MARY K. McCARTHY, M.D.
Physician, Practice Limited to Psychiatry

2311 N.W. Northrup, Suite 201
Portland, Oregon 97210-2955
Telephone: (503) 274-5417
Fax: (503) 279-8828

January 23, 2023

TO: Senate Committee on Health Care

RE: 1/23/2023 1:00 PM Public Hearing on SB 401 – Requires Oregon Health Authority to study tardive dyskinesia.

The following information is submitted in addition to my oral testimony presented today. It includes (in order):

1. The 9/2020 American Psychiatric Association Practice Guideline for treatment of patient with schizophrenia. See the second page (P 868) of the guideline (#14) relating to treatment of tardive dyskinesia.
2. The remainder of my submitted testimony is a copy of an "Appeal Letter" dated 6/8/2021 that I sent to appeal the denial for Ingrezza (a VMAT-2 medication) for one of my OHP patients. I redacted the patient identifying data from the copy I'm sending you. After this letter follow the 3 pages of American Academy of Neurology Treatment of Tardive Syndrome Guidelines (2013). Following this is a copy of the 14-page publication: "Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic review." Stanley N Caroff, J. Comp. Eff. Res. (2018) 7(2), 135–148.

I am requesting the committee review and update the evidence-based practice for OHP patients on tardive dyskinesia treatment to include the following: *Patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).*

Respectfully submitted,

M McCarthy

Mary McCarthy, MD
Psychiatrist

The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia

George A. Keepers, M.D., (Chair), Laura J. Fochtmann, M.D., M.B.I., (Vice-Chair; Methodologist), Joan M. Anzia, M.D., Sheldon Benjamin, M.D., Jeffrey M. Lyness, M.D., Ramin Mojtabai, M.D., Mark Servis, M.D., Art Walaszek, M.D., Peter Buckley, M.D., Mark F. Lenzenweger, Ph.D., Alexander S. Young, M.D., M.S.H.S., Amanda Degenhardt, M.D., Seung-Hee Hong (Systematic Review)

At its December 2019 meeting, the American Psychiatric Association (APA) Board of Trustees approved "The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia." The full guideline is available at APA's Practice Guidelines website.

INTRODUCTION

The goal of this guideline is to improve the quality of care and treatment outcomes for patients with schizophrenia, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (American Psychiatric Association 2013). Since publication of the last full practice guideline (American Psychiatric Association 2004) and guideline watch (American Psychiatric Association 2009) on schizophrenia, there have been many studies on new pharmacological and nonpharmacological treatments for schizophrenia. Additional research has expanded our knowledge of previously available treatments. The guideline focuses specifically on evidence-based pharmacological and nonpharmacological treatments for schizophrenia but also includes statements related to assessment and treatment planning that are an integral part of patient-centered care (Box 1).

Worldwide, schizophrenia is one of the top 20 causes of disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). The lifetime prevalence of schizophrenia is estimated to be approximately 0.7% (McGrath et al. 2008; Moreno-Küstner et al. 2018; van der Werf et al. 2014), although findings vary depending on the study location, demographic characteristics of the sample, the approach used for case-finding, the method used for diagnostic confirmation, and the diagnostic criteria used. Economic burdens associated with schizophrenia are high (Chapel et al. 2017; Jin and Mosweu 2017), with an estimated cost of more than $150 billion annually in the United States based on 2013 data (Cloutier et al. 2016). Schizophrenia is also associated with increased mortality, with a shortened lifespan and standardized mortality ratios that are reported to be twofold to fourfold those in the general population (Hayes et al. 2017; Heilä et al. 2005; Hjorthøj et al. 2017; Laursen et al. 2014; Lee et al. 2018; Oakley et al. 2018; Olfson et al. 2015; Tanskanen et al. 2018; Walker et al. 2015). The common co-occurrence of other psychiatric disorders (Plana-Ripoll et al. 2019), including substance use disorders (Hunt et al. 2018), contributes to morbidity and mortality among individuals with schizophrenia. About 4%–10% of persons with schizophrenia die by suicide, with rates that are highest among males in the early course of the disorder (Drake et al. 1985; Heilä et al. 2005; Hor and Taylor 2010; Inskip et al. 1998; Laursen et al. 2014; Nordentoft et al. 2011; Palmer et al. 2005; Popovic et al. 2014; Saha et al. 2007; Tanskanen et al. 2018). Increases in morbidity and mortality related to physical health in individuals with schizophrenia are likely associated with such factors as obesity, diabetes, hyperlipidemia, greater use of cigarettes, reduced engagement in health maintenance (e.g. diet, exercise), and disparities in access to preventive health care and treatment for physical conditions (Bergamo et al. 2014; De Hert et al. 2011; Druss et al. 2000; Janssen et al. 2015; Kisely et al. 2007, 2013; Kugathasan et al. 2018; Lawrence et al. 2010; Moore et al. 2015). Lack of access to adequate psychiatric treatment may also influence mortality (Schoenbaum et al. 2017). Accordingly, the overall goal of this guideline is to enhance the treatment of schizophrenia for affected individuals, thereby reducing the mortality, morbidity, and significant psychosocial and health consequences of this important psychiatric condition.

OVERVIEW OF THE DEVELOPMENT PROCESS

Since the publication of the Institute of Medicine (now known as National Academy of Medicine) report, *Clinical Practice Guidelines We Can Trust* (Institute of Medicine 2011), there has been an increasing focus on using clearly defined, transparent processes for rating the quality of evidence and the strength of the overall body of evidence in systematic reviews of the scientific literature. This guideline was developed using a process intended to be consistent with the recommendations of the Institute of Medicine (2011) and the *Principles for the Development of Specialty Society Clinical Guidelines* of the Council of Medical Specialty Societies (2012). Parameters used for the guideline's systematic review are included with the full text of the guideline. The APA

BOX 1. Guideline Statements[a]

Assessment and Determination of Treatment Plan

1. APA *recommends* **(1C)** that the initial assessment of a patient with a possible psychotic disorder include the reason the individual is presenting for evaluation; the patient's goals and preferences for treatment; a review of psychiatric symptoms and trauma history; an assessment of tobacco use and other substance use; a psychiatric treatment history; an assessment of physical health; an assessment of psychosocial and cultural factors; a mental status examination, including cognitive assessment; and an assessment of risk of suicide and aggressive behaviors, as outlined in APA's *Practice Guidelines for the Psychiatric Evaluation of Adults* (3rd edition).
2. APA *recommends* **(1C)** that the initial psychiatric evaluation of a patient with a possible psychotic disorder include a quantitative measure to identify and determine the severity of symptoms and impairments of functioning that may be a focus of treatment.
3. APA *recommends* **(1C)** that patients with schizophrenia have a documented, comprehensive, and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

Pharmacotherapy

4. APA *recommends* **(1A)** that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.*
5. APA *recommends* **(1A)** that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with an antipsychotic medication.*
6. APA *suggests* **(2B)** that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.*
7. APA *recommends* **(1B)** that patients with treatment-resistant schizophrenia be treated with clozapine. *
8. APA *recommends* **(1B)** that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.*
9. APA *suggests* **(2C)** that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.*
10. APA *suggests* **(2B)** that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.*
11. APA *recommends* **(1C)** that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.
12. APA *suggests* **(2C)** the following options for patients who have parkinsonism associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, or treating with an anticholinergic medication.
13. APA *suggests* **(2C)** the following options for patients who have akathisia associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, adding a benzodiazepine medication, or adding a beta-adrenergic blocking agent.
14. APA *recommends* **(1B)** that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).

Psychosocial Intervention

15. APA *recommends* **(1B)** that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care program.*
16. APA *recommends* **(1B)** that patients with schizophrenia be treated with cognitive-behavioral therapy for psychosis (CBTp).*
17. APA *recommends* **(1B)** that patients with schizophrenia receive psychoeducation.*
18. APA *recommends* **(1B)** that patients with schizophrenia receive supported employment services.*
19. APA *recommends* **(1B)** that patients with schizophrenia receive assertive community treatment if there is a history of poor engagement with services leading to frequent relapse or social disruption (e.g. homelessness; legal difficulties, including imprisonment).*
20. APA *suggests* **(2B)** that patients with schizophrenia who have ongoing contact with family receive family interventions.*
21. APA *suggests* **(2C)** that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.*
22. APA *suggests* **(2C)** that patients with schizophrenia receive cognitive remediation.*
23. APA *suggests* **(2C)** that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.*
24. APA *suggests* **(2C)** that patients with schizophrenia be treated with supportive psychotherapy.*

[a]Each statement includes a number rating that reflects the confidence in the statement: 1=Recommendation, indicating benefits of the intervention clearly outweigh harms; 2=Suggestion, indicating balance of benefits and harms is more difficult to judge, or the benefits or the harms may be less clear. With a suggestion, patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made. Each statement also has a letter rating for the strength of supporting research evidence (A=high; B=moderate; C=low), which reflect the level of confidence that the evidence for a guideline statement reflects a true effect based on consistency of findings across studies, directness of the effect on a specific health outcome, precision of the estimate of effect, and risk of bias in available studies.

*This guideline statement should be implemented in the context of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia.

website features a full description of the guideline development process.

RATING THE STRENGTH OF RESEARCH EVIDENCE AND RECOMMENDATIONS

Development of guideline statements entails weighing the potential benefits and harms of each statement and then identifying the level of confidence in that determination. This concept of balancing benefits and harms to determine guideline recommendations and strength of recommendations is a hallmark of Grading of Recommendations Assessment, Development and Evaluation (GRADE), which is used by multiple professional organizations around the world to develop practice guideline recommendations (Guyatt et al. 2013). With the GRADE approach, recommendations are rated by assessing the confidence that the benefits of the statement outweigh the harms and burdens of the statement, determining the confidence in estimates of effect as reflected by the quality of evidence, estimating patient values and preferences (including whether they are similar across the patient population), and identifying whether resource expenditures are worth the expected net benefit of following the recommendation (Andrews et al. 2013).

