A Modified Delphi Consensus Study of the Screening, Diagnosis, and Treatment of Tardive Dyskinesia

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ABSTRACT

Objective: A nominal group process followed by a modified Delphi method was used to survey expert opinions on best practices for tardive dyskinesia (TD) screening, diagnosis, and treatment and to identify areas lacking in clinical evidence.

Participants: A steering committee of 11 TD experts met in nominal group format to prioritize questions to be addressed and identify core bibliographic materials and criteria for survey panelists. Of 60 invited experts, 29 (23 psychiatrists and 6 neurologists) agreed to participate.

Evidence: A targeted literature search of PubMed (search term: *tardive dyskinesia*) and recommendations of the steering committee were used to generate core bibliographic material. Inclusion criteria were as follows: (1) review articles, meta-analyses, guidelines, or clinical trials; (2) publication in English between 2007 and 2017; (3) > 3 pages in length; and (4) publication in key clinical journals with impact factors ≥ 2.0. Of 29 references that met these criteria, 18 achieved a score ≥ 5 (calculated as the number of steering committee votes multiplied by journal impact factor and number of citations divided by years since publication) and were included.

Consensus Process: Two survey rounds were conducted anonymously through electronic media from November 2017 to January 2018; responses were collected, collated, and analyzed. Respondent agreement was defined a priori as unanimous (100%), consensus (75%–99%), or majority (50%–74%). For questions using a 5-point Likert scale, agreement was based on percentage of respondents choosing ≥ 4 ("agree completely" or "agree"). Round 1 survey included questions on TD screening, diagnosis, and treatment. Round 2 questions were refined per panelist feedback and excluded Round 1 questions with < 25% agreement and > 75% agreement (unless feedback suggested further investigation).

Conclusions: Consensus was reached that (1) a brief, clinical assessment for TD should be performed at every clinical encounter in patients taking antipsychotics; (2) even mild movements in 1 body area may represent possible TD; (3) management requires an overall evaluation of treatment, including reassessment of antipsychotics and anticholinergics as well as consideration of vesicular monoamine transporter 2 (VMAT2) inhibitors; and (4) informed discussions with patients/caregivers are essential.

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Tardive dyskinesia (TD) is a persistent and potentially debilitating hyperkinetic movement disorder associated with prolonged exposure to dopamine receptor blocking agents (DRBAs), such as antipsychotic medications. With expanding use of second-generation antipsychotics (SGAs) beyond schizophrenia to bipolar disorder, major depressive disorder, irritability associated with autistic disorder, and off-label indications, the number of patients at risk for developing TD continues to increase.[1–5] While SGAs were expected to be less likely to cause TD than first-generation antipsychotics (FGAs), growing evidence indicates that the risk for both continues to be significant.[6–10] A recent meta-analysis found that the prevalence of TD was 30% in patients receiving FGAs, 21% in patients receiving SGAs, and 7% in FGA-naive patients receiving SGAs (a cohort comprising relatively younger patients with lower cumulative lifetime exposure to DRBAs).[7]

In 2017, the first treatments approved by the US Food and Drug Administration (FDA) for TD in adults, valbenazine and deutetrabenazine, became available. Since then, there has been renewed interest in determining best practices for recognizing and managing TD.[11–13] In a recent commentary updating the 2013 American Academy of Neurology evidence-based recommendations,[6,14] valbenazine and deutetrabenazine were established as effective treatment and are now first-line therapies

Clinical Points

- Tardive dyskinesia remains a serious complication of treatment that may increase in significance as antipsychotics are widely used for additional indications.
- Clinicians may be unsure of screening, diagnosing, and treating TD because of outdated practice guidelines and incomplete evidence on fundamental biological mechanisms.
- Consensus agreement among a panel of experts provides guidance on best practices including routine monitoring procedures adaptable to clinical settings, diagnosing mild cases of TD, and implementing a comprehensive strategy that incorporates patient and caregiver input, review of antipsychotic and anticholinergic medications, indications for VMAT2 inhibitors, and appropriate follow-up.

for patients with troublesome TD symptoms.[14] However, many questions regarding the course, identification, and management of TD remain unresolved. In addition, agreement on screening and diagnostic criteria has been elusive, with clinicians relying on clinical experience and anecdotal evidence rather than prospective studies or formal guidelines.[11,12,15]

In this study, an initial nominal group process followed by a modified Delphi method was used to survey expert opinion on current best practices for screening, diagnosis, and treatment of TD, as well as to identify areas in which clinical evidence is lacking. The nominal group process is an open, structured meeting conducted by a trained leader to obtain agreement and organize qualitative information.[16,17] The Delphi method, a systematic group communication process, is well suited to assist in decision-making when evidence is incomplete, unclear, or unavailable.[16–19] The iterative nature of the questioning process (with feedback provided after survey rounds), participant anonymity, and a priori definitions of consensus are key features of the Delphi method, which help avoid the pitfalls of face-to-face discussions wherein group dynamics may interfere with the rational process of consensus discovery. The sequential use of a nominal group process to define and set priorities followed by a series of anonymous Delphi survey rounds has been used successfully for various medical applications from assessment of knowledge gaps to development of treatment guidelines.[20–25]

PARTICIPANTS

Nominal Group Process

A steering committee of 11 experts on TD met in a nominal group format led by a facilitator (Kimberley Riggs, MPH; Xcenda, Palm Harbor, Florida) to (1) discuss and prioritize questions to be addressed regarding the screening, diagnosis, and treatment of TD; (2) reach agreement on criteria for nomination of potential survey panelists; and (3) reach agreement on criteria for core bibliographical references (Figure 1).

Survey Panel

Recruitment efforts focused on clinical psychiatrists and neurologists from the United States or Canada who had practiced for ≥ 5 years and frequently managed patients with mental illness and TD. Additional criteria for nomination were ≥ 1 prior publication with relevance to movement disorders or antipsychotic treatment, experience as a speaker in a nonpromotional capacity on a related topic, and/or serving in a leadership position in generating recommendations on antipsychotics. Of 60 experts invited to participate, 29 agreed (including the 11 steering committee members); 1 panelist (who was also a steering committee member) dropped out for Round 2 (Figure 1). The final expert panel comprised 23 psychiatrists and 6 neurologists, the majority (62%) of whom had practices in academic institutions (Table 1). The panel saw a median of 100 patients/year with current or previous exposure to antipsychotics and a median of 20 patients/year with TD symptoms.

