Hyperkinetic Movement Disorders

New treatments were approved in 2017 for tardive dyskinesia, Parkinson’s dyskinesia, and Huntington’s chorea.

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In movement disorders, 2017 was the year of hyperkinetic disease states. Historically, most movement disorder therapy was focused on treating the off time in Parkinson’s disease (PD) or nonmotor symptoms. Therapeutic options for hyperkinetic movement disorders have been limited. In 2017, 3 new agents were approved (Table). Of these, 2 are first-available treatments for disease states without previously approved therapies. Tardive dyskinesia (TD), Parkinson’s dyskinesia, and Huntington’s chorea were the focus.

Tardive Dyskinesia

TD was first characterized in 1964 as a side effect of exposure to neuroleptic drugs. Approximately 9% of persons exposed to dopamine receptor-blocking (DRB) agents will develop TD.1,2 Tardive disorders range from the typical choreiform, athetoid, and dystonic, to the less common tremor, tics, myoclonus, and akathisia or a combination of these movements. TD typically involves the oral-buccal-lingual region but can also involve the neck, trunk, extremities, and even pharyngeal and diaphragmatic muscles.3 TD is generated by blockade and hypersensitization of the D₂ class of dopamine receptors. Age, duration of DRB treatment, history of drug or alcohol abuse, female sex, and African or Asian ethnicity are all correlated with increased risk of developing TD.4 Attempts at lowering the dose of DRB agents in use may be either not possible or unsuccessful due to management of a patient’s underlying psychiatric issues. Anticholinergics do not effectively treat TD movements. Prior to 2017, only tetrabenazine was shown to reduce TD movements effectively, but titration to an effective dose was limited by dose-responsive side effects.5

Valbenazine

Valbenazine (Ingrezza; Neurocrine Biosciences, San Diego, CA) is a vesicle monoamine transporter-2 (VMAT-2) inhibitor. The putative mechanism of valbenazine is that VMAT-2 inhibition reduces the amount of dopamine packaged into a vesicle, making less dopamine available for release at the synapse. The subsequent reduction of dopamine in the synapse is thought to reduce stimulation of the hypersensitized D₂ receptors, thereby reducing abnormal involuntary movements. Valbenazine was the first agent approved by the Food and Drug Administration (FDA) for treating patients with TD.

Both the 40-mg dose and the 80-mg dose of valbenazine show a significant reduction in TD movements in patients as measured by the abnormal involuntary movements scale (AIMS) score and compared to TD movements in patients given a placebo. Patients given the 80-mg dose demonstrated a larger reduction in the AIMS score compared to those who were given a 40-mg dose.6 In a long-term open-label extension, treatment with valbenazine provided patients with a sustained reduction of TD symptoms for as many as 48 weeks. Both a 40-mg dose and an 80-mg dose showed a significant and sustained reduction of TD symptoms. During a washout phase, patients’ AIMS scores returned to their pretreatment baseline with the discontinuation of valbenazine.7 There is no evidence that valbenazine results in parkinsonism or worsening of underlying psychiatric conditions. The main side effect of valbenazine compared to placebo is sedation.8

| TABLE. MEDICATIONS FOR HYPERKINETIC DISORDERS |
|-----------------|-----------|-----------------|
| MEDICATION       | CLASS     | INDICATION      |
| Deutetrabenazine (Austedo) | VMAT-2 inhibitor | Huntington’s disease and tardive dyskinesia |
| Valbenazine (Ingrezza) | VMAT-2 inhibitor | Tardive dyskinesia |
| Extended-release amantadine (Gocovi) | NMDA antagonist | Parkinson’s disease dyskinesia |

Abbreviations: NMDA, N-methyl-D-aspartate; VMAT-2, vesicle monoamine transporter-2.
Deutetrabenazine

Deutetrabenazine (Austedo; Teva Neuroscience, Kansas City, MO) is a VMAT-2 inhibitor approved by the FDA for the treatment of patients with chorea associated with Huntington’s disease (HD) and for the treatment of adult patients with TD.9 The main difference between tetrabenazine and deutetrabenazine is deuteration, which replaces hydrogen at key points in the tetrabenazine molecule. Deuteration is naturally occurring molecule with an extra neutron compared to hydrogen. Replacing hydrogen atoms in tetrabenazine with deuterium atoms to make deutetrabenazine results in a significantly different pharmacokinetic profile between the 2 drugs. The deuterium-carbon bond is 6 to 10 times stronger than the hydrogen-carbon bond, making metabolic breakdown of the active metabolites take more time, thus extending the half-life of the therapeutic metabolites to approximately 10 hours.10 Dosing for deutetrabenazine can be titrated to effect and given twice daily.

