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CASE REPORT

Clomipramine Misuse in a Patient with Schizophrenia

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Main Points

- Although antidepressants are theoretically safe, the abuse or misuse of antidepressant drugs is increasing.
- Individuals frequently abuse antidepressants because these are not detected in routine screening tests, are more socially acceptable, and are perceived to be safer than illicit substances.
- Indifference to side effects, the demand to prescribe higher doses of antidepressants while in remission at low doses, and progressive deterioration in functionality should suggest abuse.

Abstract

Although antidepressants are theoretically safe, the abuse of antidepressant drugs is increasingly taking place in the literature. Most cases had a history of concomitant alcohol or substance use. We present a 49-year-old female patient with a diagnosis of schizophrenia who had a clomipramine misuse history without alcohol or substance addiction. The patient gradually increased the clomipramine dose without the doctor's advice. She used clomipramine in higher doses than usual and often requested the doctors to prescribe it to relieve her complaints. Patients with a history of psychotic illness may abuse anticholinergics to reduce existing anhedonia. Therefore, our patient may have used clomipramine to alleviate the anhedonia she experienced. Tricyclic antidepressant abuse can be fatal so it is important to recognize this phenomenon.
Keywords: Antidepressant abuse, antidepressant misuse, clomipramine, drug abuse, tricyclic antidepressants

Introduction

Although antidepressants are theoretically safe, the abuse or misuse of antidepressant drugs is increasingly taking place in the literature (Evans & Sullivan, 2014; Schifano et al., 2018). The prevalence of antidepressant abuse in the general population is unknown. Studies are mostly in patients with substance addiction and the prevalence of antidepressant abuse varied between 14.2% and 40% (Darke & Ross, 2000; Dumonceau et al., 2022). Individuals frequently abuse prescription drugs, including antidepressants, because these are not detected in routine screening tests, are more socially acceptable, and are perceived to be safer than illicit substances (Evans & Sullivan, 2014; Hernandez & Nelson, 2010).

In the case reports, drugs such as tianeptine, bupropion, tranylcypromine, and amineptine are the most common, and amineptine was withdrawn from the market due to its potential for abuse (Evans & Sullivan, 2014). Among the tricyclic antidepressants, the most reported one is amitriptyline (Shenouda & Desan, 2013; Umaharan et al., 2021). Most cases had a history of concomitant alcohol or substance use, but antidepressant abuse was also reported in patients without a history of addiction (Eşsizoğlu et al., 2012; Shenouda & Desan, 2013).

To the best of our knowledge, clomipramine abuse was reported only in a 47-year-old female patient with a history of bipolar disorder (Lepping & Menkes, 2007). In this case report, we present a patient with a diagnosis of schizophrenia who had

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a clomipramine misuse history without alcohol or substance addiction.

Case Presentation

A 49-year-old, married, university graduate female patient applied to the outpatient clinic in April 2018 with complaints of palpitation, restlessness, lack of pleasure, and a feeling of tightness in her heart. The patient had been followed up with a diagnosis of schizophrenia since 2005 and was receiving ziprasidone 120 mg/day and quetiapine 50 mg/day. The patient requested to be prescribed clonazepam or clomipramine for her existing complaints. Her first complaints started when she was 25 years old with constant anxiety, tremors in her body, worry about the future, restlessness, and unhappiness. She was a teacher but was constantly worried about being fired. Then, the patient had panic attacks like a feeling of tightness in her heart, nausea, and vomiting. She applied to cardiology, but no pathology was detected. She did not apply to psychiatry and tried to cope on her own.

In 2002, she was admitted to psychiatry because her complaints still continued. She was diagnosed with panic disorder and imipramine was started at 25 mg and increased up to 75 mg/day. However, when she did not benefit, imipramine was discontinued 1 month later, and clomipramine was started at 25 mg and increased to 50 mg/day. The patient benefited partially and continued to use clomipramine 50 mg/day for 6 months. Then, because the feeling of tightness in her heart did not improve sufficiently, she applied to the psychiatrist again and clomipramine was discontinued and escitalopram 10 mg/day was started. However, the patient did not continue escitalopram because she did not benefit and started to take clomipramine again. The patient gradually increased the clomipramine dose without the physician's advice and started using 300 mg/day at the end of two and a half years. During this period, her religious pursuits and depressive symptoms increased and she became more introverted.

In 2005, she started to increase the dose of clomipramine because the complaint of tightness in her heart did not relieve, and she started to take 50 tablets of clomipramine 25 mg per day. She used this dose for about 3 days and started to wander around the house in a drowsy state, but did not go to the hospital. The patient, who regained consciousness, started to take 90 tablets of clomipramine 25 mg because of thinking that she did not benefit. When her family worried about her symptoms such as constant sleepiness and slurred speech, she was taken to the hospital and the patient was treated in the intensive care unit for a week. Then, she was hospitalized in the psychiatric ward and was diagnosed with schizophrenia due to complaints of thoughts of being followed, a constant, not improved feeling of tightness in her heart, progressive deterioration in her functionality, anhedonia, decline in social relations and activities, and intense anxiety. Oral risperidone was started and switched to the long-acting injectable form, but due to both amenorrhea and not enough improvement, olanzapine 20 mg/day and quetiapine 400 mg/day were started after 3 years. Clonazepam was started for constant anxiety in the follow-ups, and the patient increased the dose again without medical advice.

