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Case reports in psychopharmacology

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Case reports in psychopharmacology

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Editorial: Case reports in psychopharmacology

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case reports, adverse events, psychiatry, clinical pharmacist, polypharmacy

Editorial on the Research Topic
Case reports in psychopharmacology

Introduction

The papers in this Research Topic reflect a range of approaches. Some have investigated the effects of monotherapy, while others explored treatments as adjuncts. Most report on psychotropics, but a few use more novel approaches, including pharmacogenetics. Many are encouraging because they describe potential new therapeutic uses of the medications. Alternatively, some case reports describe adverse events associated with the use of well-established medications. Adverse events are an important cause of medication discontinuation in psychiatry; thus, comprehensive screening is essential during treatment (1). Some involve the case of a single patient while others present the situation of a series of patients. One case report describes a collaboration with a clinical pharmacist, who provided medication reconciliation at hospital admission and discharge in a psychiatric hospital. Some countries have developed this approach, while others still lag far behind (2, 3). The range of illnesses is broad, most with a focus on psychiatric illnesses and some also on different comorbidities, including psychiatric and somatic comorbidities.

Cases

A number of papers report on the successful treatment of schizophrenia. Jarosz and Badura-Brzoza report that the administration of combination therapy with olanzapine and zuclopenthixol was effective in reducing delusions and stabilizing mood. The treatment was well-tolerated, and sedation and extrapyramidal symptoms were not observed. Further, Renemane and Rancans explore the case of a treatment-resistant person with schizophrenia who demonstrated improvements in both positive and negative symptoms after treatment with the partial dopamine agonist cariprazine. The patient's auto-aggressive compulsive behavior was also remitted following treatment. In a case report by Wang et al., they characterize a patient with schizophrenia who experienced significant increases in symptoms when menstruating during treatment with paliperidone extended-release tablets and olanzapine. After replacing oral paliperidone with a chemically identical,

longer-lasting and more stable long-acting injection of paliperidone palmitate, she was in remission for two years.

Treatment of psychotic disorders can present a number of challenges. Logically, some papers in this Research Topic report on some of the adverse events noted during pharmacological treatment. Pjevac and Hudnik present the case of a treatment-resistant patient with schizophrenia who was treated with a number of medications: clozapine, zuclopenthixol, biperiden, flurazepam and lorazepam. The patient was believed to be experiencing anticholinergic delirium and elevated plasma clozapine level. Clozapine was gradually reduced and the dose of benzodiazepenes were lowered. The delirium gradually dissipated. Zonnenberg et al., describe the case of 5 patients with hypothermia after use of anti-psychotic treatments. They make recommendations for the assessment of the causal role of hypothermia induced by the use of antipsychotics. Preiss et al., report the case of a single patient who presented with severe hyperactive delirium after a single dose of zolpidem that was administered in combination with clozapine, aripiprazole and cariprazine. The symptom onset was rapid, occurring within a few hours. The symptoms subsided with the discontinuation of zolpidem. Torrico and Kahlon describe the case of a patient who exhibited sialorrhea after treatment with risperidone. However, concomitant treatment with clonidine reduced these symptoms, which again emerged when clonidine was removed. Levy et al., share the emergence of hyperammonemic encephalopathy after concomitant treatment with lithium and valproate semisodium for schizoaffective disorder, while Yuan et al., explore the case of a woman who developed acne after treatment with ziprasidone. Apeldoorn et al., find that buspirone worsened psychosis in a patient hospitalized for schizoaffective disorder. De Pieri et al., chart a ten year longitudinal observation of a patient with Fahr's disease and describe the psychosis related to this disorder; this is rarely described in the literature.

The reports here also demonstrate effectiveness of pharmacotherapies in other psychiatric and neurological disorders, while also describing some of the adverse events that may occur during treatment. Guo et al., describe a case of improved depression and PTSD after initiation of augmentation with prazosin. Related to this, Richardson et al., report that the symptoms of PTSD improve even after discontinuation of 2 years of therapy with prazosin. In other work, Ha and Maguire., present a case of improvement in stuttering after initiation of treatment with deutetrabenazine, while Vayisoglu found that bupropion improved symptoms of exhibitionism. Watzal et al., characterize the emergence of pneumonitis after treatment with lamotrigine as an augmentation therapy for a mood disorder. No genetic variations in metabolizing enzymes were found to explain this relationship. Correa e Castro et al. report the case of a woman who developed compulsive buying, binge eating and hypersexuality after four years of treatment with cabergoline for prolactinomas.

Inter-individual differences in response to pharmacotherapies can play an important part in determining the response to treatment. In this regard, pharmacogenetics can be beneficial in determining the potential to respond to various treatment options. Pjevac et al., present the case of 79 year old treatment-resistant patient presenting with severe depression with psychotic symptoms. Pharmacogenetic analysis involved genotyping of CYP1A2, CYP3A4, CYP2B6, CYP2C19 and CYP2D6. Based on the patient's genetic profile, a number of treatments were attempted. Ultimately, quetiapine and maprotiline were introduced, which results in a marked improvement in symptoms. Wu et al., describe the case of a patient who presented with serotonin syndrome despite the use of a relatively low dose of escitalopram. Gene detection revealed that she was a poor metabolizer due to her polymorphism of the CYP2C19 enzyme. Escitalopram was discontinued and the symptoms eventually resolved.

Makunts et al., describe the results of a synthesis of reports from the FDA Adverse Event Reporting System aimed at understanding some of the concomitant medications that may explain cardiovascular events associated with treatment with 3,4-methylenedioxymethamphetamine (MDMA). The authors found a number of cases of cardiovascular adverse events in which patients were taking one or more medications in addition to MDMA. There were no cases of cardiovascular adverse events associated with the use of MDMA on its own, which was is notable because MDMA increases blood pressure. In all cases, MDMA was taken with concomitant medications with known effects on cardiac function (e.g. SSRIs, antihistamine/anticholinergics, amphetamines).

Collaborative care, including a clinical pharmacist specialist, is one of the possible approaches for medication optimization. Stuhec & Batinic described two different cases where clinical pharmacists provided medication reconciliation at hospital admission and discharge in a psychiatric hospital. Clinical pharmacists recognized omitted medications and improved the transition of care. This service is reimbursed in Slovenia, and only clinical pharmacists can provide this service from 2023. In addition, clinical pharmacist optimized treatment outcomes and improved medication reconciliation. This case report should be replicated in a prospective study, including a larger effect size.In summary, these cases represent valuable information for daily practice. Further studies are needed to either confirm or reject these findings.

Author contributions

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

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
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Antipsychotic-Related Hypothermia: Five New Cases

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Background: Hypothermia is a potentially fatal adverse effect of antipsychotic drug (APD) use. With only 69 cases described in the literature, the condition is considered rare.

Methods: We describe five new cases, in which we estimated the role of clozapine, haloperidol, olanzapine, penfluridol, risperidone, and zuclopentixol with the aid of two structured assessment tools.

Results: In addition to APD use, all five patients described by us had been exposed to one or more additional predisposing factors for hypothermia. Therefore, with the aid of the assessment tools, the causal role of APDs was considered "possible" in four cases of moderate hypothermia and "doubtful" in the remaining one of mild hypothermia.

Conclusion: Although the best way to detect APD-related hypothermia is measuring the body temperature for a duration of at least 7–10 days after the start (or a dose increase) of APDs, the use of assessment tools to identify additional predisposing factors for hypothermia and to thus establish their causal relationship with APD use would seem to be valuable for clinical decision-making (i.e., whether or not to discontinue APD use). Further research is needed to obtain reliable prevalence figures for APD-related hypothermia and its consequences, preferably in relation with physiological changes in body temperature.

Keywords: body temperature, neuroleptic, pharmacotherapy, psychosis, schizophrenia, side effect, thermoregulation

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INTRODUCTION

Four homeless people died of exposure to cold in Portland, Oregon, during the first 10 days of 2017, after temperatures had unexpectedly dropped to −7°C (1). One of the victims was a 52-year-old woman diagnosed with schizophrenia who had lost her home a few months beforehand. She was found in a parking garage, mumbling and confused, and in the act of paradoxically undressing herself, a well-known symptom of lethal hypothermia (2). Paramedics were called to the scene, but nonetheless, the woman died within half an hour. Her fate resonated with the local community and drew attention to the need for care for the homeless. Although various obvious predisposing factors for hypothermia had been present (i.e., outdoor exposure to cold and inadequate clothing), an additional factor may well have been the use of antipsychotic drugs (APDs).

APD-related hypothermia was first described by Loughnane (3). Although its underlying pathophysiological mechanism is not entirely clear, peripheral vasodilatation *and* a failure of central thermoregulation seem to play a role (4). In spite of its potentially fatal consequences, APD-related hypothermia has received substantially less attention than its clinical counterpart,

APD-related *hyper*thermia, which has been described extensively in the context of malignant antipsychotic syndrome (5). For the purpose of a prior systematic review, we found no more than 57 original case descriptions of APD-related hypothermia, published over a time span of 50 years (i.e., 1.1 cases per year; 6). From these cases, we inferred that the risk of APD-related hypothermia is highest during the week following the initiation—or a dose increase—of APDs, notably in combination with old age, exposure to cold, the adjuvant use of benzodiazepines, and/or (subclinical) hypothyroidism. On the basis of data from drug-monitoring agencies, we moreover inferred that the prevalence of APD-related hypothermia may well be 10 times higher than that suggested by the literature (6). The publication of seven additional papers over the past 2 years, collectively describing 12 new cases, indicates that awareness of this clinically relevant condition may finally be growing (7–13). To add to the burgeoning body of literature, we here describe five cases from our own clinical practice and highlight implications for clinical practice.

METHODS

All five patients presented here were under our treatment at Parnassia Psychiatric Institute (The Hague). Patients B and D provided written permission for publication of their cases. On behalf of patients A, C, and E, written permission was obtained from their respective family members, in accordance with Dutch national guidelines. In conformity with Sund-Levander et al. (14), we defined a normal body temperature for men (measured rectally) as 36.7–37.5°C and for women as 36.8–37.1°C. Following Khasawneh et al. (15), we defined *hypothermia* as a core body temperature of <35.0°C, *mild hypothermia* as 33–35°C, *moderate hypothermia* as 28–33°C, and *severe hypothermia* as <28°C (measured rectally). In all cases, a regular digital thermometer was used. To assess and quantify the causal role of APDs in the mediation of hypothermia, we used the Adverse Drug Reaction (ADR) Probability Scale (16). For calculating the mean number of predisposing factors for hypothermia, we used the methodology developed by Brevik and Farver (17).

RESULTS

Presentation of Cases

Patient A

Patient A was a 74-year-old, unmarried Dutch man, who resided in the nursing home that is part of our psychiatric hospital. He had been diagnosed years ago with schizophrenia. His medication consisted of a zuclopentixol depot of 200 mg/week, vitamin D, acetylsalicylic acid, pantoprazole, and simvastatin. By the time we saw him, he was also using doxycycline because he was feeling ill and had slightly elevated infection parameters. The sedimentation rate was 48 mm/h (N 2–20 mm/h), and the C-reactive protein was 19 mg/l (N 0–8 mg/l). Nonetheless, a focus for the infection could not be found. Patient A presented with a body temperature of 32.5°C (measured rectally) at our outpatient department after his depot had been administered earlier that day. At the time of administration, it had been 36.8°C (measured aurically). The physical examination showed a bradycardia of 58 BPM but no other abnormalities. Patient A was diagnosed with moderate hypothermia, possibly due to the use of zuclopentixol. He was gradually rewarmed with warm blankets. His vital signs, which were being monitored, remained stable. After several hours, his body temperature normalized to 37.3°C. Although his hypothermia did not recur, the zuclopentixol depot was postponed and administered a week later. This time, the body temperature remained normal. However, during the subsequent 2 years, our patient had three more episodes of hypothermia (with temperatures of 34.6°C, measured aurically, and 33.4°C and 32.4°C, measured rectally, respectively, once while using zuclopentixol, once while using haloperidol). On all occasions, he recovered after gradual rewarming.

Patient B

Patient B was a 27-year-old, unmarried, homeless French man, who experienced psychotic symptoms, probably in the context of schizophrenia. His antipsychotic medication consisted of a weekly penfluridol depot of 20 mg. Although he did not use any additional medication, he did use heroin and cannabis. He was referred to our psychiatric hospital with a body temperature of 32.0°C (measured rectally) after the police had found him wandering the streets. He had made a confused impression and had told the police officers that he had been sleeping outdoors the night before. The outside temperature that day had ranged from 11.3 to 18.4°C (mean, 15.1°C). The physical examination revealed a bradycardia of 47 BPM. The ECG showed pointed T-tops (which were probably idiopathic or due to hypokalemia) and signs of possible left-ventricle hypertrophy. His urine tested positive for heroin and cannabis. Patient B was diagnosed with moderate hypothermia, probably due to outdoor exposure to cold and the use of penfluridol (as well as heroin and cannabis). He was gradually rewarmed, and his vital signs were being monitored. Within a few hours, his body temperature normalized to 35.6°C. The penfluridol was discontinued. Since patient B refused to use APDs any longer, a period of 18 months elapsed before he could be persuaded to switch to haloperidol 3 mg/day. After that, he experienced no more episodes of hypothermia.

Patient C

Patient C was a 77-year-old, unmarried Dutch woman, who lived in the same nursing home as patient A. She had been diagnosed with a schizoaffective disorder and was treated with haloperidol 0.5 mg twice a day and lorazepam 8.5 mg/day. She had a history of transient ischemic attacks, cerebrovascular accidents, immobility, and subclinical hypothyroidism. She presented with a body temperature of 33.4°C (measured rectally). Her behavior was unaltered, there were no signs of illness, and her intake of food and drinks was normal. On that summer's day, the weather had been warm, sunny, and dry but chilly at night (with a mean night temperature of 16.3°C). The physical examination revealed no additional abnormalities. Blood tests showed only signs of her subclinical hypothyroidism. Patient C was diagnosed with mild

hypothermia, possibly due to the use of haloperidol. She was put to bed with warm blankets. However, the following morning, her temperature dropped even further to 32.8°C. She was once again rewarmed with the aid of warm blankets. Her vital signs were monitored, and this time her body temperature stabilized within a few hours. The haloperidol was continued, and, from then onwards, her body temperature was monitored closely. Four months later, while still on haloperidol, she developed a moderate hypothermia of 32.3°C (measured rectally). After gradual rewarming, her body temperature normalized to 36.7°C. One month later, patient C died, probably due to circulatory insufficiency in the context of dehydration, developed during a state of lethal catatonia.

Patient D

Patient D was a 65-year-old, divorced Hindustani-Surinamese man, who had been admitted to our psychiatric hospital for 9 months because of a psychotic relapse. He had previously been diagnosed with schizophrenia and was being treated with a haloperidol depot. Owing to severe extrapyramidal side effects, the haloperidol was switched to clozapine 50 mg/day. As his psychotic symptoms remained unaltered and the clozapine plasma level was 0.33 mg/l (N 0.35–0.80 mg/l), the dose was increased to 62.5 mg/day. Five days later, he presented with a Glasgow Coma Score of 6 (N 15) and a body temperature of 33.2°C (measured rectally). The physical examination showed a dry, flaky skin, and reduced skin turgor; there were no other abnormalities. Patient D had suffered from hypothyroidism in the past, but his hormone levels had been adequately restored with the aid of levothyroxine 0.025 mg/day. He was diagnosed with mild hypothermia, possibly due to the use of clozapine, and referred to a somatic hospital. There, a clozapine intoxication was excluded, and he was gradually rewarmed until his body temperature and consciousness had normalized. The clozapine was discontinued. With his psychotic symptoms untreated, patient D was unable to return to his home. As a consequence, he was referred to the nursing home of our psychiatric hospital. Four months later, he was diagnosed with active neurolues (i.e., neurosyphilis or tertiary syphilis), for which he was treated with benzathine benzylpenicillin. Because his psychotic symptoms did not subside, olanzapine 2.5 mg/day was added. The hypothermia did not recur.

Patient E

Patient E was a 59-year-old, married Dutch woman, who had resided for several years in the long-stay department of our psychiatric hospital. She had been diagnosed with a schizoaffective disorder. Owing to prior therapy resistance, she was treated with a combination of clozapine, risperidone, and olanzapine. The dosage of the risperidone was 9 mg/day (the other dosages are unknown). In addition, she also used lorazepam 7.5 mg/day. Because of a manic-psychotic relapse, the dose of risperidone was increased to 12 mg/day. Ten days later, she presented with a body temperature of 34.0°C (measured rectally). Her behavior was uncontrollable, and she was continually undressing. Although her intake of food and drinks had been adequate, she also suffered from mild renal failure, with a serum creatinine of 166 μmol/l (N 50–95 μmol/l) and a renal clearance of 27 ml/min (N > 52 ml/min). Despite a thrombocyte count of 24×10^9/l (N 150–400 $\times 10^9$/l), there were no clinical signs of coagulopathy. Patient E was diagnosed with mild hypothermia, probably due to her unusual combination of APDs (especially the recent dose increase in risperidon) and her recurring state of undress. She was gradually rewarmed with the aid of warm blankets and warm drinks, under strict monitoring of her vital signs. The following day, clozapine and olanzapine were discontinued. Because the hypothermia persisted, 4 days later, the dosage of the risperidone was lowered to 6 mg/day. Additionally, amoxicillin/clavulanic acid was started in a dosage of 625 mg twice a day because of increased infection parameters [leukocyte count 11.4×10^9/l (N 4.0–10.0 $\times 10^9$/l), neutrophil count 10.49×10^9/l (N 1.5–7.5 $\times 10^9$/l), C-reactive protein 130 mg/l (N 0–8 mg/l)] in the absence of any clinical signs of infection. On day 6, her temperature normalized to 36.4°C, and the thrombocyte count also normalized. The antipsychotic treatment was continued with a combination of olanzapine 10 mg and aripiprazole 10 mg/day. Although hypothermia did not recur, patient E died three and a half years later, due to renal insufficiency.

Summary and Analysis of the Case Series

All five patients described by us had been exposed to APDs, as well as to one or more additional predisposing factors for hypothermia (**Table 1**). With the aid of the methodology developed by Brevik and Farver (17), we calculated that the mean number of these

TABLE 1 | Degrees of hypothermia and analysis of predisposing factors.

Patient	Minimum body temperature (degree of hypothermia)	Type of antipsychotic	Number of additional predisposing factors (characterization)*
A	32.5°C (moderate)	Zuclopentixol	2 (PAH, MD)
B	32.0°C (moderate)	Penfluridol	2 (PAH, M)
C	32.3°C (moderate)	Haloperidol	4 (PAH, CNS, MD, M)
D	33.2°C (moderate)	Clozapine	2 (PAH, MD)
E	33.5°C (mild)	Risperidone Clozapine Olanzapine	3 (PAH, M, O)
			Mean: 2.6 (range 2–4)

**PAH, Primary Accidental Hypothermia; CNS, Central Nervous System; MD, Metabolic Disorder; M, Medication; O, other.*

TABLE 2 | Patient scores on the Naranjo Adverse Drug Reaction Probability Scale.

Patient (sex, age)	Score per episode of hypothermia*	Medication
A (M, 74 years)	4	Zuclopentixol
B (M, 27 years)	0	Penfluridol
C (F, 77 years)	4	Haloperidol
D (M, 65 years)	3	Clozapine
E (F, 59 years)	3	Risperidone
	0	Clozapine
	0	Olanzapine

**Scoring legend:*
>9 = definitive adverse drug reaction.
5 to 8 = probable adverse drug reaction.
1 to 4 = possible adverse drug reaction.
0 = doubtful adverse drug reaction.

factors was 2.6 (range, 2–4). The most prevalent factors were advanced age (60%) and (subclinical) hypothyroidism (40%). As quantified in accordance with the Adverse Drug Reaction (ADR) Probability Scale (16), in one case, there was a doubtful, and in four cases, a possible adverse drug-related event (**Table 2**).

DISCUSSION

Contrary to the woman in Portland, none of our five patients died—at least not during a phase of hypothermia. This may well be due to the fact that none of them had been exposed to freezing, but perhaps also to the fact that they had all been under regular care, and that even patient B, the homeless man who had slept outside, had been detected in time by the police and referred to our hospital. Since systematic studies are lacking, the actual prevalence of APD-related hypothermia is unknown, as is the proportion of fatal outcomes. With APD use ranging worldwide from 3.2/1,000 in Colombia to 78.2/1,000 in Taiwan (18), the impact of ensuing hypothermia on global health must be substantial. In the present case series, we describe hypothermia in the context of clozapine, haloperidol, olanzapine, penfluridol, risperidone, and zuclopentixol use. A recent review by our group showed that APD-related hypothermia had been described before in the context of haloperidol (13 cases), clozapine (3 cases), risperidone (10 cases), and olanzapine (13 cases) use (6). As far as we know, there are no earlier publications of this type on penfluridol and zuclopentixol. Given the fact that undertreatment of psychosis has its own adverse effects on mental and physical health, quality of life, and mortality (19), the solution would not seem to lie in withholding psychotic patients from treatment with APDs, but rather in proper monitoring of the body temperature. This should be done for a duration of at least 7–10 days after starting with an APD or a dose increase (6), although some authors argue that several weeks would be even better, since hypothermia has also been described after two or more weeks (20, 21). That said, our case series indicates that even in the absence of any dose alterations, APD use may be a risk factor for hypothermia. This finding is all the more pressing, since individuals with psychosis are at risk for hypothermia anyway due to a lower mean baseline temperature and—if present—poverty and/or homelessness, which have also been established as risk factors (22–25). Although treatment of hypothermia is relatively easy and cheap (26), prevention would seem to be the solution worth striving for. If it has already set in, the goal must be early detection and treatment, preferably aided by an assessment of the causal role of APDs.

The body temperature should preferably be measured with the aid of a hypothermia thermometer. When frequent monitoring is not feasible, the method developed by Brevik and Farver (17) may be helpful to identify patients with an elevated risk of APD-related hypothermia. This method allows for a quick inventory of predisposing factors and a global impression of the severity of the ensuing risk. Still, the decision whether to continue or discontinue an APD may prove difficult. In clinical practice, this needs to be assessed in the light of the severity of the psychotic symptoms that might recur. Usually, cases of APD-related hypothermia tend to resolve—after proper monitoring and treatment—within 24–48 h. After that, only few patients tend to experience another episode of hypothermia, even after continuing the original APD or switching to another type (6). To facilitate the decision-making process, a structured assessment tool such as the ADR Probability Scale (16) may be of use, which gives an estimate of the causal role of APDs in the presence of other predisposing factors for hypothermia. If APD use was the only predisposing factor, and the causal role "possible," "probable," or "definitive" (**Table 2**), we recommend to stop or lower the dose during rewarming. If this is not possible, we advise to continue the APD under strict monitoring of the temperature and other vital functions. Finally, we recommend to review the APD treatment regimen *an sich* (e.g., proper dosage and—if possible—monotherapy). As may have been the case with our patient E, polypharmacy may add to the risk of APD-related hypothermia. After normalization of the temperature, there would seem to be no strict contraindications for reintroducing the same APD, even in its initial dose, as long as proper attention for additional predisposing factors for hypothermia is guaranteed (6).

CONCLUSIONS

With the five new cases of APD-related hypothermia here described, we add to the burgeoning literature on this underreported and still poorly understood side effect. Moreover, as far as we know, this is the first description of hypothermia in the context of penfluridol and zuclopentixol. To prevent severe APD-related hypothermia and detect it at an early stage, we recommend to measure the body temperature for a duration of 7–10 days after starting—or increasing the dose of—APDs. When this is not possible, we recommend to estimate the risk of hypothermia while also considering the role of additional predisposing factors. In cases of established hypothermia, we recommend to estimate the causal role of APDs with the aid of a structured assessment tool, such as the Naranjo Adverse Drug Reaction Probability Scale, and use the outcome to guide clinical decision-making (i.e., whether to continue or discontinue this specific APD).

LIMITATIONS

Our knowledge of APD-related hypothermia is still limited, as is our knowledge of the prevalence of idiopathic hypothermia in the general population. As a consequence, a reliable estimation of the relative risk of hypothermia due to APD use is hard to make.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and the supplementary files.

ETHICS STATEMENT

The study was exempt from testing by a medical ethical committee. All five patients presented here were under our treatment at Parnassia Psychiatric Institute (The Hague). Patients B and D provided written permission for publication of their cases. On behalf of patients A, C, and E, written permission was obtained from their respective family members.

AUTHOR CONTRIBUTIONS

CZ contributed to the conception and design of the work, and to the acquisition, analysis, and interpretation of data for the work, drafted and revised the work, gave final approval for the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JB-d-M contributed to the conception and design of the work, and to the acquisition, analysis, and interpretation of data for the work, revised the work, gave final approval for the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DR contributed to the interpretation of data for the work, revised the work, gave final approval for the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JDB contributed to the conception and design of the work, and to the analysis, and interpretation of data for the work, drafted and revised the work, gave final approval for the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CASE REPORT
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Case Report: Deutetrabenazine as an Adjunctive Treatment for Stuttering

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Childhood-Onset Fluency Disorder (Stuttering) is a neurodevelopmental disorder in which disturbances occur in the normal fluency and time patterning of speech. While the dopamine system has been well-described in its neurophysiology, there currently is no FDA-approved treatment for stuttering. Second-generation antipsychotics, which have been effective in the treatment of schizophrenia and bipolar disorder, act as dopamine D-2 receptor antagonists at the postsynaptic neuron and have been shown to reduce the symptoms of stuttering. However, the D-2 receptor antagonist and partial agonist agents carry the potential for metabolic side effects and can potentially lead to movement disorders. Deutetrabenazine, a VMAT-2 inhibitor indicated to treat hyperkinetic movement disorders, is a potential candidate in the treatment of stuttering, based on its mechanism of action in decreasing dopamine activity while not carrying the risk of metabolic adverse events.

Keywords: stuttering, deutetrabenazine, VMAT 2, D2 receptor antagonists, tardive dyskinesia (TD)

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INTRODUCTION

Stuttering is a neurodevelopmental disorder that affects 1% of the adult population in an ∼4:1 male to female ratio (1, 2). Current research on stuttering reflects a multifactorial process with physiologic etiology. Neurophysiology studies demonstrate the role of the dopamine system in the pathogenesis of stuttering, with an improvement of symptoms from treatment with dopamine D-2 receptor antagonists (3–6).

Second-generation antipsychotics act on the dopamine D-2 receptor as either antagonists or partial agonists and have been effective in the treatment of not only schizophrenia and bipolar disorder, but also have been shown, in limited trials, to improve symptoms of stuttering (7–9). In both first- and second-generation antipsychotics, there is a risk of developing drug induced movement disorders (D-IMDs), a spectrum of neurologic motor disturbances characterized by abnormally increased or decreased motor activity and function (10). D-IMDs can be distinguished into reversible or persistent, hypokinetic or hyperkinetic, and dystonic or non-dystonic classifications (10). This constellation of presentations includes acute dystonia, drug induced parkinsonism, and bradykinesia, and can precede the eventual development of the overreactive dopamine state known as tardive dyskinesia (TD). TD is a medication-induced hyperkinetic movement disorder caused by exposure to dopamine receptor-blocking agents that persists for at least 1 month after discontinuation of the offending agent (1). In comparison to other D-IMDs that present more acutely, TD is distinguished by its later, insidious onset. While the repetitive, involuntary movements may manifest as a spectrum of orofacial dyskinesia, dystonia, chorea, and tics, TD most commonly presents with oro-bucco-lingual and facial dyskinesias characterized by protruding and twisting movements of the tongue, chewing movements, blepharospasm, and pouting, puckering, or smacking movements of the lips (11).

Although the rates of D-IMDs and TD are less in second generation antipsychotic agents, such can still occur. These agents may also be associated with the potential of metabolic adverse events, but overall tend to be well-tolerated in most subjects (12). The dopamine acting agents have been shown in several studies, although many limited in scope, to be effective in the treatment of developmental stuttering. However, the studies demonstrate that not all patients respond to D-2 agents and the search for alternative mechanistic agents is warranted. A class of medications, the VMAT-2 inhibitors, are approved to treat TD in the United States, and as this case describes, may potentially serve as an adjunctive treatment in stuttering as well. The VMAT-2 inhibitors decrease dopamine activity not by antagonizing the receptor, but rather by decreasing dopamine levels in the presynaptic neuron. While VMAT-2 inhibitors predominantly decrease dopamine activity, depending on their specific compound, they may also decrease the activity of other monoamine neurotransmitters and may potentially lead to depressive symptoms.

CASE DESCRIPTION

A healthy 20-year-old Caucasian male with no family history presented with a history of stuttering at age 6 years. The patient had attended an annual 1-week intensive residential speech therapy program for eight consecutive years and continued speech therapy but experienced a poor response.

At age 14, patient sought care for his stuttering due to lack of efficacy from his speech therapy. Aripiprazole, 5 mg per day, was initiated and titrated to 30 mg per day based on his tolerability, to which the patient exhibited a positive response (1). He subsequently developed a thirty-pound weight gain over the course of 5 years above his natural growth. The patient was then switched to lurasidone 60 mg per day for 1 year and experienced

TABLE 1 | Timeline.

Month	Presentation	Treatments	Height (cm)	Weight (kg)	BMI	AIMS
1	Stuttering, non-responsive to speech therapy.	Started on aripiprazole eventually titrated to 30 mg per day.	165.74 cm	60.78 kg	22.24 kg/m^2	0
3	Stuttering stable.	Continued on aripiprazole 30 mg per day.	168.91 cm	73.03 kg	25.6 kg/m^2	0
15	Weight gain. No tardive dyskinesia.	Aripiprazole 30 mg per day Counseled on diet and exercise.	170.18 cm	86.64 kg	29.95 kg/m^2	0
20	Evaluated by endocrinology due to BMI > 30.	Aripiprazole 30 mg per day. Initiated diet and exercise program.	170.18 cm	88.90 kg	30.72 kg/m^2	0
40	Weight gain persisted. No tardive dyskinesia.	Discontinued aripiprazole 30 mg per day. Started lurasidone 20 mg, titrated to 60 mg per day.	170.18 cm	72.57 kg	24.69 kg/m^2	0
44	Stuttering worsened back to pre-treatment levels.	Increased lurasidone 80 mg per day.	170.18 cm	73.03 kg	25.2 kg/m^2	0
49	Stuttering non-responsive to lurasidone. Patient noted weight stable	Re-start aripiprazole, titrated to 30 mg per day. Tapered and discontinued lurasidone 80 mg. Topiramate titrated to 100 mg per day to prevent weight gain.	170.18 cm	Unable to obtain	Unable to obtain	0
50	Speech improved with aripiprazole. Patient noted weight stable.	Continued aripiprazole 30 mg per day and topiramate.	170.18 cm	Unable to obtain	Unable to obtain	
51	Tongue dyskinesias noted on exam and subjectively by patient. Patient noted weight stable.	Continued aripiprazole 30 mg per day. Started deutetrabenazine 6 mg per day.	170.18 cm	Unable to obtain	Unable to obtain	7
52	Tongue dyskinesia subjectively improved as noted by patient. Stuttering stable. Patient noted weight stable.	Aripiprazole 30 mg per day. Deutetrabenazine titrated to 9 mg twice per day.	170.18 cm	Unable to obtain	Unable to obtain	5
54	Stuttering stable. Patient noted weight stable.	Aripiprazole 30 mg per day. Deutetrabenazine 12 mg twice per day.	170.18 cm	Unable to obtain	Unable to obtain	2
56	Stuttering stable. Weight stable. No movements elicited on AIMS examination.	Continued aripiprazole 30 mg per day and deutetrabenazine 12 mg twice per day.	170.18 cm	69.85 kg	24.12 kg/m^2	0

Certain weight and BMI measurements were unable to be obtained due to the nature of telemedicine visits during the COVID-19 pandemic.

a thirty-pound weight loss but worsening of his speech to pre-treatment level. Patient requested to return to aripiprazole and was restarted on 30 mg per day with a resultant improvement of his speech again. Topiramate was initiated as aripiprazole was started to prevent weight gain and was proven successful. However, after 6 months of receiving aripiprazole, the patient developed minor involuntary movements of his tongue and was diagnosed as having tardive dyskinesia **Table 1**.

Deutetrabenazine was initiated at 6 mg per day, and then increased over time to 12 mg twice a day with resultant improvement of his tardive dyskinesia and further improvement of his stuttering from moderate to essentially mild on the Abnormal Involuntary Movements Scale (AIMS). The patient continues to tolerate both deutetrabenazine and aripiprazole well.

DISCUSSION

Deutetrabenazine, along with valbenazine, which have received FDA approval to treat tardive dyskinesia, may hold promise as potential pharmacologic treatments for stuttering. Such agents, as this case illustrates, may be administered concomitantly with dopamine antagonists and partial agonists to reduce dyskinetic symptoms and possibly enhance the therapy for stuttering. The patient presented in this case tolerated both aripiprazole and deutetrabenazine well, and did not experience any potential adverse events, such as depression, that may be associated with monoamine decrease.

Further research is necessary, however, to determine if such pharmacologic augmentation provides a synergism in therapeutic effect. One issue is more certain—the VMAT-2 inhibitors possess a different side-effect profile than the D-2 antagonists by avoiding metabolic concerns and the risk of long-term movement disorders. However, they themselves are not without risks such as depression, cardiac conduction delays, and muscle stiffness. Additional research with controlled studies to determine possible monotherapy or augmentation therapy of VMAT-2 inhibitors in stuttering may be warranted in the future. Given the short duration of treatment as illustrated by the case, long-term, controlled studies are required to address the potential effect of deutetrabenazine as a monotherapy in the setting of stuttering associated with tardive dyskinesia.

PATIENT PERSPECTIVE

Patient subjectively noted stuttering and tongue dyskinesias. However, the patient wishes to maintain on aripiprazole due to the improvement of his speech, in spite of the tongue dyskinesias and weight gain. Therefore, treatments of these side effects have been initiated and successful.

"Prior to starting Deutetrabenazine, I have been taking 30 mg of aripiprazole daily for stuttering. This has helped with my fluency, but I thought that my fluency could still be better. The aripiprazole was also causing uncontrolled movements in my mouth area (Dyskinesia). I was prescribed deutetrabenazine to treat my stuttering and dyskinesia. My stuttering has improved since I started taking deutetrabenazine. I feel like I am in better control of my speech. I also feel like I can more easily use the "tools" I have previously learned in speech therapy (I am no longer in speech therapy, but I remember the content of what I learned). The dyskinesia has also improved since I started deutetrabenazine; however, I still experience some uncontrolled movements in my mouth."

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

GM and CH participated directly in the patient's care. CH wrote the manuscript with support from GM. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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Conflict of Interest: The University of California, Riverside holds the patent with GM as inventor for VMAT-2 inhibitors in the treatment of stuttering. GM discloses research grants from Emalex and Teva and consulting with Vivera.

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

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CASE REPORT
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Case Report: A Case of Valproic Acid-Induced Hyperammonemic Encephalopathy Associated With the Initiation of Lithium: A Re-duplicable Finding

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Introduction: Hyperammonemic encephalopathy (HAE) is a serious adverse effect of valproate semisodium, which is facilitated by the potential for drug interaction. However, despite frequent co-prescription of valproate semisodium and lithium, the role of this combination in the occurrence of HAE has not been defined in the literature. This case report concerns the occurrence of HAE concomitant with the initiation of lithium in a 29-year-old patient who had been placed on valproate semisodium for a schizoaffective disorder.

Case Report: Due to a relapse while on a combined antipsychotic and mood-stabilizing therapy (paliperidone palmitate and valproate semisodium), a cross-taper from valproate semisodium to lithium was proposed. The initiation of lithium was accompanied by an acute confusional syndrome, an elevated serum valproate level and hyperammonemia suggestive of drug-induced HAE. The discontinuation of lithium and reduction of valproate semisodium led to neurological improvement, until a recrudescence of psychiatric symptoms justified a rechallenge of the combination within the framework of a new cross-taper. As soon as Lithium was re-initiated, an increase in the serum valproate level and hyperammonemia were again noted.

Discussion: The mechanisms of valproate-related HAE involve various metabolic pathways. In this case, exploration of the iatrogenic hypothesis focused on the imputability of concomitant cannabis use and co-prescriptions of benzodiazepines, antipsychotics, and in all likelihood, mood stabilizers.

Conclusion: Therefore, this case study suggests that Lithium plays a role in serum valproate level elevation, and supports the hypothesis of an association between an elevated serum valproate level, hyperammonemia and reversible encephalopathy. A more in-depth pharmacokinetic exploration would provide a better understanding of the mechanisms of these interactions and support for the benefit-risk balance associated with this frequent co-prescription.

Keywords: encephalopathy, hyperammonemia, lithium, interaction, valproate sodium, pharmacokinetic interaction

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INTRODUCTION

Valproic acid—marketed as valproate or valproate semisodium—is a non-barbiturate anticonvulsant drug and a GABAergic mood stabilizer. It is indicated in neurology for the management of focal or generalized epilepsy (1) and in psychiatry for the management of manic and mixed episodes in bipolar disorder, commonly employed in the course of combination treatments (2–5). In the valproate semisodium adverse effects (AE) profile, encephalopathy is described as "rare" (0.1–1%), generally transient and which regresses on discontinuation of treatment or dose reduction, but which could also lead to serious complications requiring intensive (hemodialysis) and/or resuscitative management (6, 7). While the mechanisms underlying the occurrence of these AEs is still not perfectly understood, many cases of hyperammonemic encephalopathy (HAE) have been reported in the literature (8, 9) through which various risk factors can be identified. One such risk factor is the combination of several drugs which could contribute to this AE by drug interaction (10). To date, none of these articles have mentioned the risk of iatrogenic HAE specifically associated with the co-prescription of lithium and valproate semisodium. However, this combination of drugs is common (11). Therefore, this case report concerns the concomitant occurrence of HAE with the initiation of lithium in a 29-year-old patient with schizoaffective disorder treated with valproate semisodium who was hospitalized for acute manic relapse with mood-incongruent psychotic features.

CASE REPORT

Case History

Somatically, the patient had no significant medical or surgical history, and in particular no documented drug allergy or AE. He had grade 1 obesity (99 kg, 180 cm, BMI: 30.56), was an active smoker, and had a history of addiction (cannabis) from which he had been abstinent for several years.

Psychiatrically, the patient had a history of schizoaffective disorder diagnosed at the age of 19 (illness duration of 10 years) according to DSM5 criteria (12), in combination with antisocial personality disorder and substance use disorder. Illness recurrences came in the form of acute manic psychosis, which were often triggered by a discontinuation of treatment and required multiple psychiatric hospitalizations (5 within the past 2 years), the most recent of which were by involuntary care.

Therapeutically, the initiation of long-acting injectables (LAI) in the form of Risperidone extended-release (ER) (50 mg/14 days) first of all ensured an initial period of clinical stability. However, 2 years before the onset of the current episode, a decompensation while on a single antipsychotic agent had motivated the initiation of a mood stabilizer (Valproate semisodium, 2,000 mg/d, with serum valproate concentration of 62 mg/L, within the therapeutic range of 41–100 mg/L) combined with antipsychotic treatment with paliperidone ER (100 mg/28 d). This dual therapy was then replaced by a combination of valproate semisodium (2,000 mg/day) and Risperidone (4 mg/d) in a context of absenteeism from outpatient follow-up. Six months prior to the onset of the current episode, dual therapy with valproate semisodium (2,000 mg/d) + paliperidone ER (100 mg/28 d) was re-initiated, with a well-tolerated dosage increase (to 2,500 mg/d and 150 mg/28 d, respectively, accompanied by an elevation in serum valproate levels from 67 mg/L before to 97 mg/L after drug dosage increase) without any further adjustment in the 4 months preceding this episode.

Current Episode

After a short period of clinical stability however, a further interruption of both outpatient follow-up and drug treatment was accompanied by an increase in both manic (elated mood and psychomotor agitation) and psychotic symptoms (delusions of grandeur and persecution) leading to behavioral disturbances and hetero-aggressive threats against his neighbors. After police intervention, the patient was transported to the psychiatric emergency services for medical assessment, and hospitalized without consent in a psychiatric care unit, where further examinations were performed.

During Hospitalization

Due to a relapse with a serum valproate level suggestive of drug non-compliance on admission (serological concentrations of valproate measured at 23 mg/l on admission, below the therapeutic range), the drug was re-prescribed at the usual doses and supplemented with diazepam, a benzodiazepine drug, and levomepromazine, a phenothiazine antipsychotic with tranquilizer properties. When clinical deterioration (acute manic psychosis with grandiose delusions and psychomotor agitation) again occurred under effective treatment [i.e., despite a serum valproate level within the therapeutic range (91 mg/l)], a change in mood stabilizer was proposed in an overlap-and-taper strategy, after pre-therapeutic assessment (with no outstanding features). Considering that the patient had many illness recurrences of manic polarity with psychotic symptoms, as well as a high metabolic syndrome risk valproate was replaced with lithium as mood stabilizer, which was initiated (day 0) at 400 mg/d. However, after the third administration of slow-release lithium salt, signs of fluctuating temporal disorientation signaled the onset of an acute confusional syndrome (d3). An iatrogenic etiology was immediately suspected, which led to the discontinuation of lithium the same day (d3) and the confusional syndrome was etiologically assessed.

Diagnostic Assessment and Etiological Approach

Clinically, the patient presented with psychomotor retardation, disorders of alertness and global cognitive impairment [Mini-Mental State Examination (MMSE) score of 15/30 (13); Frontal Assessment Battery (FAB) score of 3/18 (14)] with no clinical signs on general or neurological examination). Biological examinations (complete blood count, electrolytes, liver, kidney, thyroid, coagulation and vitamin workup) revealed no significant abnormality (day 3). The brain computed tomography (CT) scan (day 5) showed nothing abnormal. The electroencephalogram (EEG) (d5) showed no seizure activity but presented a pattern indicating encephalopathy (fluctuating and slowing background

activity with theta/alpha and delta waves, predominant in the posterior regions, reactive to verbal stimulation and with the change to eyes-open). Pharmacologically, serum lithium level measured 24 h after the third intake (day 3) showed subtherapeutic doses (undetectable <0.05 mmol/l; N: 0.8–1.2 mEq/l), whereas the serum valproate level was consistent with an overdose (130 mg/l) and was accompanied by a threefold elevation in serum ammonia level (182 μmol/l; N: 16–60). In addition, the blood toxicology screen showed cannabis use (THC-COOH: 16.9 ng/l) but did not suggest associated substance use.

Diagnosis

The diagnosis of *drug-induced* hyperammonemic encephalopathy (HAE) was therefore proposed, and the valproate semisodium dose was decreased under clinical supervision (2,000 mg/d on day 4, 1,500 mg/d on day 6). The neurologist recommended no other urgent course of action.

Course of the Condition

Dose reduction resulted in rapid neurological improvement, both clinically and on the electroencephalogram [check on day 7, i.e., 3 days *(steady-state*) after the first valproate semisodium dose reduction], associated with normalization of serum valproate (79 mg/l on day 7; 5 mg/l on day 10) and serum ammonia (66 μmol/l on day 7; 32 μmol/l on day 10) levels. However, regression of the encephalopathic condition quickly gave way to the reappearance of psychiatric symptoms due to the lack of effective treatment, which justified a re-increase in valproate semisodium dosage (2,500 mg/d on day 12, 5 days after the regression of the neurological disorders) and a monthly injection of paliperidone, which once again stabilized the patient without any clinical or biological adverse effect observed in 1 month (serum valproate level: 61 mg/l and serum ammonia level: 27 μmol/l on day 38, on valproate semisodium 2,500 mg/d).

Rechallenge

After requesting an opinion from a pharmacology specialist—and in the absence of documentation in the literature regarding the possibility that lithium may have contributed to the picture presented, a change in mood stabilizer was again considered at day 46 (day 0') according to the same modalities. lithium was initiated at 400 mg/d, valproate semisodium was progressively decreased (2,000 mg/d on day 0', 1,500 mg/d on day 3' [...] discontinuation on day 12') and the patient was reassessed daily. No clinical adverse effects were reported. However, biologically, the results of the test done on day 6' showed an infratherapeutic serum lithium level (0.26 mEq/l with 400 mg/d of lithium) and a 6% increase in serum valproate level compared to the test done 2 weeks earlier (89 mg/l on day 6' compared to 61 mg/l on day 38), despite a 40% decrease in the valproate semisodium dose administered since the last test (1,500 mg/d on day 6' compared to 2,500 mg/d on day 38). In addition, this elevated serum valproate level was again associated with hyperammonemia (90 mg/l), with no proven consumption of toxic substances (negative urine toxicology screen).

In Brief

The first administration of lithium salts was temporally related to an elevation of valproate serum levels, which was in turn associated with hyperammonemia and signs and symptoms of encephalopathy, which resolved after lithium discontinuation and progressive reduction of valproate semisodium dosage. The rechallenge of the combination long after the first episode then enabled a more objective examination of another increase in the serum valproate level, with more moderate hyperammonemia (without encephalopathy or associated *clinical* signs), concomitant with the re-initiation of lithium, despite a progressive decrease in the doses of valproate semisodium administered (**Figure 1**).

DISCUSSION

Several hypotheses have been put forward in the literature regarding the mechanisms of valproate-related HAE (15, 16). Valproate-related HA appears to be the result of a disturbance in the ammonia production/elimination balance, involving various metabolic pathways. In fact, in the liver, blockage of the urea cycle by the active valproate semisodium metabolites (valproyl-CoA) might be the source of an elimination defect of ammonia in the water-soluble form. To a lesser extent, in the kidneys, valproate semisodium might induce an increase in mitochondrial transport of glutamine and might stimulate the production of ammonia during the transformation of glutamine into glutamate (6, 17).

In addition to these inhibition mechanisms (N-acetylglutamate synthase) and enzyme induction (glutaminase), the effects of valproate semisodium on the metabolic pathways might also be related, one the one hand, to the production of neurotoxic derivatives of the drug [2-ene-valproate, from β-oxidation (18)] (19) and, one the other hand, to the spatial configuration of valproate semisodium which is similar to that of fatty acids (FAs). Because of this similarity, valproate semisodium and FAs might compete during transport (linked to carnitine), mitochondrial metabolization (competition with a β-oxidation enzyme and metabolic deviation of FAs toward an ω-oxidation pathway with an accumulation of hepatotoxic derivatives) and urinary elimination (minority: 0.1%) as valproyl-carnitine (6).

Therefore, a pre-existing carnitine deficiency (undernutrition, dialysis) could contribute to an elevated serum valproate level which is then maintained by the effects of valproate semisodium itself (6, 20). Consequently, L-carnitine supplementation has been suggested in case of HAE, and has shown an effect on the speed of serum ammonia normalization (not correlated to the severity of encephalopathy) but without proving its effectiveness on clinical outcomes (20, 21).

In addition to the neurotoxicity of valproate semisodium metabolites, valproate-induced HA could also be responsible for an alteration in astrocyte glutamatergic metabolism which causes cerebral edema and an increase in sensitivity to oxidative stress which is likely to contribute to the occurrence of encephalopathy (15, 18, 22).

Nevertheless, there is no systematic deterministic correlation between valproate semisodium, HA and encephalopathy. Not

Neurological symptoms	Asymptomatic patient			Confusional syndrome				Improvement			Asymptomatic patient			
Psychiatric symptoms		Manic symptoms		In the forefront of the neurological picture					Manic symptoms		Clinical stability			
Diagnostic tests						CT ⊥ EEG ⊤		EEG ⊥						
Date	D-43	D0	D2	D3	D4	D5	D6	D7	D10	D12	D38	D0'(D46)	D3'	D6'
Lithium (mg/d)	0	400		0								400		
Serum lithium level (mEq/l)				< 0.05										0.26
Semi-sodium valproate (mg/d)	2500			2000			1500		2000	2500		2000	1500	
Serum valproate level (mg/l)	91 ⊥			130 ↑↑				79 ⊥	5 ↓↓		61 ⊥			89 ↑
Serum ammonia level (μmol/l)				182 ↑↑				66 ↑↑	32 ⊥		27 ⊥			90 ↑↑

FIGURE 1 | Management summary: therapeutic strategy, clinical course and diagnostic tests. EEG, electroencephalogram; ER, extended release; NA, not administered; N, normal values →; CT, computed tomography (brain) scan; ⊤, abnormal; **?**, normal, within normal limits; ↑, elevated value, within normal limits; ↑↑, elevated value, above normal or supratherapeutic; ↓, decreased value, within normal limits; ↓↓, decreased value, below normal or subtherapeutic; ↕: discontinued; → Normal values: serum lithium level: *N* = (0.84–1.2) mg/l; serum valproate level: *N* = (41–100) mEg/l; serum ammonia level: *N* = (16–60) μmol/l.

all reported cases of valproate-related encephalopathy are accompanied by HA (16, 23) and almost half (16–52%) of the patients on valproate semisodium could have asymptomatic HA (i.e. without the occurrence of HE) (15, 23) that might not require therapeutic adjustment. Among the risk factors identified, age (0–2 years), impaired renal or hepatic function, carnitine deficiency, urea cycle disorders (including ornithine transcarbamylase deficiency), and combination therapy [particularly antiepileptic drugs (24)] appear to be associated with valproate-related HAE (10). However, no association was found between the occurrence of these AEs and the duration of treatment, the history of valproate semisodium use, the dose administered, or the serum valproate level [no dose effect (15, 23)] (10).

Therefore, if previous treatment attempts or the duration of current treatment were not protective factors for this patient regarding urea cycle, in principle, he had none of the above-mentioned *clinical* risk factors either. In hindsight, however, this study lacks information on the *biological* features that could have altered the metabolic pathways. Genetic testing for polymorphisms for the cytochrome P450 or other genes involved in mitochondrial disease leading to hyperammonemia or deficit of urea cycle has not be performed, and the presence of any urea cycle defects was not systematically assessed (plasma amino acid dosages, as well as urinary levels of orotate regarding OTC deficiency). Yet, it should be noted that serum carnitine level was not measured, but that clinical and biological improvement was rapidly observed after therapeutic adjustment without L-carnitine supplementation. Consequently, *other* parameters could have contributed to the development of HAE several years after the initiation of valproate semisodium, several months after the last adjustment in the treatment dose, and 3 days after combination with a mood stabilizer in a patient who also receives antipsychotics and benzodiazepines, associated with a recent *unusual* consumption of toxic substance (isolated cannabis use).

