Release date: August 1, 2020
Expiration date: August 1, 2021
Estimated time to complete activity:

.75 AMA Category 1 Credit™
.7 ANCC Contact hours
.75 AAPA Credits
.75 ACPE Contact hours
.75 APA Credits

Jointly provided by Postgraduate Institute for Medicine and Global Medical Education

This activity is supported by an independent educational grant from Neurocrine Biosciences.

TARGET AUDIENCE

This activity is intended for physicians, physician assistants, nurse practitioners and registered nurses engaged in the care of patients with TD.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Discuss the diagnosis, and differential diagnosis and risk factors for TD
- Identify the prevalence of TD with antipsychotics
- Use the AIMS examination

FACULTY

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Augusta University Health

JOINT ACCREDITATION STATEMENT

In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Global Medical Education. Postgraduate Institute for Medicine is jointly accredited by the American Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Postgraduate Institute for Medicine designates this continuing education activity for .75 contact hour(s) (0.075 CEUs) of the Accreditation Council for Pharmacy Education.
Universal Activity Number –JA4008162-9999-20-2153-H01-P
Type of Activity: Knowledge

CONTINUING NURSING EDUCATION

The maximum number of hours awarded for this Continuing Nursing Education activity is .7 contact hours. Designated for 0.4 contact hours of pharmacotherapy credit for Advanced Practice Registered Nurses.

CONTINUED ON PAGE S2

SUPPLEMENT TO
Current® PSYCHIATRY
AUGUST 2020 | VOL 19, NO 8
Available at www.mdedge.com/TD

Diagnosing Tardive Dyskinesia in Practice: Are We Doing Enough?

Joseph P McEvoy, MD

BOTTOM LINE:

Although the second-generation antipsychotic medications (SGAs) less frequently produce tardive dyskinesia (TD), the patient populations now treated with SGAs are more aware and distressed when TD occurs. Scheduled monitoring in direct and tele-medicine contacts is necessary for optimal outcomes.

THE EARLY HISTORY OF TD (1950s – 1980s)

Chlorpromazine became available in 1953 for the treatment of severe mental illness (SMI) (eg, schizophrenia, schizoaffective disorder, affective disorders with psychotic features), after astute clinical observation that it quieted people without putting them to sleep. Chlorpromazine produces extrapyramidal side effects (EPSE) (eg, catalepsy) in animals, and investigators used this pharmacological effect to identify new candidate agents for the treatment of SMI. Numerous similar first-generation antipsychotic medications (FGAs) (eg, haloperidol) became available, not surprisingly, all with the propensity to produce EPSE.[1]

FGAs reduce the intensity of positive psychopathology (disorganized thinking and behavior, hallucinatory experiences, and delusional beliefs) as well as the intensity of agitation in many patients with SMI, especially early in the illness course. These therapeutic effects allowed the majority of patients chronically hospitalized in state institutions to move into the community.[2]

The dose-dependent EPSE (eg, acute dystonias, bradykinesia/rigidity, tremor, and/or restlessness) associated with FGAs resemble features of Parkinson's disease (PD). In PD, *substantia nigra* dopamine neurons, whose projections ramify throughout movement-related, basal ganglia circuits like a "sprinkler system", deteriorate and die.[3] Dopamine released from these neurons sets readiness-to-move; when these dopamine neurons die (eg, PD), or when excessive doses of an FGA block the D2 dopamine (D2DA) receptors for released dopamine, readiness-to-move decreases (akinesia). As I will describe below, when D2DA receptors for dopamine in these movement-related circuits become excessively sensitive, there is an increased readiness-to-move and abnormal involuntary movements appear (chorea: eg, TD).

