP may also be able to extend the duration of effect for psychedelic-assisted treatment. There is evidence that the efficacy of psychedelic treatments attenuates over time, with estimates ranging from 6 weeks to 9 months for classic serotonergic psychedelics (34). If brief VRP sessions, administered either in a clinic or at home by patients, could extend the therapeutic effect's duration, this would make the treatment more economical and, hence, more accessible.

VRP may also make it possible to target areas of therapeutic importance in the psychedelic experience. Subjects commonly report between one and three significant events in a psychedelic dosing session. These may include episodes ranging from an encounter with a deceased relative to a visit to another planet, but subjects regard each as having thematic content and providing therapeutic benefit (35). Frequently, however, subjects report difficulty recalling these events in sufficient detail to discuss them in psychotherapeutic sessions following dosing (15, 36). VRP may make it possible to stimulate recall of these events and make the material accessible in psychotherapy.

If VRP is shown to provide therapeutic benefit, it may also be useful as an intervention for individuals with AUD who have benefitted from PAT but experienced relapse. For patients with a history of relapse following PAT, VRP sessions could be scheduled at intervals preceding periods of increased relapse risk.

VR as a tool for interrogating the role of subjective experience in PAT

There is a debate among researchers as to whether the therapeutic effect of psychedelics is mediated through the unique subjective experience made possible by these substances. Yaden et al., Bogenshutz, Ross, et al., and others argue that the subjective experience is necessary for the therapeutic effect of psychedelics and that favorable outcomes may be attributed to aspects of the subjective experience, particularly those indicating profound spiritual experiences (12, 35). Olson et al. and others contend that the correlation between subjective psychedelic experience and therapeutic outcome does not equal causation, arguing that

therapeutic efficacy depends only on the neuroplasticity induced by psychedelic agents binding to receptors (37). While each side in the debate can cite evidence supporting their contentions, no study to date has evaluated the efficacy of subjective experience alone in the treatment of AUD and depression. A trial of VRP for these conditions would make such a determination possible. Alternatively, if the experiment demonstrated therapeutic efficacy for VRP, then full or partial substitution of VRP for psychedelic agents could be considered.

Using VR to standardize set and setting

As noted above, nearly all the evidence supporting the use of psychedelic-assisted therapy has come from small studies, often open-label, and with a variety of protocols, making comparison difficult. Absent a massive infusion of research funding, it is unlikely that these limitations can be overcome in the near future.

However, VR may be able to mitigate some of these limitations. One approach to compensating for the absence of large randomized controlled trials is establishing a standard protocol for small (10–30 subjects) registered studies. To date, one of the principal sources of variation in study protocols has been their approach to dosing "set" and "setting." Here, "set" refers to the global mental state of a patient at the time of dosing and encompasses mood, expectations, beliefs, anxieties, and therapeutic intentions. "Setting" refers to the physical and social environment of the dosing session. It includes the session location, sensory elements (lighting, temperature, ambient noise), and the presence of patient care team members, usually physicians and psychotherapists. The set and setting of dosing sessions influences the subjective experience and therapeutic efficacy of psychedelic therapies (15, 35). In studies published to date, participants are usually prepared for the dosing sessions with one or more psychotherapy sessions (38, 39). There is no standardized training for therapists working with psychedelics and no validated assessment of a patient's "set" and readiness for dosing. Neither are there guidelines for settings, and these can vary from intensively controlled environments with therapists present to unmodified treatment rooms with minimal therapeutic resources.

Here, VR can play an essential role in both the set and the setting. VRP can be used to preview the subjective experience of psychedelic dosing for subjects, standardizing the set for dosing. Following this, VR applications with head-mounted displays (HMD) and noise-blocking headphones can also be used to standardize settings, obviating the need for a customized dosing area.

VR as a placebo in psychedelic research

Blinding is another area of variation in PAT studies and a frequent target of criticism. Many studies of psychedelics are open-label or lack a tenable blinding procedure (14, 35). Here, a credible VRP, albeit without a therapeutic effect, may be a way of effectively blinding study participants.

VR modalities to enhance integration in PAT

While these uses of VR, whether as a substitute for, a complement to, or an integral part of PAT, are worth exploring, the most intriguing possibility may be the potential for VR to facilitate interrogation of the mechanisms through which PAT exerts therapeutic effects. As noted above, VR, in contrast to psychedelic agents, has a period of activity that can be stopped and started according to the goals of a study. It can simulate fundamental aspects of psychedelic phenomenology and produce representations of almost any conceivable image, pattern, or geometric configuration with recent developments in artificial intelligence. These capabilities enable VR to replicate the experience of psychedelic intoxication in a way that allows for interrogation in real-time. This interrogation could directly correlate highly personal, often ineffable experiences with electrophysiological states and therapeutic outcomes. Achieving this correlation could facilitate post-dosing therapeutic integration of experiences PAT patients have characterized as profoundly meaningful and often with spiritual import. It may also allow for the continuation of the subjective experiences patients value without impacting implementation feasibility.

