ANTIPSYCHOTICS INDUCED TARDIVE DYSTONIA IN A CASE OF BIPOLAR MOOD DISORDER – A CASE REPORT
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Abstract
Atypical antipsychotics are increasingly being associated with neurological side effects. Risperidone, quetiapine, and aripiprazole have been associated with tardive dystonia among other side effects. Similarly, olanzapine has also been associated with this troublesome effect. We present here a case of Tardive dystonia associated with the use of olanzapine and other antipsychotics in an adult male suffering from bipolar mood disorder. The slight reduction in the severity of the symptoms with the stopping of olanzapine and other atypical antipsychotics, suggest the contributory role of these agents. At present the patient is on a trial of clonazepam and promethazine and is showing continuous improvement.

Keywords: Tardive dystonia, Olanzapine, Trifluperazine, Quetiapine, Clonazepam.

Introduction
Extra-pyramidal symptoms (EPS) and tardive syndromes are commonly associated with the use of typical antipsychotic drugs. Tardive dystonia (TD), a very rare side effect, estimated prevalence of Tardive dystonia with typical antipsychotics is 3% in clinical population[1], is characterized by local or general sustained, involuntary twisting movements, generally slow, which may affect the limbs, trunk, neck, or face.[2] Tardive dystonia is usually disabling and persistent, and treatment seldom results in satisfactory relief or remission of symptoms[3]. As compared to tardive dyskinesia, Tardive dystonia develops at a younger age and after shorter exposure to antipsychotic drugs. Other studies estimate tardive dystonia as a rare side effect of long-term antipsychotic use with a prevalence of 0.4% to 4.0% in neuroleptic-treated patients. [4]

Dystonia is a syndrome of sustained muscle contractions that produce twisting and repetitive movements or abnormal postures. The descriptions of the extent and severity of muscle involvement are variable, ranging from intermittent contraction limited to a single body region, to generalized dystonia involving the limbs and axial muscles. Ever since the introduction of the term, “dystonia” by Oppenhiem in the early part of the twentieth century, it has been an area of focused attention of the neurologists. In 1973, Keegan and Rajput introduced the term, “dystonia tarda” to describe drug-induced, sustained muscle spasm causing repetitive movements or abnormal postures. “Tardive dystonia” was a term introduced by Burke in 1982, the description of which required the presence of chronic dystonia, a history of antipsychotic drug treatment preceding or concurrent with the onset of dystonia, the exclusion of known causes of secondary dystonia by appropriate clinical and laboratory evaluation, and a negative family history of dystonia for definitive diagnosis[2].

The dystonia could be classified based on the region(s) of the body involved. Involvement of isolated regions like the face, neck, and arms would be labeled as focal dystonia, whereas simultaneous involvement of two or more contiguous areas would be called segmental dystonia. When the clinical picture is that of involvement of two or more noncontiguous regions, the label used is, “multifocal” and the involvement of one leg and one other body region makes it the generalized type.

The treatment of tardive dystonia requires a different therapeutic strategy from that of classic tardive dyskinesia.[5, 6] Discontinuation of the antipsychotic is recommended; however, the patient may require lifelong neuroleptic treatment. Lowering the dose may be effective but it risks the development of withdrawal emergent syndrome; this can be avoided with a gradual taper. Other agents, such as antidepressants and antiemetics, may cause or exacerbate tardive
dystonia. Elimination or reduction of these agents may help reduce symptoms. The use of atypical antipsychotics, particularly clozapine or quetiapine, minimizes but does not eliminate the risk of developing tardive phenomena.

Anticholinergics and dopamine-depleting agents may be the most effective alternatives in this patient. These classes of drugs do not have a known risk of causing the onset of tardive syndromes.

Tetrabenazine and reserpine are two commonly used dopamine-depleting agents that can be helpful in the treatment of psychotic symptoms and tardive phenomena. Reserpine can be started at 0.125-0.25 mg daily and then titrated by 0.125-0.25 mg weekly. Tetrabenazine is not yet approved in the United States but is available in Canada. The starting dose is 25 mg daily, which can be increased by 25 mg weekly or biweekly. Blood pressure should be monitored while adjusting the doses of both of these agents.

Tetrabenazine has a shorter time of onset and duration of action, as well as fewer side effects compared with reserpine. Tetrabenazine also has dopamine receptor blocking activity, which could theoretically perpetuate tardive syndromes. One study showed that tetrabenazine was effective in 80.5% of patients with tardive dystonia. Most of these patients have already been treated with botulinum toxin, anticholinergics, reserpine, and clonazepam. In an earlier study, tetrabenazine was not effective in idiopathic focal dystonia without the use of lithium.