Clinicians usually did not address the appearance of EPSE by lowering the dose of FGAs. Rather, they prescribed anticholinergic medications used with limited benefit to reduce the signs of PD. The benefit for EPSE was similarly incomplete, and anticholinergic medications produce undesirable side effects: dry mouth leading to accelerated tooth decay, constipation that is often severe, and impairment of new learning.[4]

CONTINUED ON PAGE S2

CONTINUED FROM PAGE S1

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Faculty

Joseph P. McEvoy, MD
Consulting Fees: Intra-Cellular Therapies, Sunovion
Contracted Research: Neurocrine Biosciences, Teva

PLANNERS AND MANAGERS

The PIM planners and managers have nothing to disclose.
The Global Medical Education planner and manager, Prakash Masand, MD, has disclosed the following:
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The "dopamine hypothesis" proposes that excessive, uncontrolled release ("storms") of dopamine from cells originating in the ventral tegmental area and ramifying (like a "sprinkler system") through limbic and frontal cortical circuits amplifies and disorganizes the assignment of incentive salience to items of sensory experience and intrapsychic life.[5] The abnormal, involuntary intrusion of these enhanced items disrupts normal mental activity. Random, routine sensory experiences become vivid and demand attention. Internal speech becomes loud and patients experience it as external.[6] The therapeutic effects of FGAs on positive psychopathology and agitation result from antagonism at D2DA receptors in these limbic and cortical circuits, protecting them from the "storms" of dopamine.

The FGAs offer no benefit for the enduring deficits associated with SMI: cognitive impairment, diminished initiative and expression, and neurological soft signs.[7] The enduring deficits appear to reflect the primary pathophysiology of SMI, and are not the result of the secondary pathophysiology (loss of control of ventral tegmental area dopamine neurons) of SMI. The enduring deficits are associated with loss of brain volume.

Clinicians initially failed to understand the differences between the dose-response relationships in these two dopamine "sprinkler systems". Dose-response studies[8] and, later, imaging studies,[9] demonstrated that the therapeutic antipsychotic benefit of FGAs reached a plateau at doses approximately 20% of those commonly used, and that higher doses brought only more frequent and

more severe EPSE. Brain imaging studies demonstrated that 50-60% occupancy of D2DA receptors (achievable with haloperidol doses of 2-10 mg daily) maximized the therapeutic efficacy of FGA, whereas increasing blockade beyond 60% was associated with an increasing burden of coarse EPSE. However, clinicians seeking increased therapeutic efficacy (with no chance of achieving it) continued to increase FGA doses, heedless of coarse EPSE.

In the late 1950s, the first descriptions of TD appeared.[10] It became clear that prior EPSE was a major risk factor,[11] that muffling the EPSE with anticholinergic medication offered no protection, and that the movements usually persisted even when treatment with FGAs stopped. Some cases of TD were severe and interfered with swallowing, speech, breathing, and/or walking.

Yearly risk for TD increased from 5% to 6% in young adults to 30% to 35% in those over 55 years of age. Other factors suggesting reduced brain resilience (presence of the enduring deficits,[12] or systemic illnesses such as diabetes mellitus or atherosclerotic cardiovascular disease)[13] also put patients at increased risk. The target population treated with FGAs during the early history of TD included many with cognitive deficits who reported no awareness of the TD movements, as well as no awareness of mental illness or need for treatment.[14]

No treatments were available. Lawsuits became common. The working hypothesis for the pathophysiology of TD is that D2DA receptors, denied stimulation by dopamine because of excessive blockade, become supersensitive "trip-wires" that respond excessively to random, ambient dopamine molecules in the synapse, triggering abnormal involuntary movements.[15]

THE MIDDLE HISTORY OF TD (1990s – 2010s)

Clozapine becomes available, again through serendipity, and is different from the FGAs in two major ways: (1) It does not produce any coarse EPSE or TD; and, (2) through as yet unexplained mechanisms it offers increased therapeutic benefit in reducing positive psychopathology and agitation.[16]

Clozapine's complex side effect burden precludes widespread clinical use. Pharmaceutical companies develop multiple new agents adding one of clozapine's prominent pharmacological features, strong serotonin 5HT2 antagonism (eg risperidone) to D2DA antagonism, and later also replacing D2DA antagonism with D2DA partial agonism (eg aripiprazole). These changes sharply reduce the capacity of these second-generation antipsychotic medications (SGAs) to produce coarse EPSE and reduce the frequency and severity of new cases of TD.[17]

The non-clozapine SGAs do not share clozapine's enhanced therapeutic efficacy versus positive psychopathology, nor do they reverse/reduce the enduring deficits.