Cannabis

Pharmacokinetic studies conducted on the therapeutic form of cannabis [cannabidiol—indicated in the management of symptoms related to refractory spasticity in multiple sclerosis and in syndromic seizures in children (25)] have shown a risk of hepatocyte damage with elevated transaminases (not found in the patient) during concomitant use of cannabidiol and valproate semisodium, as well as an inhibitory effect on certain isoforms of uridine-5'-diphospho-glucuronosyltransferases (UGT) and cytochromes P450 (CYP). This interaction involved in particular UGT1A6, 1A9, and 2B7 [the major valproate semisodium metabolism pathway by glucuronidation (40%) (26)] and to a lesser extent CYP2B6, 2C9, and 2C19 [also involved in valproate semisodium metabolism (27)] with an associated risk of increased serum levels of drugs metabolized by these isoenzymes. Therefore, cannabis use at the time of the first therapeutic switch could probably have contributed to an increase in serum valproate level by enzymatic inhibition [*or even* competition for UGT 1A9 and 2B7 (25)]. However, it would be difficult to explain the elevated serum valproate level observed during the second switch by this mechanism, considering that the patient was no longer using cannabis during this period.

Adjunctive Medicines

Although it has been suggested that "endogenous benzodiazepines" (the γ-aminobutyric acid pathway) contribute to the occurrence of hepatic encephalopathy (28), the role of concomitant use of benzodiazepines in the occurrence of valproate-related HAE (beyond an additional confusional effect) does not appear to be based on any tangible evidence (22). In addition, in this case, the doses of diazepam re-initiated on admission (20 mg/d) were being reduced at the time of onset of the symptoms (5 mg/d at the time of the first switch, 3 mg/d at the time of the rechallenge). Similarly, if the concomitant

administration of antipsychotics is to be taken into account in the occurrence of valproate semisodium-related AEs, a particular concern is the risk of extrapyramidal syndromes (29, 30) which do not justify special systematic precautions when antipsychotics are co-prescribed (2). For the patient, monthly injections of paliperidone were administered 18 days before the first switch, and 6 days before the second, with no documented signs of intolerance, and the dose of levomepromazine administered on admission (identical at the time of the rechallenge: 300 mg/d) (day 46) had been reduced by a factor of 6 before the first switch (55 mg/d) without preventing the occurrence of HAE.

Lithium

In order to maximize tolerability and reduce the occurrence of side effects when initiating *de novo* lithium therapy, current guidelines suggest that lithium should be administered in small divided doses, and that the dose should be titrated gradually (31–33). For this purpose, and due to the narrow therapeutic index of lithium, the mood stabilizer was initiated (D0 and D0') at 400 mg/d and no dose increase was carried out before the onset of symptoms that led to an anticipated measurement of serum drug levels (undetectable levels on D3) or before the routine therapeutic drug monitoring that was performed in an asymptomatic patient (infratherapeutic levels on D6'). Thus, despite the *apparent* temporal concordance between the initiation of lithium and the onset of HAE, neither the semiological and biological profile (isolated hyperammonemia) of the encephalopathy, nor the onset of symptoms on day 3 of initiation [given the half-life of the drug (34) and undetectable blood levels on D3] supported the hypothesis of lithium-induced encephalopathy, which was less likely in this context than a hypothesis of valproate-induced encephalopathy. However, the appearance of symptoms 3 days after the initiation of lithium and their resolution 5 days after it was discontinued (associated with the dosage reduction of valproate semisodium), in addition to a *direct* relationship, suggests the possibility of *mediation* by thium in the occurrence of valproate-related HAE.

Valproate Semisodium + Lithium Combination

The causality criteria in pharmacovigilance (35) find an intrinsic imputability of level I5, "very likely" (combining a chronological score of C3 "very likely" with a semiological score of S2 "likely"), and an extrinsic imputability rated B2 in the context of an adverse effect "not recognized in standard publications." In fact, despite frequent co-prescription of these two drugs (11), there is little data available on the co-prescription of valproate semisodium and lithium. To our knowledge, a specific search for a drug interaction when lithium and valproate semisodium are combined has only been the focus in one pharmacokinetic study (a prospective controlled crossover study against placebo) which showed no change in serum lithium level, but a "slight" increase in the serum valproate level (minimum and maximum concentrations and area under the plasma concentration-time curve) with a dual mood-stabilizing drug therapy (36). However, the AE profile was not noted to be altered in this study and the AEs documented since then appear to be more related to the *cumulative* toxicities of each drug than to an underlying drug interaction (37).

Considerations on the Association

Although this case raises the question of a pharmacokinetic interaction, the practice of prescribing lithium salts in combination with valproic acid is a common therapeutic strategy, which has interested several studies among bipolar I patients. Indeed, despite a possible increase in reported adverse events (including gastrointestinal distress, tremor, cognitive impairment, and alopecia), the authors of a literature review acknowledged that their imputability to the association rather than to one of the two molecules was not established, and that the co-administration of lithium plus valproate had generally produced favorable results, with particular benefit in patients with manic, mixed, and rapid-cycling features (38). More recently, a naturalistic study concluded that bipolar I patients on lithium plus valproate showed greater improvement in mixed, anxiety, and psychotic symptoms than those on lithium monotherapy and even suggested that a serum lithium level albeit below the reference range seemed sufficient to maintain clinical efficacy when associated with valproate (39). In the same way, a multicentric study that focused on relapse prevention in bipolar I patients showed in turn a superiority of combination therapy over valproate monotherapy, with no difference regarding adverse events and tolerability between the treatment groups (11). Thus, it seems relevant to emphasize that co-prescription of lithium and valproate is supported by evidence of clinical efficacy (acute treatment and relapse prevention) as well as safety.

CONCLUSION

This case study raises the question of a possible drug interaction between lithium and valproate, based on the observation of an increase in serum levels of valproate when co-prescribed with lithium, effects being notable as of the initiation of the mood stabilizer (below the therapeutic thresholds) with robust results on rechallenge of the dual therapy. At the same time, these observations support the hypothesis of an association between serum valproate level elevation, hyperammonemia and reversible encephalopathy in a patient with no documented history of valproate semisodium intolerance. Therefore, given the frequency of the combination in everyday psychiatric practice and the potential seriousness of the adverse effects reported, a more in-depth pharmacokinetic exploration would provide a better understanding of the mechanisms underlying these interactions, as well as enable specification of the risk factors associated with their occurrence and provide support for the benefit-risk balance associated with the prescription of these drugs.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AL: writing. EV, FM, AJ, and PB: revising. LR: revising and teaching. All authors contributed to the article and approved the submitted version.

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Binge Eating and Compulsive Buying During Cabergoline Treatment for Prolactinoma: A Case Report

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Prolactinomas are the most prevalent functional pituitary adenomas. They are usually treated clinically with dopamine agonists. The most widely used and suitable drug is cabergoline (CAB), a specific D2 dopamine agonists. Patients in prolactinoma treatment with CAB commonly report physical side effects, but aberrant behavioral changes such as increased impulsivity have also been reported recently. We report the case of a 47-year-old Brazilian woman with prolactinoma that developed compulsive buying, binge eating, and hypersexuality after four years of CAB treatment. In her psychiatric evaluation, the patient scored high levels on the following scales: Compulsive Buying Scale (CBS), Binge Eating Scale (BES), and Barratt Impulsiveness Scale-11 (BIS11). She also reported financial problems and weight gain in addition to her social and clinical problems. Impulsivity disorders may appear with the use of CAB and other dopamine agonists. We suggest that more observational studies with a large patient sample and specific regular psychiatric evaluations during treatment are necessary for patients in use of CAB, especially those treated for several years.

Keywords: prolactinoma, cabergoline, impulsivity, compulsive behavior, case report

INTRODUCTION

Prolactinomas are the most common functional pituitary adenomas, representing 60% of all clinically evident pituitary tumors (1). The first line of prolactinoma treatment is the use of dopamine agonists (2). Bromocriptine (BRC) and cabergoline (CAB) are widely used ergot-derived dopamine agonists. Quinagolide is also prescribed but is not available in Brazil (2), dopamine agonists therapy normalizes prolactin (PRL) levels in most cases, with resolution of gonadal dysfunction and infertility, besides tumor shrinkage. Dopamine agonists are generally well-tolerated, but in some cases side effects such as nausea, vomiting, nasal congestion, postural hypotension, dizziness, and syncope can occur. Rhinorrhea, painless vasospasm, pleural effusion, pulmonary or retroperitoneal fibrosis, insomnia, mood changes, and psychosis may also be reported, while the increased risk of valvular heart disease is still controversial (2, 3).

Impulse control disorder (ICD) is described as a "failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or others," according to the Diagnostic and Statistical Manual of Mental Disorders (DSM5) criteria. Pathological gambling, hypersexuality, binge eating, and compulsive shopping are included among ICDs in accordance with DSM5, even though they are classified in different DSM5 categories (4).

In addition to prolactinomas, dopamine agonists therapy can also be used in acromegaly, growth hormone secreting pituitary adenoma, Parkinson's disease (PD), and restless legs syndrome, and among these diseases, ICD is reported mainly in prolactinoma. (5) An association between dopamine agonists use and impulsivity in hyperprolactinemia was first published in 2007. Davie et al. reported on a 38-year-old woman with a microprolactinoma who developed pathologic gambling one year after initiating CAB. In 2009, Falhammar reported a second case of ICD in a 50-year-old man with a microprolactinoma treated with CAB with pathologic gambling and hypersexuality, despite low testosterone level (6).

Subsequent years witnessed an increase in case reports of dopamine agonists -induced ICDs in patients with prolactinoma, despite low doses of dopamine agonists in these patients compared to PD and restless legs syndrome. Dopamine agonists-induced ICD was assessed in many series and meta-analyses mainly in PD, but few studies in prolactinoma and only a handful with a cross-sectional design (5–9).

CASE DESCRIPTION

In 1995, a 21-year-old female patient presented galactorrhea associated with menstrual irregularity and sought medical attention. She was diagnosed with hyperprolactinemia, started BRC to control serum PRL levels, but after one month she interrupted use on her own due to gastrointestinal intolerance (vomiting) and dizziness. Approximately one year later, her initial symptoms persisted, and she resumed therapy with BRC (maximum daily dose 3.5 mg), suspended after a few months due to pregnancy, which evolved without complications. Her first magnetic resonance image (MRI) in 1996 before her first pregnancy revealed a lesion less than 5 mm in diameter in the anterior pituitary gland.

At 24 years of age, the patient appeared for medical treatment at the Endocrinology Clinic of the Clementino Fraga Filho University Hospital (HUCFF-UFRJ) in Rio de Janeiro. Her main complaints were severe headache, altered visual acuity, and amenorrhea. On physical examination, she presented galactorrhea and altered field of vision (left temporal hemianopsia and loss of upper right temporal and nasal fields). In February 1999, a new MRI revealed possible pituitary apoplexy and a 1.3 mm × 1.0 mm lesion in the right anterior pituitary, with contralateral shift of the infundibulum. She was not on dopamine agonists therapy at the time.

After this assessment, the decision was made to reintroduce BRC therapy, which was maintained until 2000 when the patient entered her second pregnancy, again without complications. Her visual campimetry improved considerably while under treatment, with good control of her PRL level.

The patient was off dopamine agonists therapy from 2000 to 2011, but due to a gradual increase in PRL level (Graph 1) associated with intense and frequent headaches, CAB was introduced in April 2011, normalizing her PRL level and leading to a reduction in headache. She experienced various physical side effects such as dizziness, vertigo, headache, nausea, vomiting, asthenia, constipation, alopecia, and edema, but no behavioral changes or mental symptoms. In 2019, a new MRI revealed an asymmetrical pituitary gland with diminished volume on the right side and encroachment of the suprasellar cistern, as well as a slight deviation of the infundibulum to the left. The optic chiasma was normal.

The initial dose of CAB was.5 mg per week, and the maintenance dose has been adjusted according to her test results over the years. Patient is currently taking two and a half pills or 1.25 mg weekly.

The patient has not reported behavioral changes or any mental complaint that impacted her daily routine so far. In 2020, she was invited for an interview with the clinical research project entitled "Physical and Behavioral Changes in Prolactinoma Patients Using Cabergoline" in partnership with the Clementino Fraga Filho University Hospital and the Institute of Psychiatry of the Federal University of Rio de Janeiro.

Patient reported no family history of substance abuse, psychiatric hospitalization, or suicide attempts. Her grandmother and son each had one previous episode of depression, but the patient had no such history herself. In her first psychiatric interview, performed for research purposes, she presented with normal physical appearance, cooperative, euthymic, with normal affect, slightly accelerated speech, regular thought process and content, normal cognition, and regular insight.

On the Mini International Neuropsychiatric Interview (MINI) (10) she was diagnosed with two previous mild depressive episodes and current binge eating disorder. She answered all the study's standardized questionnaires: Young Mania Rating Scale (YMRS) (11), South Oaks Gambling Scale (SOGS) (12), Barratt Impulsiveness Scale (BIS11) (13), Compulsive Buying Scale (CBS) (14), Binge Eating Scale (BES) (15), Sexual Functional Questionnaire (SFQ) (16). She had significantly high scores on all three of the latter.

The patient scored 24 points on BES, considered moderate binge eating disorder. She described some unusual eating behaviors such as "eating without feeling hungry" and "eating just to chew food." She even reported some event of vacuous chewing. These symptoms began in 2013 and remain at present. She gained approximately 18 kg over the years (weighting 78 kg in September 1998 and 96 kg at her last appointment in September 2020).

Patient scored 14 on CBS, considered impulsive buying behavior. She described three lifetime events: she bought 15 pairs of shoes in 2015, she began buying much more food to cook at home in 2016 and her relatives complained about it, and she reported buying jewelry on impulse (earrings, neckless, etc.), leading to financial problems.

Patient scored 94 points on BIS, considered high risk for impulsivity. On the other scales she did not score higher, but her sexual behavior stands out. Even though she did not score high in the SFQS, she described her sexuality as much more pronounced than before, with markedly increased libido and several daily episodes of masturbation.

Prolactin variations in the period is shown in **Figure 1**.

DIAGNOSTIC ASSESSMENT, INTERVENTION, AND FOLLOW-UP

The patient was instructed to taper the dose of CAB, and despite her fear of worsening PRL control, she has been able to lower the dosage. She reports feeling well with this dose reduction, but sometimes the impulses to buy and eat reemerge. She has been accompanied by the Psychiatric Outpatient Clinic for psychological support and guidance. From the patient's perspective, she presents personal, economic, and family problems. Her weight gain has generated conflict and irritability with her children. Currently (April–May 2021) she is experiencing binge eating of sweets, and her gastroesophageal reflux has worsened with her impulsive eating. She is in debt due to her impulsive shopping, which has caused various family conflicts.

DISCUSSION

Women with prolactinoma using dopamine agonists and with normal PRL levels present restored gonadal function in 80–90% of cases. These drugs recover their fertility and can conceive, regardless of tumor size (17). Pituitary tumors are classified as microadenomas (<1 cm) versus macroadenomas (⩾1 cm) (2).

The current patient with prolactinoma had no information on her initial tumor size and was already on dopamine agonists therapy (BRC was the available drug at the time). Her PRL level was 66.5 ng/ml (normal range 5–25 ng/dl). As reported, her treatment was irregular due to the clinical history of side effects from BRC, especially gastrointestinal effects. However, approximately one year after her diagnosis she became pregnant, leading to suspension of dopamine agonists as recommended by various authors (17–19).

The patient remained off medication for 11 years, which usually occurs in post-gestational periods in patients with prolactinoma (17, 18). However, she underwent annual monitoring, and her dopamine agonists therapy was resumed (this time with CAB) when her prolactin levels began to increase, and she presented altered pituitary imaging.

In the recent medical literature, the relationship between the use of dopamine agonists and impulse control disorders has been studied in patients with previous diagnosis of psychiatric diseases, as well as in healthy subjects (5–9, 20, 21). The initial focus was on patients with Parkinson's disease, who usually receive high doses of dopamine agonists (21). However, ICD has been also identified in patients with prolactinoma, who often need lower doses of this class of medications. Such disorders can lead to personal, professional, and financial losses for these patients. They are frequently underdiagnosed by their endocrinologists or general practitioners.

Physiologically, the dopamine pathways consist of the nigrostriatal pathway, related to motor function, with D2 and D3 receptors; mesocortical and mesolimbic pathway, related to

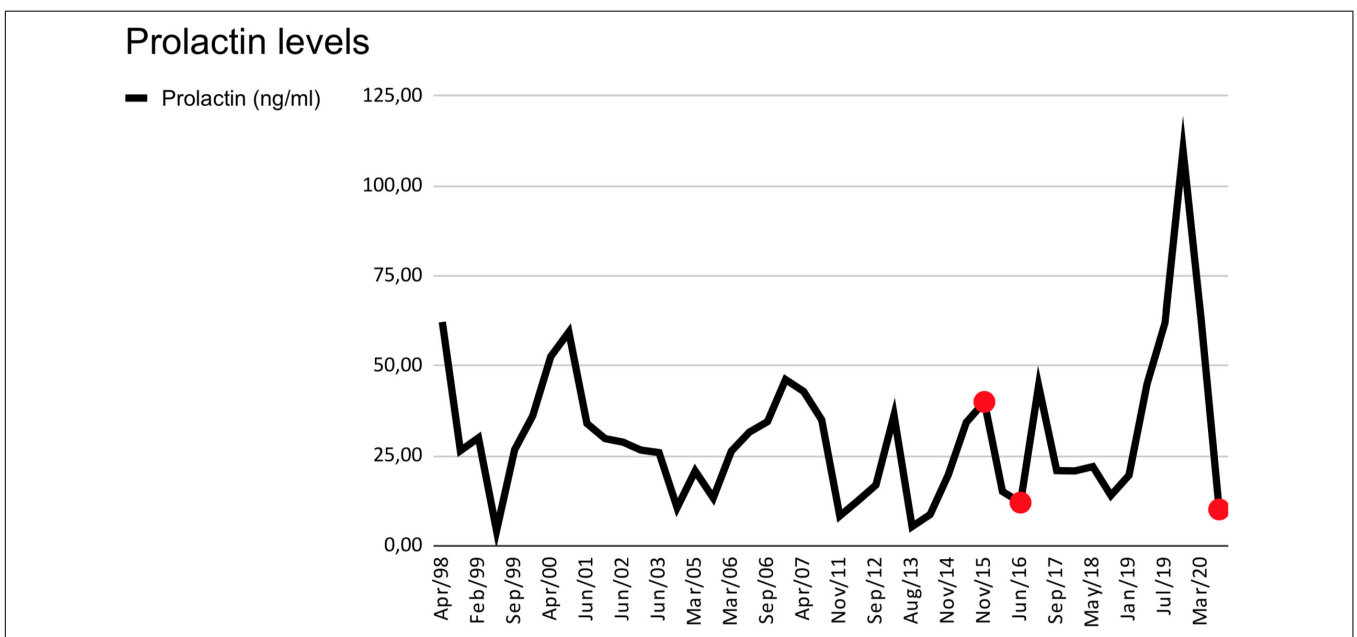

FIGURE 1 | Prolactin levels are in ng/mL. Serum levels from April 1998, to March 2020. Normal levels are from 5 to 25 ng/mL. The red dots indicate moments of major impulsive behavior.

the reward system, with D3 receptors; and tuberoinfundibular pathway, which regulates PRL secretion, with D2 receptors. Dopamine agonists must thus act on the tuberoinfundibular pathway to promote its function in PRL control. However, dopamine agonists are not specific to one kind of receptor: they also bind to D1 and D3 receptors, which produces effects on the reward system. The hypothesis of ABCB1 gene polymorphisms would also explain the occurrence of ICD, influencing or altering the function of P-glycoprotein 1 (P-gp1), a transporter protein that takes substrates from the neuron and releases them into the bloodstream, potentially causing susceptibility to dopamine agonists side effects (22, 23).

The most widely studied and reported ICDs are hypersexuality, pathological gambling, compulsive shopping, and binge eating, and their prevalence in the general population is about 8% (24). Hypersexuality is more prevalent in men; the literature reports few cases in women: 3 with CAB or BRC and 1 with quinagolide, an ergot derivative also used to treat prolactinoma (25).

According to a review article published in 2019 on psychological effects in patients with prolactinoma or PRL-secreting adenoma, independently of previous report of psychiatric illness, patients on lower or higher doses of antidepressants presented ICDs and other psychoses, mania, and worsening of depression (5–9, 23, 26).

A case-control study selected 77 patients with prolactinoma and 70 patients with non-functioning adenoma from January 2001 to December 2011; 24.68% of prolactinoma patients had a positive ICD screening assessment for hypersexuality, punding, or pathological impulses to shop or gamble, with no statistical association between tumor size, type of dopamine agonist, or duration or dosage of the medication. ICD, more specifically hypersexuality, was significantly associated with male gender (7).

Several studies also reached similar conclusions, namely that ICD appears to be associated with male gender, but without evidence regarding age (5–9, 23, 25–27). Importantly, suspension of dopamine agonists therapy in most cases led to resolution or improvement of the psychiatric disorder. However, suspension of treatment may make PRL control more difficult, indicating the need for individual assessment of the feasibility of surgical treatment, maintenance of dopamine agonists therapy, and associated psychotherapy and/or antipsychotic medication such as aripiprazole.

Frequently, the patients are underdiagnosed by their endocrinologists or general practitioners because they do not ask about such effects either for the lack of knowledge of the ICD (and consequently they do not ask about it) or for the insecurity of reducing the medication.

PATIENT'S PERSPECTIVE

In our patient, the first symptoms of impulsivity appeared after three years of treatment with CAB, that is, less than the four-year criterion of time since onset of symptoms. The symptoms were completely new in her life, since she had no previous report of mania, hypomania, or any other impulsivity disorder. Unlike other patients treated with CAB, her side effects were nearly all physical. Her impulsivity impacted her daily life, with growing financial debt, weight gain, and decreased mood. The tools to identify these complex questions were thus impulsivity scales, which helped to describe all the impulsive symptoms.

The patient experienced a decrease in her impulsivity symptoms with the reduction in her CAB dosage, thereby corroborating the close relationship between dopamine agonists and the symptoms. After her psychiatric work-up she reported an improvement in her symptoms. Despite her initial resistance to dose reduction, the patient agreed to try tapering her medication, which we are doing progressively. The patient has reported improvement in her complaints, despite occasional urges to shop and overeat.

Prolactinoma patients on dopamine agonists do not usually voice behavior changes to their physicians, nor do they even realize what is happening. Therefore, it is extremely important to proactively investigate impulsivity symptoms, given the relevant evidence of the correlation between such symptoms and dopamine agonists use. Many patients may feel too shy to admit these symptoms. We also emphasize the importance of interdisciplinarity, given that in the current case the psychiatric work-up helped identify symptoms that had not been detect during the regular clinical examination.

Clinicians must therefore pay special attention and thoroughly observe patients in on-going CAB therapy, especially after four years or more on the medication. We recommend some possible interventions such as the use of impulsivity scales for measurement in asymptomatic patients, psychiatric evaluation in cases of evident impulsive behavior, and revision of the maintenance dose, if necessary, due to possible uncontrolled impulsiveness. It is also important to inform the patient about the potential side effects, including impulsivity.

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 human participants were reviewed and approved by Comitê de Ética do Hospital Universitário Clementino Fraga Filho - UFRJ. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC was the attending psychiatrist and reported on the patient's psychiatric aspects. AA accompanied the patient under the

supervision of AV. MB, JN, and RS collaborated in the literature review, writing, and publishing. MG contributed expertise to the project. AN supervised and reviewed all versions of the manuscript related to psychiatry. AV supervised AA, MB, JN, and RS in the patient's clinical management and preparation of the article. All authors contributed to the article and approved the submitted version.

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Case report: Prazosin augmentation for treating comorbid treatment-resistant depression and chronic post-traumatic stress disorder

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Psychological trauma in childhood can lead to post-traumatic disorder (PTSD) with protracted comorbid depression, which responds poorly to conventional antidepressants. Previous studies have shown that prazosin, an α1-adrenergic receptor antagonist, can help eliminate nightmares and improve sleep quality and suicidal ideation in PTSD patients. This case report presents that prazosin had a rapid antidepressant effect in a female adolescent PTSD patient with treatment-resistant depression (TRD). Prazosin improved not only depression symptoms but also sleep quality, suicidal ideation, and cognitive function. Prazosin was well tolerated without obvious adverse effects. Our preliminary study suggests that further clinical trials are needed to determine the efficacy and safety of prazosin in treating PTSD patients with comorbid TRD.

KEYWORDS

Prazosin, post-traumatic stress disorder, treatment-resistant depression, cognitive function, sleep disturbance, comorbidity

Introduction

Physical and psychological trauma in childhood is a common precipitating and perpetuating factor for post-traumatic stress disorder (PTSD). Depression is the most common comorbidity of PTSD and often responds poorly to available antidepressants (1–3). Millions of people have post-traumatic stress disorder (PTSD) with comorbid depression (TRD) (3). Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacotherapy for treating PTSD (4, 5). However, SSRIs are largely ineffective for the core PTSD symptoms, such as insomnia and nightmares. More than half of patients with PTSD do not achieve remission after treatments with antidepressants and psychotherapy (6), or after repeated applications of the rapid antidepressant, ketamine (7, 8).

Many clinical studies have shown that prazosin, an α1-adrenergic receptor antagonist, significantly improves nightmares in PTSD (9). However, a randomized controlled trial also showed that prazosin was ineffective in alleviating sleep disturbance in PTSD veterans (10). Therefore, more clinical studies are needed to validate the efficacy

of prazosin on PTSD. Whether adding prazosin can improve the depressive symptoms in PTSD with comorbid TRD requires further investigation (11).

We here present a case of a female adolescent PTSD patient with comorbid TRD who was previously treated with a wide range of antidepressants, antipsychotics, and electroconvulsive therapy (ECT) but without achieving remission. During this admission, the patient was given low-dose prazosin as an augmenting treatment and showed remarkable improvements in PTSD and TRD symptoms.

Case report

Miss A, a 16-year-old female with a history of sexual abuse in childhood, has been hospitalized multiple times in the past two years with the diagnosis of depression and PTSD. Patient reported as a victim of sexual assault by a male neighbor when she was 8 years older. She began to suffer from depression, anxiety, and sleep problem 2 years ago. Since then, she has been hospitalized 6 times with major complaints of depression and anxiety. She also complained of sleep disturbance, nightmares, irritation, and memory loss. She often re-experienced the scenario of childhood sexual assault. She thought of killing herself and felt extremely disgusted with adult men. To manage PTSD and depression, she first was on sertraline (100 mg/day) and was late on venlafaxine XR, but with little improvement. Her anxiety was managed with diazepam (10 mg/day) and lorazepam (0.5 mg qn). One year ago, her intimate friend committed suicide from a drug overdose, and she was blamed and threatened by her friend's parents and relatives, and her symptoms worsened. She was augmented with olanzapine (2.5 mg after lunch and 5 mg at bedtime) and co-treated with four MECT and Venlafaxine XR (150 mg/d) but did not get complete remission.

Before this admission, the patient broke up with her partner and attempted to commit suicide multiple times. The patient was hospitalized with the diagnosis of PTSD with comorbid TRD. TRD was diagnosed according to DSM-5 and the failure with two successive antidepressants with adequate dose and duration. Physical exams and image studies were not

TABLE 1 Timelines of patient events and medications in current admission and follow-ups.

Date	Event	Medication/s	Comment
29/Oct-02/Nov/2020	ADMISSION (the 7th time)	Venl 225 mg/d + Ola 7.5 mg qn + Diaz 10 mg ivgtt/d*5 days + MECT(M-W-F)*2 sessions	Broke up with her partner and indulged in video games and tried to kill herself
03-08 /Nov/2020		Venl 225 mg/d + Ola 10 mg qn + Bupr 150 mg/d + Diaz 10 mg ivgtt/d*5 days + MECT(M-W-F)*2 sessions	Bupr augmentation for TRD and reducing the appetite and weight gain caused by Ola
09-18 /Nov/2020		Venl 225 mg/d + Ola 10 mg qn + Bupr 300 mg/d + MECT(M-W-F)*4 sessions	Cognitive deficit after MECT; no improvement in sleep
19/Nov/2020		Venl 225 mg/d+ Ola 10 mg qn +Bupr 300 mg/d+ Lora 1 mg qn + **prazosin** 0.25 mg qn	Add low-dose prazosin for symptoms of PTSD, especially nightmares
20-22 /Nov/2020		Venl 225 mg/d + Ola 7.5 mg qn +Bupr 300 mg/d+ Lora 1 mg qn + **prazosin** 0.25 mg qn	Down-titration Ola because of excessive sleep
23-25 /Nov/2020		Venl 225 mg/d+ Ola 7.5 mg qn + Bupr 300 mg/d+Lora 1 mg qn + **prazosin** 0.5 mg qn	Up-titration prazosin, and nightmare and depression improved
26/Nov/2020	DISCHARGE	Maintain the medications for a month	
26/Dec/2020-26/Jul/2021	Follow-up as an outpatient	Venl 225 mg/d + Ola 5 mg qn + Bupr 150 mg/d + **prazosin** 1 mg qn	Ola and Bupr Down-titration, prazosin Up-titration and Lora discontinuation. Her education continued without symptoms of PTSD or TRD relapse
27/Jul/2021-up to now	Follow-up as an outpatient	Venl 150 mg/d + Ola 2.5 mg qn + Bupr 150 mg/d + **prazosin** 1 mg qn	Venl and Ola Down-titration. Her social function is good and she feels great about herself.

Sert, sertraline; Venl, venlafaxine XR; Bupr, bupropion; Ola, olanzapine; Que, quetiapine; Diaz, diazepam; Lora, lorazepam; PTSD, post-traumatic stress disorder; MDD, major depressive disorder; TRD, treatment-resistant depression; MECT, modified electroconvulsive therapy; M-W-F, Monday-Wednesday-Friday; SAE, severe adverse event.

TABLE 2 Effects of prazosin on heart rate, blood pressure, and emotional and cognitive symptoms of patient.

	Baseline	Day 3	Day 7	Day 14	Day 28
HR	94	90	86	84	80
BP	124/84	120/80	110/74	110/78	105/75
$HAMD_{-17}$	24	18	10	4	2
HAMA	15	12	8	4	3
CAPS-5	42	28	20	14	12
DSST	45	48	52	53	66
TAT-A(s)	31	24	19	17	12
TAT-B(s)	55	52	49	40	37

HR, heart rate; BP, blood pressure; HAMD, Hamilton depression rating; HAMA, Hamilton anxiety scale; CAPS-5, the Clinician-Administered PTSD Scale for DSM-5; DSST, Digit Symbol Substitution Test; TMT, Trail-Making Test.

remarkable. The patient was put on venlafaxine XR (up to 225 mg/day), bupropion XR (up to 300 mg/d), olanzapine (up to 10 mg/day) for 3 weeks, and also received eight sessions of modified electroconvulsive therapy (MECT), but achieved no significant improvement. After informed consent, the patient was first put on prazosin at a low dosage of 0.25 mg at bedtime for 3 days with blood pressure monitored. The dose was then increased to 0.5 mg/day on day 4 and 1 mg/day on day 14 (Table 1). The patient reported no side effects and no significant change in blood pressure. The patient completed scales for depression, anxiety, PTSD, and cognitive functions before and after starting prazosin (Table 2). PTSD symptoms, depressive and cognitive symptoms improved on day 3, and continued to improve after 1, 2, and 4 weeks of treatment. The patient was discharged 4 weeks after the admission and has been followed up. The patient has been on the same medications since discharge. The patient has been doing well and not been hospitalized for mood issues and not reported side effects. She is able to continue her education. Her parents have been satisfied with the improvements. The patient consented to the publication of this case report.

Discussion

Depression is a common comorbid complication in PTSD. Like that for depression, selective serotonin reuptake inhibitors (SSRIs) are the first-line drugs for the treatment of PTSD. However, around a half percent of patients respond poorly to the treatment (4, 5). Prazosin was found to improve nightmares in PTSD and has been extensively studied in clinical trials (6, 9). In this case report, we used prazosin in addition to SSRIs to treat PTSD with comorbid TRD. We observed that the addition of prazosin in the treatment regimen gave a rapid onset of antidepressant effect and improved sleep quality, nightmares, cognitive functions, and suicidal ideation.

Previous work mainly investigated the effect of prazosin on PTSD symptoms, especially nightmares (12, 13); less attention has been paid to its possible benefit on depressive symptoms and anxiety. This female adolescent patient suffered from depression and anxiety besides PTSD symptoms. Her depression and PTSD symptoms did not respond to two SSRIs and many sessions of ECT. Adding prazosin to her treatment regimen remarkably improved not only PTSD symptoms but also depressive symptoms and cognitive impairments. Several possible reasons could explain the marked improvement of TRD in the patient by adding prazosin. Prazosin improved nightmares and sleep quality, which might lead to the alleviation of depressive symptoms and anxiety. It is also possible that prazosin itself has an antidepressant action. Preclinical studies reported that α1 antagonists such as prazosin and benoxathian exhibited antidepressant-like activity in the forced swim test and tail suspension test in rodents (14–16) although more experiments are required to support the findings. Another possibility is that prazosin may work together with SSRIs to give more potent antidepressant effects than SSRIs alone. It is worthwhile to conduct further studies to explore this possibility.

We used low doses of prazosin (0.25 to 1 mg daily), which gave marked improvements in both PTSD and depression symptoms without adverse effects. Previous studies showed that prazosin might improve nightmares in children and adolescents with PTSD with rare adverse events, and there was no significant change in blood pressure with the initiation of prazosin (17–19). The dose of prazosin used in previous studies was 1 to 16 mg daily. In adults, the dose of prazosin was up to 45 mg daily (20). The findings in our case report are consistent with previous work on adolescent patients. It was also reported that prazosin was ineffective in alleviating sleep disturbance in PTSD veterans (10). The different findings may imply that prazosin's effect may vary depending on individuals. Age, gender, and comorbidities may be important factors affecting the efficacy of prazosin. Since our current study is a case report, it provides very little information about the roles of these factors in the treatment of PTSD and its comorbid depression and anxiety. Studies with a larger sample size are needed to clarify the roles of these factors.

Conclusion

Combining low-dose prazosin and SSRIs may effectively improve PTSD symptoms and the comorbid TRD. The use of low-dose prazosin is also safe and well tolerable. However, large-scale clinical studies are warranted to study the findings in this case further.

Data availability statement

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

Ethics statement

Ethical approval was obtained from the 3rd Hospital in Huzhou Municipal, Zhejiang, China (Approval No.: AF-39). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

PG: funding acquisition and writing-original draft. YF and XZ: investigation and software. MF: data curation, investigation, and software. MQ: project administration, resources, supervision, and visualization. JH: validation and visualization. SW: conceptualization, methodology, and writing-review & editing. HC: organizing this research and writing and revising this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Schizophrenia treatment with a combination of two LAI antipsychotics: A case report

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Preventing the relapse of a psychotic episode is a challenge for the treatment of schizophrenia. Patients with schizophrenia suffer from a few to a dozen relapses in their lifetime. The use of long-acting injectable (LAI) antipsychotics in the treatment of schizophrenia is associated with less frequent recurrences of psychotic symptoms, better compliance, and better quality of life. The aim of the report is to present the findings of the successful management of treatment-resistant schizophrenia in a patient with persistent non-compliance using a combination of typical and atypical LAI antipsychotics. Since there was a history of non-adherence (irregular controls in outpatient clinics) by the patient, clozapine was not considered a therapeutic option. At the start of the treatment, olanzapine LAI was administered to the patient at a dosage of 300 mg fortnightly because of the good response and tolerance reported in the previous treatment. The treatment was continued for several weeks, and because of the persistence of constant delusions, labile affect, and aggressive behavioral tendencies, a second antipsychotic, zuclopenthyxole, was added, which was initially administered orally. After 4 weeks of combined treatment, the patient's mental state improved. There was no report of delusions, and his mood was much more stable. Zuclopenthyxole was switched to the LAI antipsychotic form due to the patient's history of persistent non-compliance, lack of insight into the disease, and the risk of aggressiveness toward others. Then, 200 mg of zuclopenthyxole decanoate was administered fortnightly. The patient was discharged from the hospital without any symptoms of delusions or hallucinations. The patient's clinical state presented negative symptoms, of which avolition and diminished social activity were dominant. The patient tolerated the treatment well, and sedation and extrapyramidal symptoms were not observed. The patient continued the injections alternately (one injection per week) to obtain regular visits to the outpatient clinic.

KEYWORDS

antipsychotics, treatment, long-acting injectable, polytherapy, treatment-resistant schizophrenia, non-compliance

Introduction

Prevention of a relapse of a psychotic episode in the treatment of schizophrenia is a challenge. Patients living with schizophrenia suffer from a few to a dozen relapses in their lifetime. Each relapse carries the risk of worsening the long-term prognosis of the disease and affects the patient's quality of life. The life expectancy of patients with schizophrenia is shorter by 15–20 years (1). Untreated psychosis and short time remission are associated with higher mortality (2), and inadequate treatment might be connected with aggressive behaviors (3). The use of antipsychotics in the treatment of schizophrenia is associated with 40% lower mortality. The risk of death is 30% lower in the group of patients who are treated with long-acting injectable (LAI) antipsychotics compared to oral antipsychotics, which is due to their neuroprotective activity (4). The first LAI, fluphenazine enanthate, was developed in 1966. Although the concept of LAIs was not initially accepted by the medical profession, many subsequent studies proved to have lower relapse rates of the disease when using LAIs in treatment. Fluphenazine enanthate was administered every 2 weeks. Almost 18 months later, fluphenazine decanoate was added to the treatment, and it was administered every 3 weeks (5). The introduction of oral second-generation antipsychotics (SGA) was supposed to be associated with better adherence rates. However, these medicines did not improve the treatment compliance of the patient. In 2001, long-acting risperidone was the first LAI SGA (6).

Antipsychotic polytherapy is used in up to 30% of patients (7) who do not respond to monotherapy. Tiihonen et al. showed that polytherapy was associated with a lower risk of rehospitalization (8). Therefore, certain types of polypharmacy may be feasible in the treatment of schizophrenia. One of the management options in treatment-resistant schizophrenia (TRS) or persistent non-compliance can be a combination of two LAI antipsychotics. TRS is defined as a history of at least two antipsychotic trials (one of them an atypical antipsychotic) with adequate doses administered at a 4–6 week period, without satisfactory responses, particularly in terms of persistent psychotic symptoms (9). The aim of this case report is to present the successful management of treatment-resistant schizophrenia in a persistently non-compliant patient using a combination of typical and atypical LAI antipsychotics.

Case report

The patient was a 34-year-old single man. He was raised by both parents, and there was no family history of mental illness. The patient had secondary education, and he was employed in Zinc Works until 2010. There was no history of alcohol or drug use. He has been treated since 2009 with a diagnosis of schizophrenia. The course of the disease was unstable, and exacerbations were mainly caused by the irregular intake of medications. Because of this fact, he was hospitalized many times, and his hospital stay lasted up to several months. The main reasons for repeated hospitalizations were disorderly behavior and aggression.

The patient was first hospitalized in a psychiatric unit in 2009 for aggressive behavior; he was aggressive with his parents and had attacked a paramedic. The patient claimed to be a trained special agent. The first symptoms were observed by his family 2 years prior, and he had become withdrawn and had broken off all contact with his friends. He used offensive language in contact with family. Perphenazine enanthate was used in his treatment, and the patient responded well to the therapy. His second hospitalization was in 2011 under similar circumstances. Treatment was attempted with risperidone and amisulpride, but there was no response. Finally, improvement was obtained with the use of quetiapine. His third hospitalization took place in January 2021. The patient received olanzapine LAI and valproic acid. However, after being discharged from the hospital, he discontinued his injections.

On 13 March 2021, he was admitted to the psychiatric department with a history of attacking people in the street, for which he was apprehended by the police. In the physical examination, obesity (BMI, 30.5 kg/m^2) and cutaneous purulent changes in the armpit area were noted, but no significant abnormalities were observed. The patient's blood pressure and heart ratio were normal. There were no abnormalities in the neurological examination. The patient negated somatic diseases except for acne inversa. In the patient's mental state examination at admission, he was noted to be conscious, oriented in time, place, and person, with normal psychomotor activity. He demonstrated signs of blunted affect, and he reported passivity experiences, saying that others could manipulate drug levels in his blood with radio waves, thus changing his moods. Additionally, he reported delusions of reference. Other abnormalities of thought included loose associations and paralogical thinking: He said that he could not be arrested because "if someone is detained illegally the building will collapse" and "This is the theory of construction." Furthermore, the patient denied attacking another person. Hallucinations or suicidal ideations were not observed. He scored 90 points on the Positive and Negative Syndrome Scale (PANSS) (Table 1). There were no abnormalities in blood tests, except for hypercholesterolemia and hypertriglyceridemia. Considering the long-term course of the disease, frequent recurrences of episodes with acute psychotic symptoms and significant behavioral disturbances, including behaviors potentially dangerous to others, it would seem that clozapine could be the drug of choice in such a situation.

However, clozapine was finally not considered a therapeutic option because of non-adherence (irregular controls in outpatient clinics) in the patient's previous history. So, the patient was treated with 300 mg of olanzapine LAI

TABLE 1 The PANSS score before and after the intervention with two LAIs.

Symptoms	Score before the intervention	Score after the intervention
P1 Delusions	7	1
P2 Conceptual disorganization	5	3
P3 Hallucinatory behavior	2	1
P4 Excitement	3	1
P5 Grandiosity	3	1
P6 Suspiciousness/persecution	3	1
P7 Hostility	3	1
N1 Blunted affect	3	3
N2 Emotional withdrawal	5	5
N3 Poor rapport	4	4
N4 Passive/apathetic social withdrawal	5	5
N5 Difficulty in abstract thinking	4	4
N6 Lack of spontaneity and flow of conversation	2	3
N7 Stereotyped thinking	3	2
G1 Somatic concern	1	1
G2 Anxiety	1	1
G3 Guilt feelings	1	1
G4 Tension	1	1
G5 Manierisms and posturng	1	1
G6 Depression	1	1
G7 Motor retardation	1	1
G8 Uncooperativeness	2	1
G9 Unusual thought content	5	2
G10 Disorientation	1	1
G11 Poor attention	2	2
G12 Lack of judgment and insight	5	2
G13 Disturbance of volition	2	1
G14 Poor impulse control	5	1
G15 Preoccupation	3	2
G16 Active social avoidance	3	3
Total	90	57

fortnightly due to good response history and tolerance to such treatment. In addition, the patient received diazepam orally at 15 mg doses/day and haloperidol orally at 15 mg doses/day. This treatment continued for several weeks, and a second antipsychotic (zuclopenthyxole) was added because of the persistence of constant delusions, labile affect, and aggressive behavior tendencies. Valproic acid was not considered due to his obesity. Initially, zuclopenthyxole was administered orally at a dosage of 75 mg/day. After 4 weeks of combined treatment, his mental state improved. There was no report of delusions, the mood of the patient was much more stable, and awareness of his symptoms was better. A temporary increase in aspartate transaminase (40, 8 U/L) and alanine transaminase (67, 2 U/L) was observed. Other blood tests and ECG reports came up with normal volumes. Zuclopenthyxole was switched to a depot form due to persistent non-compliance in previous treatment, poor insights, and the risk of being aggressive to other people. Zuclopenthyxole decanoate in 200 mg doses was administered fortnightly. The patient was discharged from the hospital on the 70th day of hospitalization. In the examination of his mental state, he was noted to be conscious and oriented in time, place, and person, with normal psychomotor activity. Blunted affect was reported. He did not report any delusions or hallucinations and did not present suicidal ideations. The patient's clinical state presented negative symptoms, of which avolition and diminished social activity were dominant. The total score was 57 points on the PANSS (Table 1). No significant abnormalities in blood tests or ECG were found. The patient tolerated the treatment well. Sedation and extrapyramidal symptoms were not observed. The patient continued taking the injections alternately (one injection per week) to obtain regular visits to the outpatient clinic. The patient received rosuvastatin at a dose of 20 mg/day and dietary recommendations (reduction of monosaccharides and animal fats) due to dyslipidemia. There were attempts to introduce individual and family therapy; unfortunately, they constantly failed. Due to the disturbances in the structure of thinking with its distinct rigidity, the therapy and psychoeducation attempts did not bring any results. Additionally, all attempts at rehabilitation procedures offered by social help were rejected by the patient. Currently, the patient remains under the care of a psychiatric outpatient clinic outside our unit; therefore, further history is unknown.

Discussion

There are few reports in the literature on the use of combined LAI antipsychotics in treatment. This case report presents the treatment of a patient with a severe and unstable course of the disease accompanied by a lack of cooperation, which resulted in aggressive behavior toward other people. The previous treatment administered to this patient seemed to be insufficient, leading to incomplete remission of symptoms, and above all, it did not alleviate dysphoria and did not improve the patient's insight. Incomplete remission and the patient's negative attitude toward the treatment resulted in permanent discontinuation of medicines, which in turn led

to a rapid deterioration of the mental state and subsequent aggressive behaviors. In the context of the above information, the patient started to be treated through a combination of two LAI antipsychotics and obtained significant clinical benefits. The combined LAI therapy was safe and well-tolerated. Better tolerance can result from the more predictable pharmacokinetics of LAI antipsychotics compared to the oral form. Side effects related to the daily peak concentration may be eliminated (10).

As a rule, the calculation of total doses for oral vs. LAI antipsychotics will usually show lower doses for the LAI (6). The data imply that there are no significant differences between LAI and oral antipsychotics regarding the risk of death (excluding suicide and accident), any extrapyramidal side effects, QTc average change, and abnormality in blood tests (11).

The basic clinical indications for LAI antipsychotic treatment in schizophrenia are as follows: unsatisfactory clinical improvement, unsatisfactory functioning improvement, and high risk of recurrence (among others: rehospitalization during the period of <12 months, interruption of oral pharmacotherapy lasting more than 2 weeks) (12). Treatment guidelines do not address combining two LAI antipsychotics. Hence, when deciding whether to use two neuroleptics at the same time, it is important to make decisions with a team of doctors, closely monitor the patient's condition, and conduct thorough documentation. When a patient does not adhere to required laboratory monitoring, clozapine cannot be an option in the management of treatment-resistant schizophrenia. In this case, it is possible to consider the combination of two LAI antipsychotics (13). In the literature, only a few case reports can be found detailing the use of combined application of typical and atypical LAI antipsychotics (14–16). In all cases, significant improvement and no adverse effects were reported.

McInnis et al. used a combination of two LAI antipsychotics in three cases of adolescents with severe psychosis and aggression (17). The research showed that the combination of LAI antipsychotics may be an effective and safe therapeutic option in adolescents.

In another case series, Fang-Ling et al. described the successful management of treatment-resistant schizophrenia in two patients. They used typical and atypical LAI antipsychotics in an alternating administration sequence. Both patients tolerated this treatment well (18).

Another case report demonstrated that the safety of combined LAI antipsychotic treatment was about the use of three LAI antipsychotics in a patient with a psychotic disorder in the course of Huntington's disease. The patient received haloperidol at a dose of 100 mg, i.m., every 7 days with simultaneous administration of risperidone at a dose of 50 mg, i.m., every 14 days and olanzapine at a dose of 405 mg, i.m., every 1 month. Side effects after administration of LAI antipsychotics were not observed (19). It seems that the use of two long-acting neuroleptics may be helpful in the treatment of drug-resistant, non-cooperative patients who present a risk of aggressive and dangerous behaviors.

Conclusion

Our case report and other cited cases show that the combination of two (or even three) LAIs can possibly be a safe therapeutic option. It seems to be an option in patients with persistent non-compliance, where clozapine is not a viable therapeutic option. Unfortunately, at this moment, there are no studies detailing the safety of the combination LAI treatment. This is an area for further research.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/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

MJ wrote the case report and article. KB-B reviewed the case report and article as senior author. Both authors contributed to the article and approved the submitted version.

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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Acne caused by ziprasidone in a young patient with bipolar disorder: A case report

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Background: Ziprasidone is a second-generation antipsychotic drug commonly used to treat schizophrenia and bipolar disorder. Acne is a common inflammatory disease of sebaceous glands in adolescents that is often co-morbid with anxiety and depression, which may reduce treatment compliance. Through unknown mechanisms, ziprasidone may cause a range of inflammatory responses. Whether ziprasidone can cause acne in young patients with bipolar disorder has not been reported.

Case summary: We report a 23-year-old woman with a 5-year history of bipolar disorder who experienced acne during use of ziprasidone. She was admitted to our hospital during 1-month aggravation of her symptoms and was diagnosed with bipolar I disorder (current or most recent episode of depression) with psychotic features. She was given ziprasidone and soon developed acne, which she never had before; the rash worsened substantially when the ziprasidone dose was increased. At the same time, levels of inflammatory factors increased. The rash resolved after ziprasidone therapy was stopped.

Conclusion: When prescribing ziprasidone to young people with bipolar disorder, clinicians should consider the potential for adverse skin reactions. It may be useful to assay levels of inflammatory markers during ziprasidone therapy and adjust the dose if necessary in order to ensure treatment compliance.

KEYWORDS

ziprasidone, acne, bipolar disorder, adverse reaction, case report

Introduction

Ziprasidone is a second-generation antipsychotic drug commonly used to treat schizophrenia and manic episodes of bipolar disorder (1, 2). Ziprasidone exerts antidepressant effects by acting as a 5-HT/D antagonist, 5HT1D receptor agonist, and inhibitor of norepinephrine/serotonin (3, 4). A systematic review and exploratory meta-analysis concluded that ziprasidone and other second-generation antipsychotics can alleviate depressive symptoms in patients with bipolar disorder (5). Ziprasidone is

generally well tolerated: it is unlikely to alter glucolipid metabolism because it weakly antagonizes the activity of M1 and H1 receptors, it does not substantially affect body weight, and it does not excessively sedate the individual (6–8). Despite its safety and efficacy, ziprasidone often prolongs QTc, which has been associated with higher risk of Torsades de Pointes tachycardia and cerebrovascular events (4, 9). The drug is also associated with extrapyramidal symptoms, headache, and insomnia (10), as well as inflammatory responses that may be related to allergic reactions (11).