In weighing the balance of benefits and harms for each statement in this guideline, our level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences. Evidence for the benefit of a particular intervention within a specific clinical context is identified through systematic review and is then balanced against the evidence for harms. In this regard, harms are broadly defined and might include direct and indirect costs of the intervention (including opportunity costs) as well as potential for adverse events from the intervention.

Many topics covered in this guideline have relied on forms of evidence such as consensus opinions of experienced clinicians or indirect findings from observational studies rather than research from randomized trials. It is well recognized that there are guideline topics and clinical circumstances for which high-quality evidence from clinical trials is not possible or is unethical to obtain (Council of Medical Specialty Societies 2012). The GRADE working group and guidelines developed by other professional organizations have noted that a strong recommendation or "good practice statement" may be appropriate even in the absence of research evidence when sensible alternatives do not exist (Andrews et al. 2013; Brito et al. 2013; Djulbegovic et al. 2009; Hazlehurst et al. 2013). For each guideline statement, we have described the type and strength of the available evidence that was available as well as the factors, including patient preferences, that were used in determining the balance of benefits and harms.

The authors of the guideline determined each final rating following parameters set forth in the "Guideline Development Process" endorsed by the APA Board of Trustees. A *recommendation* (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of the intervention clearly outweigh harms. A *suggestion* (denoted by the numeral 2 after the guideline statement) indicates greater uncertainty: although the benefits of the statement are still viewed as outweighing the harms, the balance of benefits and harms is more difficult to judge, or the benefits or the harms may be less clear. With a suggestion, patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made. Each guideline statement also has an associated rating for the strength of supporting research evidence. Three ratings are used: *high*, *moderate*, or *low* (denoted by the letters A, B, and C, respectively). These ratings reflect the level of confidence that the evidence for a guideline statement reflects a true effect based on consistency of findings across studies, directness of the effect on a specific health outcome, precision of the estimate of effect, and risk of bias in available studies (Agency for Healthcare Research and Quality 2014; Balshem et al. 2011; Guyatt et al. 2006).

GUIDELINE SCOPE

The scope of this practice guideline is shaped by the *Treatments for Schizophrenia in Adults* (McDonagh et al. 2017), a systematic review that was commissioned by the Agency for Healthcare Research and Quality (AHRQ) and that serves as a principal source of information for the guideline. The AHRQ review uses the DSM-5 definition of schizophrenia; however, many of the systematic reviews included studies that used earlier DSM or International Classification of Disease criteria for schizophrenia. Several studies, particularly those assessing harms and psychosocial interventions, also included patients with a schizophrenia spectrum disorder diagnosis. Consequently, discussion of treatment, particularly treatment of first-episode psychosis, may also be relevant to individuals with schizophreniform disorder.

Although many of the studies included in the systematic review also included individuals with a diagnosis of schizoaffective disorder, these data were rarely analyzed separately in a way that would permit unique recommendations to be crafted for this group of patients. In addition, this guideline does not address issues related to identification or treatment of attenuated psychosis syndrome or related syndromes of high psychosis risk, which were not part of the AHRQ systematic review. Data are also limited on individuals with schizophrenia and significant physical health conditions or co-occurring psychiatric conditions, including substance use disorders. Nevertheless, in the absence of more robust evidence, the statements in this guideline should generally be applicable to individuals with co-occurring conditions, including individuals who receive treatment using integrated collaborative care or inpatient or outpatient medical settings. Although treatment-related costs are often barriers to receiving treatment and cost-effectiveness considerations are relevant to health care policy, cost-effectiveness

considerations are outside the scope of this guideline and its recommendations.

The full text of the practice guideline includes a detailed description of research evidence related to the effects of pharmacological and nonpharmacological treatments in individuals with schizophrenia. It also describes aspects of guideline implementation that are relevant to individual patients' circumstances and preferences.

AUTHOR AND ARTICLE INFORMATION

APA Practice Guideline Writing Group (George A. Keepers, M.D., Chair).

Address correspondence to Jennifer Medicus (jmedicus@psych.org).

APA wishes to acknowledge the contributions of APA staff and former staff (Jennifer Medicus, Seung-Hee Hong, Samantha Shugarman, Michelle Dirst, Kristin Kroeger Ptakowski). APA also wishes to acknowledge the contribution of Amanda S. Eloma, Pharm.D, BCPP, in reviewing information related to medications in the guideline and associated tables. In addition, APA and the Guideline Writing Group especially thank Laura J. Fochtmann, M.D., M.B.I., Seung-Hee Hong, and Jennifer Medicus for their outstanding work and effort in developing this guideline. APA also thanks the APA Committee on Practice Guidelines (Daniel J. Anzia, M.D., Chair), liaisons from the APA Assembly for their input and assistance, and APA Councils and others for providing feedback during the comment period.

Am J Psychiatry 2020; 177:868–872; doi: 10.1176/appi.ajp.2020.177901

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Sample of appeal letter

June 28, 2021

TO:
Fax

Page 1 of 20

RE:
DOB:
ID#:
PA Number:

This letter serves as an appeal to the denial for Ingrezza 80 mg prescribed for the diagnosis of Tardive Dyskinesia (TD) (G24.01). In the Denial letter you mention "Please work with your doctor to see if you meet the following rules. 1) failure of tetrabenazine; and 2) failure of clonazepam."

Addressing the requirement for failure of clonazepam please note that this patient has been on another benzodiazepine (lorazepam) for many years. In looking at the recommendations for clonazepam for TD, the following is taken from the American Academy of Neurology 2013 summary guideline regarding management of tardive syndromes (TDS), including tardive dyskinesias (TDD).

GABA AGONISTS

Moderate evidence	**Based on 1 Class I study, clonazepam is probably effective in decreasing TDD symptoms short-term (approximately 3 months) and should be considered for short-term TDD treatment (Level B).**
Insufficient evidence	Data are insufficient to support or refute baclofen use in treating TDD (**Level U**).

My patient will have chronic TD secondary to his severe & chronic mental illness that will need management with antipsychotic medication ongoing most likely for the rest of his life. Therefore, it would be more appropriate to choose a treatment that has better data for long term efficacy.

Addressing the requirement for failure of tetrabenazine: In my review of the literature there is a 2018 publication by S. Caroff et al titled "Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic Review." ***J. Comp. Eff. Res.*** (2018) 7(2), 135–148. This publication summary is as follows:

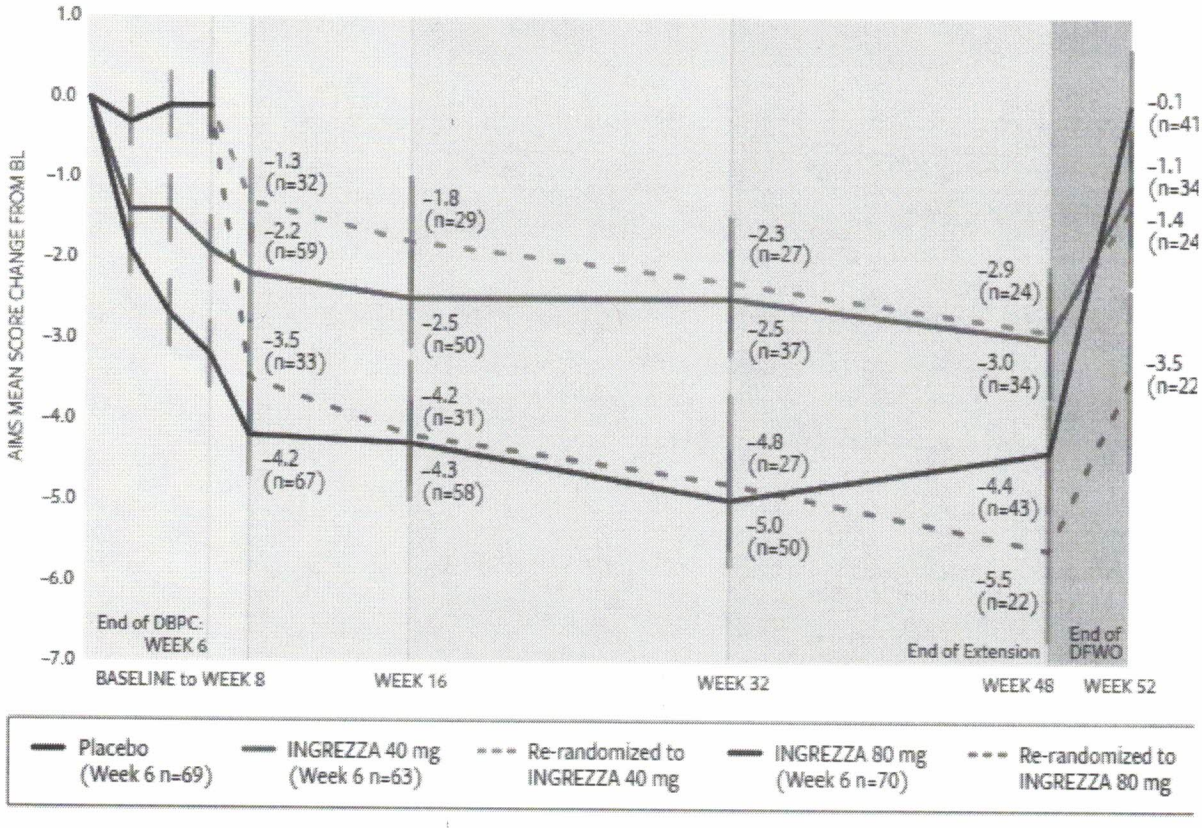
> Up to 30% of patients taking antipsychotics may develop tardive dyskinesia (TD). Recent evidence-based recommendations demonstrate an unmet need for effective TD management. This systematic review was designed to update the evidence for TD treatment, comparing two vesicular monoamine transporter 2 (VMAT2) inhibitors, tetrabenazine and valbenazine. Of 487 PubMed/Embase search results, 11 studies met the review criteria. Valbenazine efficacy was demonstrated in rigorously designed clinical trials that meet the guidelines for AAN Class I evidence. Due to differences in study designs and a lack of standardized and controlled trials with tetrabenazine, a formal meta-analysis comparing the agents was not possible. However, valbenazine appears to have fewer side effects and a more favorable once-daily dosing regimen for the treatment of TD.