VR and risk

While VR simulations involve none of risks commonly associated with psychedelic dosing, it is not without risk as a therapeutic modality. The use of any virtual reality device comes with the possibility of virtual reality sickness, a variant of motion sickness. Virtual reality sickness commonly presents with eyestrain, nausea, headache, pallor, sweating, and fatigue. After the sufferer removes the VR viewing device, virtual reality sickness generally resolves within thirty minutes. There is no indication that individuals with AUD would be more susceptible to virtual reality sickness than individuals without the disorder.

The risks posed by persons attempting to use VRP to treat AUD without medical supervision are more difficult to assess. It may be the best preventive measure for this would be to license the software solely to health care providers.

Conclusion

Psychedelics are unique among pharmacotherapies for AUD and its frequent comorbid condition, depression, and promise dramatic improvement after only one or two doses, with efficacy continuing for up to six months and possibly even longer. They also have the potential for transdiagnostic efficacy, raising the possibility that a single treatment session might provide relief for anxiety, cluster headaches, and nicotine addiction. Patients frequently characterize psychedelics as having benefits additional to treatment for an identified condition, attributing profound spiritual insight and increased empathy to dosing (38).

The unique properties of psychedelics also complicate their path to clinical implementation. Current approaches to clinical translation, medication approval, and incorporation into evidence-based practice were developed for treatments whose attributes have little in common with psychedelics. These approaches rely on systems optimized to evaluate medications with defined mechanisms of action targeted to specific diseases whose efficacy can be measured through a limited number of clinical outcomes. The assumption is that the medication in question will work roughly the same in every patient indicated for treatment and that adverse effects and clinical outcomes are consistent and dose-dependent.

Proponents of psychedelics argue that the features making them the square peg in the round hole of medication protocols are also responsible for their distinguishing therapeutic efficacy. They contend that providing patients with similar conditions with different experiences and a range of therapeutic outcomes is an advantage, evidence of the multifaceted functionality of psychedelics and their potential role in personalized treatment regimens (35). While this argument may have merit, it is unlikely that medication evaluation and implementation systems would be reconfigured to accommodate a single class of agents solely based on clinical efficacy.

Still, none of these considerations diminish the urgency of implementing new treatments for AUD or the therapeutic promise of PAT. It is worth noting in this context that the term "psychedelic" is compounded of Greek words for "mind" (psyche) and "to manifest" (deloun). The signal contribution of VR to the development of psychedelic therapy may be providing new perspectives on how the mind manifests under psychedelics and the ramifications of this manifestation. In this capacity, it can examine an issue fundamental to PAT: Do psychedelics induce a unique mental state, one possible only through a class of psychoactive substances? Or do they facilitate an intensification of consciousness, which might be accessible through intentional practice without using any drug? If establishing a reciprocal heurism between VR and psychedelics can constructively address this question, it may lead to new possibilities for PAT and new pathways to clinical implementation.

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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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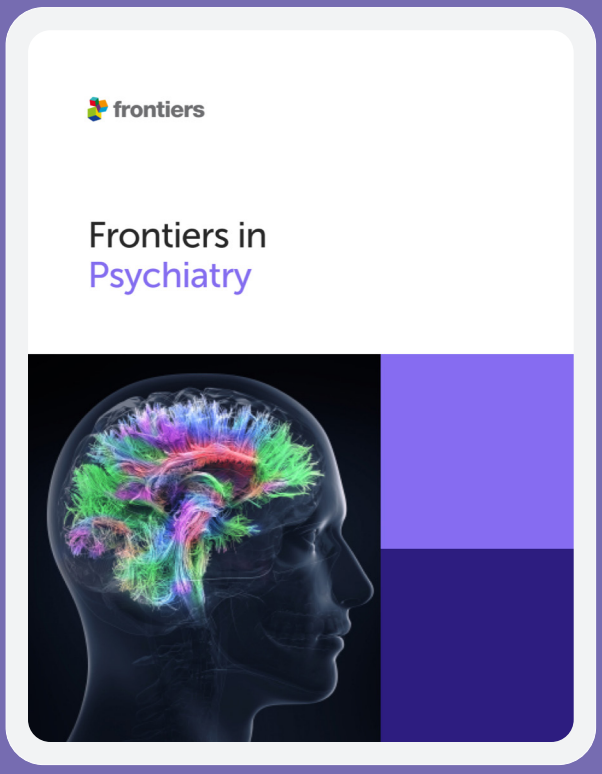

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