EVIDENCE

Core Bibliography

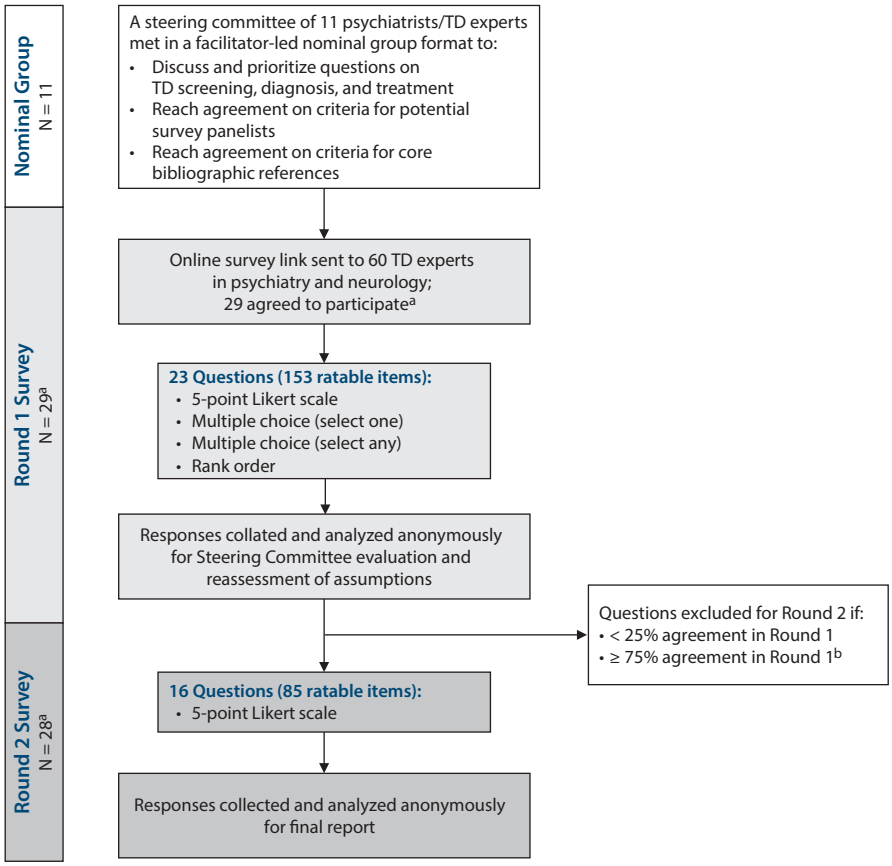
Based on a targeted literature search of PubMed (search term: *tardive dyskinesia*) and recommendations of the steering committee, a list of references was generated to serve as core bibliographic material for the survey panel to review. These references were considered essential for understanding the evidence base in current TD practice and research. Inclusion criteria for core references were (1) review articles, meta-analyses, guidelines, or clinical trials; (2) publication in English between 2007 and 2017; (3) > 3 pages in length; and (4) publication in key clinical journals with impact factors ≥ 2.0. Of 29 references that met these criteria, 18 achieved a score ≥ 5 (calculated as the number of steering committee votes multiplied by journal impact factor and number of citations divided by years since publication) and were included in the final bibliography and provided to panelists via a hyperlinked list.[1,2,6,7,10,26–38]

CONSENSUS PROCESS

Delphi Survey Procedure

Two survey rounds were conducted through electronic media from November 2017 to January 2018 and recorded anonymously (Figure 1). Responses from panelists were collected, collated, and analyzed in the aggregate by the organizer (Xcenda). To ensure a broad range of opinions was obtained, Round 1 questions were composed in multiple formats: 5-point Likert scale (select rating of 1 "strongly disagree" or "very unimportant" to 5 "strongly agree" or "very important"), multiple choice (select 1 or select any), and rank order. Anonymous raw and aggregate data from Round 1 were provided to the steering committee for Round 2 survey development, and anonymous aggregate data were provided as feedback to survey participants prior to Round 2. Questions in Round 2 were refined as follows: (1) all questions were transformed into the quantitative 5-point

Figure 1. Flowchart of Modified Delphi Process



[a]Including Steering Committee members.
[b]Unless panel feedback suggested rewording for clarity and/or additional information.
Abbreviation: TD = tardive dyskinesia.

Likert scale format; (2) if agreement of < 25% (deemed unlikely to achieve consensus) or ≥ 75% (consensus already achieved) was recorded in Round 1, the question was excluded from Round 2, unless rewording was needed for clarity or the question was revised to the Likert scale format to document the distribution of responses.

Analysis

Response outcomes defined a priori by the steering committee were "unanimous," "consensus," and "majority," representing, respectively, 100%, 75%–99%, and 50%–74% agreement among survey respondents. For questions using a 5-point Likert scale, consensus agreement was defined as a response of 4 (agree) or 5 (strongly agree); Likert scale results are reported as the percent of responses of 4 or 5 and the mean (95% confidence limits [CL]) Likert score. Final outcomes were based on Round 2 results unless consensus was achieved in Round 1.

Survey questions were organized into 3 main categories: screening, diagnosis, and treatment. Summaries of statements on which consensus agreement was obtained are

Table 1. Characteristics of Delphi Panel Respondents (N = 29)

Characteristic	Value
Primary area of practice, n (%)	
Psychiatry	23 (79)
Neurology	6 (21)
Geographic area of practice, n (%)[a]	
Northeast	14 (48)
West	8 (28)
South	8 (28)
Canada	2 (7)
Midwest	1 (3)
Practice setting, n (%)	
Academic institution	18 (62)
Community—office	6 (21)
Government—state hospital	2 (7)
Community—hospital	1 (3)
Government—federal hospital	1 (3)
Other	1 (3)
Years in practice, median	29
No. of patients currently or previously taking antipsychotic medication seen per year, median	100
No. of patients presenting with TD symptoms seen per year, median	20

[a]Respondents could select all that apply.
Abbreviation: TD = tardive dyskinesia.

Box 1. Key Consensus Results: Screening for TD

Patient Characteristics
- All patients currently taking any drug with DRB properties (eg, antipsychotics, metoclopramide) should be screened for TD[a]
- The following patient or treatment attributes contribute to high risk of TD development:
  - Current or recent treatment with a first-generation antipsychotic[a]
  - Age (ie, older age)[a]
  - Longer cumulative exposure to antipsychotics[a]
  - Acute extrapyramidal symptoms other than acute akathisia (eg, parkinsonism)

Screening Assessments
- AIMS is the standard structured assessment for screening and monitoring for severity of TD (R1)
- Semistructured assessments should be utilized in clinical practice to screen for TD (R1)
- A semistructured assessment should include (R1):
  - Patient recognition of current/recent abnormal movements as part of a review of side effects at time of assessment[a]
  - Visual observation of psychomotor abnormalities on mental status examination
  - Caregiver report of recent/current abnormal movements
  - Patient report of history of movement/psychomotor changes
  - Patient complaints about changes in movement being distressful or interfering with functioning or QoL

Screening Frequency
- Clinical assessment to screen for the development of TD in patients taking antipsychotics or other drugs with DRB properties, *regardless* of the degree of risk for TD, should be performed at every clinical encounter
- Clinical screening for TD should include routine semistructured and less frequent structured assessment of movement disorders (R1)

[a]Indicates unanimous consensus (100%). Results are listed in order of agreement, with the highest percentage of agreement listed first. All results are from Round 2, except those noted as Round 1 (R1). Consensus agreement was defined as ≥ 75% of respondents with score ≥ 4 ("agree completely" or "agree very much").
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, DRB = dopamine receptor-blocking, QoL = quality of life, TD = tardive dyskinesia.

shown in Boxes 1–3. In Round 1, 23 questions were posed, with a total of 153 items to be rated. The number of questions carried over to Round 2 was reduced to 16, with 85 items to be rated. A comparison analysis was conducted to identify consensus differences between Rounds 1 and 2 to similarly worded questions (Supplementary Tables 1–3).

