The use of clozapine and clonazepam co-administration in the treatment of a severe tardive dyskinesia: A case report

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Abstract
This is a case report of a patient who was treated with clozapine and clonazepam after he developed neuroleptic-induced tardive dyskinesia following treatment for schizophrenia. There are reports of clozapine treatment itself causing tardive dyskinesia; however, more reports have shown clozapine’s benefit for patients with neuroleptic-induced tardive dyskinesia. This is a case report of a patient with neuroleptic-induced tardive dyskinesia who benefitted from clozapine treatment with adjuvant use of clonazepam – the first such case report from Ethiopia. A 43-year-old male patient developed severe involuntary abnormal body movements mainly involving the trunk after he received chlorpromazine for 8 years for the diagnosis of schizophrenia. When the movement disorder became intolerable and disabling, the diagnosis of severe neuroleptic-induced tardive dyskinesia was established and the patient was started on clozapine with adjuvant clonazepam treatment. Following such management, the patient responded well and the dyskinetic movements were fully controlled, and the patient was able to work. Patients with severe and disabling neuroleptic-induced tardive dyskinesia can be treated and be productive if they receive treatment with clozapine, with adjuvant use of clonazepam.

Keywords
Clozapine, tardive dyskinesia, neuroleptic-induced, Ethiopia, schizophrenia, case report

Background
We present a case of a patient who started clozapine treatment after he suffered from severe tardive dyskinesia (TD) following treatment with neuroleptic. In the literature, there are mixed case reports of clozapine’s effect on TD. For example, there are reports of occurrence of TD following clozapine treatment.1,2 Systematic studies, however, have revealed that the risk of incidence of TD, associated with second-generation antipsychotics including clozapine, is lower as compared with the incidence for the first-generation antipsychotics.3,4 In fact, studies suggest that the risk and severity of TD associated with conventional antipsychotic use can be reduced through an approach that begins with a switch to an atypical antipsychotic.4 There are systematic studies which show that clozapine may have some efficacy in the treatment of antipsychotic-induced TD.5,6 Case reports have shown successful treatment of neuroleptic-induced TD with clozapine and that dosage reduction of clozapine resulted in relapse of signs of TD.7,8

The occurrence of TD has been the most daunting and intimidating experience we have been having at Amanuel Mental Specialized Hospital, the only mental health hospital in Ethiopia, which is located in the capital Addis Ababa. It is only since 2016 clozapine had been in use in the hospital. Over the years, we have been diagnosing several cases of neuroleptic-induced TD with variable severity but we couldn’t treat their TD. Since the introduction of clozapine for use in the hospital, it is believed that this might give hope to patients with TD. Here, we present a case report of a patient with neuroleptic-induced severe TD who benefitted from clozapine treatment with adjuvant use of clonazepam, and to our

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knowledge, this is the first case report of clozapine use for TD in Ethiopia.

**Case presentation**

A 43-year-old male patient, who is single and jobless at the onset of treatment, was referred to the clozapine case team in July 2017 for possible management of severe TD. The illness history of the patient is discussed here. In the year 2005, when the patient presented to the hospital for the first time, he had psychotic symptoms which lasted 1 year; at the time, he received the diagnosis of schizophrenia, catatonic type based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*) criteria. He was prescribed chlorpromazine 200 mg daily which resulted in control of symptoms and later on achievement of full remission. Later the dose of chlorpromazine was reduced to 100 mg daily, but after 6 months on the reduced dose, breakthrough symptoms appeared; then dose was restored back to 200 mg resulting in full remission again. The patient took chlorpromazine 200 mg daily for 8 years till he started to develop abnormal involuntary body movements. The first abnormal involuntary body movements were identified in August 2013. The dose of chlorpromazine was reduced gradually till 50 mg/day, and diazepam tablets were temporarily prescribed to alleviate distress. On November 2013, chlorpromazine was discontinued and the patient was prescribed risperidone 1 mg daily with gradual escalation of dose to 4 mg/day. Intermittently, benzodiazepines like diazepam and bromazepam were prescribed to alleviate distress. But the patient discontinued treatment for about 2 months with relapse of psychosis which necessitated admission. He was admitted to the hospital for the first time in June 2014; the diagnosis was schizophrenia, paranoid type with florid persecutory delusions and auditory hallucinations, as well as severe TD with involuntary choreoathetoid distressing body movements which involved the trunk. After admission, he was started on risperidone 8 mg/day along with 10 mg of diazepam with occasional addition of sedatives like promethazine 25 to 50 mg. One month later, he was discharged with hallucinations cleared but delusions still on, and dyskinetic movements still prevailing and getting worse every time. After one outpatient follow-up visit post-discharge, he discontinued treatment again. The reason for default was worsening of dyskinetic movements.

