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

Draft Background and Scope

May 8, 2017

Stakeholder Input

This scoping document was developed with extensive input from patient advocacy organizations, relevant specialty societies, practicing psychiatrists and neurologists, 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 antipsychotic agents for a variety of mental health conditions. Though prevention and treatment primarily focus on stopping or changing the offending antipsychotic agent, for some individuals there are no other effective treatment options, and symptoms can persist after discontinuing or changing antipsychotic therapy. Until recently there were no FDA approved treatments for tardive dyskinesia, and only a few off-label treatment options. For example, tetrabenazine (Xenazine®, Lundbeck), a vesicular monoamine transporter 2 (VMAT2) inhibitor, was approved in 2008 for Huntington's Disease and has been commonly used off-label for tardive dyskinesia. Recently, a new agent in this same therapeutic class was approved by the FDA for tardive dyskinesia and offers the possibility of improved outcomes with fewer side effects. 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 symptoms of tardive dyskinesia and their impact on quality of life, both physically and emotionally. They discussed 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. For psychiatrists and neurologists who treat patients with anti-psychotic agents and manage their side effects, therapy for tardive dyskinesia has primarily focused on changing the offending agent and using off-label medicines to manage symptoms. Payers have generally not focused on managing treatments for tardive dyskinesia because of a lack of FDA-approved medications and limited off-label use of other drugs by clinicians.

In addition to the above groups, input will also be solicited directly from manufacturers during the 3-week public comment period. ICER looks forward to continued engagement with 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.[1] Though initially associated with older antipsychotic agents, termed "first-generation" antipsychotics, TD also occurs with newer agents, termed "second-generation" or "atypical" antipsychotics.[2] Other medications associated less commonly with TD include antiemetics (e.g., metoclopramide) and 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 can 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 a socially stigmatizing. To assess the severity of TD symptoms and the impact of treatment, the Abnormal Involuntary Movement Scale (AIMS) has been used in clinical and research settings.[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 6 million individuals with these diagnoses on antipsychotics in the U.S.[8] Other uses can be for those with 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.

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.[2,15] 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 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 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, 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

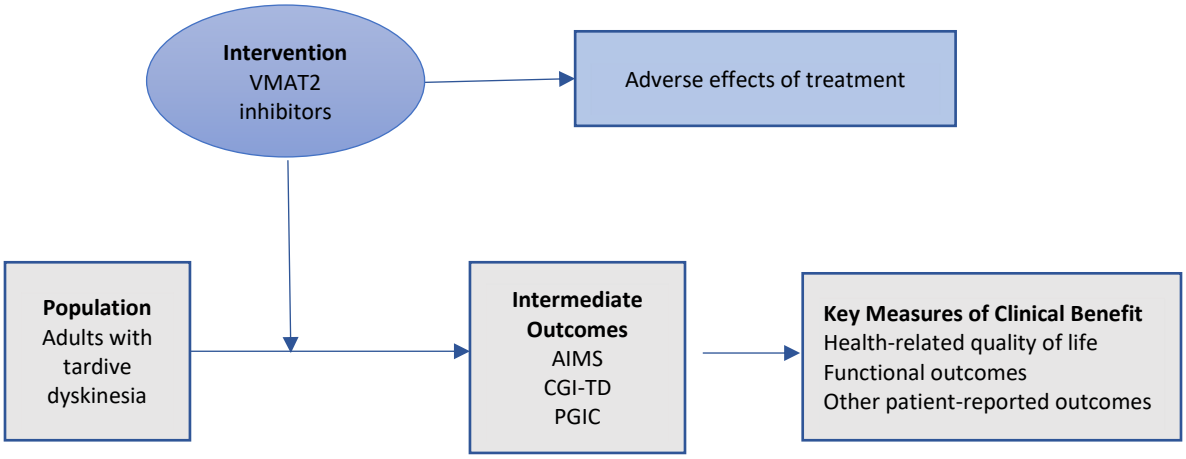
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative 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 (see page 4 for a detailed list of the agents of interest). 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. 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; (c) patients with localized tardive dyskinesia symptoms. 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. For these reasons, we will consider all VMAT2 inhibitors including those with FDA indications for TD as well as 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. 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 comparators with 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 clinicians 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
- Costs and cost-effectiveness

We will also look for evidence on additional patient-reported outcomes 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 will 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 be valbenazine (Ingrezza), and deutetrabenazine (Austedo [investigational]), and the comparators will be tetrabenazine (Xenazine [off-label use]) and no therapy. The model structure will be based in part on a literature review of prior published models of tardive dyskinesia (if available) and schizophrenia. The base case analysis will take a health-care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate analysis. The target population will consist of adult patients diagnosed with tardive dyskinesia due to use of antipsychotic 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 no tardive dyskinesia symptoms, mild tardive dyskinesia symptoms, moderate/severe 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 1, 2, and 5 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 vary to reflect differences in effectiveness between interventions. Treatment effectiveness will be estimated using outcomes such as changes in the Abnormal Involuntary Movement Scale (AIMS) and the Clinical Global Impression of Change for Tardive Dyskinesia (CGI-TD). If available, findings from network meta-analyses will be conducted to compare outcomes.

Health outcomes and costs will be dependent on time spent in each health state, treatment effects, adverse drug events (ADEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of average change in AIMS and CGI-TD, as well as quality-adjusted life years (QALYs) gained. 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. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained. Cost per change in severity of tardive dyskinesia (from moderate to mild, moderate to no symptoms, and mild to no symptoms) will also be evaluated. Threshold analyses using cost per QALYs gained will be conducted, if indicated, to assess cost and benefit thresholds needed for a variety of willingness to pay thresholds. 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.

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. These budgetary impact analyses 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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