CASE REPORT

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Safe and Effective Use of Low-Dose Clozapine for Tardive Dyskinesia in a Patient with Schizophrenia and Comorbid Epilepsy: A Case Report

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ABSTRACT

Atypical antipsychotic clozapine has a special therapeutic impact on tardive dyskinesia and treatment-resistant schizophrenia. Clozapine also has important adverse effects such as epileptic seizures. For this reason, most clinicians avoid using clozapine in patients with schizophrenia and epilepsy. Therefore, treating patients with schizophrenia, tardive dyskinesia, and epilepsy is challenging. Here, we describe the case of a 32-year-old woman who was already suffering from epilepsy, schizophrenia, and tardive dyskinesia. She experienced clozapine-related seizures. But at the same time, clozapine dose adjustments successfully improved her psychosis and tardive dyskinesia and also stabilized her epilepsy. This case study indicates that epilepsy does not preclude the use of this important agent whenever it is clinically appropriate.

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INTRODUCTION

A persistent and complex psychiatric disorder called schizophrenia is marked by delusions, hallucinations, disordered speech and behavior, and cognitive decline.[1] Tardive dyskinesia (TD) and epilepsy are 2 neurological disorders that patients with schizophrenia may also have. Tardive dyskinesia, as it is known, is a condition that causes uncontrollable, repetitive body movements like grimacing, tongue sticking, and lip-smacking. There could also be rapid twitching or slow writhing motions. Akathisia, dystonia, tics, tremor, chorea, or a mix of these are among the late-onset movement disorders that make up TD.[2] Long-term usage of dopamine receptor blockers such as antipsychotics and antiemetics is typically linked to the development of TD.[3]

It can be difficult to treat patients with TD, epilepsy, and schizophrenia because TD can progress and several antipsychotic medications can change electroencephalography (EEG) activity and lower the seizure threshold.[4,5]

When other antipsychotic medications are insufficient to treat schizophrenia and other psychotic disorders, clozapine, a potent serotonin 5HT2A-Dopamine D2 antagonist, is recommended.[6] Patients with schizophrenia who do not react to treatment, which includes at least 2 antipsychotics (olanzapine is recommended as one of these agents), are advised to switch to clozapine.[4] Furthermore, clozapine is the first atypical antipsychotic that has been formally marketed and has a distinct therapeutic impact on TD and treatment-resistant schizophrenia (TRS).[7,8] Despite having benefits in the treatment of schizophrenia, clozapine also has adverse effects, including drowsiness, constipation, hypotension, hypersalivation, weight gain, and, less frequently, agranulocytosis.[4] It also has the potential to disrupt EEG and result in epileptic seizures.[4] Clozapine-induced seizures occur at a rate of about 5%, which is greater than the rate of seizures associated with conventional antipsychotics.[9] This ratio may also increase when patients have coexisting primary epilepsy.[10] The clinical characteristics of clozapine and its usefulness in treating patients with both epilepsy and schizophrenia are poorly understood due to its infrequent use.[9] Furthermore, clozapine treatment in individuals with schizophrenia suffering concurrent epilepsy and TD is not well studied, according to our literature search. Thus, this report presents the case study of a 41-year-old woman who was suffering from TRS, TD, and comorbid epilepsy. Although this woman experienced clozapine-related seizures, the medication successfully treated her psychosis and TD through some dose adjustments.

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CASE PRESENTATION

A 32-year-old woman presented to our outpatient psychiatry clinic with episodes of "insomnia, disorganized speech, and persecutory delusions," as described by her mother. The patient had inadequate self-care and blunt affection during her mental assessment. She was normally oriented to space, time, and people. She was found to experience commanding auditory hallucinations. During examination high-amplitude, arrhythmic, postural, and kinetic tremors were observed in both hands. At the same time, the patient had repetitive chewing movements. She smacked her lips occasionally, and there was a behavior of opening and closing her mouth. These movements were involuntary, uncontrollable, and arrhythmic. On the basis of the fifth edition of the Statistical and Diagnostic Manual of Mental Disorders (DSM-5), schizophrenia was diagnosed following a psychiatric evaluation. The positive and negative syndrome scale (PANSS) was used to evaluate clinical symptoms. The patient's PANSS scores were as follows: positive scale 26, negative scale 28, and general psychopathology scale 44. Her initial clinical global impression–severity of illness (CGI-SI) score was 6. She was taking only valproate 1000 mg/day when she presented to us; this drug was prescribed for her epilepsy at age 10. Since status epilepticus was observed in the patient's first epileptic seizure, antiepileptic medication was started immediately. The patient did not have any epileptic seizures afterward, but valproate treatment was never stopped because the patient's mother also had epilepsy and due to the patient's history of status epilepticus. She had subsequently been prescribed risperidone (up to 10 mg/day) at age 22, paliperidone injection (100 mg once monthly) and olanzapine (up to 20 mg/day) at age 27, and then aripiprazole (up to 30 mg/day) at age 30, which had been maintained at therapeutic levels for over 8 weeks. Nonetheless, her complaints did not get any better. In addition, tardive dyskinetic movements appeared at the age of 28 when taking paliperidone injections and oral olanzapine.

