CNS SPECTRUMS

CME Review Article

Forgotten but Not Gone: New Developments in the Understanding and Treatment of Tardive Dyskinesia

This activity is provided by the Neuroscience Education Institute.

Additionally provided by the American Society for the Advancement of Pharmacotherapy.

American Society for the Advancement of Pharmacotherapy
Division 55, American Psychological Association

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

CME Information

Date of Release/Expiration

Released: December 2016
CME credit expires: November 2019

Learning Objectives

After completing this activity, you should be better able to:

- Discuss patient- and medication-related risk factors for drug-induced tardive dyskinesia
- Implement updated evidence-based treatment strategies for managing drug-induced tardive dyskinesia
- Explain the mechanisms and clinical data for novel agents under investigation for drug-induced tardive dyskinesia

Accreditation and Credit Designation Statements

The Neuroscience Education Institute (NEI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Neuroscience Education Institute designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit* ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Society for the Advancement of Pharmacotherapy (ASAP), Division 55 of the American Psychological Association, is approved by the American Psychological Association to sponsor continuing education for psychologists. ASAP maintains responsibility for this program and its content.

The American Society for the Advancement of Pharmacotherapy designates this program for 1.0 CE credit for psychologists.

Instructions for Optional Posttest and CME Credit

The estimated time for completion of this activity is 60minutes. There is no posttest fee nor fee for CME credits.

1. Read the article.
2. Complete the posttest and activity evaluation, available only online at www.neiglobal.com/CME (under "CNS Spectrums").
3. Print your certificate (if a score of 70% or more is achieved).

Questions? call 888-535-5600, or email CustomerService@neiglobal.com

Peer Review

These materials have been peer reviewed by an MD specializing in psychiatry to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. NEI takes responsibility for the content, quality, and scientific integrity of this CME activity.

Disclosures

All individuals in a position to influence or control content are required to disclose any financial relationships. Although potential conflicts of interest are identified and resolved prior to the activity being presented, it remains for the participant to determine whether outside interests reflect a possible bias in either the exposition or the conclusions presented.

Disclosed financial relationships with conflicts of interest have been reviewed by the NEI CME Advisory Board Chair and resolved.

Author

Jonathan M Meyer, MD, is an assistant clinical professor in the Department of Psychiatry at the University of California, San Diego School of Medicine in La Jolla, CA, and a psychopharmacology consultant for the California Department of State Hospitals. Dr. Meyer is a consultant/advisor to Forum and Teva, and is on the speakers bureaus of Acadia, Alkermes, Merck, Otsuka, and Sunovion.

No writing assistance was utilized in the production of this article.

CNS Spectrums Peer Review

All CME articles are peer reviewed in accordance with the strict standards of *CNS Spectrums* and in accordance with requirements and recommendations of the International Committee of Medical Journal Editors. The Editorial policies of the journal *CNS Spectrums* and peer review of all articles that appear in the journal is managed independently by Cambridge University Press and no financial relationship exists between the CME provider and Cambridge for this service.

Additional Peer Reviewer

Ronnie Gorman Swift, MD, is a professor in and associate chairman of the Department of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, NY, and the chief of psychiatry and associate medical director at Metropolitan Hospital Center in New York, NY. Dr. Swift has no financial relationships to disclose.

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

The **Planning Committee** has no financial relationships to disclose.

Disclosure of Off-Label Use

This educational activity may include discussion of unlabeled and/or investigational uses of agents that are not currently labeled for such use by the FDA. Please consult the product prescribing information for full disclosure of labeled uses.

Cultural and Linguistic Competency

A variety of resources addressing cultural and linguistic competency can be found at this link: www.neiglobal.com/go/cmeregs

Provider

This activity is provided by NEI, the Neuroscience Education Institute.

Additionally provided by the American Society for the Advancement of Pharmacotherapy.

Acknowledgment of Financial Support

This activity is supported by an unrestricted educational grant from Neurocrine Continental, Inc.

CNS Spectrums (2016), **21**, 16–23.
doi:10.1017/S1092852916000730

CME REVIEW ARTICLE

Forgotten but not gone: new developments in the understanding and treatment of tardive dyskinesia

*Jonathan M. Meyer**

Department of Psyshiatry, University of California, San Diego, California, USA; California Department of State Hospitals (DSH), Psychopharmacology Resource Network, Patton, California, USA

The broad use of atypical antipsychotics was expected to dramatically reduce the prevalence and incidence of tardive dyskinesia (TD), but data show that TD remains an important challenge due the persistent nature of its symptoms and resistance to numerous treatment modalities, including antipsychotic discontinuation. Recent insights on genetic risk factors and new concepts surrounding pathophysiology have spurred interest in the possibility of targeted treatment for TD. As will be reviewed in this article, the number of evidence-based strategies for TD treatment is small: only clonazepam, amantadine, ginkgo biloba extract, and the vesicular monoamine transporter 2 (VMAT2) inhibitor tetrabenazine have compelling data. Using new insights into the metabolism of tetrabenazine and the properties of its active metabolites, 2 modifications of tetrabenazine have been synthesized to improve the kinetic profile, and are currently involved in double-blind placebo controlled studies aimed at U.S. Food and Drug Administration (FDA) regulatory approval. The possible availability of these new agents, deuterated tetrabenazine and valbenazine, significantly widens the range of treatment choices for patients with TD. For clinicians with patients at risk for TD due to dopamine antagonist exposure, experience has shown that the problem of TD will be an ongoing issue in modern psychiatry, and that an appreciation of new developments in the pathophysiology of, risk factors for, and treatment of TD is crucial to managing this condition.

Received 19 September 2016; Accepted 30 September 2016

Key words: Amantadine, antipsychotic, gingko, tardive dyskinesia, tetrabenazine.