June 28, 2021
RE:
DOB:

There are now reports of patients being followed for 48 weeks on valbenazine showing 39% reduction in TD severity. The following is a graph of the outcomes with valbenazine taken from the Ingrezza (valbenazine) website.

INGREZZA provided continued reduction of TD severity through 48 weeks[1,4]

Extension study of INGREZZA 40 mg and INGREZZA 80 mg (ITT population)[1,3,4]



~39% reduction in TD severity with INGREZZA 80 mg at 48 weeks[1,4,*]

***In a post hoc analysis that included patients randomized to INGREZZA 80 mg at baseline and those who were re-randomized to INGREZZA 80 mg at Week 6.**

AIMS, Abnormal Involuntary Movement Scale; BL, baseline; DBPC, double-blind placebo-controlled; DFWO, drug-free washout; ITT, intent-to-treat.

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June 28, 2021

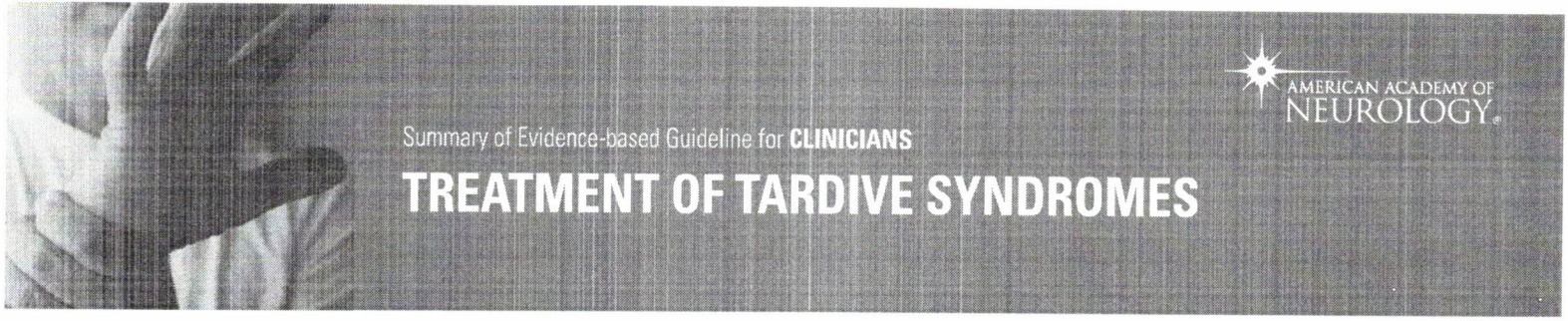
RE:
DOB:

For the above reasons I am requesting you reconsider your denial of my request for valbenazine (Ingrezza) for _____. Thank you for reviewing my request.

Sincerely,

Mary K. McCarthy, MD
Psychiatrist

enc:
1. American Academy of Neurology 2013 summary guideline regarding management of tardive syndromes (TDS), including tardive dyskinesias (TDD).
2. "Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic Review." ***J. Comp. Eff. Res.*** (2018) 7(2), 135–148.



AMERICAN ACADEMY OF NEUROLOGY

Summary of Evidence-based Guideline for **CLINICIANS**

TREATMENT OF TARDIVE SYNDROMES

This is a summary of the American Academy of Neurology (AAN) guideline regarding management of tardive syndromes (TDS), including tardive dyskinesias (TDD).

Please refer to the full guideline at www.aan.com *for more information, including definitions of the classifications of evidence and recommendations.*

Drug Warning

Some of the drugs described here may have serious side effects or other risks associated with them. For more information, visit the US Food and Drug Administration website at *www.fda.gov*.

Is withdrawal of dopamine receptor blocking agents (DRBAs) an effective TDS treatment?

Insufficient evidence	Data are insufficient to support or refute TDS treatment of DRBA withdrawal (**Level U**).

Clinical context

The American Psychiatric Association Task Force recommends antipsychotic withdrawal only in patients who can tolerate it. Despite limited evidence, clinical impression indicates that short-term withdrawal may worsen dyskinesias, whereas adding antipsychotics with stronger extrapyramidal symptoms can reduce TDS. Psychotic relapse predictors include younger age, higher baseline antipsychotic dosage, and shorter hospitalization.

Does switching from typical to atypical DRBAs reduce TDS symptoms?

Insufficient evidence	Data are insufficient to support or refute TDS treatment by changing to atypical antipsychotics (**Level U**, Class IV studies).

What is the efficacy of pharmacologic agents in treating TDS?

AMANTADINE

Weak evidence	Amantadine reduced TDS when used conjointly with a neuroleptic during the first 7 weeks (1 Class II study, 2 Class III studies). Amantadine with neuroleptics may be considered to treat TDS for short-term use (**Level C**).

ACETAZOLAMIDE

Insufficient evidence	Acetazolamide and thiamine reduced TDS in one Class III study. Data are insufficient to support or refute TDS treatment with acetazolamide and thiamine (**Level U**).

Clinical context

Only flupentixol decanoate, chlorpromazine, haloperidol, trifluoperazine, and thioridazine were tested with amantadine in these studies. The efficacy of amantadine plus other neuroleptics in TDS treatment is unknown. Because safety data are unavailable concerning long-term use of only typical neuroleptics as TDS suppressive agents and because of these agents' propensity to cause TDS, the evidence suggests only potential efficacy short-term.

FIRST-GENERATION ANTIPSYCHOTICS

Insufficient evidence	Haloperidol possibly reduces TDS movements for up to 2 weeks (2 Class II studies, 1 Class III study) but is associated with increased akinetic-rigid syndrome (1 Class II study). Data are insufficient to support or refute the use of thiopropazate in reducing oral dyskinesia (1 Class III study). Data are insufficient to support or refute the use of thiopropazate, molindone, sulpiride, fluperlapine, and flupenthixol in treating TDS (**Level U**).

Clinical context

Although haloperidol and thiopropazate possibly reduce TDS, they are not recommended because of the competing risk of akinetic-rigid syndrome. Safety data are unavailable concerning the long-term use of typical antipsychotics as TDS suppressive agents, and these drugs themselves can cause TDS; these significant risks outweigh the benefits of any short-term use of typical antipsychotics.

SECOND-GENERATION ANTIPSYCHOTICS

Insufficient evidence	Data are conflicting regarding the use of clozapine (conflicting Class III studies). Risperidone (2 Class II studies, 1 Class III study) is probably effective in reducing TDD. Olanzapine is possibly effective in reducing TDD (2 Class III studies). The safety of risperidone and olanzapine as a TDS suppressant for use beyond 48 weeks has not been addressed. There is no evidence to determine the efficacy of quetiapine, ziprasidone, aripiprazole, and sertindole in TDS treatment. **Because neuroleptic agents may themselves cause TDS and may mask its symptoms rather than treat it, these drugs cannot be recommended for TDS treatment (Level U).** Caution is advised when using risperidone or olanzapine to reduce TDS.

ELECTROCONVULSIVE THERAPY

Insufficient evidence	Data are insufficient to determine the efficacy of electrocorvulsive therapy for TDD treatment (**Level U**).

DOPAMINE-DEPLETING AGENTS

Weak evidence	Tetrabenazine (TBZ) possibly reduces TDS symptoms (2 consistent Class III studies). TBZ possibly reduces TDS symptoms (2 consistent Class III studies). TBZ may be considered in treating TDS (**Level C**).
Insufficient evidence	One study (Class III) found reserpine and α-methyldopa effective in treating TDS. Data are insufficient to determine the efficacy of reserpine or α-methyldopa in treating TDS (**Level U**).

Clinical context

TBZ reduces TDS symptoms; there is no evidence that long-term TBZ administration induces TDS, but it can cause parkinsonism.

DOPAMINE AGONISTS

Insufficient evidence	Data are insufficient to support or refute the use of bromocriptine for TDS treatment (**Level U**).

CHOLINERGIC AND ANTICHOLINERGIC DRUGS

Weak evidence	Galantamine is possibly ineffective in treating TDS (1 Class II study). Galantamine might not be considered in treating TDS (**Level C negative**).
Insufficient evidence	Data are insufficient to determine the effectiveness of other cholinergic drugs in treating TDS (**Level U**).
	Data are insufficient to determine the effectiveness of anticholinergic drugs in treating TDS (**Level U**).

BIPERIDEN (AKINETON) DISCONTINUATION

Insufficient evidence	Data are insufficient to determine the effectiveness of biperiden discontinuation in treating TDS (**Level U**, 1 Class III study).

ANTIOXIDANTS

Moderate evidence	Ginkgo biloba (EGb-761) is probably useful in TDS treatment (1 Class I study), but data are limited to inpatients with schizophrenia (**Level B**).
Weak evidence	Based on 1 Class II study, eicosapentaenoic acid is possibly ineffective in treating TDS and might not be considered (**Level C negative**).
Insufficient evidence	Based on 4 Class II and numerous Class III studies, data are conflicting regarding vitamin E efficacy in treating TDS. Data are insufficient to determine the efficacy of vitamin E (**Level U**).
	Melatonin is possibly ineffective in treating TDS at a 2-mg/d dose (1 Class II study) but is possibly effective in treating TDS at a 10-mg/d dose (1 Class II study). Evidence regarding TDS treatment with melatonin is conflicting (**Level U**).
	Data are insufficient to support or refute the use of other antioxidants, including vitamin B_6, selegiline, and yi-gan san, in treating TDS (**Level U**).

GABA AGONISTS

Moderate evidence	Based on 1 Class I study, clonazepam is probably effective in decreasing TDD symptoms short-term (approximately 3 months) and should be considered for short-term TDD treatment (**Level B**).
Insufficient evidence	Data are insufficient to support or refute baclofen use in treating TDD (**Level U**).

LEVETIRACETAM

Insufficient evidence	Data are insufficient to recommend levetiracetam as TDS treatment (**Level U**, 1 Class III study).

CALCIUM CHANNEL BLOCKERS

Moderate evidence	Diltiazem probably does not reduce TDD and should not be considered as treatment (**Level B negative**, 1 Class I study).
Insufficient evidence	Data are insufficient to support or refute nifedipine use in treating TDD (**Level U**).