We could not detect any pathological findings in the complete blood count, biochemical tests, electrocardiogram, or brain magnetic resonance imaging. We decided to start clozapine therapy in view of the refractory nature of the patient's psychosis and a 5-year history of severe TD. Baseline EEG showed alpha rhythm (Figure 1). Then, we started a 12.5 mg daily dosage of clozapine and titrated it up to 150 mg in 3 weeks. Subsequently, the patient experienced seizures that happened 2 to 3 times a day with contractions, loss of consciousness, and urinary incontinence. In her emergency service application, these episodes were reported as tonic–clonic epileptic seizures. An EEG, which was taken after her neurological consultation, was found to be consistent with her epileptic seizure (Figure 2).

During the control visit, we asked the patient to reduce the dose of clozapine to 100 mg/day. The patient was informed of the risks of continuing clozapine in terms of epilepsy. However, she preferred to continue clozapine treatment due to improvement of her tardive dyskinetic movements and psychotic symptoms. The patient had a score of 12 on the abnormal involuntary movement scale (AIMS) at the time of admission. She had a 50% improvement in her tardive dyskinetic symptoms within 2 months after the initiation of clozapine therapy. The clozapine dose in the second month was 100 mg/day, the blood concentration of clozapine was 306.7 ng/mL, and the patient's AIMS score was 6 at that point. Six months later, the patient's AIMS score had decreased to 4. Also, her psychotic signs had improved. The patient's blood values were regularly checked while she was taking clozapine. We followed up with the patient for a period of 1 year while she was on a prescribed dose of 100 mg/day of clozapine. At her last control visit, she scored "3" on the CGI-SI scale and achieved a total PANSS score of 15. At this stage, we observed no indication of worsening TD or further occurrence of epileptic seizures. We obtained a written informed consent form from the patient for this case study.

MAIN POINTS

- Clozapine has a specific therapeutic effect on tardive dyskinesia and treatment-resistant schizophrenia.
- Although there is a risk of seizures associated with all atypical antipsychotics, clozapine seems to be the one that is most closely associated with it.
- The majority of clinicians avoid prescribing clozapine to individuals who have epilepsy and schizophrenia.
- Due to the clozapine dose adjustments, our patient with treatment-resistant schizophrenia, who had previously been diagnosed with epilepsy and tardive dyskinesia, experienced a long period without seizures as well as an improvement in her psychotic symptoms and tardive dyskinetic movements.
- Epilepsy does not limit the use of clozapine when it is clinically required because it appears to be safe when used with some anticonvulsants.

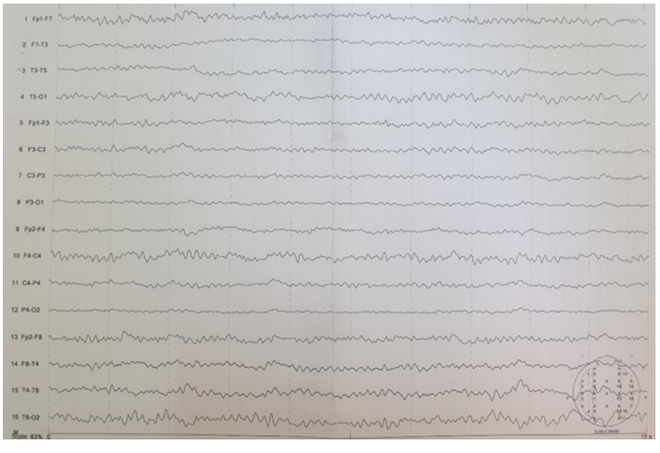

Figure 1. Baseline EEG shows slow wave and no epileptiform discharges. EEG = electroencephalography.

