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Case reports in psychopharmacology, volume III

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Editorial: Case reports in psychopharmacology, volume III

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Editorial on the Research Topic
Case reports in psychopharmacology, volume III

Mental illness can lead to severe disability and may impact quality of life, even leading to suicidal ideation. The problems associated with mental illness may be more pressing now, as the prevalence of these illnesses may have increased during the recent COVID-19 pandemic (1). Thus, there is a growing need to rise to the challenge to treat these illnesses. This is especially true in view of the fact that many of these patients are treatment-resistant (2). In this third volume of our series of case reports, the overarching theme is the treatment of (mental) illnesses with pharmacotherapies. Continuing from our previous two volumes (3, 4), we present diverse reports on various topics. Not only are there papers on novel treatments for mental illnesses, but we also highlight some new indications for established treatments. We also provide some cautionary tales about the use of some established pharmacotherapies.

The past few years seen a surge in interest in using glucagon-like peptide 1 (GLP-1) receptor agonists. Originally marketed for the treatment of Type 2 diabetes, they are now commonly used for weight management. A paper published this year found evidence that semaglutide may be effective in the treatment of alcohol use disorder (AUD) (5). Consistent with this, Hill et al. report on the successful treatment of AUD with dulaglutide, a GLP-1 receptor agonist. Due to a lapse in insurance coverage, the patient had to discontinue dulaglutide, and they relapsed to previous drinking patterns. Together, this evidence suggests that more large-scale studies are needed into determining the efficacy of GLP-1 receptor agonists for the treatment of AUD and potentially other substance use disorders.

Some mental illnesses can be challenging to manage and two papers in this volume provide some hope for novel methods of managing these disorders. For example, major depressive disorder can be difficult to manage, and many patients may lack the treatment they need. In one case report, Stuhec presents a case of successful treatment of depression by a Pharmacist in primary care. This brings hope that the treatment of depression may extend beyond the physician. Pharmacists collaborated with a general practitioner based on the collaborative practice agreement paper, which the patient also signed. Positive treatment outcomes, such as remission, were reported. This report is in line with the recent developments in Slovenia, where clinical pharmacy services are well developed (6).

In another report, on schizophrenia, Hudnik et al. present a case highlighting the role of pharmacogenetics in the treatment efficacy of olanzapine (an atypical antipsychotic, with affinity for serotonin 5-HT2A, dopamine D_2, histamine H_1, muscarinic M_1 and adrenergic $\alpha 1$ receptors) in the management of treatment-resistant schizophrenia. In our previous volume of case reports we also present the utility of pharmacogenetics (4). Thus, novel methods of treatment on the horizon may present new hope for those living with mental illnesses that are difficult to treat.

In the present volume, novel treatment strategies are also presented for two less common illnesses, genital disorder/genitopelvis dysesthesia (PGAD/GPD) and Bainbridge-Ropers syndrome. Rong et al. report on a case of persistent PGAD/GPD that was effectively treated with leuprolide, a synthetic gonadotropin-releasing hormone agonist. The patient exhibited an improvement in genital arousal symptoms as well as a decrease in scores on the Beck Anxiety Inventory and Beck Depression Inventory. Geiser et al. present a potential novel treatment for Bainbridge-Ropers syndrome, typically involving symptomatic treatment. In this report, a 28-year-old male demonstrated an almost complete improvement in challenging behavior following treatment with pregabalin, a modulator of the alpha-2-delta subunit of voltage-gated calcium channels.

Finally, two papers present novel uses of two atypical antipsychotics. Swamy et al. present a literature review and case report highlighting the need to monitor and individually tailor dose adjustments of clozapine (an antagonist at D_2 dopamine receptors and antagonist at serotonin 5-HT2A receptors) during anti-tuberculosis therapy. This is important because people with schizophrenia are at heightened risk of tuberculosis (7). As well, Goto et al. describe two cases in which aripiprazole (an antagonist at D_2 dopamine receptors and antagonist at serotonin 5-HT2A receptors, as well as a partial agonist at serotonin 5-HT1A and 5-HT2C receptors) improved auditory abnormal sensations, where traditional approaches such as antidepressants and supportive therapy were insufficient.

Even established interventions can present with new warnings over time. Yao et al. report on an 18-year-old female who developed recurrent acute myasthenia after taking lithium; this resolved after discontinuation. In another study, Zhou et al. suggest that people may develop a dependence on tiletamine (a non-competitive antagonist of the NMDA receptor), a novel psychoactive substance that has emerged in China as an additive to e-cigarettes. This is important in view of some findings that people with mental illness have greater odds of smoking (8). Finally, even commonly-used drugs can manifest with adverse events, as reported by Ahmed et al., where they present the case of a 58-year-old woman who developed bilateral peripheral oedema after low-dose escitalopram for the treatment of major depressive disorder. Complete remission of the oedema was seen within three days.

In sum, this Research Topic presents hope for new treatments of illnesses that can be difficult to manage. Even though great improvement in symptoms can be seen from novel treatment approaches, this Research Topic also highlights the need for continued monitoring of patients undergoing psychotropic treatment.

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Case report: Escitalopram-associated lower limb edema

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Escitalopram is widely prescribed for the treatment of major depressive disorder and generalized anxiety disorder with a well-documented side effects profile. Peripheral edema, however, is a rarely reported adverse reaction that warrants further work up. This paper summarizes the case of a 58-year female patient who developed transient bilateral peripheral edema following the administration of low dose escitalopram. This case underscores the necessity for clinicians to be familiar with even rare potential side effects of commonly prescribed medications. It also suggests a need for patient education regarding the importance of reporting new symptoms promptly.

KEYWORDS

edema, drug-associated, side effects, SSRIs, escitalopram

1 Introduction

Escitalopram, a selective serotonin reuptake inhibitor (SSRI), is commonly utilized in the treatment of major depressive disorder and generalized anxiety disorder due to its efficacy and relatively favorable side effect profile (1). Despite its widespread use, certain adverse drug reactions (ADRs) remain less characterized in the medical literature. Peripheral edema is infrequently associated with SSRI (1). Peripheral edema typically presents as a swelling in the lower extremities. It has been associated with a myriad of etiologies, including cardiac, renal, hepatic, or venous insufficiency, as well as several pharmacological agents (2). The incidence of drug-associated peripheral edema is often underreported and may lead to non-compliance or unnecessary medical investigations if not promptly recognized (2). We report a case of a 58-year-old-year-old female patient who developed transient bilateral peripheral edema following the administration of escitalopram. The case presents a unique instance of an adverse drug reaction (ADR) to a widely used medication, distinguished by the absence of other typical causes of edema. This is confirmed through extensive diagnostic tests. Importantly, the connection between the medication and edema is underscored by the precise timing of the reaction and the swift resolution after stopping the medication, which

substantiates a direct relationship between the two. Through this report, we aim to highlight the clinical approach to diagnosing and managing such an atypical presentation and discussing the broader implications on management with psychotropic medications (3).

2 Case presentation

A 58-year-old female, previously healthy with unremarkable medical and family history, presented with disturbed sleep. She gradually developed insomnia and appetite loss over one month, prior to her visit, and she also suffered from low mood. A full medical assessment was done in a private hospital which indicated no underline medical explanation for her symptoms. A plan was made, and she was provided with psychoeducation and a therapeutic regimen of escitalopram, initiated at a dose of 5 mg/day, for 30 days, to manage her depressive episode. Later, she presented to our outpatient department for follow up with an acute onset of bilateral lower limb swelling. This event occurred after 6 days from the commencement of the therapeutic regimen. Notably, the patient had not reported any recent alterations in her medication regimen or any significant medical history that could contribute to the current symptomatology. Upon examination, the patient exhibited bilateral peripheral edema, characterized by swelling extending from the dorsum of the feet to the mid-calves. The edema was pitting, without accompanying erythema, ulceration, or discoloration of the overlying skin, which may have suggested an inflammatory or infectious etiology. Her cardiovascular assessment did not reveal any signs suggestive of congestive heart failure, and her abdominal examination was unremarkable, discounting hepatic or renal pathology as a primary cause.

3 Diagnostic assessment

Laboratory investigations were promptly conducted, which included a complete blood count, renal function panel, which included electrolytes such as calcium, sodium, potassium and chloride, liver function panel, thyroid function tests, and a comprehensive urinalysis. The results of these tests were largely within normal parameters, excluding the common systemic causes of edema. However, the urinalysis yielded atypical findings including pyuria, hematuria, ketonuria, and hemoglobinuria, indicating a possible acute urinary pathology. Additionally, the patient's glycemic control was brought into question by an elevated HbA1c level, and liver enzyme disturbances were evidenced by increased total and indirect bilirubin, AST, and GGT levels. Serum lipid profile, C-reactive protein (CRP), B-type natriuretic peptide (BNP), and troponin T results were within normal ranges, ruling out cardiovascular causes. With the exclusion of more common etiologies and the temporal association between the initiation of escitalopram and the development of edema, a provisional diagnosis of drug-associated peripheral edema was considered. Escitalopram was subsequently discontinued and resulted in a rapid and complete resolution of edema within three days, further substantiating the causative relationship.

Patient perspective

Initially, the patient was concerned about the leg edema she started to develop, not sure the reason behind it. Following the identification and cessation of the causative medicine and the initiation of an alternate medication, the patient was happy that her leg edema was resolved quickly and still willing to adhere to her new medication. She was aware of the significance of reporting any worries and not ignoring any signs.

4 Discussion

Drug-associated edema refers to the abnormal accumulation of fluid in the interstitial spaces of the body as a result of medication. Although the edema can be frequent with some drugs, it remains inadequately understood and underdiagnosed. This poor characterization concerns both their mechanism and action. And the reporting system for peripheral edema varies from study to study. Medications from different classes have been implicated in causing edema, commonly with anticancer, antihypertensives, corticosteroids, psychotropics, and many more (4). In psychiatry, considering psychotropic drugs and their association with peripheral edema, antipsychotics and antidepressants are mostly reported. The medications with the highest rate of association were mirtazapine, olanzapine, quetiapine, risperidone and pregabalin (5). Four main mechanisms account for the etiology of drug-associated edema: sodium and water retention (renal edema), increased capillary permeability (permeability edema), lymphatic insufficiency (lymphedema), and precapillary arteriolar vasodilation (vasodilatory edema) (4).

The estimated incidence of peripheral edema can vary widely depending on the population studied and the medications involved. For example, peripheral edema is a common side effect of calcium channel blockers (CCBs), with an incidence ranging from 2% to 25% depending on the type of CCB, dosage, and duration of therapy. Amlodipine, in particular, is more likely to lead to peripheral edema compared to nondihydropyridine CCBs and newer lipophilic DHP CCBs (6). Gabapentin is another medication that can cause peripheral edema, reported at an incidence rate of 2% to 8%. The occurrence of edema seems to be dose-related and more common in the elderly population. In a pooled analysis from clinical trials, the incidence increased from 1.4% to 7.5% with doses of 1800 mg/day and up to 12.3% at 3600 mg/day. However, there are cases of edema developing at doses lower than 1800 mg/day, indicating that it might not always be dose-related (7). It's also important to note that while CCB-associated edema is a frequent issue leading to the use of diuretics, this type of edema is not caused by fluid overload, and using diuretics can pose risks, especially in older adults (6). As for the general prevalence of peripheral edema, one source suggested that approximately 20% of adults older than 50 years may experience edema (8).

In antidepressants, nearly all major classes were found to be associated with edema in a systematic review comparing them. Of these medications, trazodone is the most implicated, followed by

mirtazapine in second place and escitalopram in third. Particularly, SSRIs contributed 24.4% compared to the other classes (9). No clear conclusion is made regarding the possible etilology of anti-depressant associated edema, as most studies are case reports, but the proposed etiology involves the antagonism of α1 adrenergic receptors and 5HT2A receptors, leading to vascular smooth muscle relaxation, increased capillary vasodilatation, hydrostatic pressure, and subsequent edema (5) (9). Another possible mechanism suggests that 5-HT1B receptors are in endothelial cells, and stimulation of this receptor by increased serotonin induces vasodilation through the production of nitric oxide (NO) (10). Bilateral leg edema was reported in some cases with the use of escitalopram. Most of the patients were diagnosed with major depressive disorder and started on escitalopram in different doses, with a minimum dose ranging from 10 mg to 30 mg/day as the highest dose reported (11). In our case, the patient was started on 5 mg/day of escitalopram. The duration of the time from starting the medication to reporting the edema ranged between one week to three weeks (12). In our case, similarly, edema was reported 6 days later.

Reviewing the medication history is crucial when the cause of bilateral lower limb edema is unknown. If any medications are suspected to be associated with the edema, they must be stopped, or their dosage reduced. In addition, the basic laboratory work up should focus initially on excluding major systemic diseases, which include heart failure, renal disease, liver disease and DVT. Other possible differential diagnosis include hypothyroidism, lymphedema due to lymphatic obstruction after trauma or surgery, angioedema and urticaria secondary to allergic reaction. Systemic evaluation includes complete blood count, urinalysis, electrolytes, creatinine, blood sugar, thyroid stimulation hormone, albumin, and other tests for specific indication. Table 1 shows the suggested additional workup for the common differential diagnosis (13).

In our case, blood tests that include kidney function, liver function, urine analysis, complete blood count, thyroid function test, cardiac tests, and electrolytes showed no significant results or indication of underlying disease. Risk assessment for thrombosis was done which resulted in a very low risk for thrombotic disease. However, thrombotic assessment such duplex ultrasound and D-dimer to rule out deep vein thrombosis (DVT) were not done. Drugs interaction or adverse drug reaction are ruled out because the patient only takes lorazepam before bed (14). Medication associated edema was suspected, and escitalopram was discontinued, the edema resolved after 3 days. Despite escitalopram being a commonly prescribed medication for mood disorders, this case report highlights a rare side effect of the drug, edema. Which emphasizes the need for additional research on the side effects of SSRIs and draws attention to the significance of attentive patient monitoring, educating patients about the potential for edema development even at low therapeutic doses, and promptly reporting any such occurrences.

TABLE 1 Differential diagnosis and suggested work-up for medication-associated lower limb edema.

Differential Diagnosis	Diagnostic studies
Heart failure	ECG, Echocardiogram, chest radiograph, brain natriuretic peptide
Liver disease	ALT, AST, total bilirubin, alkaline phosphatase, prothrombin time, serum albumin
Kidney disease	Urinalysis with exam of sediment, serum lipids
DVT	D-dimer, doppler exam
Lymphedema	Abdominal/pelvic CT scan

5 Conclusion

Escitalopram associated bilateral leg edema is a side effect that should be considered when prescribing despite its rarity. Edema can occur at low therapeutic doses and in the absence of other possible medical etiologies. This indicates the further need for healthcare professionals to maintain a broad differential diagnosis when encountering peripheral edema, considering drug associated causes in the context of recent medication changes. This shows the importance of close therapeutic monitoring, blood tests, and knowledge of underlying medical issues, drug interactions, and potential adverse 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.

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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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Pregabalin treatment in a 30-year-old patient with Bainbridge-Ropers syndrome: a case-report

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Mr. X is a Swiss patient with Bainbridge-Ropers syndrome clinically and genetically diagnosed at the age of 28. He is also known to have severe intellectual disability, autism spectrum disorder and epilepsy since the age of 18. At the age of 30, he was admitted for the first time to a psychiatric crisis unit dedicated to mental disabilities for challenging behavior such as self-aggression (forceful vomiting, scratching himself, pulling out his toe and fingernails or banging his head against the wall), agitation, screaming, dropping to the ground, damaging electronic items, or even displaying hetero-aggressive gestures (trying to bite or pull hair, scratching, kicking, or punching) associated with a drop in mood, withdrawal from usual activities, a drop in social interaction and a tendency to doze off during the day. The introduction of Pregabalin leads to rapid stabilization of the clinical state, almost complete improvement in challenging behavior and gradual withdrawal of other treatments (class 2 analgesics, neuroleptics, antidepressants, and benzodiazepines). At the neurological check-up 9 months after discharge from hospital, clinical stability was confirmed by the surrounding team and the medical observation, with almost complete disappearance of auto-aggressive gestures.

KEYWORDS

Bainbridge-Ropers syndrome, ASXL3, pregabalin (PGB), autism, anxiety, epilepsy

1 Introduction

Bainbridge-Ropers syndrome (BRS) is an autosomal dominant genetic syndrome characterized by loss-of-function mutations in the Additional sex combs-like 3 (ASXL3) gene (18q12.1). It is a genetic syndrome recently discovered (2013) in the context of the genetic analysis of patients presenting with clinical features compatible with a diagnosis of Boring-Opitz syndrome. BRS is a rare syndrome with a prevalence of less than 1/1,000,000. No specific management or targeted treatment is currently known. The literature mostly focus on genetic diagnosis and clinical descriptions, which are based on non-specific descriptive signs (1, 2). They include developmental delay or moderate-to-severe intellectual disability with delayed or absent language skills, autism spectrum disorder,

non-specific facial dysmorphia, hypotonia which may evolve into spasticity with postural patterns, notably the flexion of elbows, wrists, and fingers. Other signs include growth disorders, feeding difficulties in early childhood, strabismus, behavioral disorders, epilepsy, sleep disorders with increased risk of sleep apnea linked to hypotonia, and dental anomalies (3–5).

The mutation causing this syndrome is a truncated variant affecting the gene responsible for the production of the ASXL3 protein, resulting in a reduction of ASXL3 activity (1). The function of this protein in humans is not yet well defined, but it is strongly involved in the mammalian brain development, especially in the cell fate specification during early neural development (6–8).

Consensual clinical management guidelines for ASXL3-related disorder have not yet been published. Treatment is usually symptomatic, with multidisciplinary management based on the most problematic symptoms (9).

2 Case presentation

Mr. X is a 30-year-old male patient, Swiss, Caucasian, from a non-consanguineous union. He is the second child of two siblings. The pregnancy and delivery are said to be unremarkable, with the patient's development said to be linear during the first three months of life, feeding difficulties with vomiting after bottle-feeding and no notable somatic disorders to be found. The patient subsequently showed a progressive form of overall delay in development associated with autism spectrum disorder, facial dysmorphia, hypotonia, strabismus and behavioral disorders. He therefore joined the children's sector of a social institution a few days a week and then for school days from the age of five onwards. Medically the patient is known for epilepsy since the age of 18 with notion of generalized tonic-clonic seizures and myoclonic seizures. At the age of 28, Mr. X was hospitalized in a neurological unit for status epilepticus resulting in an increase in his antiepileptic medication.

In the months following this hospitalization, the patient beneficiated from a genetic consultation given his clinical features which associated the various specific signs listed above. Following the genetic analysis, the diagnosis of Bainbridge-Ropers syndrome was made.

Regarding behavioral disorders, he has occasionally presented, since childhood, challenging behaviors, occurring periodically, without any obvious triggers and with spontaneous resolution. During these episodes, he may present with psychomotor agitation, screaming, dropping to the ground, damaging electronic items, or even displaying hetero-aggressive gestures (trying to bite or pull hair, scratching, kicking, or punching), or self-harming (forceful vomiting, scratching himself or banging his head against the wall).

Since the age of 28, he would exhibit such behavioral problem at an increasing rate of several times per day. He would also exhibit new problematic behaviors, such as pulling out his toe and fingernails. The patients' relatives describe a decline in his mood, along with him becoming withdrawn, a refusal to participate in activities, a drop in social interaction and a tendency to doze off during the day. Eating habits fluctuated, with alternating periods of food refusal and minor hyperphagia. His relatives also described episodes of hyperventilation, occurring since childhood but having increased in frequency and intensity over the recent months, particularly during periods of transition. Finally, the patient presented with a long-standing sleeping disorder, waking frequently during the night, and vocalizing in his sleep.

In view of this behavioral deterioration Fluvoxamine 150 mg/d and Risperidone 1 mg/d were introduced, with no clear improvement in symptomatology, leading to the discontinuation of Risperidone replaced by Olanzapine 10 mg/d without any clinical improvement. These are the treatments recommended to treat symptoms of irritability in patients with autism. The introduction of a treatment of proton pump inhibitor (IPP) 40 mg/j with the hypothesis of gastric reflux pain, which might explain certain challenging behaviors (eating disorders, torso laceration, etc.) led to a slight improvement in hetero-aggressive behaviors, but only transiently. Given the significant clinical deterioration over the previous month, with the onset of self-induced injuries, a tramadol-based treatment 200 mg/d was introduced with the hypothesis of dolor, in parallel to Fluvoxamine and Olanzapine, without any clinical improvement.

In view of the severity and frequency of these challenging behaviors over the previous months, he was admitted to a psychiatric crisis unit dedicated to mental disabilities. This was the patient's first psychiatric hospitalization.

Usual treatment:

Sodium Valproat tablet: 500 mg morning, 500 mg midday, 1000 mg evening

Lacosamide: 100 mg morning, 100 mg evening

Olanzapine: 10 mg/d

Fluvoxamine: 150 mg/d

Tramadol retard: 100 mg morning, 100 mg evening

Esomeprazole: 40 mg/d

Daily: Alprazolam 0.25 mg treatment for behavioral crises in reserve maximum twice a day

3 Hospital management

On his arrival, Mr. X presented several episodes of hyperventilation per day (with varying contexts: when a caregiver would address him, at the start of meals, during transitions or sometimes without any context), extremity tremors, provoked vomiting, repeated questions ("who is that?", "what is that?", "tomorrow"), regular episodes of screaming and refusal of care. These episodes pointed to a manifestation of anxiety. At the same time, the patient presented with self-aggressive behaviors such as lacerations of the torso, pulling of nails, toes, and fingers, or thermal stimulation by putting his hands under very hot water for several minutes at a time. He also presented with phases of agitation during which he would urinate on electrical outlets, spills water on the floor or on electronic equipment, try to set off alarms, or even display hetero-aggressive gestures (grabbing caregivers' hair, hitting them with feet or hands). On clinical examination, vital parameters were within normal limits (weight: 54 kg; blood pressure: 108/65 mmHg; heart rate: 71

bpm; oxygen saturation: 100%; temperature: 36.2°C). Severe intellectual disability with language delay, autism, facial dysmorphia with prominent forehead, arched eyebrows and serrated teeth, strabismus, generalized hypotonia associated with skeletal malformations: Marfanoid habitus, pectus excavatum and arachnodactyly were noted. The remainder of the clinical examination revealed self-induced nail-biting lesions on left index finger and all toes without any signs of localized infection. No cardiac, pulmonary or abdominal abnormalities were noted. Neurologically, on two occasions the patient presented with clinical manifestations strongly suggestive of epileptic seizures, despite taking his usual treatment as prescribed. Neurological observation and electroencephalogram evaluation subsequently returned to normal, suggesting an uncertain origin for these seizures. Treatment with brivaracetam 100 mg/d was added, with the aim of improving control of epilepsy. In view of the marked deterioration in the patient's behavior under Brivaracetam (psychomotor agitation with increased insomnia, major aggressiveness towards others and himself, endangerment by repeated urination onto electrical outlets, etc.) and the absence of any clear argument from the neurology specialists for potential benefits, Brivaracetam was quickly withdrawn.

Regarding gastrointestinal symptoms, the patient presented several episodes of induced vomiting at the beginning of his stay, as well as episodes of hyperventilation before meals, possibly compatible with digestive discomfort. An abdominal scanner and oeso-gastro-duodenal transit were performed in addition to an extensive laboratory work-up. Imagery examens were in the norm. Biological tests showed no obvious abnormalities.

Faced with these clinical features, and in particular the atypical self-aggressive gestures directed at his fingernail, we elaborated on the hypothesis of pain linked to an inflammatory disease of the extremities, as part of the Bainbridge-Ropers syndrome. Treatment with non-steroidal anti-inflammatory (AINS) ex officio (Ibuprofen 200 mg three times a day) was started with improvement in self-harm behaviors during three days, but with no noticeable effect on other symptoms of agitation.

To reduce the risk of iatrogenicity, Tramadol and Fluvoxamine treatments were reduced and then stopped, in view of their lack of effectiveness on behavior when they were first introduced. The Olanzapine treatment was also reduced, then replaced by a low-dose Risperidone treatment (0.5 mg/d).

As the patient had already benefited from first-line treatments for irritability in autistic patients, antidepressants for the hypothesis of an anxiety disorder diagnosis, as well as from the implementation of a conventional psycho-educational program in a patient presenting with behavioral disorders with no observed clinical effect, the differential diagnosis of the following 3 comorbidities was considered in view of the patient's clinical presentation: generalized anxiety disorder (episodes of hyperventilation, extremity tremors, provoked vomiting, repeated questions, regular episodes of screaming and refusal of care) (10), poorly controlled epilepsy and chronic neuropathic pain. However, since epileptic manifestations present atypically (maintenance of consciousness, tonic movement of the trunk without clonic movements) and EEGs show no visible abnormalities, these manifestations may also be part of behavioral symptoms related to primary or secondary anxiety. The patient's behaviors suggestive of chronic neuropathic pain (nail biting, hand burning, self-mutilation) led us to diagnose an anxiety disorder secondary to chronic neuropathic pain as the main diagnosis.

