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CASE REPORT

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Treatment of tardive dyskinesia with clonazepam: A case report

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Key Clinical Message

Clonazepam has some evidence in the treatment of tardive dyskinesia. It can be used as an alternative treatment option in situations where vesicular monoamine transporter 2 inhibitors are not available or when it is not feasible to use them.

KEYWORDS

antipsychotics, clonazepam, delusional disorder, tardive dyskinesia

1 | INTRODUCTION

Tardive dyskinesia (TD) is a movement disorder characterized by irregular, repetitive, stereotypic movements that most commonly affects movements of the tongue, lips, jaw, and face, in addition to limbs and trunks.[1,2] These abnormal movements occur mainly as a result of exposure to the dopamine blocking agents.[3,4] The word tardive comes from the Latin word "tardus" meaning late onset and dyskinesia meaning abnormal movement.[5] TD was first described by Sigwald et al. in 1959, and the term was later coined by Faurbye et al. in 1964.[6] Another entity called Tardive syndrome (TS) is more of a general term which includes any kind of neurological symptoms including hypo or hyperkinetic dyskinesias, gait disorders and sensory symptoms that develop with the use of dopamine receptor antagonists (DRA) and persists even after stopping the offending medications.[7] TD can be described as one type of TS.

The prevalence of TD among patients on antipsychotic medications ranges from 20% to 30%.[4,7] A meta-analysis of 41 studies from 2000 to 2015 found that the prevalence of TD with First Generation Antipsychotics (FGAs) was 30% and 20% with the Second Generation Antipsychotics (SGAs).[7] Solmi et al. describes the cumulative annual incidence of TD from 5.4% to 7.7% with FGAs compared to 0.8%–3.0% with SGAs in adults.[8]

Abnormal movements are a common sequela after exposure to psychotropic medications. The indications and off label prescriptions of antipsychotics have increased significantly since its discovery in 1950s.[4] Apart from psychosis, antipsychotics are also prescribed as an adjunctive treatment in mood disorders, behavioral problems like agitation and aggressiveness and even for insomnias. FGAs have greater risk than the SGAs.[9] The FGAs known to cause TD include, haloperidol, chlorpromazine, thioridazine, thiothixene, pimozide, perphenazine, and trifluoperazine. Among the SGAs, risperidone, paliperidone, iloperidone, loxapine, olanzapine, aripiprazole, ziprasidone, asenapine, lurasidone, quetiapine, and clozapine are known to cause TD. Medications other than antipsychotics causing TDs are antiemetics such as metoclopramide, prochlorperazine and antidepressants like trazodone, amitriptyline, clomipramine, amoxapine, fluoxetine, sertraline. Rarely, calcium channel blockers like cinnarizine and flunarizine have also been described to cause TD.[2]

The risk factors for TD can be classified into modifiable and non-modifiable risk factors. Modifiable risk factors can be treatment related and co morbidity related. Treatment related modifiable risk factors include, choice of antipsychotic medications, dose and duration of treatment, early manifestations of parkinsonian side effects, akathisia and acute dystonia, chronicity of illness, and co-treatment with anticholinergics. Other modifiable risk factors are diabetes, smoking, alcohol, and other substance abuse. Non-modifiable risk factors can be patient-related factors and illness-related factors. Patient related non-modifiable risk factors are higher age, female gender, Caucasian race, African descent, and genetics. Longer duration of illness, intellectual disability, brain damage, negative symptoms in schizophrenia, mood disorders, and cognitive symptoms in mood disorders are some of the illnesses related to non-modifiable risk factors.[2,7,8]

Although the exact cause for TD is not clear, several hypotheses have been proposed. One most widely accepted theory states that due to long term treatment with antipsychotics there is dopamine receptor upregulation causing hypersensitivity of postsynaptic dopamine D2 receptors.[3,6,7] However, Bashir et al. mentions two important points against this theory. First, it does not explain the persisting symptoms of TD as the receptors would be expected to reduce after discontinuation of antipsychotics and second, it doesn't explain the occurrence of TD with medications other than the antipsychotics.[7]

Neurodegenerative hypothesis states that increased oxidative stress causes damage to the neurons from the free radicals generated due to long term use of antipsychotics.[2,7,8]

The other hypothesis relevant to this case report is inactivity of the gamma amino butyric acid (GABA) system with long term treatment with antipsychotics.[3] The nigro-striatal-pallidal pathway is involved in regulating movements. This pathway also involves GABAergic neurons. It has been found that reduction of GABA level in the basal ganglia is associated with TD.[10] Reduced GABA signaling pathways causes decreased inhibitory activity in nigrostriatal circuits.[8]

