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Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value

Revised Background and Scope
June 9, 2017

Stakeholder Input

This scoping document was developed with extensive input from patient advocacy organizations, relevant specialty societies, practicing psychiatrists and neurologists, drug manufacturers and payers. These groups informed the research direction outlined in this draft scope.

Tardive dyskinesia is a serious and disabling movement disorder that affects individuals treated with dopamine receptor blocking agents, typically antipsychotic agents given for a variety of mental health conditions.[1] Until recently there were no FDA approved treatments for tardive dyskinesia, and only a few off-label treatment options. For psychiatrists and neurologists who treat patients with antipsychotic agents and manage their side effects, prevention and treatment of tardive dyskinesia has primarily focused on changing the offending agent and using off-label medications to manage symptoms. For example, tetrabenazine (Xenazine®, Lundbeck), a vesicular monoamine transporter 2 (VMAT2) inhibitor, was approved in 2008 for Huntington's disease and has been used off-label for tardive dyskinesia. For many individuals, however, there have been no effective treatment options, and symptoms of tardive dyskinesia can persist after discontinuing or changing antipsychotic therapy. Recently, two new agents in this same therapeutic class have been investigated for use in patients with tardive dyskinesia and other movement disorders. One has already been approved by the FDA for tardive dyskinesia and offers the possibility of improved outcomes with fewer side effects, and the other is currently under FDA review for this indication. As such, ICER has decided to focus attention on tardive dyskinesia for this review and consider the role of VMAT2 inhibitors.

Patients and advocacy organizations described the burden of the symptoms of tardive dyskinesia on all aspects of a patient's life, including overall quality of life. In addition to physical impairment, tardive dyskinesia can affect employment, interpersonal relationships, and have an impact on healthy lifestyles, such as diet, exercise and smoking. Patient groups discussed the primary concern of maintaining effective antipsychotic therapy, while managing the symptoms of tardive dyskinesia. They also described the dual stigma of having serious mental illness and tardive dyskinesia symptoms in a variety of social and workplace settings. For patients with persistent symptoms, there is considerable interest in new treatments that may be safe and effective.

We also solicited input from manufacturers during a 3-week public comment period. ICER looks forward to continued engagement with all of these stakeholders throughout the entire project timeline, up to and including the public meeting in December 2017. We have summarized many of the key inputs in the scoping document below.

Background

Tardive dyskinesia (TD) is a movement disorder with a delayed onset that is related to prolonged use of medications that block the dopamine receptor, most commonly antipsychotic drugs.[2] Though initially associated with older antipsychotic agents, termed "first-generation" antipsychotics, TD also occurs with newer agents, termed "second-generation" or "atypical" antipsychotics.[1] Other medications associated less commonly with TD include metoclopramide and certain antidepressants (e.g., amoxapine).[3]

The movements associated with TD can be localized or diffuse and can result in physical and psychological impairment. TD is a hyperkinetic, involuntary movement disorder that includes a range of clinical manifestations. Classic TD involves the mouth and face region which can present as lip smacking or pursing, chewing, facial grimacing, and tongue movements inside the mouth or tongue popping out. TD can also involve the limbs and trunk. This may manifest as repetitive foot tapping, finger movements, dystonic postures of the neck and trunk that can include torticollis, rocking and rotatory movements, as well as shoulder shrugging. Patients may not be aware of these involuntary movements, especially when involving the face, and thus the condition can be socially stigmatizing and may impact employment. Though there is currently no validated measure that reflects the impact of TD on a patient's quality of life, the Abnormal Involuntary Movement Scale (AIMS) has been used in clinical and research settings to assess the general severity of symptoms and the impact of treatment.[4]

