Exploring the Addictive Potential of Tranylcypromine
A Case Report

To the Editors:

Tranylcypromine is a monoamine oxidase inhibitor (MAOI) used to treat major depressive disorder. It irreversibly inhibits monoamine oxidases (MAO), a family of enzymes responsible for catalyzing monoamines, in the central nervous system and the periphery, such as the intestine and liver.[1] The approved therapeutic dose of tranylcypromine ranges from 10 to 60 mg/d. However, cases of nonmedical use have been reported, with doses exceeding 300 mg/d leading to severe complications. Nonmedical use of tranylcypromine has been reported in a few case studies, with varying doses of tranylcypromine being used. In one instance, a patient increased the dosage of tranylcypromine to an average of 500–600 mg/d for 6 weeks, exhibiting delirium and thrombocytopenia.[2] Another case involved the ingestion of 300 mg of tranylcypromine, resulting in fatal poisoning.[3] Additionally, a fatal overdose case detected tranylcypromine in combination with amphetamine and methamphetamine in the urine sample.[4] Collectively, these cases highlight the diverse range of tranylcypromine doses involved in misuse and overdose, emphasizing the potential for adverse outcomes associated with its nonmedical use.

Here, we present a case report of a patient who ingested an exceptionally high dose of tranylcypromine, reaching up to 2400 mg/d over almost 10 years. This case is notable for the severity of nonmedical use, involving doses significantly higher than previously reported. The existing literature does not extensively cover this aspect. We complied with the CARE guidelines for case reports, and written consent was obtained from the patient for publication.

CASE PRESENTATION

A 48-year-old single, heterosexual male presented to a private general hospital for an orthopedic surgery. Liaison psychiatry was consulted for follow-up due to the patient's diagnosis of major depressive disorder and his use of high doses of tranylcypromine. The patient also exhibited significant thrombocytopenia (<50 000 platelets/μL). He was using tranylcypromine 160 mg/d, with additional prescriptions including pregabalin (300 mg/d), eszopiclone (6 mg/d), and aripiprazole (5 mg/d). Although his mood remains euthymic, he continues to exhibit low insight into his condition and remains resistant to long-term treatment adherence strategies. The patient's psychiatric examination revealed a euthymic mood, reactive affect, organized thought process without delusional content, preserved volition, and low insight into his condition.

Patient Psychiatric History

The patient's psychiatric history dates back to early childhood, marked by significant emotional dysregulation and maladaptive coping mechanisms. At the age of 5, he was referred for psychotherapeutic intervention due to severe anxiety, which manifested as difficulties in social interactions and impaired distress tolerance. Over time, he demonstrated persistent impulsivity, sporadic episodes of self-injurious behaviors, and aggressive outbursts, suggesting a chronic pattern of emotional instability. By the fifth grade, these impairments culminated in academic failure, reinforcing a trajectory of psychosocial dysfunction that persisted into adulthood.

By age 18, the patient had initiated tobacco use, eventually developing a one-pack-per-day smoking habit. His exposure to psychoactive substances, including cocaine, cannabis, ecstasy, and methamphetamine, did not evolve into a formal substance use disorder, yet his behavioral pattern reflected a tendency toward compulsive exploration of psychoactive agents. At 32, he sought psychiatric treatment for alcohol use disorder, successfully achieving 2 years of remission, yet this period of abstinence was followed by the emergence of severe depression, characterized by marked anhedonia, apathy, and emotional detachment.

Despite multiple psychopharmacological interventions, his depression remained highly resistant to treatment, necessitating trials with a broad range of psychotropic medications. Over time, he exhibited a pattern of nonmedical psychotropic use, often engaging in self-directed dose escalation. His regimen included lisdexamfetamine, selegiline, amisulpride, olanzapine, amitriptyline, brexpiprazole, pioglitazone, quetiapine, mirtazapine, aripiprazole, and bupropion, yet he frequently modified prescribed doses or discontinued medications independently, undermining therapeutic stability. Notably, mirtazapine at 60 mg provided partial relief, and quetiapine significantly attenuated his impulsivity and anxiety. Yet, aripiprazole and bupropion were inconsistently used, often in abusive patterns, preventing their efficacy from being properly assessed. Despite electroconvulsive therapy (ECT) exceeding 12 sessions and multiple ketamine infusions since 2012, no lasting improvements were achieved, particularly for anhedonia.

His nonmedical stimulant use escalated, particularly with lisdexamfetamine, where he consumed up to 20 tablets of 50 mg per day, initially experiencing euphoria and heightened well-being, yet rapidly developing tolerance within a month. Similarly, his misuse extended to nonpsychiatric medications, such as metamizole, which he consumed at doses reaching 10 tablets of 500 mg daily for 1 month. However, the motivations behind this pattern remain unclear. As his depressive symptoms persisted despite multiple therapeutic strategies, tranylcypromine was introduced at 60 mg/d. However, the patient independently escalated the dosage to 2400 mg/d, reporting a profound improvement in anhedonia and depressive symptoms. This upward titration occurred progressively under multiple prescribing physicians, reflecting a pattern of doctor shopping likely facilitated by the absence of a centralized prescription monitoring system in Brazil. As tolerance developed, he sought multiple prescribers to sustain his high-dose regimen, reinforcing concerns regarding the regulatory oversight of psychotropics.