Acne is a common inflammatory disease of sebaceous glands in adolescents. It often produces undesired skin lesions and can even disfigure, reducing quality of life. Patients with acne often simultaneously suffer anxiety and depression (12).

We are unaware of reports that ziprasidone can cause acne in young patients with bipolar disorder. Here we describe a young woman with bipolar disorder who developed acne on ziprasidone therapy.

Case presentation

Chief complaints

The patient, a 23-year-old woman, was admitted to our hospital in November 2021 because of alternating episodes of depression and excitement, a condition that had persisted longer than 5 years and had worsened in the preceding month.

More than 5 years before the current admission, our patient began to manifest progressive depression of mood and energy level, loss of interest and ability to concentrate, memory loss, lazy talking, pessimism and negativity, including suicidal thoughts. Within 6 months, loss of appetite led her to lose 5 kg of body weight. At that time, she was hospitalized at our center for 12 days, diagnosed with major depressive disorder (single episode, severe) based on the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (13) and treated with unrecorded doses of sertraline. She was discharged when her condition seemed to be stable with regular medication.

At 4 years before her current admission, she unexpectedly experienced elevated emotions and inflated self-esteem, more positive self-opinion, and decreased need for sleep, with no apparent trigger or explanation. She was also more talkative than usual and sometimes could not stop talking. She would often lose focus in class. These symptoms lasted for about half a year, when she again showed depressed mood, lack of interest, loss of energy, and irritability. She also felt diminished interest in all activities most of the day. Nearly every night, she had difficulty falling asleep. She felt feelings of worthlessness and had recurring thoughts of death. She sometimes stabbed her thighs with a pen when she was upset, and she sometimes hit her head against the wall to vent emotions. She was hospitalized again at our center and was diagnosed with bipolar I disorder (current or most recent episode of depression, severe) based on the DSM-5 (13). She was given sertraline (100 mg, once a day) and quetiapine (0.15 g, once a night), and she was discharged after 14 days of treatment. After discharge, the patient took her medicine intermittently and her condition was unstable: her mood alternated between good and bad over the course of a few days.

At 11 months before the current admission, her outpatient medication was adjusted to sertraline (100 mg, once a day) and quetiapine (0.2 g, once a night), but she still took it intermittently. She became depressed and agitated again, and she felt low energy and would wake up too early. She indicated that she did not want to live anymore, wrote a suicide note, took several sleeping pills of unknown formulation and dose, and cut her wrists. Her parents sent her to a local hospital, where her wounds were sutured and she was also diagnosed with bipolar I disorder (current or most recent episode of depression, severe) based on the DSM-5 (13). She was given sertraline (150 mg, once daily), quetiapine (0.3 g, once per night), and lithium carbonate (0.25 g, twice per day). In addition, she received modified electroconvulsive therapy eight times. She was discharged 3 weeks later, when she showed no significant abnormality by electrocardiography or routine assays of blood, liver and kidney function, electrolytes, inflammatory indicators, or stool. The blood level of lithium carbonate was 5.68 μg/ml (reference value: 4.16–8.32 μg/ml).

At 3 months before the current admission, the patient gained about 4 kg and stopped taking her medication. She became excited, energetic, and sensitive; she began to spend money extravagantly; and she began to believe that others were talking about her. Her medication was adjusted to ziprasidone (40 mg, once a night) and lithium carbonate (250 mg, three times a day). The patient was offered ziprasidone after she indicated that she wanted a medication unlikely to cause weight gain. After 1 week of therapy, scattered papules and pustules appeared on her face, with some exudation. The blood level of lithium carbonate was 4.57 μg/ml (reference value: 4.16–8.32 μg/ml). The QTc interval on electrocardiography was 435 ms (reference value: <470 ms for women). She went to the outpatient dermatology clinic of our hospital, where her levels of inflammatory factors were found to be as follows: tumor necrosis factor-α (TNF-α), 4.3 pg/ml (reference, <8.1 pg/ml); interleukin-1β (IL-1β), 14.1 pg/ml (0–5 pg/ml); interleukin-6 (IL-6), 2.70 pg/ml (0.00–7.00 pg/ml); and C-reactive protein (CRP), 5.02 mg/L (<5 mg/L). She was diagnosed with acne and given vitamin A acid ointment to apply externally and minocycline hydrochloride capsules (50 mg) to take orally twice a day. The rash resolved after 2 weeks of treatment, when the levels of inflammatory factors were as follows: TNF-α, 8.2 pg/ml (reference, <8.1 pg/ml); IL-1β, 12.0

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DRESS, Drug Reaction With Eosinophilia And Systemic Symptoms; TNF-α, Tumor Necrosis Factor-α; IL-1β, Interleukin-1β; IL-6, Interleukin-6; CRP, C-reactive protein. HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale.

pg/ml (0–5 pg/ml); IL-6, 2.80 pg/ml (0.00–7.00 pg/ml); and CRP, 4.80 mg/L (<5 mg/L).

However, the patient remained excited and energetic, easily irritated, sensitive and suspicious. During follow-up in our outpatient department, the dosage of ziprasidone was adjusted to 40 mg twice a day. At this time, her levels of inflammatory factors were as follows: TNF-α, 5.0 pg/ml (reference, <8.1 pg/ml); IL-1β, 10 pg/ml (0–5 pg/ml); IL-6, 3.00 pg/ml (0.00–7.00 pg/ml); and CRP, 6.00 mg/L (<5 mg/L). After 1 week, the patient's facial acne had worsened, with papules and pustules, obvious exudate and pus. The blood level of lithium carbonate was 6.79 μg/ml (reference value: 4.16–8.32 μg/ml). The QTc interval was 447 ms (reference value: <470 ms for women). The dermatology department continued to recommend vitamin A acid ointment and minocycline hydrochloride capsules (50 mg, twice a day).

The patient and her family members felt that the acne was related to her ziprasidone, so she stopped using it. After 2 weeks, the acne improved, and no exudation or pus appeared. However, her mood remained unstable.

At 1 month before her current admission, her condition worsened: she began to show depressed mood most of the day, minimal speech and laziness, pessimism and negativity. She also experienced loss of appetite and insomnia. She could not attend school and had suicidal thoughts; she attempted suicide several times by jumping off a building.

History of past illness

Her medical history included an untreated, currently asymptomatic thyroid nodule that had originally been detected 11 months previously. She had been diagnosed with postural hypotension in January 2021, but she was currently asymptomatic. We found nothing else remarkable in her medical or family history. She denied a history of mental illness in the previous two or three generations, and she denied consuming alcohol or other psychoactive substances.

Physical examination

Physical examination on admission revealed an old suture scar about 3 cm long on the left forearm, scattered acne on the face, and no other obvious abnormality. Neurological examination showed no abnormalities.

Mental examination

Mental examination showed automatic admission, clean and appropriate dress, worried expression, self-care, passive contact, lack of concentration, self-awareness, and normal levels of intelligence and memory. She manifested several characteristics of depressive syndrome: low mood, decreased interest, energy, and activity; insomnia; as well as feelings of helplessness, worthlessness, indecisiveness, and excessive concern for physical health. She indicated a history of symptoms characteristic of manic syndrome: elevated emotions as well as high energy, inflated self-esteem, decreased need for sleep, distractibility, elevated activity, and greater talkativeness than usual. She did not report symptoms of anxiety syndrome, but she did report the following symptoms of hallucination and delusion: sensitivity, suspicion, and the feeling that others were talking about her. She also reported symptoms of sleep disorder, including difficulty in falling asleep, early waking, repeated waking during the night, and excessive dreaming. Impaired social functioning was evident.

Laboratory examinations

The following routine examinations on admission revealed no obvious abnormalities: blood composition, liver and kidney function, electrolytes, tumor markers, pre-transfusion indicators, coagulation function, urine and stool. Levels of inflammatory factors were as follows: TNF-α, 4.5 pg/ml (<8.1 pg/ml); IL-1β, 3.2 pg/ml (0–5 pg/ml); IL-6, 4.00 pg/ml (0.00–7.00 pg/ml); and CRP, 4.2 mg/L (<5 mg/L). Thyroid ultrasonography showed uneven thyroid patterns potentially suggestive of Hashimoto's thyroiditis, as well as bilateral lobular thyroid nodules suggestive of nodular goiter. Computed tomography of the chest revealed small nodules in the lower lobe of the left lung, most likely of inflammatory origin. No obvious abnormalities were found by magnetic resonance imaging of the head, color ultrasonography of the heart or electroencephalography.

Further diagnostic work-up

The patient scored 16 on the Hypomania Checking List-32, indicating a previous hypomania episode; 36 on the 24-item Hamilton Depression Scale (HAMD), indicating major depression; and 15 on the 14-item Hamilton Anxiety Scale (HAMA), indicating anxiety. Her total score on the Brief Psychiatric Rating Scale was 36, and her subscores were 8 for anxiety and depression, 12 for inactivity, 5 for thinking disorder, 3 for activation, and 8 for hostility and suspicion; these results suggested behavioral delay and impaired social functioning. She scored 6 on the Naranjo Causality Scale for determining the likelihood of an adverse drug reaction, indicating probable adverse drug reaction (14).

Final diagnosis

Based on the patient's reported symptoms and test results, the patient was diagnosed with bipolar I disorder (current or most recent episode of depression with psychotic features) according to the criteria in the DSM-5 (13).

Treatment

The patient was treated with quetiapine (0.3 g, once a night), lithium (500 mg twice a day), and agomelatine (50 mg, once a night). After consultation with the dermatology department, her acne was treated with minocycline hydrochloride capsules (50 mg, twice a day) and application of Bactroban (twice a day). During treatment, the patient's mood and her acne condition stabilized. By 2 weeks of treatment, the patient's mood was stable and her acne had improved substantially.

Outcome and follow-up

Follow-up at 3 months after discharge showed normal levels of TNF-α, IL-1β, IL-6, and CRP. She scored 6 on the HAMD, 5 on the HAMA and 5 on the Bech-Rafaelsen Mania Rating Scale. The patient's condition was stable, and acne did not reappear. She can go to school and had good tolerability of the medication. Historical and current information from this episode of care are shown in Figure 1.

Discussion

Acne is a common inflammatory disease of the sebaceous glands, which may be caused by hormones such as insulin, insulin-like growth factor-1, and androgens; bacteria; adipogenesis; or pro-inflammatory lipids (15), which activate Toll-like receptor 2 on the surface of monocytes, triggering the release of pro-inflammatory cytokines (16). Acne manifests as pleomorphic skin lesions such as papules, pustules and nodules, and it usually occurs in teenagers. In fact, acne affects nearly all individuals between 15 and 17 years old to some degree, with negative impacts on their psychological and social life (17). The prevalence of acne tends to decrease with increasing age (18), although it can still occur in young adults. Bipolar disorder may lead to abnormal lipid metabolism through mechanisms involving inflammatory responses or altered insulin sensitivity, leading to acne (19). The age of our 23-year-old patient did not place her at high risk of acne, but her bipolar disorder may have.

Many drugs can cause acne, and such drug-induced acne often shows sudden onset and involves a rash of simplex inflammatory papules or papular pustules; patients can vary widely in age at onset. Drug-induced acne is typically diagnosed based on review of medical history while taking into account drug efficacy, treatment schedule and duration, as well as improvement after drug withdrawal in the absence of additional triggers (20).

Lithium carbonate is a mood stabilizer often used to treat bipolar disorder. Long-term use of lithium or high levels of it in the blood may lead to various skin diseases, such as psoriasis and acne, predominantly in men (21). Lithium-associated acne usually occurs after 2–6 months of lithium therapy (20, 22). Although our patient had a history of lithium carbonate therapy lasting more than 6 months, it did not trigger acne during hospitalization or follow-up. In addition, the level of lithium carbonate in her blood was in the normal range, and as a female, she was inherently at lower risk of lithium-associated acne. Therefore, we do not believe her acne was related to her lithium carbonate treatment.

Ziprasidone binds strongly to D2, D3, and α1-adrenergic receptors, and with lower affinity to 5HT2A, 5HT2C, and 5HT1D receptors. It also behaves as an agonist at the 5HT1A receptor (3, 4). Therefore it is commonly used to treat schizophrenia, bipolar disorder and depression. It shows only moderate affinity for the H1 receptor and does not show a clinically relevant interaction with the M1 receptor, implying minimal effects on metabolism or body weight (4, 23). On the other hand, it prolongs QTc, which may increase the risk of death and cerebrovascular events (4, 9) and can cause inflammatory allergic reactions (11), perhaps by promoting cell proliferation and the spread of macrophages through the blood; increasing levels of oxidizing molecules such as nitric oxide, superoxide, and reactive oxygen species; increasing the levels of proinflammatory cytokines TNF-α, interferon, IL-1, and IL-6; and regulating the expression of cytokine genes.

Our patient had a long disease course and repeatedly went to the doctor to adjust her medication, but she had no history of acne. Acne began to appear only after she began to take ziprasidone, and it worsened after the dose increased, which coincided with an increase in levels of inflammatory factors. The acne improved after ziprasidone therapy was stopped, and at the same time, the levels of inflammatory factors returned to normal. In addition, our patient developed a rash after combined administration of ziprasidone and lithium carbonate, and the rash worsened substantially after an increase in the ziprasidone dose, while it resolved after termination of ziprasidone. Given that our patient did not suffer rash when she took lithium carbonate alone, and given the timing between ziprasidone use and acne onset, we believe that the acne in our patient was the result of inflammatory responses caused by ziprasidone. Future studies should examine whether combining ziprasidone with lithium carbonate increases the risk of acne.

One case report has linked ziprasidone to subacute cutaneous lupus erythematosus (24). The US Food and Drug Administration has warned that ziprasidone may be associated with a rare, potentially fatal skin reaction called "drug

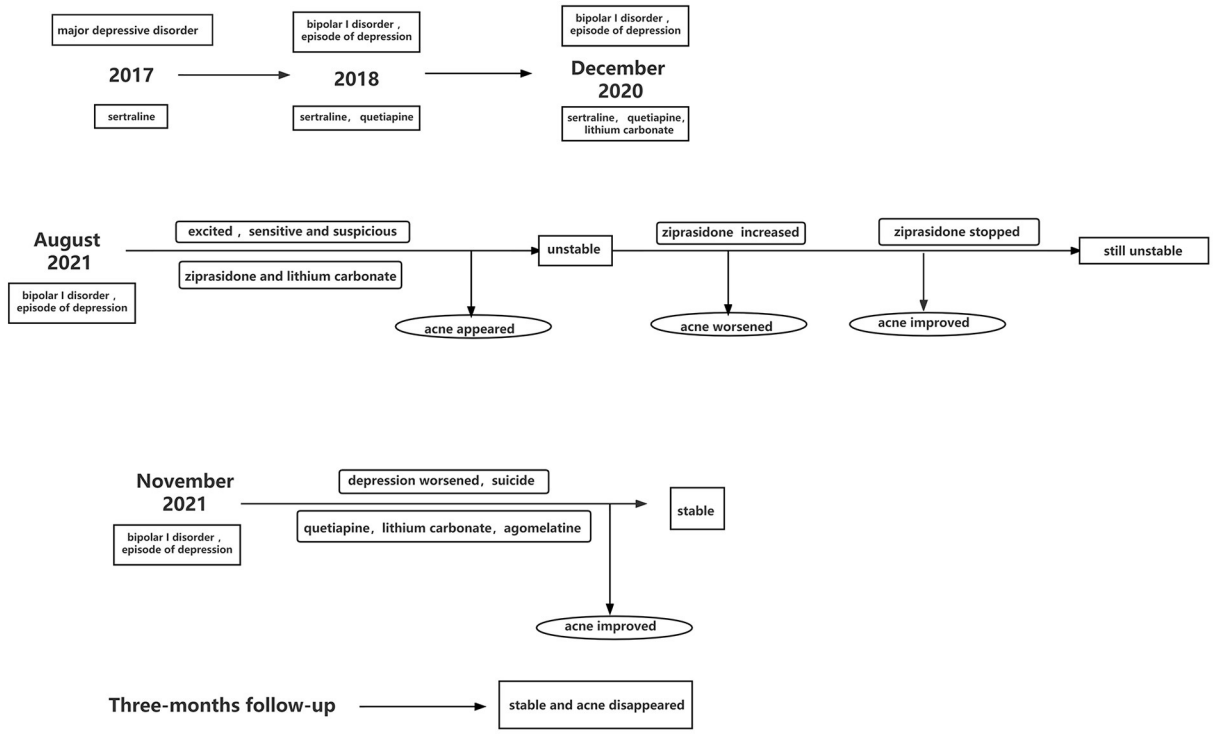

FIGURE 1
Historical and current information from this episode of care.

reaction with eosinophilia and systemic symptoms" (DRESS). Symptoms of DRESS include fever, lymph node enlargement and inflammation of other organs such as the liver, kidney, lung, heart or pancreas (25). In contrast, our patient had normal eosinophil findings, and she showed no fever, lymph node enlargement, or other manifestations of inflammation in liver, kidney, lung, heart or pancreas. Our case highlights the need to clarify how ziprasidone may contribute to adverse skin reactions in patients with bipolar disorder.

Bipolar disorder has been linked to several physical comorbidities, such as cardiovascular disease, hyperlipidemia, metabolic disease, chronic pain, asthma, diarrhea, and acne (19, 26). Acne can easily be overlooked as an indicator of bipolar disorder, since the most frequent somatic comorbidities are cardiovascular disease, metabolic syndrome, migraine and infectious disease (27). Acne has also been reported as a co-morbidity in individuals with anxiety disorder or depression disorder (28). Psychiatric disorders may cause dermatosis because psychological stress hyperstimulates the amygdala, which activates the hypothalamic-pituitary-adrenal axis, stimulating release of pro-adrenocorticotropic hormone-releasing hormone, which in turn triggers degranulation in mast cells and permeabilizes the vasculature, ultimately leading to skin inflammation (29). Our case highlights the need to pay attention to the possibility of acne or other skin diseases in patients with bipolar disorder, in addition to the more frequent co-morbidities of cardiovascular, metabolic and other somatic diseases.

Optimizing treatment should take into account the patient's perspective (30, 31), especially since psychological distress in the patient can lead to dissatisfaction with treatment and lack of compliance (32). Our patient was satisfied while using ziprasidone, which she was recommended after indicating her desire for a medication unlikely to cause weight gain. However, she felt distressed when scattered papules and pustules appeared on her face while on the drug, and when these symptoms worsened after the dose was increased. During this treatment, we provided information about the nature and causes of bipolar disorder, medication, side effects and how to cope with daily problems. She remained satisfied with the treatment and showed good compliance.

Conclusion

Acne should be considered as a potential adverse reaction when administering ziprasidone for bipolar disorder, especially to young patients. Inflammatory indicators should be checked during treatment, and the regimen should be adjusted if acne

occurs in order to ensure treatment compliance and avoid harm to the patient's psychological state or more serious outcomes.

Data availability statement

All the data on which the conclusions of this study are based are included in this article. Additional data is available from the corresponding author on reasonable request.

Ethics statement

Written informed consent was obtained from the patient and her parents for the publication of any potentially identifiable data in this article.

Author contributions

YY and XL wrote this case report. XJ, ZhiL, and YO provided clinical advice on patient management and contributed important intellectual content to the case report. ZheL was the patient's lead clinician and edited the case report for intellectual content. All authors approved the published version of the case report.

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Conflict of interest

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

Publisher's note

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Symptoms of exhibitionism that regress with bupropion: A case report

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Exhibitionistic Disorder, one of the paraphilic disorders, is a disease with an unknown etiology and causes significant distress and loss of function in the patient's life. Serotonergic antidepressants are generally preferred in the treatment of this Disorder. However, in this case, we report a patient who did not respond to serotonergic antidepressants but bupropion, an antidepressant with dopaminergic and noradrenergic activity. Therefore, bupropion should be considered a medical treatment alternative in case serotonergic antidepressants do not work efficiently in the treatment of Exhibitionism.

KEYWORDS

exhibitionistic disorder, treatment, bupropion, serotonergic antidepressants, dopaminergic activity

Introduction

Exhibitionism, one of the paraphilic disorders according to DSM-5, is a disease characterized by repetitive, sexually stimulating, intense fantasies, urges, or behaviors related to displaying the genitals to a stranger who does not expect such action for at least 6 months. It causes clinically substantial discomfort or function distortion in social, occupational, educational, or personal areas (1).

Paraphilic disorders and hypersexual behavior can be examined as behavioral disorders in the possible categorization of impulsivity and compulsivity endophenotypes as impulsivity-compulsivity disorders as a transdiagnostic psychopathological dimension together with Obsession Compulsion Related Spectrum Disorders, Substance/Behavioral Addictions, Disruptive/Impulsive Behavior Disorders. In response to the question of why impulsivity and compulsions cannot be stopped in various psychiatric disorders, it is stated that it may be due to a problem in the cortical circuits that suppress these behaviors. Impulsivity and compulsivity are hypothetically "bottom-up" neurobiological impulses, impulsivity originates from the ventral striatum, compulsivity from the dorsal striatum, and different areas of the prefrontal cortex try to suppress these stimuli "top-down" (2).

There have been case reports and studies conducted on clomipramine (3–5), fluoxetine (6, 7), fluvoxamine (8), paroxetine (9), and trazodone (10), which are antidepressants with significant serotonergic effects that are reported to be effective in the pharmacological treatment of this disorder.

A patient with Exhibitionistic Disorders did not react to serotonergic antidepressants, escitalopram, paroxetine, and sertraline but did respond to bupropion, a noradrenaline and dopamine reuptake inhibitor was addressed in this case report. However, there are no examples of Exhibitionistic Disorders responding to bupropion treatment in the literature, within the knowledge of the author of this case report.

Case

A 33-year-old male patient applied to the psychiatry outpatient clinic with his wife. As a complaint, he stated that he had painful thoughts and sexual impulses of unexpectedly revealing his genitals to persons he did not know in public, which he had difficulty resisting. He claimed that this propensity became apparent in his adolescence, but it was not to a degree of frequency that bothered him until 3 years ago. He stated that his sexually stimulating fantasies and impulses had risen significantly, virtually every day and throughout the last 3 years. At first, he preferred adult women, but then he also started tending to adult males. He admitted to three failed attempts and felt a strong feeling of remorse. He had become less social and presented social withdrawal during these 3 years. Both the patient and his wife expressed concern that he would lose his will and act, that he would get into legal problems due to these thoughts and desires, and that he would be introduced to the media. His wife corroborated her spouse, who explained that he has been married to his wife for 6 years, has a daughter, and has a regular sexual life. The frequency of sexual intercourse, which was three times per week in the first 2 years of their marriage, has dropped to one per week in the last 2 years. The patient's wife stated they had satisfactory intercourse and said she could not understand how such a feeling and behavior developed. The patient claimed that the sexual arousal he had as a result of his thoughts and drives connected to the exhibitionism was far more intense and pleasurable than the traditional sexual intercourse he experienced with his wife and that masturbating soothed him whenever he thought he was about to lose control and take action. When his symptoms began to worsen 3 years ago, he received psychotherapy for 6 months under the supervision and follow-up of a clinical psychologist. However, it did not work, so he began therapy sessions with another psychologist. He stated that there was no substantial change in him. He maintained therapy for 6 months before quitting due to financial reasons. He claimed that he suspected he had excessive testosterone hormone at the time due to the research he did on the internet, so he went to a private laboratory and had a test, but his testosterone level was average. He admitted that, despite being started on escitalopram 10 mg/day by his psychiatrist about 2 years ago, then increased to 20 mg/day a month later and used in this manner for about 6 months, there was no change in his impulses and fantasies, and he had difficulty falling asleep at night for the last 2 years; in addition, there were not any hypomanic symptoms or anything else suggestive of an attenuated mixed mood state accompanying this trouble in falling asleep noted by the patient and his wife. He said another psychiatrist he consulted ceased using escitalopram and started paroxetine 20 mg/day and trazodone 50 mg/day for sleep. He noted that trazodone helped his sleep. Despite the paroxetine 20 mg/day he was taking, there was no apparent reduction in his urges and thoughts regarding exhibitionism. He stated that in the 3-month follow-up, the dose of paroxetine was increased to 30 mg/day, and he used paroxetine at an amount of 30 mg/day for 3 months. When there was no significant effect, the dose of paroxetine was increased to 40 mg/day, but he could only use it for 3 days, and it caused nausea, dizziness, and heart palpitations. Following that, he stated that paroxetine was progressively reduced and terminated by the psychiatrist within a week, and he started taking sertraline 50 mg/day. He noted that the dose of sertraline was increased up to 200 mg/day at the end of 4 months with 1-month control. He was taking this dose for about a year, and he simultaneously started psychotherapy by a psychologist under the guidance of his psychiatrist during this period. The frequency of his impulses and fancies decreased from 7 days to 4–5 days per week. However, there was no substantial reduction in the intensity of his whims and fantasies and, therefore, the distress he caused himself.

His medical history did not reveal any remarkable features. He was not a smoker. He did not do any drugs. He said that his alcohol intake was at the level of social drinking, consisting of beer or a single raki with friends. However, he did not consume alcohol during this period since he had not participated in social activities for the previous year. In his family history, he stated that his mother had been using escitalopram for years and that the reason was unknown, but he suspected it was for depressive symptoms. The patient, who worked as a technical staff in a company, stated that he had begun to have mild concentration problems in the last few months, that he sometimes could not perceive what was said, that he forgot immediately even if he perceived it at the time and that both his boss and his colleagues noticed this.

His mood was mildly depressed, and his affection was slightly enhanced in the direction of sorrow, according to his mental state evaluation. Thoughts of guilt and concern about legal issues that could occur in the future predominated his thoughts. No indications of any personality disorders were detected. There was no evidence of perceptual deviation. His orientation was complete, and his memory test results were typical. There was no evidence of a judgment problem, and his understanding was perfect. The total blood count, vitamin B12 level, thyroid function tests, and liver and kidney findings were all within the normal reference range.

Given that the patient had not benefited from the previous selective serotonin reuptake inhibitors (escitalopram, paroxetine, sertraline), it was decided to begin bupropion 150

mg/day, which is from a different group with dopaminergic and noradrenergic effects, rather than trying another antidepressant from the same group. Sertraline was progressively reduced and terminated within a week, while trazodone was maintained in the evening for sleep. After 1 month, the patient said that the intensity and frequency of his fantasies and impulses connected to exhibitionism had diminished substantially. As a result, he felt much better morally. His inability to concentrate and distraction had vanished as if he had been suffering from a shortage of bupropion in his brain for years. When his deficit was remedied, he returned to his senses. One month later, the patient who quit taking trazodone was examined in the outpatient clinic control. He also claimed that his sleep returned to normal and that he had a few days of shallow sleep after quitting the trazodone but that his sleep pattern returned to normal in the following days. The patient was found to be in good health during the third control of the outpatient clinic in the sixth month of follow-up and was recommended to complete the medication therapy for 1 year.

Discussion

The exact etiology of paraphilia and paraphilic disorders is unknown. However, it is suggested that a combination of neurobiological, interpersonal, and cognitive processes may be involved. In Impulsive and Compulsive Disorders, including paraphilic disorders, neuroanatomically impulsivity and compulsivity map to different neuronal loops: impulsivity is a ventral striatum-dependent action-outcome learning system, whereas compulsivity is a dorsal striatum-dependent habituation system. Stimuli initiate many behaviors in the ventral loop of motivation and reward. Over time, some of these behaviors migrate to the dorsal region through a series of neuroadaptations and neuroplasticity and become habitual, meaning that impulsive behavior eventually becomes compulsive. These information spirals, which pass from one neuron cycle to another, receive regulatory inputs from the hippocampus, amygdala and other prefrontal cortex areas. Low-dose slow-release stimulants may improve people's ability to say no to an impulsive request by increasing dopamine and decreasing impulsivity in the Orbitofrontal Cortex (OFC) circuit, which is part of the prefrontal cortex (11). In our case, it was observed that the impulsive tendencies of the person decreased, and his willpower strengthened with the slow-release form of bupropion.

Dopamine may have a significant role in paraphilic disorders, according to a recent study focused on the function of neuronal transmission in these diseases. The study's researchers point out that a decrease in the activity of the dopaminergic system probably causes stereotyping of behavior and determines the psychopathological peculiarity of paraphilic localization (12). In our case, the patient with exhibitionism, a paraphilic disorder, did not react to serotonergic antidepressants but did respond to bupropion, which has a substantial dopaminergic impact, implies that the neurobiological basis of the disease may get connected to the dopamine system.

Bupropion is an antidepressant that influences noradrenaline and dopamine activity but has little impact on serotonin. Despite case reports of individuals with Exhibitionism Disorder responding to serotonergic medications (3–10), the underlying pathogenic mechanism in some instances, such as ours, may be connected to other neurotransmitters (dopamine and noradrenaline) rather than serotonin.

Although serotonergic monotherapies (Selective Serotonin Reuptake Inhibitors or Tricyclic antidepressants, mainly tertiary amines such as clomipramine, amitriptyline, and imipramine) are indicated as viable alternatives in nonviolent paraphilic disorders (13), antidepressants that primarily operate on the dopaminergic and noradrenergic systems should not be disregarded.

Further clinical research is required to explain the neurobiological mechanisms behind paraphilic disorders in general and Exhibitionistic Disorders in particular and to develop treatments.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/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

The author confirms being the sole contributor of this work and has approved it for publication.

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.

Publisher's note

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Worsening psychosis associated with administrations of buspirone and concerns for intranasal administration: A case report

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Buspirone is commonly used to treat generalized anxiety disorder and demonstrates a limited side-effect profile compared to other anxiolytics. Buspirone is considered generally safe, and neuropsychiatric adverse reactions are uncommon. There are rare clinical case reports that suggest buspirone-induced psychosis. We present a case of buspirone worsening psychosis for a patient psychiatrically hospitalized for an episode of decompensated schizoaffective disorder. The patient had a primary diagnosis of schizoaffective disorder and was treated with antipsychotics during this hospitalization, but his symptoms worsened when buspirone was administered on two separate occasions. During the first trial of buspirone, the patient exhibited traits of increased aggression, odd behaviors, and paranoia. The buspirone was discontinued after the patient admitted to hiding his pills to later consume through nasal ingestion. The second trial resulted in repeated exacerbated symptoms of paranoia related to food and substantially decreased oral intake. Considering its complex mechanism of action, buspirone is suggested to derive its neuropharmacological effects through 5-HT1A receptors. However, the drug also has been found to mediate dopamine neurotransmission. Buspirone acts as an antagonist at presynaptic dopamine D2, D3, and D4 receptors. Yet, contrary to expected outcomes, it was unable to produce antipsychotic effects and instead resulted in a substantial increase in dopaminergic metabolites. The route of administration may also play a role in the enhancement of the buspirone's effects, particularly considering that after first-pass metabolism, buspirone has approximately 4% oral bioavailability. Intranasal administration of buspirone leads to faster drug absorption by direct transport from the nasal mucosa to the brain and increased bioavailability.

KEYWORDS

adverse reaction, anxiolytic, drug abuse, nasal inhalation, methamphetamine, nasal insufflation, psychopharmacology

1. Introduction

Buspirone is a pharmacologically unique azapirone and orally administered drug approved by the Federal Drug Administration (FDA) in 1986 for the treatment of generalized anxiety disorder. Buspirone was originally developed as an antipsychotic drug but was deemed ineffective and found to be more useful for the treatment of anxiety (1). Buspirone also demonstrates a limited side-effect profile when compared to other anxiolytics (1). Buspirone is considered generally safe, with the most common reported adverse reactions being dizziness (9%), sedation (9%), headache (7%), nausea (6%), fatigue (5%), nervousness (4%), light-headedness (4%), dry mouth (3%) diarrhea (3%), depression (2%), paresthesia (2%), excitation (2%), weakness (2%), and sweating/clamminess (1%) (2, 3). Neuropsychiatric adverse reactions are not common (4–9).

There are very few clinical case reports that suspect orally administered buspirone-inducing psychosis. Buspirone is thought to have a slow onset for its anxiolytic effects. However, Friedman reported a case of the onset of delusions within 72 h after the first administered dose of buspirone that resolved within 48 h after stopping buspirone (4). Similarly, Trachman (5) reported psychosis after a single dose of buspirone 5 mg. Two childhood cases were reported after buspirone administration; one was where a patient developed loose associations, thought blocking, and odd behavior, and the other case was with worsening aggression and bizarre behavior (6). A small case series of seven patients investigated the effects of buspirone in patients with schizophrenia with limited conclusions, but ultimately, it appeared that buspirone had the potential to modify concurrent antipsychotic effects and potentially worsen extrapyramidal symptoms (7). There are also reports of buspirone possibly inducing mania (8, 10), and hypomania (9).

2. Case presentation

We present a 33-year-old Black male with schizoaffective disorder – bipolar type, generalized anxiety disorder, stimulant use disorder (methamphetamine type), phencyclidine use disorder, and cannabis use disorder. The patient's illness at baseline includes residual auditory hallucinations but no suicidal or homicidal ideations. Two months before admission, the patient's outpatient medication regimen consisted of valproic acid 1000 mg daily, buspirone 15 mg three times a day, trazodone 50 mg daily, gabapentin 900 mg daily, quetiapine 300 mg daily, and paliperidone palmitate 156 mg intramuscular injections every 4 weeks. The patient's outpatient team reported that the patient frequently nasally ingested his buspirone and had a history of difficulty with medication adherence.

Prior to admission, the patient had abandoned his domicile and 4 days later was found with alcohol intoxication by police and making suicidal statements. The patient was placed on an involuntary psychiatric hold while receiving a medical evaluation. Admission labs were unremarkable except for urine toxicology positive for amphetamines and tetrahydrocannabinol. He was endorsing bizarre and paranoid delusions, such as believing people surrounding him were aliens and demons. Furthermore, he began refusing hospital food, believing that it was poisoned.

On admission to the inpatient psychiatric unit, the patient developed increasing agitation and was offered oral haloperidol 5 mg, lorazepam 2 mg, and diphenhydramine 50 mg. Still, he refused and then later received them *via* intramuscular injections after escalating violence. The patient was offered oral risperidone 2 mg daily to target ongoing psychotic symptoms with diphenhydramine 25 mg nightly; however, the patient refused to accept those medications. He later accepted treatment with oral chlorpromazine 150 mg daily and showed some decrease in agitation.

On the 7th day of hospitalization, the patient requested that his home medication regimen be restarted and complained of uncontrolled anxiety. The patient was initiated on valproic acid 1000 mg daily and buspirone 5 mg three times a day. After 48 h of initiating buspirone, the patient exhibited increased bizarre and paranoid delusions, agitation, homicidal ideations, and disorganized thinking. The patient began refusing his oral medications, claiming he was abducted by aliens and had frequent verbal outbursts toward staff. Chlorpromazine dosage was titrated up to 300 mg daily; however, the patient continued to refuse doses frequently, and his antipsychotic medication was switched to quetiapine XR (extended-release) 300 mg. Valproic acid was also discontinued due to the patient's inability to cooperate with laboratory monitoring. Quetiapine XR was titrated up to 800 mg and then discontinued due to a lack of therapeutic response. The patient was then started on oral haloperidol and titrated to a dose of 10 mg twice daily. After 8 days, buspirone was discontinued as the patient was found to be hiding buspirone in his mouth and later admitted to reserving it for nasal ingestion. Two days after the discontinuation of buspirone, the patient was calm, in behavioral control, and cooperative with the treatment team.

The patient was on a regimen of haloperidol 30 mg daily and benztropine 4 mg daily while awaiting discharge to a locked psychiatric rehabilitation center. During that time, the patient's average daily meal intake was 76%, and his medications were switched from haloperidol to a trial of oral Risperdal and, finally, the administration of long-acting injectable paliperidone palmitate 234 mg.

On hospital day 62, the patient insisted on restarting buspirone for anxiety, which was re-initiated. Two days later, the patient's paranoid delusions about his food being poisoned returned, and his oral intake began to decline significantly. The patient only accepted pre-packaged food during that time, which was a behavioral change compared to the previous. After 4 days, the patient exhibited an increase in aggression. Clinical Global Impressions Severity scale (CGI-S) scored 6 (severely ill) at that time. Buspirone was discontinued on hospital day 72. Over the course of 10 days that the patient received buspirone, his oral intake averaged 32% daily, and he required high amounts of behavioral prompting for feeding. It was noted in behavioral notes during that time that the patient had been found to be nasally ingesting buspirone again. One day after buspirone was discontinued, the patient's meal intake increased to 83%, with adequate oral intake for the remainder of psychiatric hospitalization. In addition, the patient's Clinical Global Impressions Improvement scale (CGI-I) scored 2 (much improved). Ultimately, the patient responded

well to paliperidone palmitate 234 mg intramuscular every 4 weeks, which was continued throughout the remainder of his hospital course. Buspirone was avoided for the remainder of the hospitalization, and the patient was discharged to a psychiatric rehabilitation center.

3. Discussion

The patient described had two separate administration windows of buspirone during this hospitalization, both of which appear to have exacerbated the patient's psychosis. Additionally, the patient's presentation to the hospital included decompensated psychosis which may have been precipitated partly by intranasal buspirone abuse from his outpatient prescriptions. However, the patient also presented with medication non-compliance, alcohol intoxication, and positive urine toxicology for amphetamines and tetrahydrocannabinol; therefore, it is likely that his initial psychosis was multifactorial. During the first hospital administration of buspirone, the patient had worsening of agitation and required multiple administrations of emergency antipsychotics in addition to his scheduled regimen. During the second administration, the patient's paranoid delusions increased, and his oral intake could be used as a metric. Analyzing the average meal intake of the two periods of time immediately before and during the second buspirone administration, a student's one-tailed *t*-test reveals a significant difference: t(53 degrees of freedom) = 4.83, $p \leq 0.0001$. However, when comparing all hospitalization days of oral intake regardless of which buspirone window, there is only borderline significance that oral intake is worse on days that buspirone was administered: t(85 degrees of freedom) = 1.43, $p = 0.08$. The Naranjo (11) adverse reaction scale score was 5, indicating a probable cause between buspirone use and psychosis.

There are very limited reports between the use of buspirone and the worsening of psychosis (4–7, 12), and there are currently no conclusive reports on this reaction. Like earlier case reports published that suggest an association between psychosis and buspirone, our patient experienced worsening psychotic symptoms, including delusions, impaired thought process, hallucinations, and disorganized behavior. However, this cannot be concretely concluded as a direct result of buspirone alone due to the patient's underlying diagnosis of schizoaffective disorder. Despite this, due to the chronological association of buspirone exposure with the patient's exacerbated symptoms, it appears most likely that buspirone had a pathological influence. Diagnostically, the patient described is unable to meet the DSM-5-TR criteria for substance/medication-induced psychotic disorder due to his underlying schizoaffective disorder. Interestingly, the patient described does meet the DSM-5-TR diagnostic criteria for "other substance intoxication with perceptual disturbances" (ICD-10 code F19.122). If this adverse reaction is suspected in the future by other clinicians, it may be revealing to obtain serum levels of buspirone while psychosis is occurring, in addition to obtaining an objective and validated scale to measure psychosis, such as the Positive and Negative Syndrome Scale (PANSS).

Considering its primary mechanism of action, buspirone derives its neuropharmacological effects through 5-HT1A receptors. However, the drug also has been found to mediate dopamine neurotransmission. Initially developed as a neuroleptic, buspirone acts as an antagonist at presynaptic dopamine D2, D3, and D4 receptors, yet contrary to expected outcomes, it was unable to produce antipsychotic effects (13) and instead results in a substantial increase in dopaminergic metabolites such as homovanillic acid, norepinephrine (also from stimulation of the locus coeruleus) and its metabolite 3-methoxy-4-hydroxyphenylglycol (4, 9, 14). By inhibiting presynaptic rather than postsynaptic dopamine receptors, buspirone enhances dopamine neurotransmission by increasing the firing rate of dopamine neurons in the midbrain, similar to the mechanisms seen in the development of psychosis in schizophrenia (15). Therefore, it is possible that the worsening of psychosis while on buspirone may be due to its ability to manipulate the dopaminergic systems (16).

The route of administration may also enhance buspirone's effects, considering that after first-pass metabolism, buspirone has approximately 4% oral bioavailability (17). Although the pharmacokinetics of oral buspirone are well known, there is currently limited data about intranasal bioavailability. In Swigart (18) described a case of buspirone abuse by nasal insufflation. A study in which buspirone hydrochloride nanovesicular *in situ* gel was administered intranasally was shown to prolongate its release and increase its bioavailability, allowing for a longer duration between doses (19). This may be due to the highly vascularized nature of the nasal mucosa, larger surface area, and porous endothelial membrane as well as bypassing the first pass effect as buspirone is metabolized by the hepatic enzyme cytochrome P450-3A4 (20, 21). In a study of a buspirone nasal drug delivery system, it was found that nasal administration led to 2.10 times increase in its bioavailability (19). This demonstrates that intranasal administration of buspirone leads to faster drug absorption by direct transport from the nasal mucosa to the brain (22). Intranasal administration of buspirone has been more commonly seen in prisons (23). It is reported that patients compared the sensation they receive from nasally inhaling buspirone to a euphoric feeling that can begin within minutes to an hour of receiving the drug (23).

4. Conclusion

Although buspirone is a generally safe anxiolytic azathioprine drug, it appears to have a rare adverse reaction of exacerbating psychosis in some patients. This may be associated with the intranasal administration of buspirone, resulting in increased bioavailability, which is more commonly seen in patients with stimulant use disorder and incarceration history.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Kern Medical Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SA, RC, FH, KE, DW, and TT wrote the manuscript and formulated the analysis. All authors contributed to the article and approved the submitted version.

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 series: Continued remission of PTSD symptoms after discontinuation of prazosin

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Post-traumatic stress disorder is a debilitating chronic illness that affects 6 out of 100 adults after a severe trauma. The alpha-adrenergic antagonist prazosin, which is prescribed off-label for flashbacks and nightmares due to trauma, is often continued indefinitely due to reports of symptoms returning upon discontinuation. There is no standard guidance for a trial of discontinuation of prazosin due to intolerance or side effects. In this case series, three patients are started on prazosin leading to remission of trauma-related symptoms, and symptoms continue to remit after treatment for an average of about 2 years followed by discontinuation of the medication. There are many similarities in these case reports which serve to provide guidance as to when a trial of prazosin discontinuation may be warranted.

KEYWORDS

post-traumatic stress disorder, prazosin, trauma, nightmares, flashbacks, psychopharmacology

Introduction

Post-traumatic stress disorder (PTSD) is a chronic illness defined as more than 1 month of intrusion symptoms, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity in response to exposure of a severe trauma to death, serious injury, or sexual activity (1). According to the Veteran Affairs, about 6% of the population will experience PTSD at any point in their lives.

Prazosin is a centrally acting alpha 1-adrenergic receptor antagonist often used off-label to counteract the hyperarousal and adrenergic dysregulation seen in PTSD. The medication has been shown to effectively reduce the effects of increased systemic norepinephrine release and norepinephrine receptor sensitivity seen in PTSD (2). By extension, the reduced effect of norepinephrine is theorized to also dampen the increased startle and fear responses and improve sleep quality. Improved sleep is especially significant as 70%–87% of patients with PTSD experience sleep disruption and 60%–90% experience insomnia (3, 4). Despite being documented as beneficial for many patients, there is some controversy regarding the effectiveness of prazosin. Raskind et al. and other advocates believe strongly that clinicians should consider prazosin, although one of their clinical trials showed no improvement in nightmares or sleep quality (5). In this trial, it was thought that selection bias of clinically stable patients less likely to benefit from prazosin possibly played a role, as well as the lack of screening for sleep apnea or sleep-disordered breathing which can mask beneficial effects of prazosin (5).

While the reduction of PTSD-related nightmares has been well-documented, there appears to be a return of nightmares upon prazosin discontinuation in trials (6). In a systematic review

by Kung et al., it was noted that in several randomized controlled and open label studies, there were regular reports of distressing nightmares returning after discontinuation of prazosin (6); however, there are no reports to our knowledge documenting clear and consistent remission of nightmares after prazosin discontinuation. Unfortunately, the longest clinical trial for prazosin treatment of nightmares is 20 weeks, which may not be long enough of a treatment period for prazosin to have long-lasting effects (6).

In this case series, three patients with PTSD-related nightmares are treated successfully with prazosin and their nightmares do not return upon discontinuation of prazosin. We propose theories on the successful discontinuation of prazosin for these patients which may serve as a guide for clinicians planning to trial discontinuation of the medication due to side effects or intolerance.

Case presentations

Case 1

A female in her late 50's with a past psychiatric history of major depressive disorder (MDD) and PTSD presented to the outpatient psychiatry clinic for treatment of depression. She endured daily crying spells, hopelessness, anger, hypervigilance, avoidance of trauma cues, flashbacks of prior trauma, nightmares, insomnia, and chronic passive suicidal ideation. She had a history of prior physical, sexual and verbal abuse. Her baseline Patient Health Questionnaire-9 (PHQ-9) was 18 out of 27 and she met criteria for MDD and PTSD. The patient had tried paroxetine for MDD/PTSD in the past, but it was discontinued due to jaw clenching. Her primary care physician started duloxetine 60 mg 4 months ago but she stopped taking it 2 months ago when she started noticing jaw clenching again. Her only psychiatric medication at intake was hydroxyzine 25 mg at bedtime as needed for insomnia. She had started weekly trauma-therapy 3 months prior and felt it was helpful. The psychiatrist recommended a retrial duloxetine at a low dose to target depression, PTSD, and chronic pain, but the patient declined. To target trauma-related flashbacks and nightmares, the psychiatrist prescribed prazosin 1 mg twice daily and continued hydroxyzine 25 mg at night as needed for insomnia. Her baseline blood pressure 2 days prior was 118/84 millimeters mercury (mmHg) and pulse was 78 beats per minute (bpm). Four blood pressures measurements were obtained over the prior month and blood pressure was stable per her primary care physician: the lowest was 110/78 mmHg and the highest was 134/97 mmHg.

Two weeks later, the patient presented to the clinic and reported only taking prazosin at night because she overslept the first morning and ended up deciding not to take the morning doses. Overall, the patient felt better and denied passive suicidal ideation. She denied nightmares since starting prazosin, but still reported flashbacks. She denied dizziness, lightheadedness, or any other side effects. She was agreeable to take prazosin 1 mg twice a day to treat flashbacks and agreed to start duloxetine 20 mg daily. Four months later, the patient denied flashbacks, nightmares, avoidance, or hypervigilance related to trauma. She denied side effects from prazosin and felt she no longer needed hydroxyzine for sleep. Blood pressure and pulse were measured as 111/77 mmHg and 89 bpm. Prazosin 1 mg twice daily and duloxetine 20 mg daily were continued. Blood pressure and pulse was measured monthly by the patient's primary care physician over the following year: the lowest blood pressure over the following year was 107/75 mmHg and highest was 127/85 mmHg.

One year after starting prazosin 1 mg twice daily and duloxetine 20 mg daily, the patient requested to reduce her total number of medications and prazosin was decreased to 1 mg at bedtime. Her PHQ-9 at that time was 0. Blood pressure and pulse were measured as 127/82 mmHg and 77 bpm. Five months later, she denied recurrence of nightmares or flashbacks, was handling stressors in her life more effectively, and requested to stop prazosin completely. Prazosin was stopped, and duloxetine 20 mg daily and weekly trauma therapy were continued. Two years and 8 months after completely discontinuing prazosin, the patient continued to deny depression, flashbacks, nightmares, or other symptoms of PTSD. Her PHQ-9 score was maintained at 0.

Case 2

A female in her early 70's with a past psychiatric history of major depressive disorder and anxiety presented to the outpatient clinic for symptoms related to traumatic deaths of her son and husband over 10 years ago. She endured flashbacks and nightmares of prior trauma, hypervigilance, and avoidance of trauma cues. She denied symptoms of depression but at times felt life was not worth living when thinking about her trauma. Her baseline PHQ-9 was 5 out of 27 and she met criteria for MDD in partial remission and PTSD. In the past she took alprazolam 1 mg at bedtime for insomnia which reduced the frequency of her nightmares. Her psychiatric medications at intake included citalopram 60 mg daily for PTSD and quetiapine 25 mg at bedtime for insomnia. The psychiatrist continued her current medications and started prazosin 1 mg twice daily to target trauma-related flashbacks and nightmares. Her baseline blood pressure at this visit was 125/73 mmHg and pulse was 62 bpm. Blood pressure obtained a week prior was 128/72 mmHg and stable per her primary care physician. Trauma-focused therapy was also recommended, but the patient declined.

About 1 month after starting prazosin, the patient reported dizziness with blood pressure of 97/63 mmHg and pulse 62 bpm at her primary care physician's office, so the psychiatrist discontinued the morning dose of prazosin and recommended a cardiology consultation. One month later, she reported a decrease in trauma-related nightmares with prazosin 1 mg at bedtime and denied dizziness. Her blood pressure was 126/64 mmHg and pulse was 61 bpm. She continued to report flashbacks and requested alprazolam for anxiety related to this. The psychiatrist increased prazosin to 2 mg at bedtime for nightmares and recommended monthly blood pressure monitoring. In addition, alprazolam 0.5 mg was prescribed daily as needed for anxiety. Citalopram 60 mg was changed to escitalopram 30 mg at bedtime to address concern of QTc prolongation per the cardiology consult.

Two months later, the patient reported that nightmares were "80% gone" with the increase in prazosin, and she denied dizziness or hypotension. She continued to report flashbacks but felt she could manage triggers without therapy. She continued to take alprazolam 0.5 mg daily as needed for anxiety about once per week after trauma cues and felt it was helpful. Her PHQ-9 at this visit was 1 out of 27 and her blood pressure was 120/67 mmHg. Prazosin was increased to 3 mg at bedtime for nightmares. Fourth months later, the patient denied

nightmares and did not feel she needed quetiapine at night which was discontinued at this visit. Her blood pressure was 113/68 mmHg and continued to be measured monthly. About a year after starting prazosin 3 mg at bedtime, the patient reported increased flashbacks. She requested to try prazosin 1 mg daily in addition to 3 mg at bedtime (4 mg per day). Her blood pressure was 149/80 mmHg and pulse 88 bpm. She reported shortly afterwards that her flashbacks had stopped.

