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Clozapine-Induced Obsessive-Compulsive Symptoms and Augmentation with Clonazepam: Risks and Rationales

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ABSTRACT

Obsessive-compulsive symptoms induced by clozapine negatively affect treatment compliance. In some studies, clonazepam was shown to be beneficial in obsessive-compulsive disorder. However, in literature there are case reports of life-threatening complications associated with the combined use of clozapine and benzodiazepines. In this article, the efficacy and safety of the clonazepam augmentation were discussed in two patients who had obsessive-compulsive symptoms induced by clozapine. No life-threatening complications were detected during the follow-up period of more than two years, and the patients benefited dramatically from the addition of clonazepam. In treatment-resistant patients, clonazepam can be used with close monitoring for obsessive-compulsive symptoms associated with atypical antipsychotics.

Keywords: Atypical antipsychotics, clonazepam, clozapine, obsessive-compulsive symptoms

INTRODUCTION

The American Psychiatric Association considers clozapine the gold standard in schizophrenia treatment. However, due to the risk of serious and dose-independent side effects such as agranulocytosis, clozapine is recommended in cases resistant to at least two antipsychotic drugs (American Psychiatric Association 2021). Obsessive-compulsive symptoms (OCS) associated with clozapine effect the treatment compliance of patients negatively. Among atypical antipsychotics, clozapine is the most common associated drug with OCS, and the prevalence of OCS had been reported with varying frequency in different studies (Doyle et al. 2014, Scheltema Beduin et al. 2012, Gahr et al. 2014). Although the pathogenesis of OCS triggered by atypical antipsychotics is often associated with 5-HT-2A and 5-HT-2C antagonism, it has been suggested that the glutamatergic system may also be effective (Mak et al. 2015, Simpson et al. 2015).

Clonazepam is a long-acting benzodiazepine, and in some studies, it was shown to be beneficial in obsessive-compulsive disorder (OCD) patients (Hewlett et al. 1992, Halayem et al. 2015). In a recent study, it was determined that benzodiazepines were most commonly prescribed in OCD patients with high anxiety levels, longer disease duration, treatment-resistant, and sexual or religious obsessions (Starcevic et al. 2016). There is no information in literature regarding the effects of benzodiazepines on OCS associated with atypical antipsychotics. On the other hand, various case reports in literature reported serious complications such as respiratory depression and sudden cardiac death due to the combined use of clozapine and benzodiazepines (Borentain et al. 2002, Ramaswamy et al. 2005).

In this article, the efficacy and safety of clonazepam use in 2 patients with clozapine-induced OCS were discussed.

CASE 1

A 39-year-old, married male patient applied to our clinic in June 2018 with the complaints of sexual and religious obsessions, insomnia, loss of appetite, restlessness, guilt, not being able to enjoy life, and thoughts that people are trying to give him a message, lasting for nearly six months. The

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patient stated that he suffered heavily from sexual images, and expressions of blasphemy and insult on religious values during his prayers. It was learned that his depressive and psychotic symptoms appeared secondary to OCS. According to the patient's history, the first complaints of the patient started at the age of 17 as excessive talkativeness, decreased need for sleep, excessive spending, and aggression. He was hospitalized and treated with a diagnosis of bipolar disorder, and subsequently hospitalized many times due to recurrent manic and depressive episodes. Clozapine was started five years ago for the patient who was thought to have rapid cycling bipolar disorder and whose symptoms were resistant to treatments. The patient who benefited from clozapine 100 mg/day and lithium carbonate 1500 mg/day was in remission for the last four and half years. Venlafaxine 150 mg/day was added to his regimen in another clinic one month ago due to such complaints as sexual and religious obsessions, insomnia, restlessness, and guilt that have emerged in the last six months, but there was no improvement.

In the mental state examination, the patient's thought content included referential delusions, sexual and religious obsessions, and thoughts of guilt. His mood was depressed. The patient had compulsions to confirm all his behaviors. He had no other disease or family history of psychiatric disorders. No obvious pathology was detected in the physical examination. The complete blood count, biochemical analysis, and urine substance screening were within the normal range. The plasma lithium level was 0.82 mEq/L. The Brief Psychiatric Rating Scale (BPRS) score was 17, the Hamilton Depression Rating Scale (HAM-D) score was 26, and the Yale-Brown Obsession Compulsion Scale (Y-BOCS) score was 27 applied during the examination. The patient was hospitalized with diagnoses of obsessive-compulsive disorder and bipolar disorder, the major depressive episode with psychotic features according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) criteria.

