Tardive dyskinesia: Risk factors, prevention, and treatment

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Abstract

Background: Tardive dyskinesia is a complication of antipsychotic treatment characterized by choreiform involuntary movements affecting commonly the orofacial and buccolingual regions, but also trunk and extremities. Even though the exact etiology is not clearly understood, it is believed that upregulation of postsynaptic dopamine receptors after chronic dopamine blockade and neuronal oxidative damage may be implicated. The symptoms may be lifelong in some patients. Risk factors include advanced age, female sex, type of antipsychotic agents and routes of administration, pre existing movement disorders and general health of the patient. Multiple agents including vitamin B6, branched-chain amino acids, Ginkgo biloba, medications including beta blockers, ondansetron and benzodiazepines have been tried in the treatment of tardive dyskinesia without much success. The newly approved medications valbenazine and deutetrabenazine offer hope to these patients who otherwise had to live with this socially and functionally disabling disorder.

Methods: Literature review was conducted using keywords tardive dyskinesia, risk factors, pathophysiology, treatment, Valbenazine, and deutetrabenazine. Search engines used include Pubmed, Cochrane Review, PsycINFO, and Psychiatry Online.

Results: We have summarized the history, pathophysiology, risk factors, and management of TD including the recently approved medications.

Conclusion: Tardive dyskinesia is a disabling, long term side effect of antipsychotic use. Many risk factors predispose patients to the development of symptoms. Until recently, there were no FDA approved treatments. The newly approved medications valbenazine and tetrabenazine have shown promising results for the treatment of tardive dyskinesia.

Introduction

With the development of neuroleptic drugs, psychiatry finally had reliable medication options to treat psychotic disorders. As with most medical developments, there were downsides to these medications. Several side effects were immediately apparent. However, some side effects were more insidious. Since its discovery in the 1960's, tardive dyskinesia (TD) has been a challenging complication of antipsychotic treatment. Characterized by choreiform involuntary movements, tardive dyskinesia can cause severe distress in the life of a patient, as well as a treatment conundrum for clinicians. Most commonly seen in the oral and facial regions with notable tongue protrusions and fasciculations as well as grimacing, tardive dyskinesia symptoms can affect nearly any part of the body. While the pathophysiology of the syndrome is not clearly understood, evidence has emerged which suggests possible causes. Upregulation of postsynaptic dopamine receptors, after chronic dopamine blockade, is a likely causative factor. In addition, neuronal oxidative damage may also be associated with the symptoms. Most alarmingly, the symptoms, even with treatment and withdrawal of the offending agent, can last for years, and may possibly be lifelong.

There have been multiple risk factors postulated to be associated with the development of tardive dyskinesia. Demographics, including patient’s age, and female sex are important risk factors. As one would expect, the choice of antipsychotic agent has significant impact on the development and severity of symptoms. However, other factors involved in antipsychotic treatment, including administration schedules, may play a role. General health of the patient, including fasting glucose and pre-existing movement disorders can also predispose the patient to these symptoms.

Given the severity and persistence of the syndrome, several attempts have been made to treat tardive dyskinesia. These treatments include several natural compounds, including vitamins and amino acids, and traditional pharmaceutical therapies. Recently, for the first time, two medications valbenazine and deutetrabenazine were approved by the United States Food and Drug Administration (FDA) for treatment of tardive dyskinesia.

Pathophysiology

There appears to be an imbalance between dopamine overactivity and cholinergic underactivity [1] This is supported by the observation that patients improve initially with increasing dopamine blockade, and symptoms worsen with administration of anticholinergics. Long term antagonism of postsynaptic dopamine receptors creates a clinical picture resembling that of efferent neuronal destruction. This results in an increased concentration of post synaptic dopamine receptors [2] leading to hypersensitivity to dopamine, and to symptoms of tardive dyskinesia [3].