BUSPIRONE

Insufficient evidence	Data are insufficient to support or refute buspirone use in treating TDD (**Level U**, 1 Class III study).

Do patients with TDS benefit from chemodenervation with botulinum toxin (BoNT)?

Insufficient evidence	Data are insufficient to support or refute BoNT use to treat TDS symptoms (**Level U**).

Do patients with TDS benefit from surgical therapy?

Insufficient evidence	Data are insufficient to support or refute pallidal deep brain stimulation use in treating TDS (**Level U**, Class IV studies).

American Academy of Neurology, 201 Chicago Avenue, Minneapolis, MN 55415
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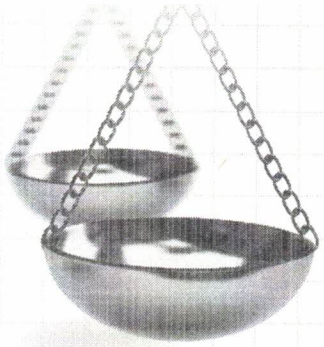
Systematic Review



Journal of Comparative Effectiveness Research

Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic review

Stanley N Caroff[1], Saurabh Aggarwal*[,2] & Charles Yonan[3]

[1]Corporal Michael J Crescenz Veterans Affairs Medical Center & the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[2]NOVEL Health Strategies, LLC, Chevy Chase, MD, USA

[3]Neurocrine Biosciences, Inc., San Diego, CA, USA

* Author for correspondence: Tel.: +1 646 717 4789; sa2@novelhealthstrategies.com

Up to 30% of patients taking antipsychotics may develop tardive dyskinesia (TD). Recent evidence-based recommendations demonstrate an unmet need for effective TD management. This systematic review was designed to update the evidence for TD treatment, comparing two vesicular monoamine transporter 2 (VMAT2) inhibitors, tetrabenazine and valbenazine. Of 487 PubMed/Embase search results, 11 studies met the review criteria. Valbenazine efficacy was demonstrated in rigorously designed clinical trials that meet the guidelines for AAN Class I evidence. Due to differences in study designs and a lack of standardized and controlled trials with tetrabenazine, a formal meta-analysis comparing the agents was not possible. However, valbenazine appears to have fewer side effects and a more favorable once-daily dosing regimen for the treatment of TD.

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Keywords: clinical trial • tardive dyskinesia • tetrabenazine • valbenazine • vesicular monoamine transporter 2 inhibitor

Tardive dyskinesia (TD) is an involuntary movement disorder induced by prolonged exposure to dopamine receptor blocking agents (DRBAs), including antipsychotics and antiemetics [1,2]. Research shows that the prescription of antipsychotics alone increased more than threefold over 10 years; conservative estimates thus indicate that approximately 5 million patients have been exposed to antipsychotics in the United States (US) [3]. Given that the estimated global mean prevalence of TD is 30% in studies of patients currently treated with a first-generation antipsychotic and 21% in those currently treated with a second-generation antipsychotic, this disorder remains a significant problem for psychiatric patients who may experience stigma, embarrassment, and impairment in social functioning (and sometimes physical functioning) as a consequence of developing TD [4]. While the prevalence of TD has been extensively studied, the associated healthcare burden is the subject of continuing investigation [3–5]. Previous studies have shown that the presence of TD in patients with schizophrenia may correlate with impaired cognition, poor response to treatment, greater risk of relapse, longer hospital stays, lower quality of life and functioning, a progressive course, and increased mortality [6].

Through the mechanism of blocking dopamine receptors, antipsychotics have proven to be highly effective and essential drugs for controlling psychotic symptoms in patients with conditions such as schizophrenia and bipolar disorder [7–10]. However, dopamine is also involved as a key neurotransmitter in other neural pathways, notably the motor circuit [7,11]. Blockade in the motor circuit may lead to upregulation and hypersensitivity of post-synaptic dopamine receptors, resulting in an increase of dopaminergic signaling and the emergence of abnormal movements associated with TD [10,12].

Vesicular monoamine transporters (VMATs) are presynaptic intracellular transmembrane proteins that have a critical role in the packaging, storage and release of dopamine and other monoamines [13]. Inhibition of VMAT2, which is the predominant isoform in the brain, interferes with dopamine uptake and storage in presynaptic vesicles, leaving dopamine to be metabolized by monoamine oxidase in the cytoplasm. The resulting decrease

Future Medicine

in dopamine concentrations available for release in the synapse [14] counteracts the heightened dopaminergic activity that follows prolonged dopamine receptor blockade, and thereby may diminish the hyperkinetic symptoms associated with TD. VMAT2 inhibitors have shown promise in the treatment of hyperkinetic movement disorders, with tetrabenazine (XENAZINE®) and deutetrabenazine (AUSTEDO™) approved in the USA for the treatment of Huntington's chorea, and more recently, valbenazine (INGREZZA®) and deutetrabenazine (AUSTEDO™) approved for treatment of TD [15–17].

Developed in the 1950s [18], tetrabenazine is currently approved for the treatment of moderate to severe TD in some countries, and has been used and studied off-label for TD in the USA [19,20]. Tetrabenazine undergoes rapid absorption and metabolism with a half-life of approximately 10 h [21], and requires multiple daily dosing [20]. As a consequence of this rapid metabolism, chorea has been shown to recur within 12–18 h after the last dose of tetrabenazine [20]. Tetrabenazine binds selectively to VMAT2, but it is the dihydrotetrabenazine (HTBZ) metabolites that have the main pharmacologic effects. However, some of these metabolites (i.e., different HTBZ stereoisomers) have affinity for other off-target receptors [22], possibly contributing to unwanted side effects that can be dose-limiting and possibly confound treatment efforts [20,23,24]. In addition, due to its tolerability and pharmacokinetic profile, use of tetrabenazine for Huntington's disease includes recommendations for CYP2D6 genotyping to screen for poor metabolizer status when exceeding doses of 50 mg/day [15].

Recognizing that TD was an important unmet medical need and that a proven TD treatment would be an important pharmacological development, the US FDA granted breakthrough status to valbenazine in 2015 and approval as a treatment for TD in 2017 [2,25]. Valbenazine is a novel and highly selective VMAT2 inhibitor that is rapidly absorbed but more slowly metabolized, with a half-life of approximately 20 h that supports once-daily dosing [22,26]. Valbenazine has two major metabolites: [+]-α-HTBZ (or R,R,R-HTBZ), which is formed by hydrolysis and is a common metabolite with tetrabenazine, and NBI-136110, which is formed by mono-oxidation. Studies have shown that these two metabolites have no affinity for other unintended targets [22]. This pharmacologic profile contributes to a lower potential for side effects and reduced concerns over pharmacokinetic drug interactions or the need to screen for CYP2D6 polymorphisms.

Due to the resurgence of interest in TD, a systematic review was conducted to consolidate available clinical outcomes from published trials for tetrabenazine, which is currently being used off-label, and valbenazine, which was recently approved, in the treatment of TD. To meet the needs of formulary review committees as well as clinicians, the original intent of this review was to provide a body of evidence to enable a direct comparison between tetrabenazine and valbenazine. The review was carried out with the intent of executing a meta-analysis of efficacy and safety data extracted from published clinical trials.

Methods

Search strategy

The PubMed and Embase databases were searched for English language publications in the date range of 1 January 1980–31 March 2017. Since reports have already been published that have reviewed earlier studies of TD with tetrabenazine [27], studies published prior to 1980 were excluded from analysis with the intention of minimizing historical bias and enhancing comparability in methodology with the more recent valbenazine trials. Search strings for each database were 'valbenazine AND tardive dyskinesia' and 'tetrabenazine AND tardive dyskinesia'. Duplicate results from these four separate searches were removed.

Criteria for study selection

Studies were selected for inclusion if they were a randomized controlled trial, single-arm study, cohort study, case series (with more than or equal to ten TD cases) or retrospective chart review. Case reports with less than ten TD cases, meta-analyses, reviews, animal studies, modeling studies, pharmacokinetic studies, chromatography studies, child/pediatric studies, guidelines, articles and letters were excluded. Results from the literature searches (i.e., study titles and/or abstracts) were screened to remove irrelevant studies based on the exclusion criteria. Results of this screening process were then further assessed by evaluating full-text articles for eligibility.

Data extraction & analysis

Full-text versions of selected studies were assessed to determine study design, sample size, study sites (single, multiple), comparator(s), efficacy and safety outcomes. For studies that reported the treatment of several movement disorders, only efficacy results pertaining to TD were reviewed and summarized. Based on available information,