However, their use expanded well beyond the SMI population primarily addressed by the FGAs. They have substantial therapeutic efficacy as adjuncts in major depressive disorder not adequately treated with an antidepressant medication alone,[18] as monotherapy or, more commonly, as adjuncts to lithium or anticonvulsant mood stabilizers for bipolar disorder,[19] and as agents to reduce disruptive behaviors in youth[20] or, off label, in agitated elderly with cognitive decline.[21]

The population exposed to SGAs is much larger than the target population for the FGAs was. Although these agents are less likely to produce TD, and moderate or severe TD than the FGAs, the number of patients exposed is greatly increased and TD continues to appear in our patients. These new populations, in particular non-psychotic patients with affective disorders and youth with behavioral disturbances, are keenly aware of TD movements when they occur. These new populations expect to resume social and occupational functioning. TD movements are readily apparent to them and to the people with whom they interact at school or work and in relationships.

Because of the other important adverse events associated with the SGAs (weight gain, insulin resistance, and dyslipidemia), and because no consistently effective and well-tolerated treatments for TD were available, attention to detection and early management of TD relaxed. However, clinicians are now searching for fewer, less obvious cases of TD in a larger population, and systematic and sensitive screening is necessary.

TABLE

Activation maneuvers

Hold arms extended in front
Let wrists go limp, hands hang loosely
Tell me five words beginning with the letter "T"
Watch the hands and face as the patient struggles to come up with words
Hold mouth wide open
Touch each finger to the thumb repeatedly. First with dominant, then with non-dominant hand
Watch the face and tongue as the patient concentrates on the movements

THE RECENT HISTORY OF TD

Valbenazine and deutetrabenazine become available, offering highly effective and well-tolerated treatments for TD.[22,23]

We want to detect cases early. TD may be more responsive to treatment when identified early. New cases of TD are likely to occur in discriminating consumers who are aware and who will be highly distressed. Even mild TD will disrupt their social and occupational functioning. These patients, who often achieve remission of their mental illnesses, want to work and have relationships.

HOW DO WE PROCEED?

Wise clinicians will include family/important others in informed consent discussions (if possible, and approved by the patient), and educate them to report coarse EPSE and any appearance of movements suggesting TD. Similarly, treatment staff and supervised living staff can report the appearance of these unwanted events. This is especially true for telepsychiatry practice, where the prescriber may have limited view of, and limited time with, the patient.

Informative videos playing in clinic waiting areas, or that can by pushed to family/important others and treatment/supervised living staff, can provide instruction as well as video examples of TD movements.

Of course, aware and distressed patients will spontaneously report coarse EPSE and new TD. Clinicians may offer queries about teeth or dentures, about speaking

TAKE-HOME POINTS

- TD continues to occur with the use of SGAs. Although the SGAs cause less TD per patient exposed, and less severe TD, clinicians prescribe them for many more indications, and many more patients.
- Patients currently taking SGAs for indications such as adjunctive treatment in major depressive disorder are discriminating consumers who will be aware of, and distressed by, even mild TD.
- In order to detect TD early, when it is most treatable and before it interferes with social and occupational functioning, clinicians must keep lines of communication open from patients, family/important others, and staff at supervised living facilities and outpatient clinics.
- Clinicians must also examine patients for coarse EPSE and TD at regular intervals.
- On-site support staff can assist busy prescribers, in particular telepsychiatry prescribers, focus their examinations to evaluate movements that may signal early TD.

and swallowing, about discomfort in constantly moving feet.