Significant differences between percent respondents (Round 2 – Round 1) were calculated at the 95% CL. In addition, where both Round 1 and Round 2 questions used the Likert scale, the mean significant difference for Likert scores (Round 2 – Round 1) was calculated. Comparisons between Round 1 and Round 2 and significance testing to identify differences were used for descriptive purposes only. Round 1 and Round 2 questions and responses, and results of the comparison analyses, are provided in Supplementary Tables 1–3. A glossary of terms used in the survey is provided in Supplementary Table 4.

CONSENSUS SUMMARY

Screening for Tardive Dyskinesia

Patient characteristics. In Round 2, unanimous consensus (100%, mean Likert score 5.0) was reached that all patients currently taking DRBAs should be screened for TD (Box 1). Unanimous or consensus agreement was reached on several patient attributes that contribute to defining high risk for TD: current or recent treatment with FGAs (100%, mean Likert score 4.9 [95% CL; 4.8, 5.1]), older age (100%, 4.7 [4.5, 4.9]), longer cumulative exposure to antipsychotics (100%, 4.9 [4.8, 5.1]), and acute extrapyramidal symptoms other than acute akathisia (75%, 4.0 [3.7, 4.3]). A majority of respondents also agreed that gender (54%, 3.5 [3.2, 3.8]) and acute akathisia (50%, 3.6 [3.2, 4.0]) contributed to defining high risk for TD (Supplementary Table 1).

Screening frequency and assessment. There was no consensus in Round 1 on the minimum duration of antipsychotic exposure within which TD may develop; however, there was majority agreement in Round 2 that the minimum duration of exposure for TD to develop was ≥ 1 month (71%, 3.9 [3.5, 4.3]), while fewer participants agreed with ≥ 3 months (57%, 3.7 [3.2, 4.2]) of exposure (Supplementary Table 1). It therefore followed that consensus was reached on screening for TD at every clinical encounter in patients taking antipsychotics regardless of the degree of risk for TD (75%, 4.1 [3.7, 4.5]) (Box 1). However, a majority replied in Round 2 that a screening assessment should be performed at least every 3 months (68%, 3.9 [3.5, 4.3]) to 6 months (61%, 3.9 [3.5, 4.3]).

Consensus (97%, 4.6 [4.4, 4.8]) was reached in Round 1 that the Abnormal Involuntary Movement Scale (AIMS)[39] is the standard structured assessment instrument for screening and monitoring TD severity (Box 1). In addition, there was consensus that brief, semistructured assessments should be used routinely in clinical practice to screen for TD (76%, 3.9 [3.5, 4.3]) and also that screening could include both routine semistructured and less frequent structured assessment (eg, AIMS) of movement disorders (79%, 4.1 [3.7, 4.5]). Unanimous or consensus agreement was reached in Round 1 that a semistructured screening assessment should include the following: patient recognition of current/recent abnormal movements as part of a review of side effects (100%), visual observation of psychomotor abnormalities on mental status examination (97%), caregiver report of recent/current abnormal movements (97%), patient report of history

Box 2. Key Consensus Results: Diagnosis of TD

Diagnostic Criteria
- The following patient or treatment attributes are important in the diagnosis of TD:
  - Involuntary movements that develop during exposure to antipsychotic medication or within 4–8 weeks of withdrawal from an antipsychotic medication[a]
  - Ruling out other movement disorders, medical conditions, or other drugs that may cause involuntary movements
  - Patient history
  - Cumulative exposure to antipsychotic medication
  - Current medication
  - Duration of involuntary movements
  - Severity of involuntary movements in affected areas
- Visual assessment as part of the routine neurologic or mental status examination is appropriate for the diagnosis of TD in a psychiatric clinical setting

Affected Body Areas
- A patient having a rating of at least mild (≥ 2 on AIMS) affecting 1 body area should be considered as possibly having TD
- TD is most often evident in orofacial musculature, although other body areas may be affected and should not be neglected

Phenomenological Movement Subtypes
- Choreoathetoid movement is important in determining the diagnosis and severity of TD[a]

Neurologic Consultation
- The following are circumstances in which a psychiatrist should consider ordering a neurologic consultation to clarify the differential diagnosis in the evaluation of patients with possible TD (R1):
  - Atypical presentation or course of a movement disorder
  - Patient has a family history of other movement or neurodegenerative disorders (eg, Huntington's disease)
  - Presence of other neurologic or systemic medical signs and symptoms
  - Psychiatrist is unsure of whether TD diagnosis is present
  - Unexpected treatment response, intolerability, or resistance of the movement disorder

[a]Indicates unanimous consensus (100%). Results are listed in order of agreement, with the highest percentage of agreement listed first. All results are from Round 2, except those noted as Round 1 (R1). Consensus agreement was defined as ≥ 75% of respondents with score ≥ 4 ("agree completely" or "agree very much").
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, TD = tardive dyskinesia.

of movement/psychomotor changes (93%), and patient complaints about changes in movement being distressful or interfering with functioning or quality of life (QoL, 86%).

Diagnosis of Tardive Dyskinesia

Diagnostic criteria. Consensus was reached on 7 criteria considered very important for the diagnosis of TD (Box 2), with majority agreement on 3 additional diagnostic criteria (Supplementary Table 2). There was consensus that visual assessment as part of the routine neurologic or mental status examination is important for diagnosing TD in a psychiatric clinical setting (82%, 4.2 [3.9, 4.5]). A majority agreed that the *DSM-5* criteria (72%, 4.0 [3.6, 4.4]) and Schooler-Kane criteria (61%, 3.8 [3.4, 4.2]) are also appropriate for diagnosing TD but that there is a need for revising standardized criteria that could be applied reliably in clinical settings (57%, 3.7 [3.2, 4.2]).

Consensus was reached that a patient with 1 rating of mild severity (≥ 2 on AIMS) affecting 1 body area should be considered as having possible TD (89%, 4.4 [4.2, 4.7]). Similar to the lack of consensus agreement on the minimum duration of antipsychotic exposure sufficient for TD to develop, there was no consensus on the minimum duration of cumulative antipsychotic exposure to include in diagnostic criteria for TD. However, a majority agreed that while there is no lower limit on the duration of exposure in patients of any age (54%, 3.7 [3.2, 4.2]), diagnostic criteria for TD may reasonably include a minimum cumulative exposure of ≥ 1 month (50%, 3.5 [3.0, 4.0]).