Attempts to gradually reduce tranylcypromine were met with significant psychological distress, withdrawal-like symptoms, and increased medication-seeking behaviors. His last psychiatrist was able to reduce the dose to 160 mg/d. Over time, his psychiatric instability necessitated three hospitalizations, each directly linked to tranylcypromine misuse.

DISCUSSION

Here, we present a case report of a 48-year-old man with a history of severe depression, alcohol use disorder, and nonmedical use of tranylcypromine, presenting a complex treatment challenge. His treatment history includes a complex array of pharmacological interventions, notably tranylcypromine, which he has used at very high doses. Although the patient reported improvement in depressive symptoms with these high doses of tranylcypromine, the nonmedical use has consistently hindered therapeutic success due to the rapid development of tolerance.

One of the significant aspects of this case is the nonmedical use of high doses

of tranylcypromine (up to 2400 mg daily). Tranylcypromine's abuse liability is likely due to its structural similarity to amphetamines. Research indicates that when tranylcypromine is used at doses above 60 mg per day, amphetamines can be detected in urine and plasma specimens.[4,5] A possible explanation for the presence of amphetamines in such specimens is the biotransformation of tranylcypromine into amphetamine and methamphetamine within the human body, given that amphetamine and methamphetamine can be identified as metabolic products following a tranylcypromine overdose. Still, these metabolites are not detected with therapeutic doses.[6] This mechanism is the proposed underlying mechanism of tranylcypromine misuse or abuse.

Addiction to tranylcypromine was first reported in 1963, 3 years after its market introduction. Since then, several studies have documented tranylcypromine abuse, with doses ranging from 120 to 600 mg/d.[7–10] Most of these reports mention a stimulant effect associated with tranylcypromine. In addition, the patient's history of nonmedical use and abuse of prescribed medications and co-occurring psychiatric disorders likely played a significant role in his propensity for tranylcypromine misuse. Despite prior use of illicit substances, he did not develop a formal substance use disorder but alcohol and tobacco. However, he consistently misused prescription psychotropic medications, including tranylcypromine, lisdexamfetamine, bupropion, and aripiprazole, frequently self-adjusting doses far beyond medical recommendations. This pattern suggests compulsive nonmedical use of prescription drugs, a phenomenon less frequently described in the literature. The patient's treatment adherence was also markedly poor, further complicating his clinical course. His lack of adherence to prescribed regimens disrupted the establishment of a stable treatment plan, likely contributing to worsening psychiatric symptoms and increased hospitalizations.

Research has consistently highlighted the high prevalence of medication nonadherence among patients with severe psychiatric disorders, which is associated with suboptimal treatment outcomes and increased healthcare utilization. Furthermore, nonadherence among psychiatric patients with a history of substance misuse—particularly those engaging in abusive use or nonmedical use of prescribed medications—has been linked to greater clinical instability and higher relapse rates. In this case, the patient's escalating doses of tranylcypromine may not only reflect its abuse potential but also underscore his significant psychiatric vulnerability, which likely exacerbated his poor clinical outcomes.

Moreover, it is pertinent to acknowledge additional explanations. An alternative rationale for the patient's requirement for escalating dosages may be his classification as a CYP2A6 ultra-rapid metabolizer.[11] Genetic polymorphisms in these metabolic enzymes are linked to an accelerated metabolism of tranylcypromine, which could result in subtherapeutic effects at standard dosages and necessitate compensatory dose increases. Additionally, methimazole, an agent that can induce hypothyroidism, was included in the patient's pharmacological history.[12] Given that hypothyroidism can present with symptoms akin to depression, it remains ambiguous whether his depressive manifestations were at least partially influenced by thyroid dysfunction or if the use of methimazole was merely coincidental. The patient also utilized *Bacopa monnieri*, an herbal supplement frequently employed in Ayurvedic medicine, which is purported to offer cognitive-enhancing and anxiolytic benefits.[13] Nevertheless, its efficacy for major depressive disorder is still unresolved, with limited clinical evidence to substantiate its effectiveness use.

In conclusion, this case report highlights the intricate challenges, and the risks and benefits associated with using tranylcypromine to target treatment-resistant depression in the context of nonmedical substance use. While tranylcypromine demonstrates efficacy in managing depressive symptoms, its liability for abuse adds complexity to the treatment. Balancing the therapeutic benefits of tranylcypromine with its potential for abuse requires vigilant monitoring and tailored interventions to address the multifaceted nature of the patient's challenges. Balancing the therapeutic benefits of tranylcypromine with its potential for misuse requires close monitoring, structured prescription practices, and comprehensive psychosocial interventions. Given the complexities of treatment-resistant depression in patients with substance misuse tendencies, a multidisciplinary approach incorporating collaborative decision-making and behavioral interventions may optimize long-term outcomes.

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