In view of this main diagnosis and these 3 differential diagnoses, we chose to introduce a molecule with a pleiotropic effect on anxiety, epilepsy and chronic neuropathic pain. We introduced a treatment with Pregabalin at an initial dose of 75 mg Q.d, doubling the dose every 5 days up to 600 mg Q.d. The introduction of Pregabalin was accompanied by a marked and rapid improvement in behavior, with significant regression in the frequency of self-aggressive gestures, episodes of self-induced vomiting and hyperventilation as well as the disappearance of episodes of hetero-aggression, destruction or urination on objects, especially electrical ones. Mr. X's behavior became increasingly appropriate, he was gradually able to take part in activities by himself or in a group. The Risperidone medication was stopped, without resurgence of problematic behaviors. The patient underwent a rheumatology consultation, which confirmed the presence of the hyperlaxity syndrome and, in the context of this syndrome, probable peripheral neuropathies. By the end of the hospital stay, the patient's residual symptoms were sleeping disturbances, improved by a treatment with of small doses of mirtazapine (15 mg/d). Somatically, following the introduction of pregabalin, the patient no longer presented with epileptic-like manifestations and episodes of vomiting regressed significantly. A few days before the patient was discharged from hospital, a new challenging behavior emerged: the patient presented episodes of fixation on female caregivers, seeking inappropriate physical contact (hair, face, private parts) and obsessively seeking the caregiver's exclusive attention. For example, if the caregiver on whom the patient has an obsession was leaving the room through a door, the patient remained behind this door for several hours at a time, banging on the door with his hands and feet. Prompt psycho-educational care, including verbal re-framing and behavioral extinction, quickly enabled to reduce the frequency and intensity of these fixations, without eliminating them altogether. This emergence at the end of hospitalization of fixations on the female caregivers could be part of a search for attention linked to an anxiety that is sometimes heightened in certain circumstances.

The patient was overall calm when discharged from the hospital, cooperating in his care, with no episodes of hyperventilation as presented in the beginning of his stay. He had a good thymia presenting with smiles and attempts to bond with caregivers. Mr. X continued to refuse certain activities, although he took part in a variety of individual and group activities (listening to music, swimming, sharing meals with other patients, etc.). He spent long periods of calm, observing his surroundings. We should mention the persistence of a few self-harm behaviors towards his toenails (right and left), but only on occasion over the last two weeks of his hospital stay and mainly in a context of frustration with deviant communication. The patient showed no hetero-aggressive gestures. He expressed himself through a few words (with a restricted lexical field and repeated verbal requests), and through pictograms. He no longer presented appetite or sleep disorders.

Treatment at discharge:

Pregabalin: 200 mg morning, 200 mg midday, 200 mg evening

Sodium Valproat: 500 mg morning, 500 mg midday, 1000 mg evening

Lacosamide: 100 mg morning, 100 mg evening
Mirtazapine: 15 mg evening
Nexium: 40 mg/d

To summarize, treatment with pregabalin, in this 30-year-old patient with Bainbridge-Ropers syndrome, permitted a clear and rapid improvement in behavior with significant regression in the frequency of self-harm gestures, hyperventilation, and disappearance of episodes of hetero-aggression, destruction or urination on objects. It also enabled complete withdrawal from neuroleptics and tramadol, cessation of antidepressant treatment with Fluvoxamine (although a small dose of Mirtazapine for sleep persisted), and cessation of daily benzodiazepine reserve medication. Somatically, it allowed the disappearance of clinical manifestations strongly suggestive of epileptic seizures, and the disappearance of episodes of induced vomiting.

Figure 1 shows the week-by-week evolution of the patient's ABC score (Antecedents, Behavior, Consequences) during hospitalization. This score is assessed by the care team in direct contact with the patient, based on a list of around sixty questions evaluating his or her behavior over the past week. Only values above the Z-score baseline of 1.0 are significant in comparison with the population with severe intellectual disability (SID).

Following discharge from hospital, the patient returns to live in his usual social institution. On his return, educational support and occupational activities were resumed. Overall, the patient remained clinically stable. He exhibited episodically challenging behaviors that he had experienced in the past, but which did not require any change in medication or adaptation of his daily routine. These episodes appeared to be mainly attention-seeking and did not endanger the patient. At the neurological check-up 9 months after discharge from hospital, clinical stability was confirmed by the surrounding team, with almost complete disappearance of auto-aggressive gestures. Mr. X was described as quiet and cooperative, with an episode of hyperventilation observed but usual in the context of a medical examination. A weight gain of around 10 kilograms and a tendency to slow down language with bradykinesia were noted.

4 Discussion

Due to the rarity of the syndrome, there is currently insufficient knowledge to propose recommendations for the specific management of patients with BRS, apart from proposing a multidisciplinary approach focused on the difficulties presented by the patient. This situation can lead to over-medicalization of patients, with a high risk of iatrogenicity associated with the multiplication of drug treatments. The clinical situation of Mr. X and the treatment with pregabalin, which allowed the almost complete cessation of all other psychiatric treatments, seem to us to be important to highlight in order to propose a therapeutic approach to this rare genetic syndrome.

Nevertheless, the complexity of the clinical presentation, the severe intellectual deficits and the patient's almost non-verbal behavior make it difficult to establish a clear diagnosis of his acute behavioral regression. The first hypothesis could be a generalized anxiety disorder with several signs suggestive of anxiety (hyperventilation, trembling, agitation, etc.). A second hypothesis could be peripheral neuropathic pain in the context of a hyperlaxity syndrome. And a third hypothesis could be a poorly stabilized epilepsy with residual epileptic seizures that may have gone unnoticed by those around the patient, but which may be experienced as unpleasant by the patient, note that hyperventilation episodes can trigger epileptic seizures, so the anxiety and epilepsy hypotheses are intertwined. Pregabalin's high affinity for the α2δ-1 and α2δ-2 subunits of high-voltage calcium channels enables it to reduce neurotransmission, with an indirect effect on the GABAergic effect. It has a recognized antiepileptic effect, as well as reducing chronic neuropathic pain. This same central effect explains pregabalin's effect on generalized anxiety (11–13). These three mechanisms all point to the central action of pregabalin. In all three of the above diagnostic hypothesis concerning the patient, pregabalin is an appropriate treatment for each of these conditions.

Fact that pregabalin had such a marked and rapid effect on this patient's challenging behaviors raises the question of a specific effect on patients with BRS in relation to the genetic mutation. There is no

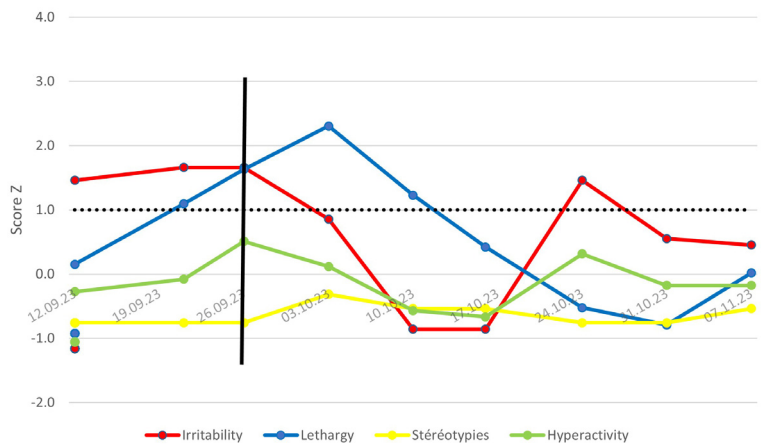

FIGURE 1
Evolution of ABC scores or Mr. X – Comparison with a population with SID.

clear link to found in the literature between the effect of pregabalin on the central nervous system and the effect of the ASLX3 protein (11–13), but the pregabalin's mechanism of action being very wide, notably at the neuronal level, the question of whether the benefits of pregabalin treatment in Bainbridge-Ropers syndrome is confirmed in other cases deserves to be explored. One of the links that could be found is that of ubiquitination failure: this is a pleiotropic phenomenon also responsible for neuropathic pain on which pregabalin acts directly, a phenomenon also linked to the ASXL3 mutation responsible for BRS (8, 12, 14, 15). This lack of knowledge concerning the direct link between BRS and the effect of pregabalin represents the main limitation of this case report. However, this is the first documented case in the literature of the net efficacy of pregabalin treatment in a patient with autism and intellectual deficiency. Whether pregabalin is effective on patients with behavioral disorders, autism or BRS, new research is needed to determine the effect of this treatment on these pathologies.

5 Conclusion

The introduction of pregabalin in this particular case of a patient with SBR and autism has led to a clear and lasting clinical stabilization. Whether this is a central effect or a pleiotropic effect on a set of syndrome-related manifestations, the question remains unanswered. However, the value of this treatment remains to be assessed for patients with BRS and autism, with the aim of providing specific, individualized care to meet the needs of these patients.

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 legal guardian/next of kin for the publication of this case report.

Author contributions

MG: Writing – original draft, Investigation, Methodology. JG: Supervision, Writing – review & editing, Validation. VG: Supervision, Validation, Writing – review & editing, Investigation, Project administration.

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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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Severe tremors induced by tiletamine e-cigarette and alcohol use: a case report

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Background and objectives: Polydrug use has caused serious harm to public health, especially involving novel psychoactive substances. Tiletamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist commonly used as a veterinary anesthetic, has recently emerged in China as an additive in e-cigarettes. However, the long-term impacts of tiletamine and its combined use with other substances remain poorly understood. This case report aims to provide further insight into the clinical manifestations and treatment of tiletamine abuse, particularly focusing on the tremors induced by polydrug use.

Case presentation: The patient had five years of intermittent alcohol use and five months of etomidate abuse. After combining tiletamine for two months, he was repeatedly hospitalized due to coarse tremors, poor sleep and appetite. Based on his substance use pattern and related outcomes, he was diagnosed with phencyclidine use disorder. Initially, intravenous diazepam (20 mg/day) effectively alleviated the tremors. During the second hospitalization, the same dose took longer to take effect, and by the third hospitalization, the dose was increased to 30 mg/day without reducing the tremors. Therefore, primidone was added and gradually titrated to 50 mg/day. The patient's tremors began to improve by the eighth day and significantly diminished by the tenth day. As we gradually replaced diazepam with lorazepam, the patient insisted on discharge.

Conclusions: Polydrug users, particularly those using NMDAR antagonists and gamma-aminobutyric acid type A receptor (GABA-AR) agonists, may be at increased risk of developing tiletamine dependence, with more severe consequences due to cross-addiction. The combination of alcohol and tiletamine could exacerbate neuroexcitotoxicity during withdrawal, potentially contributing to severe tremors. The successful management of tremors with a combination of neuroinhibitory therapies suggested an effective strategy for complex cases. Further studies are needed to better understand the long-term impacts and risks of tiletamine dependence.

KEYWORDS

tiletamine, alcohol, primidone, phencyclidine use disorder, polydrug use, withdrawal, e-cigarettes, case report

1 Introduction

In recent years, there has been a significant rise in the incidence of polydrug use, varying from 3.7%–49.7% in different western countries (1–3), elevating it to a critical public health concern. The primary consequences encompass a heightened risk of accidents or injuries, drug overdose, and fatalities (4). Polydrug use is defined as the concurrent or sequential use of multiple legal or illegal addictive substances (4). Among these, alcohol holds a prominent position due to its widespread availability; an Italian study analyzing outpatient cases revealed that 60% of abuse instances involve alcohol (5). In China, with the rapid economic development, alcohol consumption has been increasing, which has raised concerns about alcohol-related issues (6). Long-term alcoholics often experience postural tremors when they reduce or stop drinking (7). In some cases, even without complete withdrawal, long-term drinking can lead to persistent tremors, which may be related to the chronic brain damage along with other neurological issues (8). The combination of alcohol with other drugs can exacerbate adverse effects such as withdrawal symptoms, cardiovascular disease, liver damage, and behavioral abnormalities (9).

Recently, the stringent regulation of traditional drugs has prompted illegal manufacturers to explore novel psychoactive substances (NPS) as substitutes for illicit drugs. NPS that are most closely linked to psychiatric consequences include synthetic cannabinoids, novel synthetic opioids, and ketamine analogs (10). The proliferation of these substances has been facilitated by the shift from street-level drug markets to online platforms, making them more accessible to a broader audience (11). Despite efforts to control their spread, NPS continue to pose a significant challenge due to their ever-evolving nature and the difficulty in regulating them effectively (12). In China, the drug abuse pattern has also transitioned from traditional opiates to a combination of new synthetic drugs, medical anesthetics, and psychoactive substances (13). Since 2022, reports have emerged concerning the abuse of etomidate e-cigarettes in China. Due to its severe addictive potential and harmful effects, etomidate was officially regulated in China as of October 1st, 2023. Subsequently, the veterinary anesthetic tiletamine has gradually emerged as a novel drug substitute, also sold and consumed in e-cigarette form, posing a significant threat to public health and safety.

Tiletamine is a non-competitive NMDA receptor antagonist with structural and pharmacological similarities to phencyclidine (PCP) and ketamine, known for its potent analgesic and dissociative anesthetic properties (14). It is often combined with the GABA-A receptor agonist zolazepam, which provides mild sedation and effective muscle relaxation (14). Tiletamine and zolazepam are combined in a 1:1 ratio to form the compound anesthetic Telazol (Zoetis Inc., New Jersey, USA). In Asia, this anesthetic is commonly known as Zoletil (Virbac, Lyon, France). Telazol abuse has been reported since 1999 (15). Initially confined to veterinary workers (15, 16), Telazol use has expanded to include the general public (17). The primary routes of abuse include intravenous bolus (18), intramuscular injection (19), and nasal inhalation (17). Most reported cases involve recreational use, with two resulting in fatalities (15, 16), and one in a failed suicide attempt (18). Due to its societal harm, tiletamine has been classified as a controlled substance in countries including South Korea and the United States (20).

Although tiletamine is gaining popularity in other countries, its consequences remain insufficiently explored. In China, where tiletamine use is still emerging, there is no medical evidence documenting its abuse or addiction. Its long-term effects and potential dependence are not well understood, nor are the outcomes of co-use with e-cigarettes and alcohol, presenting significant challenges to treatment services and regulatory oversight. These developments highlight the urgent need for more case studies to identify the clinical symptoms and effective recovery strategies to mitigate the public health impact of tiletamine. A key concern is the movement disorders associated with tiletamine (Telazol or Zoletil) use (21, 22), which are primarily manifested as tremors in this case. Herein, we report a case of severe tremors resulting from polydrug use, primarily involving alcohol and tiletamine e-cigarettes, aiming to provide further insight into the clinical manifestations and treatment of tiletamine abuse.

2 Case

A 40-year-old male presented with recurrent limb tremors, poor appetite, and sleep disturbances, leading to repeated hospitalizations over three months. He has a long history of substance use, beginning in 2005 with ketamine (4 years), followed by heroin (3 years), and methamphetamine (6 years). After each substance, he underwent compulsory detoxification for one year. In 2019, following his last detoxification, he intermittently consumed high-proof alcohol (400–500 ml per occasion), primarily during social gatherings. In June 2023, he began using etomidate-containing e-cigarettes, which led to a car accident due to hazardous driving. He discontinued etomidate after the accident but switched to tiletamine-containing e-cigarettes in October 2023, escalating his use from a few times a week to daily (from two to six cartridges). Despite experiencing euphoria initially, he later developed depressive moods and suicidal thoughts. His alcohol consumption continued, but he did not report withdrawal symptoms. Key milestones in the patient's substance use history were illustrated in Table 1.

On November 28, 2023, the patient developed involuntary tremors in both upper limbs, which worsened with activity. He was prescribed diazepam(10mg/day), which alleviated the tremors, but his symptoms returned after resuming tiletamine use. He was hospitalized on December 4, 2023, and received intravenous diazepam(20mg/day), after which he improved and requested discharge. Upon discharge, he resumed alcohol consumption, which further reduced the tremors. He relapsed to tiletamine on January 21, 2024, and increased his dosage (eight cartridges per day). By January 27, 2024, he reduced his alcohol intake by half. On February 5, 2024, he experienced worsening tremors and was admitted to our hospital, where he received intravenous diazepam (20mg/day) with significant improvement. However, after discharge,

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TABLE 1 Key milestones in the patient's substance use history.

Duration	Abusing substance	Dose	Adverse consequences	Summaries from history and examination	Diagnosis/ treatment
2005–2008	Ketamine	The patient could not recall	ns	Dissociative symptoms, visual hallucinations, depressive moods	Phencyclidine use disorder/mandatory detoxification in a rehabilitation center for one year
2009–2011	Heroin	The patient could not recall	ns	The patient could not recall	Opioid use disorder/ mandatory detoxification in a rehabilitation center for one year
2012–2017	Methamphetamine	The patient could not recall	ns	The patient could not recall	Methamphetamine use disorder /mandatory detoxification in a rehabilitation center for one year
2018–present	High-proof liquor	400–500 ml per occasion, primarily during social gatherings, without a regular pattern, every few days	ns	ns	ns
June 2023–September 2023	Etomidate e-cigarettes	Two cartridges per occasion, every few weeks, with the exact dosage per cartridge unknown	A car accident due to hazardous driving after using etomidate	Dizziness, confusion, inability to stand, and falls after using etomidate	ns/the patient discontinued etomidate use on his own without experiencing any adverse effects after withdrawal
October 2023–February 2024	Tiletamine e-cigarettes	Increased from several times a week to daily within a month, with each session escalating from two to eight cartridges per day, with the exact dosage per cartridge unknown	A suicidal attempt	Dissociative symptoms, visual hallucinations, depressive moods, suicidal thoughts and attempts, poor appetite, sleep disturbance, unsteady gait, limb tremors, head tremors, voice tremors, dysarthria, irritability, anxiety, chest tightness, nausea, dizziness	Phencyclidine use disorder/the patients' treatment were detailed in Table 3

he relapsed and resumed previous consumption levels without drinking alcohol. On February 20, 2024, he was readmitted after his tremors worsened due to abrupt discontinuation of tiletamine, along with chest tightness, nausea, and dizziness. A review of his medical history revealed two prior admissions for limb tremors, with details of diagnoses and interventions summarized in Table 2.

The patient' s vital signs were normal upon first two admission. On the third hospitalization, he was clear with a blood pressure of 128/93 mmHg, pulse rate of 59 beats per minute, respiration rate of 20 breaths per minute, and body temperature of 36.9°C. The observable tremors in four limbs, about 5 centimeters in amplitude, intensified with voluntary movement; however, his muscle tone remained normal. He also exhibited an unsteady gait, head tremor, voice tremor, slurred articulation and variable voice intensity. Increased irritability was noted, but hallucinations and delusions were denied. Recent laboratory tests showed no abnormalities in routine blood tests, coagulation profiles, blood ammonia, electrolytes, liver and kidney function, cardiac enzymes, blood glucose, lipid profiles, or thyroid function. Urinalysis was negative for benzodiazepines, morphine, ketamine, ecstasy, methamphetamine, and buprenorphine. The electrocardiogram (ECG) showed a normal rhythm with a heart rate of 69 beats per minute. Brain magnetic resonance imaging (MRI) revealed a cavernous hemangioma in the right basal ganglia, and the electroencephalogram (EEG) showed a mildly abnormal fast-wave background. The images of the ECG and EEG are presented in Figures 1, 2 respectively.

Brain MRI showed nonspecific abnormalities in the basal ganglia, which could not suggest any organic brain disorder or explain the onset of the tremors. The patient's alcohol consumption pattern did not meet the criteria for alcohol dependence, and he did not exhibit symptoms such as sweating, elevated blood pressure, or tachycardia, thereby ruling out alcohol withdrawal as the cause of the tremors. Although we were unable to detect tiletamine using our current techniques, considering that the patient exhibited a pattern of self-reported tiletamine use (structure and potency similar to phencyclidine), characterized by high-dose consumption, intense cravings, increased tolerance, and recurrent physical and interpersonal issues meeting over two criteria from the DSM-5, we diagnosed the patient with phencyclidine use disorder.

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TABLE 2 Admission timeline.

Date of admission	Tiletamine use	Alcohol use	Days at hospital/ successive days of tiletamine use	Summaries from history and examination	Diagnosis/ treatment	Hamilton Anxiety Rating Scale
December 4, 2023	Increased from two to six cartridges per day (from a few times a week to daily)	400–500 ml of high-proof liquor per occasion, every a few days	2/33	Dissociative symptoms, visual hallucinations, depressive moods, suicidal thoughts and attempts, poor appetite, sleep disturbance, limb tremors, unsteady gait,	Phencyclidine use disorder/ intravenous diazepam 20 mg/day, intravenous fluid 1000 ml/day, sodium valproate 0.5 g/day	15
February 5, 2024	Increased from six to eight cartridges per day	Reduced by half (150–200 ml of high-proof liquor per occasion) 7 days before admission	4/14	Poor appetite, sleep disturbance, limb tremors, unsteady gait, irritability	Phencyclidine use disorder/intravenous diazepam 20 mg/day, intravenous fluid 1000 ml/day, sodium valproate 0.5 g/day	14
February 20, 2024	Eight cartridges per day	ns	12/9	Poor appetite, Sleep disturbance, unsteady gait, limb tremors, head tremors, voice tremors, dysarthria irritability, anxiety, chest tightness, nausea, dizziness	Phencyclidine use disorder/intravenous diazepam 30–20 mg/ day, lorazepam 2 mg/day, intravenous fluid 1000 ml/day, sodium valproate 0.5–1.0 g/day, olanzapine 5–10 mg/ night, primidone 25–50 mg/day	25

To manage his tremors and associated symptoms, pharmacologic treatments outlined in Table 3 were administered. He received intravenous diazepam at 30 mg/day. Due to irritability, poor sleep and appetite, oral sodium valproate (0.25 g twice daily) and olanzapine (5 mg nightly) were started. Additionally, 500 ml of intravenous fluids were given twice daily to maintain physiological stability. As his appetite improved, intravenous fluid administration was gradually discontinued. By the sixth day, his sleep, anxiety and irritability had significantly improved, with sodium valproate at 1 g/day, olanzapine at 10 mg/night and the Hamilton Anxiety Rating Scale score dropping from 25 to 10. However, tremors showed no improvement (5 centimeters in amplitude). Consequently, primidone was initiated at 25 mg nightly and gradually increased to 50 mg/day. By the eighth day, tremors began to subside (3 centimeters in amplitude), with marked improvement by the tenth day (1 centimeters in amplitude). During this period, diazepam was gradually replaced with oral lorazepam. By the twelfth day, the patient was able to walk normally, though mild tremors persisted in both upper limbs. The following day, the patient requested discharge and declined further medication. No significant adverse drug reactions occurred throughout treatment.

In the six-month follow-up conducted by phone, the patient reported no use of tiletamine e-cigarettes or tremors, while maintaining his previous pattern of alcohol consumption.

3 Discussion

To the best of our knowledge, this is the first documented case of polydrug use involving alcohol and e-cigarettes containing etomidate and tiletamine. The existing literature lacks detailed descriptions of tiletamine dependence and effective treatment recommendations. Compared to previously reported cases of tiletamine or Zoletil abuse, the primary symptom in this case was severe limb tremors. Consequently, our treatment focused primarily on addressing the tremors and successfully managed the acute withdrawal phase.

Animal studies suggest that tiletamine, when used as a sole anesthetic, can induce muscle rigidity and seizures (23), similar to the effects observed in humans after a single large dose (17). Acute tiletamine poisoning is often fatal and can result in changes in mental status, nystagmus, cardiac dysfunction, and metabolic disruption (15, 16, 24, 25), while chronic use has been associated with psychoses and behavioral abnormalities (19), with rare reports of movement disorders. For instance, Lee reported a 35-year-old man who intermittently used heroin and inhaled Telazol to reduce heroin dosage, gradually developing choreatic movements after two weeks, which were alleviated with clonazepam after two weeks (21). Similarly, a 30-year-old male who consumed 2,250 mg of Zoletil

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TABLE 3 Detailed medication administration during the third hospitalization.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Diazepam	10 mg q 8 hours IV	10 mg q 8 hours IV	10 mg q 8 hours IV	10 mg q 8 hours IV	10 mg q 8 hours IV	10 mg q 8 hours IV
Sodium Valproate	0.25 g QD 0.25 g QN PO	0.25 g QD 0.25 g QN PO	0.25 g QD 0.25 g QN PO	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO
Intravenous Fluid	500 ml Bid IV	500 ml Bid IV	500 ml QD IV	500 ml QD IV	Discontinued	
Olanzapine		5 mg QN PO	5 mg QN PO	5 mg QN PO	10 mg QN PO	10 mg QN PO
Primidone						25 mg QN PO
	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Diazepam	10 mg q 8 hours IV	10 mg q 8 hours IV	10 mg q 12 hours IV	10 mg q 12 hours IV	10 mg q 12 hours IV	10 mg q 12 hours IV
Sodium Valproate	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO	0.5 g QD 0.5 g QN PO
Olanzapine	10 mg QN PO	10 mg QN PO	10 mg QN PO	10 mg QN PO	10 mg QN PO	10 mg QN PO
Primidone	25 mg QN PO	25 mg QN PO	50 mg QN PO	50 mg QN PO	50 mg QN PO	50 mg QN PO
Lorazepam			2 mg QD PO	2 mg QD PO	2 mg QD PO	2 mg QD PO

The patient requested discharge on day 13 without receiving any medication.

over 9 days developed involuntary tremors of the lower jaw, failing eyesight, and sialorrhea one day after discontinuing the injection. The symptoms self-resolved without any intervention (22). In our case, tremors in four limbs were consistently observed in relation to tiletamine and alcohol use.

The patient's tremors were initially mild and gradually worsened. Similar symptoms have been reported in ketamine users. In a 10-year cross-sectional study in Italy involving 7,897 cases of illegal substance use, 74 cases were ketamine-related. Tremors accounted for 6.8% of the reasons ketamine users sought emergency department care, and these tremors were typically mild and transient (26). This case, however, presented with intentional tremors, dysarthria, and ataxia, suggesting a cerebellar dysfunction. Interestingly, alcohol alleviated these tremors, similar to essential tremor (ET), where alcohol activates GABA-A receptors in cerebellar granule cells, reducing tremors (27–29). Additionally, repeated ketamine administration has been shown to upregulate NMDAR expression in the frontal cortex while downregulating GABA-AR expression, paralleling the modulation observed in chronic alcohol consumption models (30). Furthermore, the increase in its subunit GRN1 and the resultant neurotoxicity are dependent on both the duration and dosage of ketamine exposure (30). Thus, we hypothesize that repeated high-dose tiletamine use may cause neurotoxicity in cerebellar granule cells, increasing excitotoxicity during withdrawal. Alcohol, a GABA-A agonist, could counterbalance this excitotoxicity. However, with prolonged use, the balance between inhibitory and excitatory neurotransmission may be reestablished and then disrupted by abrupt cessation or dose reduction of either substance, leading to tremors.

