Cost-effectiveness of valbenazine compared with deutetrabenazine for the treatment of tardive dyskinesia

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ABSTRACT

Aims: To evaluate clinical and economic outcomes associated with valbenazine compared with deutetrabenazine in patients with tardive dyskinesia (TD) using a model that accounts for multiple dimensions of patient health status.

Materials and methods: A discretely integrated condition event model was developed to evaluate the cost-effectiveness of treatment with valbenazine and deutetrabenazine in a synthetic cohort of 1,000 patients with TD who were receiving antipsychotic medication to treat an underlying psychiatric disorder. Clinical inputs were derived from relevant clinical trials or from publicly available sources. Patients were assessed over 1 year using ≥50% improvement from baseline in Abnormal Involuntary Movement Scale (AIMS) total score as the primary definition of response. Response at 1 year using Clinical Global Impression of Change (CGIC) score ≤2 was also assessed. Health outcomes included quality-adjusted life years (QALYs), life years, proportion responding to treatment at 1 year, and number of psychiatric relapses.

Results: Regardless of the definition used for response, patients treated with valbenazine were more likely to have responded to treatment at 1 year, lived longer, and accrued more QALYs than patients who received deutetrabenazine. Using the AIMS response criterion, the incremental cost-effectiveness ratio was $9,951/QALY for valbenazine compared with deutetrabenazine. By comparison, using the CGIC response criterion valbenazine dominated deutetrabenazine with valbenazine-treated patients accumulating more QALYs (3.4 vs 3.3 years) and incurring lower lifetime costs ($252,311 vs $283,208) than deutetrabenazine-treated patients.

Limitations: There are no head-to-head trials of valbenazine and deutetrabenazine, so probabilities of response used in the model were calculated based on an indirect treatment comparison of results from individual trials with one drug or the other, using only those metrics reported across trials.

Conclusions: In patients with TD, treatment with valbenazine is highly cost-effective compared with deutetrabenazine.

Introduction

Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to dopamine receptor-blocking agents (DRBAs), most commonly antipsychotics1–3, which are used by an estimated 86–90% of patients with schizophrenia and 35% of patients with affective disorders4. Characterized by repetitive, abnormal movements of the face (lip-smacking, grimacing, tongue thrusting), trunk (shoulder shrugging, pelvic thrusting), and/or extremities (foot-tapping, piano-playing finger movements), TD can lead to physical and psychological impairments, social isolation, work-related disability, and decreased quality-of-life5,6. As a consequence, some patients may be less compliant with their antipsychotic medications than they would otherwise be without TD, leading to relapse of the underlying psychiatric disorders and increased morbidity and mortality7,8. It is generally accepted that the goal of treatment with antipsychotic agents is to keep patients well in the community, and that its achievement requires clinicians to individually optimize treatment, balancing considerations of efficacy, adverse effects, and cost-effectiveness9–10.

Lifetime TD prevalence has been estimated to range from 20–50% among patients with long-term exposure to DRBAs, with increased prevalence associated with older age, female gender, smoking, and longer duration and type of antipsychotic treatment11–13. The annual incidence of new TD has been reported to be approximately 5% with older antipsychotic agents and 3% with second generation or atypical...
antipsychotics. Although the newer agents are associated with a lower incidence of TD than older antipsychotics, the newer medications are being used to treat a broader range of psychiatric illnesses beyond schizophrenia and schizoaffective disorder, including bipolar disorder, major depression, post-traumatic stress disorder, personality disorders, agitation associated with dementia, and insomnia.

Since the 1950s, when TD was first described, a number of drugs have been studied for potential effectiveness or used off-label for the treatment of TD, but none provided clear evidence of clinical benefit. In 2017, however, the US Food and Drug Administration (FDA) approved valbenazine, a novel and highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor, for the treatment of TD in adults; FDA approval of a second VMAT2 inhibitor, deutetrabenazine, followed later that year. More recently, the American Psychiatric Association (APA) released its evidence-based practice guideline for treatment of patients with schizophrenia, that includes the recommendation (based on results from randomized clinical trials) that patients with moderate-to-severe TD be treated with a VMAT2.