Initially, clozapine was increased up to 150 mg/day, venlafaxine was increased up to 300 mg/day, and lithium carbonate was continued at 1500 mg/day in the treatment of the patient. In the second week of hospitalization, the BPRS score decreased to 12 and the HAM-D score to 14, while the Y-BOCS score was graded as 25. Despite the partial improvement in psychotic and depressive symptoms, the severity of OCS was the same. It was thought that the existing obsessive symptoms could be related to clozapine since the obsessions first appeared six months ago, and the patient did not have similar complaints before. Switching to a different class of antidepressant was not considered due to the improvement in psychotic and depressive symptoms. But clonazepam was started and titrated up to 2 mg/day, considering that it would both reduce the intense anxiety level of the patient and be beneficial for his obsessions. The patient's vital signs were followed closely in terms of possible complications, but no complications were detected. At the end of the third week, complete remission was observed in patient's obsessive behaviors (BPRS: 8, HAM-D: 10, Y-BOCS: 12). The patient was discharged one month later with lithium carbonate 1500 mg/day, clozapine 150 mg/day, venlafaxine 300 mg/day, and clonazepam 2 mg/day. No complications were detected in the follow-up.

One year later, the patient was readmitted to the hospital due to a psychotic manic episode with complaints of suspiciousness, decreased need for sleep, increased energy, and aggression. No OCS was detected in the examination. The patient was discharged with partial remission with lithium carbonate 1500 mg/day, venlafaxine 150 mg/day, clozapine 100 mg/day, quetiapine 400 mg/day, and clonazepam 2 mg/day. Four months after the discharge, the patient was hospitalized due to a depressive episode with psychotic features, and no obsession was detected once again. His treatment regimen was rearranged as clozapine 100 mg/day, lithium carbonate 1500 mg/day, venlafaxine 450 mg/day, and clonazepam 2 mg/day, and he was discharged with partial remission. The follow-up of the patient continues and no complications developed during two and a half years of using clonazepam and clozapine together. His obsessions are still in remission.

CASE 2

A 36-year-old, single male patient applied to our clinic in September 2018 with complaints such as outbursts of anger, withdrawal from people, talking to himself, hallucinating, thoughts of being harmed by other people, and self-harming behaviors for about five months. The patient also had fear of attacking others and engaging in sexually deviant behaviors for two and half years. The first complaints of the patient started at the age of 18 as excessive talking, decreased need for sleep, aggression, and delusions of grandiosity. He was hospitalized with the diagnosis of bipolar disorder. The patient had recurrent hospitalizations with similar complaints. For the last two and a half years, the patient was diagnosed with schizoaffective disorder and started on clozapine treatment, for the patient's complaints could have become chronic and his functionality decreased compared to the past. The patient had been taking clozapine 600 mg/day, quetiapine 700 mg/day, risperidone 6 mg/day, sodium valproate 1000 mg/day, propranolol 40 mg/day, and flupenthixol decanoate 20 mg/2 weeks at the time of admission.

In the mental state examination, his thoughts included persecution and referential delusions, sexual and aggression obsessions, guilt, and suicidal ideations. Visual hallucinations were detected, and he had constant compulsions to confirm his obsessions. His psychomotor activity and amount of speech were decreased, and his affect was found to be blunt.

Disorganized behavior was observed occasionally. His self-care was decreased, and he had urinary and fecal incontinence. The patient had no other disease or history of substance use. His mother was also diagnosed with bipolar disorder. No obvious pathology was detected in the physical examination. The complete blood count, biochemical analysis, and urine substance screening results were normal. The plasma valproate level was 57 μg/ml. The Scale for the Assessment of Positive Symptoms (SAPS) score was 34, the Scale for the Assessment of Negative Symptoms (SANS) score was 73, and the Y-BOCS score was 32 applied during the examination. The patient was diagnosed with obsessive-compulsive disorder and schizoaffective disorder according to DSM-5 (American Psychiatric Association 2013) criteria and hospitalized.

