Evidence to Practice

Effectiveness and Value of 2 Novel Treatments for Tardive Dyskinesia

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Source of Review

The Institute for Clinical and Economic Review (ICER) developed an evidence report, including a systematic review and economic evaluation, to support a meeting of the New England Comparative Effectiveness Public Advisory Council on December 5, 2017, examining 2 new vesicular monoamine transporter 2 (VMAT2) inhibitors for tardive dyskinesia (TD).[1]

Background

Tardive dyskinesia is a repetitive, involuntary movement disorder caused by prolonged use of dopamine receptor–blocking agents (DRBAs), most commonly antipsychotic drugs.[2,3] First described in the 1950s with the introduction of antipsychotic drugs such as haloperidol,[3] the prevalence rate of TD is estimated to range from 20% to 50% of patients taking antipsychotic agents, with older age, female sex, and longer duration of treatment being risk factors. Despite approval of newer antipsychotic drugs, such as clozapine, intended to decrease abnormal movements, rates of TD are reported at 3% to 5% per year with newer and older drugs, respectively.[4] Symptoms of TD include movements of the head, neck, limbs, and trunk, such as facial grimacing, lip smacking, neck posturing, and shoulder shrugging; vary from mild to severe; and can cause physical and psychological impairment, social isolation, and work-related disability. Discontinuing use of the offending agent may not reverse and may temporarily exacerbate TD symptoms and may not be possible for patients without alternatives to treat the underlying condition. Although many treatments have been tried, there has been limited evidence to guide patients and clinicians.[5] This changed in 2017 with the first 2 US Food and Drug Administration (FDA)-approved drugs for TD, valbenazine and deutetrabenazine.

Objectives

The Institute for Clinical and Economic Review assessed the comparative clinical effectiveness, cost-effectiveness, and potential budget impact of VMAT2 inhibitors, valbenazine, deutetrabenazine, and tetrabenazine, for adults with symptoms of TD for at least 3 months and a history of use of DRBAs. Tetrabenazine, approved by the FDA in 2008 for Huntington disease, is sometimes used off-label for the treatment of TD. Because no randomized trials of tetrabenazine in patients with TD were identified, this drug is not discussed further.

Summary of Findings

The ICER review identified 2 6-week placebo-controlled randomized clinical trials of valbenazine (102 and 234 patients, respectively), and 2 12-week placebo-controlled, randomized clinical trials of deutetrabenazine (117 and 293 patients, respectively).[1] The patients included had moderate-to-severe DRBA-induced TD for at least 3 months. The primary outcome in these trials was the Abnormal Involuntary Movement Scale (AIMS), which measures the severity of TD symptoms (range, 0-28) and was assessed by blinded expert videotape review. The AIMS change thought to represent a clinically important difference is uncertain but may be approximately 2 to 3.[6] Patient-reported global impression of change was a secondary outcome reflecting overall improvement (range, 1 ["very much improved"] to 7 ["very much worse"]). The trials were of good or fair quality and of relatively short duration. No trials have compared VMAT2 inhibitors with each other.

Phase 3 trial results are presented in the **Table**. Patients receiving 80 mg and 40 mg valbenazine showed statistically significant improvements in AIMS score, compared with placebo (mean [SE] change, −3.2 [0.4] and −1.9 [0.4], respectively, vs −0.1 [0.4]; $P \leq .002$).[7] Similarly, patients receiving 36 mg and 24 mg of deutetrabenazine showed significantly greater improvement in AIMS score, compared with placebo (mean [SE] change, −3.3 [0.42] and −3.2 [0.45], respectively, vs −1.4 [0.41]; $P \leq .003$).[8] These changes are considered to be clinically meaningful. A greater percentage of patients were also classified as responders (achieved ≥50% reduction in AIMS score) relative to those receiving placebo (Table). Although there were better patient-reported improvement scores in the phase 2 trial of valbenazine,[1] the phase 3 trials did not

Table. Outcomes From Valbenazine and Deutetrabenazine Phase 3 Trials

Trial	AIMS Score[a] Baseline, Mean	AIMS Score[a] Change, Mean (SE)	*P* Value	≥50% AIMS Reduction, No. (%)	*P* Value	PGIC[b] Responders, %
Valbenazine						
80 mg/d	10.4	−3.2 (0.4)	<.001	31 (40)	<.001	24
40 mg/d	9.7	−1.9 (0.4)	.002	17 (24)	.02	32
Placebo	9.9	−0.1 (0.4)		6 (9)		42
Deutetrabenazine						
36 mg/d	10.1	−3.3 (0.42)	.001	18 (33)	.007	40
24 mg/d	9.4	−3.2 (0.45)	.003	17 (35)	.005	45
Placebo	9.5	−1.4 (0.41)		7 (12)		31

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; PGIC, patient global impression of change.

[a] Range, 0 to 28; higher score reflects worse symptoms.