In addition to the most accepted theory that the super sensitivity to dopamine is the cause of tardive dyskinesia, other factors may also be at play. Christensen, et al. [4] found neuronal loss in the basal ganglia of patients with tardive dyskinesia. This may be due to the fact that

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D2 blockade can increase the release of glutamate and aspartate [5]. Glutamate, if chronically activated, has in turn been shown to cause neuronal damage [6]. Tsai, et al. [7] showed that patients with tardive dyskinesia had higher concentrations of excitatory neurotransmitters, including N-acetylaspartate, N-acetylaspartylglutamate, and aspartate in cerebrospinal fluid (CSF) analysis compared to patients without TD symptoms.

It has been found that, among schizophrenic patients, Abnormal Involuntary Movement Scale [8] (AIMS) scores were correlated with higher N-acetylaspartate, N-acetylaspartylglutamate, aspartate, and glutamate CSF concentrations. An inverse relationship existed between AIMS score and superoxide dismutase activity, suggesting that not only do patients with abnormal movements have a higher concentration of neurotransmitters that cause oxidative stress, but also have a decrease ability to cope with oxidative stress. These trends were noted as a whole among patients with schizophrenia, and there was no correlation of these markers and AIMS scores specifically within the TD patient group [7].

A particularly concerning aspect of tardive dyskinesia is the long term possibly lifetime presence of symptoms. Zutshi, et al. [9] conducted a retrospective cohort study of patients who were diagnosed with tardive dyskinesia and discontinued their offending agent. Some of these patients received treatment for their TD, including switch to an atypical antipsychotic, beta blockers, benzodiazepines, or vesicular monoamine transporter 2 (VMAT2) inhibitors. Only 13.9% of these patients had resolution of TD, and 2.8% experienced resolution of symptoms without any treatment. However, there was a general trend toward improvement, particularly in severe cases of TD, which showed a decrease in symptoms by a factor of 2.5 (AIMS score).

**Risk factors**

There are several demographic factors and co-morbid conditions which can lead to the development of TD. Advanced age is the most important factor, as shown in a study by Yassa, et al. [10]. This study showed that amongst geriatric patients who were initiated on antipsychotic treatment, 46% met criteria for TD after 5 years of treatment. Another significant risk factor the development of TD is female sex. It has been noted that the incidence of TD in elderly women being treated with antipsychotics is as high as 30% [11]. History of alcohol abuse pre-disposes patients to development of TD [12]. Patients with mood disorders are also at risk to develop TD [13].

Pre-existing movement disorders may predispose patients to the development of tardive dyskinesia. Tenback, et al. [14] followed patients with and without extrapyramidal symptoms (EPS) for 12 months. Patients with pre-existing EPS were more likely to develop TD (3%) compared to patients without pre-existing EPS (1.6%). It has also been shown that intention tremor is a risk factor for TD [12].

Polymorphisms in the genes which code for drug-metabolizing enzymes may also enhance a patient’s risk for development of TD. Polymorphisms in the genes for the cytochrome oxidase pathway [15], catechol-O-methyl-transferase (COMT) and manganese superoxide-dismutase (MsSOD) genes [16] have been noted to increase the risk for TD.

Phenylketonuria is another risk factor for the development of tardive dyskinesia [17]. The study showed evidence that men with tardive dyskinesia have a higher plasma concentration of phenylalanine after an oral phenylalanine challenge than controls. Glucose levels may also play a role in the development of symptoms. Animal studies have shown that dopamine receptor binding sensitivity is increased in diabetic rats [18]. Given the proposed mechanism that tardive dyskinesia is caused by dopamine receptor super sensitivity, it is logical that impaired glucose tolerance would increase severity and incidence of TD symptoms. Schultz, et al. [19] found that, after controlling for age, elevated fasting glucose levels were correlated with higher AIMS scores in schizophrenic patients. However, there was no noted correlation between glucose tolerance after a 75gm glucose challenge and AIMS scores, suggesting that the baseline glucose levels, and not glucose tolerance, are implicated in the pathology of TD.

Low levels of brain-derived neurotrophic factor (BDNF) have been noted in patients with tardive dyskinesia, and BDNF serum concentrations have been found to be inversely related to AIMS scores in such patients [20]. This correlation is in line with other findings that BDNF is neuroprotective in the nigrostriatal pathway [21] and protective in neuronal damage mediated by glutamate [22].