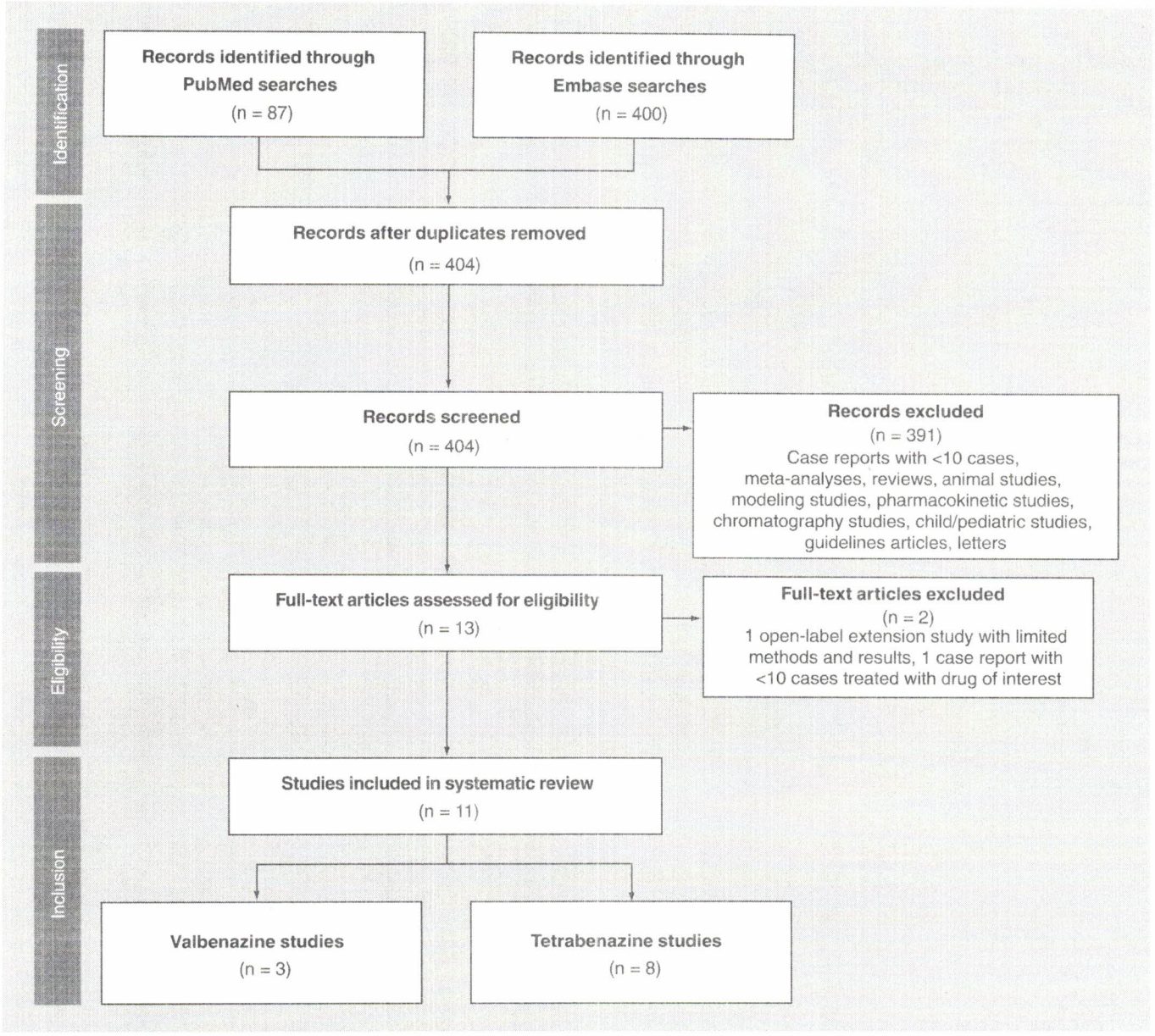

Figure 1. Results of systematic review.
Search terms: 'valbenazine AND tardive dyskinesia', 'tetrabenazine AND tardive dyskinesia'. Search criteria: English language, date range 1 January 1980–31 March 2017.

safety results were reviewed and summarized for the overall study population (i.e., any movement disorder) or only for the TD population. A meta-analysis of treatment effects was originally planned. However, as reported below, differences in study design did not allow for any meaningful comparisons across studies. Therefore, only a descriptive review of the studies is provided.

Results

Search strategy results

The initial database searches yielded 487 results, 83 of which were duplicates and thus excluded from screening. Screening of titles and abstracts resulted in the exclusion of an additional 391 studies. A total of 13 studies met criteria for this systematic review upon screening and full-text articles were assessed for eligibility (Figure 1). Four studies were identified for valbenazine: one open-label extension to a Phase II study [28]; two randomized,

double-blind, placebo-controlled trials [26,29]; and one double-blind extension to a Phase III study [30]. Eligibility assessment of these studies resulted in the exclusion of the open-label extension study [28]. Because this open-label study was only presented orally in a platform session at the 2016 American Academy of Neurology (AAN) Annual Meeting, information about the methods and results were limited. Nine studies were identified for tetrabenazine: one double-blind, crossover study [31]; and eight open-label studies, which included two case series [32,33], three long-term studies [34–36] and three retrospective chart reviews [37–39]. Full-text review resulted in the exclusion of one open-label case series [32] because only four of the 14 TD patients were treated with tetrabenazine.

A summary of the studies that met all inclusion criteria is presented in Table 1. Sample size, drug dose, duration of treatment and assessment tools varied greatly across studies. No head-to-head studies were available that compared the two interventions.

Review of tetrabenazine studies

The tetrabenazine studies included one double-blind, crossover study (n = 12) and seven open-label studies (Total n = 381; range, n = 17–149). Tetrabenazine doses ranged from 6.25 to 300 mg/day (mean doses: 37.5–175 mg/day), administered one- to three-times daily. Tetrabenazine was generally well tolerated and effective in the treatment of TD. The most common side effects were parkinsonism, drowsiness/fatigue and depression, and authors of the studies generally agreed that tetrabenazine side effects were dose related and reversible.

Two open-label studies of tetrabenazine were conducted solely in TD patients. The most recent of these was a study by Ondo *et al.* [36] that included 20 patients with TD and used the Abnormal Involuntary Movement Scale (AIMS) as an outcome measure. In addition to TD, 45% of patients also showed mild evidence of parkinsonism, and 25% had akathisia at baseline. Participants were required to stop DRBA medications and other TD treatments for ≥30 days prior to starting tetrabenazine (mean dose: 57.9 mg/day; mean treatment duration: 20.3 weeks). Participants in this study were diagnosed with a psychiatric disorder or symptoms (unspecified psychosis, schizophrenia, bipolar disorder, agitation), gastrointestinal disorder or organic brain disorder. Cessation of antipsychotic medications is often not practical in patients with chronic psychotic disorders due to the risk of relapse, and it may have confounded treatment results due to unmasking or worsening of existing TD. TD severity was assessed by a single-blinded investigator who rated videos using the standardized AIMS, both at baseline and at approximately 3 months after commencing treatment. Significant improvement ($p < 0.001$) on the motor section of the AIMS was demonstrated at the end of treatment versus baseline values; no patient had unchanged or worsened TD (Table 2). The most common adverse events (≥10%) were sedation and parkinsonism (Table 3).

The second study that included only TD patients was a case series by Watson *et al.* [33] that included 23 patients with TD who were treated with tetrabenazine (mean dose: 91.3 mg/day; mean treatment duration not reported). Severity of involuntary movements was evaluated in three regions (face/mouth/tongue, trunk, limbs) using a 5-point involuntary movement scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) and video recordings made for each patient before and during treatment. All patients in this study showed improvement with tetrabenazine treatment (range: 1–4 points) (Table 2). Side effects were minimal (all ≤10%), and the most common events were drooling and parkinsonism with tremor (Table 3).

The remaining studies were conducted in patients with various movement disorders, including TD. Among them was a crossover study by Asher and Aminoff [31] that enrolled patients with a diagnosis of TD (n = 12), Huntington's disease or dystonia. The specific psychiatric diagnoses of participants were not reported, but stable doses of antipsychotics and other medication were allowed throughout. In TD patients, the tetrabenazine mean dose was 175 mg/day. Study participants were informed of the crossover design, but were not told whether they started with tetrabenazine or placebo (although all were started on tetrabenazine) and when the crossover occurred. Participants were videotaped at baseline, 3 weeks (end of tetrabenazine treatment) and 6 weeks (end of placebo crossover); videotapes were reviewed by two blinded investigators who rated TD severity as slight, moderate or marked. The study used a 5-category rating system (marked, moderate, slight, none, worse) to assess treatment response (Table 2). Clinical significance of tetrabenazine treatment was based on TD severity being improved relative to both baseline and placebo treatment. Six of 12 patients showed marked or moderate improvement (50%). Tetrabenazine did not produce behavioral changes in participants with TD, and alteration of concomitant antipsychotics was not needed. Across all participants, the most common side effects (≥10%) were drowsiness, drooling and parkinsonism (Table 3).

Three open-label studies, conducted at a single site, investigated the effects of long-term tetrabenazine treatment on patients with TD, dystonia, Huntington's disease, Tourette's syndrome, myoclonus, tics and other movement

Table 1. Study design summary.

Study (year)	Design	Duration[†]	Population[‡]	Intervention[§]	Comparator[§]	Ref.
Valbenazine						
O'Brien *et al.* (2015) KINECT 2	Randomized, double-blind, placebo-controlled • Efficacy (AIMS) scored by two blinded video raters at baseline, weeks 2, 4 and 6 • Safety included adverse event monitoring	Treatment duration: up to 6 weeks	TD (n = 100)	Valbenazine QD 25–75 mg/day (n = 51)	Placebo (n = 49)	[29]
Hauser *et al.* (2017) KINECT 3	Randomized, double-blind, parallel-group, placebo-controlled • Efficacy (AIMS) scored by two blinded video raters at baseline, weeks 2, 4 and 6 • Safety included adverse event monitoring	Treatment duration: up to 6 weeks	TD (n = 227)	Valbenazine QD 80 mg/day (n = 79) 40 mg/day (n = 72)	Placebo (n = 76)	[26]
Grigoriadis *et al.* (2016) KINECT 3 Extension	Double-blind extension of KINECT 3 • Effectiveness (AIMS) scored by two blinded video raters at weeks 8, 16, 32, 48 and 52 • Safety included adverse event monitoring	Treatment duration: up to 48 weeks plus 4-week washout	TD (n = 198)	Valbenazine QD 80 mg/day (n = 101) 40 mg/day (n = 97)	None	[30]
Tetrabenazine						
Asher & Aminoff (1981)	Blinded crossover[¶] • Efficacy (five-category rating) scored by two blinded video raters, week 3 (active) and week 6 (placebo) • Safety included side-effect monitoring	Treatment duration: 3–24 days (titration) plus 3 weeks (stable dose) plus 3 weeks (placebo crossover)	TD (n = 12) Total (n = 32)	Tetrabenazine BID 25–200 mg/day (n = 12) (mean dose: 175 mg/day)	Placebo (n = 12) (crossover)	[31]
Watson *et al.* (1988)	Open-label, case series • Efficacy (5-point scale) in patients successfully treated with tetrabenazine was scored by an unreported number of video raters at baseline and during treatment • Safety included side-effect monitoring	Treatment duration: NR; case series follow-up duration: up to 4 years	TD (n = 23)	Tetrabenazine QD or TID: 37.5–150 mg/day (n = 23) (mean dose: 91.3 mg/day)	None	[33]
Jankovic & Orman (1988)	Open-label, long-term • Efficacy (5-point scale)[#] scored by one video rater at baseline, 6 weeks, and every 3 months • Safety included side-effect monitoring	Treatment duration: 21.1 months[††]	TD (n = 44) Total (n = 217)	Tetrabenazine: 25–100 mg/day (n = 44) (mean dose: 97.4 mg/day)	None	[34]

[†]Dosing frequency, mean dose and/or maximum dose are indicated as reported; some publications do not specify frequency or mean dose.
[‡]Some studies included patients with other movement disorders (e.g., dystonia, chorea, tic, myoclonus). For these studies a total population and TD population are reported.
[§]Intervention and comparator n-values are reported for TD patients only.
[¶]Patients were switched to placebo after 3 weeks of stable-dose tetrabenazine treatment; clinical significance of tetrabenazine treatment was based on TD severity being improved relative to both baseline and placebo treatment.
[#]These studies utilized the same 5-point scale to determine efficacy of treatment.
[††]Mean or median not specified.
[‡‡]May include many of the 44 patients from the earlier study, Jankovic & Orman (1988).
[§§]Mean dose of all patients in this study who had a hyperkinetic movement disorder.
AIMS: Abnormal Involuntary Movement Scale; BID: Twice daily; CGIC: Clinical Global Impression of Change; NR: Not reported; QD: Once daily; TD: Tardive dyskinesia; TID: Thrice daily.