However, the patient's tremors were more severe than those induced by either ketamine or alcohol withdrawal, suggesting that polydrug use may have contributed to their intensity. The combination of alcohol and tiletamine likely resulted in synergistic neuroinhibition, heightening glutamatergic activity and excitotoxicity. Previous reports have shown that tiletamine abusers are typically polydrug users with histories of NMDAR antagonist or GABAR agonist use (31). Animal studies have shown that prior exposure to alcohol significantly enhances Zoletil place preference and self-administration, highlighting the cross-addiction and compensatory effects between ethanol and NMDA antagonists (32, 33). This cross-addiction may lead to increased consumption of both substances at high doses, potentially explaining the heightened severity of tremors. Although direct human studies are limited, preclinical data suggest that alcohol and tiletamine may together produce even stronger neuroexcitotoxic effects, similar to those observed with the combination of ketamine and ethanol (34, 35). Given tiletamine's potency and effective duration between PCP and ketamine in animals (36), it is reasonable to expect tiletamine might produce even stronger neurotoxic effects in humans.

Accordingly, the tremors likely resulted from an imbalance between the excitatory glutamatergic and inhibitory GABAergic systems, exacerbated by acute withdrawal. During the first two hospitalizations, intravenous diazepam was initially effective in

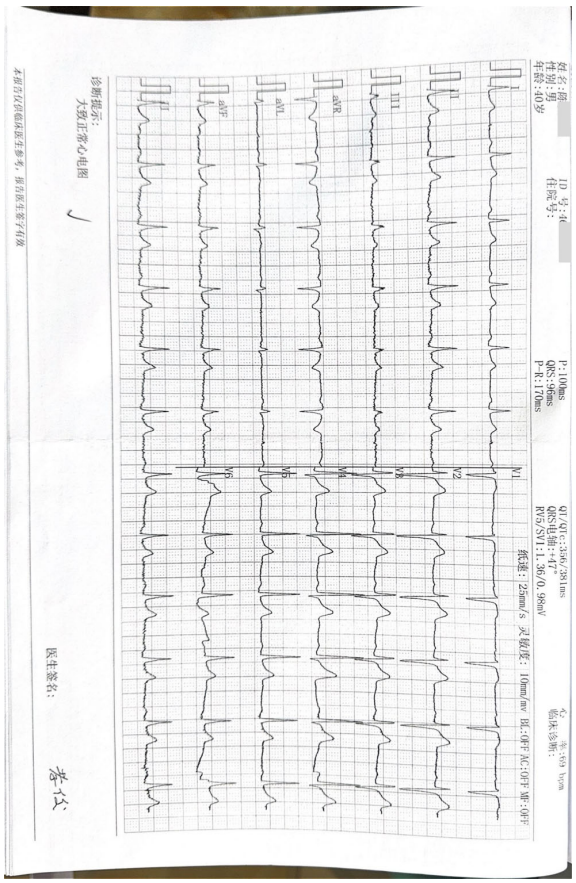

FIGURE 1
Electrocardiogram (ECG) images. The electrocardiogram showed a generally normal rhythm with a heart rate of 69 beats per minute.

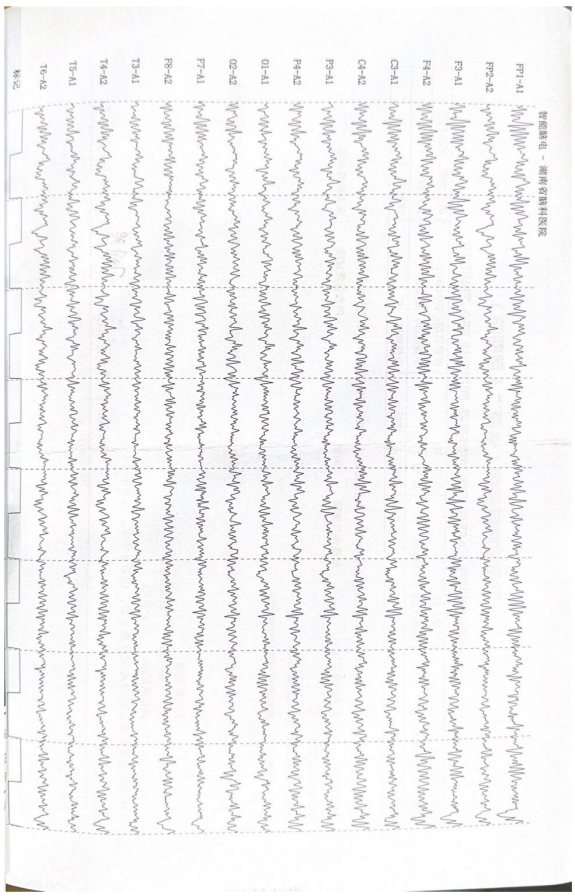

FIGURE 2
Electroencephalogram (EEG) images. The electroencephalogram showed abnormal findings with mild background activity. The primary rhythm observed during quiet wakefulness with eyes closed was a low-amplitude (5–10 μV), 15–20 Hz rhythmic activity, which appeared somewhat irregular. Bilateral symmetry was present.

controlling the tremors. However, as tolerance developed, diazepam became less effective over time, necessitating higher doses. Given that the tremors were likely linked to excitotoxicity, we administered sodium valproate to increase GABA levels and stabilize mood, in addition to primidone to alleviate the tremors. This combination led to significant improvement, suggesting that neuroinhibitory therapies could effectively address the patient's symptoms.

In addition, while deaths related to vaping products containing synthetic cannabinoids have been reported (37), and some studies have suggested that harmful constituents in vaping aerosols may cause cardiopulmonary dysfunction (38), it remains unclear whether e-cigarettes, as a medium, contribute to the dependence and neurotoxicity of tiletamine. Given the widespread use of e-cigarettes and the lack of regulatory policies on tiletamine in China, an increase in tiletamine abuse and dependence via e-cigarettes is expected, along with a potential rise in the risks associated with polydrug use. It remains uncertain whether e-cigarette use of tiletamine is more toxic than traditional methods. Vigilance is needed regarding the concurrent use of tiletamine and GABA-A agonists.

This study has several limitations. Due to constraints in testing methods, we were unable to conduct drug testing for tiletamine or quantify its amount in the e-cigarette. Given that both alcohol and tiletamine can cause neurological damage, we did not explicitly assess peripheral nerve damage in this patient, nor did we investigate potential deficiencies in vitamin B1 or B12. These factors should be considered in future clinical practice. Despite the effectiveness of pharmacological treatments in managing symptoms, improving treatment adherence in patients with complex polysubstance abuse remains challenging. In this case, the patient failed to complete the detoxification treatment during all three hospitalizations, suggesting a lack of recognition of the dangers of polysubstance abuse and insufficient motivation for withdrawal. A multi-disciplinary approach, including psychological therapy, behavioral interventions, and support groups, is crucial but difficult to implement consistently in clinical practice. Future efforts may need to focus more on prevention, with regular health education, substance use assessments, and

psychological evaluations for individuals with a history of polysubstance abuse. This proactive approach would help identify problematic behaviors, the risk of drug dependence, and any potential side effects, allowing for timely intervention and improving the long-term management of polysubstance abusers to prevent relapse.

4 Conclusion

Polysubstance abusers, particularly those using NMDA antagonists and GABA-A agonists, could be at increased risk of developing addiction to tiletamine. The concurrent use of these substances could lead to more severe consequences due to cross-addiction and their ability to counteract each other's negative effects. Long-term alcohol use induces adaptive changes in NMDA and GABA receptors, leading to faster tolerance development, requiring higher doses of tiletamine to achieve desired effects and complicating withdrawal treatment. Combined use of alcohol and tiletamine may exacerbate neuroexcitotoxicity during withdrawal by upregulating glutamatergic and NMDA receptor activity, potentially contributing to severe tremors as seen in this case. The effectiveness of adding primidone in treating tremors suggests that a combination of neuroinhibitory therapies may more effectively manage the complex tremors induced by polydrug use involving tiletamine and GABA-A receptor agonists. Further studies on tiletamine are needed to better understand its effects and potential risks on humans.

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 for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

BJZ: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SY: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. XFZ: Investigation, Methodology, Resources, Writing – review & editing. QC: Investigation, Writing – review & editing. ET: Supervision, Writing – review & editing. BZ: Methodology, Writing – review & editing. LS: Methodology, Writing – review & editing. XHZ: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript.

During the preparation of this work the authors used ChatGPT-4o in order to check grammar errors, refine language, and enhance readability to ensure that the manuscript is well-structured and adheres to academic standards. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Publisher's note

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Acute myasthenia caused by lithium: a case report

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We report the case of an 18-year-old female patient with bipolar disorder who developed recurrent acute myasthenia after taking lithium. The myasthenia resolved upon discontinuation of lithium, and this occurred twice. The results of the cranial magnetic resonance imaging (MRI), multiple sleep latency test, polysomnography, ambulatory electroencephalogram (EEG), and other tests were all negative. In summary, the patient's acute myasthenia was attributed to lithium use. Unlike previously reported cases of lithium-induced chronic and mild myasthenia symptoms, this case involved acute and widespread myasthenia with falls as the primary manifestation. The mechanism may be related to the effect of lithium on acetylcholine receptor (AChR) metabolism, neurotransmitter release, and neuromuscular junction (NMJ) stability.

KEYWORDS

lithium, myasthenia, side effect, synaptic function, neuromuscular junction

Introduction

Lithium is a commonly used to treat bipolar disorder with tremor being the most frequent neuromuscular side effect (1). Lithium intoxication can lead to symptoms such as sluggishness, ataxia, confusion, agitation, and neuromuscular excitability, manifesting as coarse tremors, fasciculations, or myoclonic jerks (2). However, lithium-induced myasthenia is relatively rare, with only six cases reported to date (3–8). These cases primarily involved chronic symptoms, such as exertional weakness, ptosis, diplopia, slurred speech, and dysphagia. In contrast, we report a case of lithium-induced acute myasthenia with recurrent falls as the primary manifestation.

History of present illness

An 18-year-old female patient with a diagnosis of bipolar disorder was admitted to the psychiatric ward after experiencing recurrent mood swings for five years. Six months prior, she had a recurrence of depression, characterized by a lack of motivation, poor sleep, and

suicidal thoughts. After starting lithium carbonate (0.3 g once daily), fluoxetine (40 mg once daily), aripiprazole (10 mg nightly), and zopiclone (7.5 mg before bed), her mood improved, motivation increased, and suicidal thoughts diminished. However, she began experiencing recurrent falls every few days.

The falls were preceded by sudden generalized weakness, with the patient falling to the ground for approximately one minute. During these episodes, her speech became very soft, and she was unable to lift her head. There were no obvious triggers, no visual disturbances, no loss of consciousness, no chest pain, palpitations, ptosis, or diplopia, no urinary or fecal incontinence. She was able to recall the events in detail.

Two months ago, her lithium dose was increased to 0.3 g three times a day, lamotrigine (25 mg once daily) was added, while zopiclone 7.5 mg before bed. Although her mood stabilized, with a significant reduction in depressive symptoms and disappearance of suicidal thoughts, the frequency of fall increased from once every few days to several times a day. Each episode of weakness lasted from 1 minute to half a day. She typically fell on her knees, causing bruising, but no other visible injuries were noted. A Holter dynamic electrocardiogram revealed a sinus heart rate with bradycardia accounting for 36.5% of the time, sinus tachycardia for 11.6%, and a longest R-R interval of 1.5 seconds. Chest CT, head CT, 24-hour EEG, and 24-hour blood pressure monitoring were all normal.

After discontinuing lithium, the patient stopped experiencing falls, though other medications remained unchanged. However, her depressive symptoms and suicidal thoughts resurfaced. Consequently, One month ago, lurasidone (20mg once nightly) was added, and lamotrigine was increased to 50mg daily. One week later, the medication was further adjusted: lamotrigine (75mg twice daily), lurasidone (40mg nightly), tandospirone (10mg three times daily), and zolpidem (10mg once before bed). Her mood improved, and she became more positive.

However, her sleepiness worsened following the medication adjustment, and the lurasidone was considered the culprit. It was discontinued two weeks ago, and lamotrigine was increased to 100mg twice daily. Her Sleepiness improved, but her depression worsened, and mood swings became more pronounced.

Treatment and follow-up in the hospital

During this hospitalization, lithium carbonate (0.3 g twice daily) was reintroduced to control the symptoms of depression, and her mood became somewhat more stable. However, her falls recurred, occurring one to several times a day. As with previous episodes, her speech volume was low, and she was unable to lift her head. There were no episodes of amaurosis, loss of consciousness, chest tightness, chest pain, or palpitation, no ptosis, or diplopia, and no urinary or fecal incontinence. Neurological examination revealed that her muscle strength in the extremities was graded at 3-, tendon reflexes were ++, and no Babinski signs were elicited bilaterally.

Relevant examinations included cranial MRI, which showed small ischemic foci in bilateral frontal lobes; cardiac ultrasound which revealed mild mitral and tricuspid regurgitation; and a Holter dynamic electrocardiogram, which revealed a sinus heart rate with bradycardia accounting for 63.3% of the time (heart rate 40-141 beats/min, average 61 beats/min), sinus tachycardia for 4.5% of the total time, and a longest R-R interval of 1.5 seconds. A 24-hour dynamic EEG was normal, and blood routine, biochemistry, vitamin B12, folate, and thyroid function were normal; A prone-standing blood pressure test was negative. Multiple nap tests revealed an average sleep latency of 19.3 min, with no Sleep Onset Rapid Eye Movement Period (SOREMP). Polysomnography from the previous night was also negative.

After the discussing the case with neurologists and cardiologists, lithium was considered the likely cause of the patient's fall. After discontinuing lithium carbonate, the fall ceased.

The patient's therapeutic regimen was adjusted to lamotrigine (100 mg twice daily), followed by oxcarbazepine (0.45 g twice daily). Her mood significantly stabilized and remained stable throughout the 1.5 years of follow-up, with no recurrence of falls or weakness.

Medical history

None.

Personal history

Both of her parents had short tempers. When she was a child, her father was often absent, and her mother would beat her. She currently has a poor relationship with her parents and is prone to conflict with them. She is a perfectionist and becomes upset if things do not go as planned. She is graduating from high school and will be attending college soon. Under great academic pressure, her performance has declined, and she feels that teachers and classmates look down on her, leading to low self-esteem.

Discussion

In this case, we hypothesized that the patient's recurrent falls were caused by the lithium for two primary reasons.

The first and most compelling reason is the temporal relationship between the administration of lithium and the onset of the falls. The patient's falls began after starting lithium and ceased upon discontinuation of the drug, which occurred twice (Figure 1). At the time of the first fall, the medications administered included lithium, fluoxetine, aripiprazole, lamotrigine, and zopiclone. Among these, only lithium and aripiprazole have been associated with an increased risk of myasthenia, while the others have not (9). Medication changes before the first fall included the discontinuation of aripiprazole and fluoxetine, and an increase in the lithium dose. At the time of the second fall, only lithium was increased, and the falls ceased immediately upon lithium discontinuation, with no other medication changes.

The second reason supporting our hypothesis is that no symptoms or examinations indicated that the falls were caused by another

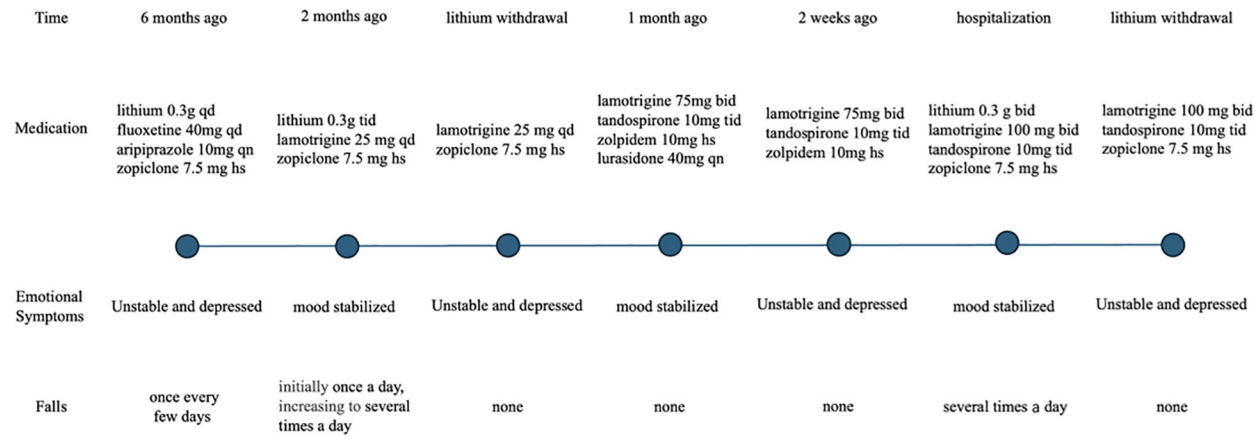

FIGURE 1
Timeline on medications, emotional symptoms and falls.

condition. The patient denied experiencing chest tightness, palpitations, or visual disturbances before the falls, and there was no loss of consciousness at the time of the falls. Cardiac evaluations, including Holter dynamic ECG, cardiac ultrasound, and blood pressure measurements (both prone and ambulatory), were all negative, ruling out cardiac syncope due to arrhythmia, valvular heart disease, or orthostatic hypotension. Additionally, the patient was able to recall the details of each fall and did not experience a loss of consciousness during the episodes and two ambulatory EEGs normal, excluding seizures as a potential cause. The patient did not report daytime sleepiness or sleep-related episodes, and the results of multiple sleep latency tests and polysomnography were negative, ruling out narcolepsy. Furthermore, there was no history of thyroid disease, and her current thyroid function tests were normal, making hypothyroidism unlikely. Conversion disorder was also not considered, as the patient showed no psychological triggers or disturbances in the integration of motor, sensory, or cognitive functions prior to the falls.

To date, six cases of lithium-induced myasthenic syndrome have been reported. The first five cases (3–7)were all characterized by chronic symptoms such as exertional weakness, ptosis, diplopia, slurred speech, and dysphagia, which were significantly improved or resolved after lithium was discontinued or its dose was reduced. The sixth case, similar to ours, involved acute myasthenia with sudden falls, but the patient had true myasthenia gravis, with lithium acting only as a precipitating factor (8). While the first five cases of lithium-induced myasthenia primarily presented with chronic symptoms and more localized muscle involvement, particularly affecting the eye and bulbar muscles, our case differed in that the patient experienced multiple episodes of acute weakness involving widespread muscle groups, including the limbs, neck, and bulbar muscles. Each episode was characterized by an abrupt onset of generalized weakness and falls. The heterogeneity in the clinical presentation of lithium-induced myasthenia is evident from these cases.

Lithium-induced myasthenia may involve several mechanisms that affect neuromuscular transmission and postsynaptic stability. First, lithium can reduce the number of acetylcholine receptors (AChRs) in skeletal muscle, potentially by affecting their synthesis, degradation, or transport (10). Lithium can also interfere with AChR metabolism, decreasing receptor stability and impairing synaptic transmission (11). Additionally, lithium inhibits agrin-induced AChR aggregation by disrupting a late step in the agrin signaling pathway, leading to abnormal AChR distribution and impaired synaptic transmission, which may contribute to muscle weakness (12). Lithium may also interfere with acetylcholine synthesis and release from presynaptic terminals, reducing neurotransmitter availability and further impairing signal transmission (13). Furthermore, lithium enhances the effects of neuromuscular blocking agents, such as succinylcholine and pancuronium, which potentiate synaptic inhibition and weaken muscle strength (14, 15). Finally, lithium appears to have a more pronounced effect on neuromuscular junctions (NMJs) in denervated muscles, exacerbating the disruption of synaptic stability and worsening muscle weakness, particularly under pathological conditions (16). These combined effects on AChR metabolism, neurotransmitter release, and NMJ stability likely contribute to the development of lithium-induced myasthenia.

The limitation of this case is that repetitive nerve stimulation or single-fiber electromyography was not performed during the patient's episodes of muscle weakness to confirm the presence of myasthenia. Additionally, despite thorough differential diagnoses, the possibility of other medications, diseases, or psychological factors contributing to myasthenia gravis cannot be completely excluded.

This case highlights the need for increased awareness among psychiatrists regarding the possibility of lithium-induced myasthenia, a potentially overlooked side effect that requires careful monitoring in patients prescribed lithium. The exact

mechanisms by which lithium induces myasthenia are still not fully understood and warrant further investigation in future 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

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

JY: Writing – original draft. RoY: Writing – original draft. XM: Writing – original draft. MJ: Writing – original draft. RuY: Writing – original draft. YS: Writing – review & editing. ND: Writing – review & editing. WC: 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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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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The role of dulaglutide in the treatment of alcohol use disorder: a case report

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Glucagon-like peptide 1 (GLP-1) receptor agonists, medications commonly employed in the treatment of type 2 diabetes mellitus, have illustrated several additional benefits, including weight loss and potentially reduce addictive cravings. Several studies have indicated that GLP-1 receptor agonists may be effective in treating Alcohol Use Disorder (AUD), for which current pharmacologic therapies are often inadequate. Proposed mechanisms include modulation of dopaminergic transmission and reduced gastric emptying, both of which reduce alcohol craving and tolerance. This case report discusses dulaglutide's ability to reduce alcohol consumption. During a visit to an outpatient behavioral health clinic, a 44-year-old male was evaluated for weight loss. His medical history revealed a BMI of 41.8, hypertension, major depressive disorder, and pre-diabetes. The individual also reported the consumption of approximately ninety beers per month and was in the pre-contemplation phase of change. As part of the treatment plan, the patient was prescribed dulaglutide to manage pre-diabetes and facilitate weight loss. During subsequent appointments, the individual not only experienced weight loss but also noted a substantial reduction in alcohol cravings and consumption. However, following a lapse in insurance coverage the following year, the individual had to discontinue his dulaglutide, resulting in a return to previous drinking patterns. Future research should focus on confirming existing animal study results in humans, with the hope that GLP-1 receptor agonists can become a mainstay treatment for AUD.

KEYWORDS

dulaglutide, alcohol use disorder (AUD), substance and alcohol use, GLP-1 receptor agonist, semaglutide

Introduction

Alcohol use disorder (AUD) affects 29.5 million individuals greater than 12 years old and is one of the top causes of avoidable deaths, causing approximately 178,000 deaths annually (1). Additionally, its costs are devastating, both on an individual and national level, contributing to nearly 12% of healthcare costs in the US (2). Despite its impact, a small percentage (less than 10% of adults with AUD) receive treatment (1).

The Alcohol Use Disorders Identification Test (AUDIT) is a screening tool developed by the World Health Organization (WHO) to help individuals recognize potential alcohol-related issues (3). It offers a standardized approach for assessing alcohol consumption and potential alcohol-related risks and is widely used by healthcare professionals around the world (3). The AUDIT quantifies a patient's frequency and amount of alcohol consumed, as well as the way it affects a patient's social and mental health (3). Patients often conceal their alcohol use and may be hesitant to seek assistance, so it is crucial for physicians to promptly screen for alcohol use disorder using screening tests to mitigate the associated risks (4).

GLP-1 receptor agonists, developed initially as diabetes medications, have gained popularity due to their ability to suppress appetite and reduce the speed of gastric emptying, resulting in weight loss (5). Additionally, these drugs have been found to potentially mitigate substance use disorders, including AUD, due to their effects on the brain-gut axis and dopaminergic centers of the brain in pre-clinical trials (5). However, research has shown that there may be more complicated mechanisms not restricted to dopaminergic signaling and the brain-gut axis, such as insulin receptors in the brain, single nucleotide polymorphisms (SNP), and neuroplasticity (6–8). These mechanisms indicate that they have the potential to become a very useful treatment in more diseases than just diabetes and while these drugs are expensive and may increase healthcare costs in the short run, it may reduce costs in the long run.

This case report serves to augment the existing body of evidence supporting the favorable impact of GLP-1 receptor agonists, not only on diabetes and weight management but also on AUD. The utilization of laboratory tests, dulaglutide titration, counseling, regular follow-ups, and periodic AUDIT screening led to notable advancements in our patient's weight loss and effectively addressed his AUD.

Case presentation

A 44-year-old male with a history of prediabetes and obesity presented at an outpatient behavioral health clinic to seek assistance with weight management and lifestyle improvement. During his visit, he weighed 275 pounds, a body mass index of 41.8 and a weight circumference of 62 inches (Figures 1–3; Table 1). The patient had a family history of obesity and been suffering from such since a back surgery. The patient's previous weight loss treatment plan involved the use of phentermine, topiramate, and Wellbutrin. Wellbutrin improved his motivation and self-esteem. However, it and the phentermine did not significantly impact his weight, and he had discontinued the phentermine prior to this behavioral health clinic visit. He also had discontinued the topiramate approximately 2 days after starting it due to a metallic taste and word-finding difficulty. Other than decreased motivation and self-esteem, the patient denied any symptoms of depression. The individual also had a documented history of hypertension and was taking hydrochlorothiazide. He was prediabetic, with a hemoglobin A1c level of 5.8%, and acknowledged a diet consisting of processed foods and low levels of physical activity.

When questioned about substance use, he mentioned drinking approximately 90 beers per month and was in the pre-contemplation phase regarding his alcohol use. He had never been treated for AUD. The patient was screened for AUD with the AUDIT, the Alcohol Use Disorder Identification Test. This 10-question screening tool aids physicians in understanding the severity of a patient's alcohol use disorder and supports them in choosing the most appropriate treatment (3). The patient's AUDIT score was 19, suggesting moderate-severe alcohol use disorder (3) (Figures 2, 3). The patient was warned about the dangers of alcohol withdrawal seizures and Wellbutrin and the decision was made that the benefit far outweighed the risk in his situation.