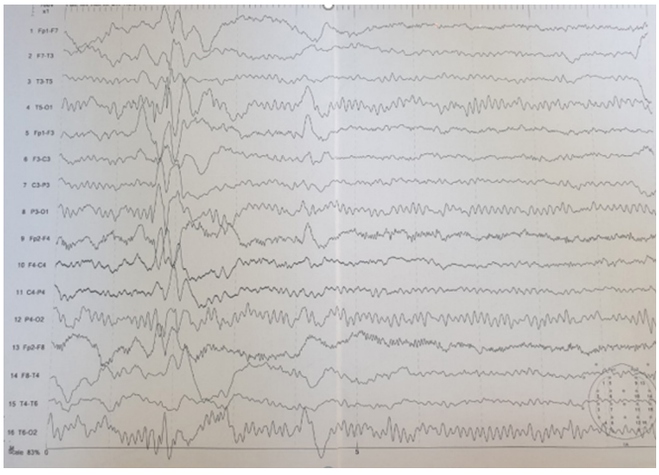

Figure 2. Second EEG showed epileptiform activity after the patient's epileptic seizure. EEG = electroencephalography.

DISCUSSION

All atypical antipsychotics are connected with a risk of seizures, but clozapine seems to be the one most strongly linked to it.[11] The majority of seizures seen as a result of clozapine administration are tonic-clonic.[9] The fact that our patient experienced her second epileptic seizure 22 years after her first epileptic attack, and 3 weeks after starting clozapine treatment suggested that her second epileptic seizure was a clozapine-induced convulsion rather than an epileptic attack. The Naranjo adverse drug reaction probability score was 7 in our patient, indicating a probable association between clozapine and her epileptic seizure.[12]

Seizures caused by clozapine are often dose-dependent; they are uncommon in patients at standard dosages (300-450 mg/day) and especially rare in those receiving low doses (150-300 mg/day).[9,11] Our patient's current history of epilepsy may have caused her epileptic seizures while on a lower dose (150 mg/day) of clozapine therapy. However, there are reports that suggest clozapine-induced seizures may not be completely dependent on the total dose or serum concentration.[11]

Although the precise cause of clozapine-induced seizures is uncertain,[11] some experts suggest that the mechanism may include the coordinated activity of many receptors. According to a study, dopamine makes the main sensorimotor cortex in adult rats less excitable.[13] By decreasing dopamine neurotransmission, clozapine may increase cortical excitability.[13] Serotonin receptors play a crucial function in the neuronal networks linked to seizures. Serotonin consumption increases cell excitability in the brain, lowers the seizure threshold, and may increase seizure frequency.[14]

According to 2 recent studies, clozapine can still be successfully continued even if a seizure does take place.[9,11] Using divalproex sodium (i.e., valproic acid) is the most common method of clozapine-induced seizure prevention. Many seizure types can be managed with its broad margin of safety, according to a study.[4] Clozapine use in patients with epilepsy is challenging, and the evidence that is currently available is inconsistent. A few studies have reported a safe treatment of epilepsy and psychosis patients with clozapine;[4,9] however, to our knowledge, no reliable data are available on the safe use of clozapine in patients with frequent or daily seizures.

Abnormal, involuntary, and arrhythmic movements in the mouth, lips, face, and arms of our patient appeared after long-term antipsychotic treatment. These abnormal movements continued long after the cessation of antipsychotic drugs. Thus, we considered these movements as TD.[2] Dopamine-depleting treatments (such as tetrabenazine, reserpine, and amantadine), γ-aminobutyric acid agonists (such as clonazepam, baclofen, and valproic acid), and anticholinergic pharmaceuticals (such as trihexyphenidyl) can all be used to treat TD.[3] Clozapine improves TD, which can be noticed in individuals who have used antipsychotics for an extended period of time.[2,7] We observed a dramatic improvement in our patient's TD within 2 months of her 100 mg/day clozapine therapy in 306.7 ng/mL blood concentration, which was in the therapeutic range.[15] As a result, our patient with TRS, who had previously known epilepsy and TD, did not have seizures for a long time because of the adjustment made in the clozapine dose, and her psychotic findings and TD also regressed. Clozapine appears to be safe when used with some anticonvulsants;[4] therefore, epilepsy does not prevent the use of this valuable drug when it is clinically necessary.

A limitation of this study is that we were unable to measure the clozapine blood concentration at the time the patient had an epileptic seizure with 150 mg/day clozapine therapy.

In conclusion, this may be an approach that enables continued maintenance of clozapine therapy with low doses in patients already diagnosed with schizophrenia, epilepsy, and TD and who do not respond to alternative treatments.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author has no conflict of interest to declare.

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