Studies that evaluated the efficacy of once-daily valbenazine included two double-blind, placebo-controlled trials, each of 6-weeks’ treatment duration, in patients 18–85 years of age with schizophrenia, schizoaffective disorder, or mood disorder – KINET 2 (25–75 mg/day) and KINET 3 (40 or 80 mg/day) — and KINET 3 extension in which patients received up to 48 weeks of valbenazine (40 or 80 mg/day) at blinded doses. KINET 4 was a long-term trial in which patients 18–85 years of age with schizophrenia, schizoaffective disorder, or mood disorder received open-label treatment with valbenazine (40 or 80 mg/day) for up to 48 weeks. The efficacy of deutetrabenazine has been established in two randomized, double-blind, placebo-controlled trials, each of 12-weeks’ treatment duration, AIM-TD (12–48 mg/day, divided doses) and ARM-TD (12–36 mg/day), in patients 18–80 years of age with schizophrenia, schizoaffective disorder, or mood disorder, and a long-term, open-label extension study (12–48 mg/day for up to 106 weeks). In the 6-week trials with valbenazine and the 12-week trials with deutetrabenazine, the primary efficacy outcome was the change from baseline to endpoint on the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1–7); both valbenazine and deutetrabenazine were observed to be statistically significantly superior compared with placebo, and to provide clinically meaningful benefits to patients. A random effects meta-analysis of efficacy and safety data from randomized, placebo-controlled trials of the VMAT2 inhibitors in patients with TD confirmed that both valbenazine and deutetrabenazine significantly outperformed placebo in reduction in AIMS total score and AIMS response rate, with no increased risk of adverse events (AEs) for the VMAT2 inhibitors as a class or with deutetrabenazine or valbenazine individually.

An indirect treatment comparison (ITC) of valbenazine and deutetrabenazine using the Bucher method showed that valbenazine 80 mg/day at 6 weeks was statistically superior to deutetrabenazine 36 mg/day at 8 weeks in AIMS total score improvement, while valbenazine 40 mg/day was statistically similar to all doses of deutetrabenazine at all time points. There were no significant differences between valbenazine and deutetrabenazine in treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to TEAEs; incidences of SAEs and treatment discontinuations were low across the studies evaluated.

An initial cost-effectiveness evaluation published shortly after FDA approval of valbenazine and deutetrabenazine (but before publication of the APA practice guideline) suggested that the clinical benefits associated with the VMAT2 inhibitors would result in increased quality-adjusted life expectancy over no treatment for TD, but that estimated lifetime cost-effectiveness of these agents would exceed commonly-cited thresholds. That analysis, however, employed a semi-Markov model, considering only four possible health states for treated patients (improved TD where patients remained on treatment, moderate-to-severe TD where patients had discontinued treatment, discontinued treatment with improved TD, and death). Additionally, it defined lifetime responders/non-responders based on whether or not patients achieved ≥50% improvement in AIMS total score using clinical inputs only from short-term trials. Moreover, the previous model assumed that treatment of TD would have no effect on clinical outcomes or the costs of treating the underlying psychiatric disorder, whereas more recent research has suggested that improvement in TD is associated with improvement in underlying psychiatric status. Given the recent APA practice guidance that recommends VMAT2 inhibitors as the only Level 1 evidence-based therapy for TD, the current study was undertaken to evaluate clinical and economic outcomes associated with valbenazine compared with deutetrabenazine in patients with TD. Further, to address some of the inherent limitations of the previous analysis we designed a model that (1) recognizes continued improvement in symptoms may occur with longer-term therapy, as measured both by the AIMS and other metrics that assess global improvements; (2) evaluates the impact of TD on management of an underlying psychiatric disorder; (3) accounts for differences in overall survival according to psychiatric disorder and presence of TD symptoms; and (4) uses a utility decrement associated with TD derived from quality-of-life assessments in a cohort of real-world patients being treated with antipsychotics.

Materials and methods

Model overview

A discretely integrated condition event (DICE) model was developed using Microsoft Excel (Microsoft Corp., Redmond, WA) to evaluate clinical and economic outcomes associated with valbenazine and deutetrabenazine treatment in a synthetic cohort of 1,000 patients with TD. The DICE model was used because of its ability to incorporate aspects of both state-transition (Markov) and discrete event simulation (of patient-level data) models. The model conceptualizes “conditions” that reflect aspects of the model or patient
attributes that persist and "events" that reflect points in time when conditions may change (Figure 1).