The EMR must cue clinicians at regular intervals to perform examinations for coarse EPSE and TD. Observe the patient at rest and during routine activity(**Table**). Use activation maneuvers to elicit movements. Remember that TD movements fluctuate and may increase with arousal and decrease with relaxation. They disappear with sleep.

Telepsychiatry, with (preferentially) or without video connections, is expanding in use.[24] One constraint is the limited visual field available to the telepsychiatry prescriber. On-site staff must report to the prescriber what family/important others see and report, or what the patient has complained of or displayed in clinic. On-site staff can adjust seating and camera location to improve visualization.

When only audio connection is available, it is especially important to include input from an informant at the patient's location who can describe the patient's movements.

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1.25 AAPA Credits
1.25 ACPE Contact hours
1.25 APA Credits
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Postgraduate Institute for Medicine

GLOBAL MEDICAL EDUCATION

This activity is supported by an independent educational grant from Neurocrine Biosciences.

TARGET AUDIENCE

This activity is intended for physicians, physician assistants, nurse practitioners and registered nurses engaged in the care of patients with TD.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Review the evidence and non-evidenced based treatments for TD
- Individualize treatment choices, giving consideration to efficacy, safety, long-term data, and unique patient characteristics
- Formulate appropriate treatment regimens considering the emergence of new FDA approved treatments for TD

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JOINT ACCREDITATION STATEMENT

In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Global Medical Education. Postgraduate Institute for Medicine is jointly accredited by the American Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Universal Activity Number –JA4008162-9999-20-2154-H01-P
Type of Activity: Knowledge

CONTINUED ON PAGE S6

Available at www.mdedge.com/TD

Evidence-Based Approaches to Optimally Manage Tardive Dyskinesia

Daniel Guinart MD and John M Kane MD

BOTTOM LINE:
Although the incidence of tardive dyskinesia (TD) is lower with second-generation antipsychotics, their use has expanded the population at risk. Prevention and early identification remain key, but for the first time we have FDA-approved treatments for TD.

Soon after the introduction of antipsychotic medications, a syndrome of involuntary movements labeled TD was reported to be associated with long-term use of these agents. At first, these reports were met with some skepticism and even denial, but gradually epidemiologic data became quite convincing that TD was a significant risk. At the same time, it took many years to establish the true prevalence and incidence across a range of populations.[1,2] As concerns mounted, clinicians found themselves with little guidance as to how to treat TD, and prevention became a major focus. Recommendations underscored the importance of only using antipsychotic medications when indications were clear, and the potential benefit outweighed the potential risks. In addition, using the lowest possible dose and being on the lookout for early signs of TD were strongly encouraged. Older age emerged as an important risk factor, as did the early occurrence of extrapyramidal side effects.[1,3]

When TD emerged, recommendations encouraged discontinuing the associated antipsychotic drug or at least lowering the dose as much as possible. In some cases, this was sufficient to ameliorate evidence of TD, but in many cases it was not. In addition, this put clinicians and patients in a difficult bind as discontinuing medication, and even lowering doses in some cases, was associated with a substantial increase in the risk of relapse, with all the potential deleterious sequelae. At the same time, TD became the focus of liability concerns and whether patients had received adequate warnings from both the medication manufacturers and the prescribing practitioner. Documentation of assessment for TD and recognition of early signs became an appropriate expectation. The fact that TD could, in the minority of cases, be severe and disabling as well as irreversible added to the concerns. It was also recognized that even mild cases could interfere with patient well-being as well as social and vocational opportunities.