The term "tardive" implies a delayed onset, commonly after at least 3 months of exposure to offending agents,[5] but examples of symptoms developing after shorter time periods have been observed. This may in part be related to the onset of TD being insidious and difficult to recognize at first. Among patients on antipsychotics, prevalence rates of TD have been estimated to be 25%,[6] with a range of 20-50%.[7] Prevalence is higher for first generation (30%) than for second generation (13-20%) agents.[6] Antipsychotic agents are most frequently used for patients with schizophrenia and schizoaffective disorder but are also used in serious mood disorders such as bipolar disease and major depression. It is estimated that there are six million individuals with these diagnoses currently receiving antipsychotics in the U.S.[8] Other uses can include personality disorders, post-traumatic stress disorder (PTSD), insomnia, and dementia. The incidence of new TD is reported to be around 5% per year with first generation antipsychotics and 3% per year with second generation antipsychotics.[9,10] Higher rates are seen in older and female patients.[11]

Treatment recommendations have been developed by the American Psychiatric Association and the American Academy of Neurology.[5,12] Avoiding long-term use of antipsychotic agents for conditions where evidence of benefit is lacking or other treatment options are available is preferred. Therapy for TD has primarily focused on decreasing and then stopping the offending agent, and switching to a different antipsychotic if such agents are still deemed necessary. It is often not possible to stop the antipsychotic immediately because TD symptoms can worsen upon withdrawal. Though patients with TD symptoms may improve with these changes, complete resolution of symptoms is rare, and long-

lasting or permanent symptoms can be seen, even in patients who successfully are taken off antipsychotics.[13,14] Therefore, other treatments have been sought to decrease symptoms of patients with TD, and guideline recommendations may change with the availability of safer and more effective treatment options.

Though a wide range of pharmacologic treatments for TD have been studied, few therapies have been shown to produce more than a slight to moderate benefit.[1,15] Tetrabenazine, approved for Huntington's disease in 2008, is a VMAT2 inhibitor that has been used off-label for TD. VMAT2 inhibition depletes dopamine storage in presynaptic vesicles, resulting in less dopamine release. Several small controlled and observational studies of tetrabenazine have shown varying improvement in symptoms, but the need for three-times per day dosing and side effects, including sedation and worsening of depression and anxiety, have limited its usefulness. Other drugs used off-label for TD have included clozapine, benzodiazepines, anti-cholinergic agents, and a number of different vitamins and homeopathic therapies. Given the limited evidence of therapeutic benefit from available treatments, there is a clear need for new therapeutics for patients with disabling symptoms due to TD.

No FDA approved drugs were available for TD prior to the approval of valbenazine in April 2017. Like tetrabenazine, valbenazine (Ingrezza™, Neurocrine Biosciences, Inc.) is a VMAT2 inhibitor, but is dosed once a day and may have a favorable side-effect profile compared to other off-label agents. Deutetrabenazine (Austedo™, Teva), a modification of tetrabenazine that slows metabolism and clearance, was approved for the treatment of Huntington's disease in April 2017, and is currently under review for a TD indication.

Report Aim

This project will evaluate both the comparative clinical effectiveness and economic impacts of VMAT2 inhibitors valbenazine, deutetrabenazine, and tetrabenazine for the treatment of adults with tardive dyskinesia. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, impact on non-medical patient quality of life, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of the Assessment

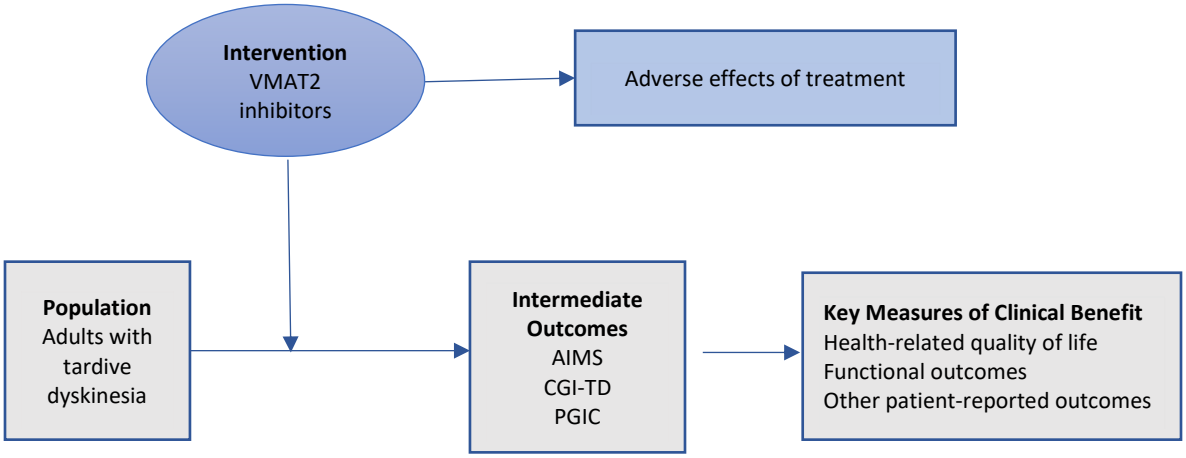
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we will seek out head-to-head studies of these interventions. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes.