Quetiapine, risperidone, and flupentixol decanoate were discontinued to simplify the treatment of the patient, and clozapine was reduced to 300 mg/day. While sodium valproate and propranolol treatments were continued, haloperidol was started orally and increased up to 30 mg/day. Biperiden 6 mg/day was added to the treatment due to the detection of rigidity in the upper extremities. Due to agitation, the patient was frequently physically restrainted. In the follow-up, the patient's self-care increased, and disorganized behaviors and psychotic symptoms decreased. On the other hand, his sexual and aggression obsessions continued, and he had intense anxiety due to these symptoms. In the second week of hospitalization, the SAPS score was 18, the SANS score was 49, and the Y-BOCS score was 29. It was thought that the obsessions might be related to clozapine since these appeared in the first month of clozapine treatment, and there was no similar symptom before. According to his history, six months after the onset of OCS, the dose of clozapine was reduced, and escitalopram was added which he used for three months, but he did not benefit from this treatment. Clonazepam 2 mg/day was added to the treatment, considering that it would be beneficial for both reducing the level of intense anxiety and his obsessions. A close vital follow-up of the patient was performed in terms of possible complications. On the same day, orthostatic hypotension was detected in the patient, but it recovered quickly. Propranolol was discontinued as it was thought to contribute to orthostatic hypotension, and then no other complications were detected. Complete response was observed in the patient's OCS in the fourth week of hospitalization (Y-BOCS: 10). After a month and a half, the patient was discharged on clozapine 300 mg/day, haloperidol 30 mg/day, biperiden 6 mg/day, sodium valproate 1000 mg/day, and clonazepam 2 mg/day. Clonazepam was reduced to 1 mg/day six months after discharge, and his obsessions continued to improve in outpatient follow-ups. The patient's follow-up continues, he has been using clonazepam for three years, and no complications have developed.

DISCUSSION

It has been reported that OCS associated with atypical antipsychotics occurred after one month at the earliest and after five years at the latest since the beginning of treatment (Lykouras et al. 2003, Lin et al. 2006). OCS developed four and a half years after the initiation of clozapine in our first patient, while it appeared one month later in our second patient. While OCS occurs in the first 12 months in most cases of clozapine, it is most common in the first 4 weeks with other atypical antipsychotics (Grover et al. 2015, Chen et al. 2008, Mahendran et al. 2007). It is suggested that slow titration of clozapine due to risk of agranulocytosis or 5-HT-2C receptor antagonism is effective in this difference (Laroche and Gaillard 2016, Khullar et al. 2001). In our first patient, OCS emerged four and a half years after starting clozapine, and there was no dose increase during this period. However, according to his medical records, he had taken cefuroxime 500 mg/day for one week for upper respiratory tract infection during the period when his obsessions emerged. The drugs with nephrotoxic potential such as cefuroxime can increase the plasma levels of other drugs by decreasing their renal excretion (Drugbank Drug Interaction Checker 2022, Yin and Wang 2016). Therefore, OCS may have occurred due to increased plasma clozapine levels in our first patient, but it is difficult to reach a definite conclusion since the plasma clozapine levels were not checked. It is suggested that blocking 5-HT-2C receptors due to long-term use of clozapine causes the development of hypersensitivity in these receptors and this triggers OCS (Khullar et al. 2001). Therefore, the emergence of OCS in our first patient, much later than expected, may also be associated with the late development of 5-HT-2C hypersensitivity. In our second patient, obsessions arose one month after starting clozapine. OCS was associated with clozapine, as the patient's clozapine dose was rapidly titrated to 200 mg/day within one month. OCS occurred while clozapine was taken at a dose of 100 mg/day in the first patient and clozapine at a dose of 200 mg/day in the second patient. Although a relationship between the dose and plasma levels of clozapine, and the prevalence and severity of OCS were found in some studies, no similar relationship was found in subsequent studies (Lin et al. 2006, Schirmbeck et al. 2011, Doyle et al. 2014, Mukhopadhaya et al. 2009).