**Patient population and perspective**

The patient population is a synthetic cohort of 1,000 patients with demographic and clinical characteristics derived from population statistics in the KINECT 3 trial. Means, standard deviations, and correlations between the KINECT 3 baseline characteristics of age, gender, AIMS score, proportion using antipsychotic medications, proportion with schizophrenia/schizoaffective disorder, proportion with bipolar disorder, proportion with major depressive disorder, and proportion with anxiety were used to generate the synthetic cohort (Supplementary Table S1). Patients could have only one underlying psychiatric condition: schizophrenia, bipolar disorder, or major depressive disorder.

The model is analyzed from a US third-party payer perspective over a lifetime horizon. Only direct costs such as drug acquisition costs, disease management costs, and relapse treatment costs are included in the analysis.

**Model inputs**

Clinical inputs, which were taken primarily from published literature that included TD treatment guidelines, clinical studies, resource use and cost studies, and health technology assessments, are shown in Table 1. Average daily TD medication doses as well as response data, as measured by the AIMS and Clinical Global Impression of Change (CGIC), were derived from an indirect treatment comparison of the VMAT2 inhibitors, based on relevant clinical trials with valbenazine and deutetrabenazine. Weibull survival functions for the time to antipsychotic treatment discontinuation were derived from published survival curves for discontinuation in schizophrenia and bipolar disorder. The hazard ratio for antipsychotic discontinuation among patients responding to TD treatment was calculated from reported persistence with antipsychotic treatment in patients following initiation of valbenazine. Annual relapse risk by antipsychotic medication usage was calculated from reported 12-month relative risks of relapse in schizophrenia and bipolar disorder. Relapse sequelae—likelihood of hospitalization, length of hospital stay, and duration of outpatient treatment—were derived from cost and cost-effectiveness studies of antipsychotics in the treatment of schizophrenia.

The mean utilities for the baseline psychiatric conditions of schizophrenia, bipolar disorder, and major depressive disorder were 0.83, 0.80, and 0.80, respectively. A utility decrement of 0.121 was applied to reflect TD, based on post hoc analyses of a recently published study that used validated health-related quality-of-life assessments (EuroQoL 5-Dimension 5-Level questionnaire) to assess the disutility of TD in a real-world cohort of patients taking antipsychotics who reported "a lot" of impact from TD symptoms, and thus would be most likely to seek treatment. Decrement of 0.081, 0.118, and 0.118 were applied to reflect relapses in schizophrenia, bipolar disorder, and major depressive disorder, respectively. Mortality was modeled using Gompertz parameters derived from survival curves for the general population that were adjusted to reflect condition-specific
hazard ratios in patients with the underlying psychiatric disorders of schizophrenia, bipolar disorder, and major depression. The hazard ratio for mortality used for patients with TD was 1.9047.

Cost inputs (in 2017 US dollars) are shown in Table 2, and include daily medication costs, annual costs to manage TD and the underlying psychiatric disorders, and costs associated with psychiatric disorder relapse. To calculate average TD medication costs, a 27% industry-wide average branded-drug discount was applied to the Wholesale Acquisition Cost of valbenazine and deutetrabenazine. Costs, quality-adjusted life years (QALYs), and life years were discounted at an annual rate of 3%.

Key assumptions

All patients begin the model simulation with TD and doses of their antipsychotic medications optimized. During the first 24 weeks of treatment with valbenazine or deutetrabenazine, patients are assessed every 8 weeks for response, defined in the base case as ≥50% improvement in AIMS total score among patients with any psychiatric condition at baseline. Each response assessment is independent of the others; patients who respond at a given assessment are assumed to suffer no disutility due to TD until at least the next assessment. A final response assessment is conducted at week 48, at which time responders continue TD treatment until death and non-responders discontinue TD treatment. Patients who discontinue one TD treatment will not attempt another.