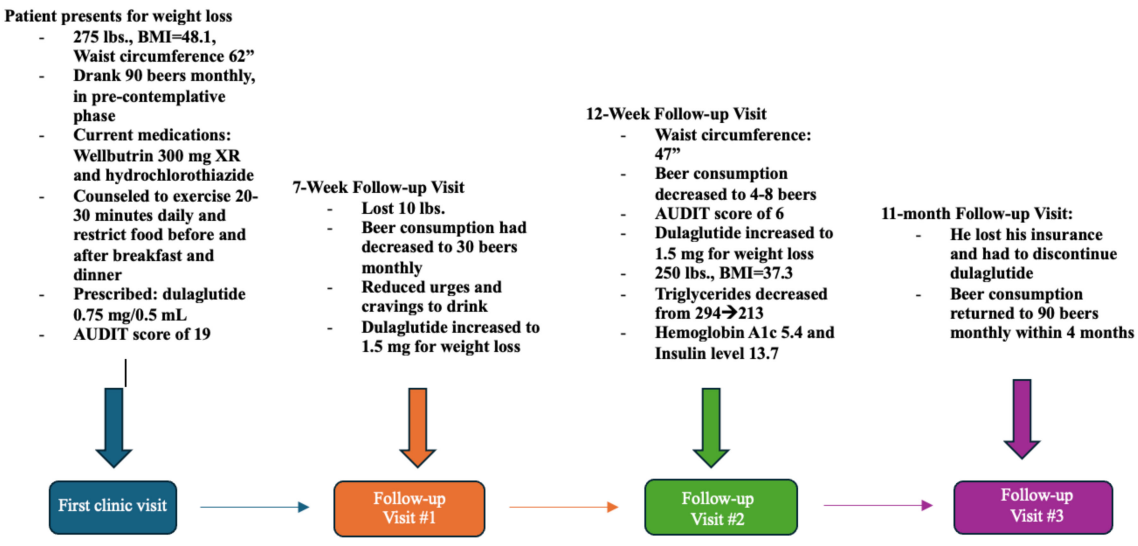


FIGURE 1
Patient visit and treatment timeline.

The Alcohol Use Disorders Identification Test (AUDIT): Interview Version

AUDIT is a 10-item screening tool to assess alcohol consumption, drinking behaviors, and alcohol-related problems. Record your patients' answers carefully and encourage them to answer the AUDIT questions in terms of standard drinks. Explain what is meant by "alcoholic drinks" by using examples of beer, wine, vodka, etc. A chart with standard drink information can be found on the other side.

Add the correct number in the answer box and sum up the total in the bottom field.

1. How often do you have a drink containing alcohol?
(0) Never [Skip to 9] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week — 4

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
(0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more — 3

3. How often do you have six or more drinks on one occasion? [Skip to question 9 if total score for questions 2 and 3 = 0]
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 3

4. How often during the last year have you found that you were not able to stop drinking once you had started?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 4

5. How often during the last year have you failed to do what was normally expected of you because of drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 3

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0

9. Have you or someone else been injured as a result of your drinking?
(0) No (2) Yes, but not in the last year (4) Yes, during the last year — 0

10. Has a relative, friend, doctor, or another healthcare professional been concerned about your drinking or suggested you cut down?
(0) No (2) Yes, but not in the last year (4) Yes, during the last year — 2

A score of 8 or more is an indication of hazardous or harmful alcohol use. **Total Score** 19

Source: Saunders JB, Aasland OG, Babor TF, et al. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption—II. *Addiction*. 1993;88(6):791–803.

FIGURE 2
The patient's first AUDIT score, a total of 19 (the maximum score is 40), was a positive screening result for AUD (9).

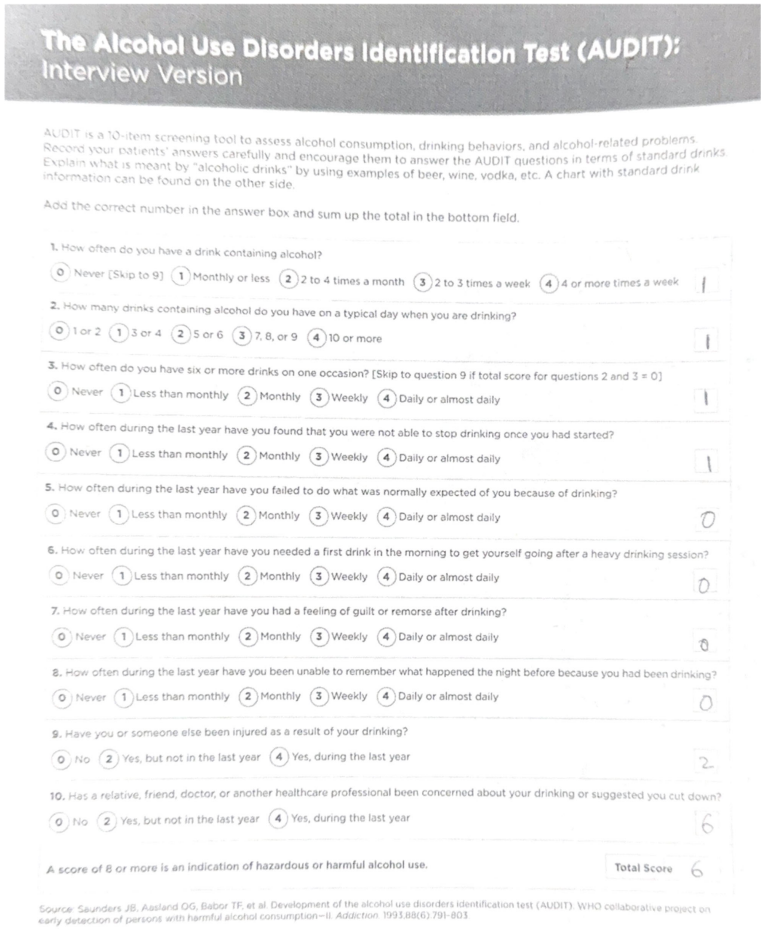
A preliminary laboratory study revealed that his insulin level was 27.4 mIU/mL, his HDL was 43, his triglycerides were 294, and his VLDL was 48. Several weight loss options were discussed, and the patient selected a weekly 0.25mg subcutaneous semaglutide injection. However, due to insurance issues, the initial prescription of semaglutide was changed to 0.75 mg of dulaglutide. The patient received behavioral counseling on nutrition and lifestyle changes, including the importance of daily exercise for 20-30 minutes, healthy eating habits, and food sequencing. The decision was also made to continue to Wellbutrin for his mood.

In his first follow-up visit seven weeks later, he reported no adverse effects from the medication and had lost ten pounds. He reported that his drinking habits had changed, and he was consuming only 30 beers per month. The patient reported feeling full after drinking and had reduced urges and cravings to drink. The patient also reported that he still was having binge eating episodes and binge drinking at times, especially in the two days prior to his next injection. During this visit, the patient agreed to increase his dulaglutide dose to 1.5 mg. He stated that he was trying to follow a healthy diet but had only minimally changed his exercise. A follow-up appointment was scheduled 5 weeks later.

In the second follow-up visit, the patient's waist circumference was 47 inches, and he reported consuming four to eight beers per month, resulting in a new AUDIT score of 6. This was considered low-risk alcohol consumption (3). His weight had decreased to 250 pounds, with a body mass index of 37.3. His repeated laboratory tests revealed a decrease in triglyceride levels from 294 to 213, with no other significant changes observed in his lipid panel. Additionally, his HbA1c had decreased to 5.4 with an insulin level of 13.7. He denied any cravings for food or alcohol during this visit and wanted to continue the same dose of dulaglutide. The patient also reported dietary improvements but still had not improved his exercise regimen. The importance of exercise was again discussed in this visit.

In the subsequent months, the patient retired from his job due to a back injury exacerbated by physical strain. Unfortunately, the loss of health insurance made it unaffordable for him to continue using dulaglutide; however, he was able to maintain his other prescribed medications. Two weeks after discontinuing dulaglutide, he began drinking again. Within four months, his consumption escalated back to his previous average of 90 beers per month.

His third follow-up appointment took place 11 months after the initial consultation. Although it was recommended that he be seen



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Add the correct number in the answer box and sum up the total in the bottom field.

1. How often do you have a drink containing alcohol?
(0) Never [Skip to 9] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week — 1
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
(0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more — 1
3. How often do you have six or more drinks on one occasion? [Skip to question 9 if total score for questions 2 and 3 = 0]
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 1
4. How often during the last year have you found that you were not able to stop drinking once you had started?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 1
5. How often during the last year have you failed to do what was normally expected of you because of drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0
7. How often during the last year have you had a feeling of guilt or remorse after drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily — 0
9. Have you or someone else been injured as a result of your drinking?
(0) No (2) Yes, but not in the last year (4) Yes, during the last year — 2
10. Has a relative, friend, doctor, or another healthcare professional been concerned about your drinking or suggested you cut down?
(0) No (2) Yes, but not in the last year (4) Yes, during the last year — 6

A score of 8 or more is an indication of hazardous or harmful alcohol use. Total Score 6

Source: Saunders JB, Aasland OG, Babor TF, et al. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction*. 1993;88(6):791–803.

FIGURE 3
Patient's second AUDIT score of 6 just 12 weeks later was a great improvement, and was below the threshold for a positive AUD screening value (9).

three months earlier, he opted to cancel this visit due to undergoing back surgery. Given that he could not utilize a GLP-1 receptor agonist for his alcohol use disorder (AUD) and that his current insurance did not cover the GLP-1 receptor agonist for weight management, he attempted treatment with naltrexone. However, he had compliance issues due to adverse side effects.

The patient and his family have conveyed that he experienced a significant reduction in alcohol consumption and effective weight management while on a GLP-1 receptor agonist, which in turn fostered improvements in his family relationships. Additionally, his wife reported that he was very compliant with the weekly GLP-1 receptor agonist injections, as she closely monitored his adherence to the treatment regimen. On the contrary, he was non-compliant with naltrexone, and no significant changes were noticed in his drinking pattern with this medication.

Discussion

Less than one-tenth of individuals with AUD received treatment in 2023, in part due to lack of effective screening and physician experience in treating AUD (1, 4). Disulfiram, acamprosate, and naltrexone are the primary pharmacological assets for AUD, but sometimes lack effectiveness (4). For example, the hepatic metabolism of naltrexone can be contraindicated for those with existing liver disease which is commonly associated with AUD (10). Additionally, patients with concurrent opioid use are also unable to use naltrexone for AUD due to precipitation of withdrawal, and acamprosate cannot be used in those with severe renal disease (4, 11). Disulfiram has very undesirable side effects, and patients often not maintain its use (4).

The left insula, hypothalamus, and orbitofrontal cortex are involved with reward, food anticipation and satiety, and GLP-1 receptors are found in these areas (5). Studies have also shown that GLP-1 decreases extracellular dopamine release and increases dopamine turnover, which decreases the reward aspect of food and alcohol (12). Multiple studies on mice have found that treatment with Exendin-4, a GLP-1 receptor agonist, reduced alcohol consumption by altering dopamine pathways (5, 12–15). In one of those studies, subjects did not have significant relapse following treatment cessation (16). It is also worth mentioning that liraglutide, which is marketed under the brand name 'Victoza,' has been shown to decrease alcohol consumption in rats by impacting the mesolimbic dopamine pathways (17).

TABLE 1 Below shows the patient's alcohol use, anthropometry, and labs with each visit.

Visit #, time since first visit	AUDIT score[1]	# Beers per month	Weight (pounds)	BMI (kg/m^2)	Waist circumference (inches)	Insulin (mIU/mL)	Triglycerides
First clinic visit, 0 days	19	90	275	41.8	62	27.4	294
Follow Up Visit #1, 56 days after	n/a	30	265	40.3	50	n/a	n/a
Follow Up Visit #2, 84 days after (labs taken 112 days after)	6	4-8	250	37.3	47	13.7	227
Follow Up Visit #3, 334 days after	N/A	90-100	278	42	64	58.9	354

[1]The Alcohol Use Disorders Identification Test (AUDIT) is a screening tool developed by the World Health Organization (WHO) to help individuals recognize potential alcohol-related issues (3).

AUD is associated with neuroplastic changes in the brain (6). Studies have shown that in those with AUD, networks affecting reward and self-control such as the striatum and orbitofrontal cortex have decreased synchronous activity, which is correlated with years of heavy alcohol consumption (6). Further, when those with AUD abstain from alcohol, their brain remains altered, leaving them more susceptible to relapsing due to mental and physical stress (18). Since GLP-1 receptors have been found to be involved with neural pathways, including the striatum, it is reasonable to consider if GLP-1 receptor agonists can affect the neuroplastic changes associated with AUD (6, 19). Our patient relapsed quickly after stopping his dulaglutide, leading us to believe that either there was not enough time for the neuroplastic changes to be affected, or it is not affecting these areas in a way that allows for remodeling.

SNPs in the GLP-1 receptor genes have clinically significant differences. One study showed that humans and mice with a GLP1R 168Ser non-wild type allele had a higher intravenous alcohol intake, as well as an increased signal intensity in the globus pallidus during a reward-seeking task (7). Similarly, mice with less expression of the 168Ser wild-type allele responded less to GLP-1 receptor agonists (7). While the current evidence is limited, the existing data on SNPs in the GLP-1 receptor genes and their role in alcohol and other substance use disorders shows promise and warrants future research.

Human studies on GLP-1 receptor agonists as a potential AUD treatment are limited, but more literature is starting to address this. A study from 2023 found that individuals taking semaglutide and tirzepatide self-reported significantly lower overall alcohol consumption and cravings (20). An observational study from January 2006-December 2023 found that of the 227, 866 individuals with AUD and comborbid obesity or type 2 diabetes studied, semaglutide and liraglutide were associated with a significantly lower risk of AUD hospitalization than those taking well-established AUD treatments (21) A systemic review from November 2024 showed that there was a significant reduction in substance use disorders in the 630 subjects prescribed either exenatide or dulaglutide for substance use disorder (22). A case series on 6 patients with positive AUD screenings significantly improved their AUD symptoms while using semaglutide for weight loss (23). Contrarily, a randomized, placebo-controlled clinical trial using exenatide once weekly did not reduce the number of heavy drinking days in 127 patients; however, the authors stated that the study population had drinking severity lower than other trials (24). Thus, the evidence for GLP-1 receptor agonists is increasing and overall promising, but the evidence for dulaglutide is explicitly smaller and requires more research.

Binge eating and substance use disorders have similarities in their pathophysiology (25). One study found that in females, excess alcohol use correlated with binge eating (25). GLP-1 receptor agonists are also utilized for weight loss, even in those without diabetes (5). These drugs both slow gastric emptying and influence receptors in reward-seeking areas in the CNS, and both may have aided in the patient's improved diet (5).

Insulin plays a significant role in regulating blood sugar levels and controlling glucose and lipid metabolism (8). Insulin resistance in the brain can also lead to an increase in alcohol intake and addiction (13). In the hypothalamus, insulin resistance can affect the brain's reward circuitry by decreasing dopamine levels in the striatum, which leads to an increased desire for alcohol and causes communication changes between brain neurons (8, 13). Our patient had a significant decrease in insulin levels after 12 weeks of treatment, which likely lowered his insulin resistance and may have contributed to his reduced alcohol cravings (13).

It is important to note that the stomach and duodenum play critical roles in alcohol metabolism and absorption (26). The stomach primarily metabolizes ethanol to acetaldehyde locally, while the duodenum is responsible for the rapid absorption of alcohol into the bloodstream (26). The delayed gastric emptying from the stomach to the duodenum following the administration of GLP-1 receptor agonists may lead to higher levels of acetaldehyde and may alter or blunt the rise in blood alcohol levels (BAC) (26). This change in the alcohol absorption curve significantly diminishes its effects and thus abuse potential, which could potentially explain the observed decrease in AUDIT scores and weekly alcohol consumption in our patient (26).

The patient presented with both weight gain and excess alcohol use. Despite the limitation of his insurance only covering dulaglutide and not semaglutide, he achieved remarkable results with his weight loss and drinking habits. The return of his cravings due to insurance issues underlines the pivotal role of insurance in patient care, as well as the need for further research on preventing rebound effects following discontinuation. Quitting his job likely acted as a social stressor and may have contributed to his relapse, but had the patient been able to stay on the dulaglutide during this stressful period, it may have helped prevent such a relapse.

Conclusion

This case report demonstrates a case of weight loss and significant alcohol use reduction in the setting of GLP-1 receptor agonist use, drugs originally used for diabetes. There has been growing literature on the benefits of GLP-1 receptor agonists on weight loss and AUD. The widespread effects of GLP-1 in the CNS, especially on the mesolimbic pathway, and the GI tract work together to reduce cravings and urges for both food and substances. Our patient's case of an approximately 93% reduction in alcohol consumption over only 12 weeks provides additional support for a new and potentially superior pharmacological treatment of AUD. While the results of this case report are promising, more extensive studies with a large number of participants and extended follow-up periods are needed to confirm these findings and establish the efficacy of GLP-1 receptor agonists as a treatment for AUD. Additionally, more research is required to understand the underlying mechanisms of GLP-1 receptor agonists in reducing cravings and urges for both food and alcohol.

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

Ethical approval was not required for the studies involving humans because informed consent was obtained, and the study was written after treatment was already initiated. 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

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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Case Report: Potential of pharmacological treatment for auditory abnormal sensations with aripiprazole: a report of two cases

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Auditory abnormal sensations encompass various subjective auditory symptoms such as tinnitus, hyperacusis, aural fullness, autophony, dysacusis, pseudo-hallucinations, and misophonia. Although tinnitus management typically includes lifestyle counseling and sound therapy, there remains no established treatment for symptoms like aural fullness or pseudo-hallucinations with unknown etiology. In cases where central sensory processing abnormalities or emotional instability are suspected, psychotropic medications may offer benefit. We report two cases in which aripiprazole, an atypical antipsychotic, was effective in treating such symptoms. In both cases, traditional approaches such as antidepressants and supportive therapy were insufficient, but aripiprazole led to marked improvement in subjective auditory symptoms. These cases suggest a potential role for pharmacological modulation of central sensory and emotional regulation in patients with auditory abnormal sensations. One involved a man with phonophobia and aural fullness, and the other a woman with tinnitus and pseudo-hallucinations.

KEYWORDS

auditory abnormal sensations, aripiprazole, pseudo-hallucinations, phonophobia, central sensory processing dysfunction

Introduction

Auditory abnormal sensations refer to a spectrum of subjective auditory complaints that are not fully explained by conventional otologic or neurologic findings. These sensations include tinnitus, hyperacusis, aural fullness, autophony, dysacusis, pseudo-hallucinations, and misophonia. While tinnitus is relatively well-studied and often managed through sound therapy and counseling strategies such as tinnitus retraining therapy (TRT) or cognitive behavioral therapy (CBT) (1, 2), other auditory symptoms remain poorly understood and lack established therapeutic options.

Auditory abnormal sensations, including tinnitus, aural fullness, and hyperacusis, are reported in approximately 10–15% of the population, with 1–2% experiencing severe functional impairment. These symptoms are associated with insomnia, anxiety, depression, and social withdrawal, resulting in a significant reduction in quality of life (QOL) (3, 4).

Patients with auditory abnormal sensations often present with significant distress and functional impairment despite normal or near-normal audiological assessments. In such cases, central sensory processing dysfunction and emotional dysregulation are increasingly recognized as contributing factors (4, 5). These central mechanisms may lead to heightened auditory perception, altered affective responses to sound, or even the misinterpretation of internally generated auditory stimuli as external sounds, such as in pseudo-hallucinations (6, 7).

Psychotropic agents, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines, have been applied in various neurotologic disorders, especially when comorbid anxiety or depression is evident. More recently, low-dose aripiprazole, an atypical antipsychotic with partial dopamine D2 receptor agonist activity and serotonin receptor modulation, has shown promise in the treatment of refractory dizziness and related sensory-emotional disorders (8, 9). These findings suggest that modulation of central neurochemical pathways may alleviate symptoms stemming from sensory-emotional dysregulation.

However, the use of aripiprazole in treating auditory abnormal sensations—particularly in cases without frank psychosis—has not been well documented. Given the overlapping pathophysiology between chronic dizziness and perceptual auditory disturbances, there is a rationale for exploring aripiprazole's utility in this context. We herein report two cases of auditory abnormal sensations—one presenting with aural fullness and phonophobia, and the other with tinnitus and pseudo-hallucinations—successfully treated with low-dose aripiprazole. These cases highlight the potential role of dopaminergic-serotonergic modulation in managing non-psychotic auditory perceptual abnormalities and provide preliminary support for pharmacologic intervention targeting central sensory processing. The sociodemographic and clinical details of these cases are summarized in Table 1.

Case 1

A man in his 40s developed aural fullness and phonophobia in his left ear after someone shouted loudly near it. The symptoms significantly interfered with his daily life, prompting him to visit a local clinic. The diagnostic assessments including pure-tone audiometry, tympanometry, speech discrimination testing, and head MRI were performed to exclude organic otological pathology. Pure tone audiometry revealed normal hearing, but he was initially diagnosed with acute sensorineural hearing loss and treated with corticosteroids, with no improvement. He was then referred to our department for further evaluation.

The severity of subjective symptoms was assessed using the Numerical Rating Scale (NRS), which ranges from 0 (no symptoms) to 10 (most severe). Generally, scores of ≤4 are considered mild, 5–6 moderate, and ≥7 severe symptom-related misperceptions (10).

The Hospital Anxiety and Depression Scale (HADS) (11) indicated mild anxiety (score 10) and mild depression (score 9). He was initially prescribed etizolam 0.5 mg/day, which led to mild symptomatic relief of both aural fullness and phonophobia (NRS 10 → 8) after two weeks. Due to his depressive tendency, vortioxetine 25 mg/day was subsequently initiated and maintained for three weeks, but no clinically significant change in auditory symptoms was observed. The patient also reported mild nausea and chose to discontinue antidepressants. Therefore, aripiprazole 1.5 mg/day was introduced as monotherapy. Two weeks later, both phonophobia and aural fullness improved (NRS 10 → 4), and at the 8-week follow-up, symptoms further decreased to NRS scores of 3.

Case 2

A 73-year-old woman with a history of migraine since youth began experiencing tinnitus and pseudo-hallucinations in December of Year X. On presentation to our clinic, audiometry revealed low-frequency sensorineural hearing loss (see Figure 1). The diagnostic assessments including pure-tone audiometry, tympanometry, speech discrimination testing, and head MRI were performed to exclude organic otological pathology. Her Tinnitus Handicap Inventory (THI) score was 62, and her HADS scores were 11 for anxiety and 12 for depression.

Despite receiving lifestyle counseling—including avoidance of silence and active redirection of attention—neither her tinnitus nor pseudo-hallucinations improved. She was then started on low-dose amitriptyline (10 mg/day) and clonazepam (0.25 mg/day), which led to only modest subjective relief, with NRS scores remaining unchanged at 9 for both symptoms after two weeks. In pursuit of greater improvement, we initiated augmentation therapy with aripiprazole 1.5 mg/day. Two weeks later, her pseudo-hallucinations had fully resolved (NRS 0), while her tinnitus persisted (NRS 9). By the 8-week follow-up, her tinnitus also showed moderate improvement, with the NRS score decreasing to 4.

Discussion

The present report highlights two cases of auditory abnormal sensations that responded favorably to low-dose aripiprazole after conventional treatment approaches had failed. The common pathophysiological thread between both cases appears to be central sensory hypersensitivity and impaired emotional regulation. These mechanisms are well documented in the context of tinnitus and hyperacusis, where dysfunctional neural networks involving the auditory cortex, limbic system, and prefrontal regions contribute to symptom persistence and distress (6, 7).

TABLE 1 Sociodemographic and clinical characteristics of the cases.

Case	Age/Sex	Main Symptoms	Psychological Background (HADS)	Clinical Background/Medical History
Case 1	40s/Male	Aural fullness, Phonophobia	HADS-A: 10, HADS-D: 9	No psychiatric or neurological history; symptoms began after loud noise exposure
Case 2	73/Female	Tinnitus, Pseudo-hallucinations	HADS-A: 11, HADS-D: 12	History of migraine since youth; no prior psychiatric treatment

Aripiprazole is a dopamine system stabilizer that acts as a partial agonist at dopamine D2 receptors and modulates serotonergic pathways through 5-HT1A agonism and 5-HT2A antagonism (12). Originally developed as an antipsychotic, it has also shown efficacy in non-psychotic conditions such as functional dizziness and somatoform disorders (6, 8, 9). These effects may reflect its ability to regulate sensory gating, emotional reactivity, and cognitive appraisal of internal stimuli —mechanisms relevant to symptoms like pseudo-hallucinations and phonophobia.

In Case 1, the patient's symptoms of phonophobia and aural fullness were resistant to corticosteroids, benzodiazepines, and even vortioxetine, an antidepressant with multimodal serotonergic action. The clear symptomatic reduction following aripiprazole introduction suggests that dopaminergic modulation played a key role in attenuating central hypersensitivity. In Case 2, pseudo-hallucinations unresponsive to low-dose tricyclic and benzodiazepine treatment were completely resolved with aripiprazole. This supports a potential role for atypical antipsychotics even in subclinical perceptual disturbances.

Aripiprazole may be particularly effective in patients whose auditory symptoms are thought to be associated with emotional dysregulation, including anxiety, depressive tendencies, or somatic symptom-related cognitive distortion. This aligns with its known dopaminergic-serotonergic modulatory action, which may reduce sensory hyperreactivity and maladaptive appraisal of internal stimuli (12). In contrast, aripiprazole is unlikely to be effective in cases where symptoms are due to identifiable organic causes, such as cochlear damage, retrocochlear lesions, or drug-induced auditory dysfunction. Careful case selection is therefore essential to optimize outcomes and avoid unnecessary pharmacological burden.