APA recommends adding selective serotonin reuptake inhibitors to the treatment, switching to other antipsychotics that are less effective on serotonergic antagonism, and applying cognitive-behavioral therapy (CBT) in patients with schizophrenia who developed OCS (American Psychiatric Association 2007). Moreover, improvement in symptoms was reported with clozapine dose reduction in patients who developed OCS (Schirmbeck and Zink 2012, Gahr et al. 2014). In our first patient diagnosed with bipolar disorder, venlafaxine and clozapine were increased gradually, and a

tendency to improvement in psychotic and mood symptoms was observed, so switching to another antidepressant or antipsychotic was not considered. In our second patient, although various approaches such as clozapine dose reduction and adding escitalopram were applied previously, no improvement was observed. Furthermore, due to the severe psychotic symptoms, clozapine was only reduced to 300 mg during hospitalization. Both patients were considered unsuitable for CBT. A decrease of more than 35% in Y-BOCS scores in OCD patients compared to pre-treatment is considered to be a complete response, and a total score of 12 or less after treatment is considered remission (Lopes et al. 2014, Mataix-Cols et al. 2016). Complete remissions were achieved in both of our patients with clonazepam treatment added to reduce intense anxiety symptoms.

Clonazepam increases GABA activity in the central nervous system and has serotonergic effects, unlike other benzodiazepines (Halayem et al. 2015). The findings regarding its efficacy in the treatment of OCD are contradictory. In an old randomized controlled double-blind study, clonazepam was found to be at least as effective as clomipramine (Hewlett et al. 1992). However, in subsequent studies, clonazepam was determined not to show a significant difference compared to placebo, neither as a monotherapy nor add-on to antidepressants (Hollander et al. 2003, Crockett et al. 2004). However, clinicians still prefer clonazepam as a strengthening agent in OCD patients (Van Ameringen et al. 2014).

There is no consensus on whether the phenomenology of OCS caused by clozapine differs from the symptoms seen in OCD patients. However, uncertainty and constant confirmation, aggression or sexually forbidden thoughts, obsessions of contagion, and hoarding are commonly reported (Doyle et al. 2014, Grover et al. 2015, Kim et al. 2012). Obsessions with sexual, religious, and aggressive content, which were also detected in our patients, are called autogenous obsessions and cause more distress than other types of obsession (Lee and Kwon 2003). Moreover, both of our patients had intense anxiety symptoms. In a study, it was reported that clinicians preferred benzodiazepines, especially in OCD patients with religious and sexual obsessions or high anxiety levels (Starcevic et al. 2016). This suggests that similar prescribing trends are common in many countries.

Concomitant use of clozapine with benzodiazepines is less preferred by clinicians due to case reports of complications such as respiratory depression and sudden death (Grover et al. 2021). Klimke and Klieser reported a case of sudden death following intravenous administration of 6 mg/day of lorazepam due to agitation on the 17th day of clozapine treatment in a 43-year-old male patient with a diagnosis of schizophrenia (Klimke and Klieser 1994). Looking at the case report, it is seen that the patient received clozapine, lorazepam, and flunitrazepam together, intravenous lorazepam was administered after refusing treatment, and the last dose of clozapine was taken 35 hours before his death. Benzodiazepines themselves alone may also cause respiratory depression when administered intravenously (Seelhammer et al. 2018). Furthermore, the authors reported no life-threatening complications in 162 patients who were administered similar combination therapies between 1986 and 1991 (Klimke and Klieser 1994). In another case report, sudden cardiac death was reported in a patient who received clozapine and lorazepam for one year (Ramaswamy et al. 2005). In a retrospective study, sudden death, and cardiac or respiratory arrest were not found in any of the 152 patients who used clozapine and benzodiazepines together (Bitter et al. 2008). However, complications such as syncope, sudden hypotensive attacks, ataxia, and loss of consciousness were not evaluated in detail in this study. In our report, orthostatic hypotension developed in the second patient on the same day he received the first dose of clonazepam. This was associated with concomitant use of clozapine-clonazepam, and propranolol was discontinued considering that it might have contributed to this side effect. After discontinuation of propranolol, no recurrence was observed.

CONCLUSION

Clonazepam may be useful in the presence of resistant OCS caused by clozapine. However, clinicians should be cautious when prescribing clozapine and benzodiazepines together. When starting clozapine, it is recommended to discontinue benzodiazepines if possible or use the lowest dose in case of agitation, ensure regular vital follow-up during titration, titrate clozapine slowly in those who receive daily basis benzodiazepine treatment, and be more careful, especially in patients with cognitive impairment, liver dysfunction and respiratory system disease (Bitter et al. 2008). These results are difficult to generalize, based on our clinical experience with the two patients, so longitudinal follow-up studies with large samples are needed.

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