Alternative scenarios were evaluated using the same assumptions, in which CGIC score ≤2 (rating of “much...
improved” or “very much improved”) was used as the definition of response among patients with any psychiatric condition at baseline, and ≥50% improvement in AIMS total score was used as the response criterion among patient subgroups defined by specific psychiatric diagnosis, use of antipsychotic medication, and employment status at baseline.

### Health and cost outcomes

The primary health outcomes to be assessed were QALYs, life years, proportion of patients responding to TD treatment at 1 year, and number of relapses. Cost outcomes included lifetime TD medication costs, antipsychotic medication costs, costs associated with management of the underlying psychiatric disorder, and costs associated with psychiatric disorder relapse. Incremental cost-effectiveness ratios (ICERs), defined as the differences in discounted QALYs between valbenazine and deutetrabenazine divided by the differences in discounted costs between those treatments, are also calculated.

### Sensitivity analyses

Deterministic sensitivity analyses (DSA) assessed the impact of varying drug acquisition costs, likelihood of response, risk of relapse, treatment discontinuation during and after the first year, the ITC odds ratio, and hazard ratio for TD mortality by ±20%. One hundred probabilistic sensitivity analysis (PSA) trials assessed the impact of simultaneously varying many of the model inputs across their probability distributions (Supplementary Table S2) on the likelihood that each intervention was cost-effective at willingness-to-pay (WTP) thresholds ranging from $0 to $300,000 per QALY (i.e. the proportion of PSA trials in which the net monetary benefit of each intervention exceeded the WTP thresholds). Two scenario analyses, one stratified by age (<55 and ≥55 years) and the other assuming no effect of response on antipsychotic treatment discontinuation, were conducted to further assess the robustness of the results to underlying assumptions and to obtain results for potentially important cohorts of patients.

### Results

#### Base case analysis

The lifetime health and total cost outcomes for patients with TD who received treatment with a VMAT2 inhibitor are shown in Table 3. In the base case analysis (i.e. ≥50% improvement from baseline in AIMS total score among patients with any underlying psychiatric condition at baseline), patients who were treated with valbenazine experienced reduced TD severity, lived longer, and accrued more QALYs compared with patients who received deutetrabenazine.

Regardless of the response criterion or subgroup analyzed, a larger proportion of patients receiving valbenazine responded to treatment at 1 year than patients receiving deutetrabenazine, resulting in an increased likelihood of continuing treatment, increased life expectancy, fewer psychiatric relapses, and increased accumulation of QALYs. In addition to being more effective, valbenazine was associated with lower total costs (i.e. “dominated” deutetrabenazine) in the analysis of patients with any psychiatric disorder at baseline when response was measured by CGIC score ≤2. In all other scenarios, the ICERs for valbenazine ranged from $9,951 (base case) to $18,888 (analysis of patients without a psychiatric condition at baseline). After 1 year of treatment, the estimated response rates for both valbenazine and deutetrabenazine were higher using the CGIC criterion of score <2 (80% and 65%, respectively) than with the AIMS criterion of ≥50% total score improvement (48% and 29%, respectively).

Drug acquisition costs were the largest contributor to total costs (Table 4) and were higher for valbenazine in all scenarios (except when response was measured using CGIC score), reflecting the higher response rates for valbenazine at 1 year resulting in increased costs as more valbenazine-treated patients continued treatment.

### Sensitivity analyses

In the base case analysis using ≥50% improvement in AIMS total score as the response criterion the model was most sensitive to the ITC odds ratio (incremental lifetime
Table 3. Lifetime health and cost outcomes of tardive dyskinesia treatment with valbenazine and deutetrabenazine.