Introduction

The term dyskinesia encompasses a broad array of hyperkinetic movement disorders with varying etiopathologies and presentations.[1,2] Management of iatrogenic dyskinesia dominates the literature, as this includes the 2 most commonly encountered etiologies: levodopa-induced dyskinesia among patients with Parkinson's disease and tardive dyskinesia (TD), which is related to medications that reduce dopamine neurotransmission via receptor antagonism (eg, antipsychotics, metoclopramide) or vesicular depletion (reserpine).[1,2] Nonetheless, clinicians should be reminded that there is a baseline rate of spontaneous dyskinesia in the general population estimated at 28.7 per 100,000 person-years, with higher rates among those with older age, female gender, and diabetes mellitus.[3] Using data from the pre-antipsychotic era and first episode studies, untreated schizophrenia is also associated with age-dependent risks for spontaneous dyskinesia, with estimated rates of 4% in first-episode patients, 12% for those under age 30 who are ill for several years, 25% for ages 30–50 years, and 40% for those 60 years or older.[4] Not only is the dyskinesia rate 3.5 times higher in antipsychotic-naive schizophrenia patients compared to matched controls, dyskinesia is also significantly more prevalent in nonpsychotic first-degree relatives compared to controls (odds ratio 1.38, 95% CI: 1.06–1.81), suggesting a common genetic basis for dopamine dysfunction that increases risk for psychosis and movement disorders.[5]

Irrespective of the demographic factors, when confronted with patients with drug-induced TD, clinicians have 3 viable options: drug discontinuation (when possible), switching to less potent dopamine antagonists, or use of adjunctive agents. For the cohort of patients who do not have a primary psychotic disorder discontinuing the offending agent is the most logical choice, but the long-term data show low rates of reversibility. In prospective

* Address for correspondence: Jonathan M. Meyer, M.D., UCSD Dept. of Psychiatry, 4225 Executive Square, Suite 1130, La Jolla, CA 92037, USA. (Email: jmmeyer@ucsd.edu)

This activity is supported by an unrestricted educational grant from Neurocrine Continental, Inc.

studies where patients had dopamine modulators withdrawn (primarily antipsychotics and metoclopramide), remission rates were extremely low (2%), and response rates to drug discontinuation were in the range of 1–20%.[6] Second generation antipsychotics generally have lower TD rates than the more potent dopamine D_2 antagonist first generation antipsychotics,[7,8] yet switching to a weaker D_2 antagonist such as quetiapine or olanzapine may be impractical for psychiatric reasons (eg, the patient requires a higher level of D_2 antagonism for optimal benefit); moreover, there are limited data to suggest reversibility of tardive syndromes upon switching to an atypical antipsychotic, with conflicting data for clozapine.[2] For patients in whom drug discontinuation does not yield substantial benefit, or who require ongoing use of dopamine blockade to treat psychiatric illness, TD management over the last 40 years necessitated choosing from an array of options, most of which demonstrated limited efficacy. However, in the past 4 years, there has been a tremendous shift away from the therapeutic nihilism surrounding TD, as the literature has been rapidly populated with papers discussing new insights into TD pathophysiology and new agents for TD management.[9,10] These insights and pharmacological advances will be discussed here, with a focus on those agents with promising clinical data that may lead to regulatory approval.

Pathophysiology of TD

Data from the early 1990s supported the concept that TD was a manifestation of D_2 receptor upregulation and supersensitivity related to chronic reduction in dopaminergic neurotransmission, primarily from postsynaptic receptor blockade.[9] Dopamine D_2 receptors are expressed on striatal medium spiny neurons and function in an inhibitory manner to reduce the velocity and amplitude of movements through activation of the so-called the indirect basal ganglia pathway.[11] The development of increased D_2 receptor sensitivity would thus be expected to induce hyperkinesia. This model was supported by in vivo animal data demonstrating the development of D_2 receptor upregulation and supersensitivity after exposure to D_2 antagonists, and by the clinical observation that withdrawal of D_2 antagonists in humans resulted in TD exacerbation[9]; however, animal data also demonstrate that these phenomena occur very quickly after drug exposure, contrary to the clinical course of TD, and are rapidly reversible after withdrawal of the dopamine antagonist, implying that the persistent forms of TD in humans may have differing mechanisms than that associated with withdrawal dyskinesia.[12,13] Moreover, while increased striatal D_2 receptor binding can be seen in patients exposed to chronic D_2 blockade, this effect is not necessarily correlated with the presence of dyskinesia in imaging or postmortem studies.[9] Although the D_2 upregulation/supersensitivity hypothesis for TD appears lacking in humans, primates exposed to clozapine or haloperidol experienced significant D_3 receptor upregulation in the haloperidol cohort, with the extent of D_3 binding in the nigrostriatal regions correlating with TD intensity.[13] There is also support for the D_3 hypothesis from genetic studies associating certain D_3 receptor polymorphisms with increased TD risk.[14] Given the large overlap in sequence homology and ligand affinity between D_2 and D_3 receptors, selective D_3 agents have only recently been developed for in vivo human neuroimaging, so future imaging studies may shed light on the viability of this concept.[15]

Genetic markers have also implicated numerous pathways involved in striatal dopaminergic signaling, including serotonin and dopamine receptor variations,[14] and polymorphisms in the gamma-aminobutyric acid (GABA) transporter[16] and $GABA_A$ receptor.[17] As will be discussed below, modulation of vesicular monoamine transporter type 2 (VMAT2) is a promising treatment modality, and several polymorphisms in the VMAT2 gene have been associated with increased TD risk.[18]