Among schizophrenic patients receiving dopamine blocking agents, specific features of their presentation may predispose them to the development of TD. Severe negative symptoms have been shown to be a risk factor [23] and it also appears that the pattern of cognitive impairment in patients with TD and severe negative symptoms is similar to that of patients with basal ganglia pathology. Pantelis, et al. [24] assessed spatial working memory in patients with and without TD and found that those with TD performed worse on spatial working memory tasks, as well as delayed-matching-to-sample tasks compared to those without TD. Interestingly, this held true for patients with orofacial TD only, and patients with truncal TD did not perform worse compared to patients without TD.

The selection of antipsychotic agent, as well as type of administration appear to be of consequence. While second generation antipsychotics display a lower risk for tardive dyskinesia as a class, the comparative risk between medications in this group also varies. Correll, et al. [25] conducted a systematic review of 11 studies of patients treated with second generation antipsychotics [26-36]. In terms of risk by age, the annual incidence was found to be higher in geriatric patients (5.3%) compared to the adult population (0.8%). No tardive dyskinesia was noted in the study in children [31]. Adults being treated with haloperidol had an annual risk of 5.4%. For second generation antipsychotics, the annual incidence of TD was as follows; olanzapine (0.0-0.5%), risperidone (0.6-0.7%, including 0.7% in a study using long-acting injectable risperidone), quetiapine (0.6-0.7%), amisulpride (1.5%), and ziprasidone (6.8%). In the studies that had significant number of geriatric patients, the annual risk for TD were 2.7% for seroquel and between 2.6%-13.4% for risperidone. Tollefsen, et al. [37] assessed patients receiving olanzapine and haloperidol for an average of 237 and 203 days, respectively. When the scores from the final two AIMS assessments for each group were analyzed, 1% of patients in the olanzapine group had met criteria for tardive dyskinesia, and 4.6% in the haloperidol group.

When tardive dyskinesia was first discovered, one common strategy to prevent the development of symptoms was to use antipsychotic medications intermittently. Such a regimen would result in less total antipsychotic exposure, which was thought to delay or prevent symptom development. However, such intermittent exposure may actually be counterproductive. Glenthoj [38] studied mice that were exposed to haloperidol for 6 months, either intermittently or continuously. It was noted that only the mice receiving intermittent doses, despite receiving a lower cumulative dose, developed TD symptoms following medication withdrawal. Harten, et al. [39] studied...
Serotonin modulates dopamine release in the striatum, a region of the brain involved in movement, and could play a role in treatment of movement disorders. Clozapine, an antipsychotic with minimal risk of EPS and tardive dyskinesia, is noted to have a favorable 5-hydroxytryptamine-2 (5HT2)/Dopamine 2 (D2) binding ratio, as well as strong 5-hydroxytryptamine-3 (5-HT3) antagonism [49]. Ondansetron, a selective 5HT3 antagonist, was administered at 12mg/day to patients in an open label study by Sirota, et al. [50] AIMS mean severity score was noted to decrease by 76%, in 13 out of 20 patients noting at least a 75% reduction in their AIMS scores. Also of note, this study showed a decrease in mean total positive and negative syndrome scale (PANSS) scores during treatment, from 95.2 at baseline to 69.6 after 12 weeks of treatment. This finding is in line with previous findings that ondansetron improves negative and cognitive symptoms in patients with schizophrenia [51].

Beta-blockers have been shown to decrease dopamine output from the striatum [52], and thus offer a novel pathway for the treatment of tardive dyskinesia. Hatcher-Martin, et al. [53] conducted a retrospective study of patients who had stopped neuroleptic treatment and had been initiated on propranolol (mean dose of 68.72mg/day). The study showed that 63.8% of patients improved with propranolol. Propranolol appears to be of added benefit in severe tardive dyskinesia. The odds of response to treatment were increased by 3.194 for every point increase in the severity of baseline tardive dyskinesia. The odds of response also increased by 1.09 for every month that the patient continued treatment, suggesting that symptom response to propranolol was gradual.