Analytic Framework

The general analytic framework for assessment of VMAT2 inhibitors for tardive dyskinesia is depicted in Figure 1.

Figure 1. Analytic Framework: Management of Tardive Dyskinesia



VMAT2: vesicular monoamine transporter 2; AIMS= Abnormal Involuntary Movement Scale; CGI-TD= Clinical Global Impression of Tardive Dyskinesia; PGIC= Patient Global Impression of Change

Populations

The population of focus for the review will be adults ages 18 and older with tardive dyskinesia. This includes individuals with TD treated in selected studies regardless of the underlying condition for which dopamine receptor blocking agents were used. In addition to children and adolescents, we will also exclude adults with movement disorders related to other conditions (e.g., Huntington's disease) or whose disorder is not thought to be medication-induced.

We will also seek evidence on key subpopulations of interest. During the open input period, stakeholders suggested evaluating subpopulations based on type of TD symptoms, including: (a) patients with incident or new onset tardive dyskinesia; (b) patients with persistent tardive dyskinesia; and (c) patients with localized tardive dyskinesia symptoms. Though stakeholders highlighted the importance of these subpopulations, they also recognized that available data may be limited. Other subgroups of interest will include age, gender, and severity of symptoms as assessed by both clinicians and patients (i.e., mild, moderate, or severe).

Interventions

Clinical experts and patient organizations advised us that it is not uncommon for patients to try various antipsychotic agents as the initial strategy for tardive dyskinesia as well as a variety of off-label medications before considering treatment options such as tetrabenazine and potentially new VMAT2

inhibitors. We also received input that insurance policies may require patients to consider other therapies that are not FDA-approved before allowing use of new VMAT2 inhibitors. Stakeholders also recognized that stopping or changing dopamine receptor blocking agents may worsen the underlying condition, and that effective and safer treatments for TD may change current clinical practice. For these reasons, we will consider all VMAT2 inhibitors, including the only currently approved therapy with an FDA indication for TD, one investigational therapy presently undergoing FDA review, and one drug used off-label. Interventions of interest are listed below.

- Valbenazine (Ingrezza™)
- Deutetrabenazine (Austedo™ [investigational])
- Tetrabenazine (Xenazine® [off-label use])

We will seek clinical evidence on all forms of the products listed above. Wherever possible, we will evaluate head-to-head trials of these interventions. Final determinations of the comparability of the VMAT2 inhibitors will be dependent on having sufficient information from the available studies to assess the relative benefits and risks. Other comparators may include placebo or other active treatments not listed above.

Comparators

As mentioned above, a variety of other types of medications are used off-label to control TD symptoms. These include the antipsychotic clozapine, benzodiazepines, anticholinergic agents (e.g., amantadine), and the anti-alcohol agent acamprosate. We will consider such comparators only if there is available randomized or higher-quality comparative observational evidence in TD populations for the purposes of this evaluation.

Outcomes

This review will examine key clinical outcomes associated with TD. We will engage with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients, and seek patient-reported outcomes or other evidence sources to enrich the available data. Initial discussion with patients, patient groups, and clinical experts indicate that clinical trials are often lacking robust information on patient-reported outcomes and burdens associated with tardive dyskinesia.