Importantly, neither patient exhibited frank psychotic features, and both tolerated aripiprazole without significant adverse effects. This expands the possible clinical use of aripiprazole into domains of non-psychotic sensory dysfunction. Nevertheless, these are preliminary observations, and placebo effects or spontaneous improvement cannot be ruled out. Controlled trials are necessary to validate these findings.

Limitations and future directions

This report presents two cases suggesting the potential efficacy of aripiprazole in treating auditory abnormal sensations. However, several limitations should be acknowledged. First, as a case report involving only two patients, the findings are insufficient to generalize the effectiveness of this medication. Second, the evaluation of subjective symptoms was based on the Numerical Rating Scale (NRS), which, while convenient, is inherently subjective and susceptible to inter-rater variability and placebo effects. Third, the possibility of spontaneous

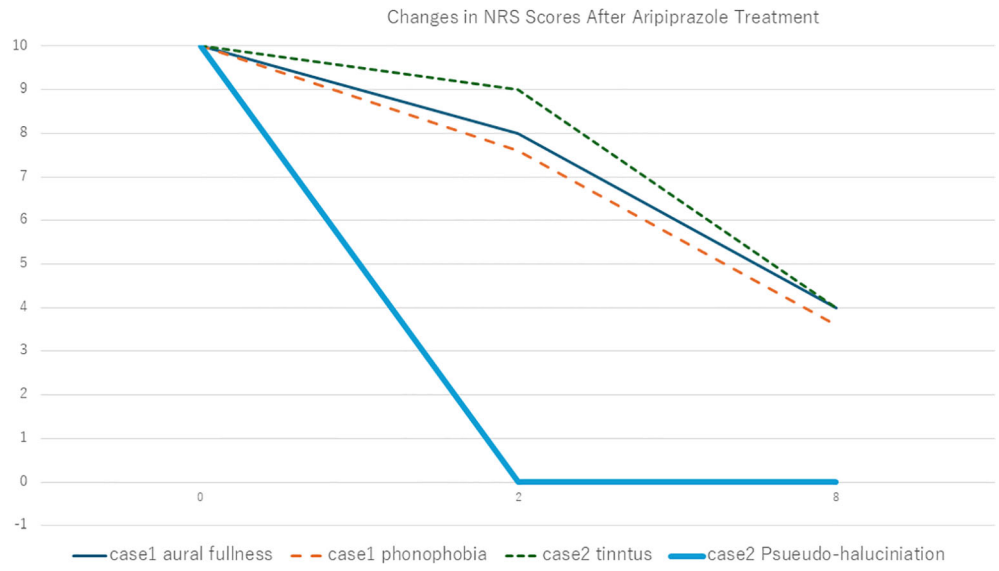

FIGURE 1
Changes in Numerical Rating Scale (NRS) scores following aripiprazole treatment in Case 1 and Case 2. Vertical axis is Numerical Rating Scale (NRS) and horizontal axis is weeks after treatment initiation.

symptom improvement cannot be entirely ruled out. Although the therapeutic effect of aripiprazole is suggested by the lack of response to prior medications, definitive conclusions require longer-term observation and controlled studies.

Furthermore, the neurophysiological mechanisms by which aripiprazole may affect sensory processing abnormalities and emotional regulation remain unclear. Comparative studies with other psychotropic agents are needed to clarify the specificity and relative efficacy of aripiprazole. Although no adverse effects were observed in either case, especially in elderly patients, drug sensitivity must be considered, and future studies should address the safety profile of aripiprazole in this population.

In light of these limitations, it is necessary to accumulate a larger number of clinical cases and to conduct prospective studies using standardized evaluation tools and objective indices. Such research will help establish the efficacy and safety of pharmacological treatment for auditory abnormal sensations in a more systematic manner.

In complex sensory-emotional cases involving auditory symptoms, collaboration with clinical pharmacists may help identify medication-related side effects or interactions, as seen in reports of drug-induced hallucinations (e.g., solifenacin, trimethoprim-sulfamethoxazole) (13, 14).

Conclusion

In the absence of standardized treatments for auditory abnormal sensations, aripiprazole may represent a promising pharmacological option by targeting central sensory processing and emotional regulation. Further clinical studies are warranted to establish its efficacy and broaden its indications in otologic psychosomatic disorders.

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 Tokai University Hospital (Tokai University Institutional Review Board for Clinical Research. 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

FG: Writing – original draft, Writing – review & editing. SK: Conceptualization, Writing – review & editing. KO: Conceptualization, Writing – review & editing. KW: Writing – review & editing.

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Clozapine and tuberculosis treatment: a case report and literature review

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Introduction: To date, clozapine is the only antipsychotic approved by the United States Food and Drug Administration (FDA) for the management of treatment-resistant schizophrenia. People with serious mental illness are at higher risk of developing tuberculosis and have worse tuberculosis recovery outcomes compared to the general population. First-line regimens for acute tuberculosis often include rifamycins and isoniazid, both of which impact clozapine metabolism and levels through induction or inhibition of the hepatic cytochrome P450 (CYP450) enzyme system. There is limited evidence, mostly from case reports, to guide clinicians in managing clozapine alongside anti-tuberculosis therapy (ATT).

Literature review: We present 5 case reports of patients with schizophrenia or schizoaffective disorder who continued clozapine while receiving ATT. In most of the case reports (n = 3), the ATT regimen included both rifampicin, a CYP450 inducer, and isoniazid, a CYP450 inhibitor. We also review pharmacokinetic properties of rifampicin and the potential impact of rifamycin-based regimens on clozapine metabolism and levels.

Case presentation: We present the case of a 35-year-old prescribed clozapine for 4 years prior to being diagnosed with pulmonary tuberculosis. The patient continued clozapine and was closely followed in both the inpatient and outpatient settings while completing a 6-month course of rifampicin, isoniazid, pyrazinamide, and ethambutol. During ATT, the patient had clozapine and norclozapine levels measured at least once monthly and maintained stability in their psychiatric symptoms through adjustment of clozapine and adjunctive antipsychotic dosages.

Conclusion: Our case supports previous reports that ATT can influence clozapine levels. Clozapine dose adjustments will likely be required to maintain clinical stability and prevent adverse effects, but the management appears to be patient-specific. We recommend closely monitoring patients' clinical status and clozapine levels during and after ATT to optimize outcomes.

KEYWORDS

tuberculosis, clozapine, case report, rifampicin, schizophrenia, drug-drug interaction

Introduction

Schizophrenia is a chronic mental disorder associated with impaired psychosocial functioning, adverse cardiometabolic outcomes, and reduced life expectancy (1). While schizophrenia affects ~1% of the global population, it is among the ten leading causes of disability, particularly among people between 25 and 54 years (2). Although antipsychotic medications are the cornerstone of treatment for schizophrenia, 1 in 3 people living with schizophrenia will continue to experience symptoms despite trialing multiple, first-line antipsychotics (3).

Clozapine remains the only FDA-approved antipsychotic for the management of treatment-resistant schizophrenia (TRS) (4, 5). Despite metabolic side effects, clozapine significantly lowers all-cause mortality and the risk of recurrent psychiatric hospitalization (6, 7). It may also remit the need for antipsychotic polypharmacy in people with TRS.

Unfortunately, the prescribing of clozapine has been limited by several factors. Clozapine is a narrow therapeutic index drug and can cause potentially life-threatening adverse effects, including intestinal obstruction, myocarditis, and agranulocytosis, the latter of which has historically mandated strict neutrophil count monitoring (5, 8). Next, clozapine is predominantly metabolized by cytochrome P450 (CYP) CYP1A2, CYP3A4, and CYP2D6 to multiple metabolites, including an active metabolite norclozapine, and is subject to drug-drug interactions that can lead to psychiatric decompensation or adverse effects. For example, aryl hydrocarbons present in cigarette smoke induce CYP1A2 activity, and people who smoke regularly may experience as much as a 50% increase in clozapine levels following smoking cessation (9, 10). The ratio of clozapine to norclozapine plasma levels, also known as the metabolic ratio, can indicate the presence of genetic polymorphisms, environmental exposures, or medications that influence CYP1A2 activity. However, routine monitoring of the metabolic ratio to predict adverse effects or therapeutic response can be challenging as the ratio can shift unpredictably following clozapine dose changes (9). While monitoring plasma clozapine levels is more common and can aid clinicians in identifying toxicity or medication non-adherence, individual levels can also fluctuate depending on patient-specific pharmacokinetic parameters (e.g., metabolism, genetics). The therapeutic range for plasma clozapine levels is generally regarded as 350 to 600 ng/mL, as studies suggest that most patients will not obtain additional benefit at levels exceeding 600 ng/mL, even though some laboratories report 1,000 ng/mL as the upper limit (11).

The impact of drug-drug interactions on clozapine safety and efficacy is critical in the context of tuberculosis treatment. People with serious mental illness are at higher risk of acquiring tuberculosis compared to the general population, and comorbid mental illness has been associated with poorer tuberculosis recovery outcomes (12). The preferred anti-tuberculosis therapy (ATT) for drug-susceptible tuberculosis consists of 2 months of daily rifampicin, isoniazid, pyrazinamide, and ethambutol followed by 4 months of daily rifampicin and isoniazid (13). Daily observed therapy (DOT), in which a healthcare worker, either virtually or in person, watches a patient take their ATT and documents completed doses, can optimize adherence and should be offered for all people receiving ATT, especially those whose clinical course may be impacted by drug-drug interactions. Of note, rifampicin and isoniazid can both affect clozapine levels via their respective induction and inhibition of multiple CYP450 isoforms, including CYP1A2 and CYP3A4 (14). Further complicating clinical decision making is evidence that acute infection itself can increase clozapine levels and the risk of toxicity, particularly in the early phases of tuberculosis (9, 15).

There are few reports describing the co-management of clozapine and ATT and no formal treatment guidelines on this topic. Here, we review the existing literature, present a successful case of clozapine management in an adult with schizophrenia receiving rifampicin and isoniazid for new-onset tuberculosis, offer suggestions for managing clozapine in ATT, and propose changes to pertinent guidelines.

Literature review

We identified 6 articles examining drug-drug interactions between clozapine and ATT. Five of these were case reports and are summarized below.

Gee et al. describe a case of a 28-year-old non-smoker with schizoaffective disorder who was taking clozapine 400 mg daily in March 2012 when they began an empiric course of rifampicin, isoniazid, pyrazinamide and moxifloxacin for presumed abdominal tuberculosis (16). Prior to starting ATT, the patient's clozapine levels generally ranged from 240–360 ng/mL. Upon starting ATT, the clozapine dose was empirically increased by 25% to 500 mg daily. The clozapine levels became sub-therapeutic within 12 days of initiating rifampicin and continued to decline to 100 ng/mL. This decline was accompanied by worsening mutism and agitation. The clozapine dose was increased to 800 mg daily, or a near doubling from baseline, resulting in levels of approximately 650 ng/mL. However, the levels quickly declined after 3 weeks to approximately 150–350 ng/mL for the remainder of ATT, despite increasing the clozapine dose to 1000 mg daily. Upon discontinuing ATT, the clozapine dose was prospectively halved and tapered by 50 mg/day over 10 days. The clozapine levels ultimately returned to therapeutic range with resolution of psychiatric symptoms at a dose of 550 mg daily. The authors recommend measuring baseline clozapine levels and preemptively increasing the dose upon initiating rifampicin, monitoring clozapine levels at least once weekly during therapy, and tapering the clozapine dose over 7–10 days following discontinuation of rifampicin to prevent adverse events.

Peritogiannis et al. report a case of a 30-year-old with schizophrenia who was prescribed a 6-month course of rifampicin 600 mg daily for pulmonary tuberculosis and maintained on clozapine 300 mg daily (17). The patient's smoking status was not documented. After two weeks, the patient experienced reduced sialorrhea and sedation but relapse of their psychiatric symptoms. The clozapine dose was titrated to 550 mg

daily in the following month with minimal improvement in their psychiatric symptoms. Sedation, sialorrhea and clinical efficacy returned within 7 days of completing rifampicin and the clozapine dose was reduced to 500 mg daily. Clozapine levels were not measured due to laboratory technical difficulties. The authors endorse individualization of clozapine doses during ATT but do not issue specific dosing or monitoring recommendations.

Joos et al. report a case of a 33-year-old smoker with schizophrenia taking clozapine 400 mg daily at the time of starting rifampicin 600 mg daily, isoniazid 300 mg daily, pyrazinamide 2000 mg daily, and ethambutol 1600 mg daily for pulmonary tuberculosis (18). Three weeks after initiating ATT, their clozapine levels declined from a baseline level of 240 ng/mL to approximately 80 ng/mL. This decline was accompanied by restlessness and delusional thinking. Clozapine was increased by 50% to 600 mg daily with minimal improvement in psychiatric symptoms or clozapine levels. Rifampicin was switched to ciprofloxacin 1000 mg/day; within 3 days, the patient's clozapine levels returned to therapeutic range with improvement of their psychiatric symptoms. The authors concluded that clozapine levels declined by 600% 2–3 weeks after the initiation of rifampicin due to CYP enzyme induction but increased following discontinuation of rifampicin due to CYP enzyme inhibition by isoniazid. The authors recommend monitoring clozapine levels upon discontinuation of rifampicin but do not provide titration or monitoring schedules.

Grover et al. describe a case of a 31-year-old non-smoker with schizophrenia who had been on clozapine 125 mg daily for 7 years with clinical stability (19). The patient was diagnosed with pulmonary tuberculosis and initiated on rifampicin 600 mg daily, isoniazid 300 mg daily, pyrazinamide 1400 mg daily, and ethambutol 1000 mg daily. After two months of ATT, the patient developed persecutory delusions and auditory hallucinations that progressed despite more than doubling the clozapine dose to 300 mg daily. Isoniazid was switched to levofloxacin 750 mg daily, which may have contributed to five months of persistent psychiatric symptoms and subsequent admission to an inpatient behavioral health unit. The patient's symptoms began to improve 6 weeks following completion of ATT, and they were discharged on clozapine 300 mg daily. The authors do not report clozapine levels or issue monitoring or titration recommendations.

Angelini et al. describe a case of a 65-year-old with schizophrenia and unknown smoking status maintained on clozapine 200 mg twice daily who was initiated on a 9-month course of isoniazid 300 mg daily for tuberculosis (20). Their pre-treatment clozapine level was 397 ng/mL. Nine days after initiating isoniazid, the clozapine level increased by 90% to 756 ng/mL, and the clozapine dose was decreased by 25% to 150 mg twice daily. On day 20 of isoniazid therapy, the clozapine level declined to 527 ng/mL, and the dose was further reduced by 50% from baseline to 100 mg twice-daily. Fifty-four days after discontinuing isoniazid, the clozapine level decreased to 239 ng/mL, and the patient was maintained on clozapine 100 mg twice-daily. However, one month later, the patient exhibited worsening psychiatric symptoms, which resolved after returning to 200 mg twice-daily. The authors recommend monitoring clozapine levels but do not specify a dose titration or monitoring schedule.

Case report

ZZ is a 35-year-old with a history of obesity, schizophrenia, psoriasis and tobacco use. ZZ was treated with clozapine for four years during which their dose was titrated to a maximum of 900 mg daily in response to ongoing, functionally impairing psychotic symptoms with no significant side effects from clozapine other than sialorrhea. At a routine outpatient psychiatry visit, their clozapine dose was decreased from 900 mg nightly to 800 mg nightly to address new concerns for weight gain; aripiprazole 5 mg daily was initiated to target persistent auditory hallucinations and delusions. At this visit, their clozapine and norclozapine levels were 972 and 358 ng/mL, respectively.

ZZ was admitted to the hospital 18 days later for nausea, vomiting, cough, and malaise. Although ZZ denied adverse effects, on hospitalization day 6, their clozapine dose was decreased by nearly 20% from 800 mg nightly to 650 mg nightly to avoid clozapine toxicity in the setting of acute infection and cessation of smoking during hospitalization. After a period of diagnostic uncertainty, pulmonary tuberculosis was diagnosed by acid-fast bacilli stain and Mycobacterium tuberculosis positive culture from a sputum sample. On hospital day 16, ZZ began a 6-month course of ATT: 6 months of rifampicin and isoniazid; pyrazinamide and ethambutol stopped after 7 and 9 weeks respectively following negative sputum cultures and testing that confirmed sensitivity to rifampicin and isoniazid. In anticipation of CYP450 enzyme induction by rifampicin, ZZ's clozapine dose was gradually increased by 25 mg daily to 750 mg nightly; aripiprazole was titrated to 15 mg daily over the following 3 weeks. These dose adjustments were made in collaboration with a clinical pharmacist. Clozapine and norclozapine trough levels were drawn at least once weekly and ZZ was regularly seen by the inpatient psychiatry consult team throughout the hospitalization. Although ZZ exhibited some worsening delusional content following the initial dose decrease, they did not deteriorate in their clinical status. On hospital day 35, ZZ was discharged on clozapine 750 mg nightly and aripiprazole 15 mg daily alongside daily observed ATT. ZZ has been seen by their outpatient psychiatrist and had clozapine and norclozapine levels drawn at least once monthly since discharge. Over the following 6 months, their clozapine dose was adjusted to 950 mg nightly and their aripiprazole to 20 mg daily for worsening intensity in delusional content. These adjustments were also made in consultation with a clinical pharmacist. Following these dose increases, ZZ reported drooling which was managed with the addition of glycopyrrolate but maintained stability in their psychiatric symptoms. ATT was completed after 6 months. ZZ's clozapine and norclozapine levels increased appreciably 13 days afterwards and the clozapine dose was adjusted downwards by 50 mg per day 19 days following discontinuation of ATT (See Figure 1). ZZ's psychiatric and ATT doses are listed in

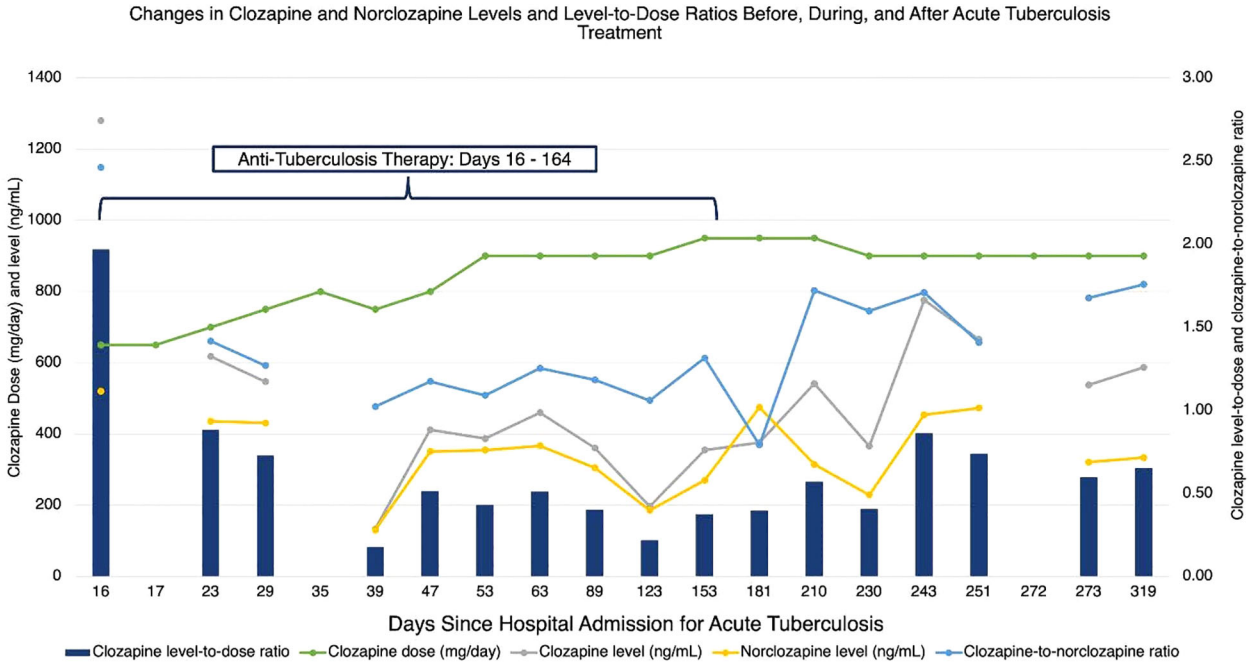

FIGURE 1
Changes in clozapine and norclozapine levels and level-to-dose ratios before, during, and after acute tuberculosis treatment.

TABLE 1 Psychiatric and anti-tuberculosis medication doses.

Time	Medication (mg/day)					
	Clozapine	Aripiprazole	Rifampicin	Isoniazid	Pyrazinamide	Ethambutol
Days Before Hospitalization						
17	800	5				
Day of Hospitalization						
6	650	10				
15	650	10	600	300	1500	1200
19	700	10	600	300	1500	1200
20	750	10	600	300	1500	1200
30	750	15	600	300	1500	1200
Days After Hospitalization						
1	800	15	600	300	2000*	1600*
2	750	15	600	300	2000	1600
5	800	15	600	300	2000	1600
15	900	15	600	300	2000	1600
19	900	20	600	300	2000	1600
29	900	20	600	300	2000	**Discontinued**
47	900	20	600	300	**Discontinued**	–
93	950	20	600	300	–	–

(Continued)

TABLE 1 Continued

Time	Medication (mg/day)					
	Clozapine	Aripiprazole	Rifampicin	Isoniazid	Pyrazinamide	Ethambutol
Days After Hospitalization						
164	950	20	**Discontinued**		–	–
180	900	20	–	–	–	–
Years After Hospitalization						
1.5 years	900	20	–	–	–	–

*The doses of pyrazinamide and ethambutol were increased in accordance with weight-based dosing recommendations.
Gray color indicates they were not receiving that treatment at that time.
The bold values are to indicated when certain treatments were discontinued.

Table 1, while their absolute neutrophil counts and clozapine and norclozapine levels are listed in Table 2.

In reflecting on their experience, ZZ appreciated that their wishes were taken into account during their diagnostic workup and treatment. Specifically, they recalled being grateful that their wishes around avoiding a mediastinoscopy during initial diagnostic investigation were honored. While they understood and were agreeable to their treatment plan, they also shared that they were frustrated by their lengthy hospital stay; this inpatient stay, more than subsequent daily outpatient ATT, was particularly frustrating for ZZ. ZZ was hopeful that their experience, and this article, could be helpful to others in a similar situation.

Discussion

While there are few case reports describing the co-management of clozapine and ATT, our case report and the series summarized above illustrate common themes: patients who were previously stable on clozapine are at risk of worsening psychiatric symptoms, alongside declining clozapine levels, after starting rifampicin-containing ATT. Specifically, clozapine levels decline 1–3 weeks after starting rifampicin, often necessitating clozapine dose increases by as much as 50-150%, and recover only gradually, often more than 30 days, after rifampicin cessation. In the absence of comprehensive studies in this area, we offer the following recommendations:

We recommend monitoring clozapine levels at least once weekly during rifampicin therapy and for 8–12 weeks following its cessation, particularly for patients who are exposed to environmental factors that affect clozapine disposition (e.g., cigarette smoking or medications that influence CYP1A2 activity). Ideally, clozapine levels can be timed synergistically with neutrophil monitoring or DOT visits to minimize laboratory burden. However, we acknowledge that socioeconomic factors, including housing insecurity and geographic inaccessibility to an outpatient behavioral health provider, can influence the feasibility of this monitoring and titration schedule. In these circumstances, stability in clozapine levels and the patient's symptoms during the first 4 weeks of therapy may allow for once monthly monitoring. The remittance of adverse effects, such as sialorrhea, could indicate a reduction in clozapine levels and prompt recurrent monitoring. We favor adjusting clozapine in larger than typical increments of 50–100 mg/day given the significance of CYP450 enzyme induction by rifampicin. While preemptive dose increases in clozapine could be necessary in some circumstances such as limited follow up or slow lab turnaround times, preferably clozapine doses should be adjusted based on close monitoring of clozapine levels. This is especially true early in treatment when the level is difficult to predict due to complex patient-specific factors (e.g. inflammatory effects, the specific ATT regimen, initial clozapine dose). If a patient's clozapine dose requirement during ATT exceeds or is anticipated to exceed 900 mg daily, the addition of a second antipsychotic that is primarily metabolized by CYP2D6 (e.g., aripiprazole) or one with minimal CYP metabolism (e.g., amisulpride) could be considered. We recommend that psychiatric practitioners consult with an infectious disease specialist and a clinical pharmacist to weigh the risks and benefits of rifamycin-sparing regimens, which could interact less significantly with clozapine. Finally, we encourage the inclusion of the clozapine-ATT interaction in tuberculosis treatment and general antimicrobial reference guides.

The findings observed in our patient case are explained largely by rifampicin's impact upon clozapine metabolism, specifically delayed CYP450 enzyme induction following rifampicin initiation and delayed CYP450 enzyme de-induction upon its cessation. CYP1A2 and CYP3A4 are major substrate pathways, accounting for approximately 30 – 55% and 20% of clozapine biotransformation, respectively. CYP2C19 and CYP2D6 are also involved as minor substrate pathways (9). Rifampicin is a moderate inducer of multiple CYP450 enzymes but is an especially potent inducer of CYP3A4 (21, 22). Enzyme induction due to rifampicin can be significant and unpredictable enough to require substantial dose modifications of concomitant CYP450 substrates or avoidance of rifampicin altogether. For instance, rifampicin is contraindicated in people taking most protease inhibitors due to the risk of antiviral failure (23). Rifampicin's inductive effects may also be potent enough to outweigh CYP450 inhibition by other medications. Although isoniazid is a moderate inhibitor of CYP2C9 and CYP3A4, our literature review suggests that co-administration of isoniazid and rifampicin results in net enzyme induction and enhanced metabolism of CYP450 substrates such as clozapine.