Phenomenology and differential diagnosis. Consensus and unanimous agreement were reached in Round 1 (93%, 4.7 [4.4, 5.0]) and Round 2 (100%, 4.8, [4.7, 4.9]) that choreoathetoid movement was an important subtype in determining both diagnosis and severity of TD (Box 2). There was majority agreement on the importance of dystonic (64%, 3.8 [3.4, 4.2]) and stereotypic (57%, 3.6 [3.2, 4.0]) subtypes and majority agreement for akathisia (55%, 3.5 [3.1, 3.9]) in Round 1 only (Supplementary Table 2). Consensus was reached in Round 1 for circumstances in which a psychiatrist should consider requesting a neurologic consultation to clarify diagnosis in the evaluation of patients with possible TD: atypical presentation or course of a movement disorder (93%); presence of other neurologic or systemic medical signs and symptoms (90%); family history of other movement or neurodegenerative disorders such as Huntington's disease (90%); uncertainty whether a TD diagnosis is present (86%); and unexpected treatment response, intolerability, or treatment resistance of the movement disorder (86%).

Treatment of Patients With Tardive Dyskinesia

Comprehensive management of psychopharmacology. Consensus was reached in Round 1 on several components of a treatment approach for patients with TD: discussion of treatment options with patients and caregivers (100%), review and possible modification of both antipsychotic (100%) and anticholinergic regimens (86%), and treatment of TD with a vesicular monoamine transporter 2 (VMAT2) inhibitor (100%). More broadly, there was consensus or

majority agreement in Round 1 on 12 important patient or treatment factors to take into account when determining the best treatment approach (Box 3 and Supplementary Table 3).

Unanimous agreement was reached in Round 1 that severity, stability, and risk of relapse of the underlying psychiatric disorder were important considerations for modifying antipsychotic regimens as part of the management of patients with TD (100%, 4.8 [4.7, 5.0]). There was also consensus that availability of alternative (antipsychotic and non-antipsychotic) treatments for the underlying psychiatric disorder was an important consideration (97%, 4.6 [4.4, 4.8]) and that antipsychotic tapering should be considered in patients who can be safely withdrawn from antipsychotic therapy (93%, 4.6 [4.3, 4.9]). For patients who could not be safely withdrawn from antipsychotic therapy, possible options or modifications to antipsychotic treatment included consensus on switching from an FGA to an SGA (78%, 4.1 [3.7, 4.5]) or clozapine (79%, 4.0 [3.6, 4.4]) and majority agreement on reducing dose (60%, 3.9 [3.5, 4.3]) or switching from a more to a less potent antipsychotic (54%, 3.5 [3.1, 3.9]). For anticholinergic management, consensus was reached in Round 1 that providers should consider modifying anticholinergics (97%, 4.6 [4.4, 4.8]) but that the presence and severity of acute extrapyramidal side effects and dystonia must be considered (90%, 4.4 [4.2, 4.7]). In Round 2, a majority of participants agreed that modification of treatment with anticholinergics may include reducing the dose (71%, 3.9 [3.5, 4.3]), discontinuation by tapering (68%, 4.0 [3.6, 4.4]), or switching to amantadine (54%, 3.6 [3.2, 4.0]).

VMAT2 inhibitors and treatment response. Consensus was reached on 4 factors to consider when deciding on prescription of VMAT2 inhibitors to treat TD: as part of an overall and integrated, pharmacologic treatment plan (97%, 4.9 [4.8, 5.1]); the patient's condition and needs (97%, 4.6 [4.4, 4.8]); if a patient and caregiver request, prefer, or agree to this treatment option (86%, 4.3 [4.0, 4.6]); and after the response to antipsychotic maintenance or modifications is determined (75%, 4.0 [3.6, 4.4]) (Box 3 and Supplementary Table 3). There was consensus in Round 1 that tolerability (93%), efficacy (86%), safety (86%), and ease of use (79%) affect selection of a specific VMAT2 inhibitor and majority agreement that previous VMAT2 treatment (69%), cost (69%), patient or caregiver preference (66%), and label indication (55%) are important in selecting a specific drug (Supplementary Table 3). A consensus (82%, 4.4 [4.1, 4.7]) of respondents agreed that if a VMAT2 inhibitor was ineffective, not tolerated, or declined by a patient, the next step was to switch to another VMAT2 inhibitor before considering other agents. No Delphi question in either round addressed long-term treatment practices of TD with VMAT2 inhibitors.

Finally, there was consensus on the most useful measures of a minimal clinically important difference in response to treatment for TD in a given patient: subjective clinical global impression of at least much improved (82%, 4.4 [4.1, 4.7]); subjective patient report of improvement in distress, functioning, or QoL (82%, 4.3 [4.0, 4.6]); and subjective patient global impression of at least much improved (78%, 4.3 [4.0, 4.6]). A majority agreed that a minimal clinically important difference in response to treatment could also be measured by a ≥30% decrease in total AIMS score (items 1–7) (68%, 4.0 [3.7, 4.3]).

Trends in Convergence of Agreement

Comparisons between individual items in Round 1 and Round 2 and significance testing to identify differences for descriptive purposes only are provided in Supplementary Tables 1–3. Items that reached Round 2 consensus and were comparable between rounds (ie, rated in both Round 1 and Round 2) showed a mean absolute change of 10% in agreement between panelists and 0.2 in Likert scores. Statistically significant change between rounds in categorical ratings of agreement or continuous Likert scores was found in 19/69 (28%) of items rated in both rounds. Of the total 153 original items rated by panelists in Round 1, consensus or unanimous consensus was achieved for 60/153 (39%), which increased to 64/153 (42%) at the end of Round 2. Majority agreement remained about the same between rounds (39/153 [25%] in Round 1 and 36/153 [24%] after Round 2). Conversely, items rejected as unlikely to achieve agreement (ie, <25% agreement) increased from 30/153 (20%) after Round 1 to 37/153 (24%) after Round 2, while the number of items for which panelists were unable to reach majority agreement (ie, 25%–49% agreement) fell from 24/153 (16%) after Round 1 to 16/153 (10%) after Round 2. In summary, the final study findings revealed that consensus or at least majority agreement had been achieved for 100/153 (66%) of queried items such that no further significant changes in responses were anticipated.

DISCUSSION

Our panel of TD experts convened for this study provided a cross-sectional view of opinions on best clinical practices in the screening, diagnosis, and treatment of TD. Consensus was reached in several areas, while absence of consensus identified areas where data are lacking and further study is desirable.