Four months after taking prazosin 1 mg daily and 3 mg at bedtime, the patient had a kidney biopsy after diagnosis of a kidney mass, and prazosin was discontinued after hemothorax and hypotension complications in the hospital. Prior to this hospitalization, her blood pressure was measured as 142/84 mmHg and it was unclear if prazosin contributed to the hypotension. She denied the return of nightmares or flashbacks after prazosin was discontinued. One and a half years after discontinuing prazosin, the patient continued to deny flashbacks, nightmares, or other symptoms of PTSD. Her PHQ-9 score was 0.

Case 3

A female in her late 50's with a past psychiatric history of major depressive disorder and generalized anxiety disorder presented to the outpatient psychiatry clinic for poor sleep and symptoms related to past trauma. She reported nightmares with fear of going to sleep, flashbacks, and anxiety related to prior physical abuse. Her baseline PHQ-9 was recorded as 14 out of 27, 1 month prior by her therapist; however, recorded symptoms were due to nightmares and flashbacks from PTSD. She did meet criteria for PTSD and MDD in full remission. Her psychiatric medications at intake included fluoxetine 20 mg daily for mood, aripiprazole 20 mg daily for mood, and trazodone 50 mg at bedtime as needed for insomnia. She reported the aripiprazole may have caused an occasional tremor but was unsure. The psychiatrist increased her fluoxetine to 30 mg daily for PTSD symptoms and started prazosin 1 mg at bedtime to target trauma-related nightmares. Aripiprazole was continued at 20 mg daily. Her most recent blood pressure was 162/70 mmHg and pulse 68 bpm. Her blood pressure the month prior was 151/74 mmHg and stable per her primary care physician. She was already in weekly trauma-focused therapy and found it helpful. One month after starting prazosin she denied nightmares or flashbacks and reported her sleep had improved. Her blood pressure was 145/85 mmHg and continued to be measured monthly by her primary care physician. She requested the medications be kept the same due to grieving a death in the family at that time.

Eight months after starting prazosin, the patient continued to deny trauma-related nightmares and flashbacks, and only complained about occasional night-time awakenings. Shortly after this appointment, a family member suffered a medical emergency, and she reported new nightmares related to this. Her blood pressure was 162/88 mmHg. Prazosin was increased to 2 mg at bedtime, and 2 months later she denied nightmares, reported sleeping 8 h each night, and her PHQ-9 score was 0. Her blood pressure was measured as 155/86 mmHg. At this visit, the patient complained of worsening hand tremor. She was started on primidone 100 mg twice daily by her neurologist and aripiprazole was slowly tapered to 2 mg daily over the next 2 years due to possible contribution to the tremor. Blood pressure was measured monthly over the next 2 years: the lowest blood pressure was 110/90 mmHg and highest was 162/88 mmHg.

More than 2 years after taking prazosin 2 mg at bedtime, the patient reported flashbacks and nightmares were returning after her boyfriend threatened her. Her blood pressure was 134/78 mmHg. Prazosin was increased to 1 mg twice daily (morning and afternoon) for flashbacks and 2 mg at bedtime for nightmares. One month later she denied flashbacks or nightmares and her blood pressure was measured as 134/72 mmHg. Unexpectedly, all of the patient's psychotropics, including fluoxetine, aripiprazole, prazosin, and trazodone were discontinued and not restarted during hospitalization for somnolence due to possible contribution to the condition. Four months later, she reported some anxiety but denied nightmares or flashbacks. She requested fluoxetine be restarted for anxiety. The psychiatrist prescribed fluoxetine 20 mg daily and trazodone 50 mg at bedtime as needed for insomnia. Ten months after prazosin was discontinued, the patient continued to deny flashbacks, nightmares, or other symptoms related to prior trauma. Her PHQ-9 score was 0. She felt her mood was good while taking fluoxetine and participating in trauma-focused therapy.

Discussion

The primary treatment for PTSD is trauma-informed cognitive behavioral therapy (7). For patients that prefer pharmacotherapy or do not have access to therapy, the medications approved by the Food and Drug Administration for PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine (8). The Veteran Affairs also recommends the SSRI paroxetine and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine (7, 9). Off-label medications for PTSD include anti-adrenergic agents such as prazosin, atypical antipsychotics, and mood stabilizers (10).

Prazosin is an alpha-adrenergic antagonist often prescribed off-label for PTSD-related nightmares. It is worth noting that there is variation in recommendations for how to utilize prazosin for PTSD. In a systematic review of PTSD treatments by Martin et al., prazosin was noted to be first-line recommended treatment for PTSD-related nightmares in two guidelines, while other guidelines recommended it as third-line or provided no guidance at all (11). In addition, the effective dose of prazosin for nightmares tends to vary in case reports from 0.25 mg up to 50 mg daily (12, 13). Recommendations based on guidelines suggest that prazosin be started at a low dose and titrated to an effective range of 3–16 mg/night (14); however, long-term efficacy has not been established. In our case series, one patient's final daily dose of prazosin was 1 mg and the two other patients' final daily doses were 4 mg, divided into two or three doses. Each patient reported a complete resolution in PTSD symptoms at these doses, suggesting that some patients may not require higher doses for prazosin to be effective.

First-dose hypotension is a known phenomenon of prazosin and other alpha-antagonists that leads to postural hypotension and possible syncope after the first dose of the medication. It is more common in patients taking beta blockers or diuretics. This side effect of prazosin has been minimized in PTSD clinical trials by utilizing a small starting dose of 1 mg and slowly titrating by 1 mg every few days (15). None of the patients in our case series experienced first-dose hypotension; however, one patient did experience hypotension and dizziness within a few weeks. In all patients in this case series, there were standing medications that increased risk of hypotension when prazosin was added. In the first case, duloxetine, an SNRI, was added which has additive effects with prazosin and may increase risk of hypotension; fortunately, the patient did not experience any side effects, but blood pressure was monitored monthly. This patient was also taking hydroxyzine 25 mg, but there are no known interactions with prazosin. In the second case, the patient was

taking citalopram (later changed to escitalopram due to concern for QTc prolongation) and quetiapine when prazosin was added twice daily. Quetiapine and prazosin have additive effects and can increase the risk of hypotension including orthostasis and syncope. This patient did experience symptomatic hypotension, likely due to this increased risk, and the prazosin dose was decreased. Prazosin was then able to be more slowly titrated and quetiapine was eventually discontinued. In the scenario of a co-occurring medication with risk of hypotension, it would be better to start prazosin at once daily instead of twice daily and with slower titration. Alprazolam was also added at bedtime which has no known interactions with prazosin. In the third case, the patient was taking fluoxetine, aripiprazole, and trazodone when prazosin 1 mg at bedtime was added. Like quetiapine, aripiprazole also has the increased risk of hypotension when added with prazosin. However, the patient did not have any side effects from the addition of prazosin, likely due to starting at 1 mg and a slower titration. In addition, the dose of aripiprazole was lowered to 2 mg due to tremor as prazosin was titrated, likely contributing to better tolerance of the medication.

In each of these cases, there were multiple similarities which could account for the resolution of flashbacks and nightmares related to PTSD; however, there were also many differences further implicating the import role of prazosin (Table 1). In the first and third case, trauma-based therapy was already in motion before prazosin was even started, which could lead to the resolution of symptoms itself (16). However, the patient in the second case declined therapy and still had resolution of flashbacks and nightmares. The number of years the patients reported experiencing PTSD symptoms prior to starting prazosin varied greatly and did not appear to impact treatment (Table 1). The main similarity between all three cases are prazosin combined with an SSRI or SNRI. In the second and third case, the patients' PTSD symptoms had not resolved fully even after having been prescribed an SSRI prior to the first appointment, suggesting that prazosin has a role to play in reducing these symptoms.

All three patients described nightmares and flashbacks as disturbing symptoms which prazosin has been shown to target. We propose that the increase in serotonin/norepinephrine in the brain responsible for long-term brain changes along with decreased autonomic arousal from prazosin led to resolution of PTSD symptoms. SSRIs increase serotonin in the brain and SNRIs additionally increase norepinephrine, but the exact treatment mechanisms for PTSD are unknown. In a study by Fernandez et al., SSRI treatment increased activation in the dorsolateral prefrontal cortex and supplementary motor area during emotion regulation after 6 months of treatment (17). In comparison, symptom reduction with prazosin occurs within a few weeks by preventing the norepinephrine-induced release of corticotropin releasing factor and reducing flight or fight and startle response (18).

In clinical trials by Raskind et al., the discontinuation of prazosin led to the recurrence of PTSD symptoms; however, the average length of these trials is 8 weeks (4, 5, 19, 20). The understanding of varying prazosin doses on the discontinuation and remission of PTSD are limited currently. The patients in the above cases each achieved continued remission of PTSD symptoms despite varied dosing that ranged between 1 mg nightly to 4 mg daily split between two or three doses, suggesting that a high dose is not needed for remission upon discontinuation. The most significant aspect of the cases in this series are the combination of an SSRI or SNRI with prazosin within an average of 1 to 3 years, which allowed the patients to discontinue prazosin without recurrence of PTSD symptoms. In one study by Ketenci et al., treatment with prazosin increased norepinephrine levels significantly in the amygdala and rostral pons and thus increased GABA, thought to inhibit fear conditioning in stressed rats (21). This was thought to decrease stress and defensive behaviors before a trauma stimulus (21). The clinical trial timeline of 8 weeks is likely not enough time for long-term changes in the brain from prazosin to come to effect. These three cases support that the synergistic effect of SSRI/SNRI with prazosin for about 2 years (average 28 months) prior to discontinuation of prazosin might be enough time for permanent brain changes to persist (Table 1).

A limitation of this case series is that it is a small sample size of patients seen by only one psychiatrist. However, the patients in this case provide unique cases that have not been published in the past regarding successful remission of PTSD symptoms after discontinuation of prazosin. This case series serves to add to the literature of prazosin utilized for treatment of PTSD symptoms and can be used as a guide for discontinuation of the medication. Continued research on the effects of prazosin discontinuation and remission of PTSD is recommended.

Conclusion

This case series involved the treatment of PTSD with recommended psychotherapy and an SSRI or SNRI along with addition of prazosin for distressing arousal symptoms including flashbacks and nightmares. Combining an SSRI or SNRI with prazosin for an average of about 28 months before discontinuation of prazosin may prevent recurrence of

TABLE 1 Comparison of timelines between the three cases.

	Case 1	Case 2	Case 3
Approximate # of years of PTSD symptoms prior to prazosin	51	20	6
SSRI/SNRI prior to prazosin	None	Citalopram	Fluoxetine
Trauma-focused therapy	Yes	No	Yes
Starting prazosin dose	1 mg AM and HS	1 mg AM and HS	1 mg HS
Last prazosin dose	1 mg at HS	1 mg AM and 3 mg HS	1 mg AM, 1 mg in afternoon, and 2 mg HS
Approximate # of months until prazosin discontinued	21	20	42
Approximate # of months of remission after prazosin discontinued	32	18	10

AM: in the morning; HS: at night.

symptoms. This case serves to provide guidance as to when a trial of prazosin discontinuation may be warranted due to intolerance, side effects, or reducing polypharmacy. Further studies would be helpful in elucidating these trends to promote further guidance in how to prevent re-emergence of flashbacks and nightmares due to PTSD after successful treatment.

Patient perspective

Case 2: "I felt fine. I did not have any side effects (from prazosin) … there were no negative effects … it worked over a period of time. It alleviated the nightmares and helped me sleep. Before, I would go to sleep but I would wake with horrific nightmares and would shake from head to toe, and then I would not be able to go to sleep. With prazosin, I wasn't having nightmares anymore for quite a while. I wanted to see if I could go without the prazosin and if they would stay away, and they did. There was no breakthrough. The prazosin took care of nightmares long-term."

Data availability statement

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

Ethics statement

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

Author contributions

CR, JY, JS, and MF contributed equally to the formulation of these cases. All authors contributed to the article and approved the submitted version.

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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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Concomitant medications associated with ischemic, hypertensive, and arrhythmic events in MDMA users in FDA adverse event reporting system

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3,4-Methylenedioxymethamphetamine (MDMA) is currently being investigated as an adjunctive treatment to therapy for posttraumatic stress and other anxiety related disorders in clinical trials. Within the next few years MDMA-assisted therapy is projected for approval by regulatory authorities. MDMA's primary mechanism of action includes modulation of monoamine signaling by increasing release and inhibiting reuptake of serotonin, norepinephrine, and, to a lesser extent, dopamine. This pharmacology affects sympathomimetic physiology. In controlled trials, special attention has been given to cardiovascular adverse events (AEs), because transient increases in heart rate and blood pressure have been observed during the MDMA-assisted therapy sessions. Finding and quantifying the potential drivers of cardiac AEs in clinical trials is difficult since only a relatively small number of participants have been included in these studies, and a limited set of allowed concomitant drugs has been studied. In this study a more diverse set of reports from the FDA Adverse Event Reporting System was surveyed. We found 17 cases of cardiovascular AEs, in which the individuals had taken one or more substances in addition to MDMA. Interestingly, all of those concomitant medications and illicit substances, including opioids, stimulants, anticholinergics, and amphetamines, had been previously associated with cardiovascular AEs. Furthermore, in none of the reports MDMA was marked as the primary suspect.

KEYWORDS

3,4-methylenedioxymethamphetamine, MDMA, adverse events, cardiovascular, schaemia, hypertension, arrhythmia

Introduction

3,4-methylenedioxymethamphetamine also known as MDMA or its street name Ecstasy, is currently a schedule I controlled substance in the United States and the European Union, and a Class A substance in the United Kingdom. There is growing interest in MDMA's utilization in psychiatry based on promising efficacy and safety findings from multiple controlled clinical trials including a Phase 3 study for MDMA assisted therapy for post-traumatic stress disorder (PTSD) (1–5).

MDMA's psychoactive effects are due to its complex pharmacology, including modulation of release and reuptake of serotonin, norepinephrine, and dopamine (6–9), and an increase in oxytocin levels (10). The efficacy of MDMA in PTSD treatment is attributed to supporting fear-extinction learning an increased ability to confront adverse memories, and improved social and interpersonal interactions (5, 11–13).

However, due to the monoamine neurotransmission modulation, cardiovascular physiology may be affected as well (14–16). Arrhythmia-related adverse events (AEs), in addition to hypertensive and ischemia-related AEs have been reported in literature (17–20). In controlled clinical trials in both healthy volunteers and patients with PTSD, AEs of transient increases in blood pressure and heart rate were observed along with muscle tightness, decreased appetite, nausea, hyperhidrosis, and feeling cold (4, 21).

Considering the polypharmacy often present in PTSD populations due to other comorbid conditions such as substance use (22, 23), anxiety (24), depression (25), sleep (26) and pain disorders (27), and the respective treatment drugs, further MDMA AE evaluation is warranted using the FAERS database. This is particularly important since the clinical trials excluded many of these medications, and there is potential for drug–drug interactions (28).

In this study, we evaluated arrhythmic, ischemic, and hypertensive AE reports in MDMA users from the FDA Adverse Event Reporting System (FAERS). These AEs were reviewed in submissions where MDMA was reported to be used alone or with additional therapeutics or illicit substances. The contribution of concomitant drugs and substances to the risk of cardiovascular AEs was evaluated.

Methods

FDA adverse event reporting system

FAERS is a repository of AEs submitted to the FDA through MedWatch (Forms 3,500/3500A) (29) by consumers, legal representatives, healthcare professionals, sponsors and manufacturers.

FAERS was initially intended for post-marketing drug and biologic safety surveillance to detect and re-evaluate drug safety signals that may have been missed in smaller scale controlled trials. However, the database includes reports of drugs still under investigation and Schedule I substances, making it a useful resource to evaluate safety of substances not yet approved by the FDA and other regulatory authorities. Reporting use of unapproved or illegal substances is important, since those agents may be the culprits of the adverse events wrongly attributed to concomitant therapeutics.

Combining and normalizing data sets

FAERS/AERS quarterly data sets, each including a data subset (demographics, drug, indication, outcome, reaction, report source), were downloaded individually from the FDA public repository in dollar sign-separated text format (30–32). At the time of the study FAERS/AERS contained 18,274,795 reports from January 2004 to September 2022. It was convenient to standardize the multiple data tables into a unified single table structure. A set of Unix shell scripts was used for data restructuring and filtering (33). The partially missing fields, relevant to the current analysis, in the MDMA reports were only in the demographic section (age, weight, sex), and were comparable to the rest of the database.

Case selection

Cases where one of the reported drugs included the terms methylenedioxymethamphetamine, 3,4-methylenedioxymethamphetamine, midomaphetamine, midomafetamine, MDMA, ecstasy, were selected into the MDMA cohort for review. A total of 1,475 reports were selected. Further, cases where reports were submitted by a healthcare professional were selected to avoid reporting bias and add clinical relevance to the reports. The resulting cohort was queried for AEs with Preferred Terms (PT) based on the following Standardized MedDRA queries (SMQs) (34) consisting of a series of specific terms intended to select key symptoms or diagnoses: Torsade de pointes/QT prolongation (level 1 SMQ), Arrhythmia related investigations, signs and symptoms (Level 2 SMQ), Cardiac arrhythmia terms nonspecific (level 3 SMQ), Supraventricular tachyarrhythmias (level 4 SMQ), Hypertension (Level 1 SMQ), Ventricular tachyarrhythmias (Level 4 SMQ), Tachyarrhythmia terms, nonspecific (Level 4 SMQ). A comprehensive list of both narrow and broad scope SMQ PTs used in the query can be found in Supplementary Table S1. Cases were selected if at least one narrow scope PT or two or more broad scope PTs were reported. Reports were further individually reviewed to exclude duplicate submissions from multiple reporting sources resulting in 17 unique reports with AEs of interest (Figure 1). No other inclusion and exclusion parameters were applied in the case selection. All of the screened cases were included in the study ($n = 17$).

Results

A total of 17 unique cases were reviewed in this study. There were no reports where MDMA was taken as a single agent and ischemic, hypertensive, or arrhythmic AEs were reported. All cases included concomitant medications with known associated cardiac function abnormalities. There were a total of four cases matching the *Torsade de pointes/QT prolongation* SMQ search criteria (Supplementary Table S1). In *all* of the cases, MDMA was taken with concomitant medications (SSRIs, antihistamines/anticholinergics, amphetamines) with known effects on cardiac function (Table 1). These cases included one report of ventricular fibrillation which matched the *Ventricular tachyarrhythmias* SMQ search query (Table 2). The *Supraventricular tachyarrhythmia* SMQ query produced three reports with one report overlapping with *Torsade de pointes/QT prolongation* SMQ terms (Table 3). The *Cardiac arrhythmia terms nonspecific* SMQ search produced two reports with concomitant reported cocaine, opioid, benzodiazepine, gamma hydroxybutyrate, and cannabis use (Table 4). There were two reports in the *Arrhythmia related investigations, signs and symptoms* query, both based on three broad scope AE PTs (Supplementary Table S1), one of which (case #6) overlapped with the *Supraventricular tachyarrhythmia* query (Table 5). The *Myocardial infarction* SMQ based search produced one report of an AE of troponin increased, where MDMA was taken with clozapine (Table 6). The *Tachyarrhythmia terms nonspecific* SMQ search produced no reports. The *Other ischaemic heart disease* query found

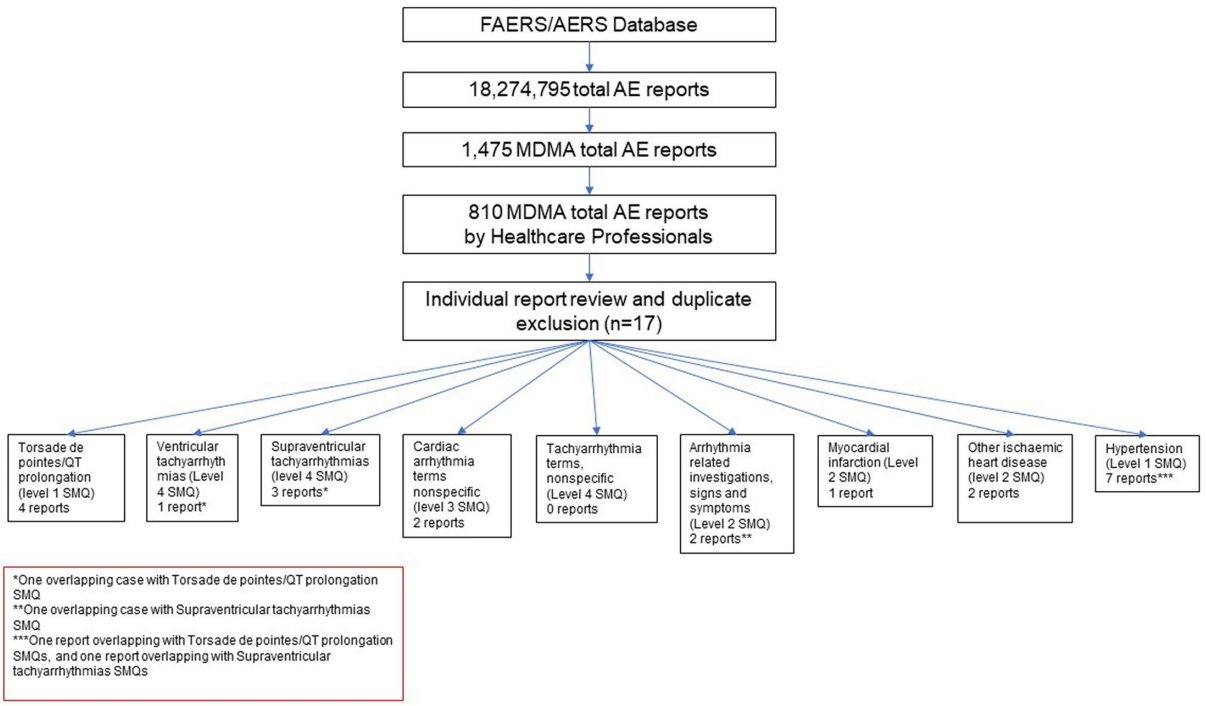

FIGURE 1
MDMA Cardiac AE report selection flowchart.

two unique reports and the 'Hypertension' query produced seven reports with two overlaps with *Torsade de pointes/QT prolongation* and *Supraventricular tachyarrhythmias SMQs* (Table 7). There were seven *Hypertension* SMQ cases with two reports overlapping with *Torsade de pointes/QT prolongation* and *Supraventricular tachyarrhythmias* SMQs (Table 8).

The summary of all of the cases, with the concomitant medications organized by class, is provided in Table 9.

Discussion

In this study, we evaluated AEs related to arrhythmias, hypertension, and ischemia in MDMA reports from the FDA adverse Event Reporting System (See Supplementary Table S1). There were no reports of those AEs in cases where MDMA was the sole reported drug. A limited number of 17 cases associated with MDMA use, reported in the last ~18 years, were evaluated. Interestingly, in every single case, MDMA was not reported as the primary suspect of those AEs. Furthermore, in all the cases, all listed concomitant drugs except one, acetaminophen, had known cardiac function related effects and were marked as primary suspects. There were two unique acetaminophen overdose cases that reported MDMA as a concomitant drug. Additionally, 76% of the reports included two or more drugs or illicit substances associated with arrhythmic, ischemic, or hypertensive AEs. It is interesting to note that in majority of the cases, illicit substances were taken in combination with psychoactive prescription medications supporting previous observations that substance use and abuse are often comorbid with psychiatric disorders. While individuals with mental health are more susceptible to misuse/abuse of illicit substances, this correlation is more complex and multidimensional as misuse/abuse may themselves lead to psychiatric disorders (35, 36).

There is still the possibility that MDMA contributed to the cardiovascular AE due to its sympathomimetic mechanism of action or CYP2D6-mediated drug–drug interaction(s) (37, 38). However, it was neither a sole culprit nor a primary suspect in any of the reported cases. The United Nations Office of Drugs and Crime estimated the number of people who report MDMA/ecstasy use to be nearly 20 million people (39). Surprisingly, considering this number, the number of reported MDMA cases with cardiovascular AE in FAERS/AERS was surprisingly low. Despite the fact that MDMA, as a known sympathomimetic, transiently increases blood pressure which is also observed in clinical trials, the number of FAERS reports on hypertension is relatively low, supporting the transient nature of this observation.

Study limitations. Due to the voluntary nature of FAERS/AERS reporting, with the exception of spontaneous reports from sponsors/manufacturers, the data presented only represents a subset of actual cases and should not be confused with actual population frequencies. Additionally, since the manufacturing and distribution of MDMA is not regulated, it is not clear whether the reported compound was pure MDMA or if it was laced with another compound not caught by the conventional drug tests. Information on the ingested MDMA dose and how the presence of MDMA was evaluated is missing from the reports, since case narratives are kept confidential by the FDA due to privacy concerns. Detailed medical and psychiatric history of the individuals in the reports were also not available. However, all of the 17 cases presented

TABLE 1 Torsade de pointes/QT prolongation (level 1 SMQ) cases in FAERS/AERS.

Case # (number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
1 (6)	15	F	DE	ps:cetirizine ss:ecstasy	Drug interaction **Electrocardiogram qt prolonged** Toxicity to various agents Urine amphetamine positive	HO	MD HP
2 (2)	25	M	AU	ps:sertraline ss:midomafetamine	Abdominal pain upper Aggression Alanine aminotransferase increased Aspartate aminotransferase increased Blood potassium decreased **Blood pressure increased** Decreased appetite Disorientation Drug abuse **Electrocardiogram qt prolonged** **Heart rate increased** Muscle rigidity Nausea Oxygen saturation decreased Serotonin syndrome **Sinus tachycardia** Vomiting Weight decreased	OT	HP
3	25	M	US	ps:sertraline ss:cocaine ss:midomafetamine c:st john's wort	Abdominal pain upper Aggression Alanine aminotransferase increased Aspartate aminotransferase increased Blood potassium decreased Decreased appetite Disorientation Drug abuse **Electrocardiogram qt prolonged** Nausea Oxygen saturation decreased Serotonin syndrome Vomiting Weight decreased	OT	HP
4	unk	unk	TR	ps:amphetamine ss:mdma	Cardiac arrest Cardioversion Coma scale abnormal Hyperthermia Hypotension Seizure Toxicity to various agents **Ventricular fibrillation**	HO OT	MD

unk, unknown; M, male; F, female; DE, Germany; AU, Australia; US, United States; TR, turkey; ps, primary suspect; ss, secondary suspect; c, concomitant; HO, hospitalization; OT, other serious (important medical event); HP, health professional; MD, physician.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

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TABLE 2 Ventricular tachyarrhythmias (Level 4 SMQ) cases in FAERS/AERS.

Case #	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
4*	unk	unk	TR	ps:amphetamine ss:mdma	Cardiac arrest Cardioversion Coma scale abnormal Hyperthermia Hypotension Seizure Toxicity to various agents **Ventricular Fibrillation**	HO OT	MD

*This case also matches the Torsade de pointes/QT prolongation SMQ criteria (see Table 1).
unk, unknown; TR, turkey; ps, primary suspect; ss, secondary suspect; HO, hospitalization; OT, other serious (important medical event); MD, physician.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

TABLE 3 Supraventricular tachyarrhythmias (level 4 SMQ) cases in FAERS/AERS.

Case #(number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
5(2)	19	F	FR	ps:fluoxetine ss:cannabis ss:citalopram c:3 4 methylenedioxymethamphetamine c:cocaine c:methylphenidate	Agitation **Blood pressure increased** Clonus Coma scale abnormal Hallucination visual Hypertonia Respiratory acidosis **Sinus tachycardia** Tonic convulsion Toxicity to various agents	HO OT	MD
6(3)	55	F	IT	ps:acetaminophen ss:bromazepam ss:carbamazepine ss:trazodone c:methylenedioxymethamphetamine c:morphine c: tramadol c: codeine c: naloxone c: pregabalin	**Atrial fibrillation** Bradycardia Bradypnoea Hepatitis acute Hypokalaemia Hypotension Hypothermia Loss of consciousness Mydriasis Overdose Product use in unapproved indication	HO LT OT	HP

(Continued)

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TABLE 3 (Continued)

Case #(number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
2(2)*	25	M	AU	ps:sertraline: ss:midomafetamine	Abdominal pain upper Aggression Alanine aminotransferase increased Aspartate aminotransferase increased Blood potassium decreased **Blood pressure increased** Decreased appetite Disorientation Drug abuse **Electrocardiogram qt prolonged** **Heart rate increased** Muscle rigidity Nausea Oxygen saturation decreased Serotonin syndrome **Sinus tachycardia** Vomiting Weight decreased	OT	HP

*This case also matches the Torsade de pointes/QT prolongation SMQ criteria (see Table 1).
M, male; F, female; FR, France; IT, Italy; AU, Australia; ps, primary suspect; ss, secondary suspect; c, concomitant; HO, hospitalization; LT, life threatening; OT, other serious (important medical event); HP, health professional; MD, physician.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

TABLE 4 Cardiac arrhythmia terms nonspecific (level 3 SMQ) cases in FAERS/AERS.

Case #	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
7	unk	unk	GB	ps:fentanyl ss:alprazolam ss:clonazepam ss:cocaine ss:diazepam ss:gamma hydroxybutyrate ss:heroin ss:methylenedioxymethamphetamine ss:oxazepam ss:tramadol HCl	**Arrhythmia** Cardiac arrest Coma scale abnormal Death Drug abuse Seizure Toxicity to various agents	DE HO OT	HP
8	23	M	FR	ps:pregabalin ss:cannabis sativa subsp. indica top ss:cocaine ss:midomafetamine	Coma Drug abuse **Heart rate irregular** Partial seizures	HO	MD

unk, unknown; M, male; F, female; FR, France; IT, Italy; AU, Australia; ps, primary suspect; ss, secondary suspect; c, concomitant; HO, hospitalization; LT, life threatening; OT, other serious (important medical event); HP, health professional; MD, physician.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

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TABLE 5 Arrhythmia related investigations, signs, and symptoms (Level 2 SMQ) cases in FAERS/AERS.

Case #(number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
6 (3)*	55	F	IT	ps:acetaminophen ss:bromazepam ss:carbamazepine ss:trazodone c:methylenedioxymethamphetamine c:morphine	Atrial fibrillation **Bradycardia** Bradypnoea Hepatitis acute Hypokalaemia Hypotension Hypothermia **Loss of consciousness** Mydriasis Overdose Product use in unapproved indication	HO LT OT	HP
9	unk	unk	GB	ps:acetaminophenss:amphetamine ss:aspirin ss:buprenorphine ss:cannabis ss:cocaine ss:codeine ss:diamorphine ss:diclofenac ss:ecstasy ss:ibuprofen ss:methadone ss:morphine	Abdominal pain Abdominal symptom Accident at work Adverse event Aggression Back pain Cardiac disorder **Cardio respiratory arrest** Cerebrovascular accident Chest pain Depressed level of consciousness Diabetic complication Exposure to unspecified agent Fall Gunshot wound Hemorrhage Headache Injury Laceration **Loss of consciousness** Malaise Multiple allergies Overdose Physical assault psychiatric symptom Respiratory disorder Respiratory distress Road traffic accident Seizure Sexual abuse Stab wound Substance abuse Suicidal ideation **Syncope** Toxicity to various agents	HO OT	MD

*This case also matches the Supraventricular tachyarrhythmias SMQ criteria (see Table 3).

unk, unknown; F, female; GB, Great Britain; IT, Italy; ps, primary suspect; ss, secondary suspect; c, concomitant; DE, death; HO, hospitalization; OT, other serious (important medical event); LT, life threatening; HP, health professional; MD, physician.

The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

TABLE 6 Myocardial infarction (Level 2 SMQ) cases in FAERS/AERS.

Case #	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
10	unk	M	AU	ps:clozapine ss:ecstasy	**Troponin increased**	HO	MD

unk, unknown; M, male; AU, Australia; ps, primary suspect; ss, secondary suspect; c, concomitant; HO, hospitalization; MD, physician.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

TABLE 7 Other ischaemic heart disease (level 2 SMQ).

Case # (number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
11(3)	unk	unk	AU	ps:fentanyl ss:alcohol ss:buprenorphine ss:cannabinol ss:cocaine ss:codeine ss:hydromorphone ss:methadone ss:methamphetamine ss:midomafetamine ss:morphine ss:olanzapine ss:oxycodone ss:promethazine ss:quetiapine ss:tapentadol ss:tramadol HCl	**Arteriosclerosis coronary Artery** Aspiration Asthma Cardiac valve disease Cardiomegaly Cardiomyopathy Emphysema Fibrosis Hepatic cirrhosis Hepatic fibrosis Hepatic hypertrophy Hepatic steatosis Hepatitis Intentional self injury Kidney fibrosis Nephrosclerosis Overdose Pneumonia Pulmonary oedema Toxicity to various agents Ventricular hypertrophy Death	DE OT	HP
12(6)	22	F	AU	ps:morphine sulfate ss:acetaminophen ss:furosemide ss:methadone HCl ss:methamphetamine ss:methylenedioxymethamphetamine ss:metoclopramide	Hepatitis c **Myocardial ischaemia** Pulmonary oedema Toxicity to various agents Death	DE OT	MD

unk, unknown; M, male; AU, Australia; ps, primary suspect; ss, secondary suspect; c, concomitant; HO, hospitalization; MD, physician.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

in the study were submitted by healthcare professionals (*Form*-3,500), thus some level of clinical adjudication prior to reporting is expected.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Ethics statement

Ethical approval was not provided for this study on human participants because Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Study utilized de-identified postmarketing data available online to the

TABLE 8 Hypertension (Level 1 SMQ) cases in FAERS/AERS.

Case # (number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
2 (2)*	25	M	AU	ps:sertraline ss:midomafetaminea	Abdominal pain upper Aggression Alanine aminotransferase Increased Aspartate aminotransferase increased Blood potassium decreased **Blood pressure increased** Decreased appetite Disorientation Drug abuse Electrocardiogram qt prolonged Heart rate increased Muscle rigidity Nausea Oxygen saturation decreased Serotonin syndrome Sinus tachycardia Vomiting Weight decreased	OT	HP
13	44	M	FR	ps:diazepam ss:alcohol ss:cannabis ss:cocaine ss:lsd ss:mdma ss:tabacum inhalation	Drug abuse Gamma glutamyltransferase increased **Hypertension** Hypertriglyceridaemia	HO	MD
14	24	F	FR	ps:alprazolam ss:amphetamine ss:midomafetamine	**Hypertension** Somnolence Suicide attempt Tachycardia	OT	PH
15 (3)	32	M	FR	ps:pregabalin ss:midomafetamine ss:clonazepam ss:prazepam	Drug abuse **Hypertension** Somnolence Victim of crime	OT	PH

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TABLE 8 (Continued)

Case # (number of duplicates)	Age	Sex	Country	Concomitant medications	Adverse events	Outcome	Reported by
16	unk	unk	unk	ps:sodium valproate ss:benzocaine ss:mdai ss:methylenedioxymethamphetamine ss:mirtazapine c:amoxicillin c:levomepromazine c:orphenadrine	**Blood pressure increased** Cyanosis central Dizziness Malaise Methaemoglobinaemia Off label use Oxygen saturation decreased PO2 increased Respiratory rate increased	HO	MD
5(2)**	19	F	FR	ps:fluoxetine ss:cannabis ss:citalopram c:3 4 methylenedioxymethamphetamine c:cocaine c:methylphenidate	Agitation **Blood pressure increased** Clonus Coma scale abnormal Hallucination visual Hypertonia Respiratory acidosis **Sinus tachycardia** Tonic convulsion Toxicity to various agents	HO OT	MD
17	unk	M	FR	ps:buprenorphine ss:alcohol ss:methylenedioxymethamphetamine	Agitation Delirium drug abuse **Hypertension** Injection site inflammation	HO	PH

*This case also matches the Torsade de pointes/QT prolongation SMQ criteria (see Table 1).

**This case also matches the Supraventricular tachyarrhythmias SMQs criteria (See Table 3).

unk, unknown; M, male; F, female; FR, France; AU, Australie; ps, primary suspect; ss, secondary suspect; c, concomitant; HO, hospitalization; OT, other serious (important medical event); HP, health professional; PH, pharmacist; MD-physician.

The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

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TABLE 9 Concomitant drugs associated with cardiac function related AEs in MDMA cases summarized by class.

Report number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
MDMA	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Opioid agonists/ antagonists						****	***		*****		***** ****	**					*
Amphetamines, NET/DAT inhibitors				*	*						*	*		*			
Benzodiazepines						*	***						*	*			
Cocaine			*		*		*	*	*		*		*		*		
Hydroxybutyrate							*										
Antihistamines/ anticholinergics	*										*					**	
SSRIs/SSRAs/ antidepressants		*	**		**	*										**	
Gabapentinoids						*		*							*		
Alcohol											*		*				*
Cannabinoids					*			*	*		*		*				
Antipsychotics										*	**						
LSD													*				
NSAIDS									***								

The number of* corresponds to the number of drugs in the listed drug class included in the report. NET, norepinephrine transporter; DAT, dopamine transporter; SSRI, selective serotonin reuptake inhibitor; SSRA, selective serotonin releasing agent; LSD, lysergic acid diethylamide; NSAID, nonsteroidal anti-inflammatory drug.
The bold values are the terms of the adverse events related to the study focus (hypertensive, ischaemic, and arrhythmic).

public. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TM performed the research. TM, DD, LJ, AB, and RA designed the study, drafted the manuscript, and reviewed the final version. RA processed the data sets. All authors contributed to the article and approved the submitted version.

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Conflict of interest

TM, DD, and LJ were employed by MAPS Public Benefit Corporation. AB was employed by Tulip Medical Consulting LLC.

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1149766/full#supplementary-material

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Case report: Treatment-resistant schizophrenia with auto-aggressive compulsive behavior—Successful management with cariprazine

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The present case report describes a patient with treatment-resistant schizophrenia and auto-aggressive compulsive behavior who was effectively treated with a third-generation antipsychotic medication, cariprazine. The diagnosis was made 12 years ago, and the patient has been hospitalized 14 times and undergone various antipsychotic treatments. Despite receiving both inpatient and outpatient care, the patient's response to treatment has been only partial, and he has been classified as a treatment-resistant case. Therefore, the patient was switched to cariprazine, which led to significant improvements in both positive and negative symptoms, as well as the complete reduction of auto-aggressive compulsive behavior. These improvements contributed to the patient's overall social functioning and the achievement of remission, while also avoiding polypharmacy and eliminating the metabolic side effects associated with previous treatments.

KEYWORDS

treatment-resistant schizophrenia, cariprazine, aggressive compulsive behavior, treatment of schizophrenia, antipsychotics

1. Introduction

Schizophrenia is a chronic psychiatric disorder affecting major thought processes such as perception, thinking and behavior. It is characterized by three major symptom domains: positive, negative and cognitive. Given these symptoms, schizophrenia has a major impact on the functioning and quality of life of patients, as they cause disruptions to work and school performance as well as to social relationships.

Studies estimate that about 30% of patients will develop treatment-resistant schizophrenia (TRS). The development of the concept of TRS was associated with the introduction of the second-generation antipsychotic drugs in dichotomic terms of response or no response to previous drug (1). The advancement of psychiatry science, using of integrated biopsychosocial approach and a multi-level assessment of treatment response lead to formulate concepts such as remission, much closer to the idea of recovery and functional recovery, based on patients' social functioning level (2). Up to now, TRS is defined as the presence of persisting symptoms despite two or more antipsychotic trials with adequate dose and treatment duration as well as documented medication-adherence (3). One of the defining features of TRS is the persistence of positive symptoms (4), yet cognitive or negative symptoms may also persist (5). Patients with TRS tend to have more severe symptoms, worse cognitive functioning and therefore higher costs to the healthcare providers (6).

In addition, it further increases the burden on families and caregivers as they need to spend significant amount of their time and income on patient-care activates, having a negative impact on family life (6–8). It is important to note that TRS affects not only the patient and their family, but also the medical team responsible for their care. Healthcare professionals may develop negative attitudes such as pessimism, therapeutic nihilism, and lack of intellectual curiosity toward these patients (6). These patients come to be perceived and labeled as 'difficult' (6, 9).

In order to provide clinical guidance on the identification and management of TRS, a research group was launched who developed and published a guideline (6). According to their view, re-evaluation of treatment plan is needed in case of non-response to two different antipsychotic medications including clozapine, consideration of adjunctive treatment with non-pharmacologic therapies and sharing of decision-making process among the treatment team, patient, and family, in order to choose the most adequate treatment plan. Finally, the authors suggest monitoring for potential markers of TRS such as high dose of antipsychotics, frequent hospitalisations, and ineffective polypharmacy.

Obsessive-compulsive symptoms in schizophrenia are clinically significant, may manifest in the prodromal or acute phase of the disorder, and have a prevalence rate of 12 to 20% (10, 11). Clinical studies report that obsessive-compulsive symptoms (OCS) not only increase the severity of symptoms and worsens the prognosis of schizophrenia but also causes the patient to respond poorly to conventional antipsychotic treatment, and generally have worse outcomes in social functioning (10–12).

Aggression is a significant concern in individuals with schizophrenia, and it can manifest in various forms, including auto-aggression as a compulsive symptom. According to recent meta-analysis data, the pooled prevalence of aggression is reported as 33.3% (13). Additionally, the estimated prevalence rates for verbal aggression, property-oriented aggression, auto-aggression, and physical aggression are 42.6, 23.8, 23.5, and 23.7%, respectively. In another cross-sectional study, several associated factors for aggressive behavior among patients with schizophrenia were identified, including male gender, unemployment, previous history of aggression, psychotic symptoms, drug nonadherence, poor social support, and alcohol use (14).

Scientists have discussed if this condition is a pure comorbidity or a subtype of schizophrenia. The term schizo-obsessive disorder refers to a clinical spectrum of disorders with characteristics of schizophrenia and obsessive compulsive disorder (OCD) (11, 12). Some studies have pointed out that schizo-obsessive disorder can be considered a subtype of schizophrenia and not a distinct clinical entity (11). Nevertheless, the OCD with psychotic features and absent insight is distinguished in the diagnostic and statistical manual of mental disorders fifth edition (DSM-5) (15). Similarly, the international classification of diseases 11th version (ICD-11) has specified insight levels for OCD as good to fair insight or poor to absent insight (16). Another aspect of relationships is iatrogenic OCS secondary to atypical antipsychotics, particularly clozapine, which appear to have a role in inducing or exacerbating OCS (11, 12, 17). Currently, there is no consensus on the management of OCS in TRS patients, but this does not mean that the condition cannot be improved, rather that these improvements may take time and experimentation.

Cariprazine is a third-generation antipsychotic with dopamine D_2-D_3 partial agonist with preferential binding to the D_3 receptors (18). The exceptional receptor profile and tolerability is a potential beneficial value of this drug. Cariprazine is effective in the treatment of schizophrenia and may be particularly beneficial for the negative symptoms of this disorder. It is approved for the treatment for schizophrenia by the European Medicines Agency (19) and additionally for the treatment of depressive and manic/mixed episodes associated with bipolar I disorder by the Food and Drug Administration (20). It further showed efficacy in the adjunctive treatment of major depressive disorder (21). In schizophrenia, cariprazine showed statistically significant superiority in the treatment of acute patients (22–24) and in long-term relapse prevention (25) over placebo. Furthermore, it statistically significantly outperformed risperidone in the treatment of patients with persistent, predominant negative symptoms (26).

The present case report describes a TRS patient with auto-aggressive compulsive behavior that was managed successfully with switching to cariprazine.

2. Case presentation

2.1. Background history

A 35-year-old Caucasian male does not have a family history of mental illness or substance abuse disorder. Early developmental progression was without any delay. During adolescence, the individual experienced tension, decreased energy, and symptoms of agoraphobia, leading to three visits to a child psychologist. The individual later pursued vocational education and became a potter, and then worked part-time as an assistant of a social worker. He lived alone and had not been in a romantic relationship until his current episode of illness.

2.2. Interventions and their outcomes

The first notable complaince appeared when he was 23 years old. He developed tension, obsessive thoughts and auto-aggressive compulsive behavior, he used to beat walls with his fist. After a consultation with a psychiatrist he was diagnosed with obsessive-compulsive disorder according to DSM-5 (300.3) (15) and Sertraline 100 mg/day was prescribed. However, after 2 months of gradually increasing the dosage to 150 mg/day, there was no improvement in the patient's mental state. The patient's therapy was then switched to Clomipramine, starting with an initial dose of 150 mg and gradually increased to 300 mg/day. Despite 2 months of treatment, the patient's compulsive behavior was not controlled, and Paroxetine was prescribed with a gradual titration to 60 mg. After 2 months of treatment, Risperidone was added to the therapy at a dosage of 2 mg/day, but there was no significant improvement in the patient's clinical symptoms.

The patient became socially avoidant, experienced a decreased in motivation and ability to initiate and persist in self-directed purposeful activities, and started neglecting the hygiene. First psychotic symptoms manifested 2 months prior to being admitted to a psychiatric hospital, and characterized by auditory

hallucinations, thoughts echo, thought insertion and delusion of control. Furthermore, he engaged in self-harming behavior by hitting himself in the face, which resulted in severe bruising.

Due to the above-described symptoms, the patient was admitted to the hospital. Subsequently, a structured psychiatric assessment interview was conducted, revealing that the patient met the criteria for Schizophrenia (295.90) as per the DSM-5. Diagnostic testing to exclude any organic, neurological, somatic or psychoactive substance etiology of psychosis were performed. Patient's vital signs, biochemical blood test, C-reactive protein, glucose level, total bilirubin, alanine aminotransferase, urea, urinalysis, and thyroid hormones were within normal limits. The rapid plasma reagin test, HIV serology, Hepatitis B and C surface antigen and urine drug tests were negative. Magnetic resonance imaging showed no pathology of the brain. No paroxysmal activity was registered on the electroencephalogram. A chest x-ray showed no abnormalities in the lungs. Psychometric psychological assessment revealed signs of endogenous type of mental disorders. Thinking process is characterized with lose of associations, paralogy, abstract reasoning was based on insignificant facts. No reductions were observed in sensory memory, short-term memory, and long-term memory. The personality was characterized by passive social withdrawal, emotional and social isolation. Neurological and somatic status were without abnormalities. Substance use disorder evaluations did not reveal any substance or alcohol dependence syndrome. The patient did not have any depressive, manic or hypomanic episodes; therefore, affective disorders were ruled-out.

At the inpatient psychiatry unit, the patient received haloperidol 15 mg/day, divalproate 1500 mg/day, trihexyphenidyl 6 mg/day and diazepam up to 20 mg/day in combination with rehabilitation. His symptoms partially improved and after discharge, the patient continued the outpatient treatment.

In total, the patient had 14 hospital admissions; the last one was in May 2021. The reasons for hospitalization were psychotic exacerbations, safety reasons due to aggressive compulsive behavior, and decline in social functioning. He was involved in out-patient care, and demonstrated good compliance, and adherence to recommended treatment regimens. Throughout this period of the illness, auditory hallucinations, thoughts echo, thought insertion, delusions, social withdrawal, motor retardation, poor attention, disturbance of volition, poor impulse control, auto-aggressive behavior and decline in social functioning were persisted. Over the past 12 years, different treatment schemes were applied. For at least 4 months, he received the following therapy regimes in these years: olanzapine 40 mg per day; risperidone 6 mg, trihexyphenidyl 6 mg; risperidone up to 6 mg, trihexyphenidyl up to 8 mg, clozapine 200 mg per day; olanzapine 20 mg, haloperidol 10 mg, buspirone 30 mg, trihexyphenidyl 6 mg per day; haloperidol 15 mg, clozapine 150 mg, trihexyphenidyl 6 mg per day; clozapine 400 mg, mirtazapine 15 mg, divalproate 1,000 mg daily; amisulpiroid 600 mg, clozapine 75 mg, divalproate 1,500 mg, trihexyphenidyl 6 mg per day. Clozapine up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. The patient refuses to receive long-acting injectable antipsychotics. Despite ongoing treatment, the patient achieving only a partial response in terms of above-described symptoms. An overview of inpatient and outpatient pharmacological treatments 12-year time line summery listed in Table 1.

The patient was treated on an outpatient basis in January 2022 with a medication regimen that included amisulpride 400 mg/day, clozapine 100 mg/day, mirtazapine 30 mg/day, and trihexyphenidyl 4 mg/day. Despite treatment, the patient continued experiencing severe auditory hallucinations, thought insertion, social withdrawal, motor retardation, disturbance of volition, poor impulse control, and auto-aggressive behavior. He engaged in self-mutilation by hitting his own face, which caused subcutaneous hemorrhage. Assessment of total score on the Positive and Negative Syndrome Scale (PANSS) (27) was 86 with positive sub-score of 15, negative sub-score of 24 and general sub-score of 47. The Global Assessment of Functioning (GAF) (28) score was 20, and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (29) showed a score of 22 that indicates severe level of symptoms. His body mass index (BMI) was 30.5 kg/m^2 (height = 190 cm, weight = 110 kg).

Due to persistent symptoms and low functioning, the patient's medication regimen was changed without cross-titration to cariprazine 6 mg/day, clozapine 100 mg/day and mirtazapine 30 mg/day. In the first 2 weeks, the patient experienced extrapyramidal side effects in the form of a moderate tremor in his fingers, thus trihexyphenidyl 4 mg/day was prescribed. Otherwise, patient showed good tolerability. A time line summary of pharmacological treatment, clinical picture and scores of psychometric scales after switching to cariprazine presented in Table 2.

After 2 months, the severity of auditory hallucinations, thought insertion, social withdrawal, motor retardation, disturbance of volition and poor impulse control decrease to moderate level. He developed partial control of auto-aggressive behavior. The patient started working two times a week. Due to the improvement, clozapine was discontinued, and the dose of mirtazapine was decreased to 15 mg/day.

Four months after the first administration of cariprazine 6 mg/day, the severity of positive and negative symptoms were defined as mild. The patient reported interest in hobby, communication with acquaintances, and started physical activities.