It has been reported that the remission rates of TD are widely variable.[3] It is also considered as irreversible sometimes.[11] The consequences of TD are distressing to the patients and their caregivers and to some degree to the clinicians who initiated the treatment. The physical, emotional and social consequences of TD have been described to have direct bearing in the clinical outcome, functional recovery and survival.[10] Studies have found that there are correlations between TD and impaired cognition, poor response to treatment, greater risk of relapse, longer hospital stays, lower quality of life and functioning, a progressive course and increased mortality.[5,11]

Effective treatment therefore is very important not only to improve the associated distress and improve the quality of life but also to strengthen the therapeutic relationship geared towards alleviating the primary psychiatric conditions for which the medications were given. The first line treatment of TD is vesicular monoamine transporter 2 (VMAT 2) inhibitors. However, clinical dilemmas could occur when VMAT 2 inhibitors are not available, if they are not feasible to use or if their use does not yield improvement.

Here we present a case of successful treatment of TD with clonazepam.

2 | CASE HISTORY AND EXAMINATION

A 50-year-old businessman and father of four children was admitted to the Psychiatry ward of Jigme Dorji Wangchuck National Referral Hospital for assessment of change in behavior and personality. Detailed psychiatric history and mental state exam revealed that he had been having delusions which were predominantly grandiose in nature with some secondary persecutory delusions. Apart from these delusions, his other mental faculties were preserved. There was no history suggestive of underlying mood disorders, especially that of manic episodes or chronic psychosis nor was there a positive history of substance use such as cannabis. Patient's wife confirmed that there was no past history of psychosis. His functionality was affected primarily due to secondary paranoia. Blood investigations excluded nutritional deficiencies, tuberculosis, viral infections including HIV, and syphilis. Brain MRI showed generalized atrophy of the brain and no other abnormalities.

A diagnosis of Delusional disorder, grandiose type, and first episode, currently in acute episode, was made with reference to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5). He was treated with oral tablet chlorpromazine 200 mg at night and risperidone 4 mg at night. He responded to these antipsychotics and was discharged on the same dose of medications. He was followed up in the psychiatry outpatient unit and his delusions were disappearing and his functionality was beginning to improve. Apart from akathisia and mild bilateral digital tremors there were no other significant adverse effects of medications.

3 | METHODS (DIFFERENTIAL DIAGNOSIS/INVESTIGATION/TREATMENT)

However, his family members brought him to the OPD after 7 months of taking chlorpromazine with complaints

of repeated protrusion of tongue for the last 1–2 months. It had become distressing to him as the protrusion interfered with eating food, when conversing with people and while working. It disappeared only during sleep. His basic activities of daily living were affected as he required assistance in taking bath or eating food at times. There was no change in the dosages of medications that could have precipitated the abnormal irregular movements. There was no family history suggestive of movement disorders or other neurological disorders. Examination revealed that there was irregular chewing like movements in the jaw in addition to protrusion of his tongue irregularly. There was no problem with his teeth, and he did not wear dentures. Non-rhythmic bilateral digital tremors were also noticed. There were no other choreoathetoid movements of limbs or trunks. He exhibited a slowed, shuffling gait. His blood investigation reports were unremarkable. There were no abnormalities to suggest an alternate cause for his abnormal irregular repetitive movements.

In summary, our patient was on chlorpromazine (FGA) and risperidone (SGA) for 7 months duration for delusional disorder. He developed dyskinetic movements in his jaw in addition to the tongue which interfered with his basic and instrumental activities of daily living comprising his day-to-day functioning. We couldn't elicit an alternative cause for this movement disorder. Therefore, a diagnosis of tardive dyskinesia was made using the Schooler Kane criteria. His Abnormal Involuntary Movement Scale (AIMS) score during the first visit was positive as he scored mild in the lips and perioral area (puckering), moderate in the jaw (chewing) and severe in the tongue.

Chlorpromazine was tapered off over a period of 1 week and he was observed for about 3 weeks without any additional medications. According to the patient's wife, the irregular chewing like jaw movements and protrusion of tongue persisted with some deterioration as she reported an increase in "difficulty in feeding" him with "increasing spells of tongue protrusion." Then he was started on clonazepam 0.5 mg once at night and the dose gradually escalated up to 2.5 mg once at night. He was gradually tapered off risperidone and replaced with quetiapine for the underlying psychosis and sleep disturbances. His AIMS score during follow ups were improving as observed by reduction in the severity of the scores in his lips and perioral area (puckering), jaw and in the tongue.

4 | CONCLUSIONS AND RESULTS (OUTCOME AND FOLLOW UP)

He achieved complete remission of symptoms after 4 months of treatment with clonazepam. He was weaned off from clonazepam and was maintained on a low dose of quetiapine. His wife reported "his feeding has become easier as a result of spells of tongue protrusion and irregular chewing like jaw movement reducing greatly." He has returned to his occupational functioning and is able to carry out his basic and instrumental activities of daily living at present as we write this case report.