Clozapine, an atypical antipsychotic, not only has low rates of TD, but has been shown to benefit patients with TD who were previously on other antipsychotics. Spivak, et al. [54] studied patients who met criteria for TD and previously on another antipsychotic, switched to clozapine. At the conclusion of the 18-week trial, mean AIMS scores had improved by 74%, with significant improvement in most patients by week 5.

Benzodiazepines have been studied in the treatment of TD symptoms as well. Bhooopathi [55] reviewed 3 studies on the use of benzodiazepines in patients with TD, the conclusion of which showed little evidence of improvement in symptoms. However in our clinical experience, we have seen significant improvement in many cases.

A new drug valbenazine, a VMAT2 inhibitor, was the first drug to be approved for the treatment of tardive dyskinesia by the FDA in 2017. Hauser, et al. [56] studied patients receiving valbenazine at doses of 80mg daily, 40mg daily, and placebo for six weeks. At the study end, those who received 80mg/day had a mean decrease of 3.2 in their AIMS scores (effect size 0.90), while those receiving the lower 40mg/day or placebo saw a decrease of 1.9 and 0.1, respectively. Differences from baseline AIMS scores were significant as early as week 2. Significant response, defined as an AIMS score improvement of at least 50%, was seen in 40% of the group receiving 80mg/day, 23.8% of the 40mg/day group, and only 8.7% in the placebo group. In terms of safety, the most common side effects reported were somnolence (5.3% in the treatment group vs 3.9 in the placebo group), akathisia (3.3% vs 1.1%), and dry mouth (3.3% vs 1.3%). There were no significant changes in physical examination, electrocardiogram, or routine laboratory tests. No difference in suicidal ideation was noted between groups. Following this study, an extension study of 42 weeks was conducted. In this extension study, patients received daily doses of either 40mg or 80mg of valbenazine. At the end of this study, both groups of patients saw improvement in AIMS scores, with a decrease in mean AIMS scores of 3 and 4.8, respectively. Following this treatment period, there was
Tardive dyskinesia presents a complex challenge to clinicians, and potentially life altering complications to patients. Assessing the incidence of TD is difficult, as many patients are not aware of their symptoms, and often a patient’s symptoms may go unrecognized by their clinician. There is evidence that the syndrome is caused by upregulated postsynaptic dopamine receptors and oxidative neuronal damage, however a clear explanation of the pathology remains elusive. The risk of developing TD is greater in elderly patients, possibly due to increased sensitivity to dopamine blocking agents, or to naturally occurring chronic neuronal oxidative damage. Long term administration of antipsychotics is a key risk factor in the development of TD, however studies measuring lifetime antipsychotic use are dependent on accurate medication history for patients, which may be challenging. The expanded use of second generation antipsychotics has reduced the risk of tardive dyskinesia. A meta analysis of 11 studies showed the annual incidence of TD for patients being treated with haloperidol was 5.4% while the incidence was lower with atypical antipsychotics, including olanzapine (0-0.5%), risperidone (0.6-0.7%), quetiapine (0.6-0.7%), amisulpride (1.5%) [26-36]. It was noted that clozapine has a low risk for TD, however the incidence of other side effects such as agranulocytosis and the requirement for frequent laboratory monitoring limit clozapine use. While some natural products have been shown to offer some benefit, such as BCAA’s and Vitamin B6, studies involving these agents are typically of small sample sizes, and resulted in only modest benefit. It was also noted that while patients taking vitamin B6 saw improvement in symptoms greater than those receiving placebo, there was no correlation between serum levels and symptom improvement. Two recently approved medications, valbenazine and deuteretabenazine, have been shown to improve symptoms in clinical trials. More long term studies are needed to evaluate the long term risks and benefits of these medications.

Our review is limited because it is an unstructured one. As more long term studies are conducted, a more cohesive assessment of these medications can be made.

Conclusion
Tardive dyskinesia is a very disabling and grotesque disorder, which did not have any FDA approved treatment until recently. The newly approved medications like valbenazine and tetrabenazine offer hope to these patients who otherwise would have to live with this condition causing potential social and clinical morbidity.

Disclosures
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