Table 1. Study design summary (cont.).

Study (year)	Design	Duration[†]	Population[‡]	Intervention[§]	Comparator[§]	Ref.
Jankovic & Beach (1997)	Open-label, long-term • Efficacy (5-point scale)[#] scored by one video rater at baseline, and every 3–6 months • Safety included side-effect monitoring	Mean treatment duration: 35.4 months	TD (n = 93) Total (n = 400)	Tetrabenazine: 25–200 mg/day (n = 93)[‡‡] (mean maximum dose: 96.9 mg/day)	None	[35]
Ondo *et al.* (1999)	Open-label, long-term • Efficacy (AIMS) scored by one blinded video rater at baseline and ~3 months • Safety included adverse event monitoring	Mean treatment duration: 20.3 weeks	TD (n = 20)	Tetrabenazine TID: 25–150 mg/day (n = 20) (mean dose: 57.9 mg/day)	None	[36]
Paleacu *et al.* (2004)	Open-label, retrospective chart review • Efficacy (CGIC) composite score of patient/caregiver • Safety included side-effect monitoring	Mean treatment duration, 22 months; chart review period: 4 years	TD (n = 17) Total (n = 118)	Tetrabenazine BID or TID: 12.5–150 mg/day (n = 17) (mean dose: 76.2 mg/day)	None	[37]
Kenney *et al.* (2007)	Open-label, retrospective chart review • Efficacy (5-point scale)[#] scored by chart review at baseline, and every 3–6 months • Outcomes noted upon withdrawal • Safety included adverse event monitoring	Mean treatment duration: 2.3 years; chart review period: 8 years	TD (n = 149) Total (n = 490)	Tetrabenazine: 12.5–300 mg/day (n = 149) (mean dose, 60.4 mg/day)[§§]	None	[38]
Miguel *et al.* (2017)	Open-label, retrospective chart review • Efficacy (three-category rating) scored by chart review at baseline and during treatment • Outcomes noted upon withdrawal • Safety included side-effect monitoring	Mean treatment duration: 40 months; chart review period: 9 years	TD (n = 35) Total (n = 111)	Tetrabenazine: 6.25–225 mg/day (n = 35) (mean maximum daily dose: 37.5 mg/day)	None	[39]

[†]Dosing frequency, mean dose and/or maximum dose are indicated as reported; some publications do not specify frequency or mean dose.
[‡]Some studies included patients with other movement disorders (e.g., dystonia, chorea, tic, myoclonus). For these studies a total population and TD population are reported.
[§]Intervention and comparator n-values are reported for TD patients only.
[¶]Patients were switched to placebo after 3 weeks of stable-dose tetrabenazine treatment; clinical significance of tetrabenazine treatment was based on TD severity being improved relative to both baseline and placebo treatment.
[#]These studies utilized the same 5-point scale to determine efficacy of treatment.
[††]Mean or median not specified.
[‡‡]May include many of the 44 patients from the earlier study, Jankovic & Orman (1988).
[§§]Mean dose of all patients in this study who had a hyperkinetic movement disorder.
AIMS: Abnormal Involuntary Movement Scale; BID: Twice daily; CGIC: Clinical Global Impression of Change; NR: Not reported; QD: Once daily; TD: Tardive dyskinesia; TID: Thrice daily.

disorders. The use of concomitant medications and specific psychiatric disorders were not reported in these studies. Response to tetrabenazine was scored approximately every 3–6 months by a single examiner, using a 5-point Likert scale to rate abnormal movements (1 = marked improvement, 2 = moderate improvement, 3 = mild to moderate improvement, 4 = poor or no improvement, 5 = worsening). In the 1988 study [34], 44 patients with TD received tetrabenazine 25–100 mg/day, with a mean treatment duration of 21.1 months. The majority of patients showed moderate to marked improvement of TD (Table 2). In the 1997 study [35], which appears to have included patients from the 1988 study who were still receiving treatment, the mean maximum tetrabenazine dose in patients with TD (n = 93) was 96.9 mg/kg and the mean treatment duration was 35.4 months. The percentage of patients who had moderate to marked improvement in this study was similar to the earlier study (93 and 71%, respectively; Table 2). The 2007 retrospective chart review [38] did not include patients who commenced treatment prior to 1997, thus excluding patients from the previous reports. The mean dose was 60.4 mg/day and mean duration was 2.3 years

Table 2. Efficacy summary.

Study (year)	Efficacy summary	Ref.
Valbenazine		
O'Brien *et al.* (2015) KINECT 2†	• AIMS score, LS mean change from baseline to week 6 (primary end point): -0.2 placebo, -2.6 valbenazine ($p = 0.001$) • AIMS response at week 6 (≥50% improvement from baseline): 19% placebo, 49% valbenazine ($p = 0.002$) • CGI-TD score, LS mean at week 6: 3.1 placebo, 2.2 valbenazine ($p < 0.001$) • CGI-TD response at week 6 ('much improved' or 'very much improved'): 16% placebo, 67% valbenazine ($p < 0.001$)	[29]
Hauser *et al.* (2017) KINECT 3†	• AIMS score, LS mean change from baseline to week 6 (primary end point): -0.1 placebo, -3.2 valbenazine 80 mg ($p < 0.001$) • AIMS score, LS mean change from baseline to week 6: -0.1 placebo, -1.9 valbenazine 40 mg ($p = 0.002$) • CGI-TD score, LS mean at week 6: 3.2 placebo, 2.9 valbenazine 80 mg (ns), 2.8 valbenazine 40 mg (ns) • AIMS response at week 6 (≥50% improvement from baseline): 9% placebo, 40% valbenazine 80 mg ($p < 0.001$), 24% valbenazine 40 mg ($p = 0.02$)	[26]
Grigoriadis *et al.* (2016) KINECT 3 Extension	• AIMS score, mean change from baseline to week 48: -4.8 valbenazine 80 mg, -3.0 valbenazine 40 mg • CGI-TD score, mean at week 48, 2.1 valbenazine 80 mg, 2.4 valbenazine 40 mg • AIMS response at week 48 (≥50% improvement from baseline): 52% valbenazine 80 mg, 28% valbenazine 40 mg • CGI-TD response at week 48 ('much improved' or 'very much improved'): 76% valbenazine 80 mg, 59% valbenazine 40 mg • After treatment washout (week 52), increases in AIMS and CGI-TD response rates indicated that TD severity was reverting toward baseline levels	[30]
Tetrabenazine‡		
Asher & Aminoff (1981)	• Improvement scale with five possible categories: marked, moderate, slight, none, worse • Marked or moderate improvement with tetrabenazine: 60% of ten patients who completed the study • No change with tetrabenazine: 40% of ten patients (two discontinued and were not included in these analyses)	[31]
Watson *et al.* (1988)	• 5-point severity scale: score range, 0 (none) to 4 (severe) • Score of 3 or 4 (moderate/severe) at baseline: 83% of 23 patients • Score of 1 or 2 (none/minimal) after tetrabenazine: 87% of 23 patients	[33]
Jankovic & Orman (1988)	• 5-point global response scale: score range, 1 (marked reduction in abnormal movements and excellent improvement in function) to 5 (worsening in movement disorder and some deterioration in function) • Mean score after tetrabenazine: 2.3 in 44 patients • Score of 1 or 2 (marked/moderate improvement): 71% of 44 patients	[34]
Jankovic & Beach (1997)	• 5-point global response scale: score range, 1 (marked reduction in abnormal movements and excellent improvement in function) to 5 (worsening in movement disorder and some deterioration in function) • Score of 1 (marked improvement) after tetrabenazine: 89% of 93 patients • Score of 2 (moderate improvement) after tetrabenazine: 4% of 93 patients	[35]
Ondo *et al.* (1999)	• AIMS total score: assessed by patients (self-rating) and video raters • Mean percent improvement with tetrabenazine (self-raters): 60% improvement (from 9.1 to 3.6; $p < 0.001$) • Mean percent improvement with tetrabenazine (video raters): 54% improvement (from 17.9 to 8.2; $p < 0.001$)	[36]
Paleacu *et al.* (2004)	• 7-point CGIC score: range, -3 (marked worsening) to +3 (marked improvement) • Score of 1 (mild improvement) after tetrabenazine: 18% of 17 patients • Score of 2 (moderate improvement) after tetrabenazine: 35% of 17 patients • Score of 3 (marked improvement) after tetrabenazine: 6% of 17 patients	[37]
Kenney *et al.* (2007)	• 5-point global response scale: score range, 1 (marked reduction in abnormal movements and excellent improvement in function) to 5 (worsening in movement disorder and some deterioration in function) • Score of 1 or 2 (marked/moderate improvement) after initiating tetrabenazine: 84% of 149 patients • Score of 1 or 2 (marked/moderate improvement) after long-term tetrabenazine: 86% of 149 patients	[38]
Miguel *et al.* (2017)	• 3-category response scale: 1 (improved and asymptomatic), 2 (improved but symptomatic), 3 (poor or no clinical response) • Score of 1 or 2 (any improvement) after tetrabenazine: 77% of 35 patients	[39]

†Significance in these studies is reported as compared with placebo.
‡All tetrabenazine studies except Watson *et al.* (1988) and Ondo *et al.* (1999) included patients with other hyperkinetic disorders; results are only presented for patients with tardive dyskinesia.
AIMS: Abnormal Involuntary Movement Scale; CGIC: Clinical Global Impression of Change; CGI-TD: Clinical Global Impression of Change-Tardive Dyskinesia; LS: Least square; ns: Not significant; PGIC: Patient Global Impression of Change.