5 | DISCUSSION

TD is a potentially irreversible iatrogenic movement disorder with negative physical, emotional, and social consequences. With increasing indications and off label use of antipsychotic medications, it is important to not only prescribe antipsychotic medications but also to monitor and treat the side effects accordingly.

The diagnosis of TD can be made either using the DSM criteria or the Schooler Kane criteria as follows:[5]

a. Symptoms occur for at least 3 months of antipsychotic therapy.
b. Abnormal involuntary movements must occur in two or more body regions (mild) or one body region if symptoms are moderate to severe as determined by the AIMS scale.
c. There are no other conditions that might cause abnormal movements.

The case described above fulfills the mentioned criteria of TD. He was on chlorpromazine (FGA) and risperidone (SGA) for 7 months. He had dyskinetic movements in his jaw in addition to the tongue. Repeated and irregular protrusion of tongue interfered with his basic and instrumental activities of daily living comprising his day-to-day functioning. There was no family history suggestive of movement disorders. His neurological examinations ruled out possible focal neurological deficits and his blood investigation and brain imaging studies were not significant to account for the dyskinetic movements.

The best management for TD is prevention.[12] However, sometimes it is inevitable not to prescribe antipsychotics in the presence of compelling indications. Nevertheless, a prescribing physician should be aware of the risk factors for TD, prescribing doses of antipsychotics and regularly monitor and follow up for movement disorders.

VMAT 2 inhibitors such as valbenazine and deutetrabenazine have been approved for treatment of TD by the FDA[6,8] and is the first line drug to treat TD. However, it is not available in our setting. Therefore, an alternate treatment, clonazepam was considered which has some evidence in the treatment of TD. The American Academy of Neurology grades clonazepam as grade B level of evidence

which means it is probably effective in the treatment of TD.[6,7,13]

The first step in the management involves stopping the most probable causative agent or the antipsychotic medications and ruling out other possible causes. However, this may not be as easy. Patients often require long term antipsychotic medications. In such cases, switching to less dopamine selective medications like quetiapine or clozapine could be preferred. Stopping antipsychotic medications should not be done at once, it should be tapered and stopped.[14] Withdrawal emergent dyskinesias are dyskinesias which occur upon stopping, change or dose reduction of antipsychotic medications.[14] It is one of the differentials for TD which resolves on its own with time in about 4–8 weeks.[14] In the case we described, antipsychotic medication was stopped gradually over a week's period. His symptoms persisted for 3 weeks and it was in fact deteriorating more consistent with TD. Chlorpromazine was tapered first considering its higher propensity to cause TD than risperidone. Gradually, risperidone was also tapered and he was put on less dopamine selective antipsychotic, quetiapine.

Although cessation of chlorpromazine and risperidone could have contributed to the remission of his TD symptoms, we believe that the fact clonazepam did actually facilitate the recovery. This is because his TD symptoms were deteriorating when he was being observed before clonazepam was started. His TD symptoms started to diminish after he was put on clonazepam and as the dose was gradually increased the response was even better.

The use of Clonazepam in the treatment of TD was studied from the 1970s–1980s and since then several case reports have reported its success.[15,16] Clonazepam is a long-acting benzodiazepine. Benzodiazepines bind to GABA type A receptors allosterically and increase the frequency of chloride channel opening thereby hyperpolarizing the neurons.[7,10] The GABAergic system has been involved in the pathophysiology of TD and reduction of GABA levels in the basal ganglia have been found in association with TD.[7,10] Additionally, Chih Chun et al. described that a significant number of patients did not exhibit improvement in their symptoms with VMAT2 inhibitors, and that dopamine blockage may not be the only reason in genesis of TD.[10]

Furthermore, in a 12 week, double-blind, randomized, placebo crossover trial of 19 chronically ill patients with TD taking the FGAs, clonazepam treatment reduced dyskinesia scores by 37% compared with placebo.[6] Doses up to 4.5 mg/day of clonazepam have been used and reported in some studies.[5,10] However, it has also been reported that benzodiazepines do induce TD[5] and reappearance of TD symptoms have been reported with cessation of benzodiazepine treatment.[15]

In our case, he was weaned off from clonazepam gradually with a slight increase in the dose of quetiapine. He was followed up to assess for reemergence of his symptoms and at the time of writing this case report he did not exhibit any symptoms of TD.

AUTHOR CONTRIBUTIONS

Bikram Chhetri: Conceptualization; data curation; methodology; project administration; writing – original draft; writing – review and editing. **Dawa Gyeltshen:** Methodology; project administration; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The ethical clearance was sought from IRB, Khesar Gyalpo University of Medical Sciences of Bhutan: Ref. no. IRB/Approval/PN/2022/007/564, dated April 8, 2022.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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