There was unanimous consensus that all patients receiving DRBAs must be screened for TD. Consensus results on screening procedures identified several important patient attributes that contribute to high risk for TD, including current and type of antipsychotic use, older age, longer cumulative exposure to antipsychotics, and acute extrapyramidal symptoms. Although there was a lack of consensus on the minimum duration of cumulative antipsychotic exposure for TD to develop, a majority of panelists suggested that at least 1 month could be considered a minimum threshold. This was consistent with the consensus opinion that patients should be screened for TD at all clinical encounters regardless of risk for TD or, according to the majority of panelists, no less frequently than every 3 to 6 months.

Improved understanding of the onset of TD is of critical clinical importance in developing guidelines for screening.

Box 3. Key Consensus Results: Treatment of TD

Treatment Approach
- The following strategies should be considered as part of your treatment approach (R1):
  - Discussion of treatment options with patients and caregivers[a]
  - Review and consider modifying antipsychotic regimen[a]
  - Treatment of TD with VMAT2 inhibitor[a]
  - Review and consider modifying anticholinergic regimen
- The following are important considerations when deciding on treatment approach (R1):
  - Severity of TD symptoms
  - Severity of underlying psychiatric disorder
  - Phenomenology of TD symptoms (eg, dystonia)
  - Psychiatric stability on current treatment regimen
  - Current antipsychotic medication
  - Current acute extrapyramidal side effects
  - Patient psychiatric history (eg, suicide attempts, hospitalizations, severe psychosis, etc)
  - Patient-reported subjective awareness, distress, and impact of movements on functioning and QoL
  - Current anticholinergic medication

Management of Antipsychotics
- The following are important considerations in modifying antipsychotic regimens as part of TD management (R1):
  - Severity, stability, and risk of relapse of the underlying psychiatric disorder[a]
  - Availability of alternative treatments for the underlying psychiatric disorder
- For patients who can be safely withdrawn from antipsychotic therapy (ie, for whom alternative therapies are approved and available [antidepressants, etc]), providers should consider tapering the antipsychotic agent (R1)
- The following options should be considered when modifying antipsychotic treatment for patients with TD who are unable to be withdrawn from antipsychotic therapy:
  - Switch to clozapine
  - Switch from a first-generation antipsychotic to a second-/third-generation antipsychotic

Management of Anticholinergics
- As part of TD management, providers should consider modifying anticholinergic agents (eg, reduce dose, taper off) (R1)
- In considering whether to modify anticholinergic regimens as part of TD management, the presence and severity of acute extrapyramidal side effects and dystonia must be considered (R1)

Use of VMAT2 Inhibitors
- The following should be considered in the prescription of VMAT2 inhibitors as part of TD management:
  - As part of an overall and integrated, pharmacologic treatment plan
  - Depends on a patient's condition and needs
  - If a patient and caregiver request, prefer, or agree to this treatment option
  - After the response to antipsychotic maintenance or modifications is determined
- The following patient- or drug-specific factors impact selection of a specific VMAT2 inhibitor (R1):
  - Tolerability
  - Safety
  - Efficacy
  - Ease of use
- If a VMAT2 inhibitor is ineffective, not tolerated, or declined by a patient, the next step is to switch to another VMAT2 inhibitor before using other agents

TD Treatment Response
- The most useful measures of a minimal clinically important difference in response to TD treatment are as follows:
  - Subjective patient report of improvement in distress, functioning, or QoL
  - Subjective clinical global impression of "much improved"
  - Subjective patient global impression of "much improved"

[a]Indicates unanimous consensus (100%). Results are listed in order of agreement, with the highest percentage of agreement listed first. All results are from Round 2, except those noted as Round 1 (R1). Consensus agreement was defined as ≥ 75% of respondents with score ≥ 4 ("agree completely" or "agree very much").
Abbreviations: QoL = quality of life, TD = tardive dyskinesia, VMAT2 = vesicular monoamine transporter 2.

Conventional acceptance of a delayed onset of 3 months or more serves as a helpful cutoff to distinguish TD from acute drug-induced movement disorders (eg, parkinsonism), to decrease frequency of formal screening, and potentially to distinguish persistent TD from withdrawal dyskinesias. However, the time point that differentiates withdrawal dyskinesias from permanent TD is not completely clear, and there is evidence that early TD detection can improve patient outcomes.[12] Recommendations in previous guidelines that suggest screening for TD at intervals of 6 months or more are thus likely to miss a significant percentage of early cases of TD, preventing timely intervention and possibly reducing chances of remission.[40,41] Uncertainty over the process of TD development reinforces the need for prospective studies of differential TD risk among SGAs based on dose and cumulative exposure to better inform screening guidelines. While prospective studies are ideal, retrospective analyses using large case registries would also provide useful information on vulnerability and risk factors related to type of drug prescribed and risk estimation.

Regarding instruments for assessing the severity and extent of TD, the AIMS has achieved widespread acceptance as an objective measure. The AIMS has been highly effective at enhancing clinician adherence with routine TD

monitoring and screening and fostering standardization and comparability between research trials.[39,42,43] However, the complete AIMS examination and rating procedure may be time-consuming to conduct in a busy clinical practice, and efforts to develop and validate an abridged, simplified AIMS or other semistructured instrument for routine clinical encounters are worthwhile. This may include incorporating patient and caregiver observations as well as strengthening training on the visualization of abnormal movements as part of the psychomotor component of the mental status examination. In fact, while consensus was reached that the AIMS is the standard assessment tool, consensus also was reached that semistructured assessments could be used to screen for TD in clinical practice at each visit, in combination with a more formal AIMS examination performed at less frequent intervals, with extra time set aside for completion.

Consensus results identified several important diagnostic criteria for TD, including unanimous consensus that involuntary movements developing during current or recent antipsychotic treatment may be indicative of TD. Similar to the lack of consensus on the minimum duration of antipsychotic exposure for TD screening purposes, there was a lack of consensus on the minimum duration of exposure for diagnostic purposes as well, although a majority suggested a minimum duration of ≥ 1 month. In addition, there was consensus that 1 rating of mild (AIMS score ≥ 2) in 1 body area should be considered as an indication of possible TD. Research criteria for the diagnosis of TD based on AIMS scores developed by Schooler and Kane were critical in standardizing the diagnosis across clinical and epidemiologic research studies[44]; however, observation of mild movements in 1 body area in a clinical practice setting may be sufficient for the diagnosis of TD as previously proposed by Glazer et al.[45] Recognition of mild signs of TD such as tic-like orofacial or lingual movements or increased eye blink frequency may be critical for early treatment intervention and prevention of worsening or generalization of movements.

While unanimous consensus was reached that choreoathetoid movement was important in determining the diagnosis and severity of TD, there was a lack of consensus on the level of importance of other movement subtypes such as dystonia and stereotypy. There has been considerable study on the phenomenology and differentiation of movement disorders, but the relevance of TD subtypes to treatment and prognosis remain subjects for future research.[46–49] There also remains a pressing need for formal guidelines, recommendations, and training to aid clinicians in the differentiation of TD versus other drug-induced and idiopathic movement disorders, especially in the context of the availability of VMAT2 inhibitors, which can have very different effects on movement disorders other than TD.

