Tardive Dyskinesia (TD) is in the borderzone of psychiatry and neurology. In absolutely simple terms, it is the neurological complication of psychotropic medications. Though it was first characterized in 1964, it remains under recognized with limited treatment options.

Estimates for the prevalence of TD varies widely, but one recent study projected that TD is present in nine percent of the population exposed to antipsychotics. Overall incidence has declined with decreasing use of typical (first generation) antipsychotics. However, the growing use of antipsychotics due increasing indications and off-label use may potentially increase the number of patients that can develop TD.

The Spectrum of Tardive Disorders
The DSM-5 defines TD as a medication induced disorder that can occur with exposure to dopamine receptor blockers. Generally, the duration of exposure that can result in TD is variable from a few months to a few years. Tardive movements typically involve oro-buccal-lingual movements but can also involve neck, trunk, and extremities. They can range greatly between subtle and severe, impacting daily activities and social function. In a majority of cases, TD is irreversible and persists after discontinuation of offending medication, however, cases of reversible TD have been reported after short-term exposure.

The Abnormal Involuntary Movement Scale (AIMS) is a standardized scale to quantify the severity of abnormal movements. A modified scale can be administered easily to measure and follow the severity of the TD movements longitudinally. However, the scale is infrequently administered in clinical settings by psychiatrists and neurologists. Tardive disorders range from the typical choreoform, athetoid, dystonic, to the less common tremor, tics, myoclonus, and akathisia, or a combination of these movements.

Pathology of Tardive Dyskinesia
Tardive movements are generally caused by dopamine receptor blockers, most commonly first generation and to a less degree second generation neuroleptic medications. Other common causative medications are metoclopramide and prochlorperazine. Uncommon causes of TD are TCAs, SSRIs, antiepileptic medications, lithium, and stimulants.

The generally accepted hypothesis is that a blockade of the dopaminergic system causes hypersensitivity of the D2 receptors. Other dopaminergic receptors’ (D3 & D4) hypersensitivity is also implicated in the development of TD. While relatives of patients with TD have been observed to also develop TD, no specific gene has been implicated in the development of TD. Known factors that increase risk of developing TD are age, duration of dopamine receptor blocker (DRB), history of drug or alcohol use. Women and African or Asian Americans also have a higher likelihood of TD.

Management of Tardive Dyskinesia
Currently there is no generally accepted TD management algorithm. Since TD is caused by dopamine blockage, initial treatment includes gradual removal of the dopamine blocking agents. Many times, DRB agents cannot be removed, as these agents are used for a variety of illnesses (such as...
gastrointestinal and psychiatric). Under these circumstances, treatment recommendations include agents such as quetiapine or clozapine. These therapies are less potent DRBs with adrenergic, histaminergic, and muscarinic mechanisms of action. Given these conditions, it is essential to discuss with the treating psychiatrist the potential need for cessation, dose reduction, or medication change.21

If the removal, reduction, or change of the DRB is not possible, consider if the TD is focal or non-focal in nature. Botulinum toxin can be useful in treating focal dyskinesia and is worth considering. Other reported cases of persistent non-focal TD have been treated with propranolol, amantadine, levateracitam, clonazepam, vitamin B6, and gingko biloba. Medication use is largely based on the experience of the prescriber and potential side effect profile. A number of medications have been utilized for non-focal TD, however few studies have demonstrated efficacy.12,13

Tetrabenazine (TBZ), a VMAT-2 inhibitor approved in the US for Huntington’s chorea since 2008, is a mainstay therapy for severe TD. It has been used “off-label” for management of moderate to severe TD in the absence of any approved therapy, as studies have demonstrated a 60 percent reduction in TD symptoms with use of 150mg dose per day.14 However, numerous factors limit broad utilization in TD; these include sedation, akathisia, depression, suicidal ideation, multiple daily doses, and expense.

Another VMAT-2 inhibitor that’s been investigated for the treatment of TD is deutetrabenazine (DTZ or Austedo, Teva), a novel twice-daily agent that was recently approved for Huntington’s disease. It contains deuterium, a non-toxic hydrogen molecule that changes the pharmacokinetic profile of TBZ. In the AIM-TD study, which compared placebo versus 12mg, 24mg, and 36mg doses of DTZ, the 24mg and 36mg dose showed a statistically significant reduction in the AIMS score vs placebo at 12 weeks. DTZ was also well tolerated without worsening depression or somnolence. DTZ is not currently approved for treatment of TD.15,16

The newest agent to enter the market is valbenzine (VBZ or Ingrezza, Neurocrine), a novel once-daily dosed VMAT-2 inhibitor specifically studied in TD population that was approved in April. It is the first and only approved agent specifically for the treatment of TD.17 VBZ was studied in patients with schizophrenia and bipolar disorders. It can be added on to the existing psychiatric medication without altering of psychotropic medications. According to Tremor 3 study data, 40mg and 80mg doses of VBZ reduced TD symptoms as per the AIMS, compared to a minimal placebo response over six weeks. There was a dose dependent response with the 80mg dose, providing a greater reduction of the AIMS score as compared to the 40mg dose. Open-label extension data show sustained reduction of AIMS score up to 48 weeks.18,19

The starting dose of VBZ is 40mg daily for one week, increasing to 80mg daily dose. Patients with CYP3A4 inhibitors or moderate hepatic impairment should stay on the 40mg dose of VBZ.20 Common side effects include somnolence and akathisia. Of note, VBZ did not worsen depression or exacerbate underlying psychiatric symptoms, nor did it increase suicidal ideation.

Conclusion
TD is a disabling iatrogenic movement disorder with limited treatment options. Historically, numerous medications have been tried with limited success or limited tolerability. The recent approval of Ingrezza and potential approval for Austedo will increase awareness of TD among physicians and patients. However, given the paucity of treatment options for so long, the availability of TD specific treatment poses new challenges about access, cost, and overcoming physician apathy. VBZ allows treatment of TD without altering the psychiatric medication and potentially worsening mental health. This changes the treatment options of TD from reduction, removal, or trial and error options, to a focused option that can be added on to existing psychiatric medications.

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