Lack of Support for the Use of VMAT-2 Inhibitors for the Treatment of Tics in Tourette Syndrome

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In the current issue of JAMA Network Open, Coffey et al report the results of Alternatives for Reducing Tics in Tourette syndrome (ARTISTS 2), a phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study of the reversible vesicular monoamine transporter 2 (VMAT-2) inhibitor deutetrabenazine for the treatment of Tourette syndrome. A total of 158 children and adolescents were enrolled across 52 sites in 10 countries. Participants were randomized to high-dose deutetrabenazine (up to 48 mg per day, adjusting for weight and cytochrome P450 2D6 status; n = 52), low-dose deutetrabenazine (up to 36 mg per day; n = 54), or placebo (n = 52). Clinically significant depression, a history of suicidal ideation within 2 years, or a prior suicidal attempt were criteria for study exclusion. The primary efficacy endpoint was change from baseline to week 8 in the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) for high-dose deutetrabenazine. Although a numeric improvement in the YGTSS-TTS favoring deutetrabenazine compared with placebo was observed at the end of the 4-week titration period, the difference was not significant at week 8 (least-squares mean difference, -0.8 points; 95% CI, -3.9 to 2.3 points; P = .60). Also, there were no significant differences between groups for key secondary end points. Depression was recorded in 4 participants (8%) in the high-dose group, 1 participant (2%) in the low-dose group, and in 0 participants in the placebo group. One participant in the high-dose group and 1 in the placebo group reported suicidal ideation during the study period. Among the more common treatment-emergent adverse events (TEAEs), somnolence was reported in 8 participants (15%) and fatigue in 5 participants (10%) in the high-dose group vs 1 participant (2%) and 0 participants, respectively, in the placebo group. Body weight increased by a mean of 2.2 kg in participants in the high-dose deutetrabenazine group compared with those in the placebo group.

Neuroleptic drugs are well accepted to be the most efficacious medications to treat moderate-to-severe tics in those with Tourette syndrome and other tic disorders. From a retrospective medical record review, Billnitzer and Jankovic reported that neuroleptic drugs provided moderate to marked benefit in 80.5% of 268 patients with Tourette syndrome. Neuroleptic drugs carry the risks of hyperglycemic metabolic complications, parkinsonism, and QTC prolongation. Although these and most other side effects can be regularly managed by lowering medication dosages or by switching to other neuroleptic medications, these agents carry appreciable risk for inducing tardive dyskinesia. Across 12 trials lasting at least 1 year (mean participant age, 39.7 years; n = 28 051; followed for 463 925 person-years), the annualized tardive dyskinesia incidence in the psychiatric population was 3.9% for second-generation and 5.5% for first-generation antipsychotic drugs. However, in distinction, in a 2011 literature review, only 20 potential cases of tardive dyskinesia in patients with Tourette syndrome were identified. Moreover, in only 2 of these cases, the reviewing authors considered there to be compelling evidence of tardive dyskinesia with persistence of symptoms upon neuroleptic withdrawal. Since this literature review, there do not appear to be any additional reported cases, including no identified cases in 2 large retrospective chart reviews totaling 789 patients with Tourette syndrome.

Tetrabenazine was the first of 3 developed VMAT2 inhibitors, which nonselectively deplete monoamines, including dopamine, serotonin, norepinephrine, and histamine, from presynaptic nerve terminals. Tetrabenazine was approved by the US Food and Drug Administration in 2008 to treat chorea in adults with Huntington disease. More recently, deutetrabenazine was approved for
the treatment of adults with tardive dyskinesia or with chorea associated with Huntington disease, and valbenazine was approved more specifically to treat adults with tardive dyskinesia. The newer agents are considered equally efficacious to tetrabenazine but are suggested to be better tolerated. Also, deutetrapobenazine is more conveniently dosed twice daily and valbenazine at once daily, compared with the required dosing for tetrabenazine (>50 mg at 3 times per day). Although tardive dyskinesia has not been reported with VMAT-2 inhibitor use, notably, these agents are contraindicated in individuals with inadequately treated depression or suicidal ideation and carry black box warnings of these risks.

The ARTISTS 2 fixed-dose study followed the ARTISTS 1 flexible-dose titration study of 119 participants assessed for a total of 12 weeks, including an initial titration period, which also failed to demonstrate efficacy. Valbenazine additionally failed to demonstrate efficacy in 2 phase 2, randomized, double-blind, placebo-controlled, fixed-dose studies of the treatment of Tourette syndrome: 1 in 120 adults (T-Forward) and 1 in adolescents and children (T-Force GREEN). Furthermore, in the valbenazine studies, TEAEs were particularly frequent. For instance, in T-Forward (124 adults), 95.2% of the 80 mg valbenazine group and 73.8% of the 40 mg valbenazine group vs 52.5% of the placebo group reported TEAEs, most commonly somnolence, fatigue, akathisia, and headache.

Negative clinical trials, including the somewhat surprising results of the trials of VMAT-2 inhibitors for Tourette syndrome, demand scrutiny for potential explanations for their failures. To my knowledge, the deutetrapobenazine and valbenazine study investigators themselves have not offered cogent explanations for their negative findings. For one, the studies appeared to have been adequately powered for the similar YGTSS-TTS primary efficacy end points. The maximum study dosages of deutetrapobenazine and valbenazine reached the recommendations of the US Food and Drug Administration, and the extent of TEAEs, particularly in higher dosing groups, supports that these dosages were adequate. Although Coffey et al bring positive light to the improvement in YGTSS-TTS favoring deutetrapobenazine compared with placebo at the end of the 4-week titration period, this result is seemingly best explained by a placebo effect. Considering the frequency of TEAEs, a high proportion of the participants who were treated with a VMAT-2 drug were surely unblinded to the fact that they were receiving a drug and not a placebo; therefore, they would have been more likely to have perceived a benefit early on. The lack of benefits in primary and secondary measures at 8 weeks should support this impression.

In summary, the available results from several large controlled clinical trials unfortunately do not suggest effectiveness of VMAT-2 inhibitors for the treatment of tics in patients with Tourette syndrome. Furthermore, it is not evident from these studies that the side effect profile of the VMAT-2 inhibitors is clearly favorable over that of neuroleptic drugs, especially in that neuroleptic drugs can be prescribed in the presence of coexistent depression or suicidal ideation, which are not uncommon in patients with Tourette syndrome. Considering the demonstrated efficacy of neuroleptic medications for Tourette syndrome and the paucity of reports of tardive dyskinesia in patients with Tourette syndrome, neuroleptic drugs arguably should be considered a mainstay for treating moderate-to-severe Tourette syndrome. For milder cases, in particular with coexistent ADHD, α-agonists can be prescribed. Additional evidence from noncontrolled studies suggest efficacy from topiramate and from tetrahydrocannabinol, either as dronabinol or, where legal, as medicinal marijuana. Last, Comprehensive Behavioral Intervention for Tics, a nonmedication alternative for the management of tics, should be recommended for all patients where available. Unfortunately, there is a paucity of trained therapists in this type of therapy, and insurance coverage can be difficult to obtain. Thus, a worthwhile goal for Tourette societies would be to prioritize means to train more therapists in Comprehensive Behavioral Intervention for Tics.
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REFERENCES