Managing the interaction between clozapine and ATT can be challenging for several reasons. Firstly, beyond the small number of published case reports, there is limited evidence to inform clozapine titrations or monitoring during ATT; the 2024 tuberculosis

TABLE 2 Clozapine doses, levels and ratios before, during, and after anti-tuberculosis treatment.

Days since hospital admission	Days since initiating anti-TB treatment	ANC (cells/μL)	Clozapine (ng/mL)[1]	Norclozapine (ng/mL)	Clozapine-to-Norclozapine ratio[2]	Clozapine dose (mg/day)	Clozapine level-to-dose ratio
-58	-72		972	358	2.71	900	1.08
16	2		1280	520	2.46	650	1.97
23	9	2720	618	436	1.42	700	0.88
29	15		547	431	1.27	750	0.73
35	21					800	
39	25	4090	134	131	1.02	750	0.18
47	33	2550	412	351	1.17	800	0.52
53	39	2520	387	355	1.09	900	0.43
63	49	2030	460	367	1.25	900	0.51
89	75	2410	361	305	1.18	900	0.40
123	109	2320	197	186	1.06	900	0.22
153	139	1830	355	270	1.31	950	0.37
181	167	2140	376	475	0.79	950	0.40
210	196	2150	542	315	1.72	950	0.57
230	216	2640	366	229	1.60	900	0.41
243	229		776	454	1.71	900	0.86
251	237	2280	666	473	1.41	900	0.74
273	259	2210	538	321	1.68	900	0.60
319	305	2140	587	334	1.76	900	0.65

[1]In clinical practice, 350 ng/mL is considered the lower threshold for clozapine efficacy. While some laboratories designate 600 ng/mL as the upper threshold, patients may experience clinical benefit at levels as high as 1000 ng/mL.
[2]A clozapine-to-norclozapine ratio below 1.32 may indicate CYP1A2 induction by medications (such as carbamazepine) or smoking. A ratio above 2.00 may indicate CYP1A2 inhibition by medications (such as fluvoxamine) or acute changes in clozapine metabolism during medical illness.
Gray color means the lab value was not available or not drawn/collected.

guidelines published by the American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America (ATS/CDC/ERSIDSA), for instance, make no mention of clozapine (13). Secondly, rifamycin-based regimens are among the most effective and shortest treatments for drug-susceptible tuberculosis. Thirdly, as clozapine is typically reserved for patients who have not responded to multiple antipsychotics, switching clozapine to circumvent drug-drug interactions is not pragmatic for most patients. Adding a second antipsychotic during antituberculosis therapy may protect against decompensation. However, options are limited as most antipsychotics are at least partially metabolized by the CYP450 enzyme system (9, 24). Next, a range of additional factors, including genetic polymorphisms, pregnancy, smoking status, and acute infection itself, can influence CYP450 enzyme activity (9, 25). Finally, people with serious mental illness are at higher risk of being lost to follow-up, experiencing poorer tuberculosis recovery outcomes, and inhabiting environments associated with enhanced tuberculosis transmission (such as correctional facilities and housing shelters) than the general population. Delaying treatment in this population can have grave consequences for both the individual patient and public health (26).

Our case adds to the body of literature and provides important insights into the co-management of clozapine and ATT. ZZ's clozapine levels increased between hospitalization and ATT initiation. We attribute this to smoking cessation during hospitalization and the impact of clozapine on inflammatory cytokines and CYP450 enzyme system. Severe infection and clozapine itself can lead to alterations in interleukin-6, interleukin-1, interferon-ɣ and tumor necrosis factor-α leading to decreases in CYP1A2 and the body's capacity to metabolize clozapine (8, 14, 24, 27). Additionally, clozapine's effects on muscarinic and histaminic receptors and cytokine signaling cascades may cause immunosuppressant effects that, in turn, render patients more vulnerable to acquiring tuberculosis. Clozapine's immunologic impacts may explain observations that clozapine led to an increased risk for tuberculosis and can lead to reactivation of latent tuberculosis (28).

As anticipated, ZZ's clozapine levels steadily declined 9 days after starting ATT. The clozapine levels and clozapine-to-norclozapine ratios remained below pre-treatment levels for the remainder of ATT, reflective of ongoing CYP450 enzyme induction.

On days 53 and 123 of ATT, the treating psychiatrist noted an increase in delusional thought content and increased the clozapine dose by 50 mg daily. This mild worsening of psychiatric symptoms may be explained by declines in the clozapine-to-norclozapine ratios. Multiple factors, including possible resumption of smoking or changes in inflammatory cytokine signaling during ATT, could explain this decline, While the investigators in prior case reports overcame lower clozapine levels or ratios by doubling the clozapine dose, ZZ's pre-treatment clozapine dose was near the typical dose ceiling of 900 mg per day, rendering a dose increase of this magnitude infeasible and potentially unsafe. In contrast to prior case reports, ZZ's clozapine dosages were only adjusted upwards by 15-20% from baseline. Proactive increases in ZZ's aripiprazole dosage may have protected against psychiatric decompensation, as aripiprazole is predominantly metabolized by CYP2D6. Our case suggests that adjunctive antipsychotic therapy may be effective when baseline clozapine doses are near the recommended daily maximum. Of note, aripiprazole prescribing recommendations recognize metabolism by CYP3A4 and suggest the dose be increased in the presence of strong CYP3A4 inducers (29).

ZZ's course following the completion of ATT also differs from prior case reports. While ZZ's clozapine levels and clozapine-to-norclozapine ratio increased after rifampicin therapy ended, they did not reach pre-treatment levels, despite ZZ's clozapine dose being higher than pre-treatment. In contrast to prior reports, ZZ did not require dramatic clozapine dose adjustments following discontinuation of rifampicin to prevent clozapine toxicity. ZZ also received most of their ATT in the outpatient setting, via directly observed therapy, to ensure adherence. Our case highlights the need for close collaboration among multiple disciplines across transitions of care, both inpatient and outpatient, including consult/liaison and outpatient psychiatry services, local or territorial public health services, infectious disease specialists, and pharmacy services. ZZ continues to exhibit psychiatric stability and adherence to clozapine and aripiprazole.

Limitations

While our case report has key advantages, including the reporting of medication doses and clozapine and norclozapine levels before, during and after ATT, there are limitations. The trends observed in ZZ may be partially explained by non-medication factors, including genetics and smoking status, and therefore may not be applicable to all patients receiving clozapine. Similarly, while the combination of clozapine and aripiprazole appears to have been effective for our patient, we cannot definitively conclude that antipsychotic polypharmacy will protect against psychiatric decompensation in people receiving clozapine and standard ATT.

Finally, while we offer recommendations, we emphasize these are based on the case reports and literature reviewed here and represent the opinions of the authors. Additional research, as well as soliciting recommendations from larger groups of clinicians and experts would strengthen and refine the recommendations proposed.

Conclusion

Our case and literature review underscore important issues in the management of ATT among adults receiving clozapine. Clozapine levels can fluctuate dramatically in response to acute illness, smoking status, and the initiation of rifamycins, but these shifts may not always be accompanied by adverse effects or worsening psychiatric symptoms. Additionally, these fluctuations may be delayed by as much as 3 weeks following rifampicin initiation; clinicians should be mindful of levels slowly returning to concentrations seen prior to ATT after rifampicin is discontinued. When feasible, routine monitoring of clozapine and norclozapine levels can be useful to capture the magnitude of the drug interaction and guide clozapine dosing during and after ATT. Close monitoring of a patient's psychiatric status is necessary as recurrence of symptoms is not uncommon after starting ATT. In our experience, pre-emptive dose adjustments, frequent monitoring of levels, and close outpatient clinical assessments were all necessary to maintain clinical stability and prevent clozapine toxicity.

Data availability statement

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

Ethics statement

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

NS: Visualization, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. JJ: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. BW: Validation, Writing – original draft, Writing – review & editing. AS: Visualization, Writing – original draft, Formal analysis, Conceptualization, Writing – review & editing, Supervision. CE:

Writing – review & editing, Conceptualization, Supervision, Writing – original draft, Formal analysis, Visualization.

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Case Report: I want more olanzapine: pharmacogenetic insights into a patient's preference for high-dose olanzapine

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Olanzapine is an effective antipsychotic agent, but its metabolism shows considerable interindividual variability. We present a case of a patient with treatment-resistant schizophrenia who consistently required and preferred high-dose olanzapine (40–60 mg/day) for symptom control. The patient reported improved motivation and energy following the reduction of adjunctive antipsychotics.

Methods: The patient's clinical course and treatment history were retrospectively reviewed. Plasma olanzapine levels were measured to assess systemic drug exposure, and pharmacogenetic testing for CYP1A2, CYP2D6, CYP3A4, and CYP3A5 polymorphisms was performed using PCR-based genotyping.

Results: Genotyping revealed CYP1A2 -163AA genotype, consistent with an ultrarapid metabolizer phenotype, and CYP2D6 *1/*9 genotype, indicating slightly reduced but overall normal enzyme activity. At 40 mg/day, the olanzapine trough level was 51 ng/mL—lower than expected for a non-smoker—suggesting enhanced metabolic clearance. This pharmacokinetic profile, shaped by genetic predisposition and smoking, likely necessitated higher olanzapine doses to reach therapeutic levels. Discontinuation of haloperidol and risperidone was associated with improved subjective energy and engagement.

Conclusion: This case illustrates how pharmacogenetic variability may influence antipsychotic efficacy and tolerability. The patient's ultrarapid CYP1A2 metabolism and smoking status likely reduced olanzapine exposure, warranting higher doses for clinical response. Pharmacogenetic profiling may provide valuable insights into individual treatment needs and support more personalized approaches in complex psychiatric cases.

KEYWORDS

case report, CYP1A2, CYP2D6, genetic polymorphism, olanzapine, personalized psychopharmacotherapy, pharmacogenetics, treatment resistance

Introduction

Olanzapine is one of the most extensively studied second-generation antipsychotics due to its commonly perceived efficacy, good tolerability, and significant metabolic side effects. In phase 1 of the CATIE schizophrenia study, olanzapine demonstrated superior outcomes on primary efficacy measures compared to the other second-generation antipsychotics and perphenazine (1). It is however important to note that the primary outcome measure in question was "all-cause discontinuation", therefore the apparent superiority of olanzapine may, in part, be attributed to its high subjective tolerability. Due to its strong binding affinity for serotonergic 5-hydroxytryptamine 2A receptor (5-HT_{2A}) receptors, olanzapine is associated with a lower incidence of subjectively distressing adverse effects, such as parkinsonism, akathisia, and other dysphoric experiences linked to excessive dopaminergic type 2 (D2) receptor blockade (2, 3). Some authors have suggested that olanzapine's efficacy may rival that of clozapine among patients with treatment-resistant schizophrenia (TRS), but this may represent an overestimation due to differences in inclusion criteria across studies. Although olanzapine has not consistently been shown to match the efficacy of clozapine when rigorous TRS criteria are applied, it may offer benefits for a specific subgroup of therapeutically resistant patients. Gannon and colleagues reviewed studies evaluating the efficacy, safety, and tolerability of high-dose olanzapine. Based on their analysis of 10 studies, they concluded that olanzapine doses exceeding 20 mg/day may be more effective than haloperidol and commonly used second-generation antipsychotics in TRS cases where clozapine is either intolerable or contraindicated (4).

Olanzapine is primarily metabolized by the cytochrome P450 enzyme CYP1A2 or via direct glucuronidation. Because of enzyme induction, smokers tend to have lower serum concentrations and higher clearance rates of olanzapine compared to nonsmokers. The therapeutic effects are attributed to olanzapine, while its metabolism mainly serves as a pathway for inactivation and elimination. The resulting metabolites,10-N-glucuronide and 4N-glucuronides, are considered pharmacologically inactive or, in the case of 4-Ndesmethylolanzapine, minimally active but clinically insignificant. In addition to tobacco use, sex also has a significant impact on metabolism. However, there is not sufficient data supporting the necessity for the dose adjustment in individuals with faster metabolism. In contrast, there is some evidence that lower doses are required in individuals with slower metabolism—such as women, older adults, and non-smokers (5, 6). Olanzapine serum concentrations show strong correlation with cerebrospinal fluid levels and can be readily measured; therefore, therapeutic drug monitoring is a valuable tool for optimizing treatment efficacy and ensuring patient safety (7). Several studies with differing methodologies show a high degree of agreement on the plasma level response threshold for olanzapine at 23 ng/ml (8–10).

In this case report, we present a patient with TRS and poor tolerability to clozapine, who was consequently treated with a combination of antipsychotics with only partial effectiveness, until a high dose of olanzapine led to satisfactory remission. Particularly notable was the patient's consistent personal preference for higher doses of olanzapine. Pharmacogenetic testing of CYP1A2 and CYP2D6 revealed specific genetically determined metabolic characteristic, which may potentially explain the good response and the expressed preference for high daily olanzapine dose, the partial efficacy and side effects observed with clozapine, as well as patient's reluctance to risperidone and haloperidol.

Case description

A 36-year-old male patient with a diagnosis of schizophrenia, previously treated at another facility, first attended our outpatient unit in June 2022. He did not have any other medical conditions requiring treatment up until then and had no family history of psychiatric disorders. He was a smoker, smoking up to one pack of cigarettes a day, but denied consuming alcohol or prohibited psychoactive substances, although he disclosed smoking marihuana occasionally in his youth.

We reconstructed the patient's preceding treatment history based on the available medical records and the patient's own account. He was first admitted to an intensive psychiatric care unit at the age of 20 years in 2006. Due to psychotic symptoms, he was prescribed olanzapine 5 mg and lorazepam 1 mg QHS. He was discharged after four days, at his own request and against medical advice, but in accordance with the absence of legal criteria for involuntary treatment. He discontinued the prescribed antipsychotic medication. In March 2009 he sought help in the psychiatric emergency unit due to intense fear and anxiety. He presented with persecutory ideations. His friends and family described that he reported on acoustic hallucinations, passivity experiences, and telepathy. According to collateral reports, he had become progressively withdrawn and inactive, and his relationship with his parents had become increasingly strained. He was voluntarily admitted to in-hospital treatment at the intensive psychiatric ward of the University Psychiatric Clinic Ljubljana. A diagnostic work-up following the protocol for first-episode psychosis included a physical and neurological examination, routine blood tests (including complete blood count, liver and kidney function tests, thyroid function, and inflammatory markers) and serological testing for infectious and autoimmune causes (e.g., HIV, syphilis, and antinuclear antibodies). The results of all aforementioned tests were normal, a head CT revealed no structural abnormalities, and an electroencephalogram (EEG) was also performed to exclude seizure activity. Treatment with amisulpride up to 600 mg/day TID and later olanzapine up to 20 mg/day QHS was initiated. Due to an inadequate response to consecutive trials of two antipsychotic medications and the persistence of psychotic symptoms, treatment with clozapine was initiated. Olanzapine was discontinued, and clozapine was slowly titrated alongside amisulpride 400 mg/day BID up to 500 mg/day BID. Following the introduction of clozapine, the patient's condition gradually improved with a significant reduction in positive symptoms. He was discharged with a recommendation to continue treatment in the outpatient setting at a facility in another

location, which was more suitable at the time, given his living arrangements.

Between 2009 and 2019, he attended regular check-ups, at first once a month, later once every two months. Amisulpride was gradually discontinued with no recorded deterioration in his mental state. Due to continuous complaint of excessive daytime sedation and hypersalivation the dose of clozapine was slowly tapered to 350 mg/day QHS. Despite the lower dosage, the patient frequently reported hypersalivation and expressed a desire to discontinue the treatment. At the same time, he often complained of insomnia, for which his treating psychiatrist prescribed zolpidem 5 mg as needed at bedtime.

In October 2019, he was hospitalized for the third time at the intensive psychiatric ward of the University Psychiatric Clinic Ljubljana due to a deterioration in his mental state following complete discontinuation of treatment. After an incident of aggression in his home environment, he was admitted involuntarily. He exhibited acute psychotic symptoms and psychomotor agitation. Upon admission, treatment with risperidone and lorazepam was initiated to manage agitation; later clozapine was reintroduced. In the third week of hospitalization, the patient developed a high fever, reaching 38.8°C. As a precaution, clozapine—at that time administered at a dose of 75 mg/day—was temporarily discontinued. The elevated body temperature was attributed to a localized inflammatory process in the right mandibular region, which required surgical drainage and a course of antibiotic therapy. Following completion of the antibiotic treatment, the patient became reluctant to resume clozapine due to previously experienced adverse effects, particularly severe hypersalivation. Given the need to address residual psychotic symptoms and the patient's unwillingness to resume previously effective clozapine treatment, the attending psychiatrist adopted a polypharmacological approach. His condition gradually improved, and he was discharged with olanzapine 20 mg/day QHS, risperidone 8 mg/day BID, haloperidol 4 mg/day TID, and clonazepam 3 mg/day TID.

Following his discharge in December 2019 and until his enrollment in our outpatient service, the patient continued outpatient treatment under the care of his previous psychiatrist. He attended monthly check-ups, during which clonazepam was gradually tapered and eventually discontinued. Good control of positive psychotic symptoms and adherence to the prescribed treatment were documented. However, the patient continued to report excessive daytime sedation alongside persistent sleep difficulties, for which he was occasionally prescribed zolpidem at a dose of 5 mg. Due to persistent complaints of insomnia after unsuccessful attempts with non-pharmacological interventions as well as trazodone, the treating psychiatrist increased the olanzapine dose to 30 mg/day, after which the patient reported an improvement in sleep. Weight gain was observed during the course of the prescribed treatment, and the patient was referred to a weight management program organized by the local primary health care center.

The patient expressed a preference to continue treatment at our outpatient unit, citing its proximity to his place of residence as a matter of convenience. He presented for an initial consultation in June 2022. At this time, he was prescribed olanzapine 30 mg/day QHS, risperidone 8mg/day, haloperidol 4mg/day TID, and trazodone 50 mg in the evening. The latter was ineffective in treating his persistent insomnia, and he admitted to having discontinued it. He was free of acute psychotic symptoms and demonstrated insight into the nature of his condition and the need for maintenance antipsychotic therapy. He again emphasized experiencing severe and persistent sleep disturbances. In addition, he reported excessive daytime sleepiness and a lack of motivation. He was overweight with a BMI of 36, had normal ECG without QTc prolongation, and presented with no clear extrapyramidal side effects of medication. Routine blood tests revealed mixed dyslipidemia, for which rosuvastatin was subsequently initiated. Given the patient's polypharmacy and established metabolic syndrome, we proposed a gradual adjustment of his pharmacotherapy to transition to a metabolically more favorable monotherapy. At first the dose of olanzapine was gradually tapered at a rate of 5 mg per month. After two months, at a dose of 20 mg/day, the patient voiced his objection to further dose reduction. He expressed a preference to continue olanzapine while discontinuing other medications. He reported that olanzapine was the most effective treatment for his symptoms, caused the least muscular tension, and was the only medication that alleviated his insomnia. In the period between follow-up appointments, the patient frequently contacted the outpatient clinic, repeatedly requesting additional prescriptions specifically for olanzapine, often citing various reasons such as having lost his medication. Upon confrontation, the patient admitted to taking olanzapine at a higher dose than prescribed as he found it helpful for sleep. He also disclosed that, on rare occasions when unable to fall asleep, he took up to 60 mg. He reported adhering to the prescribed regimen for the other medications but felt they were ineffective. He experienced fatigue and lack of motivation following the morning doses. The patient was thoroughly educated about the negative impact of olanzapine on metabolic health. Nevertheless, he persisted in his preference for olanzapine, explicitly stating, 'If it's acceptable, I would like to continue taking 40 mg of olanzapine, as it is the only thing that helps me sleep.' Taking into account the patient's preferences and to maintain adherence to maintenance treatment, we agreed to prescribe olanzapine at a dose of 40 mg/day QHS. Concurrently, a plan was established for the gradual tapering of the other two antipsychotic medications. The patient was encouraged to adopt a healthy, balanced diet and engage in regular physical activity with the goal of weight reduction.

As a safety measure and to objectively assess treatment adherence, a trough plasma level of olanzapine was measured using liquid chromatography–mass spectrometry (LC-MS). A venous blood sample was obtained 12 hours after the patient's last evening dose of olanzapine. The analysis revealed a plasma olanzapine concentration of 51 ng/mL. The patient reported a consistent daily intake of 40 mg of olanzapine in the evening. The dose of haloperidol was gradually tapered until discontinuation, and the dose of risperidone was also reduced. Following the discontinuation of haloperidol, and while receiving olanzapine 40

mg/day QHS and risperidone 6 mg/day TID, the patient spontaneously reported experiencing increased motivation and energy throughout the day. He reported improved ability to engage in physical activity. No worsening of psychotic symptoms was observed during this period.

To elucidate potential pharmacogenetic factors underlying the patient's atypical therapeutic response and preference for higher olanzapine doses, a targeted analysis of common functional polymorphisms in the CYP1A2, CYP2D6, CYP3A4, and CYP3A5 was conducted after obtaining informed consent. A graphical representation of the patient's treatment history is provided in Figure 1.

Methods

Pharmacogenetic testing was performed using DNA extracted from peripheral blood leukocytes with the E.Z.N.A. SQ Blood Kit II (Omega Bio-tek), following the manufacturer's protocol. Copy number variations in CYP2D6, including gene deletions (CYP2D6*5) and duplications (CYP2D6*xN), were assessed using long-range PCR (Biotechrabbit GmbH) and confirmed by gel electrophoresis.

Single-nucleotide variants (SNVs) in CYP1A2 (rs762551, *30) and CYP2D6 (including common variants such as *3, *4, *6, *9, *10, *17, *41) were analyzed using KASP genotyping assays (LGC

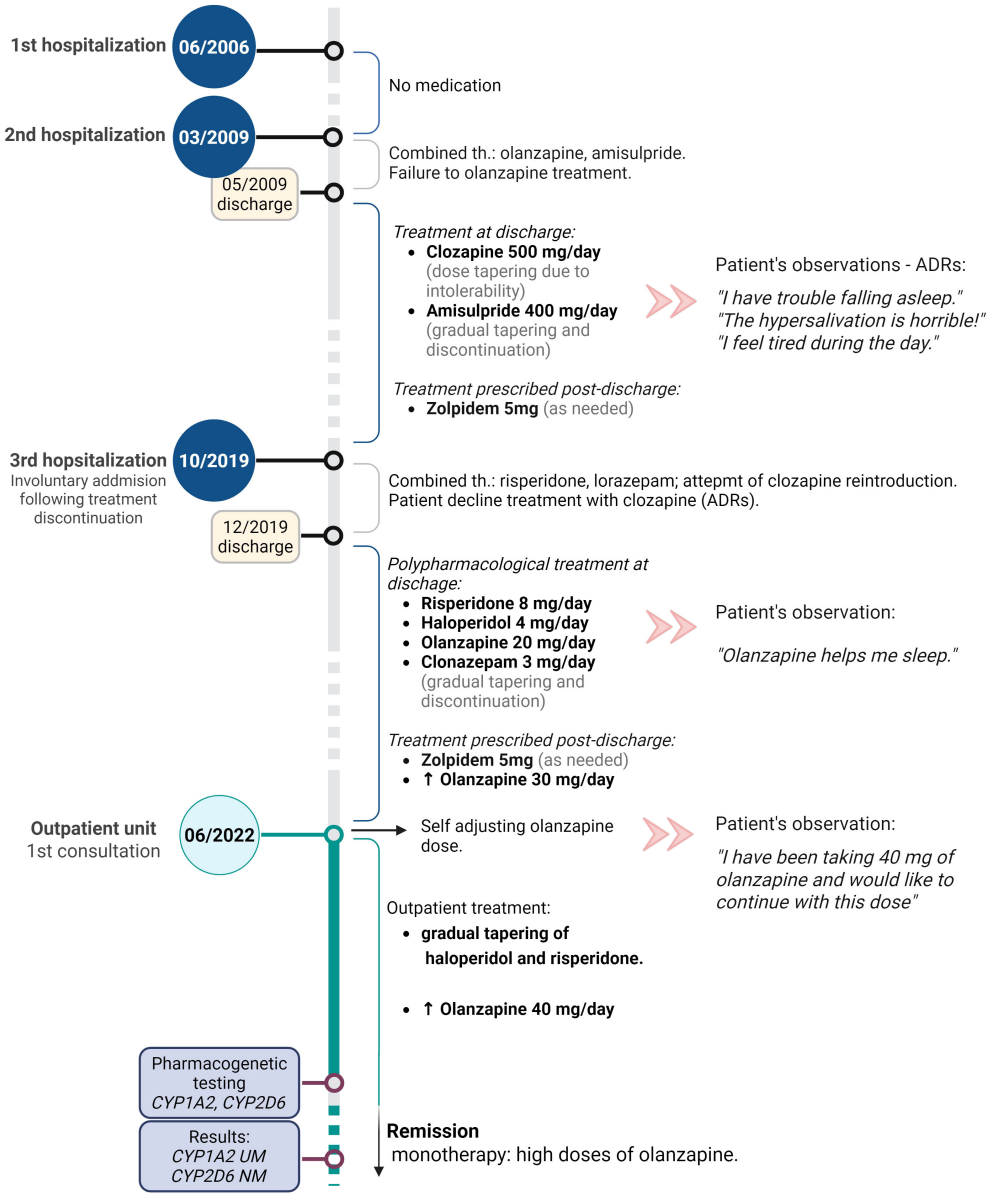

FIGURE 1
Graphical representation of the patient's treatment timeline, including antipsychotic dosing, medication changes, and key clinical events.

Biosearch Technologies), which detect allele-specific PCR products via fluorescence. All assays were performed in duplicate with appropriate positive and negative controls.