Other hypotheses have been advanced over the years related to in vivo animal data, and clinical and genetic human studies. The involvement of free radicals and other oxidative mechanisms was suggested 2 decades ago on the basis of animal and a small number of human studies.[19] These hypotheses fell into disfavor due to the inconsistent results from vitamin E trials,[20] but they have not been completely abandoned, as some genetic studies point to increased risk among those with polymorphisms in the free radical scavenger enzyme superoxide dismutase and related anti-oxidative enzymes[9,21] and to markers related to systemic inflammation.[22] Recent animal studies have indicated that peroxisome proliferator-activated receptor (PPAR) agonists exhibit neuroprotective properties, leading to exploratory studies of the PPAR-gamma agonist pioglitazone and PPAR-alpha agonist fenofibrate in rat models of TD, with positive results.[23] The observations that phenylketonuria was associated with TD risk and that administration of large phenylalanine doses worsened dyskinetic symptoms in patients with TD led to the hypothesis that failure to clear central nervous system phenylalanine might underlie TD pathophysiology. Branched chain amino acids compete with phenylalanine for transport across the blood–brain barrier, and their use was associated with TD improvement in a number of studies; however, most of these were open label and were performed by investigators at 1 institution.[24] No new studies have appeared in the past decade.

Among the more novel findings from genetic association studies are loci associated with development, cellular signaling, and neuroplasticity.[9,11] That TD might be best viewed as a disorder of synaptic plasticity has

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

emerged as a leading unifying hypothesis that brings together basic science and genetic findings with the clinical observation that TD shows limited reversibility after withdrawal of offending agents.[11] While striatal D_2 receptor hypersensitivity might be the initial manifestation of D_2 antagonist exposure, ongoing D_2 blockade creates secondary effects on the plasticity of glutamatergic synapses of striatal interneurons. Aberrant glutamatergic signals to cortical structures that also have impaired plasticity results in a situation wherein withdrawal of dopamine antagonists fails to generate the expected symptomatic reversal.[9] Not only does this model suggest that certain glutamate-based strategies might be effective for TD,[9] but it also explains why signal interruption via surgical pallidotomy or bilateral deep brain stimulation (DBS) of the internal part of the globus pallidus (GPi) have been reported as beneficial in those with intractable TD.[25]

Imaging studies and peripheral markers in schizophrenia patients with TD reflect this underlying cellular dysfunction. Reduced basal ganglia and thalamic volume is seen among those with TD, with the greatest reductions found in the caudate nucleus.[26] S100B is a calcium binding protein expressed by astrocytes and involved in numerous cell regulatory processes. Peripheral S100B levels are increased after central nervous system cellular insults, and data in schizophrenia patients not only reveal higher S100B levels among those with TD, but also that serum S100B levels positively correlate with abnormal movement rating scale scores.[27]

Treatment

After an extensive review of the literature, the American Academy of Neurology (AAN) found few evidence-based therapies for TD in 2013 and concluded that the following agents are either not recommended, or have insufficient data to support (or refute) their use: acetazolamide, bromocriptine, baclofen, buspirone, diltiazem, galantamine, eicosapentaenoic acid, levetiracetam, vitamin E, vitamin B6, thiamine, selegiline, melatonin, nifedipine, yi-gan san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy, α-methyldopa, reserpine, and pallidal DBS.[28] The AAN review also noted that data are insufficient to support or refute TD improvement by withdrawing causative agents or switching from typical to atypical antipsychotics.[28] Vitamin E in particular had proponents based on early small case series, but these findings failed to replicate in larger controlled studies.[2,29] Evidence for branched chain amino acid preparations also remains inconclusive due to the paucity of controlled studies.[2]

Among the small number of evidence-based options are clonazepam, ginkgo biloba, amantadine, and tetrabenazine. In a double-blind, crossover, 12-week, placebo-controlled study, clonazepam (mean dose 3.5 mg/d) was associated with 35% improvement in dyskinesia symptoms (n = 19), although tolerance developed after 5–8 months of use in the 5 subjects whose treatment continued up to 9 months.[30] The investigators noted that a 2-week washout was sufficient to restore the antidyskinetic effect of clonazepam. Of the 4 published studies of amantadine use, 2 employed double-blind, placebo-controlled, crossover designs. The first, an 18-week trial, reported 15% improvement in dyskinesia ratings on an amantadine dose of 300 mg/d,[31] while the second study randomized patients to amantadine 100 mg/d or placebo for 2 weeks each (with a 4-day washout between treatment arms) and found a 22% reduction in abnormal involuntary movement scale (AIMS) scores.[32] Extract of ginkgo biloba (EGb) is an antioxidant that possesses free radical scavenging properties. A standardized extract (EGb-761) was examined in a 12-week, double-blind, placebo-controlled trial in which inpatients with schizophrenia and TD were randomly assigned to EGb-761 240 mg/d (n = 78) or placebo (n = 79). EGb-761 was well tolerated, with 96.8% of subjects completing the study. There was a significantly greater decrease in endpoint AIMS total score in the patients treated with EGb-761 compared to the placebo cohort ($p < 0.0001$), with ≥30% reduction in AIMS noted in 51.3% of EGb-761 but only 5.1% of the placebo group.[33]

By the 1960s, it was known that TD was the result of increased dopamine signaling, and this led to the search for agents that could modulate dopamine neurotransmission without directly antagonizing postsynaptic receptors. Reserpine's effect on presynaptic vesicle monoamine content would not be elucidated until the 1960s; however, by the mid-1950s it was known that reserpine had antipsychotic properties and was useful for movement disorders such as Huntington's disease, but with significant tolerability issues related to orthostasis.[34,35] Tetrabenazine (TBZ) was developed in the 1950s as an antipsychotic based on in vivo models that predicted reserpine-like effects, but with markedly reduced orthostasis risk.[36] The first TD study with TBZ was published in 1972 with the authors rationalizing the choice of TBZ due to its lower risk for hypotension than reserpine.[37] Though TBZ has been available in Canada, Great Britain, and Europe for decades, it was not approved in the US until August 15, 2008, with an indication for the management of chorea in patients with Huntington's disease.