Another month later, auditory hallucinations and thought insertion disappeared. He had full control of auto-aggressive behavior. This improvement enabled mirtazapine to be discontinued too.

After 6 months of treatment with cariprazine 6 mg/day, the patient began to become socially active again, he demonstrated absent of auditory hallucinations and thought insertion, and he does not engage in auto-aggressive behavior. At this point, the PANSS total score was 43 with positive sub-score of 10, negative sub-score of 11 and general sub-score of 22, meaning an overall reduction of 50%. The GAF score was 67, which is fairly good as a score of $\geq$60 points is considered as demonstrating adequate functioning (30). The Y-BOCS score decreased to 3, and the patient's BMI to 26.3 kg/m^2. The PANSS scores prior to switching to cariprazine and after 6 months of therapy with cariprazine presented in Figure 1.

TABLE 1 Inpatient and outpatient pharmacological treatments attempt 12-year timeline summary with duration of treatment at least 4 months.

Duration of treatment	Pharmacological treatment/Daly dose	Comments
7 months	Haloperidol 15 mg Divalproate 1,500 mg	Trihexyphenidyl 6 mg/day was administrated to manage parkinsonism. Diazepam up to 20 mg was administrated for 2 months to manage anxiety. Partial response to treatment.
4 months	Olanzapine 40 mg	Partial response to treatment.
4 months	Risperidone 6 mg	Trihexyphenidyl 6 mg/day was administrated to manage parkinsonism. Partial response to treatment.
7 months	Risperidone 6 mg Clozapine 200 mg	Trihexyphenidyl 8 mg/day was administrated to manage parkinsonism; Clozapine up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. Partial response to treatment.
8 months	Olanzapine 20 mg Haloperidol 10 mg Buspirone 30 mg	Trihexyphenidyl 6 mg/day was administrated to manage parkinsonism. Partial response to treatment.
7 months	Haloperidol 15 mg Clozapine 150 mg	Trihexyphenidyl 6 mg/day was administrated to manage parkinsonism; Clozapine up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. Partial response to treatment.
6 months	Clozapine 400 mg Mirtazapine 15 mg Divalproate 1,000 mg	Clozapine up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. Partial response to treatment.
9 months	Amisulpiroid 600 mg Clozapine 75 mg Divalproate 1,500 m,	Trihexyphenidyl 6 mg/day was administrated to manage parkinsonism; Clozapine up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. Partial response to treatment.
8 months	Amisulpride 400 mg Clozapine 100 mg Mirtazapine 30 mg	Trihexyphenidyl 4 mg/day was administrated to manage parkinsonism; Clozapine up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. Partial response to treatment. The patient was switched to cariprazine from this therapy.

TABLE 2 Outpatient care timeline summery of pharmacological treatment, clinical picture and psychometric scales.

Date Duration	Pharmacological treatment	Description of clinical presentations	PANSS, GAF, Y-BOCS, BMI
Jan 2022 Baseline	Cariprazine 6 mg Clozapine 100 mg Mirtrazapine 30 mg EPS after 2 weeks Trihexyphenidyl 4 mg	Severe auditory hallucinations, thought insertion, social withdrawal, motor retardation, disturbance of volition, poor impulse control, auto-aggressive behavior. Severe impairment in personal grooming. He stopped brushing his teeth, playing the guitar, leaving the house, going to work or doing sports. Tension accompanied by an irresistible desire to hit himself. He engaged in self-mutilation and bet himself in the face, leading to subcutaneous hemorrhage. In order to avoid self-harm, the patient lied on his bed all day.	PANSS = 86 GAF = 20 Y-BOCS = 22 BMI = 30.5 kg/m2 High = 90 cm Weight = 110 kg
Mar 2022 8 weeks	Cariprazine 6 mg Mirtrazapine 15 mg Trihexyphenidyl 4 mg	Moderate auditory hallucinations, thought insertion, social withdrawal, motor retardation, disturbance of volition, poor impulse control, auto-aggressive behavior (partial control). The patient was finally able to get out of his bed, go outside and started working two times a week.	
May 2022 16 weeks	Cariprazine 6 mg Mirtrazapine 15 mg Trihexyphenidyl 4 mg	Mild auditory hallucinations, social withdrawal, motor retardation, disturbance of volition, poor impulse control, auto-aggressive behavior (partial control). The patient was able to play the guitar for 20 mins and started boxing with a trainer for three times a week.	
Jun 2022 20 weeks	Cariprazine 6 mg Trihexyphenidyl 4 mg	Absent of auditory hallucinations, thought insertion and autoagressive behavior. Started working full-time at a woodworking manufacturer. He was glad to be able to do sports and play the guitar again, although for a limited amount of time.	
Jul 2022 24 weeks	Cariprazine 6 mg Trihexyphenidyl 4 mg	The patient began to become socially active again, rarely experiences tensions and the urge to hit himself, he does not engage in aggressive behavior and his auditory hallucinations seized. The patient was able to do sports and play the guitar without any time-limitation.	PANSS = 43 GAF = 67 Y-BOCS = 3 BMI = 26.3 kg/m2 High = 190 cm Weight = 95 kg

PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; BMI, body mass index; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; EPS, extrapyramidal symptoms.

3. Discussion

The disorder manifested in adolescence and retrospectively, a prodromal phase of schizophrenia can be detected with neurosis-like symptoms such as tension, anxiety, decreased energy and agoraphobia. The acute phase start at the age of 23, characterized by auditory hallucinations, thoughts echo, delusion of passivity, obsessive thoughts, tension and aggressive compulsive behavior. Throughout the course of the disorder, the patient developed passive social withdrawal, motor retardation, poor attention, disturbance of volition, poor impulse control and active social avoidance. The patient had 14 readmission to mental hospitals, often because he were discharged before he had adequately recovered, that describe the revolving door phenomenon (31).

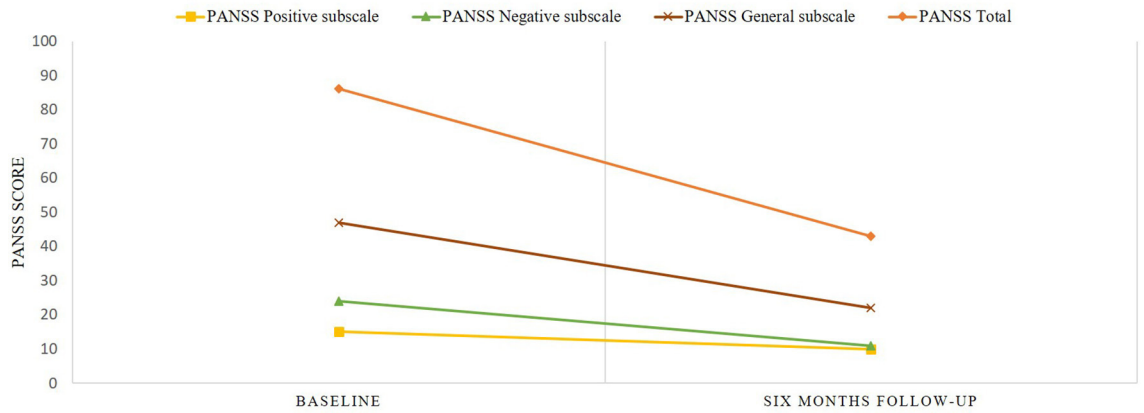

FIGURE 1
Changes of PANSS scores prior and after initiation of the treatment with cariprazine.

This highlights the importance of providing comprehensive and effective treatment and support to individuals with mental illness to prevent the revolving door phenomenon from occurring.

Despite receiving continuous pharmacological treatment in the form of both first- and second-generation antipsychotics in various combinations, it exemplifies a "difficult to treat" condition. The treatment response was only partial, and complete remission was not achieved. The case meets the criteria for treatment-resistant schizophrenia (TRS) as per the consensus guidelines of the Treatment Response and Resistance in Psychosis Working Group, given the reasons outlined above (5). The patient had active and persistent symptoms for over 12 weeks with impaired functioning and at least 6 weeks of treatment with an appropriate usage of two antipsychotics from different drug profiles at doses equivalent to over 600 mg chlorpromazine per day, and he was also compliant.

Throughout the course of schizophrenia, different approaches of pharmacological treatment were tried without sufficient improvement. Clozapine is wellknown and defined as the first-line medication for the management of TRS with evidence from several studies (32). For instance, the patient did not response to clozapine 400 mg/day and the up-titration was impossible due to side effects such as sedation, hypersalivation and weight gain. In terms of cariprazine, there is some evidence supporting its effectiveness in TRS patients, however it is only based on case reports (33–35). While both cariprazine and clozapine have affinity for dopamine D2 and D3 receptors, their receptor profiles differ in terms of partial agonism vs. antagonism. Clozapine primarily acts as an antagonist at multiple receptors, including dopamine D1, D2, D3, and D4 receptors, serotonin 5-HT2A, 5-HT2C, 5-HT3 receptors, and histamine H1 receptors (32). Cariprazine, on the other hand, acts as a partial agonist at dopamine D2 and D3 receptors and as an antagonist at serotonin 5-HT2A receptors (18). While clozapine exhibits broader antagonistic effects on serotonin receptors, both medications antagonize 5-HT2A receptors. Similarities in receptor profiles can potentially be associated with comparable treatment efficacy. Another possible explanation for the effectiveness of cariprazine in this case could be attributed to a comparison of dose equivalents between cariprazine 6 mg and clozapine 400 mg, where the dose equivalent for cariprazine is ~1.5 times higher (36).

Unfortunately, the use of clozapine in schizophrenia patients with obsessive-compulsive behavior could lead to the worsening of OCS (11, 12, 17). Indeed, in the present case, such symptoms of the patient did not change significantly during clozapine treatment according to the medical records as monitored by standardized rating scales.

Several studies have provided evidence of aripiprazole efficacy in improving symptoms and achieving remission in patients with TRS (37, 38). Additionally, several case reports demonstrated effective use of aripiprasole in OCD (37). Aripiprazole and cariprazine share similarities in their receptor profiles, particularly in their partial agonist activity at dopamine D2 and D3 receptors. This partial agonism may contribute to their ability to stabilize dopamine activity in the brain. Additionally, both aripiprazole and cariprazine display antagonistic effects on serotonin 5-HT2A receptors, which may further contribute to their overall pharmacological effects.

Although a recent study summarizing evidence from clinical trials and real-world studies recommend cross-titration in case of switching from another antipsychotic to cariprazine (39), in this case the authors decided to switch from amisulpride 400 mg/day to cariprazine 6 mg/day without cross-titration due to the severity of symptoms. This abrupt switching strategy was well tolerated by the patient.

Based on the results, the present case demonstrates the efficacy of cariprazine in the treatment of psychotic, negative symptoms and self-aggressive compulsive behavior in a TRS patient. After 6 months of therapy, 50% of the PANSS reduction. The GAF improvement was detected and indicates adequate day-to-day functioning, which was unimaginable previously. Reviewing the literature, this is also supported by other studies focusing on the efficacy of cariprazine in hostility (40, 41). For instance, a recent *post-hoc* analysis looked at the pooled data from three randomized,

placebo-controlled, phase 2/3 studies with patients who had acute exacerbation of schizophrenia and found that with cariprazine there was a significant improvement in hostility compared to patients treated with placebo as measured by the PANSS-derived Marder hostility subscale (40).

Another important aspect in this case is the prevention of further polypharmacy—the combination of more than one antipsychotics and/or antidepressants—with cariprazine. After the fifth month of cariprazine treatment, the patient stopped any other medication and received only cariprazine as monotherapy.

Since the patient received the highest recommended dose, 6 mg/day, a side-effect in the form of hand tremor was induced which was then compensated with anticholinergic medication. Otherwise, the medication was welltolerated. Another safety aspect in this case was metabolic symptoms. It is a wellknown fact that TRS patients belong to a high-risk group of developing metabolic syndrome due to the widespread use of polypharmacy treatment with second-generation antipsychotics as well as due to general lifestyle (40). Given the fact that cariprazine is metabolically neutral, the patient lost 15 kg body weight and his BMI became close from class obese to only class overweight. Moreover, clozapine and mirtazapine, medications that have high metabolic risk, were discontinued and with the reduction of negative symptoms, the patient changed his lifestyle and became more active. It is important to note that the patient did not change his eating regime or the amount of food intake.

Finally, given the fact that the switch to cariprazine prevented further hospitalization of the patient, this case reduced the healthcare costs of the provider as well.

All in all, this is an example of continuous treatment efforts and maintenance of therapeutic optimism that finally resulted in symptom improvement. Nonetheless, it is crucial to continue to follow up the patient in the future in order to understand further changes in symptoms, control tolerability and social functioning. More evidence is needed regarding the long-term effectiveness of cariprazine in TRS schizophrenia with auto-aggressive compulsive behavior.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient to publish this case.

Author contributions

LR and ER contributed to the design and conception of the manuscript and data analysis and revision of subsequent versions. LR wrote the first draft of the manuscript. Both authors contributed to the article and approved the submitted version.

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Conflict of interest

ER during the last 3 years has received research grants from Gedeon Richter and Lundbeck, and is a member of advisory panels for Abbvie, Gedeon Richter, Grindex, Janssen Cilag, Lundbeck and Servier.

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

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Case report: Interstitial pneumonitis after initiation of lamotrigine

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The second-generation anticonvulsant lamotrigine is widely used in the psychiatric field as a mood stabilizer or antidepressant augmentation therapy. Although particularly older anticonvulsants are known for their potential to cause hypersensitivity syndromes, newer antiepileptic drugs do hold a certain risk as well. Presenting a case of a 32-year-old male inpatient of African ethnicity suffering from a primary severe depressive episode in the course of a recurrent major depressive disorder, we report the occurrence of a rapid-onset drug-induced pneumonitis. Herewith, the interstitial pneumonitis occurred after the initiation of 25 mg lamotrigine as an augmentation therapy. Except for the clear temporal correlation between the administration of lamotrigine and the onset of pneumonitis, we did not reveal any further potentially causal diagnostic hints. Importantly, no relevant genetic variations of metabolizing enzymes or drug interactions resulting in lamotrigine overdosage as a potential cause of toxicity were identified. Our experience with a potentially life-threatening adverse drug reaction shortly after the initiation of the largely well-tolerated lamotrigine suggests a potential side effect under the second-generation anticonvulsant although similar adverse events are deemed to be very rare.

KEYWORDS

lamotrigine (LTG), interstitial pneumonitis, adverse events, case report, pulmonary condition

1. Introduction

Lamotrigine is an antiepileptic drug, primarily applied in the treatment of epileptic syndromes as a mono-therapeutic regimen or as an add-on therapy in children and adults (1). In addition, lamotrigine is approved as a mood stabilizer in affective disorders and is also frequently administered as augmentation antidepressant therapy (2–4). Similar to other anticonvulsants, lamotrigine is known to be able to provoke hypersensitive adverse reactions—even though less frequent than in older anticonvulsant medication such as phenytoin, carbamazepine, or phenobarbital (5–7). Considering its balance of efficacy and tolerability, lamotrigine ranks among first-line drugs for the treatment of bipolar disorders with the exception of acute manic episodes or conditions requiring rapid symptom control (3). Lamotrigine is eliminated via a hepatic route, whereby the metabolic inactivation through N-glucuronidation is primarily catalyzed by UGT1A4 (8). Interestingly, many

polymorphisms could be identified in the coding regions of this enzyme, which result in corresponding changes in its catalytic activities. Moreover, a higher frequency of *UGT1A4* heterozygous mutations was reported in African populations compared with those in Caucasians (9). Indeed, the homozygous genotype was associated with better efficacy of lamotrigine (10).

2. Case description

In April 2022, a 32-year-old male inpatient of African ethnicity with a history of post-traumatic stress disorder (PTSD), recurrent major depressive disorder (MDD), and focal epilepsy was admitted to a psychiatric ward of a university department due to a current severe major depressive episode (MDE) that was accompanied by psychosomatic symptoms with predominant chronic pain. The patient presented physically fit apart from well-controlled arterial hypertension and the pronounced pain syndrome mentioned before. The psychosomatic character of the pain as primary etiology was assumed after the exclusion of physical causes and detailed anamnesis, which revealed a close temporal correlation between the reaggravation of pain and a recent stressful life event. Moreover, he received repeated neurosurgical interventions for traumatic brain injury between 2013 and 2020. At the time of admission, he received mirtazapine 60 mg, quetiapine 100 mg, pregabalin 600 mg, levetiracetam 1,000 mg, and 7 mg diazepam per day in addition to analgesics (dexibuprofen 800 mg and tramadol 400 mg) as well as lisinopril 20 mg. (CAVE: An off-label dose of 60 mg mirtazapine can only be administered after close therapeutic drug monitoring, because of CYP enzyme alterations necessitating higher doses and in special institutions enabling such therapeutic decisions. This was processed accordingly in an earlier admission of this patient.) Considering the current severe MDE and the known epileptic syndrome, lamotrigine at a dose of 25 mg once a day was added as an antidepressant augmentation strategy.

Two days after admission, respiratory deterioration of the patient was evident, whereby he became acutely unwell with shortness of breath, tachycardia (pulse rate 120/min in comparison with 105/min on admission), and oxygen saturation dropping to 55% on air during sleep. Subsequently, supplemental oxygen via a nasal cannula (starting at 2–3l/min) and inhalation therapy with short-acting beta-agonists were employed, and a comprehensive diagnostic workup was promptly initiated. On auscultation, the chest of the patient was clear. He had no rash, and his cardiovascular, abdominal, and neurological examinations remained without findings. His ECG was normal with no evidence of ischemia, and his blood pressure remained stable. His chest radiograph showed bipulmonal spotty opacities but no pleural effusion. Although the increased CRP (up to 8.73 mg/dl) was indicative of an infection, procalcitonin, markers of autoimmune response or rheumatologic origin, microbiology (blood cultures), and virology (nasal swab—including SARS-CoV-2, RSV, and influenza) results were negative.

3. Diagnostic assessment

Upon suspicion of pneumonia, empirical antibiotic treatment with cefotaxime 2 g three times a day was administered. As

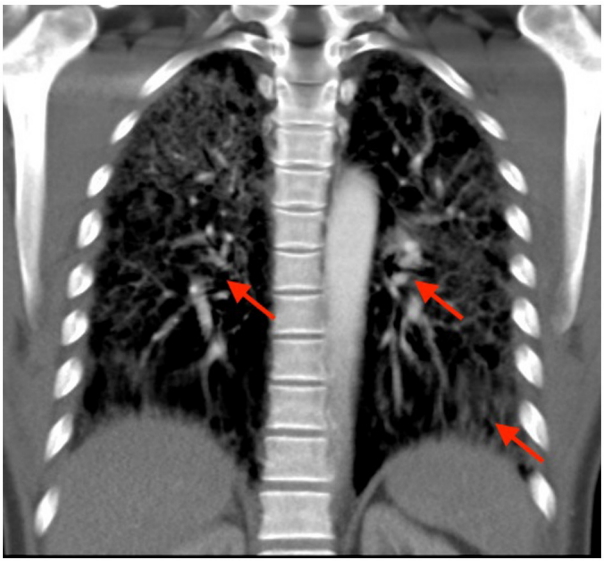

FIGURE 1
Computed tomography scan showing extensive bronchial wall thickening, interlobular septal thickening, and ground glass haziness on both lower lobes with bilateral hilar and mediastinal lymphadenopathy (pathological alterations marked with red arrows).

the patient exhibited a constantly decreasing and insufficient oxygen saturation and required supplemental oxygen up to 9l/min (BGA: pO2 56 mmHg, pH 7.45), he was transferred to the intensive care unit (ICU) on the 6th day after admission, where high-flow oxygen nasal cannula therapy (50l/min, FiO2 70%) was provided and his antibiotic treatment was adapted (piperacillin 4 g/tazobactam 0.5 g three times a day and azithromycin 500 mg once a day) (until the arrival of the negative microbiology results) while psychopharmacotherapy was maintained unchanged. Additionally, a corticoid therapy (starting with 500 mg of prednisolone) was introduced once interstitial pneumonitis was suspected. The latter diagnosis was substantiated using chest computed tomography revealing extensive bronchial wall thickening, interlobular septal thickening, and ground glass haziness on both lower lobes with bilateral hilar and mediastinal lymphadenopathy (Figure 1).

Because of an unremarkable history of substance abuse, familial predispositions, use of tobacco, or relevant exposures, the diagnostic workup described earlier, and as the initiation of lamotrigine augmentation was the only change in his medication at the onset of the respiratory symptoms, lamotrigine-induced pneumonitis was presumed as the most likely diagnosis. Accordingly, lamotrigine was discontinued (Figure 2), and the patient's oxygen demand decreased continuously. As the patient's general condition improved rapidly within a week and the patient was cardiorespiratory stable without supplemental oxygen, we were able to continue his treatment at the psychiatric ward. Subsequently, his corticoid therapy could be gradually reduced and discontinued. Concurrently, an antidepressant augmentation with quetiapine extended release 100 mg (two tablets 50 mg XR) and an antidepressant combination with milnacipran 200 mg per day were established. While a significant improvement of the depressive symptoms was achieved under the abovementioned

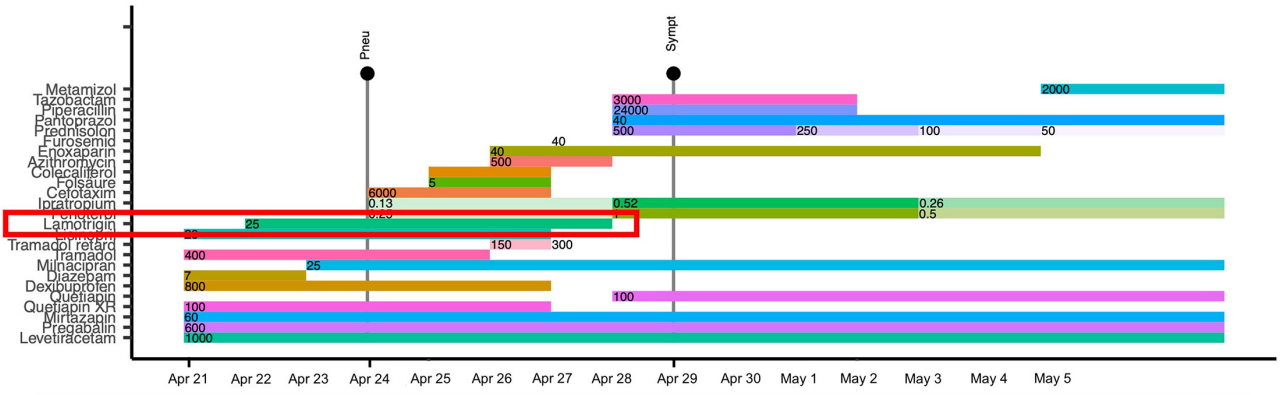

FIGURE 2
Graph showcasing a timeline of the case with the onset of pneumonitis and subsequent symptom reduction. Pneu, Onset of pneumonitis; Sympt, Improvement of symptoms; Apr, April; Folsäure, folic acid.

treatment optimization, a clinically meaningful reduction in his psychosomatic symptoms manifesting as chronic pain was attained after pregabalin was increased to 1,200 mg per day. This is clearly an off-label dose that can only be titrated up according to kidney function (as pregabalin is eliminated predominantly renally), under close observation for potential side effects as well as therapeutic drug monitoring, and was tolerated well in the present case. Additionally, a reduction of perseveration in pain-related thoughts was successful after adding risperidone 2 mg at night. After treatment optimization, a final therapeutic drug monitoring revealed drug levels within the therapeutic range. Contemporaneously with the drug adaptations, the patient experienced relief from the burden of stressful life circumstances resulting in a significant reduction of not only depressive symptoms but also pain. Therefore, from a diagnostic point of view, the initially suspected diagnosis of a persistent pain disorder in the context of the psychiatric multimorbidity seemed confirmed.

4. Discussion

The present case report portrays severe respiratory deterioration that occurred in an adult African male inpatient immediately after the introduction of lamotrigine and that required intensive internal treatment. The consequently presumed diagnosis of a lamotrigine-induced interstitial pneumonitis is supported by previous singular observations on anticonvulsant hypersensitivity syndrome (ACHS), lamotrigine-associated pneumonitis, and the so-called drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with lung involvement (11–15). Previous reports portray both subacute and acute progressions of lamotrigine-induced pulmonary changes. Some describe concomitant skin alterations. In the present case, we were able to observe an acute progression over a couple of days and an isolated pulmonary affection. To exclude the possibility of a lamotrigine overdosage, even though lamotrigine was carefully introduced with a minimum daily dosage of 25 mg, we carried out genetic screening for variations in metabolizing enzymes and checked for possible drug interactions. Unfortunately, plasma concentrations were not measured during the acute phase. In addition to *UGT1A4*, we evaluated polymorphisms in *ABCG2*, *HLA-B*, and *SLC22A1*. For *HLA-B* (16) and *SLC22A1*, we found no relevant alleles associated with lamotrigine levels or toxicity according to pharmgkb.org. For the polymorphism *ABCG2 421C > A*, as found in our patient, an interaction with valproate on the steady-state disposition of lamotrigine with greater troughs was shown. However, the effects were contrary in patients receiving lamotrigine monotherapy with mildly lower troughs (17). Apart from a serious interaction of quetiapine and mirtazapine because of their effect on the QT interval, the interaction check did not show up any drug interactions for lamotrigine. As the diagnostic workup revealed unremarkable results, a hypersensitivity reaction to certain metabolites remained most likely as described in other hypersensitivity reactions to anticonvulsants (18). According to the Naranjo Scale, an algorithm for estimation of the likelihood of an adverse clinical event being actually caused by a specific drug, the pulmonary condition classifies as a probable adverse drug reaction (19). Moreover, the case was systematically documented and extensively discussed in the course of our national (ÖAMSP) and international (AMSP; Institut für Arzneimittelsicherheit in der Psychiatrie - Institute for Drug Safety in Psychiatry) psychopharmacotherapeutic conferences, whereby all medication-related adverse events are considered due to established protocols.

Our experience with a potentially life-threatening adverse drug reaction following the application of the largely well-tolerated lamotrigine might raise awareness for potential side effects under second-generation anticonvulsants including those that are deemed to be very rare (20). Although an altered lamotrigine metabolization seemed unlikely as a triggering factor in the present case and there are no data supporting a higher risk of lamotrigine intolerance in African populations, healthcare professionals might be encouraged to consider genetic testing, particularly on the occurrence of side effects and in the case of treatment resistance. Further research including the transparent documentation of side effects is needed to be able to estimate the risk of hypersensitivity reactions to second-generation anticonvulsants.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/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

VW wrote the case report including the first draft of the manuscript that was further elaborated and critically revised by LB. All authors were meaningfully involved in the performance of the reported therapy and the treatment of the patient, managed the literature search, and reviewed and approved the final manuscript.

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Conflict of interest

GF has received consultant/speaker honoraria from Janssen and Angelini. CK has received travel grants and consultant/speaker honoraria from AOP, Roche Austria, Janssen, and LivaNova. Within the last 3 years, DR has received grant/research support from Janssen and Lundbeck; he has served as a consultant or on advisory boards for AC Immune, Janssen, Roche, and Rovi and he has served on speakers bureaus of Janssen and Pharmagenetix, he also received honoraria from Gerot Lannacher, Janssen and Pharmagenetix, and travel support from Angelini and Janssen. Within the last 3 years, LB has received travel grants and consultant/speaker honoraria from Alpine Market Research, Angelini, Biogen, Diagnosia, Dialectica, Janssen, Lundbeck, Market Access Transformation, Medizin Medien Austria, Novartis, Schwabe, and Universimed. RF has received consulting fees from Janssen-Cilag.

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

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Pathophysiology and management of risperidone-induced sialorrhea: case report

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Background: Among antipsychotics, sialorrhea is most associated with clozapine, and when it occurs, it is uncomfortable, socially stigmatizing, and can contribute to medication non-adherence. Risperidone has a generally negligible muscarinic activity compared to clozapine, and yet, multiple reports of severe sialorrhea associated with risperidone have been reported.

Case presentation: This case report describes risperidone-induced sialorrhea that was unintentionally masked by simultaneous clonidine administration that was intended to treat hypertension. Interestingly, sialorrhea was present but mild when clonidine was present; however, when risperidone was further titrated and clonidine removed, a significant worsening of sialorrhea developed. Sialorrhea did not respond to treatment with anticholinergic medication.

Conclusion: The pathophysiology of antipsychotic-induced sialorrhea is complex and varies between antipsychotics. Risperidone-induced sialorrhea is suspected of having prominent adrenergic pathophysiology that is likely composed of highly viscoelastic saliva (high protein content), differing from the more commonly encountered clozapine-induced sialorrhea. Risperidone-induced sialorrhea is reported as more likely to respond to dose reduction and treatment with α2-adrenergic receptor agonists or β-adrenergic receptor antagonists and less likely to respond to anticholinergic (antimuscarinic) medications.

KEYWORDS

antipsychotics, adverse reactions, psychopharmacology, second-generation antipsychotics, schizophrenia, iloperidone

Background

Sialorrhea is a known potential adverse reaction of antipsychotic medications; however, its incidence varies among antipsychotics, and its pathophysiology is not unanimous. Salivary flow is predominantly under parasympathetic (cholinergic) control, but the sympathetic (adrenergic) system also modulates saliva production (1). Among antipsychotics, sialorrhea is most associated with clozapine, and when it occurs, it is uncomfortable, socially stigmatizing, and can contribute to medication non-adherence (2). Clozapine (including metabolites) has a generally high muscarinic activity compared to the other antipsychotics, which significantly contributes to sialorrhea when it occurs. In contrast, risperidone has a generally negligible muscarinic activity; and yet, multiple reports of severe sialorrhea associated with risperidone have been reported (3–6). This difference demonstrates that sialorrhea as an adverse reaction of antipsychotics has a complex pathophysiology and that the saliva itself in antipsychotic-associated

sialorrhea may have different make-up depending on cholinergic vs. adrenergic stimulation proportions. We present a case of risperidone-induced sialorrhea masked by clonidine that demonstrates risperidone's adrenergic properties having a significant contribution to saliva overproduction.

Case report

A 46-year-old Caucasian male with a medical history of hypertension and psychiatric history of schizoaffective disorder, depressed type, presented to the behavioral health unit with paranoid ideation and aggression. He had previously tolerated quetiapine at 800 mg but was medication non-adherent for an unknown duration of time prior to this presentation. On admission, his vitals were normal except for hypertension (154/94 mmHg). Urine toxicology screening was negative, and his labs were unremarkable. On hospital day 1, he was started on risperidone 1 mg twice daily to treat psychosis. On hospital day 2, risperidone was increased to 1.5 mg twice daily. Simultaneously, the patient was started on clonidine 0.1 mg twice daily for ongoing hypertension. Clonidine was chosen for short-term use, as it was unclear if the patient had chronic hypertension in early hospitalization. As hypertension continued, on hospital day 3, amlodipine 10 mg daily was added to his regimen with titration of risperidone to 2 mg twice daily. On hospital day 4, the patient exhibited mild sialorrhea [drooling severity score: 3, moderate (2, 7, 8)] along with mild muscle rigidity and was administered benztropine 2 mg intramuscular for extrapyramidal symptoms that alleviated the rigidity only. Throughout that night, his blood pressure remained elevated, prompting consultation with internal medicine, who recommended discontinuing his clonidine and adding lisinopril 20 mg daily. The final hypertension regimen for hospitalization was lisinopril 20 mg daily and amlodipine 10 mg daily.

The next day, on hospital day 5, risperidone was also titrated to 6 mg daily. After the discontinuation of the clonidine, the patient had significantly worsened thick mucinous saliva and was found to have cogwheel rigidity with masked facies (Figure 1). In response, he started on a benztropine 2 mg daily but had no alleviation of severe mucinous sialorrhea and was wearing a towel over his shoulder due to the amount [Drooling severity scale rating: 5, profuse (2, 7, 8)]. The patient utilized atropine 1% ophthalmic drops (administered orally sublingually) but still had minimal relief of sialorrhea despite frequent use. His worsening rigidity and sialorrhea on hospital day 6 prompted medication changes, including discontinuing risperidone and benztropine and starting olanzapine 10 mg daily. After the medication changes, the patient's sialorrhea and rigidity began to subside and eventually resolved. The patient was later transitioned to quetiapine 300 mg prior to discharge and did not experience any further psychotropic-induced adverse reactions.

Discussion

Case analysis and scientific implications

This case report describes risperidone-induced sialorrhea unintentionally masked by simultaneous clonidine administration intended to treat hypertension. Interestingly, sialorrhea was present but mild when clonidine was present; however, when risperidone

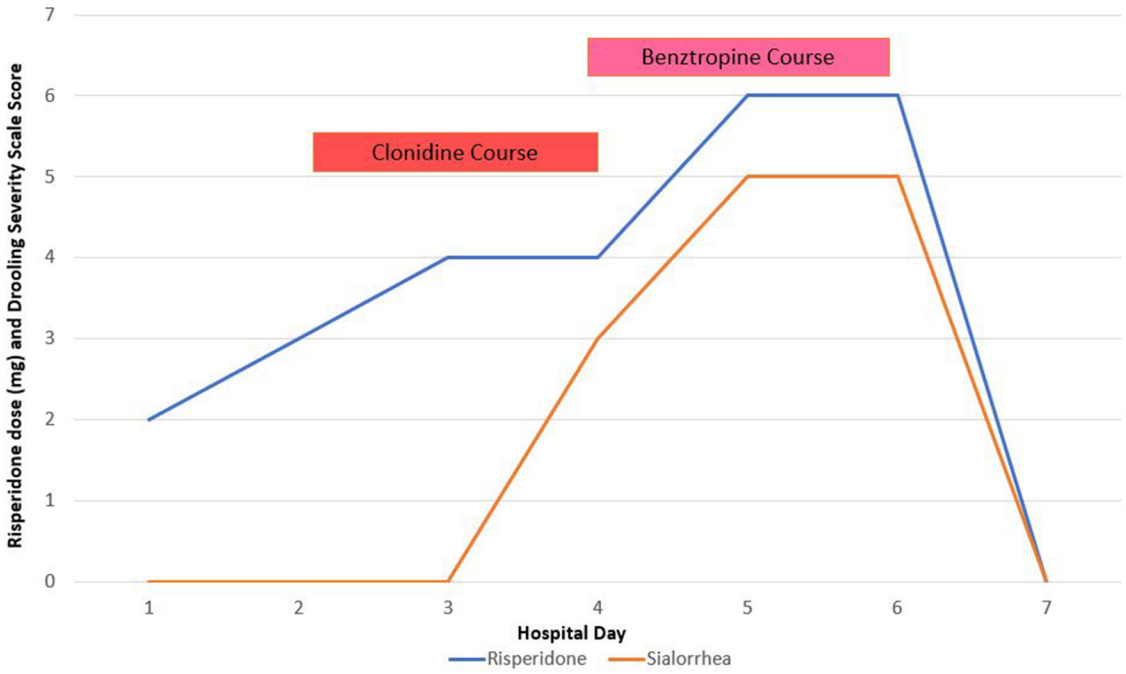

FIGURE 1
Medication course and adverse event timeline.

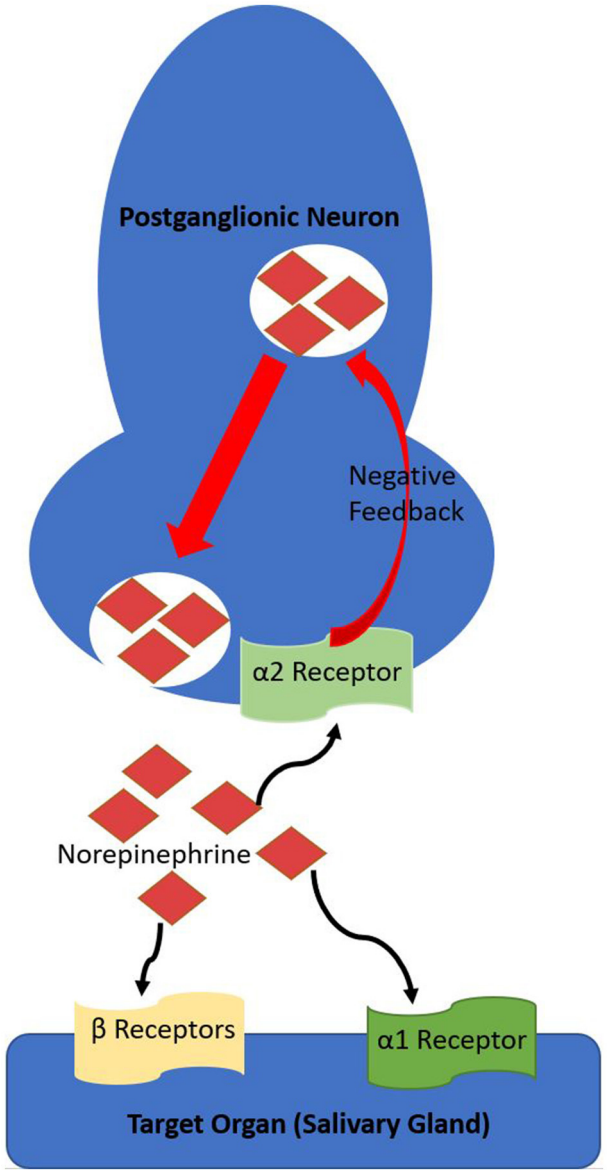

FIGURE 2
Overview of the sympathetic (adrenergic) pathway and α_2-adrenergic receptor role in negative feedback. The α_2-adrenergic receptor is a Gi-coupled metabotropic receptor, decreasing intracellular cAMP, thereby decreasing exocytosis.

was further titrated and clonidine removed, significant worsening of sialorrhea developed, and this was scored by the drooling severity scale. There was no relief of sialorrhea with benztropine and minimal relief with atropine. Clonidine, an α_2-adrenergic receptor agonist, did alleviate sialorrhea and suggests that risperidone's α_2-adrenergic receptor antagonism is a key mechanism in risperidone-induced sialorrhea. We hypothesize that risperidone-induced sialorrhea has higher protein content (higher viscosity) compared to clozapine-induced sialorrhea due to risperidone's adrenergic stimulation mechanism. Although salivary composition analysis was not obtained in this patient, the physical examination did reveal congruent thick mucinous saliva. To investigate this hypothesis further, future cases that suspect risperidone-induced sialorrhea are suggested to obtain saliva composition analysis.

Fundamentals of saliva production

Saliva production is a constant process, but the amount and viscoelasticity (protein content and viscosity) are dependent on multiple factors, including proportions of sympathetic vs. parasympathetic stimulation and circadian rhythm (1). Mastication induces parasympathetic stimulation, predominately by M_1 and M_3-Muscarinic receptors, which produces copious saliva of low protein concentration (low viscoelasticity) (1, 2). M_4-muscarinic receptors stimulation also appears to increase saliva output (2, 9). Sympathetic (adrenergic) stimulation results in saliva production of lower volume but higher protein concentration (high viscoelasticity) (1, 2). α_2-adrenergic receptors provide negative feedback for sympathetic stimulation (Figure 2), decreasing salivary flow when stimulated (10). Antagonism of α_2-adrenergic receptors increases salivation by disinhibition, leaving α_1-adrenergic and β-adrenoreceptors unopposed to induce a protein-rich, catecholamine-concentrated, and increased rate of flow hyper-salivatory state (10). The α_2-adrenergic hypersalivation mechanism was demonstrated in multiple studies utilizing yohimbine, a potent α_2-adrenergic antagonist (11, 12).

Hypothesized pathophysiology of risperidone-induced sialorrhea

Risperidone and clozapine are both second-generation (atypical) antipsychotics but have differing neuroreceptor affinity across their mechanisms of action (Table 1); these differences are responsible for their differing therapeutic efficacies as well as their most common adverse reactions. We hypothesize that risperidone-induced sialorrhea is likely a result of potent α_2-adrenergic antagonism. Risperidone-induced sialorrhea may have some pathophysiological contributions from its antimuscarinic activity; however, these neuroreceptor affinities are far less potent than its α_2-adrenergic antagonism.

Clozapine-induced sialorrhea is much more common than risperidone-induced sialorrhea, and its pathophysiology is more robustly studied. Clozapine-induced sialorrhea is a result of clozapine's potent M_4-muscarinic partial agonism and its metabolite norclozapine having potent muscarinic agonism (15). Clozapine-induced sialorrhea likely has some pathophysiological contribution from α_2-adrenergic antagonism, but it is not as potent at this neuroreceptor in comparison to M_3 and M_4 muscarinic receptors or to risperidone. This likely results in lower viscoelastic saliva compared to risperidone-induced sialorrhea, but no direct comparisons are documented, and it also probably slightly varies from case to case. An additional pathophysiological mechanism of sialorrhea from clozapine results from decreased laryngeal peristalsis and inhibition of swallow reflex from its potent muscarinic modulation (16), which is likely less contributory in risperidone-induced sialorrhea.

TABLE 1 Antipsychotic receptor binding affinities.

	M_1-muscarinic receptor	M_3-muscarinic receptor	M_4-muscarinic receptor	α_2-adrenergic receptor	Dopamine D_2 receptor	Serotonin 5-HT_{2A} receptor
Risperidone	>10,000	>10,000	>10,000	8	3.8	0.15
Paliperidone	>10,000	>10,000	>10,000	80	2.8	1.2
Clozapine	1.4	109	27	158	210	2.59
Quetiapine	120	1,320	660	80	770	31

Data is represented by the equilibrium constant (K_i), the nanomolar amount required to block 50% of the specified receptor. Pharmacokinetically, the lower an equilibrium constant (K_i), the stronger a receptor is bound (2, 13, 14).

TABLE 2 Summary of salivary flow by the agonism or antagonism associated with common antipsychotic mechanisms of action.

Receptor	Saliva flow modulation by receptors of interest			
	M1-muscarinic receptor	M_3-muscarinic receptor	M_4-muscarinic receptor	α_2-adrenergic receptor
Agonism	Increased flow	Increased flow	Increased flow	Decreased flow
Antagonism	Decreased flow	Decreased flow	Decreased flow	Increased flow (increased viscoelasticity)

Viscoelasticity describes protein concentration in saliva (1, 2, 9, 10).

Management of risperidone-induced sialorrhea

Sialorrhea is uncomfortable for the individual experiencing it and has significant psychosocial implications. Wet clothing may result in social stigmatization and embarrassment. The need to carry towels and "spit cups" can impair vocational functioning (2). The psychosocial complications of antipsychotic-induced sialorrhea may be a reason for a patient to self-discontinue their medication treatment (17, 18). Therefore, it is paramount to manage this adverse reaction in cases the therapeutic benefit of risperidone is substantial. Further, managing sialorrhea reduces the risk of its medical complications, which can include choking sensation, dysphonia, irritated, and macerated skin in perioral areas, cheilitis, sleep disturbance, and aspiration (2).

Switching antipsychotics or reducing the dose of risperidone would be an optimal first step in managing suspected risperidone-induced sialorrhea. If risperidone-induced sialorrhea only occurs after titrating risperidone to a high dose, tapering down to a previously tolerated lower dose may be considered (3, 4), although this will likely congruently decrease its antipsychotic effectiveness. Many of the therapeutic benefits of risperidone are also due to its conversion to its active metabolite of paliperidone. Paliperidone has a 10-fold weaker affinity for α_2-adrenergic antagonism compared to risperidone (Table 2). Therefore, patients who benefit from the antipsychotic effects of risperidone but develop mild-moderate sialorrhea on it may be able to maintain similar treatment efficacy by transitioning to paliperidone and monitoring for a reduction in sialorrhea. However, paliperidone-induced sialorrhea has also been reported (19). Risperidone metabolism utilizes cytochrome P450 enzymes 2D6 and 3A4, and genetically inherited impaired activity of these enzymes may lead to the predisposition of risperidone-induced adverse reactions, including sialorrhea (20).

As described in this case report, clonidine has been reported as alleviating risperidone-induced sialorrhea, hypothesized due to its properties as a centrally acting α_2-adrenergic receptor agonist. Similarly, Gajwani et al. (5) also reported a case of risperidone-induced sialorrhea that did not respond to benztropine but was alleviated with clonidine. Other medications in this class include lofexidine, guanfacine, guanabenz, α-methyldopa, and moxonidine, but have not been reported in the literature as an attempted treatment for risperidone-induced sialorrhea (2). β-adrenergic receptor antagonists such as propranolol are theoretically another treatment option for risperidone-induced sialorrhea. This treatment would aim to halt the unopposed β-adrenergic receptors resulting from risperidone's α_2-adrenergic antagonism (Figure 2) (2). β-adrenergic receptor antagonists are known to decrease salivary viscoelasticity but not necessarily the volume of saliva (21).

Anticholinergic (antimuscarinic) medications are commonly prescribed medications for treating clozapine-induced sialorrhea. Atropine ophthalmic drops are frequently used and administered sublingually and on the inside of the cheeks, with many patients reporting relief of sialorrhea (22). We predict that due to likely differences in pathophysiology for clozapine vs. risperidone-induced sialorrhea, selective and non-selective anticholinergic (antimuscarinic) medications are less likely to relieve risperidone-induced sialorrhea, despite some efficacies reported with clozapine-induced sialorrhea. Still, risperidone dose reduction and the addition of diphenhydramine were reported as therapeutic in one case of risperidone-induced sialorrhea (6); and another case was treated with risperidone dose reduction down to a previously tolerated dose and adding biperiden (4).

Conclusions

The pathophysiology of antipsychotic-induced sialorrhea is complex and varies between antipsychotics. Risperidone-induced sialorrhea is suspected of having prominent adrenergic

pathophysiology, likely composed of highly viscoelastic saliva (high protein content), differing from the more commonly encountered clozapine-induced sialorrhea. Risperidone-induced sialorrhea is reported to be more likely to respond to dose reduction, treatment with α_2-adrenergic receptor agonists or β-adrenergic receptor antagonists, and less likely to respond to anticholinergic (antimuscarinic) medications.

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 human participants were reviewed and approved by Kern Medical Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

TT and AK formulated the analysis and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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: Hyperactive delirium after a single dose of zolpidem administered additionally to psychopharmacotherapy including clozapine

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The non-benzodiazepine hypnotic zolpidem is frequently administered as a short term psychopharmacotherapy for insomnia. Although it is well-established in a broad clinical routine and often well-tolerated, severe delirium and complex sleep behavior were reported in rare cases. Hereby, it remains unclear whether zolpidem's potential for delirium might be enhanced when combined with further psychopharmacotherapeutics. The present case report portrays a young male Caucasian inpatient with schizoaffective disorder, who was admitted due to severe hyperactive delirium after a single dose of zolpidem 10 mg that was administered in addition to already established psychopharmacotherapy including clozapine 200 mg/day, aripiprazole 15 mg/day and cariprazine 4.5 mg/day. In detail, disorientation, agitation, confabulations, bizarre behavior, and anterograde amnesia occurred shortly after ingestion of zolpidem and gained in intensity within a couple of hours. Once zolpidem was discontinued, the abovementioned symptoms subsided completely and did not reoccur. Since a clear temporal association could be drawn between the intake of zolpidem and the onset of hyperactive delirium, the present clinical experience should serve as a cautionary note for combining potent sedative-hypnotics and substances with anticholinergic properties, even in young adults in a good general condition. Moreover, our case argues for the necessity of further research into the pathomechanism of the interaction potential of non-benzodiazepines as zolpidem, especially with substances exerting anticholinergic properties, which are known for their potential to precipitate delirium. Therefore, the metabolic pathways of the concurrently administered substances should be further taken into account.

KEYWORDS

hyperactive delirium, anterograde amnesia, non-benzodiazepine, zolpidem, clozapine

1. Introduction

Zolpidem is a gamma-aminobutyric acid ($GABA_A$) receptor agonist of the imidazopyridine class that is primarily indicated for a short term (≤4 weeks) psychopharmacotherapy of insomnia (1). It acts as rapid and short-acting potent sedative with only minor anxiolytic, anticonvulsant, and muscle-relaxant properties (2). As agonist at the benzodiazepine receptor component of the GABA alpha-receptor complex, zolpidem mediates an inhibition on excitatory neurons. It is predominantly eliminated via the hepatic route into three pharmacologically inactive metabolites, mainly through the cytochrome P450 isoenzyme CYP3A4 (1, 2).

In patients with insomnia, efficacy of this non-benzodiazepine hypnotic has been shown to be comparable with benzodiazepines, while being less addictive. Although nausea, dizziness, drowsiness, and diarrhea have been described as common adverse effects (AEs) (1–3), zolpidem is commonly well-tolerated and largely accepted by the patients. Despite its broad employment in the clinical routine, severe AEs like anterograde amnesia, delirium, and complex sleep behavior have been observed occasionally and in some cases have led to grave incidents in patients and those around them (3–12). Whether zolpidem's potential for delirium might be triggered when combined with further psychopharmacotherapeutic agents has, however, not been systematically investigated yet. This might be of clinical relevance especially in case of combination treatments with agents exerting anticholinergic effects, which are known for their potential to precipitate delirium.

Here, we report a case of a young male Caucasian inpatient, who was admitted due to severe hyperactive delirium with disorientation, agitation, confabulations, bizarre behavior, and anterograde amnesia after a single dose of zolpidem 10 mg.

2. Case description

On the 20th September 2022, a 34-year-old male patient of Caucasian ethnicity with a history of schizoaffective disorder of predominantly mixed type (ICD-10: F25.2, DSM-5: 295.70) was admitted to a general psychiatric ward of the Medical University of Vienna, Austria due to acute disorientation, agitation, and bizarre behavior. According to his spouse and parents, the patient had woken up around midnight of the day of admission and presented in a state of acute confusion and agitation. Contrary to a normal episode of sleep inertia, the aforementioned symptoms continued to intensify. Reportedly, the patient was partially oriented and not able to fall asleep again due to his state of agitation. He claimed to suffer from "a storm of thoughts" and elicited bizarre behavior with out of context comments and actions (e.g., denying the presence of his spouse beside him in bed despite her actual presence as well as consistently interpreting idiomatic expressions in a literal sense). Because his symptoms did not mitigate until midday, he was admitted to the psychiatric ward, where he had been receiving treatment in the course of the known schizoaffective disorder before. His daily medication upon admission comprised clozapine 200 mg, cariprazine 4.5 mg, aripiprazole 15 mg, and doxycycline 300 mg (cariprazine had been additionally prescribed by his outpatient psychiatrist for the past 2 weeks due to insufficient clinical improvement). On the ward the patient continued to present perplexed, only partially oriented in a fluctuating manner (e.g., believing it was winter and later realizing it was fall, or asserting that they had visited a winter's market before admission), and with vivid confabulations (e.g., claiming to have been fed oranges in front of the clinic and subjectively recalling arriving with a large bag instead of a small backpack, persistently searching for the abovementioned bag). He was not physically aggressive in any way toward others or himself. However, due to the hyperactive delirium and the state of agitation a constant 1:1 supervision by medical staff was necessary.