Pharmacogenetic testing was performed using DNA extracted from peripheral blood leukocytes with the E.Z.N.A. SQ Blood Kit II (Omega Bio-tek, USA), following the manufacturer's instructions. Copy number variations in CYP2D6, including gene deletion (CYP2D6*5) and duplication (CYP2D6*xN), were assessed using long-range PCR

(Biotechrabbit GmbH, GER) and confirmed by gel electrophoresis. Single-nucleotide variants

(SNVs) in CYP1A2 (-163C>A (rs762551)), CYP2D6 (*3, *4, *6, *9, *10, 14A/B, *17, *41),

CYP3A4 (*22) and CYP3A5 (*3, *6, *7) were analyzed using KASP genotyping assays (LGC Biosearch Technologies, UK). All analyses were performed in duplicate along with appropriate controls.

Results and discussion

Summary of the genotyping analysis and the patient's phenotypes is presented in Table 1. Considering the genotypes and resulting phenotypes, we attempted to retrospectively elucidate the drugs' pharmacokinetics to explain the patient's treatment response and preference for high-dose olanzapine, although evidence-based recommendations for treatment selection in such cases are not yet established.

The presence of the CYP1A2 -163AA genotype indicates homozygosity for a genetic variant in the promoter region of the CYP1A2 gene that increases inducibility and thereby gene expression. This could lead to accelerated metabolism of certain drugs when coadministered with the inducers of this enzyme. Consequently, the efficacy of certain antipsychotics that are primarily (e.g., olanzapine, asenapine, thiothixene, trifluoperazine) or partially (e.g., clozapine) metabolized through CYP1A2 (11). Numerous studies suggest that CYP1A2 activity is more strongly influenced by CYP1A2 expression levels than by genotype alone (12, 13). Polycyclic aromatic hydrocarbons present in tobacco smoke are common inducers of CYP1A2. Smokers have lower plasma concentrations of olanzapine compared to non-smokers, with a reported mean decrease in trough levels of up to 35–45% (14). Increased olanzapine clearance due to CYP1A2 induction lowers exposure (area under the curve) and shortens drug half-life. Subtherapeutic levels may occur in smokers at standard olanzapine doses (e.g., 10 mg/day). This may lead to reduced efficacy, increased risk of relapse, or the need for higher doses, although the clinical relevance and need for dose adjustment are disputed, and no clear evidence-based treatment recommendations are available.

The effect of smoking on enzyme induction is theoretically more pronounced in individuals with the CYP1A2 -163AA genotype, which is associated with the phenotype of ultrarapid metabolizer (UM) (15). In the case of the patient presented, we hypothesize that accelerated olanzapine metabolism contributed to a significantly reduced concentration-to-dose ratio. This pharmacokinetic profile may explain the patient's subjective preference for higher doses. The administration of elevated doses (40–60 mg) likely compensated for enhanced metabolic clearance by achieving higher peak plasma concentrations shortly after ingestion. This, in turn, may account for the patient's reported sedative effects only at higher doses, as supported by olanzapine's concentration-time kinetics. These observations are consistent with the known pharmacological characteristics of olanzapine, wherein peak plasma levels play a critical role in mediating sedative and anxiolytic effects (5). The proposed cumulative effects on olanzapine pharmacokinetics are illustrated schematically in Figure 2.

One limitation of this study is the absence of direct assessment of CYP1A2 expression, which would have provided definitive evidence of enhanced enzyme induction. However, CYP1A2 activity was indirectly inferred through measured olanzapine plasma concentrations and the patient's clinical response. Plasma olanzapine levels were measured following the initiation of high-dose olanzapine, primarily to objectively assess adherence, as the patient's persistent request for higher doses was atypical compared

TABLE 1 Summary of the genotyping analysis and the patient's phenotypes.

Gene	Analyzed polymorphisms	Genotype	Phenotype
CYP1A2	-163C>A	-163AA	UM (ultrarapid metabolizer)
CYP2D6	*3, *4, *5, *6, *8, *9, *10, *14A/B, *17, *41, xN	*1/*9	NM (normal metabolizer)
CYP3A4	*22	*1/*1	NM (normal metabolizer)
CYP3A5	*3, *6, *7	*3/*3	PM (poor metabolizer)

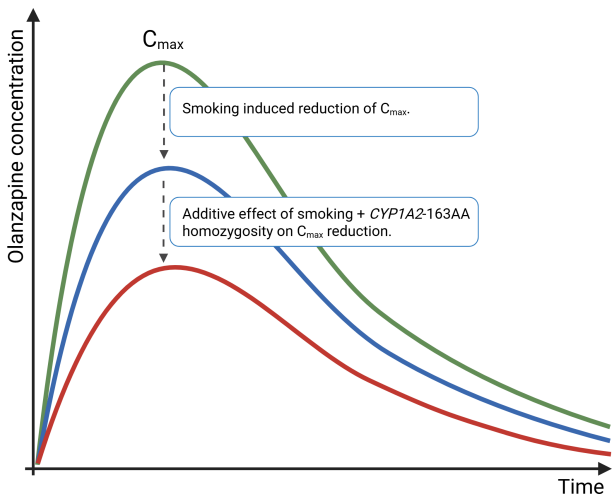

FIGURE 2
Schematic representation of the proposed impact of smoking and CYP1A2 phenotype on olanzapine pharmacokinetics, illustrating reduced plasma concentrations and altered peak–trough dynamics. The schematic is based on published data describing olanzapine pharmacokinetics and the known effects of smoking and specific CYP1A2 metabolic phenotypes on drug metabolism (5, 14, 15).

to standard clinical experience. The measured trough plasma concentration of olanzapine was 51 ng/mL at a nightly dose of 40 mg (QHS). This value supports the hypothesis of accelerated olanzapine metabolism in this patient. Previous pharmacokinetic studies have demonstrated an approximate conversion factor of 2 between daily dose and expected 12-hour trough levels in nonsmokers, suggesting that a 40 mg daily dose would typically yield a trough concentration of approximately 80 ng/mL in the absence of metabolic inducers or individual metabolic variations (16). The observed discrepancy further supports the presence of enhanced olanzapine clearance, potentially due to a combination of smoking and genetic factors influencing CYP1A2 inducibility.

The patient developed features of metabolic syndrome during high-dose olanzapine treatment, raising safety concerns. However, due to his strong preference for continuing olanzapine and resistance to switching to a potentially more metabolically favorable antipsychotic, management focused on lifestyle modifications and the initiation of statin therapy to address hyperlipidemia. No other clear adverse drug reactions (ADR) were observed. The measured trough plasma concentration of 51 ng/mL exceeds the previously proposed therapeutic response threshold of approximately 20 ng/mL for the majority of patients (17). On the other hand, concerning safety and tolerability, previous studies have demonstrated that high-dose olanzapine treatment—and even trough plasma concentrations exceeding 200 ng/mL—can be well tolerated by a substantial subset of patients (18, 19).

Furthermore, the patient's CYP1A2 metabolic phenotype likely contributed to a suboptimal therapeutic response to clozapine. Increased CYP1A2 activity can lead to faster clearance of clozapine, resulting in lower plasma concentrations and reduced clinical efficacy. While CYP3A4 and CYP3A5 enzymes also influence clozapine metabolism—particularly its conversion to norclozapine— (20, 21) they were likely less influential in this case. The patient was a normal metabolizer for CYP3A4 and a poor metabolizer for CYP3A5, suggesting minimal impact on overall clozapine clearance from these pathways. The increased production of norclozapine, clozapine's major metabolite, may have affected the side effect profile. Norclozapine has weaker antipsychotic properties, a longer half-life, and is associated with hypersalivation (sialorrhea) (22, 23). Although plasma levels were not measured during clozapine treatment, the patient's report of severe hypersalivation—ultimately contributing to his refusal of clozapine reintroduction during his third hospitalization—is consistent with this proposed mechanism.

The patient also carried CYP2D6 *1/*9 genotype which is according to current guidelines associated with the normal metabolizer (NM) phenotype, albeit with slightly reduced enzymatic activity (activity score 1.5) (24). Nevertheless, the slightly reduced enzymatic activity may still result in slower conversion of risperidone to its active metabolite, paliperidone. This may lead to higher plasma concentrations of risperidone relative to paliperidone, without significantly affecting the total active moiety. In individuals with reduced CYP2D6 enzymatic activity, this could result in disproportionately higher risperidone levels, potentially leading to increased D2 receptor occupancy at a given daily dose. Haloperidol is primarily metabolized by CYP3A4 and, to a lesser extent also CYP2D6. We excluded the potential impact of CYP3A4 and CYP3A5 genotypes on haloperidol metabolism, as the patient was a normal CYP3A4 and poor CYP3A5 metabolizer. However, the patient's mildly reduced CYP2D6 enzymatic activity may have influenced plasma concentrations of haloperidol. All above-described mechanisms could hypothetically have led to enhanced D2 receptor blockade during the period of polypharmacological treatment when haloperidol and risperidone were co-administered in the presented patient. Although no extrapyramidal symptoms were described, excessive D2 receptor blockade can exacerbate negative and cognitive symptoms and attenuate reward-related processing leading to impairments in motivated behavior, hedonic experience, and emotional expression (25). Although not assessed using objective measures, the patient's reported increase in motivation and energy throughout the day, along with improved capacity to engage in physical activity following the tapering of haloperidol and risperidone, may reflect a reduction in excessive D2 receptor blockade.

Apart from the proposed pharmacokinetic mechanisms that may hypothetically explain the patient's preference for high-dose olanzapine, this case also warrants consideration of potential non-therapeutic use or misuse-like behavior involving olanzapine. Recent literature highlights a notable potential for misuse and abuse among certain atypical antipsychotics. Although no definitive mechanism of action underlying possible reinforcing effects has been clearly established, agents such as olanzapine and quetiapine may elicit non-therapeutic seeking behavior in some individuals, likely due to their pronounced sedative and anxiolytic properties (26). Unlike substances with well-established misuse potential, reports of olanzapine abuse in the literature remain relatively scarce (27). However, the present case may be alternatively interpreted through the lens of misuse and drug-seeking behavior commonly observed in substance use disorders.

Conclusions

This case illustrates how pharmacogenetic and pharmacokinetic factors may underlie atypical treatment responses in psychiatry. The patient's CYP1A2 -163AA genotype, combined with smoking, likely led to accelerated olanzapine metabolism, possibly explaining the need for higher doses to achieve therapeutic effects and contributing to clozapine inefficacy and hypersalivation. Additionally, the CYP2D6 *1/*9 genotype may have altered risperidone and haloperidol metabolism, potentially increasing D2 receptor blockade and dampening motivation and affect—effects that improved after discontinuation of these agents. Although routine genotype-guided prescribing is not yet supported by sufficient evidence, this case illustrates how pharmacogenetic testing may provide useful insights in selected treatment-resistant patients. Further research is needed to clarify its role in personalized psychopharmacology.

Data availability statement

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

Ethics statement

Ethical approval was not required for the case report involving humans in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

LK: Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing, Methodology. IK: Data curation, Writing – original draft, Writing – review & editing. TB: Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. VD: Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. JB: Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. MP: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Successful treatment of PGAD/GPD with leuprolide: a case report

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Persistent genital arousal disorder/genitopelvic dysesthesia (PGAD/GPD) is a rare clinical condition of uncertain etiology. It is characterized by involuntary genital arousal occurring in the absence of sexual interest or desire, and may be accompanied by abnormal sensations in the pelvic and reproductive regions. PGAD/GPD exerts a profound negative impact on patients' physical and mental health, severely impairing daily functioning and, in some cases, leading to suicidal ideation. This case highlights the potential role of COVID-19 as a triggering factor in the development of PGAD/GPD. The marked improvement in symptoms following treatment with leuprolide suggests that dysregulation of gonadotropin/GnRH signaling may constitute a key pathogenic mechanism underlying this condition. We anticipate that this successful treatment case will provide valuable insights into the etiology and treatment strategies of PGAD/GPD.

KEYWORDS

leuprolide, case report, treatment, PGAD, generalized pareto distribution (GPD)

Introduction

Persistent genital arousal disorder/genitopelvic dysesthesia (PGAD/GPD) is a rare condition affecting women's sexual health, occurring at any age but most commonly after puberty (1). The condition is characterized by sudden and frequent spontaneous genital arousal, often accompanied by genitopelvic sensory abnormalities. Its nature differs from sexual arousal associated with sexual desire or subjective arousal. Symptoms of PGAD/GPD are typically not alleviated through masturbation or orgasm. It is fundamentally distinct from hypersexuality, which is defined by excessive sexual desire that may or may not include persistent genital arousal, whereas PGAD/GPD involves persistent genital arousal in the absence of sexual desire (2). This condition primarily affects women. Due to the unique nature of its symptoms, patients often experience psychological distress, including shame and guilt. Severe cases may be accompanied by anxiety, depression, or even suicidal ideation, significantly impairing quality of life.

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TABLE 1 Relevant laboratory examinations and BAI and BDI scores before, during and after treatment.

	Initiation of Leuprorelin	1 month after Leuprorelin treatment	2 months after discontinuation	4 months after discontinuation	22 months after discontinuation
date of hospital visiting	2013.02.17	2023.03.25	2023.07.07	2023.09.08	2025.03.21
LH(IU/L)	26.2	1.27	<0.01	3.64	15.87
FSH(IU/L)	45.86	5.8	10.62	21.58	41.88
E2(pmol/L)	24.33	<55.07	<55.07	<55.07	<55.07
T(nmol/L)	<0.1	<0.01	0.1	0.18	0.46
P(nmol/L)	0.6	0.71	1.27	0.72	0.77
PRL(mIU/L)	848.8	232.36	189.25	134.51	148.02
DHEAS (umol/L)	–	1.3	1.3	1.2	1.6
BAI score	23	10	6	6	6
BDI score	16	9	4	4	4

LH, Luteinizing Hormone; FSH, Follicle-stimulating Hormone; E2, Estradiol; T, Testosterone; P, Progesterone; PRL, Prolactin; DHEAS, dehydroepiandrosterone; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

However, there is currently limited global understanding of this condition, with only a few reports available. Existing treatment approaches are primarily exploratory in nature. Clinical efficacy remains poor, and follow-up data are scarce. Here, we report a case of PGAD/GPD treated with leuprolide, which demonstrated marked clinical improvement and was followed for nearly two years. The results are summarized below.

Case report

A 77-year-old female patient presented to our endocrinology outpatient clinic in February 2023 with a chief complaint of "recurrent spontaneous genital arousal for over 50 days." At the time of presentation, she expressed shame and reluctance to speak, and her medical history was primarily provided by family members. Approximately 50 days after recovering from a COVID-19 infection, she developed spontaneous genital arousal characterized by sudden urges that were not alleviated by intercourse. These symptoms were accompanied by lower limb weakness, pelvic congestion, a burning sensation, and suicidal thoughts. There was no genital swelling or pain. Subsequently, the symptoms recurred intermittently with increasing frequency and duration, eventually becoming persistent without spontaneous resolution. Three days prior to presentation, hormonal tests conducted at another hospital confirmed postmenopausal status, and pelvic MRI revealed no significant abnormalities. Her medical history includes a modified radical mastectomy for right breast invasive ductal carcinoma performed seven years ago at another institution. Postoperatively, she has been maintained on 2.5 mg of letrozole daily. She denies any history of anxiety, depression, or hyperactive sexual desire. Menarche occurred at age 14, and menopause at age 50. She has had four pregnancies and has one son and one daughter. She has reported low spontaneous sexual desire over the past 20 years.

Based on a comprehensive analysis of the patient's medical history and clinical presentation, a diagnosis of PGAD/GPD was made. The patient expressed recurrent suicidal ideation and demonstrated a strong desire for treatment. She was informed that no evidence-based treatment guidelines currently exist for PGAD/GPD, and that available therapeutic approaches are largely exploratory. Following approval from the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University and written informed consent, a monthly subcutaneous injection of 3.75 mg leuprolide acetate sustained-release microspheres was initiated. Before treatment and during follow-up, the patient completed assessments using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI). Prior to treatment, the BAI score was 23 (15–25 indicates mild anxiety), and the BDI score was 16 (greater than 15 suggests possible depression), indicating mild anxiety and possible depression (Table 1, Figure 1).

The patient reported a worsening of genital arousal symptoms within the first three days following leuprolide administration, which gradually improved after one week. One month later, symptoms showed marked improvement, with the BAI score reduced to 10 and the BDI score reduced to 9. Follow-up hormone levels were consistent with the physiological changes expected after Gonadotropin-Releasing Hormone Analog (GnRHa) therapy. Two months after treatment, the symptoms were largely absent, with only occasional brief recurrences that resolved spontaneously. At the three-month follow-up, the patient reported complete remission of symptoms, and leuprolide therapy was discontinued, with BAI and BDI scores of 5. Over the three-

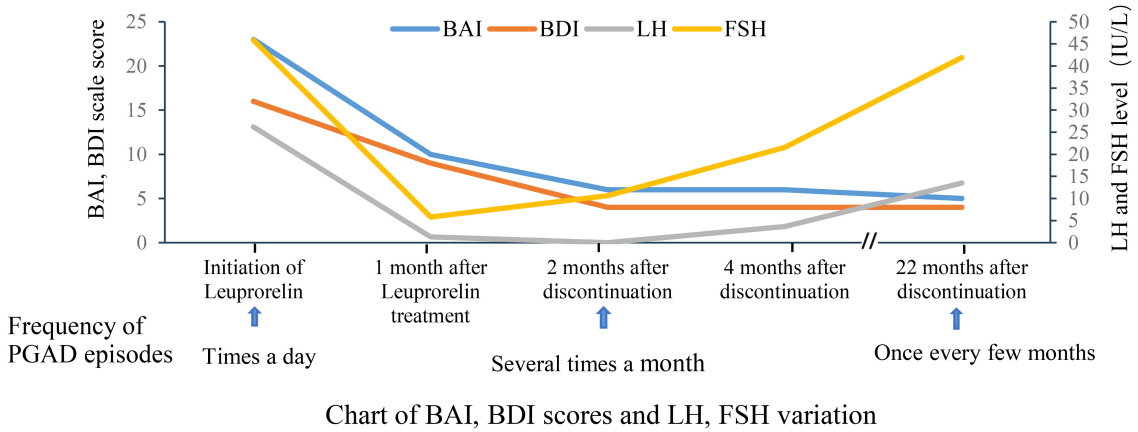

FIGURE 1
Changes in BAI and BDI Scores and LH Levels.

month treatment period, three injections of leuprolide acetate sustained-release microspheres were given.

One month after discontinuing leuprolide, approximately 10 days following reinfection with COVID-19, a mild recurrence of sexual arousal symptoms was noted, though milder than previous episodes. The main symptom was a burning sensation in the perineal region, which typically occurred during leisure time and resolved with cognitive distraction. Two months after discontinuation, the patient returned for a follow-up visit and reported that symptoms had largely resolved, with occasional recurrence triggered by watching videos on a smartphone, which resolved with focused distraction. Re-evaluation of sex hormones showed that LH and FSH levels remained below postmenopausal baseline. The BAI score was 6, and the BDI score was 4. Four months after medication discontinuation, the patient reported two episodes over the preceding two months, both of which resolved quickly with mild intensity. Follow-up hormone levels indicated a gradual return of FSH and LH to postmenopausal levels. The BAI and BDI scores remained stable at 6 and 4 (Table 1, Figure 1), respectively. After seven months without medication, the patient experienced a resurgence of symptoms following attendance at a wedding banquet. These episodes lasted approximately 30 minutes and were accompanied by lower limb weakness and mild pelvic discomfort. Symptoms recurred intermittently every 2–3 days over a three-month period before resolving spontaneously. At the 22-month telephone follow-up, the patient reported mild and transient episodes of spontaneous genital arousal, which resolved without intervention. Hormone reassessment confirmed postmenopausal status with LH levels persistently lower than baseline. The BAI and BDI scores were 6 and 4, respectively.

Discussion

In 2001, Leiblum and Nathan first reported five cases of Persistent Sexual Arousal Syndrome (PSAS) in women, characterized by symptoms of unrelieved genital arousal (3). Considering that the condition was primarily genital in nature rather than sexual, Leiblum renamed it Persistent Genital Arousal Disorder (PGAD) in 2006 (4). In 2019, the International Society for the Study of Women's Sexual Health (ISSWSH) convened a panel of experts to re-evaluate the terminology. The panel recognized that PGAD did not fully capture the range of symptoms experienced by patients with genitopelvic dysesthesia (GPD). As a result, the term PGAD was broadened to encompass GPD. The term PGAD/GPD maintains a primary focus on persistent arousal symptoms while acknowledging the associated physical manifestations (1).

Currently, the epidemiological characteristics and pathophysiological mechanisms of PGAD/GPD are not well understood. Due to its unique symptoms and privacy concerns, many patients experience self-shame or even guilt, which often leads to avoidance of medical consultation or delayed treatment. Additionally, clinicians frequently lack sufficient understanding of the condition, further contributing to the unclear epidemiological characteristics of this disorder to date. Epidemiological studies conducted abroad have reported prevalence rates ranging from 0.6% to approximately 3% (5, 6), suggesting that a considerable number of individuals may be affected globally. Limited information exists on the pathophysiology of PGAD/GPD, partly due to the absence of validated animal models for experimental study. Although a few international case reports have proposed various etiological hypotheses in recent years, these are generally unsupported by robust clinical or laboratory evidence due to the small number of cases. Current hypotheses include vascular changes, central or peripheral nerve dysfunction, Tarlov cysts, psychological, pharmacological, dietary, and hormonal factors, neurotransmitter imbalances, mechanical pressure on genital structures, or a combination of these (7–9). Given the limited understanding of disease mechanisms, clinical management remains largely exploratory, focusing on presumed etiologies. Systematic evaluations of treatment efficacy and safety through clinical trials are lacking. Most therapeutic approaches are drawn

from case reports and may involve trigger removal, local anesthetics, cognitive-behavioral therapy, mindfulness techniques, hypnotherapy, pelvic floor physical therapy, electroconvulsive therapy, pharmacological therapies (such as antidepressants, anxiolytics, GnRHa, among others), or surgical intervention in cases involving Tarlov cysts (10–12). Reported outcomes for these treatments vary significantly. Deka et al. reported the successful treatment of a case of PGAD/GPD using leuprolide, but the treatment lacked psychological assessment and follow-up data after discontinuation of treatment (13). Our case report further supports the potential efficacy of GnRHa in PGAD/GPD management and contributes detailed symptom tracking and follow-up information across the treatment continuum.

The patient exhibited marked spontaneous genital arousal symptoms following two laboratory-confirmed COVID-19 infections. The underlying mechanism is hypothesized to involve COVID-19-mediated activation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) and subsequent symptom development and exacerbation of PGAD/GPD. During the initial phase of leuprolide treatment (within the first three days post-injection), the patient's symptoms worsened, which may be attributed to the "flare-up effect" induced by GnRH agonists. Subsequently, symptoms rapidly improved, likely due to suppression of the HPG axis. Based on laboratory test results and clinical progression, we speculate that leuprolide may suppress pulsatile GnRH secretion, thereby inhibiting pituitary luteinizing hormone (LH) levels and improving the patient's symptomatology. Following the discontinuation of leuprolide acetate, both LH and FSH levels gradually returned to pre-treatment values; however, the patient's symptoms did not worsen significantly. Potential underlying mechanisms include the following: (1) GnRHa may induce a "resetting" effect on the HPG axis, thereby suppressing hormonal signaling pathways associated with PGAD/GPD (14); (2) GnRHa may modulate relevant neuroendocrine pathways through epigenetic mechanisms (15). Furthermore, 22 months after treatment cessation, FSH returned to pre-treatment levels, while LH remained relatively suppressed. This may be attributable to the more potent and sustained inhibitory effect of GnRHa on the LH secretion pathway (16). The dissociation between LH suppression and the recovery of FSH to pre-treatment levels may indicate a stronger correlation between LH dynamics and clinical manifestations. Notably, a significant positive correlation between LH and sexual arousal has been well-documented, as demonstrated by studies on male and female pre-ovulatory libido peaks (17, 18). Additionally, BAI and BDI scores showed significant improvement (Figure 1, Table 1), suggesting that anxiety and depressive symptoms may be secondary to the underlying physical condition. This may partially account for the limited efficacy of current international treatment regimens that rely solely on psychotropic medications for managing PGAD/GPD.

Notably, the incidence of central precocious puberty among adolescents has significantly increased during the COVID-19 pandemic. For example, in a cohort study of school-aged girls in Shanghai, the incidence of precocious puberty in 2020 was significantly higher than in 2016–2019, accompanied by elevated GnRH levels (19). GnRH neurons originate from the olfactory bulb, develop in the olfactory cortex, and eventually mature in the hypothalamus (20). COVID-19 infection is frequently associated with olfactory dysfunction, and live viruses have been isolated from hypothalamic tissue, supporting the hypothesis of direct viral effects on hypothalamic regulation (21). To date, no studies have specifically investigated the impact of COVID-19 on LH levels in postmenopausal women. A recent meta-analysis reported that, compared to the control group, COVID-19 patients exhibited significantly elevated LH levels, a marked reduction in the FSH/LH ratio, and no significant changes in estradiol concentrations (22). Additionally, post-COVID-19 infection has been linked to increased expression of Kiss1 and its receptor GPR54, which is believed to enhance GnRH pulse frequency (23). GnRH and its receptors are not only localized in the hypothalamus but are also widely distributed throughout the limbic system and cerebral cortex, particularly the prefrontal cortex, where they play roles in regulating sexual desire and impulse control via modulation of the dopaminergic (DA) pathway (24, 25). Although the mechanism by which COVID-19 infection triggers PGAD/GPD by interfering with the HPGA axis remains unclear, COVID-19 infection and its associated physiological and psychological changes may disrupt the GnRH pulse rhythm and amplitude, potentially contributing to its onset.