[b] Range, 1, "very much improved" to 7, "very much worse," with patients reporting 1 or 2 classified as PGIC responders.

demonstrate significant differences (Table). Adverse effects of valbenazine and deutetrabenazine included drowsiness, fatigue, headache, and akathisia (feeling of restlessness/inability to remain still). Discontinuation rates of valbenazine (at 6 weeks) and deutetrabenazine (at 12 weeks) compared with placebo were 6% vs 5%, and 4% vs 3%, respectively. Rates of depression or suicidal ideation for either drug were similar to placebo.

The Institute for Clinical and Economic Review conducted a lifetime cost-effectiveness analysis using simulation models of valbenazine and deutetrabenazine for treating the symptoms of TD, compared with placebo. Patients with TD initiated a medication trial resulting in either response and continuation or nonresponse and discontinuation, after which they entered the model and cycled through 4 health states: (1) improved TD in which patients continued treatment, (2) moderate-to-severe TD due to lack of treatment efficacy or stopping due to adverse effects, (3) improved TD despite discontinuing therapy, and (4) death. The primary outcomes of the model included discounted total payer costs, quality-adjusted life years (QALYs) gained, and incremental cost-effectiveness ratios, using a health care system perspective over a lifetime horizon. The QALYs were modeled using published utility estimates for moderate-to-severe TD vs no TD. A full utility benefit was applied to the percentage of responders with at least a 50% reduction in AIMS score, representing a bias in favor of the therapies. Uncertainty was addressed through sensitivity analyses of key model inputs. Valbenazine and deutetrabenazine both resulted in increased costs and increased QALYs, compared with placebo. The incremental cost-effectiveness ratios over a lifetime horizon were approximately $752 000 and $1.101 million per QALY for valbenazine and deutetrabenazine, respectively. Varying key model parameters within reasonable ranges did not result in either drug showing cost-effectiveness ratios below the upper limit of the generally accepted ratio of $150 000 per QALY. In addition, probabilistic sensitivity analyses showed low likelihood of either drug approaching this cost-effectiveness threshold.

Cost inputs for calculating potential budget impact were derived from our cost-effectiveness model. Potential budget impact was defined as the total 5-year cost of introducing either of the VMAT2 inhibitors into standard clinical practice, including net drug prices, adverse event costs, and any medical cost offsets. We estimated a prevalent population of 360 000 adults with moderate-to-severe TD due to antipsychotic drugs. Across the 5-year time frame, the total potential budget impact for this population is approximately $22.5 billion, or $4.5 billion per year.

Limitations on the Evidence

In the clinical trials, objective clinical improvement assessed by expert reviewers was not reflected in subjective patient-reported outcomes. The reason for this is unclear, but if some patients are less aware of their TD symptoms, such as those with psychotic disorders, they may be less able to assess the impact of treatment. The clinical trials of these agents were of short duration, but patients may have to take these drugs indefinitely. Although valbenazine and deutetrabenazine seem to be well tolerated, their long-term effectiveness and safety compared with placebo or other treatments remain to be determined. Future studies should evaluate predictors of long-term response and functional improvement such as patient age, symptom duration, and continued use of the antipsychotic drug that causes TD symptoms, and pragmatic trials should include patients with comorbid conditions and other mental disorders encountered in routine clinical practice. Limitations of the cost-effectiveness model include the following: current TD severity measures may not reflect disease burden on overall quality of life; a lack of long-term data on discontinuation of TD medication due to adverse events; and lack of data on nondrug costs of TD and subpopulations that may differ from the typical TD patient.

Policy Discussions

The evidence report indicated that there was adequate evidence of a similar positive net health benefit based on the primary outcome from treating patients with either valbenazine or deutetrabenazine. However, given incremental cost-effectiveness ratios that far exceed commonly used thresholds, the report noted that the high cost of lifelong treatment with valbenazine and deutetrabenazine may be unsustainable, leading insurance companies to be reluctant to cover these medications. Additionally, high patient copayments for these specialty medications may limit their use in practice, even if clinical benefit is seen. The potential budget impact of $4.5 billion per year is far in excess of ICER's estimated threshold for novel therapies, which is anchored to US economic growth indicators.[9] Nevertheless, there was substantial interest from patients and clinicians in using these medications given that TD is a debilitating disease with limited treatment options.

Conclusions

For patients with moderate-to-severe TD symptoms due to use of DRBAs that persist after withdrawal of the offending agent or for those without alternative treatment options for the underlying condition, valbenazine and deutetrabenazine demonstrated short-term, modest objective improvement but inconsistent subjective patient-reported improvement. At current pricing, their cost-effectiveness and potential budget impact far exceed common thresholds, and because the clinical trials were short-term, many questions remain about long-term benefits and harms. Thus, despite being approved by the FDA, there is little rationale to prescribe these drugs for the treatment of tardive dyskinesia.

ARTICLE INFORMATION

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