Consensus was reached on several principles for managing patients who develop TD, as part of a comprehensive treatment approach. First and foremost is informed discussion with patients and caregivers on the diagnosis, prognosis, and treatment options, with consideration of symptoms, functioning, QoL, history, and efficacy and tolerability of treatments. In addition, consensus was reached that possible modification of antipsychotic/anticholinergic regimens and treatment with VMAT2 inhibitor should be considered. Depending on the character, severity, stability, and risk of relapse of the underlying psychiatric disorder, a majority of the panel thought that antipsychotics could be maintained, tapered off, or possibly switched from FGAs to other SGAs or clozapine at the discretion of the treating practitioner. It should be noted, however, that evidence supporting or refuting these prescribing decisions is insufficient, such that further research on the impact of antipsychotic discontinuation or modification on the course of patients with TD is needed.[14,50,51] Similarly, a decision has to be made whether adjunctive anticholinergics should be maintained, tapered off, or switched to amantadine. While anticholinergics may be effective for some acute drug-induced movement disorders (eg, parkinsonism), they generally worsen choreiform and stereotyped forms of TD.[8,46] In contrast to other antidyskinetic agents that have been studied, VMAT2 inhibitors have been demonstrated to be effective in reducing TD symptoms, and 2 drugs in this class (valbenazine and deutetrabenazine) are now considered first-line treatment for TD.[14] If one of these VMAT2 inhibitors is ineffective or intolerable, a majority of panelists felt that a second should be tried; however, additional research is needed to provide evidence on comparative efficacy of available VMAT2 inhibitors as well as alternative agents. While other agents may be tried empirically off-label, to date no other specific antidyskinetic agent has been proven effective for treatment of TD.[6,14]

Limitations

Although substantial data on TD have accumulated over decades, the continuing controversies and gaps in knowledge lend themselves to a consensus process to identify areas of need and inform future research. Within the essential parameters of iterative rounds, anonymity, and feedback between rounds, the Delphi process has offered flexibility across studies in modified form. In this study, the Delphi rounds were preceded by a nominal group meeting that enabled the identification of criteria for panelists and the core bibliography, and the identification and organization of critical clinical questions. This format of combining these consensus techniques has been suggested and implemented in previous studies.[24,25] A large number of questions were selected for review, reflecting the uncertainty on the range of screening, diagnosis, and treatment aspects of TD that have been included in previous clinical guidelines, often on an arbitrary basis without solid evidence. To inform reassessment of recommendations, a comprehensive approach in posing questions was considered desirable. Outcome measures in Delphi studies also can vary substantially, with categorical criteria for consensus ranging from 50% to 80% of respondents in agreement.[25] In this study, consensus was set at 75% of panelists in agreement, which is among the more stringent criteria.

While the Delphi process has been well accepted as a standardized, systematic technique for surveying the current state of knowledge in many areas of health care, the major limitation in its use is that it is based on opinions of selected individuals rather than objective measurements, evidence-based investigations, or systematic review of the extant literature.[16,17,25] Another potential limitation is the total number and expertise of the panel participants.[20] To ensure a broadly representative sample, panelists who met academic and clinical criteria were recruited across disciplines, from different institutional and clinical settings throughout the United States and Canada, and provided with a core bibliography.

The ideal number of rounds in a Delphi process has been debated,[19] but a minimum of 2 to 3 rounds has been considered sufficient.[25,52–54] The current study employed just 2 rounds of questioning, but after 2 rounds, questions had been improved, consensus or majority agreement had been achieved on 66% of key issues, and no significant changes in responses were further anticipated. Comparison of categorical findings between rounds indicated that Round 2 results generally reinforced and provided further clarity on areas of consensus (or lack thereof) in Round 1. Further, mean Likert scores in both rounds generally correlated with categorical findings. The first round of questions was far-reaching to elicit a wide breadth of opinions and included a range of open-ended formats, on which panelists could comment as well as provide answers. Feedback on the first round was used to revise and streamline questions for the second round, to provide more incisive questioning to facilitate conclusions on whether or not agreement could be achieved. Second round questions were also converted to quantitative form as Likert scales to better capture the strength and distribution of responses.

Clinicians are advised to review policies and guidelines within their governmental jurisdictions and facilities, which likely differ on procedures for monitoring and managing TD, underscoring the need for prompt development of national standards and guidelines that can be applied across practice settings. Finally, financial support for this study was obtained from a pharmaceutical manufacturer of a VMAT2 inhibitor. The breadth and diversity of expert panel participants, who were selected by the steering committee members based on academic and clinical credentials only, served to mitigate potential bias introduced by commercial sponsorship. Survey questions were specifically designed to address a broad and comprehensive clinical approach to assessing and treating TD within the context of overall pharmacologic management, including the use of antidyskinetic agents other than VMAT2 inhibitors. Furthermore, the live meeting and analytics were handled by a third-party organizer.

CONCLUSIONS

Recent availability of 2 FDA-approved VMAT2 inhibitors for treatment of TD suggests that new guidelines to advance best practices in the identification and management of TD could prove worthwhile. Although substantial knowledge has been generated through ambitious and rigorous investigations over decades, gaps in our understanding of the fundamental biology of TD remain. In addition, there continues to be a compelling need to provide training on best practices for preventing TD and diagnosing and managing patients who develop TD. Using a combined sequential nominal group and modified Delphi process, our study provides an overview of current opinions on screening, diagnosis, and treatment of TD. Consensus was reached regarding several key aspects, including that brief screening for TD should be performed at every clinical encounter in all patients taking antipsychotics, that even mild movements in 1 body may represent possible TD, that management of TD requires an overall reassessment of pharmacologic treatment including antipsychotics and anticholinergics and the use of VMAT2 inhibitors, and that informed discussions with patients and caregivers are essential. Several areas requiring further study were identified, including the minimum duration of cumulative antipsychotic exposure for TD to develop, the need for prospective studies on the risk of TD associated with the duration and type of antipsychotic exposure, and the long-term course and prognosis of TD. There is also a pressing need for evidence-based guidelines and procedures for screening, diagnosis, and treatment of TD in clinical settings.