Conclusions

In conclusion, PGAD/GPD is a complex and under-recognized disorder with a potentially multifactorial etiology. Treatment should be individualized to target the most likely underlying cause, as hormone-suppressive therapy may not be suitable for all patients. The present report describes a unique clinical scenario (a surgical history of breast cancer), thereby providing a formal indication for GnRHa use. However, given that the application of GnRHa for PGAD/GPD is off-label and the lack of randomized controlled trial data supporting its application, the generalizability of this approach remains limited. Nevertheless, it offers novel insights into the pathophysiology of the disease and potential strategies for clinical management. Given women's relatively conservative attitudes toward "sex," as exemplified by the patient in this case who was hesitant to speak during her initial outpatient visit, feelings of shame and embarrassment may prevent patients from actively seeking medical help. In addition, clinical physicians generally lack sufficient understanding of PGAD/GPD. Through this case, we aim to raise awareness among both patients and clinicians—including but not limited to endocrinologists, urologists, gynecologists, psychiatrists, and neurologists—to improve recognition and treatment of PGAD/GPD in future clinical practice.

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 the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University. 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

WR: Formal Analysis, Writing – original draft, Data curation, Investigation. HZ: Writing – review & editing, Supervision. HF: Validation, Supervision, Visualization, Writing – review & editing, Methodology.

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Conflict of interest

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Case Report: Clinical pharmacist prescriber in depression treatment in primary care settings: clinical case focused on prescribing practice

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Introduction: Pharmacotherapy of depression represents a significant challenge in the management of depression in primary care. Although effective treatments have been available, many patients are still not adequately managed. Clinical pharmacists represent one of the possible strategies in the management, although this practice is rarely seen outside the United Kingdom and the United States.

Aim: The aim of the case was to evaluate the impact of clinical pharmacist prescribers on depression treatment.

Methods: A longitudinal, observational, case-based medication review by a pharmacist prescriber was conducted for a 63-year-old Slovenian patient in a primary care ambulatory setting. The review included three structured medication review assessments performed by a clinical pharmacist prescriber at defined intervals: first observation, two months post-intervention, and six months after first observation. The pharmacists conducted medication reviews and prescribed medications like physicians, operating within a collaborative practice agreement as dependent prescribers. Predefined outcomes included diabetes management (HbA1c and blood glucose), lipid levels (S-LDL), pain (Visual Analogue Scale [VAS]), depression (Patient Health Questionnaire-9 [PHQ-9]), and quality of life (assessed via EQ-5D-VAS). The patient's complete medication regimens were reviewed, focusing on dosage appropriateness, indication matching, potential drug-drug interactions, and medication adherence.

Results: A 63-year-old male Slovenian patient diagnosed with depression, type 2 diabetes with polyneuropathy, and hypothyroidism underwent two medication reviews between December 2024 and July 2025. The pharmacist prescribed amitriptyline and semaglutide (accepted by the patient's physician). Notable improvements were observed in glycemic control (HbA1c reduced from 9.9% to 8.2%), and quality of life (EQ-5D-VAS score improved from 30/100 to 80/100). Depression symptoms also resolved, with the PHQ-9 score improving from 11 to 4.

Conclusions: This case study demonstrates that interventions by a clinical pharmacist prescriber during the medication review process resulted in improved clinical outcomes in the treatment of depression, as well as enhanced quality of life. It represents an important contribution to the development of pharmacist prescribing roles in depression management within primary care settings outside of the United Kingdom and the United States.

KEYWORDS

depression, pharmacist prescriber, clinical pharmacy, ambulatory care, medication review

1 Introduction

Major depressive disorder (depression) represents a significant global disease burden (1). According to the World Health Organization (WHO) report, depression is especially prevalent in primary care, where its burden is increasing significantly. WHO projections indicate that by 2030, depression will be the leading cause of disease burden worldwide (2). Depression rates in Central Europe, including Germany, have been rising. In Germany, the 12-month prevalence of unipolar depression is estimated at approximately 7.7%, with major depression accounting for around 6.0% of the population (3).

Although effective pharmacological and non-pharmacological treatment options are available, many patients still do not receive adequate care (4). According to a study by Kessler and colleagues, fewer than 50% of patients with depression in primary care receive adequate treatment (4). The study reported that 51.6% of patients with 12-month depression received healthcare treatment, and of these, only 41.9% received adequate care (4). Similar challenges exist in Germany, where most general practitioners (GPs) report poor communication with psychiatrists. GPs are responsible for diagnosing and managing the majority of depression cases in primary care, with 64.1% of outpatient incidental depression patients receiving treatment exclusively from GPs. A significant barrier to effective depression management in primary care is the lack of collaboration between GPs and psychiatrists (5).

Furthermore, adherence to depression treatment guidelines is often poor. For example, in primary care in the Netherlands, adherence to treatment guidelines was only 42% (6). German researchers have emphasized the urgent need for collaborative healthcare models to address obstacles arising from fragmented mental health care systems. In cases of inappropriate treatment or progression of depression, patients are at risk of developing treatment-resistant depression (TRD), which is significantly more challenging to manage. TRD often requires augmentation strategies, such as the addition of lithium, antipsychotics, or esketamine (7, 8).

Furthermore, depression is two to three times more prevalent among individuals with multimorbidity. The presence of multiple chronic conditions complicates depression management and often limits adherence to clinical guidelines, which are typically not designed with this patient population in mind. A systematic review included 40 studies that found a weak but statistically significant association between the number of chronic conditions and the severity of depressive symptoms [$r = 0.26$ (95% CI 0.18–0.33), $p < 0.001$] (9).

These limitations and existing gaps in the treatment of depression, particularly in patients with multimorbidity, highlight the pressing need for more effective, interdisciplinary collaboration in primary care. Involving a broader range of healthcare specialists, including clinical pharmacist prescribers, may provide a valuable strategy to enhance treatment outcomes and address current deficiencies in care delivery. Traditionally, psychiatrists have treated depression, but its high prevalence has shifted much of the treatment responsibility to the primary care level (2, 4). In some countries, including Slovenia and Germany, most antidepressants and other related medications are prescribed by general practitioners (GPs) (5, 10). In this context, primary care represents a crucial setting for collaboration between GPs and clinical pharmacists in treating depression (10).

Clinical pharmacists collaborate with GPs in various ways, including conducting medication reviews and, in some cases, prescribing (11, 12). The authors of the position paper highlighted that clinical pharmacists are not adequately integrated into mental health care, including the treatment of depression, and proposed the establishment of nationally reimbursed services to address this gap. In several European countries, the role of clinical pharmacists in depression management remains underrecognized, and they are often not included as members of multidisciplinary care teams. In this context, the authors emphasized the importance of implementing reimbursed clinical pharmacy services, citing Slovenia as an example where clinical pharmacists provide medication reviews at the national level. Additionally, they referred to the United Kingdom, where pharmacist prescribers are an established part of the primary care system (12).

Numerous trials have demonstrated that clinical pharmacists can improve adherence to treatment guidelines through medication reviews, even when they do not have prescribing authority (10). Medication reviews by clinical pharmacists are among the most effective strategies to optimize depression treatment. For instance, a study by Stuhec and Lah showed that interventions through

medication reviews in Slovenian ambulatory settings in a primary health center led to a 40% increase in adherence to depression treatment guidelines—a significant improvement (n=30 patients) (13). The acceptance rate of GPs was 55%, and most of the recommendations were based on medication switching and dose adjustments (13). These studies demonstrate that clinical pharmacists' medication reviews in ambulatory settings within primary health centers contribute to improved treatment outcomes and may support more effective management of depression. Pharmacist prescribers represent an important additional resource, potentially enhancing care through further prescription, either independently (without prior approval) or dependently (in collaboration with a physician's permission).

Although prescribing has traditionally been the domain of physicians, this role has expanded to include other healthcare professionals such as clinical pharmacists and nurses (14). Clinical pharmacists have been recognized as independent prescribers in the United Kingdom for over 20 years (15). In the United States, clinical pharmacists prescribe medications through various protocols (e.g., Collaborative Care Agreements), allowing them to prescribe for depression in some regions (16). Pharmacist prescriber roles are also being developed in Australia, New Zealand, and Slovenia (10, 17).

The European Society of Clinical Pharmacy (ESCP), in its position paper, emphasized the need for clinical pharmacists to develop the competencies required for prescribing in mental health, including depression, across Europe and beyond (12). They noted that pharmacist prescribing in mental health remains underdeveloped, except in the UK and certain parts of the US (12).

In this context, the main aim of this paper is to present a case of a patient with depression in which a pharmacist prescriber provided medication review, additional dependent prescribing, and ongoing monitoring. A secondary aim is to present the rationale for the global development of such services. We acknowledge that this case description does not constitute a full study but serves as an important starting point for the development of the pharmacist prescriber role.

2 Methods

A longitudinal, observational, case-based medication review by a clinical pharmacist was conducted for a 63-year-old Slovenian patient in a primary care ambulatory setting. Patients were referred to the pharmacist prescriber by GPs based on clinical complexity, such as the presence of depressive symptoms and multimorbidity, as well as medication-related problems, including critical drug-drug interactions and polypharmacy. The review included three structured medication review assessments performed by a clinical pharmacist at defined intervals: first observation, two months post-intervention, and six months after first observation. The pharmacists conducted medication reviews and prescribed medications like physicians, operating within a collaborative practice agreement as dependent prescribers. Predefined outcomes included diabetes management (HbA1c and blood glucose), lipid levels (S-LDL), pain (Visual Analogue Scale [VAS]), depression (Patient Health Questionnaire-9 [PHQ-9]), and quality of life (assessed via EQ-5D-VAS). The patient's complete medication regimens were reviewed, focusing on dosage appropriateness, indication matching, potential drug-drug interactions, and medication adherence.

The patient is part of a national pre-post prospective study involving clinical pharmacist prescribers working in primary care ambulatory settings in Slovenia. The clinical pharmacist prescriber conducts a medication review (advanced medication review, type 3 according to the Pharmaceutical Care Network Europe-PCNE) and may initiate or adjust therapy as needed (extra service to medication review) (10, 11). Medication reviews type 3 (advanced medication review) have been reimbursed in Slovenia and recognized as a pharmacist service since 2017, but clinical pharmacists do not have prescribing rights (10). Medication review type 3 is based on a patient's medication history, relevant patient information, and clinical data. It addresses all critical aspects outlined by the PCNE, including drug interactions, side effects, unusual dosages, adherence issues, drug-food interactions, effectiveness concerns, over-the-counter medication problems, unindicated medications, missing indications, and dosage issues (10, 11). This study researched clinical pharmacists prescribers. In this study, clinical pharmacists can prescribe medications under a collaborative agreement, which must be approved by both the GP and the patient before prescribing and monitoring begin. Consent for participation in the study may also be cancelled by the patient or the physician for the duration of the study.

Clinical pharmacist prescribers may prescribe and monitor medications listed in the collaborative practice agreement until the third patient visit (six months after the initial visit). After each prescription by the clinical pharmacist prescriber, the GP must approve the prescription, making this a pharmacist-dependent prescribing model. GPs make a final decision on all prescription acceptance. In 2024, the Slovenian National Medical Ethics Committee granted ethical approval for the study (N#0120-330/2024-2711-3). Informed consent was obtained from this patient. The CARE guidelines were followed in the preparation of this manuscript.

3 Case report

A 63-year-old Slovenian male patient with a diagnosis of major depressive disorder, type 2 diabetes mellitus complicated by peripheral polyneuropathy, obesity (body weight >120 kg), and hypothyroidism underwent three structured medication reviews on 4 December 2024, 11 February 2025, and 3 July 2025. His medical history included major depressive disorder, angina pectoris, hypertension, insomnia, neuropathic pain, and type 2 diabetes. Laboratory results collected during the first pharmacist visit showed a normal complete blood count, normal liver enzymes, and normal liver function tests. However, the serum creatinine level was elevated, and the glomerular filtration rate (GFR) was calculated at 46 mL/min. The patient also had elevated levels of

glycated hemoglobin (HbA1c, 9.9%) and triglycerides (4.97 mmol/L; normal 0.6-1.7 mmol/L). There was no history of dementia or smoking.

Patient was treated with multiple medications, including pregabalin 300 mg daily, quetiapine 25 mg at bedtime, vortioxetine 15 mg daily, furosemide 40 mg daily, pantoprazole 20 mg daily, levothyroxine 25 mcg daily, aspirin 100 mg daily, perindopril/indapamide 8 mg/2.5 mg daily, rosuvastatin/ezetimibe 20 mg/10 mg daily, dapagliflozin/metformin 5 mg/1000 mg twice daily, two types of insulin (as part and glargine), trimetazidine 35 mg twice daily, and fenofibrate 250 mg daily. The GP was not fully satisfied with the clinical outcomes (e.g., depression, elevated HbA1c and polyneuropathy) and referred the patient to the clinical pharmacist in December 2024 for medication review. In addition, the GP specified in the collaborative practice agreement that clinical pharmacists could prescribe, modify or discontinue all medications within the medication list, including medication initiation if necessary and monitor patients for up to 6 months.

At the initial visit (4 December 2024), clinical pharmacists conducted a comprehensive medication review and initiated changes to pharmacotherapy. Modifications were prescribed due to suboptimal therapeutic outcomes in the management of depression, diabetes, and pain. Depression symptoms were assessed using the PHQ-9, with a score of 11 indicating the absence of remission. Health-related quality of life was evaluated using the EQ-5D Visual Analogue Scale (VAS), with a score of 80/100, and pain was assessed using the VAS, with the patient reporting severe pain intensity (VAS score: 10/10).

Based on the assessment, the clinical pharmacist initiated amitriptyline at 25 mg twice daily with a plan to titrate to 50 mg twice daily and semaglutide at 3 mg daily, increasing to 7 mg daily after two weeks. Quetiapine was discontinued. The patient's GP accepted all proposed medication changes.

At the follow-up visit on 5 February 2025 (two months after the initial consultation), the clinical pharmacist reassessed treatment outcomes and conducted a second medication review. The patient reported marked improvements, particularly in depressive symptoms and pain. Objective improvements included a reduction in HbA1c from 9.9% to 8.2%, an increase in estimated GFR from 46 to 63 mL/min, improved quality of life (EQ-5D-VAS score 80/100), and decreased pain intensity (VAS score: 5/10). The PHQ-9 score decreased from 11 to 4, indicating remission of depressive symptoms. No additional pharmacological changes were recommended at this visit. However, the clinical pharmacist provided counselling on the importance of adherence to fenofibrate therapy, as the patient reported inconsistent use, which was reflected in elevated triglyceride levels (9.5 mmol/L).

A third medication review was conducted at the third visit on 5 July 2025 (six months after the initial consultation). The patient reported sustained improvement compared to the baseline visit, with outcomes consistent with those observed at the second visit. Glycemic control improved (HbA1c: 8.8% vs 9.9% at baseline), and depressive symptoms remained in remission with a PHQ-9 score of 4. Pain intensity further decreased (VAS score: 3/10). The EQ-5D-VAS score was 80/100 at the third visit. Triglyceride levels improved significantly, decreasing to 2.8 mmol/L. No further pharmacotherapy adjustments were deemed necessary. A summary of the case report, including key outcomes, is presented in the Table 1.

4 Discussion

This case report highlights the potential for clinical pharmacist prescribers to contribute to improved clinical outcomes, which constitutes the primary objective in the management of depression. In Slovenia, clinical pharmacists have been integrated into the healthcare system since 2017, where their role primarily focus on medication review without prescribing (10). In this context, the present case introduces a novel approach compared to previous Slovenian studies (10), where clinical pharmacists were limited to

TABLE 1 Summary of the case report: key dates, medications, and clinical outcomes.

Outcome scales	Medication review N#1	Medication review N#2	Medication review N#3
Date	4 December 2024	4 December 2024	4 December 2024
Medication Changes	Pharmacist initiated amitriptyline at 25 mg twice daily with a plan to titrate to 50 mg twice daily and semaglutide at 3 mg daily, increasing to 7 mg daily after two weeks. Quetiapine was discontinued. Accepted by the general practitioner.	No additional pharmacological changes were recommended at this visit. However, the clinical pharmacist provided counselling on the importance of adherence to fenofibrate therapy.	No changes. No additional pharmacological changes were recommended.
Levels of glycated hemoglobin (HbA1c)	9.9%	8.2%	8.8%
Patient Health Questionnaire-9 (PHQ-9) score	11/27 (no remission)	4/27 (remission)	4/27 (remission)
EQ-5D Visual Analogue Scale (VAS) score	10/10	5/10	3/10
EQ-5D visual analogue scale (EQ-5D-VAS) score	30/100	80/100	80/100
Triglyceride levels	4.97 mmol/L	9.5 mmol/L	2.8 mmol/L

conducting medication reviews, and the role of pharmacist prescribers had not yet been described. The integration of pharmacist prescribers represents a significant advancement in collaborative care within primary care settings. Future studies will involve a larger number of patients managed by pharmacist-dependent prescribers, which will also open the way for investigating the role of pharmacist-independent prescribers in clinical practice.

Patients with depression frequently present with multimorbidity, and this complex case illustrates how clinical pharmacists—through medication review, ongoing monitoring, and prescribing—can support GPs in achieving favorable clinical outcomes. In this case, both depression and type 2 diabetes with associated polyneuropathy improved, with remission achieved. In addition, the patient and the GP reported that quality of life improved significantly by approximately 50%. The positive impact of clinical pharmacist interventions on quality of life was also demonstrated in our previous study involving 24 patients, in which clinical pharmacists monitored patients without having prescribing authority (18). The case also demonstrates significant clinical improvements, as the patient's quality of life increased by 50% on the EQ-5D-VAS, which exceeds the threshold for clinical significance (19). This improvement was further supported by clinical remission on the PHQ-9 and was corroborated by the patient's self-reported improvements.

The prevalence of pain in patients with depression is estimated to be approximately 65%, according to a pooled analysis of multiple studies (20). This highlights the complexity often encountered in primary care and underscores the potential role of clinical pharmacists in optimizing pharmacotherapy. In this case, the clinical pharmacist prescribed amitriptyline, an antidepressant, following clinical guidelines for pain and depression treatment (21). Additionally, semaglutide was prescribed to support glycemic control and weight management, particularly relevant for this patient with obesity (weight >120 kg) and type 2 diabetes. The intervention significantly reduced HbA1c levels, consistent with evidence-based recommendations for using GLP-1 receptor agonists in this patient population (22). The pharmacist prescriber also educated the patient on medication adherence, which contributed to a significant decrease in the patient's triglyceride levels by the final visit. The patient had not taken fenofibrate between the first and second visits, which explained the elevated triglyceride levels observed at that time.

Evidence from primary care settings suggests that medication reviews conducted by clinical pharmacists in the context of mental health care are associated with favorable outcomes, including reductions in polypharmacy, fewer drug-drug interactions, and enhanced adherence to treatment guidelines (13, 14). In addition to conducting medication reviews, clinical pharmacists are authorized to prescribe guideline-recommended pharmacotherapy and to monitor patients longitudinally in some countries. This model of care remains novel in many European countries, where medication prescribing and monitoring have traditionally been the sole responsibility of physicians. Notably, the United Kingdom has been recognized for expanding the scope of clinical pharmacists, including prescribing for depression (23). This case highlights that pilot trials involving pharmacist prescribers are also feasible and valuable in countries where clinical pharmacists do not yet have prescribing rights. In Slovenia, where this service is currently in development, a pilot trial has been approved and conducted. In contrast, clinical pharmacy in other Central European countries has not reached the same level of advancement as in Slovenia (24). In Slovenia, three key clinical pharmacy services—delivered in ambulatory primary care, hospital outpatient settings, and through seamless care models—are reimbursed by the national insurance company and well-established, providing a crucial foundation for the development of pharmacist prescribing roles (23). Notably, clinical pharmacy services in Slovenia are more developed than in some wealthier neighboring countries, such as Italy and Austria (24).

A 12-month pilot study conducted in Scotland involving 75 patients demonstrated that clinical pharmacists, acting as independent prescribers, were able to initiate and modify pharmacological treatment for depression and generalized anxiety disorder (GAD) without requiring direct referral to GPs. Pharmacological interventions included antidepressants and anxiolytics. The study reported clinical remission or treatment response in most patients, with reductions in PHQ-9 and GAD-7 scores by 45% and 50%, respectively. Pharmacists prescribed treatment following diagnoses established by GPs (23). In a randomized controlled trial conducted in a primary care setting in the United States, Finley et al. evaluated the outcomes of 75 patients managed by clinical pharmacist prescribers compared with 50 patients receiving standard care. Pharmacists operated as dependent prescribers under a collaborative practice agreement in an ambulatory care environment. After six months, the intervention group demonstrated significantly higher medication adherence rates than the control group (67% vs. 48%; odds ratio = 2.17; 95% CI: 1.04–4.51; $P = 0.038$). Patient satisfaction scores were significantly greater in the intervention group, and provider satisfaction was also high. Although clinical improvement was observed in both groups, the between-group difference was not statistically significant (25). Another study in the United States evaluated the impact of clinical pharmacists acting as dependent prescribers under collaborative practice agreements. This prospective, nonrandomized proof-of-concept study was conducted from July 2006 to December 2007 and included 151 patients with depression. Statistically significant reductions were observed in PHQ-9 scores from baseline to endpoint (11.5 ± 6.6 to 5.3 ± 4.7; $P < 0.0001$). The clinical response rate was 68%, with a remission rate of 56%. Moreover, the intervention was associated with a reduction in projected annual healthcare costs per patient (16).

Comparable findings were reported by Adler et al. in a 6-month randomized study involving 533 patients with depression and/or dysthymia in U.S. primary care settings (26). In this trial, clinical pharmacists provided in-person and telephone consultations, supporting GPs and patients in selecting, dosing, and adjusting antidepressant therapy. Antidepressant utilization rates at six months were significantly higher in the intervention group than in controls (57.5% vs. 46.2%; $P = 0.03$). However, differences in symptom severity did not reach statistical significance (26).

In addition to the studies previously mentioned, a meta-analysis examining the impact of pharmacists on depression treatment has been published, including 12 studies and a total of 2,133 patients (18). The results demonstrated a significantly higher number of patients with good adherence in the pharmacist intervention group compared to usual care (relative risk = 1.39; 95% CI: 1.11–1.75), as well as improved medication adherence scores (standardized mean difference = 0.32; 95% CI: 0.07–0.56). However, no statistically significant differences were observed in clinical rating scales or quality of life measures (27). The meta-analysis did not restrict inclusion to studies where pharmacists were authorized to prescribe medications; instead, it included a wide range of pharmacist-led interventions, including medication therapy management, adherence counselling, and educational support related to depression and antidepressants.

Several limitations of this case should be acknowledged. The findings from a single case cannot be generalized, which represents a significant limitation of this study. The findings are derived from a single case report, and further studies with larger sample sizes are necessary to confirm these results. The follow-up period was limited to six months, as defined by the scope of a pilot trial approved by the Slovenian National Medical Ethics Committee. Additionally, clinical pharmacists in this case did not have independent prescribing authority, as such rights are not currently granted in Slovenia. This limitation may have constrained the potential impact and evaluation of the intervention. This case should be replicated in studies with larger sample sizes to confirm the findings.

Nonetheless, the case highlights several positive aspects. Over the past decade, the role of clinical pharmacists in Slovenia has expanded significantly, with the introduction of reimbursed clinical pharmacy services such as medication reviews and reconciliation. Incorporating prescribing rights would represent a logical step in enhancing medication review services. This case demonstrates that clinical pharmacists, collaborating with GPs, can effectively monitor patients and contribute to improved treatment outcomes. These findings align with the Committee of Ministers' Resolution CM/Res (2020)3 on the Implementation of pharmaceutical care for the benefit of patients and health services and with the principles endorsed by the European Society of Clinical Pharmacy (28, 29).

This case also highlights that established and reimbursed medication review services within the country provide a necessary starting point for the development of pharmacist prescriber roles. General practitioners are already familiar with clinical pharmacy practices, including medication reviews, and have established effective team-based collaboration with ambulatory clinical pharmacy services in primary care settings.

5 Conclusion

This case report demonstrates that an ambulatory clinical pharmacist prescriber can effectively contribute to improved clinical outcomes in the treatment of depression through collaborative care with GPs in primary care settings. Such collaboration has the potential to address existing treatment gaps and enhance patient monitoring in depression management. Although these findings are encouraging, a larger-scale clinical study is necessary to confirm or refute these results.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: 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 Slovenian National Medical Ethics Committee granted ethical approval for the study (N#0120-330/2024-2711-3). 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

MS: Writing – original draft, Writing – review & editing.

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Conflict of interest

The 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.

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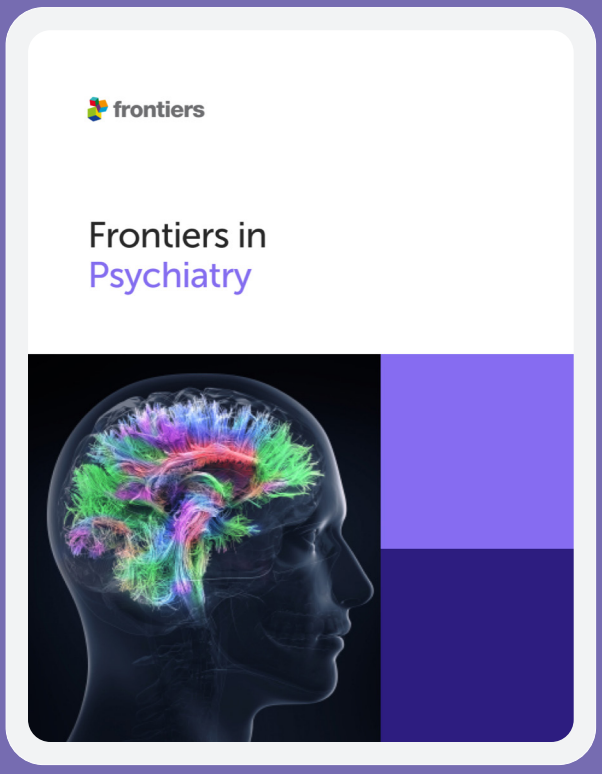

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