About 2 to 3 months after default of treatment, his psychotic symptoms got worse to the level necessitating physical restraint with chains. He was admitted for the second time in September of the same year. His treatment was restarted with risperidone and benzodiazepines, and with occasional use of promethazine. The abnormal involuntary movements got worse with involvement of neck and both hands in addition to the trunk and shoulders. The movements were described as neck and back extension with swinging of both arms. He was refusing or unable to be interviewed due to the distress from the dyskinetic movements. The treatment was shifted to olanzapine 10 mg daily. But he had been given fluphenazine decanoate depot injection of 12.5 mg at the onset of the second admission which resulted in the occurrence of acute dystonia for which the anticholinergic trihexyphenidyl was given orally at 5 mg/day. The dystonic reactions were alleviated by trihexyphenidyl. Following 10 weeks of inpatient treatment, the patient was discharged with some improvement of psychotic symptoms. His previous medications were discontinued, and he was started on olanzapine 20 mg/day and clonazepam 2 mg/day at discharge.

At outpatient follow-up, the patient continued to have frequent relapse of symptoms and signs of psychosis, including homicidal intent. Risperidone was later restarted due to unavailability of olanzapine. He was admitted for the third time in October 2016 to the emergency department and was discharged 3 weeks later after he was treated with risperidone, and later olanzapine 20 mg/day; he also had received clonazepam. However, at outpatient follow-up visit, he reported that the abnormal body movements were worsening further and that he was being disabled due to which he was contemplating on suicide. He also started smoking cigarettes one pack daily to alleviate his distress. After this, the treating psychiatrists decided to consult the clozapine case team. In March of the same year, the patient was admitted for the fourth time with intention of starting him on clozapine. He was on risperidone 4 mg/day and clonazepam 2 mg/day when he was transferred to the clozapine case team in July 2017. At the onset of treatment, the TD movements were continuous and vigorous all the time except during sleep when movements disappeared. During the daytime, when he was awake, he was diaphoretic from the vigour of the muscle contractions and usually got exhausted and dehydrated. Abnormal Involuntary Movement Scale (AIMS) total score prior to the onset of treatment was 34. All necessary evaluation and workup were conducted, and the patient was declared fit to start clozapine treatment.

After all preconditions were fulfilled, the patient’s previous medications were discontinued and he was started on clozapine treatment according to the dose escalation protocol starting from July 2017. Dose increment continued with all necessary monitoring. Soon after the start of treatment with clozapine, the dyskinetic movements increased and became distressing; he was given intravenous diazepam to alleviate his distress every time he had distress from the dyskinetic movements. Few days after the onset of clozapine treatment, clonazepam was also prescribed a dose of 4 mg/day, given divided twice daily. But dose of clonazepam was reduced to 2 mg/day, when dyskinetic movements started to show a decrease in intensity few days later. One month after the onset of clozapine treatment, the patient said he was better and requested to be discharged despite continued dyskinetic movements which episodically got exacerbated. He was free of psychotic symptoms, however. He was advised on coping...
mechanisms with ways of relaxing himself; clonazepam was discontinued and he was discharged in consultation with his relatives. Upon discharge, he was on clozapine 400 mg/day divided twice, with higher dose in the evening and clonazepam 2 mg to be taken on a need basis (10 tablets were dispensed). Two weeks later, during outpatient visit, the patient reported that he was better than before but still has occasional worsening of symptoms, which necessitated clonazepam use; the total score of AIMS was 19 at the time. Early October 2017, the patient presented with exacerbation of dyskinetic movements with sweating and exhaustion, and requested to be admitted again. He was admitted and was soon given intravenous diazepam 10 mg to stabilize him. He was prescribed clonazepam again at 2 mg/day and was also given haloperidol at 1.5 mg/day in a desperate attempt to suppress movements, but to no avail; haloperidol was discontinued 3 weeks after it was started.