Table 3. Safety summary.

Study (year)	Safety summary	Ref.
Valbenazine		
O'Brien *et al.* (2015) KINECT 2	• Discontinuation due to TEAEs: 10% placebo, 10% valbenazine • Serious TEAEs: 4% placebo, 0% valbenazine • Any TEAE: 33% placebo, 49% valbenazine • Three most common TEAEs with valbenazine: fatigue (10 vs 4% placebo), headache (10 vs 4% placebo), decreased appetite (8 vs 0% placebo)	[29]
Hauser *et al.* (2017) KINECT 3	• Discontinuation due to TEAEs: 5% placebo, 6% valbenazine 40 mg, 6% valbenazine 80 mg • Serious TEAEs: 4% placebo, 6% valbenazine 40 mg, 8% valbenazine 80 mg • Any TEAE: 43% placebo, 40% valbenazine 40 mg, 51% valbenazine 80 mg • Three most common TEAE with valbenazine (combined 40 and 80 mg): somnolence (5 vs 4% for placebo), akathisia (3 vs 1% for placebo), dry mouth (3 vs 1% for placebo)	[26]
Grigoriadis *et al.* (2016) KINECT 3 Extension[†]	• Discontinuation due to TEAEs: 13% valbenazine 40 mg, 18% valbenazine 80 mg • Serious TEAEs: 13% valbenazine 40 mg, 16% valbenazine 80 mg • Any TEAE incidence: 62% valbenazine 40 mg, 76% valbenazine 80 mg • Four most common TEAEs (combined 40 and 80 mg): headache (7%), urinary tract infection (7%), diarrhea (6%), dizziness (6%)	[30]
Tetrabenazine[‡]		
Asher & Aminoff (1981)	• Discontinued study due to side effects: 9% of 32 total patients treated with tetrabenazine • Three most common side effects: 30% drowsiness, 12% drooling, 9% parkinsonism	[31]
Watson *et al.* (1988)	• Two reported side effects in 23 TD patients treated with tetrabenazine: 9% drooling, 4% parkinsonism with tremor	[33]
Jankovic & Orman (1988)	• Three most common side effects in 217 total patients treated with tetrabenazine: 24% parkinsonism, 13% drowsiness/fatigue, 11% depression	[34]
Jankovic & Beach (1997)	• Discontinued study due to side effects: 23% of 400 total patients treated with tetrabenazine • Three most common side effects: 37% drowsiness/fatigue, 29% parkinsonism, 15% depression • Incidence of side effects may have been high because treatment strategy was to increase dose until evidence of efficacy or intolerability	[35]
Ondo *et al.* (1999)	• Of 20 TD patients treated with tetrabenazine, 1 discontinued due to sedation • Five patients reported mild sedation • Five patients had evidence of mild parkinsonism (based on neurologic examination)	[36]
Paleacu *et al.* (2004)	• Discontinued study due to side effects: 3.5% of 118 total patients treated with tetrabenazine; 12% of 17 TD patients (both TD patients discontinued for somnolence and weakness) • Four most common side effects in 118 total patients: 6% somnolence/weakness/apathy, 5% parkinsonism, 2% depression, 2% akathisia	[37]
Kenney *et al.* (2007)	• Discontinued study due to adverse events: 17% of 448 total patients • Four most common adverse events: 25% drowsiness, 15% parkinsonism, 8% depression, 8% akathisia • Age was found to be a significant predictor of parkinsonism ($p < 0.0001$)	[38]
Miguel *et al.* (2017)	• Discontinuation due to adverse events: 16% of 108 total patients treated with tetrabenazine; 23% of 40 TD patients • Reported adverse events in all patients: 27% parkinsonism, 13% psychiatric disorder, 2% other movement disorder (not specified), 10% other side effects (not specified) • Reported adverse events in TD patients: 35% parkinsonism, 8% psychiatric disorder, 3% other movement disorder (akathisia), 8% other side effects (somnolence, rash, mental confusion)	[39]

[†]Safety results not reported in Grigoriadis *et al.* (2016); results were provided by Neurocrine Biosciences, Inc. (data on file).
[‡]All tetrabenazine studies except Watson *et al.* (1988) and Ondo *et al.* (1999) included patients with other hyperkinetic disorders; based on availability, safety results are presented for all patients and/or TD patients as indicated. Descriptive terms ('side effects' or 'adverse events') are based on terminology used in the published study.
TD: Tardive dyskinesia; TEAE: Treatment-emergent adverse event.

(all movement disorder patients, n = 490). Response rates did not vary over time, with the majority of TD patients showing moderate to marked improvement both after initiating treatment, and after long-term treatment with tetrabenazine (Table 2). Adverse events that occurred in ≥10% of tetrabenazine-treated patients (all movement disorders) in these studies were parkinsonism, drowsiness/fatigue, depression, insomnia and nervousness/anxiety (Table 3). Up to 23% of patients discontinued tetrabenazine treatment due to adverse events.

The tetrabenazine studies also included retrospective chart reviews by Paleacu *et al.* [37] and Miguel *et al.* [39]. Both studies examined the effects of tetrabenazine on TD and other movement disorders in patients who did not respond to other medications. The use of concomitant medications and specific psychiatric diagnoses were not reported in either study. In the chart review by Paleacu *et al.* [37], mean treatment duration was 22 months and mean dose was 76.2 mg/day (all movement disorder patients, n = 188). Improvement of movement disorders was rated using a Clinical Global Impression of Change scale, with scores ranging from -3 (marked worsening) to +3 (marked improvement). Approximately 60% of patients included in this chart review showed any improvement (mild, moderate and marked) of TD (Table 2). Side effects included somnolence, weakness, apathy and parkinsonism, but none of the reported side effects occurred in >10% of all patients (Table 3). In the chart review by Miguel *et al.* [39], mean treatment duration was 40 months and mean maximum daily dose was 37.5 mg/day (TD patients, n = 35). Clinical response was based on comparison of baseline with follow-up visits using a 3-category rating system (improved and asymptomatic, improved but symptomatic, poor or no clinical response). Charts showed that the majority of patients with TD exhibited clinically meaningful improvement based on assessment of any improvement with treatment (Table 2). The most common adverse events (≥10%) were parkinsonism, depression, anxiety and worsening of pre-existing psychiatric disorder (Table 3).

In addition to examining the effects of tetrabenazine on TD and other movement disorders, Kenney *et al.* [38] and Miguel *et al.* [39] reported the effects of treatment cessation. Both studies showed that movement disorder severity reverted when tetrabenazine was interrupted for as little as 1 week or discontinued permanently.

Review of valbenazine studies

The valbenazine studies included: two randomized, double-blind, placebo-controlled trials, both with 6-week treatment duration; and one long-term, uncontrolled, extension trial with treatment of up to 48 weeks (Total n = 327). Valbenazine was administered once daily in all studies. In the Phase II study (KINECT 2; n = 100) [29], doses ranged from 25 to 75 mg/day and 76% of subjects reached maximum dose. In the Phase III study (KINECT 3; n = 227) [26] and its long-term extension (n = 198) [30], valbenazine-treated patients received 40 or 80 mg/day.

The valbenazine studies included adults with TD and stable schizophrenia/schizoaffective disorder or mood disorder. Stable regimens of concomitant medications for management of medical and psychiatric disorders were allowed. Changes in TD were assessed by consensus between two centralized video raters using standardized AIMS [40] assessments at baseline and at each study visit. Central AIMS video raters were blinded to treatment and to study visit.

Change in the AIMS total score (items 1–7) from baseline to week 6 was the primary end point for KINECT 2 and KINECT 3, and both studies showed significant improvement in ratings of severity of TD with valbenazine compared with placebo ($p < 0.001$; Table 2). Least squares mean differences between valbenazine and placebo were 2.4 in KINECT 2 and 3.1 (with the 80 mg/day dose) in KINECT 3. The long-term KINECT 3 extension study showed sustained improvement in the AIMS total scores through the end of valbenazine treatment (week 48), but TD reverted toward baseline levels of severity 4 weeks after treatment withdrawal at the end of the trial (week 52) (Table 2). The percentages of participants achieving a rigorous AIMS response threshold, defined as a ≥50% total score improvement from baseline, were significantly higher with valbenazine compared with placebo in both studies (KINECT 2, 49 vs 18%; KINECT 3, 40% [80 mg/day] and 24% [40 mg/day] vs 9%; all $p < 0.05$).

The Clinical Global Impression of Change-TD (CGI-TD) [40], which was scored by an onsite investigator who was blinded to treatment, indicated clinically meaningful but not statistically significant improvements with valbenazine compared with placebo in KINECT 3 (Table 2). In the KINECT 2 study, however, results for CGI-TD response, defined as a rating of 'much improved' or 'very much improved' (score ≤ 2), were significantly greater for valbenazine compared with placebo ($p < 0.001$), and significantly more patients showed a response with valbenazine (67 vs. 16%, $p < 0.0001$).

Similarly, in the KINECT 3 extension study, improvements in scores from baseline through week 48 were maintained in AIMS total and the CGI-TD scores (Table 2). The proportion of patients maintaining a response was sustained based on both the CGI-TD scores (76% [80 mg/day]; 59% [40 mg/day]) and ≥50% improvement in AIMS scores (52% [80 mg/day]; 28% [40 mg/day]).