In 2 placebo-controlled clinical trials and 1 long-term open-label study, deutetrabenazine was studied as a potential treatment for patients with PD. One placebo-controlled trial was a flexible-dose trial in which patients with PD were given a dose that was titrated and individualized or a placebo.11 In the other, patients were given 1 of 3 fixed doses of deutetrabenazine (12 mg, 24 mg, or 36 mg daily in divided doses) or placebo.12 Both studies measured changes in patients’ AIMS score compared to their baseline score for a period of 12 weeks. Patients who were given a titrated, individualized dose of deutetrabenazine had statistically significant improvements in their AIMS compared to patients who were given the placebo. The mean deutetrabenazine dose for treated persons was 38.8 mg per day at the end of the 6-week titration period and 38.3 mg per day at the end of the total 12 weeks of treatment.11 In the trial with fixed doses of deutetrabenazine, patients given 36 mg per day group had a significantly improved AIMS total score at 12 weeks compared to those who were given placebo (–3.3 points vs –1.4 points; P < .05). In an exploratory analysis, significant reduction in patients’ AIMS score was observed after 2 weeks of treatment.12 Dose reductions were required in 4% of patients taking deutetrabenazine due to adverse events vs 2% of patients taking placebo. Depression and suicidality were relatively stable.11,12 The benefit of deutetrabenazine is that it can be individualized and titrated to effect to minimize side effects in patients with HD and TD.

Parkinson’s Disease Dyskinesia

PD dyskinesia is frequently bothersome to patients, causing embarrassment in social situations. When severe, PD dyskinesia can lead to reduction in functional status and quality of life. Treatment options for PD dyskinesia are limited. Reducing the levodopa dose may help, but this is often at the cost of reduced control of PD symptoms. Another approach is to fractionate the levodopa dose resulting in more frequent but smaller doses or adding adjunct medication to provide steadier dopaminergic stimulation.1 Deep brain stimulation is effective in improving PD dyskinesia, although the inherent invasiveness and stringent criteria restrict its use to a smaller group of patients.13-15 The N-methyl-D-aspartate (NMDA) receptor is been implicated in the pathogenesis of dyskinesia. Amantadine, first introduced as an antiparkinsonian drug in the 1960s, has anti-dyskinetic effects attributed to NMDA receptor antagonism.16-18 Unfortunately, use of amantadine was limited by loss of antidyksinesia benefits several months into treatment due to tachyphylaxis. Balancing therapeutic dosing and adverse effects of amantadine was also challenging.19-20 Immediate-release amantadine received a level C recommendation by the American Academy of Neurology as being “possibly effective in reducing dyskinesia.”21

Extended-Release Amantadine

A new, extended-release formulation of amantadine (Gocovri; Adamas, Emeryville, CA) taken once daily at bedtime, is the first FDA-approved treatment for PD dyskinesia. The extended-release formulation provides a slow, steady release of the medication at night during sleep, and reaches the optimal serum level during the most active hours of the day. This in turn causes levels of the drug in the bloodstream that are approximately double that seen with immediate-release amantadine and reduces titration challenges for amantadine considerably.22-25

There were 2 clinical trials that provided the pivotal data for extended-release amantadine. The studies enrolled 126 and 77 participants, respectively; dyskinesia reduction was measured by the standardized Unified Dyskinesia Rating Scale (UDysRS). Patients treated with extended-release amantadine had a 37% to 46% reduction in dyskinesia compared to patients treated with placebo. The difference was sustained throughout the duration of the study.26-28 Extended-release amantadine was well-tolerated overall. The most commonly encountered adverse effects were hallucinations, orthostatic hypotension, and livedo reticularis, and all were generally classified as mild. Visual hallucinations were the most common reason for discontinuation of extended-release amantadine.

Extended-release amantadine was studied in an open-label long-term extension trial, and treated patients had sustained reduction of dyskinesia. The drug was well-tolerated with 80% of patients continuing to take the drug for up to 88 weeks. This trial included 61 patients treated with deep brain stimulation or patients who had previously experienced dyskinesia while taking immediate-release amantadine.24,27 Extended-release amantadine addresses a significant unmet need in management of dyskinesia and medical optimization of PD.

Huntington’s Disease

Huntington’s chorea is a motor manifestation of HD. Chorea describes involuntary movements involving various parts of the body that affect gait, daily function, and social interactions.28
Deutetrabenazine

The first HD trial studied the effects of 12 weeks of deutetrabenazine treatment on chorea in patients with HD who were not taking dopamine receptor blockers or modulating drugs. The total maximal chorea (TMC) score was reduced by 21% with return to baseline after 1 week of washout. Patients treated with deutetrabenazine also had improvements on the Patient Global Impression of Change, Clinician Global Impression of Change, Short Form—36 Physical Functioning subscale and the total motor score compared to patients taking a placebo. The discontinuation rate was only 2% for both the group taking deutetrabenazine and the group taking placebo. Suicidal ideation was present in 2% of patients taking deutetrabenazine compared to none who were taking placebo. Depression occurred in 4% of patients taking deutetrabenazine and in 7% of those taking placebo. These data suggest that deutetrabenazine can treat chorea in HD, is more tolerable than previous treatments, and may transform care for patients with HD.

Summary

Many of those living with TD, PD dyskinesia, or HD have limited therapeutic options. The availability of these medications will reduce functional impairment of patients with these conditions. All 3 medications are novel formulations of pre-existing medications or novel medications designed to provide easier dosing, better efficacy, and tolerability than their predecessors. The medications were studied in the specific disease state for which each was approved, including disease-specific safety measurements. Hopefully the momentum of new therapeutics will provide treatment options for other hyperkinetic movement disorders such as generalized dystonia, tic disorders, and Tourette’s syndrome.

Disclosures

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