Against this backdrop, there continued to be no proven effective and safe treatments for TD. Then, in the 1990's clozapine was approved for the treatment of severely ill patients with schizophrenia who fail to respond adequately to antipsychotic treatment. Although no attempts were made to garner an indication for clozapine in the treatment of TD, it became apparent that the risk of TD with clozapine treatment was extremely low if at all present.[4] Therefore, it seemed reasonable to many clinicians to switch patients with TD (particularly severe cases who needed ongoing antipsychotic treatment) to clozapine with the hope that it would either "treat" TD or allow it to gradually remit. A metanalysis of 4 studies[5] did confirm a significant impact of switching to clozapine on the severity of TD.

Previous research from our group had indicated a substantial reduction in TD risk with the second-generation medications. None appeared to be as safe as clozapine in this regard, but our estimates suggested that they were associated with as little as one-fifth the risk associated with first generation medica-

CONTINUED FROM PAGE S5

CONTINUING NURSING EDUCATION

The maximum number of hours awarded for this Continuing Nursing Education activity is 1.1 contact hours. Designated for 0.9 contact hours of pharmacotherapy credit for Advanced Practice Registered Nurses.

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Faculty

John Kane, MD
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Daniel Guinart, MD
Consulting fees: Otsuka America Pharmaceuticals, Janssen Pharmaceuticals

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The PIM planners and managers have nothing to disclose.
The Global Medical Education planner and manager, Prakash Masand, MD, has disclosed the following:
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3) Type in **15582** at the top of the page, "Find Post-Test/Evaluation by Course", and click enter
4) Click on the activity title when it appears
5) Choose the type of credit you desire
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For Pharmacists: Upon completion of the online evaluation, your credit will be submitted to CPE Monitor. Pharmacists have up to thirty (30) days to complete the evaluation and claim credit. Please check your NABP account within thirty (30) days to make sure the credit has posted.

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tions.[6] However, simultaneously some newer medications were also receiving indications for the treatment of specific affective disorders and gaining much wider utilization in that context. At the same time, more recent estimates suggested that the incidence of TD on the newer medicines was significantly lower, but not as low as originally thought.[7] Therefore, even though the risk of TD was lower, the number of people exposed to these medications increased substantially, and therefore more cases of TD began emerging.

The American Academy of Neurology[8] reviewed a number of off-label treatments for TD that were being utilized with mixed benefits, and often a limited database to support their effectiveness: tetrabenazine, reserpine, Vitamin E, melatonin, Vitamin B6, and donepezil. They suggested that clonazepam, ginkgo biloba, and amantadine were off-label indications that had shown some benefit. In a small-scale 18 week, double-blind, crossover study of amantadine and neuroleptics in the treatment of TD, the

TABLE 1

Dosing Strategies

Valbenazine	Deutetrabenazine
40 mg/day x 7 days, then 80m g/day	6 mg/day bid × 7 days with food up to 48 mg/day
QTc prolonged 1-2 msec	Above 24 mg/day assess for QTc prolongation
Lower dose when co-treatment with strong CYP2D6	Lower dose when co-treatment with strong CYP2D6 and CYP3A4 inhibitors
Once-daily dosing	Twice daily dosing
	Boxed warning (suicidal ideation/depression)

results indicated that amantadine is significantly better than placebo in the management of TD and that there is little risk of exacerbating psychosis.[9] In a subsequent study[10], 22 TD patients with a mean age of 52 years participated in a double-blind, placebo-controlled, crossover design to receive either amantadine or placebo for 2 weeks followed by a washout period of 4 days. Subsequently, the groups were crossed over, and the procedure repeated. Participants received amantadine (100 mg) or placebo. TD was assessed by means of the Abnormal Involuntary Scale (AIMS). With amantadine, the average total AIMS reduction was 21.81%. On the contrary, with placebo treatment, no reduction was noted.

Thaker at al[11] reported on clonazepam in a 12-week double-blind, placebo- controlled, randomized crossover trial in 19 TD patients who were being treated with concomitant antipsychotics. They reported a 35% decrease in dyskinesia ratings on clonazepam. Some tolerance developed after long-term treatment, but 2 weeks off clonazepam was reported to restore its antidyskinetic effects.