Valbenazine was generally well tolerated, especially considering that most participants were taking a concomitant antipsychotic medication (KINECT 2, ≥40% of patients; KINECT 3, 86% of patients) [26,29]. The most common adverse events that were reported with valbenazine were fatigue, headache, somnolence and reduced appetite (all ≤10%) (Table 3). In the long-term extension study, headache and urinary tract infection (7% each) were the

most common adverse events. Psychiatric status remained stable throughout valbenazine treatment and no other clinically relevant safety signals were observed.

Discussion

This review demonstrates that published studies of tetrabenazine and valbenazine in the treatment of TD were widely different in design, treatment duration, daily dosing/administration, allowance of concomitant psychiatric medications, methods for clinical evaluation, outcome measurements and patient characteristics including the presence or absence of underlying psychiatric disease. Because of these differences, conducting a direct comparison by means of a formal meta-analysis was not feasible; nor has any study been conducted that directly compares tetrabenazine with valbenazine in the treatment of TD or any hyperkinetic movement disorder. However, given the current resurgence of interest in VMAT2 inhibitors for the treatment of TD, a descriptive and comparative review of these studies is warranted.

Tetrabenazine is approved in the USA only for the treatment of chorea associated with Huntington's disease [15], but is commonly used off-label for TD. The tetrabenazine studies reported here demonstrated significant improvement in TD, although none of the studies included randomization or parallel-group placebo controls, and the studies varied widely in use of prospective versus retrospective designs, standardized outcome measures (e.g., AIMS), blinded conditions, videotaping and adequately powered sample sizes (only two studies included >50 patients with TD) [35,38]. Two long-term studies reported that TD severity reverted when tetrabenazine was discontinued, though this was noted through retrospective chart review and not investigated as part of the study design [38,39]. Tetrabenazine required dosing up to three-times daily, but was reported to be generally safe and well tolerated both short- and long term. The maximum daily dose for tetrabenazine as indicated for the treatment of Huntington's chorea was generally adhered to in all studies, except in Asher and Aminoff [31] where the recommended maximum daily dose was exceeded almost twofold. Nearly all studies with tetrabenazine documented changes in psychiatric status (depression) and secondary movement disorders (parkinsonism, akathisia) as frequent side effects of treatment. Adverse events were found to be dose related and reversible upon dose reduction. Limited information is available regarding the reasons for study discontinuation, but they include side effects, intolerability, lack of efficacy and travel/financial difficulties [35,38].

Valbenazine was recently approved in the USA for the treatment of adults with TD [17]. The randomized and controlled studies included in this systematic review demonstrated significant improvement in ratings of the severity of TD with valbenazine when compared with placebo [26,29]. In KINECT 3, the mean change from baseline in AIMS total score and AIMS $\geq$ 50% response indicated an effect with valbenazine after 2 weeks of treatment [26]. Preliminary results from the long-term study showed sustained improvement of TD, with decline toward baseline TD levels following treatment withdrawal [17,30], suggesting that ongoing treatment is required to maintain symptom reduction. Final reports for this study and additional long-term studies are pending (i.e., a 52-week open-label study [NCT02405091] and a 72-week rollover study [NCT02736955]). Valbenazine required only once-daily dosing, and was reported to be safe and well tolerated both short and long term. Importantly, psychiatric status was not altered by valbenazine and no safety signals were detected for secondary abnormal movements (i.e., parkinsonism, akathisia), even with the use of concomitant antipsychotic medications. The most common reasons for study discontinuation were withdrawal of consent, adverse events and loss to follow-up [26,35]. More research is needed to address some important questions about valbenazine and other VMAT2 inhibitors. Key topics include complete recovery or remission of TD symptoms, effects of valbenazine across different body regions (e.g., orofacial region versus limbs), and factors that may affect treatment response (e.g., demographics, TD severity and duration, DRBA type and duration of treatment).

The current systematic review highlights some of the key methodological differences between published clinical studies of tetrabenazine and valbenazine. As summarized in the evidence-based AAN guidelines for TD treatment, tetrabenazine studies present Class III and IV evidence, with a resultant Level C recommendation (possibly effective) [27]. Based on the trial design, it seems reasonable to expect that the valbenazine studies would constitute Class I evidence (i.e., randomized controlled trial in a representative population with clearly defined eligibility criteria, a clearly defined primary outcome, blinded treatment allocation and adequate sample size for drop-outs and statistical testing), which would be translatable to Level A evidence for treatment recommendation (i.e., established efficacy for the given condition/disorder in a specified population).

For this review, one aspect of the AAN Class I criteria that may warrant additional discussion is the requirement that the clinical trial be conducted in a representative population with presentation of relevant baseline charac-

teristics. By clearly defining TD (based on prior DRBA exposure and AIMS assessment), including patients with a psychiatric diagnosis (i.e., schizophrenia, schizoaffective disorder, mood disorder), and allowing concomitant psychiatric medications including both first- and second-generation antipsychotics, the valbenazine trials were specifically designed to be reflective of real-world patients. In contrast, the tetrabenazine studies largely omitted any reporting of psychiatric status and concomitant medication use in their patient populations; moreover, many of the studies included patients with an array of abnormal movement disorders. In addition, the AIMS was used in all valbenazine trials to assess TD at baseline, and evaluate postbaseline improvements, whereas only one tetrabenazine study implemented this scale to evaluate efficacy [36]. The American Psychiatric Association has emphasized the importance of utilizing standardized scales for TD evaluation in clinical research [41] and the FDA currently requires that TD trials use the AIMS to demonstrate efficacy.

Differences in dosing and administration are another important clinical and formulary consideration. As reported in this systematic review, the tetrabenazine studies used doses ranging from 6.25 to 300 mg/day, administered up to three-times daily. In contrast, once-daily dosing of valbenazine may improve medication adherence, particularly in patients with psychiatric disorders [38,39]. There is no established dose of tetrabenazine specifically for TD, which may have contributed to the wide variance in tetrabenazine dosing regimens used in reported studies [42,43]. From a formulary perspective, unit dose costs can be estimated for valbenazine but not for tetrabenazine.

Finally, this review highlights some of the key differences between the two drugs in terms of side effects and patient safety. One important distinction is the association between tetrabenazine and secondary movement disorders such as parkinsonism and akathisia in patients with TD, which were negligible in the valbenazine studies. Other potential differences that have been identified by the FDA based on their review of clinical trial results with tetrabenazine in Huntington's disease versus valbenazine in TD, which may not be exactly comparable, can be found in the product labels (e.g., no black-box warning for suicidality/depression or any other warning/precautions for valbenazine) [15,17].

Limitations

As is often the case with systematic reviews [44], one of the main limitations of this analysis was the paucity of details available in some publications, especially the observational tetrabenazine studies. Moreover, as discussed earlier, the heterogeneity of the studies precluded the possibility of conducting a more formal meta-analysis. Therefore, only descriptive summaries could be provided and any interpretation of the results should be considered qualitative in nature. Although purposefully broad search terms were used to capture as many potential articles of interest within PubMed and Embase (i.e., the most frequently used literature databases in the USA), it is possible that this review did not include relevant publications that were only indexed in other databases. However, it seems reasonable to assume that the publications included in this review are adequately representative.

Conclusion

Studies of tetrabenazine and valbenazine for TD indicate that both VMAT2 inhibitors have published evidence of efficacy in the treatment of TD. However, the overall evidence for the efficacy of tetrabenazine is limited by the lack of randomized and placebo-controlled trials, differences across available studies (e.g., no standard dosing, differences in patient selection criteria), and no standardized outcome measures for assessing TD [41]. As would be expected with a recently approved medication, the clinical trials confirming the efficacy of valbenazine in the treatment of TD were larger, well controlled and more rigorously designed than the studies with tetrabenazine. Since the trial design and resultant data available for the two agents varied greatly, a meta-analysis and direct comparison were not possible. However, evidence from the clinical trials suggests that valbenazine is better tolerated and easier to administer, as predicted by the relative pharmacokinetics and off-target binding properties of the two drugs. Ongoing and future research on the effects of VMAT2 inhibitors on TD and other movement disorders is warranted.

Future perspective

Tetrabenazine has been used off-label to treat TD for decades, but valbenazine was recently approved for treatment of TD in adults. Evidence for the effectiveness of these drugs provides support for the mechanism of VMAT2 inhibition as a rational strategy for reducing the severity of TD movements. The approval of valbenazine in the context of the unmet need for treatment of TD, which interferes with social and occupational functioning for thousands of patients receiving antipsychotic therapy, is likely to transform clinical practice. No studies are yet available that directly compare the effects of valbenazine and tetrabenazine in patients with TD. Another

VMAT2 inhibitor, deutetrabenazine, has been approved for the treatment of chorea in Huntington's disease, and more recently for TD, based on the results of two clinical trials (NCT02195700, NCT02291861) [45,46]. With publication of these controlled clinical studies for deutetrabenazine, a future meta-analysis of VMAT2 inhibitors specific for the treatment of TD may be possible.

Executive summary

Background

- Tardive dyskinesia (TD) associated with chronic exposure to dopamine-receptor blocking drugs may have a significant effect on social and occupational functioning.
- A systematic review was conducted to summarize clinical studies results for two vesicular monoamine transporter 2 inhibitors, tetrabenazine and valbenazine, with the intent to execute a meta-analysis.

Results

- Systematic PubMed and Embase searches (January 1980–March 2017) yielded 487 results; 11 studies were included for review.
- Treatment with once-daily valbenazine (three studies) indicated clinically meaningful and statistically significant improvements in TD severity relative to placebo. Valbenazine was safe and well tolerated, both in short- and long-term studies. The most common adverse events were fatigue, headache and somnolence.
- Tetrabenazine (eight studies), which required dosing of one- to three-times daily, also significantly improved TD and was well tolerated. The most common adverse events were parkinsonism, drowsiness/fatigue and depression.

Conclusion

- Results of this systematic review showed the valbenazine studies to be larger and more rigorously designed than the earlier tetrabenazine studies, providing robust evidence in support of the recent US FDA decision affirming valbenazine as the first approved treatment for TD.
- Since the study designs and subjects were vastly different, a meta-analysis or other direct comparison of the two agents was not possible.

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