While the mechanism that differentiated reserpine's and TBZ's clinical properties was not understood, by the mid-1980s it became clear that integral membrane transporters were necessary to package neurotransmitters

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

into synaptic vesicles of presynaptic neurons (Figure 1).[38] This discovery led to the characterization of multiple vesicular transporters, including those with specificity for acetylcholine,[39] or for monoamines such as dopamine, serotonin, norepinephrine, epinephrine, and histamine.[40] The vesicular monoamine transporter (VMAT) was found to exist in 2 isoforms (VMAT1 and VMAT2) that vary in distribution: VMAT1 is expressed mainly in the peripheral nervous system, while VMAT2 is expressed mainly in monoaminergic cells of the CNS.[41] TBZ's improved tolerability profile was related to the fact that it was a specific and reversible VMAT2 inhibitor, while reserpine was an irreversible and non-selective antagonist of both VMAT isoforms. TBZ and reserpine also have different binding sites on VMAT2 (Figure 2).

Investigation of TBZ's metabolism revealed that it is rapidly and extensively converted into 2 isomers, α-dihydrotetrabenazine (DH-TBZ) and β-DH-TBZ, which have high affinity for VMAT2 and are the pharmacologically active agents.[42,43] The α-DH-TBZ isomer is metabolized via cytochrome P450 (CYP) 2D6 and 3A4 into inactive metabolites, while β-DH-TBZ is metabolized solely via 2D6.[44,45] Due to the short half-life of DH-TBZ and the existence of 2D6 polymorphisms, use of TBZ for Huntington's disease carries recommendations for thrice daily (TID) dosing, and for CYP 2D6 genotyping to screen for poor metabolizer status when exceeding 50 mg/d.[46] To obviate these issues, 2 different pharmacological strategies were explored to moderate TBZ's metabolism, to permit once-daily dosing, and also to improve tolerability.

Deutetrabenazine

The use of the stable isotope deuterium to replace selected hydrogen atoms in a molecule can result in a compound with similar pharmacodynamic properties but different kinetics, as the carbon-deuterium covalent bond requires 8 times more energy to break than a carbon-hydrogen bond.[47] A deuterated form of TBZ deutetrabenazine (Deut-TBZ) was synthesized (Figure 3) with such purpose in mind. While the active metabolites of Deut-TBZ retain the VMAT2 affinity of the nondeuterated DTBZ forms, the substitution of deuterium for hydrogen at specific positions markedly slows the

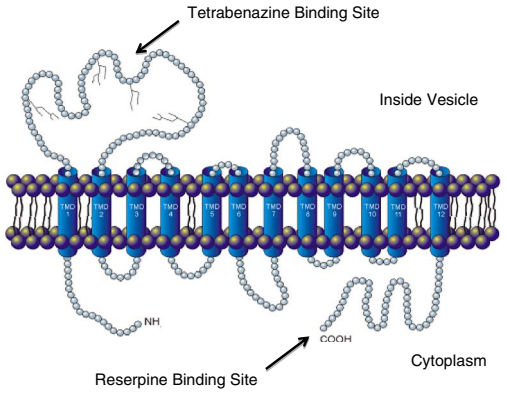

FIGURE 2. VMAT2 structure.[46] Adapted from: Jankovic J, Clarence-Smith K. Tetrabenazine for the treatment of chorea and other hyperkinetic movement disorders. Expert Review of Neurotherapeutics 2011; 11(11):1509-2, reprinted by permission of the publisher Taylor & Francis Ltd. (http://www.tandfonline.com).

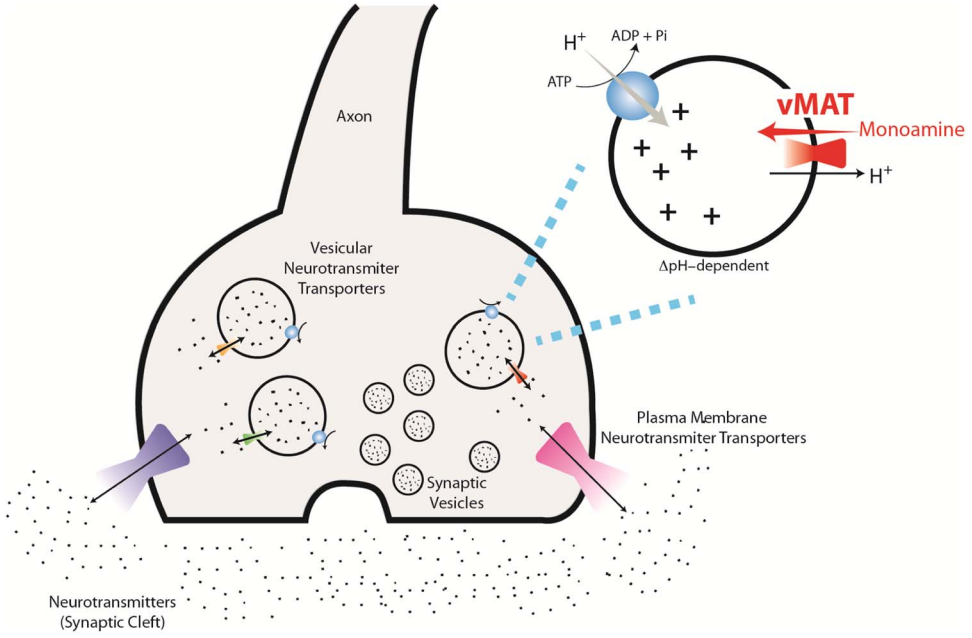

FIGURE 1. Location and function of VMAT. ADP: adenosine biphosphate, ATP: adenosine triphosphate, VMAT: vesicular monoamine transporter.