Zhang et al[12] reported on inpatients with DSM-IV-diagnosed schizophrenia and TD (n=157) in a mainland China Veterans Affairs psychiatric hospital who were randomly assigned to 12 weeks of treatment with either ginkgo biloba 240 mg/d (n=78) or placebo (n=79) in a double-blind manner. Ginkgo biloba treatment significantly decreased the AIMS total score in patients with TD compared with those who were given placebo (2.13 ± 1.75 vs -0.10 ± 1.69; P< .0001), with 40 (51.3%) and 4 (5.1%) patients achieving response in the ginkgo biloba and placebo treatment groups, respectively. A few case reports have suggested some efficacy of lesioning surgery (ie pallidotomy or thalamotomy). A greater number of case series of series have assessed the effects of deep brain stimulation applied to the internal globus pallidus. Recently, a class II study provided level C evidence for use of deep brain stimulation (DBS) of the globus pallidus internus (GPi) in patients with TD. Although the precise pathogenesis of TD remains to be elucidated, the beneficial effects of GPi-DBS in patients with TD suggest that the disease may be a basal ganglia disorder.[13]

Vesicular monoamine transporter (VMAT) inhibitors are agents that can reduce the amount of monoamines that are packaged in vesicles for release into the synaptic cleft. Tetrabenazine is a reversible VMAT-inhibiting medication that was approved in 2008 for the treatment of chorea associated with Huntington's disease. Tetrabenazine has a short half-life requiring more than 1 dose per day (up to 3 times). Titration is necessary. There are no major prospective trials in TD with 4 open label studies and 2 retrospective reports.[14] Two small randomized double-blind, placebo-controlled, crossover trials have been reported.[15,16] Both showed positive effects of tetrabenazine utilizing doses between 100 and 200 mg. The most frequent side effects included daytime drowsiness, drooling or sialorrhea, insomnia, restlessness and anxiety, parkinsonian features, and mild postural hypotension. The adverse effects resolved with continued administration or with reduction in dosage.

Deutetrabenazine is a deuterated form of tetrabenazine that provides a longer half life and slower metabolic clearance allowing for twice daily dosing. There are fewer peak-trough variations and it has proven to be better tolerated than tetrabenazine. In addition, there was no difference from placebo in measures of depression, which had been a concern with tetrabenazine.[17,18] Deutetrabenazine was approved by the FDA for the treatment of TD in August 2017.

Valbenazine is a novel VMAT2 inhibitor, an active agent that is slowly converted to 2 active metabolites that are highly selective for VMAT2. It has a half-life of 20 hours, allowing for once daily dosing. It was approved by the FDA for the treatment of TD in April of 2017. The clinical trials that were designed and implemented in the programs to test both new drugs were state of the art, and included centralized, blinded, expert raters to conduct the key outcome assessments. They both involved dou-

TABLE 2

Monitoring Patients on VMAT Inhibitors

- Monitor all patients taking dopamine-depleting drugs for
  - Depression
  - Suicidality
  - Parkinsonism
- Psychiatric conditions
  - When DRBA is prescribed for psychiatric conditions and patient treated with VMAT-i
    - Monitor the underlying psychiatric condition
  - In studies of deutetrabenazine and valbenazine for TD
    - All patients maintained psychiatric medications
    - Psychiatric conditions remained stable
- Longer-term data needed to assess impact of manipulation of dopamine system
  - On psychotic or mood disorder
  - In patients outside of clinical trial populations

Abbreviations: DRBA, dopamine receptor-blocking agents; TD, dardive dyskinesia; VMAT, vesicular monoamine transporter.