Regarding diagnostics, the patient's vital signs, urinary drug test, blood alcohol levels, and electrocardiography (ECG) were unremarkable. A comprehensive blood analysis showed normal results, with the exception of slightly elevated levels of alkaline phosphatase (139 U/L, RI: 40–130 U/L) and alanine transaminase (78 U/L, RI: <50 U/L). Plasma levels of clozapine were within therapeutic range, while aripiprazole showed values slightly below. In addition, The pharmacogenetic cytochrome P450 testing to determine drug-metabolizing capacity of the liver enzymes revealed an ultra-rapid metabolizer genotype for isoenzyme 1A2, with other findings of negligible importance. Moreover, during the last admission in August 2022 cranial magnetic resonance imaging (MRI) yielded no pathological findings, while a cerebrospinal fluid (CSF) analysis had shown elevated liquor/serum levels of borrelia antibodies. Tests for CSF pleocytosis, CXCL13-protein, borrelia-PCR, and borrelia culture turned out to be negative. The absence of neuroborreliosis-specific clinical symptoms, such as erythema migrans or cranial nerve palsy, in addition to no reported tick bites within the last 2 years, led to the interpretation of this finding as either a false-positive result or suggestive of an asymptomatic past infection (13). Nonetheless, in accordance with recommendations from the university department of neurology and in line with current guidelines (14), the patient has received a prophylactic antibiotic treatment with doxycycline from the 2nd Sept. to the 23rd Sept. 2023 (21 days).

Regarding the patient's history, the schizoaffective disorder first manifested 1.5 years prior, characterized by hyperactivity and vivid delusions without hallucinations or disorientation. In previous admissions, he mainly exhibited a depressed mood and mild delusions, effectively managed upon his last discharge in August 2022. The patient had no history of substance use disorder nor further relevant comorbidities. Of notable importance was the positive family history, specifically the occurrence of suicide during a severe depressive episode in the patient's older brother in 2007. Concerning his psychopharmacotherapy, the patient had previously taken zolpidem 10 mg on an as-needed basis, which was well-tolerated at the time. Subsequently, zolpidem was discontinued prior to the initiation of clozapine and aripiprazole. Moreover, the patient experienced a previous brief episode with disorientation and audiovisual hallucinations under clozapine 200 mg/day and bupropion 150 mg/day, which resolved quickly after discontinuing both. Clozapine was later incrementally and successfully reestablished due to its effectiveness in treating the patient's schizoaffective disorder.

Toward the evening of admission, the symptoms finally subsided, and 17 h after their initial onset the patient was fully oriented again and did not experience any residual symptoms. Remarkably, suffering from anterograde amnesia he claimed

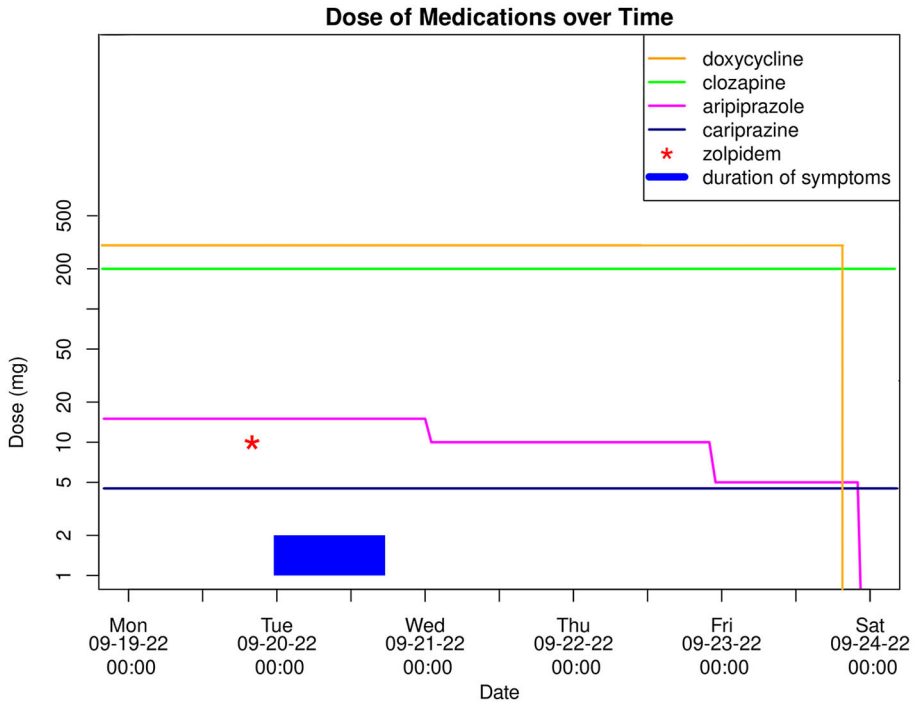

FIGURE 1
Graph showcasing a timeline of the case with dosage of medication (logarithmic scale) and duration of symptoms.

to have fallen asleep in his bed at home and woken up in hospital. According to the patient's report, he had taken an single dose of zolpidem 10 mg ~4 h before the incident because of sleep disturbances without prior consultation of his outpatient psychiatrist. In the course of his inpatient treatment optimization, he was asked to avoid taking zolpidem in the future, while his ongoing antipsychotic combination treatment with clozapine 200 mg/day and cariprazine 4.5 mg/day was continued. Due to similar pharmacological properties of cariprazine and aripiprazole, which may potentiate AEs when combined (15), the latter was gradually discontinued (see Figure 1). During the following observation period of 6 days, none of the aforementioned symptoms reoccurred and the patient could be discharged from the hospital in a fully remitted state.

Upon follow-up approximately 8 months later, the patient reported to have remained stable on the unchanged medication without experiencing any further delirious symptoms. He attributed the delirious episode to zolpidem and reported abstaining from its use since then.

3. Discussion

The present case illustrates the occurrence of hyperactive delirium with anterograde amnesia in a young adult Caucasian male after a single dose of zolpidem 10 mg that was taken additionally to already established antipsychotic as well as an antibiotic treatment. The presumed causal association with zolpidem is supported by the fact that symptoms of delirium initiated shortly after ingestion of zolpidem, terminated after an approximate equivalent of five half-life circles of the drug (2), and did not reoccur once zolpidem was discontinued. According to the Naranjo Scale, which is an algorithm used to determine the likelihood of a specific drug causing an adverse clinical event, this case of hyperactive delirium can be classified as a probable adverse drug reaction to zolpidem (16). Moreover, this case was systematically documented and thoroughly discussed during one of our national psychopharmacotherapeutic conferences conducted by ÖAMSP (Austrian Institute for Drug Safety in Psychiatry), where medication-related adverse events are regularly evaluated in accordance with established protocols.

In this context it is noteworthy that in <1% of available patient cases, zolpidem has shown to elicit complex sleep behavior or delirium (17), sometimes resulting in significant self-harm or harm to others (5–7, 12). This non-benzodiazepine substance selectively binds to the benzodiazepine omega1-receptor subtype in the central nervous system, specifically to the alpha-1 subunit. The omega1-receptor subtype is implicated in memory loss (18), contributing to anterograde amnesia, while binding at the alpha-1 subunit seems essential for the hypnotic/sedative effects and other adverse events of zolpidem (19). These hypnotic AEs and delirium, according to literature, are dose-dependent and more common in older individuals (5, 6).

Nevertheless, zolpidem was taken only once at a standard dose and previously had been tolerated well, indicating that it could not be solely responsible in eliciting delirium in our patient. The involvement of doxycycline was ruled out, as there is currently no evidence suggesting its association with delirium, either independently or in interaction with zolpidem or antipsychotics (20). In rare cases of acute neuroborreliosis delirium

was sometimes observed, typically accompanied by inflammatory signs (e.g., CSF pleocytosis) and neurological symptoms including paresis (21). Yet our patient did neither exhibit neurological symptoms nor signs of CSF pleocytosis and received ongoing antibiotic treatment, rendering the involvement of neuroborreliosis highly unlikely.

Clozapine, however, with its anticholinergic properties is known for the potential to elicit delirium (22). It can be posited that the combination of zolpidem with clozapine might have been a leading factor in the development of delirium, especially considering the prior occurrence of delirium induced by clozapine in this patient. Additionally, zolpidem, cariprazine, aripiprazole, and to some extent clozapine undergo hepatic metabolism via CYP3A4 (23). Competitive inhibition of CYP3A4 by these drugs could have raised zolpidem plasma levels, potentially playing a role in the onset of delirium. Furthermore, we are aware that the lack of titration of zolpidem from 5 to 10 mg may have exacerbated the condition. Lastly, the observed slightly elevated alanine transaminase levels might have pointed to already mildly impaired liver functioning, in turn further increasing zolpidem plasma levels and therefore its hypnotic effects.

Another potential contributing factor to the observed AEs could be explained by the D2 receptor competition associated with the antipsychotics aripiprazole, cariprazine (both characterized by long elimination half-lives), and clozapine. However, given that aripiprazole did not reach therapeutic plasma concentrations and was gradually discontinued only after the complete resolution of all AEs, the impact of D2 receptor competition in the development of delirium in this patient may be considered relatively minor.

4. Conclusion

Our experience with a patient exhibiting severe hyperactive delirium with anterograde amnesia after a single standard-dose of zolpidem in addition to already established psychopharmacotherapy including clozapine, arpipiprazole and cariprazine serves as a cautionary note for combining potent sedative-hypnotics with other psychopharmacotherapeutics sharing the same metabolizing pathways, even when treating young adults who are in good general condition. While it's important to acknowledge the limitations of generalizing from a single case report, the significance of this particular incident should not be overlooked, as it resulted in our patient's inadvertent hospitalization. Average daily doses of zolpidem have been reported to result in grave consequences for several patients and those around them before (4–6, 12). Although AEs of zolpidem are usually time-limited and fully reversible, they may bear a relevant hazard potential. Hence, further research should be conducted into the pathomechanism of the interaction potential of non-benzodiazepines like zolpidem, especially with substances exerting anticholinergic properties, which are known for their potential to provoke delirium. Furthermore, the present case report provides a valuable argument for routine laboratory evaluation including genetic testing of cytochrome P450 enzyme activity, which would inform in advance about the individual metabolizing status and therefore possible vulnerability to drug-related AEs.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/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

MP wrote the case report including the first draft of the manuscript that was further elaborated and critically revised by LB. All listed authors were meaningfully involved in the performance of the reported therapy and the treatment of the patient and managed the literature search and have reviewed and approved the final manuscript.

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Conflict of interest

GF has received consultant/speaker honoraria from Janssen and Angelini. RF has received consultant/speaker honoraria from Janssen and LivaNova. Within the last 3 years, RF has received a Principial Investigator grant, consultation fees, and speakers honoraria from Janssen, Principial Investigator grants from Alkermes and Liva Nova, and speakers honoraria from Lundbeck. Within the last 3 years, LB has received travel grants and/or consultant/speaker honoraria from Alpine Market Research, Angelini, Biogen, Diagnosia, Dialectica, Janssen, Lundbeck, Market Access Transformation, Medizin Medien Austria, Novartis, Schwabe and Universimed.

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

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A case report—"When less is more": controlled inpatient reduction of anticholinergic burden in a patient with clozapine-resistant schizophrenia

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The functional status of an individual with schizophrenia is the defining factor in their quality of life and is closely associated with cognitive abilities, which are impaired in individuals with schizophrenia and considered to be the core symptom of the disorder. The use of psychopharmacotherapy can also have a significant impact on cognitive functioning. The relationship between clozapine treatment and cognitive impairment in individuals with schizophrenia is an intricate one. While some studies have reported a positive effect of clozapine on learning and memory, other studies have found that patients treated with clozapine experienced a decline in cognitive functioning in particular areas. In particular, attention and memory have been shown to deteriorate with rising plasma levels of clozapine. This effect may be attributed to its anticholinergic effect. A reduction in the medication related to anticholinergic burden has been previously found to improve cognitive abilities. In the presented case, we describe a psychotic relapse with delirium symptoms in a patient on clozapine treatment with potentially toxic clozapine blood level. The symptoms of delirium subsided after a clozapine dose adjustment. Gradually lowering the initially very high anticholinergic burden improved the patient's cognitive functioning.

KEYWORDS

anticholinergic burden, treatment-resistant schizophrenia, cognition, clozapine blood level monitoring, delirium

Introduction

Clozapine is the most efficient medication for treatment-resistant schizophrenia, which occurs in ~30% of schizophrenia patients, 12–20% of whom are clozapine-resistant (1, 2). Despite its superior efficacy and antipsychotic, anti-aggressive, anti-suicidal, and anti-impulsive properties, it is reserved for resistant cases due to its potentially severe side effects (3). Close monitoring for agranulocytosis, myocarditis, and intestinal obstruction is necessary. Only 40% of resistant schizophrenia patients, however, will fully respond to clozapine, and of these, between 40 and 70% will develop clozapine resistance over time (4). Other side effects, such as weight gain, hypersalivation, sedation, tachycardia, and seizures, can complicate treatment and require additional medications (5).

Cognitive impairment is among the core features of schizophrenia, and clozapine's prominent anticholinergic properties may further compromise cognitive function. Joshi et al. showed that patients with schizophrenia with higher cumulative ACB (Anticholinergic Cognitive Burden Scale) scores had significantly greater cognitive impairment, with

optimistic preliminary results after lowering the anticholinergic burden (6). The ACB scale assigns a dose-independent rating to each medication based on its anticholinergic properties. This is not an exact or accurately quantifiable measure of anticholinergic burden, but rather an estimate that takes into account the known characteristics and data of each given medication. When anticholinergic side effects are present or best avoided, such as in geriatric patients, or are a clinically evident problem, the scale is useful in determining which medications contribute significantly to the anticholinergic burden and can support clinicians in making an informed decision to optimize the prescribed medication regimen. Additionally, delirium has been described as an uncommon side effect of clozapine treatment, probably due to its central anticholinergic properties (7). Clozapine's low antidopaminergic activity in combination with simultaneous acetylcholine decreases may also contribute to the development of delirium, especially hyperactive forms (8).

In the case presented, we describe a real-life clinical example of treatment-resistant schizophrenia in which symptoms of the underlying psychotic disorder overlap with adverse effects of clozapine and other prescribed medications. This case is an example of complex polypharmacy. The objective is to elucidate the clinical importance and complexity associated with distinguishing between primary symptoms and potential adverse effects of medications. Our main emphasis lies on anticholinergic side effects, particularly the cognitive impairment resulting from the anticholinergic burden of medications. These cognitive impairments may coincide with the inherent cognitive deficits observed in schizophrenia. Furthermore, in the case presented, anticholinergic delirium is shown to overlap with acute exacerbations of positive symptoms. This represents an important issue, as polypharmacy is extremely common in the treatment of schizophrenia. Our aim is to emphasize the significance of identifying and distinguishing between the primary symptoms and medication-related adverse effects and to demonstrate the benefits, in this case in terms of cognitive and functional status, of adjusting the medication accordingly. Additionally, we would like to stress the benefits of an interdisciplinary approach in cases of complex polypharmacy, in particular consultation with a clinical pharmacist, as this has previously been shown to improve clinical outcomes (9).

Case description

A 57-year-old female patient with treatment-resistant and arguably clozapine-resistant schizophrenia on clozapine treatment presented with acute psychotic symptoms. She exhibited bizarre delusions, auditory and possibly tactile and visual hallucinations, and disorganized speech, and there were reports of aggressive tendencies. The patient had been treated for paranoid schizophrenia since 1995. During this period, she had been hospitalized several times in our clinic due to acute exacerbations of psychotic symptoms. In 2016, with her consent, she was admitted to a specialized long-term care facility because of an impairment in social functioning and a severely diminished capacity for independent functioning.

Initially, the subjects was prescribed the same medications and dosages as in the long-term care facility, i.e., clozapine 700 mg/day divided into three daily doses, zuclopenthixol decanoate 200 mg LAI every 2 weeks, zuclopenthixol 25 mg/day (oral), biperiden 6 mg/day, flurazepam 15 mg at bedtime, and lorazepam 5.5 mg/day. This placed the patient at high risk for confusion, falls, or death due to the high anticholinergic burden on the ACB scale. There were no reports of recent changes in any of the medications.

During the first week on the ward, she exhibited marked variability in observed clinical presentations, with persistent reports of auditory hallucinations and bizarre delusions as well as superimposed reports of episodes of extremely disorganized behavior with escalations of psychomotor agitation, apparent disorientation, and confusion. These episodes usually occurred at night and were related to severe insomnia, which led to the use of additional benzodiazepines or haloperidol. The nursing staff regularly reported that she seemed to be experiencing visual hallucinations during these periods.

We hypothesized that the patient was experiencing episodes of delirium, possibly anticholinergic delirium. A general workup, including a clinical examination, laboratory tests, and microbiologic assays, was performed to exclude other possible precipitating factors or causes of delirium. A plasma clozapine level was obtained during Week 2 of hospitalization; the results were 1,130 μg/L, markedly above the current consensus for the minimum plasma level required to achieve a clinical response (350 μg/L) and also above the recommended laboratory alert level of 1,000 μg/L (10). The patient, however, did not present with other possible symptoms of clozapine toxicity (seizures, hypersalivation, tachycardia, hypotension, sedation, coma, and respiratory depression). Possible partial epileptic seizures were excluded by the EEG. We consulted an in-hospital clinical pharmacist and proceeded to gradually reduce the clozapine dose by ∼25 mg per week, reaching 450 mg/day by Week 11. This resulted in a plasma clozapine level of 435 μg/L at Week 15 of hospitalization. The clozapine/N-desmethylclozapine ratio also shifted from 1.82 to 0.98 (both levels obtained at steady-state conditions). The relatively high doses of benzodiazepines prescribed could, of course, further worsen the delirium, so we gradually reduced the dose but decided against abrupt discontinuation to avoid severe withdrawal symptoms, given that the patient had been on these medications for a long time leading up to this hospitalization. The signs of delirium slowly dissipated. The sleep-wake cycle was re-established, and there was no need for flurazepam or additional hypnotic medication at bedtime.

To further reduce the anticholinergic burden, biperiden was gradually withdrawn, and the interval between doses of zuclopenthixol 200 mg LAI was increased to every 4 weeks. To avoid possible rebound symptoms, the anticholinergics were gradually tapered, and we regularly screened for a possible worsening of psychotic features. In the case of biperiden, no information was provided by the long-term care facility as to why this medication was prescribed in the first place, but no signs of movement disorders were recorded following its discontinuation. Additionally, to ensure sufficient control of the symptoms of the primary disorder, clozapine therapy was augmented with the addition of amisulpride, 1,000 mg/day by Week 21, and lamotrigine, 200 mg/day by Week 17. Her Mini-Mental State Examination

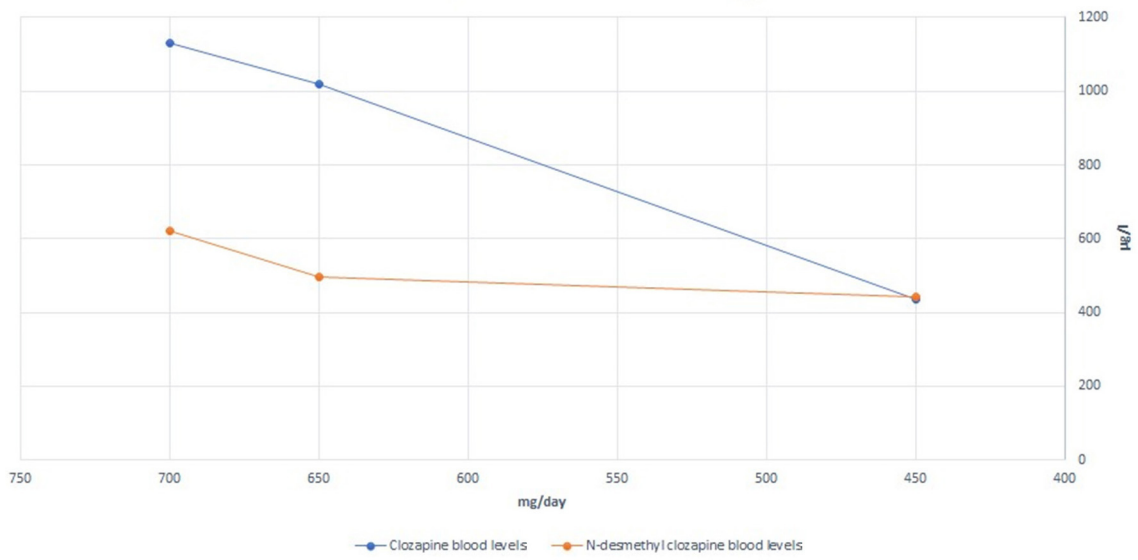

FIGURE 1
Clozapine blood level monitoring.

scores improved from 13/30 on Week 10 to 22/30 on Week 21.

In total, the patient was hospitalized for 22 weeks. She was discharged from the hospital with the following medications: clozapine 450 mg/day, amisulpride 1,000 mg/day, lamotrigine 200 mg/day, zuclopenthixol 200 mg LAI every 4 weeks, zuclopenthixol 30 mg/day, divided into three daily doses, and lorazepam 6.5 mg/day, divided into three daily doses, and with the option of a gradual dose reduction in the long-term care facility. In an attempt to improve her cognitive function even further, an acetylcholinesterase inhibitor was empirically added to her medications prior to discharge. She was prescribed a transdermal patch with 9.5 mg of rivastigmine/day. A detailed presentation of the changes in medications and recorded clozapine and N-desmethylclozapine levels is shown in Figure 1 and Table 1.

Discussion

The functional status of an individual with schizophrenia is the defining factor in their quality of life and is closely associated with cognitive abilities, which are impaired in people with schizophrenia and are considered to be the core symptom of the disorder. The use of psychopharmacotherapy can also have a significant impact on cognitive function.

The relationship between clozapine treatment and cognitive impairment in people with schizophrenia is an intricate one. While some studies have reported a positive effect of clozapine on learning and memory, other studies have found that patients treated with clozapine experienced a decline in cognitive function in specific areas. In particular, attention and memory have been shown to deteriorate with increased plasma levels of clozapine (11, 12). This effect may be due to its anticholinergic activity. A reduction in the medication related to anticholinergic burden has previously been found to improve cognitive function (13).

In this case, the initial plasma clozapine levels were distinctly above the reported plasma levels, beyond which no additional antipsychotic benefit is to be expected in most individuals, while dose-dependent adverse effects become increasingly likely (10, 14). Given both the high anticholinergic burden due to the clozapine plasma levels and other anticholinergic medications, an expected cognitive deficit was objectively shown using the mini-mental state examination. We would also like to point out the possible effect of the change in the clozapine/N-desmethylclozapine ratio between the first and second plasma levels obtained. It has previously been suggested that the ratio of clozapine to N-desmethylclozapine may independently influence cognitive performance due to the different muscarinic agonist/antagonist action profiles between clozapine and N-desmethylclozapine (15). In the present case, the clozapine/N-desmethylclozapine ratio changed to a theoretically favorable lower value. The major enzymes involved in clozapine conversion to N-desmethylclozapine are CYP1A2 and CYP3A4 (16). In the absence of any additional exposure to an enzyme inducer (e.g., smoking, carbamazepine, omeprazole, or phenytoin), this change after a gradual clozapine dose reduction suggests that the N-desmethylation process was previously saturated. Additionally, when administered together, clozapine and zuclopenthixol could potentially compete for the same metabolizing enzymes, specifically CYP3A4 (17), potentially increasing the levels of one or both drugs in the absence of an enzyme inhibitor.

The substantial improvement in cognitive function after clozapine dose reduction and anticholinergic burden reduction suggests cognitive dysfunction to be at least partially secondary to medication side effects and not exclusively a

TABLE 1 Timeline.

		Treatment	Problems
Week 1–4	November	Zuklopentixol 25 mg/day Biperiden 6 mg/day Fluzepam 15 mg/day Lorazepam 5.5 mg/day Clozapine 700–650 mg/day Zuklopenthixol long-acting 200 mg/2 weeks	22.11. Brief psychiatric rating scale (BPRS) = 57 Delirium observation scale (DOS) = 52 7.11. Therapeutic drug monitoring (TDM): 1,130 µg/l 28.11. TDM: 1,020 µg/l Psychosis, delirium
Week 5–8	December	Zuklopentixol 30 mg/day Biperiden 3 × 2 mg-ex at week 8 Lorazepam 4 mg/day Flurazepam 15 mg/day Clozapine 525 mg/day	29.12. Anticholinergic burden score (ACB): 7 Mini-mental state examination (MMSE): 13/30 Psychosis
Week 9–12	January	Clozapine 450–400 mg/day Zuklopentixol 50 mg/day Lorazepam 7.5 mg/day Fluzepam 15 mg/day Lamotrigine 25–100 mg/day Zuklopentixole LAI 200 mg/4 weeks	30.1. ACB: 5 MMSE: 13/30 Psychosis Cognitive impairment
Week 13–16	February	Clozapine 450 mg/day Zuklopenthixole 30 mg/day Lorazepam 7.5 mg/day Lamotrigine 150–200 mg/day Amislupride 600 mg/day Zuklopentixole LAI 200 mg/4 weeks	
Week 17–22	March–April	Zuklopentixole 20 mg/day Clozapine 450 mg/day Lamotrigine 200 mg/day Amisulpride 1,000 mg/day Lorazepam 6.5 mg/day Rivastigmine patch 9.5 mg/day Zuklopentixole LAI 200 mg/4 weeks	15.3.2023- MMSE: 22/30 22.3.: ACB 4

feature of the primary disorder. In addition, it is important to note that benzodiazepines can also markedly contribute to cognitive impairment, so further gradual reduction of the benzodiazepine may lead to additional improvements in her cognitive status.

In clozapine-resistant schizophrenia, antipsychotic polypharmacy is a common practice. Since prominent auditory hallucinations and delusions in the patient persisted despite clozapine plasma levels being above the estimated response threshold on admission (14), clozapine therapy had been augmented with zuclopenthixol, adding to the cumulative anticholinergic burden. Even though the literature does not favor any particular antipsychotic drug as an augmentation to clozapine therapy in cases of inadequate response or residual psychotic symptoms, from a pharmacodynamic perspective, the addition of amisulpride may be beneficial if supplementary dopamine receptor blockade is desired without increasing the anticholinergic burden. Additionally, the reduction in clozapine dose along with the addition of amisulpride has previously been shown to significantly reduce adverse effects compared to monotherapy (18).

Furthermore, clozapine's potent central anticholinergic activity is a risk factor for the development of delirium. As described in the present case, this complication of clozapine treatment, or arguably clozapine toxicity, given the very high plasma levels, led to further worsening of the patient's cognition and functional status. The incidence of delirium in patients treated with clozapine is estimated to be ∼5% (19) but may be underrecognized in clinical practice due to the difficulty in identifying and differentiating signs of delirium in psychotic patients. A misdiagnosis of delirium as an exacerbation of the underlying psychotic disorder may lead to a counterproductive and potentially dangerous escalation of the drug dose that precipitated the state of delirium.

Conclusions

Antipsychotic polypharmacy is extremely common in the management of treatment-resistant schizophrenia. As is evident in the present case, adverse effects of medications can overlap with the primary symptoms of the underlying disorder, and differentiating between the two can present an important clinical challenge and should influence treatment decisions. The anticholinergic burden can severely impair the cognitive and functional abilities of individuals with schizophrenia, but the clinical case presented demonstrates that a gradual and controlled reduction of the anticholinergic burden, with screening for potential worsening of psychotic symptoms, may be an approach to consider in improving functional outcomes. Further research and real-life clinical data are of course needed to support any conclusions, as this case represents only anecdotal data and is an example of extensive polypharmacy, which represents an important limitation for generalization.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1222177/full#supplementary-material

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Case report: application of pharmacogenetics in the personalized treatment of an elderly patient with a major depressive episode

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Background: Pharmacogenetic analyses can predict interpersonal differences in response to psychopharmacotherapy, which greatly facilitates the selection of the most effective medication at optimal doses. By personalizing therapy in this way, we can minimize adverse drug reactions (ADR) and prevent polypharmacy. Most psychotropic medications are metabolized by the cytochrome P450 enzymes CYP2D6, CYP2C19, and CYPA3A4, which influence drug metabolism and concentration, affecting both efficacy and the occurrence of ADR. The relationships between genetic variations and enzymatic activity allow pharmacogenetic analysis to provide important data for optimal drug selection. The following case report illustrates the impact of pharmacogenetic analysis on the course of pharmacologic treatment in an elderly patient with a major depressive episode.

Methods: We present a case of a 79-year-old patient treated for severe depression with psychotic symptoms. We collected data on treatment selection and response to treatment before and after pharmacogenetic analysis. For pharmacogenetic analysis, common functional variants in *CYP1A2*, *CYP3A4*, *CYP2B6*, *CYP2C19*, and *CYP2D6* were genotyped, and corresponding evidence-based treatment recommendations were prepared.

Results: The patient suffered from lack of efficacy and serious ADR of several medications, resulting in worsening depression and treatment resistance over the course of several months of treatment. Pharmacogenetic analysis provided important insights into the patient's pharmacokinetic phenotype and allowed us to personalize treatment and achieve remission of the depressive episode.

Conclusion: In the case presented, we have shown how consideration of pharmacogenetic characteristics in an individual patient can improve treatment outcome and patient well-being. Knowledge of the patient's pharmacogenetic characteristics helped us to personalize treatment, resulting in complete remission of psychopathology. Due to the complexity of psychiatric disorders, the efficacy of combinations of different medications, which are often required in individual patients, cannot be clearly explained. Therefore, it is of great importance to conduct further pharmacokinetic and pharmacogenetic studies to better assess gene-drug interactions in psychopharmacotherapy.

KEYWORDS

personalized therapy, pharmacogenetics, cytochrome P450 enzymes, depression, antidepressants, antipsychotics, case report

1. Introduction

Interindividual differences in response to pharmacotherapy play an important part in the treatment of mental disorders. Pharmacotherapy is effective only in a relatively small proportion of patients with mental disorders. In addition to the variable therapeutic effect, ADR of varying intensity often occur. A treatment-resistant form of depression, defined as an inadequate therapeutic response despite adequate treatment with two or more antidepressants, occurs in approximately 30% of patients with depression (1). Similarly, in the treatment of psychotic disorders, only about one-third of patients achieve good long-term remission (2). Additional medications can be used to mitigate the ADR, or if the therapeutic effect is insufficient, combination or augmentation therapy with other medications can be considered. The concomitant use of multiple medications is relatively common, despite the higher risk of ADR. Poor patient adherence to therapy is due, at least in part, to ADR and inadequate therapeutic effect (3). An important determinant of response to therapy is individual pharmacokinetic and pharmacodynamic variability. Common functional variants in genes that code for enzymes, membrane transporters, and therapeutic targets are reflected in interindividual differences in treatment response. Most antidepressants and antipsychotics are metabolized by cytochrome P450 enzymes in the liver, e.g., CYP2D6, CYP2C19, and CYPA3A4. These enzymes were an early focus for clinical use of pharmacogenetics in psychiatry because of the close relationship between genetic variants and enzymatic activity (4). Therefore, pharmacogenetic analysis can provide important data that influence optimal drug selection. Finding the most effective dose with minimal ADR is a critical step toward personalized therapy.

In this case report, we illustrate the importance of considering pharmacogenetic data and recommendations in clinical practice by presenting the case of a patient in whom the application of recommendations successfully changed the course of a previously unsuccessful treatment for a severe depressive episode.

2. Case description

A 79-year-old retired teacher was treated for 164 days at the University Psychiatric Clinic Ljubljana (UPCL) for severe depression with psychotic symptoms. She had no previous history of psychiatric treatment. After the death of her husband, she had been living alone for 10 years. She was physically healthy and did not take any medication regularly. There were no particular problems in her family history, and she did not report any substance use disorder.

The patient's course of treatment is schematically presented in Figure 1.

The first symptoms of depression appeared around 6 months before hospitalization, including anxiety, concerns about her health, lack of will, and anhedonia. Over time, the anxiety and lack of will worsened, her appetite decreased, and she suffered from insomnia. During an outpatient psychiatric evaluation, she was diagnosed with a moderate depressive episode. Initially, she was prescribed escitalopram 10 mg daily, which was switched to mirtazapine due to lack of efficacy. Due to deterioration in daily functioning and self-care, she temporarily moved in with her daughter. After 3 weeks of therapy with 30 mg of mirtazapine daily, improvements in mood, insomnia, and increased energy were noted. However, her concern for her own health and the well-being of her loved ones intensified and gradually took on delusional features. She firmly believed that her digestion had stopped and that something terrible was about to happen to her daughter and grandchildren. In addition to 30 mg of mirtazapine, risperidone was administered at a dose of 0.5 mg three times daily during a follow-up visit. This resulted in increased agitation, despair, a recurrence of decreased willpower, and increased anxiety. The delusional beliefs persisted. Due to the severity of her symptoms, she was admitted to the UPCL.

On admission and for the first few days, she showed marked depressed mood, depressive delusions, delusional interpretations of bodily sensations, and possibly cenesthetic hallucinations. She was, however, fully conscious and oriented, although somewhat suspicious in her interactions. There was no evidence of formal thought disorder, and her cognitive abilities appeared to be intact. She described passive thoughts of death but had no acute suicidal ideation. Initially, therapy was continued with mirtazapine and risperidone. Lorazepam 0.5 mg was additionally prescribed three times daily because of increased anxiety. Motor restlessness was observed and attributed to possible akathisia or depression-related agitation. Other extrapyramidal symptoms (EPS) were also noted: mildly increased muscle tone in the upper limbs and neck, and mild and symmetrical postural tremor. Risperidone was discontinued due to akathisia and EPS. Because of the poor efficacy of mirtazapine monotherapy, combined antidepressant therapy was initiated. A combination of sertraline and olanzapine was introduced. Despite a daily dose of up to 20 mg olanzapine and up to 100 mg sertraline, psychotic symptoms persisted, so aripiprazole was additionally administered. However, as severe akathisia occurred at a dose of 10 mg aripiprazole daily, aripiprazole was replaced by 1 mg brexpiprazole daily. Psychotic symptoms decreased slightly, and she was able to focus on other topics in conversations. At the same time, she continued to receive 75 mg sertraline, 30 mg mirtazapine, 15 mg olanzapine, and 1 mg lorazepam three times daily. Akathisia persisted for several days even at a low dose of 1 mg brexpiprazole daily, but then subsided without a change in medication, resulting in a recurrence of delusions and anxiety. We initiated medication monitoring and found that she had not been taking the prescribed medication, which we attributed to ADR and secondary persecutory delusions. After starting medication monitoring, sertraline 200 mg daily and olanzapine 15 mg daily were confirmed to be ineffective, and brexpiprazole was discontinued because of persistent akathisia. We decided to introduce venlafaxine 75 mg daily. In addition to lorazepam 1 mg three times daily, she also

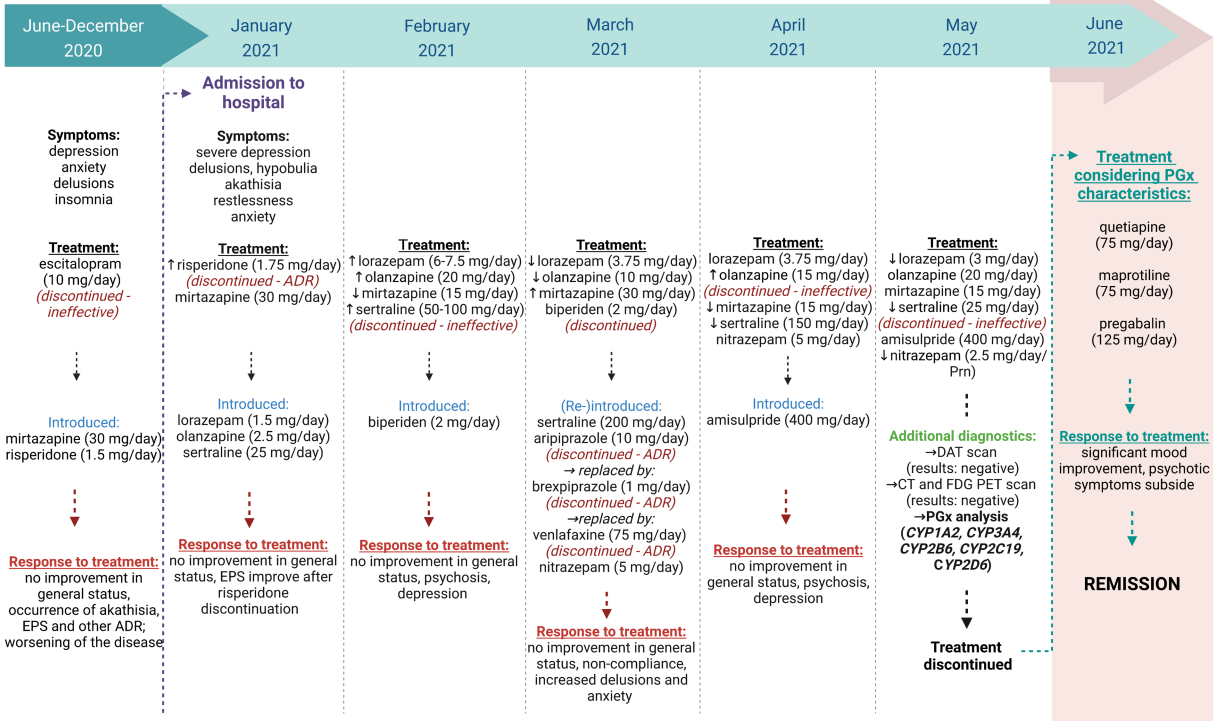

FIGURE 1
A schematic presentation of the patient's treatment. Created with Biorender.com.

received biperiden 2 mg and olanzapine 20 mg daily. Because of the persistent EPS, a neurologic examination was performed, which revealed mild asymmetric bradykinesia and hypokinesia in the upper limbs (UPDRS stages 1 and 2), Parkinsonian posture, and gait disturbances. Dopamine transporter scintigraphy (DaTSCAN) was performed to confirm presynaptic dopaminergic impairment. The patient had not previously undergone any of the other planned diagnostic tests (CT, EEG) because she had refused them due to her psychotic experiences. Five days after starting venlafaxine 75 mg daily, marked akathisia and reactive worsening of anxiety reappeared. Venlafaxine was therefore discontinued. We temporarily increased lorazepam dose to 1.25 mg in the morning, 2.5 mg in the afternoon, and 2.5 mg in the evening. We also tried amisulpride and gradually increased the dose to 400 mg daily. The dose of sertraline was decreased to 150 mg daily, while mirtazapine was reduced to 15 mg in the evening. Lorazepam was administered regularly, with the dose adjusted to 1 mg three times daily. Nitrazepam 5 mg was introduced for the treatment of insomnia. This also resulted in a slight decrease in anxiety, and akathisia subsided. However, nihilistic and other depressive delusions with bizarre content persisted. With decreased anxiety, a CT brain scan and EEG could be performed, which showed no abnormalities. Laboratory results showed no significant deviations from normal (thyroid hormones, complete blood count, liver function tests, electrolytes, vitamin B12, and folic acid levels). A PET-CT scan with FDG revealed mild diffuse cortical hypometabolism, which was not characteristic of neurodegenerative disease. DaTSCAN excluded parkinsonism due to presynaptic dopaminergic dysfunction. The clinical picture still included depressed mood and depressive delusions. She participated little in ward activities and required considerable assistance with daily activities. In her free time, she tended to withdraw from the company of other patients on the ward.

The examinations performed excluded the differential diagnoses of early-stage dementia or Parkinson's disease. A clinical psychological examination was performed, but its results were inconclusive because the patient was unable to participate properly. However, based on the low cognitive screening test results (MMSE 25/30, ACE 83/100), some type of dementia syndrome was suspected. The cognitive decline was consistent with the picture of pseudodementia associated with depression.

Due to therapeutic inefficacy of various drug combinations (olanzapine, risperidone, sertraline, mirtazapine, amisulpride) and pronounced ADR with several drugs (aripiprazole, brexpiprazole, risperidone, venlafaxine), a pharmacogenetic analysis was performed.

DNA was isolated from the blood sample collected in EDTA-containing using the E.Z.N.A. SQ Blood Kit II (Omega bio-tek), according to the manufacturer's instructions. The presence of *CYP2D6* gene deletion (*5) or duplication (*xN) was tested using long-range PCR (Long-Range PCR, Biotechrabbit GmbH) and the amplicons were visualised after agarose gel electrophoresis. The other genetic variants (*CYP1A2**1F; *CYP3A4**22; *CYP2B6**4, *6, *9; *CYP2C19**2, *3, *4A/B, *5, *6, *8, *10, *9, *17; and *CYP2D6**3, *4, *6, *8, *9, *10, *14A/B, *17, *41) were analysed using commercial KASPar SNP Genotyping Assay kits (LGC Group), which enable the detection of products using fluorescence. All analyses were performed in duplicate in the presence of appropriate negative and positive controls for all genotypes and additional control samples.

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

Gene	Polymorphism	Patient's genotype	Polymorphic allele contribution	Patient's phenotype
CYP1A2	*1F	***1F/*1F**	Increased enzyme activity	UM (DPWG)
CYP3A4	*22	*1/***22**	Decreased enzyme activity	IM (DPWG)
CYP2B6	*4, *6, *9	*1/***4**	Increased enzyme activity	RM (CPIC)
CYP2C19	*2, *3, *4A/B, *5, *6, *8, *10, *9, *17	*1/***17**	Increased enzyme activity	NM (DPWG) RM (CPIC)
CYP2D6	*3, *4, *5, *6, *8, *9, *10, *14A/B, *17, *41, xN	*1/***41**	Decreased enzyme activity	NM (DPWG, CPIC)

NM, normal metabolizer; IM, intermediate metabolizer; RM, rapid metabolizer; UM, ultra-rapid metabolizer; DPWG, Dutch Pharmacogenomic Working Group; CPIC, The Clinical Pharmacogenetics Implementation Consortium.
Marked in bold are polymorphic alleles that are present in the patient and contribute to changes in the activity of metabolizing enzymes.

3. Results and discussion

The patient presented here experienced a plethora of treatment failures, both in terms of inefficacy and ADR (see Figure 1). Based on the list of prescribed drugs and their metabolic pathways, *CYP1A2*, *CYP3A4*, *CYP2B6*, *CYP2C19*, and *CYP2D6* were selected for genotyping for various genetic polymorphisms. Genotyping results and their corresponding phenotypes are shown in Table 1.

Briefly, typical antipsychotics (chlorpromazine, fluphenazine, perphenazine, promethazine, thioridazine), some selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are metabolized predominantly *via* CYP2D6, whereas the metabolism of atypical antipsychotics (aripiprazole, brexpiprazole, iloperidone, risperidone), noradrenergic specific serotonergic antidepressants (NaSSAs), haloperidol, and venlafaxine is also catalyzed by CYP3A4 (5). Clozapine and olanzapine are metabolized predominantly via CYP1A2 and to a lesser extent *via* CYP2D6 and CYP3A4, while most SSRIs are metabolized primarily via CYP2C19 (5–7). Finally, CYP2B6 is an important enzyme for the metabolism of sertraline (8).

The presented patient carries two polymorphic alleles (*CYP2D6**41, *CYP23A4**22) that contribute to lower activity of metabolizing enzymes, which could lead to impaired conversion of drugs into inactive metabolites, resulting in a higher risk of developing ADR. On the other hand, lower activity could also lead to lower drug efficacy if the parent compound needs to be activated *via* these enzymes. For other CYP enzymes analysed, the patient carries multiple polymorphic alleles (*CYP1A2**1F, *CYP2C19**17, *CYP2B6**4) that result in increased enzyme activity, meaning that the patient could be susceptible to decreased drug efficacy as active compounds are neutralized shortly after drug administration.

Considering the genotypes and phenotypes, many of the treatment-related problems can be explained. Treatment was initiated with the administration of mirtazapine as an atypical tetracyclic antidepressant and risperidone as an atypical antipsychotic. During the course of treatment, mirtazapine proved ineffective, whereas risperidone led to the development of extrapyramidal symptoms (EPS), with akathisia being the most severe. CYP1A2, CYP2D6, and CYP3A4 are responsible for the metabolism of mirtazapine, the latter two being the most important (9, 10). Unfortunately, the lack of efficacy of mirtazapine cannot be explained by the fact that the activity of the crucial metabolizing enzymes was decreased. There is still no strong evidence or pharmacogenetic recommendations for mirtazapine and its gene interactions. Similarly, there are no dose adjustment recommendations for risperidone in *CYP2D6**1/*41 (NM). However, decreased CYP2D6 enzyme activity suggests a tendency for drug-gene interactions to cause the occurrence of ADR in risperidone treatment, although no clinically relevant associations have been demonstrated to date (11). Nevertheless, plasma concentrations of 9-hydroxyrisperidone, the equipotent metabolite of risperidone, are known to be decreased in carriers of *CYP2D6**41, implying higher plasma concentrations of risperidone (11, 12). Since risperidone is more likely to cross the blood–brain barrier than 9-hydroxyriperidone, this may explain the development of ADR originating from the central nervous system, and thus EPS (13).

When the patient's treatment was continued, olanzapine also proved ineffective. This may have been because the patient was a *CYP1A2**1F/*1F (UM). Carriers of this genotype metabolize olanzapine more rapidly than normal metabolizers, resulting in significantly lower concentrations of the active drug compound in the blood. CYP2D6 and CYP3A4 also contribute to the metabolism of olanzapine, but to a much lesser extent (11).

Sertraline is extensively metabolized in the liver via several different CYP enzymes, CYP2C19 being the most important. However, CYP2B6, CYP2D6, and CYP3A4 also play a role. Slightly lower serum concentrations of sertraline and its active form have been demonstrated in Scandinavian patients with the *CYP2C19* *17 allele (14), suggesting that this phenotype may contribute to lower efficacy of sertraline as observed in the presented patient. Currently, there is insufficient evidence and pharmacogenetic recommendations for the *CYP2C19**1/*17 phenotype (NM) based on the Dutch Pharmacogenetic Working Group (DPWG), but there are recommendations based on a combination of genotypes for *CYP2B6* and *CYP2C19* according to the Clinical Pharmacogenetics Implementation Consortium (CPIC). Because the patient carries two alleles (*CYP2C19**17 and *CYP2B6**4) associated with increased metabolism of sertraline to a less active compound, it is recommended to consider titrating sertraline to a higher maintenance dose or switching to a clinically appropriate alternative antidepressant that is not predominantly metabolized by CYP2C19 or CYP2B6 if a patient does not respond adequately to the recommended initial/maintenance dose of sertraline (15, 16). In addition, lower CYP2D6 and CYP3A4 activity in the presented patient could affect the response to sertraline. However, there is no clear evidence for the clinical relevance of dose adjustments or the occurrence of ADR/efficacy during treatment with sertraline in these phenotypes. Therefore, the patient's non-response to sertraline treatment is more

likely related to increased activity of CYP2C19 and CYP2B6. Knowledge of the patient's *CYP2C19* genotype/phenotype could also explain the ineffectiveness of escitalopram, the first medication prescribed to the patient when she was diagnosed with a depressive episode. CPIC, but not DPWG, provides the explanation that patients carrying the *17 allele may have lower plasma concentrations of escitalopram, indicating increased metabolism of escitalopram to a less active compound and thus a lower likelihood of clinical benefit. If PGx information were available earlier, the patient's depression could be successfully treated before hospitalization by increasing the escitalopram dose as recommended by the CPIC (8).

Because the patient did not respond well to the above therapy, the medication was changed to aripiprazole, brexpiprazole, and venlafaxine. After the introduction of the new treatment regimen, several ADR occurred that can be explained, at least in part, by the patient's pharmacogenetic characteristics. All of these drugs are metabolized mainly via CYP2D6. Since the patient was a carrier of the CYP2D6*41 allele, metabolism *via* this enzyme might be reduced, leading to higher plasma concentrations of the drugs and thus to various ADR (8, 11). Importantly, there are pharmacogenetic recommendations for the *CYP2D6*-aripiprazole gene-drug pair, but only for the "poor metabolizers" (PM). These recommendations state that patients with a *CYP2D6* PM phenotype should not be given more than 10 mg/day or 300 mg/month (68%–75% of the normal maximum dose of aripiprazole) (11). In addition, aripiprazole plasma concentrations may also be elevated due to genetically low CYP3A4 activity, further increasing the risk for the occurrence of ADR (11). Because brexpiprazole is metabolized in a similar manner to aripiprazole, similar consequences in terms of plasma concentrations and possible ADR are expected. Pharmacogenetic recommendations for brexpiprazole state that half the normal dose should be used for *CYP2D6* PMs, which is even less compared to aripiprazole (11). In addition, the patient experienced akathisia while taking venlafaxine. The akathisia could possibly be explained by the fact that the patient was a carrier of *CYP2D6**41, meaning that venlafaxine was metabolized to a lesser extent to O-desmethylvenlafaxine. Heterozygous *CYP2D6**1/*41 are currently classified as NM, so there are no recommendations for patients with this genotype.