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

breakdown of metabolites, resulting in a pharmacokinetic profile with longer metabolite duration of action, greater active drug exposure (Figure 4), and less impact of 2D6 genotype on drug exposure, eliminating the need for genotyping.[47,48] Deut-TBZ was first studied in Huntington's chorea in a 13-week, double-blind, placebo-controlled, parallel-group study in which 90 patients were randomized 1:1 to receive Deut-TBZ or placebo twice daily.[48] The study involved an 8-week titration period and 4-week maintenance period followed by a 1-week washout. The maximum daily Deut-TBZ dose was 48 mg, but was reduced to 36 mg in those receiving a strong CYP 2D6 inhibitor (bupropion, fluoxetine, or paroxetine). No dose modification was needed based on 2D6 genotype. There was a 36.4% reduction in total maximal chorea score for Deut-TBZ compared to 14.4% for placebo.[48] Importantly, adverse effects were comparable between both groups, with 1 drop-out in the Deut-TBZ arm vs 2 in the placebo arm. The only adverse event occurring in ≥5% of Deut-TBZ subjects and at a rate ≥2 times that of placebo was somnolence: 11.1% for Deut-TBZ vs. 4.4% for placebo.

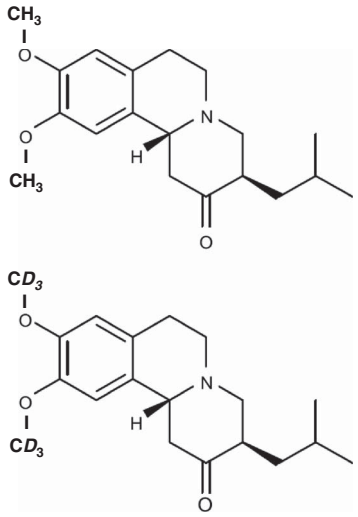

FIGURE 3. Structures of tetrabenazine and deutetrabenazine.

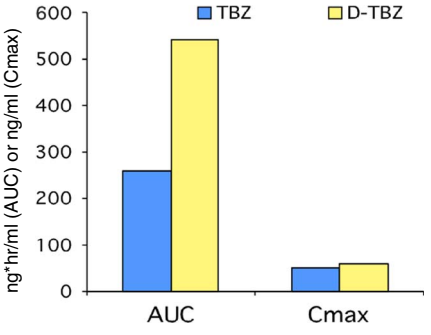

FIGURE 4. Kinetics of tetrabenazine and deutetrabenazine.[47]

A subsequent TD study was performed in a similar design with 117 subjects randomized in 1:1 manner to Deut-TBZ or placebo.[49] The population demographics were as follows: mean age 54.9 ± 9.8 years, 59% female, 79% Caucasian, 80.5% of whom were receiving ongoing dopamine antagonists, mean TD duration of 75.0 ± 81.9 months. The mean baseline AIMS score for items 1–7 was 9.6 ± 3.9, with 85.8% of subjects having AIMS ≥ 6. Study treatment retention was high, with 6 drop-outs in the Deut-TBZ arm vs 7 in the placebo arm. There was a mean 3.0 point decrease in AIMS for Deut-TBZ compared to 1.4 for placebo ($p = 0.019$). Among those with baseline AIMS ≥ 6, there was a 3.4 point decrease in AIMS for Deut-TBZ compared to 1.9 for placebo ($p = 0.027$). There were no adverse effects that occurred in ≥5% of Deut-TBZ subjects and at a rate ≥2 times the rate in placebo.

Valbenazine

Each of TBZ's active metabolites α- and -DH-TBZ possess multiple chiral centers, yielding a total of 8 possible isomers (Figure 5), each of which has different VMAT2 activity.[45,50] Characterization of isomers with greatest VMAT2 affinity (Table 1) led to the development of valbenazine, a prodrug that is metabolized into the most active DH-TBZ isomers.[45] Importantly, valbenazine was designed to be metabolized slowly, and thereby minimize high peak plasma concentrations, decrease peak-to-trough ratios, and reduce inter-subject variability. The T_{Max} for the active metabolites is 4–10 hours with a

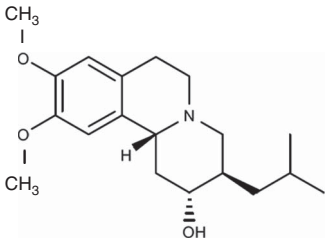

FIGURE 5. Dihydrotetrabenazine.

TABLE 1. Dihydrotetrabenazine (DH-TBZ) isomer affinity for VMAT2 (Ki ± SEM nM)[50]

Isomer	Ki ± SE (nM)
(2R,3R,11bR)-DH-TBZ	3.96 ± 0.40
(2S,3S,11bS)-DH-TBZ	23,700 ± 2350
(2S,3R,11bR)-DH-TBZ	13.4 ± 1.36
(2R,3S,11bS)-DH-TBZ	2460 ± 333
(2R,3S,11bR)-DH-TBZ	71.1 ± 6.66
(2S,3R,11bS)-DH-TBZ	4630 ± 350
(2S,3S,11bR)-DH-TBZ	593 ± 69.7
(2R,3R,11bS)-DH-TBZ	1253 ± 314