| Modeled scenario | QALYs (discounted) | LYS (discounted) | Responders at Year 1, % (undiscounted) | Relapses, n (undiscounted) | Total discounted costs (2017 US $) | Incremental costs/ QALY (discounted) |
|------------------|---------------------|------------------|----------------------------------------|---------------------------|----------------------------------|-------------------------------------|
| Deutetrabenazine | 3.113               | 4.239            | 29                                     | 3.006                     | $191,618                         | $9951                               |
| Valbenazine      | 3.231               | 4.266            | 48                                     | 2.958                     | $192,794                         |                                     |
| Response criterion: >50% improvement in AIMS score in patients with any psychiatric disorder at baseline (base case) | | | | | | |
| Deutetrabenazine | 3.162               | 4.274            | 29                                     | 2.714                     | $188,291                         |                                     |
| Valbenazine      | 3.280               | 4.299            | 48                                     | 2.657                     | $189,962                         | $14,109                             |
| Response criterion: >50% improvement in AIMS score in patients with any psychiatric disorder at baseline | | | | | | |
| Deutetrabenazine | 3.131               | 4.355            | 29                                     | 3.553                     | $185,630                         |                                     |
| Valbenazine      | 3.250               | 4.378            | 49                                     | 3.501                     | $187,510                         | $15,866                             |
| Response criterion: >50% improvement in AIMS score in patients with major depressive disorder at baseline | | | | | | |
| Deutetrabenazine | 3.102               | 4.299            | 29                                     | 3.437                     | $183,006                         |                                     |
| Valbenazine      | 3.222               | 4.325            | 49                                     | 3.385                     | $185,124                         | $17,637                             |
| Response criterion: >50% improvement in AIMS score in patients with schizophrenia at baseline | | | | | | |
| Deutetrabenazine | 3.106               | 4.181            | 29                                     | 2.770                     | $195,839                         |                                     |
| Valbenazine      | 3.225               | 4.208            | 48                                     | 2.696                     | $197,446                         | $13,474                             |
| Response criterion: >50% improvement in AIMS score in patients using antipsychotic medications at baseline | | | | | | |
| Deutetrabenazine | 3.147               | 4.279            | 29                                     | 2.951                     | $193,459                         |                                     |
| Valbenazine      | 3.263               | 4.300            | 48                                     | 2.878                     | $195,385                         | $16,547                             |
| Response criterion: >50% improvement in AIMS score in patients who are employed at baseline | | | | | | |
| Deutetrabenazine | 3.217               | 4.385            | 29                                     | 3.127                     | $195,739                         |                                     |
| Valbenazine      | 3.332               | 4.402            | 49                                     | 3.052                     | $197,677                         | $16,897                             |
| Response criterion: >50% improvement in AIMS score in patients without a psychiatric condition at baseline | | | | | | |
| Deutetrabenazine | 3.521               | 4.493            | 30                                     | 0.000                     | $152,659                         |                                     |
| Valbenazine      | 3.638               | 4.509            | 49                                     | 0.000                     | $154,868                         | $18,888                             |
| Scenario analysis: age <55 | | | | | | |
| Deutetrabenazine | 3.303               | 4.500            | 29.9                                   | 3.210                     | $200,796                         |                                     |
| Valbenazine      | 3.418               | 4.515            | 49.5                                   | 3.119                     | $202,812                         | $17,474                             |
| Scenario analysis: age ≥55 | | | | | | |
| Deutetrabenazine | 2.941               | 4.006            | 28.5                                   | 2.872                     | $184,057                         |                                     |
| Valbenazine      | 3.059               | 4.036            | 47.0                                   | 2.791                     | $185,544                         | $12,593                             |
| Scenario analysis: no effect of response on antipsychotic treatment discontinuation | | | | | | |
| Deutetrabenazine | 3.112               | 4.239            | 29.0                                   | 3.110                     | $190,943                         |                                     |
| Valbenazine      | 3.230               | 4.266            | 47.9                                   | 3.124                     | $191,937                         | $8436                               |

Abbreviations. AIMS, Abnormal Involuntary Movement Scale; CGIC, Clinical Global Impression of Change; LY, life year; QALY, quality-adjusted life year.

Table 4. Lifetime discounted costs (2017 US $) of tardive dyskinesia treatment with valbenazine and deutetrabenazine.