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Supplementary Material

Article Title: A Modified Delphi Consensus Study of the Screening, Diagnosis, and Treatment of Tardive Dyskinesia

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List of Supplementary Material for the article

1. Table 1 Survey Responses and Statistical Comparisons—Screening for TD
2. Table 2 Survey Responses and Statistical Comparisons—Diagnosis of TD
3. Table 3 Survey Responses and Statistical Comparisons—Treatment of TD
4. Table 4 Glossary of Terms

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Supplementary Table 1. Survey Responses and Statistical Comparisons – Screening for TD

***** indicates significant difference (R2-R1) at the 95% CL. [a]Questions are worded exactly as they were worded in the survey and are presented by topic (actual order of survey questions varied from R1 to R2). Responses are listed in order of agreement in Round 2 (or in Round 1 if question was not asked in Round 2), with the highest percentage of agreement first. [b]For Likert scale questions, percent of respondents with score ≥4 ("agree completely" or "agree very much"); for rank order questions, percent of respondents with top-3 ranking. [c]At the 95% confidence level.
Abbreviations: AIMS, Abnormal Involuntary Movement Scale; CL, confidence limits; DRB, dopamine receptor-blocking; EPS, extrapyramidal symptoms; QoL, Quality of life; MC, multiple choice; MSD, mean significant difference; R1, Round 1; R2, Round 2; SD, standard deviation; SE, standard error of the mean; TD, tardive dyskinesia.

	Round 1 (N=29)				Round 2 (N=28)				Difference (R2-R1)	
Question[a]	Question Type	Respondents, %[b]	Likert score, mean (95% CL)	SD/SE	Question Type	Respondents, %[b]	Likert score, mean (95% CL)	SD/SE	%	MSD[c] (Likert score)
PATIENT CHARACTERISTICS										
Which patients should be screened for TD? (R1) **To what extent would you agree that the following patients should be screened for TD? (R2)**										
- Patients currently taking any drug with DRB properties	MC	72			Likert	100	5.0	0/0	+28*	
- Patients having taken drug with DRB properties within the past year	(select	62	-	-	scale	68	4.0 (3.7, 4.3)	0.9/0.2	+6	-
- Patients currently taking any antipsychotic with DRB properties	any)	66				-	-	-	-	
- Patients having taken drug with DRB properties at any time		37				29	3.0 (2.7, 3.3)	0.9/0.2	-9	
What patient or treatment attributes contribute to how high risk for TD is identified? (R1) **To what extent do you agree that the following patient or treatment attributes contribute to how high-risk for TD is identified? (R2)**										
- Current/recent treatment with 1st generation antipsychotic	MC	100			Likert	100	4.9 (4.8, 5.1)	0.4/0.1	0	
- Age	(select	97			scale	100	4.7 (4.5, 4.9)	0.5/0.1	+3	
- Cumulative exposure to antipsychotic	any)	93				100	4.9 (4.8, 5.1)	0.4/0.1	+7	
- Acute EPS symptoms other than acute akathisia		86				75	4.0 (3.7, 4.3)	0.8/0.2	-11	
- Gender		72				54	3.5 (3.2, 3.8)	0.8/0.2	-18	
- Acute akathisia		55				50	3.6 (3.2, 4.0)	1.0/0.2	-5	
- Concomitant anticholinergic treatment		45	-	-		46	3.3 (2.9, 3.7)	1.0/0.2	+1	-
- Psychiatric diagnosis		59				39	3.3 (3.0, 3.6)	0.9/0.2	-20	
- Comorbid medical condition		48				39	3.1 (2.8, 3.4)	0.9/0.2	-9	
- Race/ethnicity		-				21	2.7 (2.3, 3.1)	1.0/0.2	-	
- Treatment non-adherence		31				18	2.6 (2.3, 2.9)	0.9/0.2	-13	
- Comorbid alcohol/substance abuse		28				18	2.6 (2.2, 3.0)	1.0/0.2	-10	
MINIMUM DURATION OF ANTIPSYCHOTIC EXPOSURE (FOR SCREENING PURPOSES)										
The frequency of screening for patients who are currently taking antipsychotics or other drugs with DRB properties should take into account that TD may develop within which of the following durations of exposure? (R1) **To what extent would you agree that TD may develop within the following minimum cumulative durations of exposure to antipsychotics or other drugs with DRB properties? (R2)**										
- At least 1 month	MC	41			Likert	71	3.9 (3.5, 4.3)	1.0/0.2	+30*	
- At least 3 months	(select	34			scale	57	3.7 (3.2, 4.2)	1.3/0.3	+23	
- No lower limit	one)	-	-	-		36	3.3 (2.8, 3.8)	1.4/0.3	-	-
- At least 6 months		17				-	-	-	-	
- At least 12 months		3				-	-	-	-	

SCREENING ASSESSMENTS										
How much do you agree with the following? (R1)										
- AIMS is the standard structured assessment - Semi-structured assessment should be utilized in clinical practice to screen for TD - Structured assessments should be utilized in clinical practice to screen for TD - Clinical screening for TD should include either semi-structured or structured assessment of movement disorders	Likert scale	97 76 69 59	4.6 (4.4, 4.8) 3.9 (3.5, 4.3) 3.9 (3.5, 4.3) 3.8 (3.4, 4.2)	0.6/0.1 1.0/0.2 1.2/0.2 1.1/0.2	-	-	-	-	-	-
What should a semi-structured assessment include? (R1)										
- Patient recognition of current/recent abnormal movements as part of a review of side effects at time of assessment - Visual observation of psychomotor abnormalities on mental status examination - Caregiver report of recent/current abnormal movements - Patient report of past history of movement/psychomotor changes - Patient complaints about changes in movement being distressful or interfering with functioning or QoL - Other	MC (select any)	100 97 97 93 86 17	-	-	-	-	-	-	-	-
SCREENING FREQUENCY										
How much do you agree with the following? (R1)										
- Patients at high risk for TD should be screened more frequently than patients at low risk - In patients at increased risk, assessment should be done every 3 months and every 6 months with treatment using 1st and 2nd/3rdgeneration antipsychotics, respectively - Clinical assessment of abnormal involuntary movements should be conducted every 6 months in patients taking 1st generation antipsychotics and every 12 months in those taking 2nd/3rd generation antipsychotics - All patients currently taking any antipsychotics or other drugs with DRB properties should be screened for TD at same frequency regardless of risk	Likert scale	86 79 52 52	4.3 (4.0, 4.6) 4.0 (3.7, 4.3) 3.5 (3.1, 3.9) 3.5 (3.1, 3.9)	0.8/0.2 0.9/0.2 1.0/0.2 1.2/0.2	-	-	-	-	-	-
How much do you agree with the following? (R1)										
- Clinical screening for TD should include routine semi-structured and less frequent structured assessment of movement disorders - Semi-structured assessments should be administered at same frequency for 1st generation and 2nd/3rd generation antipsychotics - Structured assessments should be administered at same frequency for 1st generation and 2nd/3rd generation antipsychotics	Likert scale	79 69 62	4.1 (3.7, 4.5) 4.0 (3.6, 4.4) 3.6 (3.1, 4.1)	1.0/0.2 1.1/0.2 1.4/0.3	-	-	-	-	-	-