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

half-life of approximately 20 hours, allowing once-daily dosing.[51] Due to the limited range of metabolites (2), it was also designed to limit off-target receptor binding that was theoretically possible with certain DH-TBZ isomers.[45] Data from a randomized, 6-week, double-blind, placebo-controlled, dose-titration study in subjects with TD was published in 2015 (n = 100).[51] The population demographics were as follows: mean age 56.2 ± 10.3 years, 57% male, 79% Caucasian, 73% of whom were receiving ongoing antipsychotic treatment, mean TD duration of 7 years. The mean baseline AIMS score for items 1–7 was 8.0 ± 4.0. The valbenazine starting dose was 25 mg, and this could be escalated in 25 mg increments every 2 weeks to a maximum of 75 mg. At study endpoint, 75% of subjects were on the maximum dose, and there were no study drop-outs due to adverse events in the valbenazine cohort. There was a mean 3.6 point decrease in AIMS for valbenazine compared to 1.1 for placebo ($p = 0.0005$), with lower baseline severity and mood diagnosis (vs schizophrenia spectrum) moderating factors that improved treatment response.[52] The following adverse events occurred in ≥5% of valbenazine subjects and at a rate ≥2 times that of placebo: fatigue: 9.8% for valbenazine vs 4.1% for placebo; headache: 9.8% for valbenazine vs 4.1% for placebo; decreased appetite: 7.8% for valbenazine vs 0% for placebo.

A subsequent 6-week study using similar design was presented in 2016 using dosing data derived from the prior trial.[53] In this design 234 subjects with TD were randomized in a 1:1:1 manner to placebo, valbenazine 40 mg once daily or valbenazine 80 mg once daily. Completion rates were high (87.6%), with only 2 drop-outs due to adverse events in each of the placebo and 40 mg arms, and 3 in the 80 mg group. There were no adverse events in either valbenazine arm that exceed 5% in frequency and were ≥2 times that of placebo. Subject demographics were similar to the prior trial but with higher baseline AIMS scores: mean 10.4 ± 3.6.[53] The prior trial demonstrated a least squares mean 2.5 point difference in AIMS score between valbenazine and placebo, while for this trial the least squares mean change from baseline to week 6 was 3.1 points between valbenazine 80 mg (-3.2) and placebo (-0.1) ($p < 0.001$). The effect size (Cohen's *d*) was large, at 0.90.

Conclusions

There have been significant advances in the understanding of schizophrenia pathophysiology, but knowledge of tardive dyskinesia has lagged behind. As with other complex disorders, genetic load and environmental factors impose risks. Besides exposure to dopamine modulating agents, sources of oxidative stress may be another contributing factor to TD development. Recent data indicate that the final common pathway for persistent TD may relate to aberrations in synaptic plasticity, while the model of receptor upregulation/supersensitivity applies more appropriately to withdrawal dyskinesia, with its high rates of reversibility. On the other hand, TD shows very low rates of improvement after antipsychotic discontinuation, indicating a more durable problem with persistently abnormal synaptic connections.[9]

Although the developments discussed above have suggested some potential evidence-based treatment options, such as ginkgo biloba extract,[33] clinicians have been discouraged by positive case reports for a variety of agents, many of which have limited high-level evidence for TD treatment.[28] However, more rigorous clinical research with the VMAT2 inhibitor tetrabenazine has amassed a considerable evidence base for TD treatment.[54] Importantly, characterization of TBZ's metabolic pathway and the activity of its isomers has yielded 2 divergent strategies for optimizing response to TBZ: (1) deuterated tetrabenazine (Deut-TBZ), where the substitution of deuterium for selected hydrogen atoms increases bond strength 8-fold, delays breakdown of active metabolites, and minimizes variability in drug exposure based on 2D6 genotype; and (2) valbenazine, a prodrug for the active TBZ isomers. Both of these options appear effective in phase 3 studies, with kinetic profiles that permit once-daily dosing and obviate the need for 2D6 genotyping.

Given the widespread use of antipsychotics in the management of schizophrenia, bipolar mania, bipolar depression, and adjunctively for unipolar depression, persistent TD will remain a clinical feature of modern psychiatry. The resurgent interest in TD has led to valuable insights into pathophysiology and mechanisms for TD management. The clinical development of 2 new compounds based on the older but useful agent tetrabenazine has yielded therapies that that may be soon available for treatment of this vexing problem. With the routine use of atypical antipsychotics, many clinicians have developed the perception that persistent TD was a thing of the past. For those who work with the chronically and persistently mentally ill, or who are unfortunate to have higher functioning mood patients with this disorder, TD is an issue that clearly is not gone, and should not be forgotten.

Disclosures

Dr. Meyer reports having received speaking or advising fees from Acadia, Alkermes, Forum, Merck, Otsuka-USA, Sunovion, and Teva.

REFERENCES:

1. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 1: treatment of levodopa-induced dyskinesia. *Drugs*. 2016; **76**(7): 759–777.