Outcomes of interest from clinical trials will include:

- Symptom improvement (Abnormal Involuntary Movement Scale [AIMS], Clinical Global Impression of Tardive Dyskinesia [CGI-TD])
- Patient reported outcome (Patient Global Impression of Change [PGIC])
- Health-related quality of life
- Treatment-related adverse events (e.g., somnolence, suicide, worsening of underlying mental health illness)
- Discontinuation due to adverse events

- Disease-specific outcome measures and compliance with therapy (related to the underlying condition for which a dopamine receptor blocking agent is being used)
- Costs and cost-effectiveness

We will also look for evidence on additional patient-reported outcomes, such as employment, disability status, social engagement, overall well-being, as available. Importantly, long-term use of antipsychotics is also associated with the development of other extrapyramidal symptoms and movement disorders, but the focus of this assessment will be on TD symptoms only.

Evidence tables will be developed for each selected study and results will be summarized in a qualitative fashion; meta-analysis may be used to quantitatively summarize outcomes for the therapies of interest. In addition, we will consider network meta-analysis to combine direct and indirect evidence of effectiveness if available data permit.

Timing

Evidence on intervention effectiveness will be derived from studies of any duration, as long as they meet the study design criteria set forth above and measure the outcomes of interest.

Settings

All relevant settings will be considered, including outpatient/clinic, office, and home settings.

Simulation Models Focusing on Comparative Value

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. The interventions will include valbenazine (Ingrezza™) and deutetrabenazine (Austedo™ [investigational]). Depending on the availability of evidence, the comparators considered for inclusion will be tetrabenazine (Xenazine® [off-label use]) and no specific TD therapy. The model structure will be based in part on a literature review of prior published models of tardive dyskinesia (as available) and underlying conditions commonly treated with antipsychotic agents associated with tardive dyskinesia. The base case analysis will take a health-care system perspective (i.e., focus on direct medical care costs only). Data permitting, we will undertake cost-effectiveness analysis using a modified societal perspective as a scenario analysis.

The target population will consist of adult patients diagnosed with tardive dyskinesia due to use of dopamine receptor blocking agents. As mentioned in the clinical evidence section, antipsychotic agents are most frequently prescribed to patients diagnosed with schizophrenia and schizoaffective disorders; mood disorders such as bipolar disease and major depressive disorder; and conditions such as personality disorders, PTSD, insomnia, and dementia. The model will consist of health states including moderate/severe tardive dyskinesia symptoms, improved tardive dyskinesia symptoms, and death. A cohort of patients will transition between states using one-year cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons of one, two, and five years.

Base-case model inputs will include the probability and impact of symptom improvement, quality of life, and health care costs. Probabilities, costs, and other inputs will reflect differences in effectiveness between interventions. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to drug costs and the treatment of serious adverse events.

Health outcomes and costs considered will be determined by time spent in each health state, costs and utilities associated with those health states, treatment effects, adverse drug events (ADEs), and treatment discontinuation. The health outcome of each intervention will be evaluated in terms of quality-adjusted life years (QALYs) gained as well as the average change in Abnormal Involuntary Movement Scale (AIMS) and Clinical Global Impression of Change for Tardive Dyskinesia (CGI-TD). Cost per change in improvement of tardive dyskinesia (from moderate/severe base state to improved state) will also be evaluated. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained. Threshold analyses using cost per QALYs gained will be conducted to assess cost and benefit thresholds needed for a variety of willingness to pay thresholds.

Additional analyses of potential QALY gains from clinically indirect effects, such as improved outcomes due to adherence to antipsychotic and other medications, as well as potential productivity effects will be considered based on available evidence. One-way sensitivity analyses will be conducted to assess the impact of individual model inputs on outcomes. Probabilistic sensitivity analyses will be conducted to assess the impact of important model parameters simultaneously. Sensitivity analyses will also include adjustment to the utility weights associated with tardive dyskinesia to reflect potential bias associated with assessing utility in patients with the common underlying comorbid conditions.

In an additional analysis, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment price and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating product uptake and calculating potential budget impacts can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

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