| Modeled scenario | TD medication | AP medication | Disease management | Disease relapse | Total |
|------------------|---------------|---------------|--------------------|-----------------|-------|
| Deutetrabenazine | $137,589      | $16,036       | $25,841            | $13,095         | $191,618 |
| Valbenazine      | $140,240      | $16,164       | $23,529            | $12,766         | $192,794 |
| Response criterion: >50% improvement in AIMS score in patients with any psychiatric disorder at baseline (base case) | | | | | |
| Deutetrabenazine | $231,644      | $16,423       | $22,485            | $12,655         | $283,208 |
| Valbenazine      | $201,595      | $16,976       | $20,979            | $12,761         | $252,311 |
| Response criterion: >50% improvement in AIMS score in all patients regardless of psychiatric condition at baseline | | | | | |
| Deutetrabenazine | $138,305      | $13,770       | $24,137            | $12,078         | $188,291 |
| Valbenazine      | $141,677      | $14,419       | $22,175            | $11,691         | $189,962 |
| Response criterion: >50% improvement in AIMS score in patients with bipolar disorder at baseline | | | | | |
| Deutetrabenazine | $140,726      | $14,443       | $17,817            | $12,644         | $185,630 |
| Valbenazine      | $144,097      | $14,919       | $20,275            | $11,691         | $187,950 |
| Response criterion: >50% improvement in AIMS score in patients with major depressive disorder at baseline | | | | | |
| Deutetrabenazine | $138,657      | $14,526       | $19,245            | $10,579         | $183,006 |
| Valbenazine      | $142,645      | $15,229       | $22,275            | $9,992          | $185,124 |
| Response criterion: >50% improvement in AIMS score in patients with schizophrenia at baseline | | | | | |
| Deutetrabenazine | $136,316      | $15,579       | $29,974            | $13,969         | $195,839 |
| Valbenazine      | $139,837      | $16,342       | $28,089            | $13,168         | $197,446 |
| Response criterion: >50% improvement in AIMS score in patients using antipsychotic medications at baseline | | | | | |
| Deutetrabenazine | $137,170      | $16,043       | $27,101            | $13,146         | $193,459 |
| Valbenazine      | $140,949      | $16,782       | $25,134            | $12,520         | $195,385 |
| Response criterion: >50% improvement in AIMS score in patients who are employed at baseline | | | | | |
| Deutetrabenazine | $139,801      | $15,703       | $26,591            | $13,644         | $195,739 |
| Valbenazine      | $143,568      | $16,378       | $24,561            | $13,170         | $197,677 |
| Response criterion: >50% improvement in AIMS score in patients without a psychiatric condition at baseline | | | | | |
| Deutetrabenazine | $144,486      | –             | $8,173             | –               | $152,659 |
| Valbenazine      | $148,863      | –             | $6,005             | –               | $154,868 |

Abbreviations. AIMS, Abnormal Involuntary Movement Scale; AP, antipsychotic; CGIC, Clinical Global Impression of Change; TD, tardive dyskinesia.
costs for valbenazine compared with deutetrabenazine ranging from −$53,022 to $39,410), the acquisition cost of valbenazine 80 mg (incremental lifetime costs compared with deutetrabenazine ranging from −$21,771 to $24,123), and acquisition cost of deutetrabenazine 48 mg (incremental lifetime costs compared with deutetrabenazine ranging from −$14,167 to $16,519). Tornado plots for the DSA of lifetime costs and QALYs of valbenazine compared with deutetrabenazine are provided in Figure 2. Sensitivity analysis results demonstrated that, in almost all cases, valbenazine remained cost-effective compared with deutetrabenazine when varying model inputs by ±20%. In all analyses, incremental lifetime costs of valbenazine treatment compared with deutetrabenazine remained below a threshold of $50,000. Only when the ITC odds ratio was decreased by 20% did the QALYs associated with deutetrabenazine treatment exceed those associated with valbenazine.