The more common side effects of dopamine-depleting agents are drowsiness, Parkinsonism, depression, and orthostatic hypotension. These side effects are dose-dependent and responsive to dose reduction. The combination of both anticholinergics and dopamine-depleting agents can be helpful in refractory cases.

In terms of other potential options, botulinum toxin is most effective in focal dystonia. Clonazepam is usually more effective in treating dystonic features compared with classic tardive dyskinesia. On the basis of the treatment of dystonia, up to 12 mg daily divided into 3 doses may be effective in this patient, but side effects may limit dose titration. Other gamma-amino butyric acid (GABA)-mimetic agents, such as valproate and baclofen, may also be helpful.

**CASE REPORT**

A 56-year-old male, married, Hindu, resident of Vadodara, k/c/o Bipolar 1 Mood disorder with hypertension and diabetes (controlled) on regular treatment since 13 years presented to DHIRAJ HOSPITAL PSYCHIATRY OPD and was admitted (IPD NO 1112040050) with complaints of recent onset of discomfort in lower back, difficulty in initiation at the time of walk and patient dragged his feet to move forward rather than lifting them. However, when he was set in motion at once, he completed his walk by taking rapid dragging fast steps. Then again when he was asked to stop and to turn back again to walk, he took a turn by moving a full circle, by dragging his feet and then started to walk. Patient felt that sudden stretching of muscles of his upper leg posed difficulty in walking, as well as restricted his body movements. He was not able to maintain an erect posture and would tend to fall on either side while standing up from a sitting position. Due to the restrictions with the body movements, he would require assistance in standing and walking. Despite this, he was driving about 300 km approximately everyday for work and was adamant accepting help from his wife and brother.

History relates back from last 13 years when he was apparently asymptomatic. He started behaving abnormally and was diagnosed a sufferer of Bipolar Mood disorder. He was managed with olanzapine, antidepressants, benzodiazepines and mood stabilizers (divalproex sodium) for psychotic and mood symptoms. Improvement and subsequent remission of the mood symptoms of the patient provided the treatment team with an opportunity to stop olanzapine. The discomfort in the neck and the abnormal movement of the neck muscles which he developed during course of this treatment, persisted over the next three months' period when he was off olanzapine without any significant change, even with a trial of propranolol, trihexyphenidyl, and promethazine injection. Reintroduction of olanzapine (at a dose of 2.5 mg per day) after a gap of three months for the reemergence of some behavioral features led to a slight aggravation of the already existing abnormal movement and posturing of the neck.
Patient since 2005 after few months of receiving antipsychotic drug (Olanzapine,Trifluperazone) and mood stabilizers had some of the above mentioned (difficulty in speaking, difficulty in walking, tremors and slowness of movements)features. Due to these symptoms patient was also shown to the physician and levodopa, carbidopa was started. Patient took opinion from neurophysician and started treatment, after which symptoms worsened and Quetiapine was omitted. He was treated for parkinsonian symptoms after which tremors improved, but the abnormal movement of trunk and face continued.

During the course of the illness, the patient has been investigated for the presence of any neurological illness as the cause of his abnormal movements. His MRI scan of the brain, serum and urine copper levels, slit lamp microscopy for the KF ring, complete blood count, TLC, DLC, and USG of the abdomen did not reveal any abnormalities. There was no improvement with the treatment received so far.

Than later after admission in DGH, On Neurological Examination patient had
1. Difficulty in initiation of the movement of the body.
2. Jerky movements while walking.
3. Jerky movements of the muscles of the left side of the face.
4. Impaired coordination.
5. Ataxia.
6. Positive glabellar tap.
7. Sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures.
8. Difficulty in writing not associated with doing any other activity with hand. Other neurological examination was normal
The diagnosis of Tardive Dystonia was made and trial of clonazepam and promethazine was given and patient showed improvement. Antipsychotic and mood stabilizers were stopped.

Present status and future plan
The patient is showing continuous improvement at present. A comprehensive approach including patient education and supportive care is also being given side by side. Physical therapy and well-fitted braces are also being designed to improve posture and to prevent contractures. Various muscle relaxation techniques have also been taught as adjunct to current medical treatment. Clozapine has been used to treat antipsychotic-induced tardive dystonia, with some investigators suggesting that tardive dystonia may selectively respond to clozapine (2,4,10). So, clozapine can be used in near future in this patient, so that patient gets the benefit of antipsychotic without developing tardive dystonia.

REFERENCES