However, regardless of the current phenotype classification, several studies reported that allele*41 decreases the activity of the enzyme to a greater extent as agreed between CPIC and DPWG in 2019 (17–19). Indeed, a consensus has been reached that the NM phenotype is assigned when the activity score is between 1.25 and 2.25, whereas a value below 1.25 indicates a IM phenotype (20). According to this consensus, the contribution of the *CYP2D6**41 allele to decreased enzyme activity is estimated to be 0.5, implying that the *1/*41 diplotype has a total score of 1.5 and is therefore NM. Doubts about this consensus on scores were recently raised by the group of Jukić et al. (18), who demonstrated that the activity score for the *CYP2D6**41 allele is close to 0.18, especially when risperidone, aripiprazole, and venlafaxine are administered (0.14, 0.26, and 0.21, respectively), and is not equal to 0.5 as assumed by the consensus. Similar results were obtained by Haslemo et al. (19), who found in their study of a large patient population that the score for residual enzyme activity was only 9.5% in the case of venlafaxine administration. Considering these data, the presented patient could be classified as IM rather than NM.

Finally, CYP2D6 activity could also be reduced by sertraline, which is a known weak inhibitor of CYP2D6 (21). With a consequent reduction in CYP2D6 activity, the patient's CYP2D6 phenotype could shift toward IM or even PM. This could increase the likelihood of ADR due to treatment with risperidone, aripiprazole, brexpiprazole, and venlafaxine, all taken concomitantly with sertraline.

Once the pharmacogenetic results were available, the patient's genetic characteristics were considered when deciding about the new course of treatment. Because certain drugs were selected for which there were no corresponding pharmacogenetic recommendations, their doses were titrated slowly and carefully. Quetiapine, an atypical antipsychotic, is metabolized mainly via CYP3A4 (22). Because of the patient's decreased CYP3A4 activity, quetiapine was introduced slowly and under close monitoring. We started with a dose of 12.5 mg in the evening and gradually increased it to 75 mg in the evening. Similarly, maprotiline, a tetracyclic antidepressant, was introduced with caution because of its metabolism via CYP2D6 and CYP1A2 (23). We started with an initial dose of 25 mg and gradually increased it to 75 mg daily. In the titration phase, we focused on the joint effects of maprotiline and quetiapine, particularly with regard to the possible anticholinergic ADR and QTc interval prolongation. For the treatment of anxiety, pregabalin, which is metabolized by the liver to a very low extent (24), was administered at a dose of 25 mg in the morning and at noon and 75 mg in the evening. The patient's mood improved markedly within 4 weeks, and psychotic symptoms disappeared completely.

4. Conclusion

In the case presented, we have shown how consideration of pharmacogenetic characteristics in an individual patient can improve treatment outcome and patient well-being. Treatment without consideration of patients' pharmacogenetic characteristics resulted in ineffective therapy even at high or maximal doses of antidepressants and antipsychotics. In addition, low doses of some antidepressants and antipsychotics caused the occurrence of serious and complicating ADR. Knowledge of the patient's pharmacogenetic characteristics helped us to personalize treatment, resulting in complete remission of psychopathology. However, due to the complexity of psychiatric disorders and the combinations of different medications that are often required in individual treatment, response and efficacy cannot be clearly explained. As is often observed in pharmacogenetic studies of cytochrome enzyme gene alleles, some results are consistent with expectations based on previous data from the literature, whereas others aren't. Therefore, it is of great importance to conduct additional pharmacokinetic and pharmacogenetic studies to better assess gene-drug interactions. This knowledge will help us to adjust dosage and combinations of prescribed drugs to personalize the treatment and increase its safety and efficacy.

Data availability statement

The data presented in the case report are available upon reasonable request. Further inquiries may be directed to the corresponding authors.

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(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MP, JB, and VD contributed to conception and design of the case report. MP organized the data. ST and TB performed the pharmacogenetic analysis. MP, ST, TB, and JB wrote the first draft of the manuscript. TB and ST created the figures. All authors contributed to the article and approved the submitted version.

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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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Paliperidone long-acting injection in the treatment of an adolescent with schizophrenia with fluctuating mental symptoms during menstrual period: a case report

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Background: The treatment of schizophrenia, a chronic disabling psychiatric disorder, mainly relies on antipsychotics to control the disease and improve clinical symptoms. Various medication options are available, and differences in treatment effects, even for the same medication, have been noted. Treatment efficacy is correlated with the patient's sex, age, and physical condition. When a drug fails to achieve the desired effect or the symptoms are unstable, the drug dose is often increased or a change in medication is advised according to the patient's situation.

Case presentation: We report the case of a 16 years-old girl with schizophrenia and apparent psychotic symptoms. According to the genetic testing results, the symptoms were effectively controlled, and she was discharged from the hospital with the prescription of paliperidone sustained-release tablets. During the follow-up, her symptoms fluctuated during menstrual period, causing her great distress. Furthermore, her compliance gradually declined during the following 2 years of treatment, and the medication was often discontinued. We changed the drug from an oral tablet to an injection preparation while maintaining the active ingredients of the drug. The patient's symptoms were significantly controlled, and no fluctuation of symptoms occurred during the menstrual cycle.

Conclusion: Long-acting antipsychotic injections can be administered to female adolescents with schizophrenia who experience fluctuating psychotic symptoms during menstruation. This technique can ensure both consistency of medication and improvement in clinical symptoms.

KEYWORDS

paliperidone extended-release tablets, paliperidone palmitate injection, schizophrenia, menstrual cycle, adolescent

Background

The long-term maintenance treatment of schizophrenia mainly relies on drugs, including oral preparations and intramuscular injections; most patients are treated with oral drugs. However, the efficacy of oral drug therapy may be influenced by various factors. Clinicians usually adjust the dose or type of oral medication according to the patient's condition (1). The range of antipsychotic drugs available is limited. Thus, before switching medications, clinicians should consider many factors, including the patient's tolerance to the drug, absorption and metabolic rates, and the patient's hormone levels. However, changes in hormone levels in women during clinical treatment are usually an easily overlooked factor.

As the pathogenesis of schizophrenia is not fully understood, current antipsychotics have certain limitations (2). Symptoms fluctuating with the menstrual cycle have been widely reported in women with schizophrenia; the occurrence of premenstrual psychosis and recurrence of psychotic features despite adherence to antipsychotic medications at the onset of or during menstrual cycle in adolescent girls and young women have been reported (3). Furthermore, symptoms in patients with schizophrenia reportedly change at different stages of the menstrual cycle (premenstrual, menstrual, and post-menstrual). Therefore, targeted treatment measures must be applied in such cases (4). For patients with poor treatment effectiveness or with disease fluctuation, clinicians usually increase the dose gradually, change the type of drugs, or administer combination drugs according to the patient's mental symptoms, physical condition, compliance, and drug interactions, and constantly adjust the treatment plan to select the appropriate antipsychotic drugs. Switching medications requires re-titration, which may cause fluctuating symptoms. Furthermore, dose escalation or combination therapy may also reduce patient adherence to therapy. Additionally, it is necessary to weigh the advantages and disadvantages of changing drugs to maximize patient benefits. Another option would be changing the form of the same drug; however, the effectiveness of this strategy in female patients with fluctuating mental symptoms during menstruation has not been reported.

Here, we report the case of a 16 years-old girl with schizophrenia who presented with recurrent psychotic symptoms during the menstrual cycle and was managed using a long-acting injection of the same drug.

Case presentation

Chief complaints

A 16 years-old female patient was admitted to the hospital in September 2018. Six months before admission, the patient had been depressed after an argument with classmates at school and had frequent dizziness, slowness, and inattention at home. She could hear someone scolding her out of thin air, felt that her stomach is "talking" and will spread her ideas to her classmates, suspected that her classmates were discussing her affairs, and needed to repeatedly ask others to ensure that her classmates did not hear her swear words. Gradually, she became inattentive, talked to herself, did not take the initiative to communicate with classmates or family members, often felt nervous and afraid, slept poorly at night, and her academic performance decreased significantly.

Personal history and family history

Since childhood, she had been introverted, sensitive, cared about others' opinions, and had almost no interests. Her parents divorced 4 years ago, and she lived with her mother; however, the patient had good support from family members.

History of past illness

The patient was in good health, had never smoked or consumed alcohol, and had no family history of mental disorders. She did not report any major adverse life events. Both the patient and her family denied any substance abuse. She had no history of violent, agitated, or suicidal behavior during her illness.

Physical examination and laboratory examinations

Routine blood tests did not reveal any unusual findings. No abnormalities were found in liver, kidney, and metabolic function; coagulation tests; transfusion; immunity; routine urine examination; and procalcitonin and adrenocorticotropic hormone levels. Magnetic resonance imaging of the head showed a 2.5 × 1.3 cm hypointense shadow with clear borders in the left middle skull base and compression of the left temporal lobe. There was no ventricular pools enlargement or midline structures displacement. An arachnoid cyst was observed at the base of the left middle skull. After consultation with a neurosurgeon, no special treatment was suggested for the findings. Cerebrospinal fluid (CSF) protein levels and white blood cell counts were also examined. The D2R antibody titer detected by cell-based assays in the serum sample showed a ratio of 1:32, whereas the CSF sample showed negative findings. The other 15 autoimmune encephalitis antibodies, including anti-N-methyl-D-aspartate receptor (NMDAR) and anti-contactin-associated protein (CASPR), paraneoplastic antibodies, and oligoclonal bands, were negative in both samples. Thyroid ultrasound showed a nodule in the right lobe of the thyroid, which could be nodular goiter. Cardiac, abdominal, urological, and gynecological ultrasonography revealed no abnormalities. Chest computed tomography, electrocardiography, and electroencephalography did not show any abnormalities. The results of hormone examination showed a prolactin level of 13.8 μg/L and estradiol level of 107.4 pmol/L.

Further diagnostic work-up

The Brief Psychiatric Rating Scale (BPRS) (5) score was 92, Hamilton Depression Scale (HAMD) score was 8 (6), Hamilton Anxiety Scale (HAMA) score was 9 (7), and Hypomania Checklist (HCL-32) score was 7 (8). This suggests that the patient had no obvious symptoms of depression, anxiety, or hypomanic episodes.

Final diagnosis

The patient was diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (9).

Treatment

After diagnosis, the medications were gradually adjusted to a maximum dose of aripiprazole (15 mg twice daily) and olanzapine (10 mg twice daily) to control the psychiatric symptoms. Modified electric convulsive therapy was administered 10 times during hospitalization. However, the treatment efficacy was poor. At that time, the patient has been titrated to the maximum dosage of medications, yet the therapeutic response remains inadequate. Given this situation, it is imperative to refine the treatment plan. Consequently, genetic testing was considered indispensable for making a well-informed decision regarding the most suitable treatment drugs. Consequently, we proceeded directly with genetic testing to identify the appropriate treatment drugs. The antipsychotic drug metabolism gene test and *DRD2* gene test results suggested that the patient might response better to olanzapine, clozapine, risperidone, and aripiprazole; with a low risk of weight gain. Furthermore, the *HTR1A* gene test results suggested that she had a high chance of improvement of negative symptoms with several of these drugs. Patient DNA was genotyped using Mass ARRAY time-of-flight mass spectrometry (Sequenom Inc., United States) and real-time PCR (ABI VIIA7 real-time PCR Instrument, ABI Inc., United States). The gene test results are presented in Table 1 and Figure 1.

Olanzapine and clozapine are mainly metabolized and cleared by CYP1A2 metabolizing enzyme. The *CYP1A2* gene test results suggest that the patient was a CYP1A2 fast metabolizer with normal metabolic rate and normal sensitivity to olanzapine and clozapine. The dopamine receptor encoded by *DRD2* gene and pentraxin 1A receptor encoded by *HTRIA* gene are the targets of olanzapine and clozapine. Risperidone and aripiprazole are mainly metabolized and cleared by CYP2D6-metabolizing enzymes. The *CYP2D6* gene test results suggest that the patients was a CYP2D6 intermediate metabolizer, with reduced metabolism rate and increased sensitivity to risperidone and aripiprazole, and had an increased risk of neurological adverse effects, suggesting that the drug dose should be adjusted in conjunction with drug quasi-monitoring, and that the patients should be alerted to the occurrence of adverse drug reactions.

The active ingredient of paliperidone is an active metabolite of risperidone. Its pharmacological effect is similar to that of risperidone but it has a more direct effect. Considering the patient's age and other factors, paliperidone extended-release tablets (3 mg in the morning and 9 mg in the evening) and olanzapine tablets (5 mg in the morning and 10 mg in the evening) were finally used to control psychiatric symptoms. After continuous drug treatment (Table 2), the patient's psychiatric symptoms improved significantly, and her sleep improved. She had occasional verbal hallucinations and sense of insecurity and was discharged in October 2018. The drug plasma level examination results at the time of discharge indicated that the patient's blood concentration of paliperidone was 48 ng/mL, which falls within the recommended treatment reference range outlined in the consensus guidelines for monitoring drugs used in neuropsychopharmacologic therapy, ranging from 20 to 60 ng/mL (10).

Follow-up period and outcome

After being discharged from the hospital, the patient insisted on a monthly outpatient follow-up. During the patient's continuous follow-up for more than 2 years, her treating physician found an interesting phenomenon. The patient's symptoms fluctuated every time during her menstrual cycle, and the patient complained that she was "back to the state she was in before hospitalization." She also had a significant weight gain, gaining 8 kg in approximately half a year after discharge. Her blood test results showed prolactin level of 34.6 μg/L (normal range 4–23 μg/L). The patient complained that she had been taking her medication as prescribed and denied any increase or decrease in the dosage or missed doses. To quantify these symptoms, in addition to blood monitoring for hormone levels (prolactin and estradiol) (Table 3), we used the Positive and Negative Syndrome Scale (PANSS) to assess the severity of the patient's symptoms at each outpatient follow-up visit. Throughout the treatment period, paliperidone (6 mg twice daily) was used as the main medication in combination with clozapine (50 mg twice daily). The treating physician adjusted the type and dose of medication according to the patient's symptoms; however, a stable effect was not achieved, and the symptoms fluctuated periodically with the menstrual cycle. The main medications used during the follow-up period after the patient's discharge from the hospital, with each medication adjusted as a treatment regimen are presented in Tables 4–6.

The patient, an adolescent female diagnosed with schizophrenia, experienced worsening psychiatric symptoms during each menstrual period. The blood concentration of paliperidone ranged from 12 to 18 ng/mL when her menstrual cycle began. However, outside of her

TABLE 1 Gene test results.

Test site	rs ID	cDNA change	Test results
*CYP1A2*1F*	rs762551	C>A	CA (heterozygous mutation)
*CYP2D6*5*		Gene deletion	Wild homozygote (not missing)
*CYP2D6*10*	rs1065852	100C>T	TT (homozygous mutation)
*CYP2D6*41*	rs28371725	2988G>A	GG (wild-type homozygous)
*CYP3A5*3*	rs776746	6986A>G	AG (homozygous mutation)
DRD2	rs1799732	-141C Ins/Del	Ins/Ins (wild-type homozygous)
HTR1A	rs6295	c.-1019G>C	GC (heterozygous mutation)

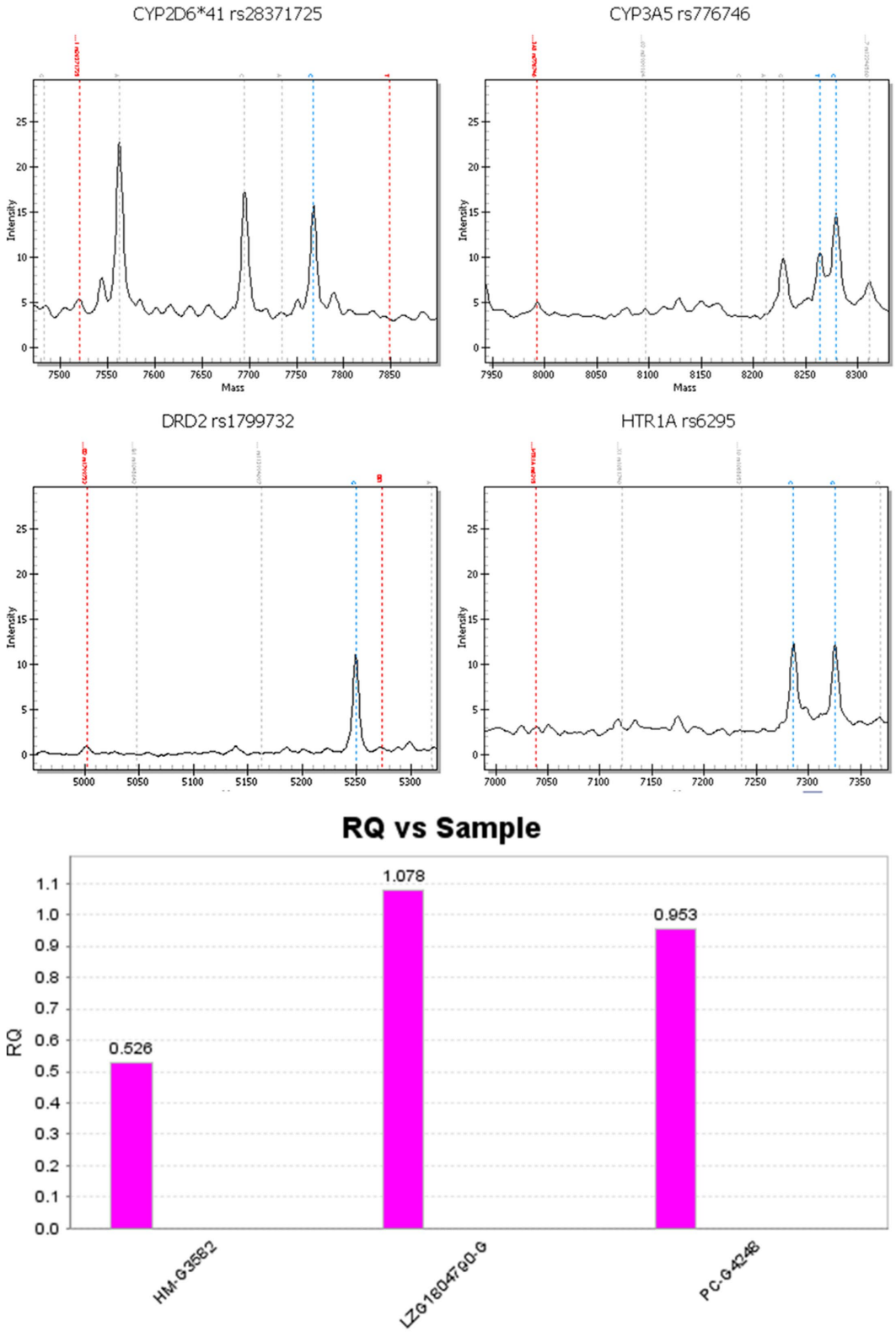

FIGURE 1
RQ vs. sample. Note: From left to right, the three samples are: CYP2D6*5 positive sample (gene deletion control), sample to be tested, CYP2D6*5 non-deletion sample (wild type control).

menstrual period, the plasma level of paliperidone ranged from 30 to 55 ng/mL. The patient was currently receiving the maximum therapeutic dose of paliperidone as approved by the medication's label, and the treating physician opted not to further increase the dosage. There were several reasons for this decision. Firstly, the patient and her parents were reluctant to exceed the maximum dose specified on

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TABLE 2 Course of medication during hospitalization.

Days after admission	1	7	15	30	35	45 (discharge)
Drugs	Aripiprazole	Aripiprazole	Aripiprazole	Aripiprazole	Paliperidone extended-release tablets	Paliperidone extended-release tablets
	Olanzapine tablets	Olanzapine tablets	Olanzapine tablets	Olanzapine tablets	Aripiprazole	Aripiprazole
					Olanzapine tablets	Olanzapine tablets
Maximal dose, mg/d[a]	10	20	30	30	3	12
	2.5	7.5	15	20	15	0
					20	15

[a]Listed in the same vertical sequence as the drugs in the row above.

TABLE 3 Blood test results of prolactin and estradiol for six consecutive months.[a]

Month		1	2	3	4	5	6
PRL (μg/L)		32.7	34.9	36.5	32.8	33.7	34.2
E_2 (pmol/L)	The third day after menstruation	114.9	110.7	112.6	110.4	111.8	114.3
	Menstrual period	69.6	72.8	79.4	70.9	67.6	74.5

APRL, prolactin; E_2, estradiol.
[a]After informed consent was obtained from the patient and her family, the hormone levels were monitored on the first and third days after menarche for 6 months.

TABLE 4 Antipsychotic treatment between 2018 and 2019.

Sequence of therapeutic schedule	1	2	3	4	5
Drugs	Paliperidone extended-release tablets	Paliperidone extended-release tablets	Paliperidone extended-release tablets	Paliperidone extended-release tablets	Paliperidone extended-release tablets
	Olanzapine	Olanzapine	Olanzapine	Aripiprazole	Olanzapine
		Aripiprazole Tablets	Aripiprazole		Aripiprazole
Maximal dose, mg/d[a]	12	12	9	12	12
	15	20	10	0	20
		5	5		10

[a]Listed in the same vertical sequence as the drugs in the row above.

TABLE 5 Antipsychotic treatment between 2020 and 2021.

Sequence of therapeutic schedule	6	7	8	9	10
Drugs	Paliperidone extended-release tablets	Paliperidone extended-release tablets	Paliperidone extended-release tablets	Paliperidone extended-release tablets	Paliperidone palmitate injection
	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine
				Paliperidone palmitate injection	
Maximal dose, mg/d[a]	12	9	9	3	150 (per month)
	100	100	100	100	100
				150 (per month)	

[a]Listed in the same vertical sequence as the drugs in the row above.

the label. Additionally, the attending physician believed that even with an escalation of paliperidone dosage, achieving the desired plasma concentration during the patient's menstrual cycle might remain challenging.

Finally, the patient had been taking antipsychotic drugs for a long time, which led to elevated prolactin and significant weight gain. These factors, along with the stigma of adhering to medication during school, may have contributed to the patient's poor medication

TABLE 6 Antipsychotic treatment from August 2021 to 2022.

Sequence of therapeutic schedule	11	12	13
Drugs	Paliperidone palmitate injection	Paliperidone palmitate injection	Paliperidone palmitate injection
	Aripiprazole	Aripiprazole	Aripiprazole
	Clozapine	Clozapine	Clozapine
Maximal dose, mg/d[a]	100 (per month)	100 (per month)	100 (per month)
	10	5	5
	50	50	25

[a]Listed in the same vertical sequence as the drugs in the row above.

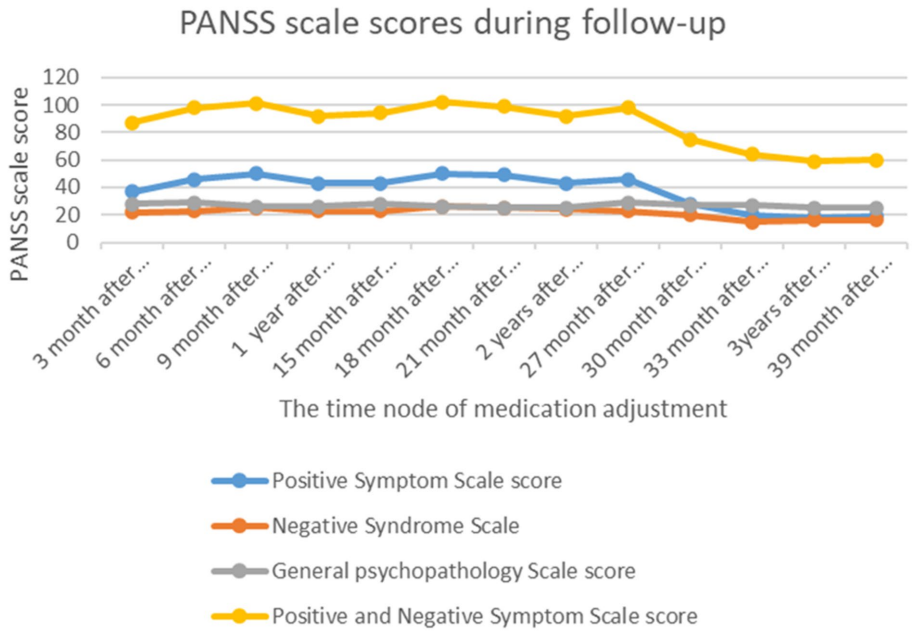

FIGURE 2
PANSS scale score trend chart during follow-up. Note: The patient was followed up every 3 months after discharge, and the attending clinician adjusted the medication according to the patient' chief complaints and symptoms and evaluated her symptoms using the Positive and Negative Syndrome Scale.

adherence. On a follow-up visit in August 2020, her attending physician attempted to adjust her treatment after communication with the patient and her family, and after obtaining informed consent, replaced oral paliperidone with a chemically identical, longer-lasting, and more stable long-acting injection of paliperidone palmitate. The starting dose was 150 mg, and 1 week later, the injection was administered intramuscularly at a monthly dose of 100 mg. After switching to the injectable preparation, the patient's condition was stable, and so far, no further psychiatric symptoms have occurred for more than 2 years, either at ordinary times or during the menstrual cycle. The blood concentration of paliperidone ranged from 25 to 53 ng/mL. Currently, the patient's condition is well controlled.

The trend of the patient's scores on the corresponding PANSS scale over the course of more than 3 years of follow-up is shown in Figure 2. The scores decreased significantly after the medication was adjusted to paliperidone injectable injection (30 months after discharge), indicating that the patient's overall psychiatric symptoms were significantly controlled.

Discussion

In the present case, the patient's medical history revealed obvious hallucinations, delusions, incoherent speech, off-topic answers, tension, withdrawal behavior, decreased emotional expression, and a lack of motivation. After experiencing the symptoms, the patient showed a significant decline in academic performance, interpersonal communication, and other aspects of functioning that lasted for 6 months. The overall symptoms met the diagnostic criteria for schizophrenia according to DSM-5. The patient was a young woman with a slow onset and long course of disease. The examination results showed normal thyroid function; thus, eliminating the diagnosis of mental disorders caused by thyroid disease. CSF examination ruled out autoimmune encephalitis. The patient denied substance abuse and had a negative urinalysis result, which eliminated the possibility of a psychiatric disorder caused by psychoactive substances. Previously administered antipsychotics (paliperidone modified-release tablets and olanzapine) were effective; however, fluctuations in psychiatric symptoms, such as recurrent auditory hallucinations, increased

delusions, and increased alertness, were observed. These symptoms were similar to those reported previously and the patient did not report any new symptoms. Almost all symptom fluctuations were related to the menstrual cycle. The patient and her family members reported that she had been taking the medications as prescribed and she had not taken any other medication on her own that could have caused changes in blood levels.

Numerous studies have shown that the physiological cycle can cause fluctuations in psychiatric symptoms in patients with schizophrenia (4, 11–13). Estrogen and prolactin are the two major hormones associated with these fluctuations. Estrogen has a protective effect against psychosis, which worsens when estrogen levels are low during the pre- and post-menstrual cycles (14). Estrogen levels vary during different stages of the physiological cycle (11). Psychiatric symptoms may appear or worsen during the declining phase of the menstrual cycle, that is the first week after the start of menstruation, when the corpus luteum shrinks and the blood levels of progesterone and estrogen are low. However, during the ovulatory and luteal phases, estrogen levels are higher, and patients may experience fewer psychiatric symptoms. Estrogen has an antagonistic effect on dopamine and 5 HT and can change the mental traits of patients by regulating the release and metabolism of dopamine and 5 HT (15). When estrogen levels are low during menstruation, the antagonistic effect of estrogen on dopamine and 5 HT is weakened, which may lead to the worsening of psychotic symptoms (12).

Furthermore, changes in prolactin levels are associated with symptom fluctuations in patients with schizophrenia (16, 17). In this case, the patient's hormone levels were within the normal range before treatment; however, after a period of drug treatment, the prolactin level was observed to be significantly higher than normal, which also verified that antipsychotic drugs could cause hyperprolactinemia (18). Prolactin affects the function of the anterior pituitary gland and hypothalamus. Studies have shown that patients with high prolactin levels are less responsive to treatment (19). Higher prolactin levels are associated with more severe positive (20) and negative (21) psychotic symptoms in patients with uncontrolled symptoms. This finding is consistent with the patient's performance in this case.

Alternatively, changes in a female's menstrual cycle may affect the pharmacokinetics of a drug, thereby affecting the blood concentration of oral or injected drugs. At different stages of the menstrual cycle, female patients may experience changes in the efficacy or side effects of medications. This may be related to the effect of estrogen on the liver enzyme system, which is one of the main sites for drug metabolism (22). Most antipsychotic drugs are metabolized by CYP1A2, CYP2C19, CYP2D6, and/or CYP3A4 (10). Both estrogen and progesterone are substrates of CYP1A2, and have an inhibitory effect on this enzyme (23). This may result in high drug plasma concentrations in females when the hormone levels are high (e.g., premenopausal) and relatively low concentrations when the hormone levels are low (e.g., postmenopausal). This may affect the action of drugs, including clozapine and olanzapine (24).

Risperidone and paliperidone are mainly metabolized by CYP2D6 (22). In the present case, the patient was an intermediate metabolizer of CYP2D6, with a low metabolic rate and high sensitivity to risperidone and aripiprazole. Such patient may have higher enzyme activity, thereby accelerating the metabolism and excretion of drugs and leading to a decrease in blood drug concentration. When the level of estrogen in the body decreases, the synthesis of CYP2D6 is reduced, thus slowing down the metabolic rate of oral drugs and impairing their efficacy. In our patient, the blood concentration of paliperidone was below the normal range when her menstrual cycle began but remained within the normal range outside of her menstrual period. An increase in the blood drug concentration also makes the side effects of drugs relatively obvious, causing discomfort to patients (24). Therefore, when the efficacy of a previously effective antipsychotic drug dose is reduced during the estrogen decline phase, increasing the dose may not a treatment option because it may increase the risk of adverse effects. Thus, eliminating the first metabolic pathway by changing the drug type or delivery method will ensure improvement in the therapeutic effect in such cases.

For long-acting injections, the drug release rate is relatively stable, and drug metabolism is not affected by the patient's sex (25, 26); thus, the blood drug concentration is relatively less affected by the menstrual cycle and hormones. In contrast, metabolism of oral drugs is more complex and may be influenced by the menstrual cycle. Estrogen has a greater effect on the blood concentration of oral psychiatric drugs than that of long-acting injectable drugs during the menstrual cycle.

In the clinical treatment of schizophrenia, continuous adjustment of drug types and doses and optimization of medication strategies are important. Ensuring drug efficacy, conducting early and timely intervention, reducing corresponding adverse reactions, and improving the treatment compliance of patients are common challenges faced by clinicians. The general clinical course of treatment using atypical antipsychotics involves increasing the dose or combining atypical antipsychotics with other drugs. In this case, medication adjustments were also made for 3 years, but with poor results. To rule out the effect of changes in blood drug concentration during the menstrual cycle and a decrease in patient medication compliance, the attending physician decided to change the form of medication without changing the type. Therefore, the oral form was changed to a long-acting injection, which ensured that the drug concentration in the patient's body remained within the therapeutic range. The long-acting injection is not only superior to oral dosage forms in improving patient compliance and preventing recurrence (27, 28) but can improve patients' social function earlier and for a longer duration (29). The treatment results of the patient confirmed that the long-acting injection provided a durable and stable improvement in psychiatric symptoms.

Therapeutic drug monitoring (TDM) and pharmacogenomic testing are indispensable tools in common clinical practice. TDM allows healthcare professionals to fine-tune medication dosages, ensuring that patients receive the optimal amount of a drug to achieve the desired therapeutic effect while minimizing side effects. On the other hand, pharmacogenomic testing takes personalized medicine to the next level by analyzing an individual's genetic makeup to predict their response to specific medications. It aids in selecting the most appropriate drugs and dosages based on genetic factors, reducing the risk of adverse reactions and improving patient safety. Together, TDM and pharmacogenomics help deliver more effective, safer, and patient-centered healthcare. In our patient, during the onset of her menstrual cycle, the blood concentration of paliperidone fell below the established therapeutic range. However, outside of her menstrual period, the paliperidone concentration consistently remained within the therapeutic range. The results of genetic monitoring showed that paliperidone, an intermediate metabolizer, is safe and effective for patients, and switching to a different formulation of the same drug,

rather than increasing doses or introducing drug combinations, may be a solution to fluctuations in symptoms during specific periods. In clinical practice, TDM and genetic testing should be performed in a timely manner to identify effective drugs for targeted treatment.

Conclusion

For female patients with schizophrenia with effective drug treatment, if the mental symptoms fluctuate periodically with the physiological cycle, and the effect of drug adjustment is not satisfactory, we recommend replacement with a similar long-acting injectable agent. Based on this case, we suggest that changes in hormone levels should be monitored in female adolescents during treatment and other forms of drugs that are less affected by hormones, such as long-acting injections should be administered. This may help to achieve the desired therapeutic effect. However, further high-quality research is required to promote the development of such formulations.

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), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

FW: Project administration, Writing – review & editing, Investigation, Conceptualization, Data curation, Writing – original draft. JC: Writing – original draft, Resources, Supervision, Writing – review & editing. LG: Writing – review & editing, Data curation, Formal analysis, Software. ZgL: Data curation, Formal analysis, Software, Writing – review & editing. ZeL: Conceptualization, 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.

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Serotonin syndrome caused by a CYP2C19-mediated interaction between low-dose escitalopram and clopidogrel: a case report

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Background: Serotonin syndrome has been recognized as a serious adverse reaction to antidepressants and is characterized by sudden or severe autonomic nerve dysfunction and neuromuscular symptoms. Without an accurate diagnosis and prompt treatment, serotonin syndrome progresses rapidly and can be life-threatening. It is usually related to the dose of 5-hydroxytryptamine drugs, and the dose is the basis for diagnosis. Therefore, serotonin syndrome induced by low-dose antidepressants rarely occurs, and clinicians are more likely to misdiagnose patients who take low-dose antidepressants with similar symptoms. Here, we present a case study of serotonin syndrome caused by a relatively low dose of escitalopram, which is not common in past references.

Case summary: The patient was a 74-year-old Asian woman with a 42-year history of schizophrenia. After 6 weeks of antidepressant treatment, our patient presented with characteristic myoclonus in the lower limbs and closed eyes with fluttering. Initially, she was misdiagnosed with neuroleptic malignant syndrome (NMS) due to antipsychotic medication and was treated accordingly, even with discontinuation of clozapine. However, her symptoms persisted, and then therapeutic drug monitoring was initiated with the involvement of a clinical pharmacist. Eventually, she was diagnosed with serotonin syndrome due to escitalopram levels reaching the warning level. Subsequently, the patient's treatment was modified, and her clinical outcome was satisfactory without any other serious adverse reactions. Gene detection was also performed, and a cytochrome P450 enzyme (CYP) 2C19-mediated interaction between low-dose escitalopram and clopidogrel seems to be a possible mechanism.

Conclusion: Data on this is extremely scarce, and to the best of our knowledge, serotonin syndrome caused by low-dose antidepressants has not yet been discussed to any great extent in the literature. Our case provides more clinical experience in the treatment of serotonin syndrome.

KEYWORDS

serotonin syndrome, CYP2C19, escitalopram, clopidogrel, case report

Introduction

Serotonin syndrome is a potentially life-threatening adverse drug reaction caused by excessive 5-hydroxytryptamine (5-HT) activity in the synaptic space, which results in a variety of symptoms involving the central and peripheral nervous systems (1). Changes in mental state, autonomic nerve dysfunction, and neuromuscular symptoms such as myoclonus, ocular flutter, myotonia, and hyperreflexia are some of its typical manifestations (2). Its symptoms are diverse and easily confused, making diagnosis and treatment difficult.

The formation of 5-HT is the most important link in the pathogenesis of serotonin syndrome. 5-HT is produced by the hydroxylation and decarboxylation of L-tryptophan (3). Its amount and function are tightly regulated by reuptake inhibition mechanisms, feedback loops, and metabolic enzyme combinations. Initially, 5-HT is stored in vesicles by vesicular monoamine transporters after generation. When nerve cells are stimulated by the outer axon, 5-HT is released into the synaptic space. At the same time, the presynaptic 5-HT receptor acts as a feedback loop to inhibit the exocytosis of vesicles (4). The released 5-HT binds to the prominent posterior membrane receptors and produces a corresponding effect. Meanwhile, a reuptake inhibition mechanism returns 5-HT to the cytoplasm of presynaptic neurons, where it is reabsorbed by vesicles and then metabolized by type A monoamine oxidase (5). When the reuptake is inhibited, the level of 5-HT in the synaptic cleft increases (6). Excessive 5-HT activation binds to the appropriate receptors when present in doses above a threshold, leading to serotonin syndrome and a range of symptoms. As different 5-HT receptors are distributed on different types of neurons, such as the cerebral cortex, hypothalamus, gastrointestinal tract, blood vessels, and bronchial smooth muscle (7, 8), the symptoms of serotonin syndrome tend to be diverse.

However, the variety of symptoms makes diagnosis difficult, and many conditions have similar symptoms to those of serotonin syndrome. Without careful identification, it is easy to misdiagnose, especially in patients with mental disorders who are taking multiple antipsychotic drugs at the same time. Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction to a dopamine antagonist that is often misdiagnosed as serotonin syndrome (2). Due to their different treatment methods and withdrawal strategies, clinical misdiagnosis can lead to serious outcomes. In addition, serotonin syndrome is often caused by high-dose antidepressants or a drug combination containing higher levels of 5-hydroxytryptamine (9), and low-dose antidepressant-induced serotonin syndrome rarely occurs.

Here, we present a case study of serotonin syndrome caused by a relatively low dose of an antidepressant. Serotonin syndrome occurred despite medication, with escitalopram at only 5 mg/day. Because of the routine antipsychotic treatment, at first, the patient was mistakenly diagnosed with NMS. Eventually, therapeutic drug monitoring (TDM) and genetic testing helped us identify serotonin syndrome and explain the possible pathogenesis.

Case description

Patient presentation

The patient was a 74-year-old Asian woman with a 42-year history of schizophrenia. On February 23, 2023, she was admitted to the hospital due to auditory hallucinations and a behavioral disorder, which had been worsening for 2 days. Her medical history was as follows (Table 1).

Treatment course

After admission, the patient was treated with clozapine 275 mg/day, and risperidone 3 mg/day in combination with clopidogrel 75 mg/day because of her history of cerebral infarction. In addition, our patient was receiving rosuvastatin 10 mg qn and estazolam 1 mg qn for hyperlipidemia and insomnia, respectively. She had a history of hypertension and was not receiving antihypertensive medication because her current blood pressure was normal. However, 4 days after admission, her blood pressure was 188/95 mmHg and she was prescribed valsartan 80 mg/day. On the same day, our patient was less active and depressed, so risperidone was discontinued and escitalopram 5 mg/d was added to improve depression. During treatment, the patient received intermittent potassium chloride for her persistent hypokalemia.

After 6 weeks of admission (April 13, 2023), our patient incidentally showed insomnia, agitation, refusal to eat, nervous expression, tachypnea, tremor in the lower extremities, confusion, negativism, and diaphoresis, with neurological pathological signs being all negative. Vital signs were as follows: blood pressure 196/106 mmHg, heart rate 118 beats/min, respiratory rate 30 breaths/min, and temperature 36.7°C. Initial physical examination revealed: eyes closed with fluttering; increased muscle tension; myoclonus; hyperreflexia; and bilateral plantar tremor. Laboratory findings showed that creatine kinase (CK) was 267.2 IU/L. Combined with her symptoms and medications, she was initially diagnosed with neuroleptic malignant syndrome (NMS) (Table 2).

Intravenous fluids, diazepam 5 mg injection, and propranolol 10 mg were started to relieve the symptoms, and the clozapine was immediately stopped. However, there was little change in her symptoms over the following 24 h. Moreover, what confused us was that the concentration of clozapine in our patient was 105.1 ng/mL, much lower than the normal level. On April 15, 2023, although the patient's breathing was more stable than before, her lower extremities remained tense and jittered involuntarily. The timeline for our patient was as follows (Figure 1).

Such a triad of autonomic dysfunction, neuromuscular excitement, and mental state changes could also be considered a serotonin syndrome, according to the literature (10). Therefore, TDM and gene detection were introduced despite the low dose of escitalopram. The results showed that the escitalopram level was 210.9 ng/mL, which was much higher than the cutoff, and the polymorphism of CYP2C19 was typical of poor metabolizers (PMs). Combined with the patient's current symptoms, she was diagnosed with serotonin syndrome (Table 1).

Escitalopram was then discontinued. In the following 2 days, the patient's blood pressure rose to 204/84 mmHg, and heart rate reached 145 beats/min. Intravenous fluids were used to promote drug metabolism, and captopril 25 mg was given orally as needed for antihypertensive therapy. The patient's myoclonus persisted, and her CK increased to 716.8 IU/L on April 17. Given that the half-life of escitalopram is 30 h, its metabolites last longer, and an elderly patient needs more time to eliminate escitalopram, the increase in laboratory

TABLE 1 Medical history of our patient.

Time	Etiology	Presentation	Diagnosis	Treatment	Prognosis
December 1980	Acute mental disorders following postpartum infection with high fever	Insomnia, hooey, irritability, and aggressive behavior	Schizophrenia	Chlorpromazine, perphenazine (Dose is unclear)	Stable and able to resume work
October 1984	Self-induced medication withdrawal and relapse	Insomnia, talking to self, disorganized behavior and speech, aggressive behavior, and inability to care for herself	Schizophrenia	Chlorpromazine 600 mg qd, perphenazine 32 mg qd	Stable and able to resume work
Hospitalized three times (Exact dates are unknown)	Self-induced medication withdrawal and relapse	Insomnia, talking to self, hooey, aggressive behavior, and inability to care for herself	Schizophrenia	Chlorpromazine 450 mg qd	Stable
July 2007	Self-blame and guilt after fatigue	Insomnia, crying alone, socially withdrawn, staying away from family, inability to care for herself, and aggressive behavior	Schizophrenia with depression	Clozapine 300 mg qd	Stable, and can do housework, with medication adherence
October 24, 2015	Depressed about the death of her father	Poor mood, often self-blame	Schizophrenia with depression	Clozapine, amisulpride (Dose is unclear)	Stable
(The exact date is unknown)	The patient discontinued amisulpride after discharge and only took clozapine				
July 2022	Refuses medication	Socially withdrawn, disorganized behavior	Schizophrenia	Clozapine 250 mg qd, risperidone 3 mg qd	Stable
February 2023	Self-blaming and depressed because her husband needed to undergo surgery. She had suddenly banged her head against the wall after dinner.	Self-blame and guilt, melancholy, and self-harm	Schizophrenia	Clozapine 275 mg qd, risperidone 3 mg qd	

results 2 days after her discontinuation seemed to be normal (Figure 2). Over the next 4 days, the patient presented with intermittent jittering, negativism, and myoclonus. On April 21, 2023, her hyperreflexia, myoclonus, lower extremities tremor, and ocular flutter subsided, blood pressure gradually returned to 140/72 mmHg; CK returned to normal; and her escitalopram level decreased to 23.9 ng/mL. Subsequently, the patient developed other physical conditions, which included recurrent pneumonia and gastric bleeding, and was admitted to another hospital. After the completion of treatment, she returned to our hospital and was discharged in the following weeks.

Discussion

At present, with the substantial increase of antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), and 5-HT and NE reuptake inhibitors (SNRIs), the burden of serotonin in patients is increasing, and serotonin syndrome has become an urgent clinical problem (11). Due to its diverse and non-specific manifestations, serotonin syndrome is easily ignored, misdiagnosed, or exacerbated if not carefully evaluated, especially in elderly patients with a prescribing cascade. For example, hypertension caused by serotonin syndrome may be considered to be a deterioration of the patient's primary condition, while tremor may be regarded as common adverse reaction. Anxiety and increased muscle tone may be mistakenly attributed to the patient's mental state. Although the early clinical symptoms of serotonin syndrome are often mild to moderate, individuals can quickly deteriorate without active recognition and care (12). Therefore, it is necessary to improve clinicians' understanding of serotonin syndrome.

According to the Hunter criteria, the typical clinical manifestation of serotonin syndrome is a triad of autonomic dysfunction, neuromuscular excitement, and mental state changes (13). Clonus (spontaneous, inducible, and ocular) is the most important hallmark of Hunter criteria, and this neuromuscular characteristic is closely related to serotonin syndrome. Although other adverse drug reactions may initially be mistaken for 5-HT toxicity, careful examination of specific neurological features, such as clonus, hyperreflexia, and tension, makes it possible to differentiate it from other conditions (Table 3). The most common confounding antipsychotic syndrome is NMS, due to the similarity of symptoms between them. Also, some patients with mental disorders take antipsychotic and antidepressant drugs at the same time to treat psychiatric disorders with depression, making it difficult to distinguish between them.

We went back to the clinical course of this patient. Along with rigidity, NMS is characterized by bradyreflexia, whereas serotonin syndrome mainly manifests as neuromuscular symptoms such as myoclonus, ocular flutter, and hyperreflexia (14), which were observed in our patient. The increased muscle tone in our patient was mainly in the lower limbs rather than in all muscle groups, which differs from NMS (15). No fever was observed in our patients. In fact, almost 90% of NMS

patients are characterized by a temperature above 38°C; therefore, the absence of fever in our patient was also helpful in excluding a diagnosis of NMS. Indeed, fever is not a typical symptom of serotonin syndrome (16). The patient showed significant agitation, which was different from the stupor caused by NMS (1). In addition, the patient's symptoms continued after clozapine withdrawal, which was inconsistent with NMS.

TABLE 2 Results of laboratory tests.

Variable	Value (reference range)
Blood chemistry and serology	
Total protein (g/L)	77.9 (60.0–83.0)
Albumin (g/L)	42.1 (35.0–50.0)
Globulin (g/L)	**35.8** (15.0–35.0)
Prealbumin (mg/L)	306.0 (200.0–400.0)
Total bilirubin (umol/L)	13.0 (0–23.0)
Direct bilirubin (umol/L)	3.2 (0–7.0)
Aspartate aminotransferase (IU/L)	21 (5–50)
Alanine aminotransferase (IU/L)	20 (7–40)
Alkaline phosphatase (U/L)	92.8 (40–150)
Lactate dehydrogenase (IU/L)	**264** (109–245)
γ-Glutamyltransferase (IU/L)	25 (7–50)
Sodium (mmol/L)	142.2 (137.0–147.0)
Potassium (mmol/L)	3.09 (3.5–5.3)
Chloride (mmol/L)	101.6 (99.0–110.0)
Creatinine (umol/L)	63.7 (45.0–104.0)
Urea nitrogen (mmol/dL)	7.2 (2.9–8.2)
Creatine kinase (IU/L)	**267.2** (26–174)
Creatine kinase-MB fraction (IU/L)	**25.1** (0–25.0)
Hematology	
Red blood cells ($\times10^{12}$/L)	4.85 (3.5–5.13)
Hemoglobin (g/L)	**151** (110–150)
Hematocrit (%)	45.1 (34.0–51.0)
White blood cells ($\times10^{9}$/L)	**19.7** (4.0–10.0)
Platelet count ($\times10^{9}$/L)	**348** (100–300)
Neutrophil percentage (%)	**92.6** (50–70)

The bold values means pathologic changes in the laboratory report.

The core symptoms of NMS are bradyreflexia, lead pipe rigidity in all muscle groups, coma, and hyperthermia, in contrast to the hyperreflexia and clonus seen in serotonin syndrome. Some of the symptoms, such as agitation, refusal to eat, nervous expression, tachypnea, CK elevation, and diaphoresis, are common to both NMS and serotonin syndrome (17). Lower limb tremors, myoclonus, and hyperreflexia are unique to serotonin syndrome. Since our patient had been taking clozapine, while the dose of escitalopram was rather low (5 mg/d), it is easy to mix up these two diagnoses. Unlike NMS, serotonin syndrome should not be considered an extremely rare idiosyncratic reaction to drugs but rather a form of 5-HT toxicity based on elevated concentrations that can occur in patients of any age (2). Considering the above, it was less likely to diagnose NMS in our patient. Thus, overall, the occurrence of hyperreflexia, increased lower extremity tension, myoclonus, agitation, ocular flutter, and high escitalopram concentration in our patient supported the diagnosis of significant serotonin syndrome.

Given that our patient continued to have certain symptoms after discontinuing clozapine and CK increased after discontinuing escitalopram, we also need to be aware of clozapine discontinuation withdrawal symptoms, which are similar to those of serotonin syndrome and include clozapine's cholinergic withdrawal symptoms and serotonergic withdrawal symptoms (Table 4).

Clozapine's cholinergic withdrawal symptoms, also known as "cholinergic rebound," are characterized by a series of mental and physical clinical features that include nausea, vomiting, confusion, insomnia, and dystonia (18). Symptoms usually appear within a few days and last for weeks or longer. This is thought to be caused by overactivity of the cholinergic system. Although some symptoms, such as insomnia and dystonia in cholinergic rebound, partly overlap with our patient's symptoms, the timing was not consistent with clozapine withdrawal. Before clozapine was discontinued, our patient had insomnia. In addition, cholinergic rebound does not appear as spontaneous clonus, whereas it was the core symptom of the serotonin syndrome that appeared in our patient.

Serotonergic withdrawal symptoms are very similar to those of serotonin syndrome. The only difference is the medication. Serotonergic withdrawal symptoms are usually associated with clozapine withdrawal, which is related to its 5-HT_{2A} antagonist effect.

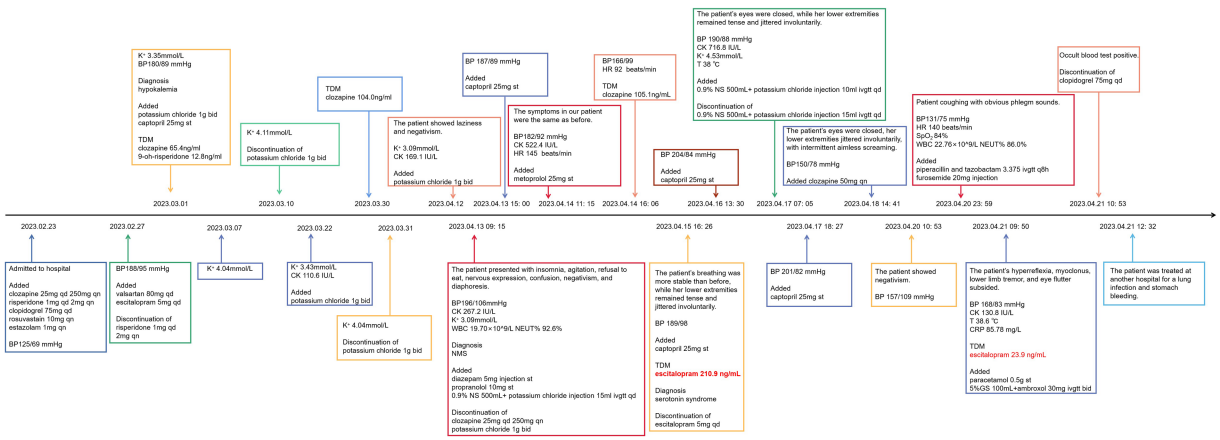

FIGURE 1
Case report timeline.