Gradually, however, the dyskinetic movements started to decrease, and he was discharged from hospital 1 month after admission on clozapine 400 mg/day and clonazepam 2 mg/day. However, the dyskinetic movements were not adequately controlled, and the dose of clozapine was raised gradually to reach a dose of 500 mg/day, while clonazepam dose was raised to 4 mg/day. At the beginning of August 2018, the patient reported that the abnormal body movements were markedly decreased and that he did not consider them a problem anymore. After this, the dose of clonazepam was reduced to 2 mg/day with plan to taper and discontinue the drug. The patient started to work, but after dose reduction of clonazepam, the dyskinetic movements started to show increment to intolerable levels. Finally, since the end of August 2018, the treating team decided to keep the dose of clonazepam to 4 mg/day divided twice and to continue that dose indefinitely together with clozapine 500 mg/day divided twice daily. Since that time, the dyskinetic movements almost disappeared and were unnoticeable; the score of AIMS reached to a low level of 3. The patient was stable and effective at work with marked satisfaction with treatment. He adhered to treatment and continued to come for follow-up by himself. The benefit the patient got from the treatment started inspiring other patients with similar problems who started joining the programme of clozapine treatment to overcome their enormous suffering.

Discussion and conclusion

Discussion

TD is an iatrogenic human hyperkinetic movement disorder associated with chronic antipsychotic drug treatment. Considerable reduction of manifestation of neuroleptic-induced TD has been described in the literature with use of clozapine. The dosage of clozapine required could be high, and long period of treatment may be required. Even if the exact mechanism of action of clozapine’s efficacy is not clearly understood, it is believed that clozapine works by acting on the changes in the brain’s striatal system which are caused by prolonged blockade of dopamine receptors due to prolonged use of antipsychotic medications. Continued use of clozapine is necessary to suppress the dyskinetic movements, and studies have shown that dose reduction resulted in relapse of the abnormal body movements, and its cessation resulted in rebound of TD movements. Due to its adverse effect profile and the need for strict monitoring, the benefit of clozapine mainly is for patients with moderate to severe manifestations of TD for whom switch to clozapine treatment is warranted. While clozapine monotherapy could be efficacious to reduce TD movements, some case reports show use of clozapine together with other medications. It is the belief of the authors that the use of adjunctive clonazepam has contributed to the response of the patient. The concomitant use of clonazepam was initiated with intention of alleviating anxiety and to help relax the patient; however, some literature show that the benefit of benzodiazepines in treating TD movements could have association with the pathophysiologic changes in the brain of the patient who has the movement disorder. Traditionally, factors mediating TD have been sought in striatal dopaminergic transmission; however, several incompatibilities have developed between the characteristics of the dopaminergic model and the presentation of the disorder. Defective GABAergic (gamma aminobutyric acid) transmission within the basal ganglia has also been targeted as the possible putative pathophysiologic mechanism in TD. The involvement of both dopaminergic and GABAergic mechanisms in the pathophysiology of neuroleptic-induced TD probably explains the effectiveness of concurrent administration of clozapine and clonazepam for patients in order to effectively control the disorder.

Conclusion

Clozapine has effectively controlled severe and debilitating TD movements in our patient, when administered concurrently with clonazepam. The patient was fully stabilized with complete relief and return to full functioning.

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Availability of data and materials

The datasets used in the write-up of this case report are not publicly available because the data are taken from the medical record of the patient.
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Informed consent
Written informed consent was obtained from the patient for their anonymized information to be published in this article. The patient had given informed consent to undergo treatment with clozapine, and for the case to be written and sent for publication. The patient was competent enough to give informed consent.

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