TABLE 3

Practice Pearls in TD

- Prevention is key
  - Use DRBAs only in patients for whom they are indicated
  - Use DRBAs in the lowest possible dose for the shortest duration necessary to treat the condition
- Screen for movement disorders in patients taking a DRBA
  - Systematically evaluate for TD or acute movement disorders at regular intervals
  - Use the AIMS to assess TD symptoms
- Diagnose before treating
  - Confirm the diagnosis of TD before treating
  - Refer to a movement disorders specialist if diagnosis is uncertain

Abbreviations: AIMs, Abnormal Involuntary Movement Scale; DRBA, dopamine receptor-blocking agents; TD, tardive dyskinesia.

ble-blind, placebo-controlled trials, utilizing the AIMS as the primary outcome measure.

The AIM-TD trial[19] is an example of the development trials that were conducted with deutetrabenazine. This was a 12-week, fixed dose trial involving 298 patients who had experienced TD for at least 3 months and were randomly assigned to 1 of 3 doses of deutetrabenazine (12, 24, or 36 mg) or placebo. Both the 24 and 36mg doses showed significant superiority over placebo. Serious adverse effects were reported in 6% of placebo patients and 3% to 8% of those receiving active treatment. The most common side effects were somnolence, headache, fatigue, and insomnia. The ARM-TD trial[20] was a Phase 2B study, which showed similar results. A long-term extension study with TD patients (N=343) from Phase III trials was also conducted.[21] Follow-up visits took place at week 4, 6, 15 and then every 13 weeks until week 106. Items of depression, anxiety, and suicidality were assessed, as well as the AIMS. Improvement on the AIMS continued and was generally sustained. No significant increase in adverse effects occurred.

Kinect 3[22] was a Phase III study and an example of the trials conducted with valbenazine. This was a 6-week, double-blind, placebo-controlled, parallel, fixed-dose study of doses 40 and 80 mg vs. placebo in 234 moderate to severe TD patients who continued to receive whatever antipsychotic medication they had been receiving. Both doses proved to be significantly superior to placebo on the primary efficacy variable: change from baseline on the AIMS. Serious adverse effects were reported in 3.9% of placebo and 6.6% of valbenazine patients. The most common side effects were fatigue, headache, and decreased appetite. Subjects eligible to continue for an additional 42 weeks (subjects on placebo re-randomized to 40 or 80 mg)[23] showed sustained improvement on valbenazine, but with movements recurring during a washout.

In a Phase II, 6-week, double-blind, placebo-controlled study,[24] 109 adult males and females with moderate or severe TD were randomized to different treatments. One cohort took 50 mg valbenazine for 6 weeks and the other group received 100 mg in the first 2 weeks, then the patients were down titrated to 50 mg for the final 4 weeks of this study. The 50 mg dose did not significantly improve AIMS scores, but the 100 mg dose reduced symptoms when scored via a blinded central video AIMS assessment at the end of the 100 mg dosing interval. A long-term 48-week, open-label treatment study was also conducted[25] followed by 4 weeks drug-free treatment (total 52 weeks). Adults with TD 3 months duration before screening were eligible and all started on 40 mg/day valbenazine for 4 weeks then the dose was escalated to 80 mg/day. The dose was reduced to 40 mg if tolerability was an issue. When medication was withdrawn at week 48 for 4 weeks, 43% of those who had been on valbenazine 80 mg continued to be rated much/very much improved and 33% of those on the 40 mg dose remained much/very much. So, despite some reemergence of symptoms, the gains remained substantial.

Conclusions

Both of these new drugs represent the first FDA-approved treatments for TD and are very welcome additions to our therapeutic armamentarium. There are some differences in dosing requirements and safety precautions, as indicated in ***Table 1***.

There have been no head-to-head comparisons to determine whether there are any differences in efficacy or effectiveness. A recent meta-analysis[26] indicated consistent efficacy for both drugs across 4 separate studies for each. The two VMAT-2 inhibitors, valbenazine and deutetrabenazine, are effective in treating TD, both acutely and long-term. However, some patients will experience a recurrence of symptoms when medication is discontinued. Monitoring guidance is presented in ***Table 2***.

We should also keep in mind the practice pearls listed in ***Table 3***.

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