In the PSA (Figure 3), valbenazine dominated deutetrabenazine in 46% of simulations, was cost-effective at a threshold of $50,000/QALY or less in 11% of simulations, was cost-effective at a threshold greater than $50,000/QALY but less than $100,000/QALY in 10% of simulations, or cost
effective at a threshold greater than $100,000/QALY in 21% of simulations. In 12% of simulations, valbenazine was found to be less effective but also less costly than deutetrabenazine. In no simulation was valbenazine found to be more costly and less effective than deutetrabenazine. The cost-effectiveness acceptability curves for valbenazine and deutetrabenazine are shown in Figure 4. Compared with valbenazine, deutetrabenazine is generally not a cost-effective option at any WTP threshold ≤$300,000.
The results of the two scenario analyses are shown in Table 3. Total lifetime discounted QALYs and costs were slightly higher for patients <55 years of age and were slightly lower for patients ≥55 years of age; the ICERs for both age groups were 25–76% greater than for the base case. Total lifetime discounted QALYs were practically both age groups were 25/C21 slightly lower for patients by AIMS scores. This may reflect the limited applicability of greater probability of response at 1-year than that measured for response to treatment was associated with a substantially disutility associated with TD symptoms. The base case model showed that, compared with deutetrabenazine, treatment with valbenazine resulted in more patients responding at 1-year, longer life expectancy, fewer relapses of the underlying psychiatric condition, and improved quality-of-life measured by QALYs for patients with TD. These findings were consistent across the various scenarios that were modeled; however, the analysis that used a CGIC score ≤2 as the definition for response to treatment was associated with a substantially greater probability of response at 1-year than that measured by AIMS scores. This may reflect the limited applicability of the AIMS to assess subjective well-being, quality-of-life, social stigma, or occupational burden associated with TD/C20, and underscores the importance of including multidimensional perspectives of patient health when gauging the psychosocial impact of TD.

Model results using the CGIC criterion for response further demonstrated that valbenazine was more effective and less costly than deutetrabenazine (i.e. valbenazine dominated deutetrabenazine). Compared with deutetrabenazine, the ICER for valbenazine ranged from $30,897/QALY when response was defined as CGIC score ≤2 to $9,951/QALY when response was defined as ≥50% improvement in AIMS total score in patients with any psychiatric disorder at baseline. In the other modeled scenarios, the ICERs for valbenazine compared with deutetrabenazine ranged from $13,474/QALY to $18,888/QALY, values that are well within thresholds suggested by research evaluating societal WTP for health gains/C21. The current analysis may underestimate the value of VMAT2 inhibitors, since the outcome measures typically used in clinical trials (that provided the clinical inputs utilized in this DICE model) may not adequately capture the full range of impact that TD can have on patients and caregivers, especially in terms of social isolation and the ability to work/C28. It would be expected that patients whose TD is successfully treated with valbenazine or deutetrabenazine would experience more time employed than those receiving no treatment; however, lacking adequate source data to model employment, its impact was not factored into calculations of costs or QALYs in this analysis.

Several limitations of this study should be considered. First, the model assumed that responders to treatment with valbenazine or deutetrabenazine at 1 year would remain on medication and continue to respond indefinitely. Although safety and efficacy data from trials with continuous TD treatment for longer than 1 year are not available, it is almost certain that some patients would discontinue treatment, either for lack of efficacy or adverse events, meaning that the model may have overestimated time on treatment and underestimated discontinuation risk, resulting in an overestimation of both costs and QALYs. Second, although serious adverse events occurred infrequently in clinical trials and at rates similar to placebo, the effects of adverse events on outcomes and costs were not included in the model. Third, there are no head-to-head trials of valbenazine and deutetrabenazine, so probabilities of response were calculated based on an ITC of the results from individual trials with one drug or the other. Although the ITC sought to adjust results according to each compound’s direct comparisons with placebo, it is possible that differences in study designs and patient characteristics may have affected the outcomes reported in the individual clinical trials. Finally, the response to treatment metrics used in this study – while typical of clinical trials – are not specifically designed to measure impairment in subjective well-being, functioning, and quality-of-life. Without information from patient-reported outcomes, caregiver measures, functional scales, and quality-of-life questionnaires, the value of VMAT2 inhibitors in the management of TD may be underestimated.

Conclusions

In patients with TD, treatment with valbenazine was associated with longer life expectancy and better quality-of-life, measured by QALYs, compared with deutetrabenazine. Over a lifetime horizon, valbenazine was more effective than deutetrabenazine, and either less costly or associated with increased costs well below established cost per QALY thresholds, depending on the response criterion evaluated. The effect of reduced TD symptoms on the use of antipsychotic agents and psychiatric relapse should be further explored and new, validated measures that accurately reflect patient and caregiver perspectives on disease burden and quality-of-life are needed. The results of this study may assist payers in making more fully informed decisions regarding treatment of TD.

Transparency

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Declaration of financial/other interests

RD, MS, and CY are employees of Neurocrine. MLG and AC are employees of Evidera, which provides consulting and other services to bio-pharmaceutical companies. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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