The patient, who had been followed up in our clinic since 2012, was started on many antipsychotic drugs, including clozapine, but could not be continued due to side effects or insufficient improvement. In 2015, ziprasidone was started and increased up to 120 mg/day. The patient mostly benefited from this treatment and functionality was increased. No abnormality was detected in the periodic blood tests and electrocardiogram. However, it was determined from the records that there was her request for the prescription of clomipramine or clonazepam occasionally for reducing the tightness in her heart. To date, the patient's misuse of antidepressants has not been evaluated in detail.

In the mental state examination, she was conscious, oriented, and had no obvious psychotic symptoms. She had a euthymic mood but her affect was blunted. She did not have any physical disease and alcohol or substance abuse. No apparent pathology was found in the physical and neurological examination. Vital signs were normal. Normal sinus rhythm was detected in the electrocardiogram, and the QTc was calculated as 410 milliseconds. The patient, whose treatment regimen was not changed, was given psychoeducation about prescription drug abuse. The harmful effects of using drugs without medical advice or increasing the dose of drugs were discussed. Warning notes about the antidepressant misuse were included in the patient's follow-up notes, and she was followed closely. The patient's consent was obtained for this case study.

Discussion and Conclusion

The abuse of prescription drugs is on the rise, but the ambiguity about the differences in terms such as abuse or misuse in the literature limits epidemiological data (Hernandez & Nelson, 2010; Huang et al., 2006). Misuse is generally considered to be the inappropriate use of a drug to relieve symptoms without seeking medical advice or following recommendations. On the other hand, the use of the drug for a non-medical purpose, especially to achieve euphoria, is considered abuse (Jaber et al., 2015). Our patient used clomipramine in higher doses than usual and often requested the physicians to prescribe it. She continued this attitude with the thought that the drug would relieve her complaints, which she described as a feeling of tightness in her heart. Therefore, it is more appropriate to consider this phenomenon as a misuse.

Several mechanisms were proposed for the abuse of tricyclic antidepressants. First, tricyclic antidepressants with tertiary amine structure, including clomipramine, have more anticholinergic and antihistaminergic effects than those with secondary amine structure (Fava & Papakostas, 2010). Because the anticholinergic effects create a kind of "high" sensation, patients abuse these drugs (Peles et al., 2008). Anticholinergic effects with dose increase progress in the form of a distorted perception of time, sedation, and hallucinations (Evans & Sullivan, 2014). Patients with a history of psychotic illness or neuroleptic use may also abuse anticholinergics to reduce existing anhedonia (Dose & Tempel, 2000). Therefore, our patient did not use clomipramine mainly to achieve euphoria but may have used it to alleviate the anhedonia she experienced. Furthermore, antihistamines were shown to potentiate the action of opiates in animal and human models (Halpert et al., 2002). Thus, tricyclic antidepressants may also potentiate the effects of various illicit substances (Miller et al., 2019). Lastly, since tricyclic antidepressants are substrates of CYP2D6, they compete with some illicit substances and may cause elevated plasma levels (Nelson, 2017). There was no illicit

substance use in our patient, and these mechanisms explain mostly the higher incidence of antidepressant abuse in addicted patients.

In the case reported by Lepping and Menkes, a 47-year-old female patient with bipolar disorder and cluster B personality disorder stated that she abused clomipramine to trigger the manic switch (Lepping & Menkes, 2007). Interestingly, as in our patient, no substance use history was described. However, our patient used clonazepam occasionally to relieve her symptoms. In a study with patients who were in the methadone maintenance program, it was found that benzodiazepines and tetrahydrocannabinol positivity in urine was found to be significantly higher in patients who abused amitriptyline compared to those who did not (Peles et al., 2008). In the same study, patients with a history of abuse of both benzodiazepines and amitriptyline had higher depression scale scores (Peles et al., 2008). Therefore, as in our patient, patients abuse antidepressants and benzodiazepines in order to relieve their depressive symptoms.

Tricyclic antidepressants can cause life-threatening side effects such as QTc prolongation, cardiac arrhythmias, and epileptic seizures, especially at high doses (Fanoe et al., 2014; Johannessen Landmark et al., 2016). Therefore, tricyclic antidepressant abuse can be fatal. The risk increases due to the interactions that occur since most of the patients also have illicit substance abuse (Dumonceau et al., 2022; Peles et al., 2008). Irregular attendance to appointments, the desire to be prescribed drugs earlier, indifference to side effects, the demand to prescribe higher doses of antidepressants while in remission at low doses, and progressive deterioration in functionality should suggest abuse (Evans & Sullivan, 2014). Therefore, clinicians should be vigilant to recognize antidepressant abuse.

Informed Consent: Written informed consent of the patient was obtained for publishing a scientific article.

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