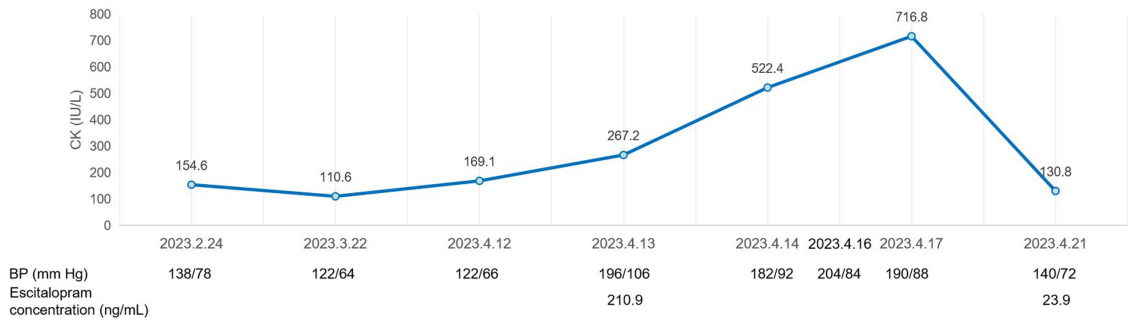

FIGURE 2
A graphic representation of the clinical course of the patient with serotonin syndrome, showing laboratory values during hospitalization.

TABLE 3 Typical clinical presentation according to the Hunter criteria.

Category	Signs and symptoms
Neuromuscular	Clonus (inducible, spontaneous or ocular)
	Tremor
	Hyperreflexia
	Hypertonicity
Autonomic	Diaphoresis
	Maximum temperature > 38°C
Mental state	Agitation

TABLE 4 Differences in withdrawal symptoms between serotonin syndrome, neuroleptic malignant syndrome (NMS), and clozapine discontinuation withdrawal symptoms.

	Classification	Symptoms	Core symptoms
Adverse drug reaction	Serotonin syndrome	The classic triad of clinical features is altered mental status (with anxiety, agitation, and confusion), autonomic nervous system hyperactivity (with diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea), and neuromuscular hyperactivity (muscle rigidity, hyperkinesis that includes myoclonus and tremor, hyperreflexia, and bilateral Babinski sign).	Hyperreflexia and clonus
Idiosyncratic reaction	Neuroleptic malignant syndrome	Agitated delirium, confusion, lead pipe rigidity, cogwheel tremor, hyperthermia with body temperature greater than 40°C, profuse diaphoresis, tachycardia, hypertension, and tachypnea	Bradyreflexia, lead pipe rigidity in all muscle groups, coma, and hyperthermia
Withdrawal symptoms from clozapine discontinuation	Serotonergic symptoms	Agitation, diaphoresis, clonus, and hyperreflexia	Hyperreflexia and clonus
	Cholinergic symptoms (cholinergic rebound)	Nausea, vomiting, confusion, insomnia, and dystonia	Dystonia
	Withdrawal-associated psychosis	Delusions, hallucinations, and thought disorder (TD), including formal thought disorder (FTD) and content thought disorder	Delusions, hallucinations
	Catatonia	Stupor, posturing, and echo phenomena	Stupor, posturing, and echo phenomena

Long-term use of clozapine can lead to upregulation of serotonin receptors, and sudden withdrawal produces a response similar to serotonin syndrome (19). Theoretically, any drug with a 5-HT_{2A} antagonist effect will produce serotonin withdrawal symptoms. However, the patient's symptoms had appeared before clozapine withdrawal. They had manifested as a more central serotonin syndrome. Therefore, this stage can rule out the possibility of serotonergic symptoms caused by clozapine withdrawal. After clozapine withdrawal, the patient still presented with the previous symptoms without showing new ones. Crucially, due to the lack of antipsychotic treatment during serotonin syndrome, the psychiatric symptoms that appeared in our patient on April 18, 2023, manifested as yelling; therefore, clozapine 50 mg was re-used for treatment. It should be noted that our patient's psychiatric symptoms were partly controlled after treatment, while the serotonin syndrome did not improve. If the patient's current serotonergic symptoms were caused

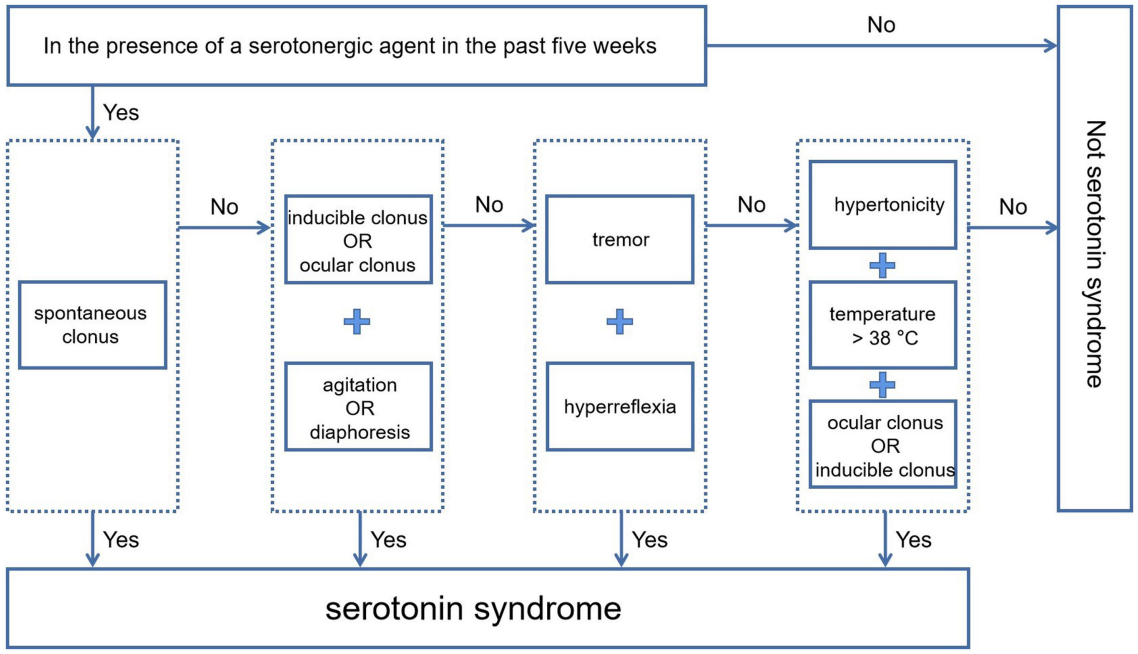

FIGURE 3
Decision rules of the Hunter serotonin toxicity criteria.

by clozapine withdrawal, the symptoms would have disappeared after clozapine reintroduction. On the contrary, the patient's symptoms gradually subsided after discontinuing escitalopram, ruling out the possibility that the serotonergic symptoms were caused by clozapine withdrawal. In fact, her symptoms had little to do with clozapine. Symptoms appeared when clozapine was still being taken at a dose of 275 mg; symptoms did not subside after clozapine withdrawal; symptoms did not worsen or subside when clozapine was re-introduced. This helped us exclude the diagnosis of serotonergic withdrawal symptoms in our patient after discontinuing clozapine.

In fact, there were two extreme situations in the patient that we also had to take into account, namely, the possibility of gradual regression of NMS after clozapine withdrawal and the regression of serotonergic symptoms after clozapine withdrawal. Before the symptoms appeared, our patient did not discontinue any medication, not even clozapine. After she did, the symptoms did not subside. Therefore, the possibility that the symptoms were caused by clozapine discontinuation was excluded.

Although serotonin syndrome has many similarities to NMS, its diagnosis based on Hunter criteria is not difficult, due to some core symptoms. It is important for clinicians to be aware that patients' current complex symptoms may be related to serotonin syndrome. Once such a connection is established, serotonin syndrome is not difficult to diagnose according to the decision rules of the Hunter Serotonin Toxicity criteria (Figure 3).

Before evaluation based on decision rules, clinicians should have a full understanding of the use of prescription drugs and overdoses, illicit substances, and dietary supplements, which is critical to determining whether Hunter criteria are applicable and whether all of these medications are related to the development of serotonin syndrome. The use of 5-HT drugs or interactions that produce 5-HT tryptamine activity is the basis of the diagnosis. Second, a detailed physical examination should be carried out. The physical examination should include a focused assessment of deep tendon reflexes, clonus, and muscle rigidity, in addition to an assessment of pupil size and reactivity, dryness of the oral mucosa, intensity of bowel sounds, skin color, and sweating. The neuromuscular features of clonus and hyperreflexia are highly diagnostic of serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity may overwhelm other neuromuscular findings and mask the diagnosis. Finally, screening for serotonin syndrome should be carried out strictly in accordance with Hunter criteria.

Cases of serotonin syndrome requiring hospitalization are easy to diagnose because severe symptoms (such as bilateral, symmetric clonus in the legs more than in the arms) are not common in other cases. The combination of non-specific autonomic manifestations, a series of possible signs and symptoms, and the lack of definitive laboratory tests makes it less likely to diagnose mild cases, although such cases are also less likely to be fatal. In addition, the risk of serotonin syndrome caused by a single therapeutic dose is low (20). The emergence of serotonin syndrome is often a combination of several drugs.

Since serotonin syndrome is a drug-induced condition, an accurate drug history is necessary for diagnosis. A wide variety of drug types and combinations can cause serotonin syndrome, and the final common pathway is thought to involve a net increase in serotoninergic neurotransmission. In addition to SSRI excess, drugs that inhibit 5-HT metabolism, increase 5-HT synthesis, increase 5-HT release, and promote 5-HT1 receptor activation can cause serotonin syndrome. There are many drug combinations that can cause serotonin syndrome. 5-HT toxicity most commonly occurs when two or more drugs that increase 5-HT are used simultaneously, especially if they increase 5-HT in

different ways (21). It is worth noting that the combination of SSRI and monoamine oxidase inhibitor (MAOI) can significantly increase the risk of serotonin syndrome. SSRIs inhibit the reuptake of 5-HT and increase the level of 5-HT in the synaptic cleft. MAOIs can reduce the degradation of monoamine neurotransmitters, such as 5-HT, and significantly increase its level. Therefore, the combination of these two drugs should be strictly prohibited. The sequential use of these two drugs should also maintain a 14 day interval.

To date, there is little agreement on the effect of the serotonin concentration on serotonin syndrome. Some studies suggest that an increase in serotonin levels is likely to lead to serotonin syndrome (12). Therefore, the determination of serum 5-HT levels can be used as the basis for the diagnosis of serotonin syndrome. Other researchers believe that there is no laboratory test to confirm the diagnosis of serotonin syndrome, and the level of 5-HT concentration has no practical significance for the diagnosis (22), because the local concentration of nerve endings is the cause of the physiological effects of serotonin syndrome (23). Although the role of 5-HT concentration in serotonin syndrome is still controversial, most studies generally believe that high doses of SSRI drugs or drug behaviors that can produce high serotonin effects can lead to serotonin syndrome (2, 24). The concentration of escitalopram in our patient reached a staggering 210.9 ng/mL, exceeding the warning level, which significantly supported the diagnosis of serotonin syndrome.

Aggregation of 5-HT caused by high concentrations of SSRIs leads to serotonin syndrome, which was confirmed by the blood concentration in our patient, but how did she reach such a high concentration with a relatively low dose of escitalopram? Drug interactions are a factor that cannot be ignored. Escitalopram is a well-known SSRI that is mainly metabolized by CYP2C19, a highly polymorphic enzyme known to cause individual differences in pharmacokinetics (25). Clopidogrel is a thiophene-pyridine prodrug that also needs to be metabolized by CYP2C19 to form active thiol derivatives that selectively and irreversibly inhibit $P2Y_{12}$ receptors (26). The serotonin syndrome here seemed to occur due to an interaction between these two drugs. To date, only escitalopram-increasing effects of clopidogrel through pharmacodynamic synergism have been reported (27), and there are no such reports of clopidogrel-increasing effects on the pharmacodynamics and pharmacokinetics of escitalopram. In light of this, we examined the CYP2C19 polymorphism and surprisingly discovered that it was typical of poor metabolizers (PMs), as evidenced by the presence of two nonfunctional alleles (CYP2C19 *2/*3). The metabolism of both escitalopram and clopidogrel was slowed down. That means, at first, the serum level of escitalopram slowly increased or balanced as a result of the comprehensive effect of poor metabolism of CYP2C19, continuous exogenous intake, and metabolism. However, clopidogrel, which is metabolized by the same enzyme, was also introduced at the same time, which seriously slowed down the metabolism of escitalopram. As a result, one month later, the level of escitalopram steadily increased to a dangerous level, resulting in serotonin syndrome. It should be noted that our patient was taking clozapine, an atypical antipsychotic drug with partial $5\text{-}HT_{2A}$ antagonism, which can also delay serotonin syndrome (28). The withdrawal of clozapine may, instead, partially aggravate the symptoms of serotonin syndrome. Therefore, overall, explaining the reason how serotonin syndrome caused by low-dose of escitalopram and why the syndrome developed so slowly.

We do not believe that our patient developed serotonin syndrome using such a low dose of escitalopram alone. The patient's platelet control was acceptable during the combination of clopidogrel and escitalopram, whereas gastric bleeding symptoms occurred after the discontinuation of escitalopram, indicating a significant increase in clopidogrel active metabolites after CYP2C19 metabolism. This may be the initial combination of overloaded drug metabolism causing CYP2C19 to "run at full load" due to its PMs. Although escitalopram can affect platelet activation and increase the effect of clopidogrel, clopidogrel activation is reduced due to the PMs of CYP2C19, and patients have no risk of bleeding. When escitalopram was removed, CYP2C19 remained operating at full load and then converted more clopidogrel to an active metabolite, thus resulting in gastric bleeding. This further indicates that there is a co-occupancy of CYP2C19 in the combination of escitalopram and clopidogrel, causing a decrease in the metabolism of both drugs. To put it another way, escitalopram, when taken alone at a dose of 5 mg/d in our patient, does not lead to accumulation and is metabolized by CYP2C19, similarly to clopidogrel. It is precisely because of the combination of the two drugs, which are both metabolized by CYP2C19, and the patient's low enzyme activity leads to serotonin syndrome.

Other drugs that may affect the metabolism of CYP2C19 may also affect the metabolism of escitalopram, e.g., enzyme inhibitors and enzyme inducers. Inhibitors can hinder the metabolism of escitalopram, increase its concentration in the body, and cause drug overdose poisoning. Inducers may accelerate the metabolism of escitalopram and reduce its efficacy. CYP2C19 enzyme inhibitors and inducers are shown in Table 5.

To our knowledge, there have been no reports of serotonin syndrome caused by low-dose escitalopram in combination with clopidogrel. Only one case has been reported that was caused by low-dose citalopram. The report described a 40-year-old male patient who developed serotonin syndrome within 3 h of taking citalopram 30 mg (29). The effective dose of escitalopram in this case was relatively high, in contrast to our patient. Since it is generally associated with high doses of serotonergic drugs, the serotonin syndrome in our patient is quite rare. Meanwhile, cases of serotonin

TABLE 5 CYP2C19 enzyme inhibitors and inducers.

Classification	Inhibitor	Inducer
	Esomeprazole, Omeprazole, Fluconazole, Voriconazole, Chloramphenicol, Artemisinin, Isoniazid, Fluoxetine Hydrochloride, Indomethacin, Sodium Valproate, Oxcarbazepine, Fluvastatin, Lovastatin, Nicardipine, Amiodarone, Zafirlukast, and Oral contraceptives, etc.	Rifampicin, ritonavir, dexamethasone, Ginkgo preparations, and St. John's wort

syndrome related to poor metabolizers of CYP2D6 have also been reported (30, 31).

Conclusion

In older adults on low-dose antidepressants, drug interactions, and low metabolic enzyme activity can lead to serotonin syndrome, which is likely to be ignored by doctors in the majority of cases. Additionally, it is easy to overlook mixed symptoms when dealing with serotonin syndrome, and unintentionally increasing medication dosages or adding medications with high levels of 5-HT could result in serious clinical events.

Although the combination treatments of clopidogrel and escitalopram did not cause serotonin syndrome in most patients, it is still necessary to be alert for drug accumulation in patients with poor metabolism of CYP2C19, which may still be fatal in some special cases. Early detection, TDM and genetic testing, active intervention, and treatment are essential for the further management of serotonin syndrome.

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. Written informed consent was obtained from the patient and her relatives, and the information was de-identified to protect anonymity.

Author contributions

JW: Writing – original draft. JY: Writing – original draft. KQ: Validation, Writing – review & editing. JJY: Validation, Writing – review & editing. CZ: Validation, Writing – review & editing. XL: Validation, 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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Case report: 10 years follow-up of psychosis due to Fahr's disease complicated by a left temporal stroke

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Fahr's disease (FD) is a rare disorder, characterized by basal ganglia calcification and presenting with movement disorders, speech impairment, cognitive deficits, and neuropsychiatric symptoms. Psychotic disorders related to FD are barely described in the literature, and knowledge is missing concerning pathophysiology, course, and management. Here, we report on the long-term follow-up of a patient who had three acute episodes of FD-psychosis characterized by bizarre delusions and behavioral disorganization, without hallucinations. Genetic and metabolic causes of FD were ruled out. In all three episodes, olanzapine monotherapy rapidly and completely resolved psychosis, without inducing metabolic syndrome and extrapyramidal symptoms. In addition to the acute decompensations, the patient presented a tame, introverted, industrious, and perfectionistic personality, which we could interpret as the "*parkinsonian personality*" described for many other basal ganglia disorders. Moreover, bizarre appearance, reduced affectivity, abulia, concrete speech, and stiff motricity in the context of a mild asymmetric extrapyramidal syndrome characterized the mental status. The cognitive profile was initially marked by executive difficulties and partial agnosia, with an IQ of 86. In the course of 10years, the patient suffered from an ischemic stroke in the left superior temporal gyrus, which provoked a decline in memory and executive functions, without any impact on the psychiatric picture. Antiphospholipid antibody syndrome emerged as the underlying cause; thus, for the first time in the literature, an overlap of FD and antiphospholipid antibody syndrome is described here. This case report stresses once more the need for better integration of psychiatry and neurology and for the investigation of secondary causes of late-onset psychosis.

KEYWORDS

Fahr's disease, Parkinson personality, psychosis, diagnosis, antipsychotics

Introduction

Fahr's disease (FD) is a rare disorder (prevalence <1 out of 1,000,000), identified by progressive brain calcifications of internal globus pallidus, caudate, putamen, dentate nuclei, and thalamus (1, 2).

The pathogenesis of FD is incompletely understood; a calcification of small vessels' walls and perivascular space occurs, ultimately extending to neurons. A defect in iron transport and a free radical production at the level of the blood–brain barrier are considered as pathogenetic *primum movens*. Thus, microvascular stenoses initiate a cycle of impaired blood flow, neural tissue injury, and mineral deposition (1, 3).

FD is sporadic in most cases, but it is rarely inherited in an autosomal dominant fashion due to mutations in solute carrier 20A2 (SLC20A2), platelet-derived growth factor beta (PDGF-beta), platelet-derived growth factor beta receptor (PDGFR-beta), and Xenotropic and Polytropic Retrovirus Receptor 1 (XPR) genes.

FD needs to be distinguished from Fahr's syndrome in which basal ganglia calcifications are attributed to metabolic, mitochondrial, infectious, toxic, or traumatic causes (1, 4).

FD's typical age of onset is in the 3rd to 5th decade of life, being extrapyramidal syndrome the most common presentation. Affected individuals display parkinsonism, ataxia, dystonia, seizures, myoclonus, speech impairment, cerebellar dysfunction, orofacial dyskinesias, and chorea (1, 2, 4). Cerebrovascular disorders were described in many cases of FD (5, 6). Neuropsychiatric symptoms are common in FD, including major cognitive impairment, frontal lobe syndrome, mania, depression, and personality change (4, 7). So far, few cases of FD-psychosis have been described (8–14).

Treatment for FD is usually symptomatic, while no disease-modifying measures exist to limit the progression of brain calcification (1, 2).

Even if FD-psychosis is a known phenomenon, in-depth knowledge of clinical features, comorbidities, course, and treatment is lacking. For the first time in the literature, we describe a long-term follow-up of a patient with non-hereditary idiopathic FD, developing multiple psychotic episodes in the course. Moreover, the patient represents the first case in the literature of antiphospholipid antibody syndrome comorbid with FD, leading to a left-superior parietal stroke.

Case report

Mr. B is a Caucasian man, who was born in 1961. No pregnancy and/or perinatal problems are known nor is there a delay in the early development. Since the age of 8 years, he was admitted to a special school due to unspecified learning difficulties, corresponding to a 2 years delay compared to the norm. Mr. B was then able to move to an ordinary school at the age of 14 years, but he did not obtain the graduation. After a practical education, he worked as a store manager for 13 years and then, until 2008, as a delivery boy for his religious community. His only relevant medical antecedent was cranial trauma with peri-circumstantial amnesia at the age of 8 years; he has no family history of movement disorders or psychosis, but his only brother has a slight intellectual disability and is institutionalized.

In 2012, without any provoking factor, Mr. B suffered from a psychotic episode characterized by bizarre mystic and persecutory delusions accompanied by congruent hallucinations, requiring hospitalization due to psychomotor agitation and lack of insight. An idiopathic brief psychotic episode was diagnosed, and after administration of olanzapine 10 mg, symptoms got completely remitted in 7 days. The same treatment was continued for relapse prevention.

After 2 years, following olanzapine withdrawal for 4 months in accordance with the psychiatrist, a novel brief psychotic episode ensued. The patient was arrested by the police on the street while walking barefoot; upon interrogation, he explained that this way he would have found a wife the same day, a delusion that was also mixed with some of the mystic contents known from the previous episode. Again, a 7 days hospitalization and the resumption of olanzapine 10 mg made full remission.

After discharge, he was addressed for a neurological assessment: a predominant right hypokinetic rigid extrapyramidal syndrome was observed, attributed mostly to FD, and to olanzapine treatment only to a lesser extent. A brain MRI displayed abnormal calcium deposits at the level of the basal ganglia, especially of the pulvinar, leading to a diagnosis of FD. Magnetic resonance angiography and venography excluded intracranial large-vessel stenosis, aneurysm, vascular malformation, or dural sinus thrombosis. The contrast-enhanced MRI excluded abnormal parenchymal or leptomeningeal enhancement. An endocrinological evaluation ruled out hyperparathyroidism and other causes of a phospho-calcic metabolism imbalance since repeated blood dosages of total calcium, ionized calcium, phosphates, parathyroid hormone, and 25-hydroxy-vitamin D showed no abnormalities. After this comprehensive neurological and endocrinological assessment, the two psychotic episodes were evaluated as a form of FD-psychosis.

Extensive genetic testing (SLC20A2, PDGF-beta, PDGFR-beta, and XPR) was realized, but no pathogenetic mutation was found in homo- or heterozygosis.

Because of the subjective difficulties in reading, writing, and calculating a neuropsychological realized. It resulted overall normal, even if some executive difficulties and a partial agnosia emerged, with an IQ of 86 (see Table 1 for the summary of testing).

In 2018, olanzapine was interrupted again in accordance with the psychiatrist, considering the 4 years disease-free interval and the risk of metabolic syndrome and of a worsening of extrapyramidal symptoms with this medication. After 3 weeks of drug withdrawal, Mr. B developed an acute confusional state and a seizure due to hyponatremia (124 nM) secondary to potomania. Once the ion imbalance was resolved, mental status turned out to be characterized by an incoherent and disorganized thought process, and thought content was occupied by the delusional idea of having killed his brother from a distance, which generated feelings of guilt and shame. Moreover, the obsessional fear that he or someone else was going to die emerged for some days. Once more, olanzapine reintroduction at a dosage of 15 mg resolved the acute episode. After a month, a maintenance dose of 10 mg was left and is still effectively taken.

In January 2022, the patient complained of a subjective decline in memory and executive functions, mirrored by a Montreal Cognitive Assessment test (MoCA) score drop from 26 to 23 points (see Table 1). A novel brain MRI revealed an ischemic stroke in the left superior temporal gyrus (see Figure 1), without any other relevant difference compared to previous MRIs. A duplex of the sovra-aortic vessels and a long-term Holter exam of the cardiac rhythm revealed no abnormalities; meanwhile, the echocardiography showed a right–left shunt of moderate severity, confirmed by means of a transcranial duplex. The laboratory examination showed the positivity of the B2GP1 antibodies (53.3 UI/L at time 0, 61.6 UI/L after 6 weeks), leading to a diagnosis of antiphospholipid antibody syndrome. Anticoagulation with warfarin was introduced and is still ongoing. A comprehensive neuropsychological evaluation showed a general slowing and deficits of selective attention, verbal episodic memory, recognition of fear, and verbal autoactivation.

The last brain MRI in 2022 displayed stability of the basal ganglia calcifications and of the ischemic lesion but a hippocampal atrophy (class MTA 0 bilaterally) and a microvascular leukoencephalopathy (Fazekas 1 grade).

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TABLE 1 Summary of neuropsychological deficits at multiple time points.

Cognitive function	Test	Results	Interpretation
24.04.2014			
Mental flexibility	Color trail test; WAIS-III subtest code	NA	Lower limit of normality
Attention	Color trail test; WAIS-III subtest code	NA	Moderate impairment
Verbal IQ	WAIS-III	Total score 86 pts, performance score 84 pts	Lower limit of normality
19.01.2016			
Global assessment	MoCA test	Total score 24/30 pts (−1 pt. mini trail, −1 pts serial subtractions, −1 pt. fluency, −3 pts delayed recall)	Lower limit of normality
Executive functions	BREF scale	Total score 16/18 pts (− 1 pt. fluency, − 1 pt. Go/noGo)	Lower limit of normality
11.01.2017			
Global assessment	MoCA test	Total score 24/30 pts (−1 pt. mini trail, −1 pts serial subtractions, −1 pt. fluency, −3 pts delayed recall)	Lower limit of normality
Executive functions	BREF scale	Total score 16/18 pts (− 1 pt. fluency, − 1 pt. Go/noGo)	Lower limit of normality
19.12.2018			
Global assessment	MoCA test	Total score 25/30 pts (−1 pt. clock, −1 pt. fluency, −2 pt. free recall, −1 pt. orientation)	Normal
10.01.2020			
Global assessment	MoCA test	Total score 26/30 pts (−1 pt. clock, −1 pt. fluency, −1 pt. free recall, −1 pt. orientation)	Normal
25.01.2022			
Verbal fluency	Animal categories	23 pts	Pathological
Phonemic fluency	Words starting with "P"	19 pts	Lower limit of normality
Mental flexibility	Color trail test	1st part 85″, 2nd part 210"	Pathological
Inhibition	Stroop Victoria test	24"	Pathological
Verbal memory	Immediate recall	14 pts	Lower limit of normality
Episodic memory	Doors test	Part A 9 pts, part B 5 pts	Lower limit of normality
Attention	WAIS-III subtest code	35 pts	Pathological
Emotion recognition	Mini-SEA test	Fear not recognized in 4/5 attempts	Pathological
15.02.2022			
Global assessment	MoCA test	23/30 pts (−3 pts executive functions, −1 pt. verbal fluency, −1 pt. abstraction, −2 pts delayed recall)	Pathological

Pt/pts, point/s; NA, not available; WAIS, Wechsler adults inventory scale; IQ, intelligence quotient; MoCA, Montreal cognitive assessment; BREF, rapid battery for the frontal efficiency; Mini-SEA, mini-social cognition and emotional assessment.

Nowadays, Mr. B is independent in the activities of daily living and in self-care; he lives alone in an apartment, and he benefits from a disability monthly paycheck and works part-time in a laundry. He displays a poor relational and intimate life: he is not in a couple relationship, has a social life restricted to a religious community, and his sister remains his main support figure.

The patient's personality is tame and naïve, characterized by interpersonal inhibition and social withdrawal and also by obsessive traits such as perfectionism, ritualism, over-conscious behavior, and love for habits. Currently, Mr. B presents no positive psychotic symptoms and behavioral abnormalities, but his appearance is bizarre and aloof; he gives the examiner a sense of strangeness and coldness in a context of reduced affectivity and stiff motricity. Mr. B always reports feeling good but displays apathy, abulia, and anhedonia instead, and his speech is concrete and oversimplified. From the motor point of view, Mr. B presents an asymmetric bradykinetic-amimic extrapyramidal syndrome and bucco-facial dyskinesias, as detailed in Table 2.

Beyond the three psychotic episodes, psychiatric status and personality profile remained remarkably steady, with no meaningful variations through the years; after each psychotic episode, Mr. B was able to recover his previous level of functioning, without personal and cognitive impairment nor residual psychotic symptoms; a decline was only due to the ischemic stroke.

The patient persistently showed good insight, with a full understanding of the motor symptoms of FD and of the three episodes of FD-psychosis. Accordingly, he has been taking olanzapine for a long time with perfect adherence and categorically refused a novel attempt at withdrawal or a switch to a different medication.

Discussion

FD is a rare neurological condition having multiple dimensions; FD-psychosis is one of them, whose pathophysiology, course, and

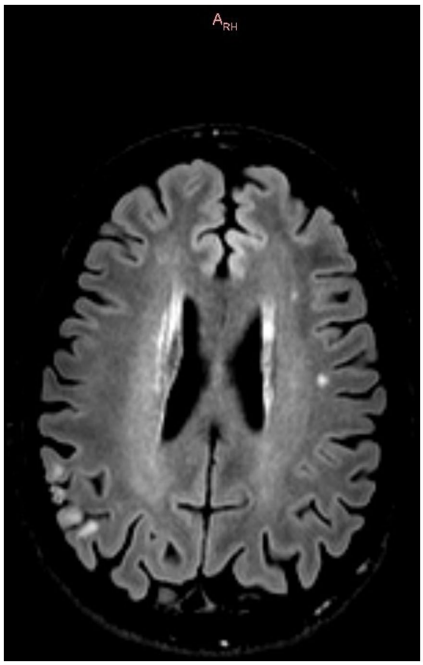

FIGURE 1
3T brain MRI displaying basal ganglia calcification and left temporal stroke, 15.11.2023.

TABLE 2 MDS-UPDRS III, 05.08.2022.

ITEM	Left	Right
3.1 Speech	0/4	
3.2 Facial expression	2/4	
3.3 Rigidity	2/4	2/4
3.4 Finger tapping	2/4	1/4
3.5 Hand movements	1/4	1/4
3.6 Pronation-supination movements of hands	2/4	2/4
3.7 Toe tapping	1/4	1/4
3.8 Leg agility	1/4	1/4
3.9 Arising from chair	0/4	0/4
3.10 Gait	0/4	0/4
3.11 Freezing of gait	0/4	0/4
3.12 Postural stability	0/4	0/4
3.13 Posture	0/4	0/4
3.14 Global spontaneity of movement	0/4	0/4
3.15 Postural tremor of hands	0/4	0/4
3.16 Kinetic tremor of hands	0/4	0/4
3.17 Rest tremor amplitude	0/4	0/4
3.18 Constancy of rest tremor	0/4	0/4
TOTAL	19/132	

MDS-UPDRS III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale, 3rd section; cutoff scores to define mild/moderate and moderate/severe levels are 32/33 and 58/59, respectively.

treatment remain poorly understood. The present case is unique in terms of follow-up length. Moreover, attention should be given to the overlap with a left superior temporal stroke resulting from an antiphospholipid antibodies syndrome and to an episode of psychogenic polydipsia. This latter is an impulsive phenomenon unknown in FD but possibly linked to basal ganglia dysfunction (15).

Mr. B presented a "parkinsonian personality," arising in the context of a basal ganglia disorder (e.g., Parkinson's disease) and defined as a compulsive, industrious, introverted, morally rigid, cautious, punctual, quiet, and inflexible character, with low novelty seeking (16). Psychotic episodes of Mr. B were not in line with this personality structure but similar to schizophrenic delusions, normally arising on the grounds of a paranoid or schizotypal personality (17).

In fact, acute psychotic symptoms consisted of the delusion of persecutory type, bizarre and disorganized behavior, and in a lesser component thought process impairment. These features were in line with other case reports (8, 18), but Mr. B differed in the absence of hallucinations (10, 12–14, 18) and of obsessive-compulsive symptoms (10). The onset of psychosis was late (51 years), in line with the typical age of onset of FD (1, 2, 4) and with some cases of FD-psychosis (8–10, 13). On the contrary, other cases of FD-psychosis had an early onset (11, 12, 14). Mr. B was determined as a sporadic case of FD-psychosis after an extensive search for genetic causes of the disorder and an investigation into affected relatives. Quite the opposite, any of the other cases of FD-psychosis in the literature underwent genetic testing, and only for one of them, a familial nature was acknowledged (14).

We observed a complete remission of Mr. B's acute psychotic episodes and a return to the same baseline level of functioning, without decline, which differentiates FD-psychosis from schizophrenia. In fact, each acute episode of schizophrenic psychosis takes a toll in terms of cognitive, social, and personal functioning, and often residual psychotic symptoms persist (19).

The concomitance of ischemic stroke with FD has already been described (5, 6, 20) and linked to genetic mutations related to FD in two cases (21, 22). Calcification in the walls of small vessels has been implicated as the potential cause (6). In addition to this possible mechanism, we describe for the first time in the literature the comorbidity of FD with a phospholipid antibodies syndrome, interpreted as the cause of stroke. The parietal ictus had no consequences on psychopathology but only on cognitive functioning. This finding is surprising considering the role of the area in behavioral disorganization (23) and in the pathogenesis of psychosis (24).

In the 10 years clinical history of Mr. B, treatment was specific for FD-psychosis, without medication to address other dimensions of FD. Response to olanzapine was complete and sustained, with no induction of metabolic syndrome nor of a significant movement disorder; in fact, the patient presents a mild extrapyramidal syndrome, mostly attributed to FD. Olanzapine withdrawal led to multiple psychosis relapses, proving that long-term medication was needed; the ischemic stroke did not pose the need for a change in this respect. The choice of olanzapine was motivated by the concern that an antipsychotic with a stronger anti-dopaminergic effect would have worsened the extrapyramidal syndrome. Our choice was in line with a previous case that was effectively treated with olanzapine alone (18) or combined with fluoxetine to address concomitant obsessive symptoms (10). However, other cases treated with low-dose risperidone (12, 13), with risperidone plus oxcarbazepine (11), with low-dose haloperidol (9), or with risperidone plus haloperidol (8)

that had an equally positive outcome in the short-term, without developing a movement disorder. These findings indicate that all antipsychotics could be rapidly effective in inducing remission of FD-psychosis. Clozapine is possibly a valuable therapeutic option, often used for psychosis in Parkinson's disease and other basal ganglia disorders due to the low impact on the extrapyramidal system (25). However, the high potential for sedation and metabolic syndrome relegates its use to treatment-resistant schizophrenia (26).

Our case report presents many strengths, such as the length of the observation period, the multidisciplinary follow-up, the availability of neuropsychological and neuroradiological data, and the careful mental status evaluation at multiple time points. The overlap between FD and antiphospholipid antibodies syndrome is unprecedented. However, some limitations can be found: the diagnosis of FD was delayed and posed only after the second psychotic episode. Second, in-depth neuropsychological testing was realized only twice, while the cognitive follow-up was mainly based on screening instruments such as the Montreal Cognitive Assessment (MoCA) and the rapid battery for the frontal efficiency (BREF) scales. Moreover, concerning the first neurocognitive evaluation, we only had a qualitative evaluation of the outcome of many tests, with the raw results not available in the clinical records. Last, a formal evaluation for personality disorders was missing.

In conclusion, our report underlines the necessity of excluding organic causes in front of an acute psychotic onset, especially at an age range atypical for a first episode of schizophrenia. Imaging and laboratory exams should be integrated into psychiatry clinical practice in order to diagnose organic mental disorders. FD-psychosis remains a poorly studied phenomenon, deserving further investigation to reach an in-depth knowledge about pathophysiology and clinical management.

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 individual(s) 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

MP: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. GP: Supervision, Validation, Writing – review & editing. JB: Supervision, Validation, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Clinical pharmacist interventions in the transition of care in a mental health hospital: case reports focused on the medication reconciliation process

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The transition of care represents a key point in the hospital admission and discharge process. A comprehensive transition could lead to fewer medication-related problems. The hospital clinical pharmacist could help in the transition of care process with a comprehensive medication reconciliation process, which has been poorly described in mental health hospitals. This study presents two clinical cases in which hospital clinical pharmacists identified omitted medications and other medication-related issues, including medication errors, during the transition of care in a mental health hospital. These positive experiences may encourage other countries to establish similar collaborations with hospital clinical pharmacists in mental health hospitals.

KEYWORDS

psychiatry, hospital clinical pharmacist in psychiatry, transition of care, medication reconciliation, case report

Introduction

The transition of patients between different healthcare settings and levels of healthcare is one of the most important therapeutic challenges, as medication errors often occur (1, 2). Medication errors are associated with a higher incidence of adverse effects and higher treatment costs and are responsible for many hospital admissions (1, 2). Medication errors occur at all levels of outpatient and inpatient care. At present, most occur at the admission, ward transition, and discharge from the hospital and back to primary care, so appropriate medication reconciliation is needed (2). The prevalence of medication errors in Scottish hospitals was 7.5% (4,710 patient charts were reviewed) (3). According to the results of the study by Santell et al., 22% of medication errors occur on admission to the hospital, 66% during ward transition, and 12% at the time of discharge, which means that these points are critical in the likelihood of medication errors and need to be particularly highlighted in the healthcare team and effective protective strategies are needed within each healthcare system (4). In a French prospective observational study, of all included all adult patients 29.4% had at least one unintended medication discrepancy, and most were medication errors. Most were omissions (59.3%), and potential severity was observed

in almost 40% of patients. The authors proposed different interventions for medication error minimizing, including medication reconciliation, which lead to fewer medication errors (5, 6).

Medication reconciliation is the process of identifying the most accurate list of all medicines a patient is taking, including the data on the name, dosage, frequency, and route of administration of each medicine. Different healthcare professionals could participate in this process (7). Physicians and nurses predominately do medication reconciliation, but hospital clinical pharmacists and pharmacy technicians in some countries also provide medication reconciliation. The medication reconciliation process included five key steps: list the patient's current medications, list the medications currently needed, compare the lists, make a new list based on the comparison, and communicate the new list to the patient and caregivers (8). In a retrospective chart review study by Smith and Mango ($n = 720$ charts), the researchers investigated the role of the hospital clinical pharmacist in the medication reconciliation process at hospital admission (6). They found that medication accuracy increased from 45.8 to 95% per patient ($p < 0.001$) and medication reconciliation increased from 44.2 to 92.8% ($p < 0.001$) (6). In a randomized prospective study conducted in Norway (201 patients), researchers found that the hospital clinical pharmacists spent significantly less time than the nurses for medication reconciliation (22.9 min for pharmacists and 32.2 min for nurses). Physicians agreed significantly more often with the pharmacist than nurses, which shows who could provide the best possible medication reconciliation process in the hospitals (9). More studies on this topic, including pharmacoeconomic studies, are needed. This would provide better evidence of the hospital clinical pharmacist's work within the medication reconciliation process. The World Health Organization recommends the important role of the hospital pharmacist in the medication reconciliation process in daily practice and encourages hospital clinical pharmacists to participate in this process (10).

In this context, the main aim of this case report is to describe two clinical cases from the mental health hospital, showcasing the successful collaboration between hospital clinical pharmacists and psychiatrists in the medication reconciliation process.

Case reports

Case 1

A psychogeriatric female patient was admitted to Slovenia's mental health hospital because of anxiety and depression. In addition, the patient suffers from arterial hypertension and heart failure. At the admission, on the patient's chart, she had the following medications: levothyroxine 75 mg daily, levothyroxine 50 mcg daily (each second day), bisoprolol 1.25 mg daily, esomeprazole 20 mg daily, ursodeoxycholic acid 500 mg daily, mirtazapine 15 mg daily, alprazolam 0.25 mg twice daily, and fixed combination of perindopril, indapamide, and amlodipine 5/1.25/5 mg. The hospital clinical pharmacist provided the best possible medication history and reconciliation within 24 h after admission. He provided the best possible medication history (check the entire medication history through the ePrescribing system and previous discharge papers) in communication with the patient. He recommended to the attending physician rosuvastatin 10 mg initiation because of elevated low-density lipoprotein cholesterol levels (3.72 mmol/L) and the final cardiovascular risk evaluation (Framingham scale). The attending psychiatrist accepted this recommendation. On the day of discharge, the patient's psychiatrist prepared a discharge paper for her. Hospital clinical pharmacists checked the discharge paper and patient's chart, and he recognized that levothyroxine 75 mg and the correct dosing of perindopril, indapamide, and amlodipine 5/1.25/5 mg were missing on the discharge paper (compared chart and discharge paper). Hospital clinical pharmacists then reconciled medication with the attending psychiatrist, who accepted both proposals and corrected the discharge paper. The hospital clinical pharmacists then provided a personal medication card to the patient before discharge and explained all the details about pharmacotherapy (gave the card to the patient and included it in the system—each physician in Slovenia would be able to check it immediately in the electronic system). The patient had a good understanding of her medication because the hospital clinical pharmacist discussed medication names, indications, and dosing with her.

Case 2

A female patient was admitted to the mental health hospital in Slovenia because of bipolar disorder, which has been treated for many years. In addition, she has arterial hypertension, gout, type II diabetes, and heart failure. At the admission, the following medications were listed on the patient's chart: atorvastatin 40 mg daily, torasemide 5 mg daily, perindopril 4 mg daily, acetylsalicylic acid 100 mg daily, nebivolol 5 mg daily, quetiapine sustained release form 200 mg daily, quetiapine 100 mg daily, and valproic acid 500 mg once daily. The hospital clinical pharmacist provided the best possible medication history and reconciliation within 24 h after hospital admission. He provided the best possible medication history (check the entire medication history through the ePrescribing system and previous discharge papers) in communication with a patient. He recommended to the attending psychiatrist some medication changes (adding omitted medications: metformin 1,000 mg twice daily, linagliptin 5 mg daily, and allopurinol 100 mg daily). The hospital clinical pharmacist recognized the omitted medications by checking the ePrescribing system and in communication with the patient and compared this information with the patient's chart. The attending psychiatrist accepted these recommendations after a discussion with the hospital clinical pharmacist. On the discharge day, her psychiatrists prepared a discharge paper. The hospital clinical pharmacist checked the discharge paper and patient's chart, and he did not recognize any medication-related problems (e.g., omissions or medication discrepancies). Hospital clinical pharmacists then provided a personal medication card to the patient before discharge and discussed medication names, indications, and dosing with her and her relatives; thus, the patient understood her medication well.

Discussion

Elderly patients with mental disorders are often treated with many medications concomitantly (e.g., polypharmacy) and have many medication-related issues during the transition of care, representing an important point for collaboration. These aspects are mostly

excluded from randomized controlled trials and meta-analyses, although the topic is highly relevant for daily practice and medication optimization (11, 12). This study adds substantial value to the existing literature by highlighting the significance of hospital clinical pharmacist interventions within the medication reconciliation process in mental health hospitals, a topic not well-described in this part of Europe. These cases may serve as a catalyst for researchers to conduct trials investigating the impact of hospital clinical pharmacists within the medication reconciliation process in mental health hospitals, which can either confirm or challenge our findings.

Clinical pharmacy in psychiatry is included in the treatment processes in some European Countries. This approach is well-known in the United Kingdom and the United States. However, in most European countries, clinical pharmacists are still not regular team members of the ward healthcare team, which was shown in a systematic review published in 2020 (64 studies) (13). The authors found that incorporating psychiatric hospital pharmacist input into interprofessional healthcare teams was the most common pharmacist practice in psychiatric and neurological settings and was associated with significant improvements in patient-level outcomes (13). Oliveira et al. reported positive results of hospital pharmacist-led medication reconciliation in the acute psychiatric ward (14). Their study included 148 admitted patients, and collaboration with psychiatrists was needed in 74% of patients while clarification with psychiatrists was needed in 359 discrepancies (84.12% "drug omission," 5.57% "drug substitution," 6.96% "dose change," and 3.34% "dosage frequency change") (14). The results show the important role of hospital clinical pharmacists in the medication reconciliation process in a psychiatric hospital. Stuhec and Tement reported that hospital clinical pharmacists' interventions in the daily rounds in a psychiatric hospital led to fewer medication-related problems, representing an appropriate collaboration with psychiatrists (12). The medication reconciliation process at the transition of care represents a unique opportunity for such collaboration.

These cases show the importance of hospital clinical pharmacist recommendations and their activities within the medication reconciliation process. The first case describes that the inclusion of the hospital clinical pharmacist in the medication reconciliation at the hospital admission can lead to fewer medication-related problems. Hospital pharmacists did not recognize any omitted medications but recognized an untreated condition (hypercholesterolemia), which is in line with the study by Stuhec and Tement, where they showed fewer medication-related problems in inpatients with mental disorders in the ward rounds including clinical pharmacists (12). Comorbidities are frequent in patients with mental disorders, especially elderly patients with schizophrenia. Collaboration with hospital clinical pharmacists can lead to fewer medication-related problems and help psychiatrists deal with comorbidities (e.g., diabetes) (11, 15). This issue was studied in clozapine clinics in the United States. After the clinical pharmacist's recommendations, the researchers checked the clinical consequences of metabolic and cardiovascular monitoring. The researchers found that pharmacist clinics had statistically higher rates of metabolic and ECG monitoring (glucose 48% vs. 11%, $p < 0.001$; lipids 61% vs. 7.1%, $p < 0.001$; ECG 15% vs. 0%, $p = 0.001$) (15). This study shows that collaboration with hospital clinical pharmacists could lead to better monitoring in patients with clozapine. Hospital pharmacists also could recognize medication-related problems in the discharge paper, which were solved before the patient's discharge, increasing medication accuracy. This study also highlights the importance of appropriate monitoring, which should be carried out by healthcare professionals at all levels of healthcare. This also emphasizes the need for successful collaboration among pharmacists, physicians, and nurses across various healthcare settings, such as primary care, hospitals, and outpatient clinics. In this context, pharmaceutical services facilitate a smooth transition for patients between primary care and hospitals, which was shown in this study.

The second case shows the important role of hospital clinical pharmacists in medication reconciliation at admission. Omitted medications are seen frequently, and hospital clinical pharmacists can recognize them and recommend medication changes to the attending psychiatrist (16). In this case, the patient with diabetes continued with her medications for diabetes, which were omitted at the admission. In one Slovenian study, which included 108 patients with a median age of 73, 42% of medical records were considered completed medical records. The researchers found that 72.4% of the listed drugs were associated with medication discrepancies. The most discrepancies were often found both in the medication order (76.2%) and discharge letter (69.9%) (16). The authors reported a high rate of discrepancies and the need to implement medication reconciliation, including the participation of hospital clinical pharmacists.

In addition, these cases show the positive impact of this service on the transition of care. From 2023, hospital clinical pharmacists will be doing medication reconciliation in Slovenia. This service is reimbursed (e.g., 50 EUR/patient), meaning that the national insurance company pays extra for each patient in mental health hospitals and can hire clinical pharmacists. Only hospital clinical pharmacist specialists can take over this healthcare program. This process (named seamless care) includes medication reconciliation at admission (including the best possible medication history) and discharge and personal medication card (at the discharge). Hospital clinical pharmacists must be included in the team, have full access to patients and all datasets, and provide medication reviews. All processes have been defined inside this Sub Act (e.g., best possible medication history, medication reconciliation at admission, medication reconciliation at discharge, personal medication card before discharge, and home dispensing) (17, 18).

These case reports are subject to a number of limitations. Clinical outcomes were not measured with any approved scale, and only two cases were included. The following limitation concerns single-hospital clinical pharmacists who provide this service in a psychiatric hospital. To validate these findings, studies employing prospective observational data are required.

Conclusion

This case study shows that hospital clinical pharmacists could recognize many medication-related problems during the admission and discharge processes, emphasizing the important role of hospital clinical pharmacists in the transition of care in a mental health hospital. Further studies are needed to confirm/reject these findings.

Data availability statement

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

Ethics statement

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

Author contributions

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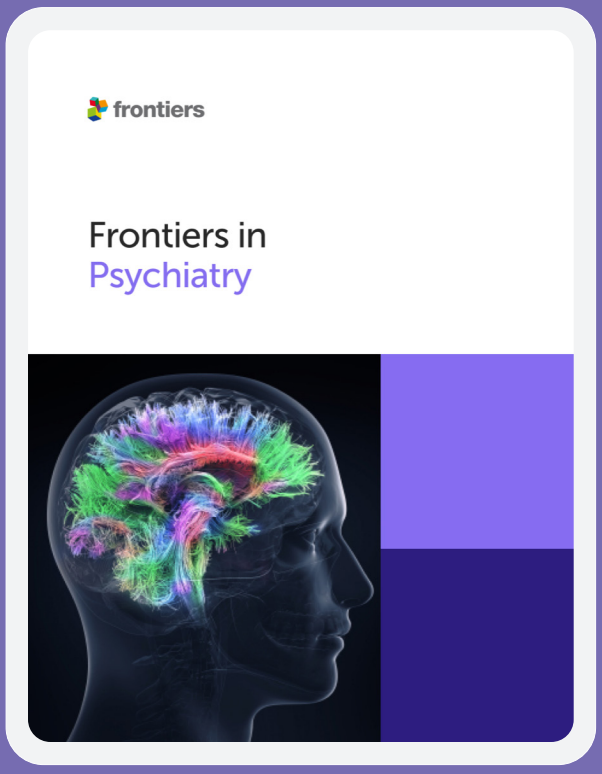

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