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

2. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 2: treatment of tardive dyskinesia. *Drugs*. 2016; **76**(7): 779–787.
3. Merrill RM, Lyon JL, Matiaco PM. Tardive and spontaneous dyskinesia incidence in the general population. *BMC Psychiatry*. 2013; **13**(1): 152–160.
4. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. *J Clin Psychiatry*. 2000; **61**(Suppl 4): 10–14.
5. Koning JPF, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull*. 2010; **36**(4): 723–731.
6. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics*. 2014; **11**(1): 166–176.
7. Ryu S, Yoo JH, Kim JH, *et al*. Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-elderly schizophrenic patients unexposed to first-generation antipsychotics: a cross-sectional and retrospective study. *J Clin Psychopharmacol*. 2015; **35**(1): 13–21.
8. Kinon BJ, Kollack-Walker S, Jeste D, *et al*. Incidence of tardive dyskinesia in older adult patients treated with olanzapine or conventional antipsychotics. *J Geriatr Psychiatry Neurol*. 2015; **28**(1): 67–79.
9. Teo JT, Edwards MJ, Bhatia K. Tardive dyskinesia is caused by maladaptive synaptic plasticity: a hypothesis. *Mov Disord*. 2012; **27**(10): 1205–1215.
10. Rana AQ, Chaudry ZM, Blanchet PJ. New and emerging treatments for symptomatic tardive dyskinesia. *Drug Des Devel Ther*. 2013; **7**(6): 1329–1340.
11. Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. *Parkinsonism Relat Disord*. 2014; **20**(Suppl 1): S113–S117.
12. Casey DE. Tardive dyskinesia: pathophysiology and animal models. *J Clin Psychiatry*. 2000; **61**(Suppl 4): 5–9.
13. Mahmoudi S, Levesque D, Blanchet PJ. Upregulation of dopamine D3, not D2, receptors correlates with tardive dyskinesia in a primate model. *Mov Disord*. 2014; **29**(9): 1125–1133.
14. Segman RH, Goltser T, Heresco-Levy U, *et al*. Association of dopaminergic and serotonergic genes with tardive dyskinesia in patients with chronic schizophrenia. *Pharmacogenomics J*. 2003; **3**(5): 277–283.
15. Le Foll B, Wilson AA, Graff A, Boileau I, Di Ciano P. Recent methods for measuring dopamine D3 receptor occupancy in vivo: importance for drug development. *Front Pharmacol*. 2014; **5**(1): 161.
16. Son WY, Lee HJ, Yoon HK, *et al*. Gaba transporter SLC6A11 gene polymorphism associated with tardive dyskinesia. *Nord J Psychiatry*. 2014; **68**(2): 123–128.
17. Inada T, Koga M, Ishiguro H, *et al*. Pathway-based association analysis of genome-wide screening data suggest that genes associated with the gamma-aminobutyric acid receptor signaling pathway are involved in neuroleptic-induced, treatment-resistant tardive dyskinesia. *Pharmacogenet Genomics*. 2008; **18**(4): 317–323.
18. Zai CC, Tiwari AK, Mazzoco M, *et al*. Association study of the vesicular monoamine transporter gene SLC18A2 with tardive dyskinesia. *J Psychiatr Res*. 2013; **47**(11): 1760–1765.
19. Lohr JB, Browning JA. Free radical involvement in neuropsychiatric illnesses. *Psychopharmacol Bull*. 1995; **31**(1): 159–165.
20. Lohr JB, Kuczenski R, Niculescu AB. Oxidative mechanisms and tardive dyskinesia. *CNS Drugs*. 2003; **17**(1): 47–62.
21. Cho CH, Lee HJ. Oxidative stress and tardive dyskinesia: pharmacogenetic evidence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; **46**(1): 207–213.
22. An HM, Tan YL, Shi J, *et al*. Altered IL-2, IL-6 and IL-8 serum levels in schizophrenia patients with tardive dyskinesia. *Schizophr Res*. 2015; **162**(1–3): 261–268.
23. Grover S, Kumar P, Singh K, Vikram V, Budhiraja RD. Possible beneficial effect of peroxisome proliferator-activated receptor (PPAR)–alpha and gamma agonist against a rat model of oral dyskinesia. *Pharmacol Biochem Behav*. 2013; **111**(1): 17–23.
24. Richardson MA, Small AM, Read LL, Chao HM, Clelland JD. Branched chain amino acid treatment of tardive dyskinesia in children and adolescents. *J Clin Psychiatry*. 2004; **65**(1): 92–96.
25. Pouclet-Courtemanche H, Rouaud T, Thobois S, *et al*. Long-term efficacy and tolerability of bilateral pallidal stimulation to treat tardive dyskinesia. *Neurology*. 2016; **86**(7): 651–659.
26. Sarró S, Pomarol-Clotet E, Canales-Rodríguez EJ, *et al*. Structural brain changes associated with tardive dyskinesia in schizophrenia. *Br J Psychiatry*. 2013; **203**(1): 51–57.
27. Zhang XY, Xiu MH, Chen da C, *et al*. Increased S100B serum levels in schizophrenic patients with tardive dyskinesia: association with dyskinetic movements. *J Psychiatr Res*. 2010; **44**(7): 429–433.
28. Bhidayasiri R, Fahn S, Weiner WJ, *et al*. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013; **81**(5): 463–469.
29. Soares KV, McGrath JJ. Vitamin E for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2001;(4): CD000209.
30. Thaker GK, Nguyen JA, Strauss ME, Jacobson R, Kaup BA, Tamminga CA. Clonazepam treatment of tardive dyskinesia: a practical GABAmimetic strategy. *Am J Psychiatry*. 1990; **147**(4): 445–451.
31. Angus S, Sugars J, Boltezar R, Koskewich S, Schneider NM. A controlled trial of amantadine hydrochloride and neuroleptics in the treatment of tardive dyskinesia. *J Clin Psychopharmacol*. 1997; **17**(2): 88–91.
32. Pappa S, Tsouli S, Apostolou G, Mavreas V, Konitsiotis S. Effects of amantadine on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Clin Neuropharmacol*. 2010; **33**(6): 271–275.
33. Zhang WF, Tan YL, Zhang XY, Chan RC, Wu HR, Zhou DF. Extract of Ginkgo biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2011; **72**(5): 615–621.
34. Chandler JH. Reserpine in the treatment of Huntington's chorea. *Med Bull (Ann Arbor)*. 1955; **21**(4): 95–100.
35. Lazarte JA, Petersen MC, Baars CW, *et al*. Huntington's chorea: results of treatment with reserpine. *Proc Staff Meet Mayo Clin*. 1955; **30**(16): 358–365.
36. Quinn GP, Shore PA, Brodie BB. Biochemical and pharmacological studies of RO 1-9569 (tetrabenazine), a nonindole tranquilizing agent with reserpine-like effects. *J Pharmacol Exp Ther*. 1959; **127**: 103–109.
37. Kazamatsuri H, Chien C, Cole JO. Treatment of tardive dyskinesia. I. Clinical efficacy of a dopamine-depleting agent, tetrabenazine. *Arch Gen Psychiatry*. 1972; **27**(1): 95–99.
38. Scherman D, Weber MJ. Characterization of the vesicular monoamine transporter in cultured rat sympathetic neurons: persistence upon induction of cholinergic phenotypic traits. *Dev Biol*. 1987; **119**(1): 68–74.
39. Roghani A, Feldman J, Kohan SA, *et al*. Molecular cloning of a putative vesicular transporter for acetylcholine. *Proc Natl Acad Sci U S A*. 1994; **91**(22): 10620–10624.
40. Erickson JD, Eiden LE, Schafer MK, Weihe E. Reserpine- and tetrabenazine-sensitive transport of (3)H-histamine by the neuronal isoform of the vesicular monoamine transporter. *J Mol Neurosci*. 1995; **6**(4): 277–287.

41. Erickson JD, Schafer MK, Bonner TI, Eiden LE, Weihe E. Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. *Proc Natl Acad Sci U S A*. 1996; **93**(10): 5166–5171.
42. Kilbourn M, Lee L, Vander Borght T, Jewett D, Frey K. Binding of alpha-dihydrotetrabenazine to the vesicular monoamine transporter is stereospecific. *Eur J Pharmacol*. 1995; **278**(3): 249–252.
43. Kilbourn MR, Lee LC, Heeg MJ, Jewett DM. Absolute configuration of (+)-alpha-dihydrotetrabenazine, an active metabolite of tetrabenazine. *Chirality*. 1997; **9**(1): 59–62.
44. Mehanna R, Hunter C, Davidson A, Jimenez-Shahed J, Jankovic J. Analysis of CYP2D6 genotype and response to tetrabenazine. *Mov Disord*. 2013; **28**(2): 210–215.
45. Muller T. Valbenazine granted breakthrough drug status for treating tardive dyskinesia. *Expert Opin Investig Drugs*. 2015; **24**(6): 737–742.
46. Jankovic J, Clarence-Smith K. Tetrabenazine for the treatment of chorea and other hyperkinetic movement disorders. *Expert Rev Neurother*. 2011; **11**(11): 1509–1523.
47. SEC Form S-1 Registration Statement of Auspex Pharmaceuticals, Inc. December 20, 2013. https://www.sec.gov/Archives/edgar/data/1454189/000119312513481239/d627086ds1.htm. Accessed 7/1/2016.
48. Huntington Study Group, Frank S, Testa CM, Stamler D, *et al*. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. *JAMA*. 2016; **316**(1): 40–50.
49. Anderson KE, Factor SA, Hauser RA, *et al*. A randomized, double-blind, placebo-controlled trial of deutetrabenazine for the treatment of tardive dyskinesia (ARM-TD). Poster presented at: The American Psychiatric Association Annual Meeting; May 14–18, 2016; Atlanta, GA.
50. Yao Z, Wei X, Wu X, *et al*. Preparation and evaluation of tetrabenazine enantiomers and all eight stereoisomers of dihydrotetrabenazine as VMAT2 inhibitors. *Eur J Med Chem*. 2011; **46**(5): 1841–1848.
51. O'Brien CF, Jimenez R, Hauser RA, *et al*. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Mov Disord*. 2015; **30**(12): 1681–1687.
52. Josiassen RC, Remington G, Burke J, *et al*. Valbenazine (NBI-98854) is effective for treating tardive dyskinesia in individuals with schizophrenia or mood disorder. Poster presented at: The American Psychiatric Association Annual Meeting; May 14–18, 2016; Atlanta, GA.
53. Marder S, Knesevich MA, Hauser RA, *et al*. KINECT 3: a randomized, double-blind, placebo-controlled phase 3 trial of valbenazine (NBI-98854) for tardive dyskinesia. Poster presented at: The American Psychiatric Association Annual Meeting; May 14–18, 2016; Atlanta, GA.
54. Leung JG, Breden EL. Tetrabenazine for the treatment of tardive dyskinesia. *Ann Pharmacother*. 2011; **45**(4): 525–531.

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press

Optional CME Posttest and Certificate

CME Credit Expires: November 30, 2019

CME Posttest Study Guide

NOTE: The posttest can only be submitted online. *The below posttest questions have been provided solely as a study tool to prepare for your online submission.* ***Faxed/mailed copies of the posttest cannot be processed*** *and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.*

1. Positive data for which of the following compounds provide compelling evidence that antioxidant treatment can improve tardive dyskinesia symptoms?
   A. Reserpine
   B. Ginkgo biloba extract
   C. Vitamin E
   D. N-Acetylcysteine
   E. 2 and 3
   F. B, C, and D

2. Which of the following models is the best explanation for the persistence of tardive dyskinesia symptoms in most patients after withdrawal of antipsychotic medication?
   A. Neurotoxicity
   B. Abnormal synaptic plasticity
   C. Postsynaptic receptor upregulation
   D. Postsynaptic receptor supersensitivity
   E. All of the above

3. Which of the following agents has positive data from double-blind, placebo-controlled trials for the treatment of patients with tardive dyskinesia?
   A. Deuterated tetrabenazine
   B. Tritiated tetrabenazine
   C. Valbenazine
   D. 9-Fluororeserpine
   E. A and C
   F. A, B, and C
   G. A–D

Optional CME Online Posttest and Certificate Instructions

There is no posttest fee nor fee for CME credits.

1. Read the article.
2. Complete the posttest and activity evaluation, available only online at www.neiglobal.com/CME (under "CNS Spectrums").
3. Print your certificate, if a score of 70% or more is achieved.

Questions? call 888-535-5600, or email CustomerService@neiglobal.com

https://doi.org/10.1017/S1092852916000730 Published online by Cambridge University Press