How often should a semi-structured assessment be administered for patients taking antipsychotics or other drugs with DRB properties? (R1) **To what extent do you agree that clinical assessment to screen for the development of TD in patients taking antipsychotics or other drugs with DRB properties, <u>regardless</u> of the degree of risk for TD, should be performed at the following? (R2)**										
- Every clinical encounter	MC	66			Likert	75	4.1 (3.7, 4.5)	1.1/0.2	+9	
- Once every 3 months	(select	10			scale	68	3.9 (3.5, 4.3)	1.0/0.2	+58*	
- Once every 6 months	one)	14				61	3.9 (3.5, 4.3)	1.2/0.2	+47*	
- At least once a month		3				-	-	-	-	
- Once every 12 months		3	-	-		-	-	-	-	-
- Other		3				-	-	-	-	
- At least once a week		0				-	-	-	-	
- Once every 9 months		0				-	-	-	-	
- >12 months		0				-	-	-	-	
To what extent do you agree that clinical assessment to screen for the development of TD in patients taking antipsychotics or other drugs with DRB properties, who are <u>not at high risk</u> for tardive dyskinesia (e.g., younger age, 2nd generation antipsychotics), should be performed at the following? (R2)										
- At every clinical encounter					Likert	68	3.8 (3.3, 4.3)	1.3/0.2		
- At least every 3 months	-	-	-	-	scale	61	3.6 (3.2, 4.0)	1.1/0.2	-	-
- At least every 6 months						54	3.8 (3.4, 4.2)	1.2/0.2		
To what extent do you agree that clinical assessment to screen for the development of TD in patients taking antipsychotics or other drugs with DRB properties, who are at high risk for tardive dyskinesia (e.g., older age, 1st generation antipsychotics), should be performed at the following? (R2)										
- At every clinical encounter					Likert	93	4.5 (4.2, 4.8)	0.8/0.2		
- At least every 3 months	-	-	-	-	scale	71	3.8 (3.3, 4.3)	1.0/0.2	-	-
- At least every 6 months						61	3.8 (3.4, 4.1)	1.3/0.2		

Supplementary Table 2. Survey Responses and Statistical Comparisons – Diagnosis of TD

***** indicates significant difference (R2-R1) at the 95% CL. [a]Questions are worded exactly as they were worded in the survey and are presented by topic (actual order of survey questions varied from R1 to R2). Responses are listed in order of agreement in Round 2 (or in Round 1 if question was not asked in Round 2), with the highest percentage of agreement first. [b]For Likert scale questions, percent of respondents with score ≥4 ("agree completely" or "agree very much"); for rank order questions, percent of respondents with top-3 ranking. [c]At the 95% confidence level.

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; APA, American Psychiatric Association; CL, confidence limits; DISCUS, Dyskinesia Identification System: Condensed User Scale; DSM-5, The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ESRS, Extrapyramidal Symptom Rating Scale; QoL, quality of life; MC, multiple choice; MSD, mean significant difference; R1, Round 1; R2, Round 2; SD, standard deviation; SE, standard error of the mean; TD, tardive dyskinesia.

	Round 1 (N=29)				Round 2 (N=28)				Difference (R2-R1)	
Question[a]	Question Type	Respondents, %[b]	Likert score, mean (95% CL)	SD/SE	Question Type	Respondents, %[b]	Likert score, mean (95% CL)	SD/SE	%	MSD[c] (Likert score)
DIAGNOSTIC CRITERIA										
How important are the following criteria to the diagnosis of TD? (R1) **To what extent do you agree that the following criteria are very important for the diagnosis of TD? (R2)**										
- Signs/symptoms (R1)/involuntary movements (R2) that develop during exposure to antipsychotic medication or within 4-8 weeks of withdrawal from an antipsychotic medication	Likert scale	93	4.6 (4.4, 4.8)	0.6/0.1	Likert scale	100	4.9 (4.8, 5.1)	0.4/0.1	+7	Yes
- Patient history		86	4.4 (4.1, 4.7)	0.7/0.1		93	4.5 (4.3, 4.7)	0.6/0.1	+7	No
- Ruling out other movement disorders/medical conditions/other drugs that cause involuntary movements		93	4.7 (4.5, 4.9)	0.6/0.1		93	4.7 (4.5, 4.9)	0.6/0.1	0	No
- Cumulative exposure to antipsychotic medication		83	4.2 (3.8, 4.6)	1.1/0.2		86	4.4 (4.0, 4.8)	1.0/0.2	+3	No
- Current medication		83	4.4 (4.1, 4.7)	0.9/0.2		85	4.3 (3.9, 5.1)	0.9/0.2	+2	No
- Duration of signs and symptoms (R1)/involuntary movements (R2)		93	4.4 (4.1, 4.7)	0.9/0.2		82	4.3 (3.9, 4.7)	1.1/0.2	-11	No
- Severity of dyskinetic (R1)/involuntary (R2) movements in affected areas		72	4.0 (3.6, 4.4)	1.2/0.2		79	3.9 (3.5, 4.3)	1.1/0.2	+7	No
- Presence of abnormal (R1)/involuntary (R2) movements prior to medication initiation		86	4.3 (3.9, 4.7)	1.2/0.2		71	4.0 (3.6, 4.4)	1.1/0.2	-14	No
- Frequency and regularity of involuntary movements		-	-	-		64	3.8 (3.4, 4.2)	1.1/0.2	-	-
- Number of areas affected by dyskinetic (R1)/involuntary (R2) movements		66	3.7 (3.3, 4.1)	1.2/0.2		57	3.6 (3.2, 4.0)	1.2/0.2	-9	No
- Patient-reported subjective awareness, distress, and impact of movements on functioning and QoL		62	3.8 (3.3, 4.3)	1.3/0.2		36	3.1 (2.6, 3.6)	1.3/0.3	-26*	No
- Presence of psychiatric comorbidity		41	3.2 (2.8, 3.6)	1.1/0.2		21	2.5 (2.1, 2.9)	1.1/0.2	-20	Yes
Please rate the following on the appropriateness (based on practicality, value, etc.) for use in clinical practice to diagnose patient with TD. (R1) **Please indicate the extent to which you agree that the following are appropriate criteria for the diagnosis of TD in a psychiatric clinical setting. (R2)**										
- Visual assessment as part of the routine neurologic/mental status examination	Likert scale	-	-	-	Likert scale	82	4.2 (3.9, 4.5)	0.8/0.2	-	-
- DSM-5		72	3.9 (3.5, 4.3)	1.1/0.2		72	4.0 (3.6, 4.4)	1.1/0.2	0	No
- Schooler-Kane AIMS criteria		62	3.7 (3.2, 4.2)	1.3/0.2		61	3.8 (3.4, 4.2)	1.1/0.2	-1	No
- There is a need for revised standardized criteria for making a diagnosis of TD in a psychiatric clinical practice setting		-	-	-		57	3.7 (3.2, 4.2)	1.3/0.2	-	-
- Glazer et al AIMS		48	3.3 (2.9, 3.7)	1.1/0.2		-	-	-	-	-
- APA Practice Guideline		41	3.3 (2.9, 3.7)	1.0/0.2		-	-	-	-	-
- Patient reported subjective awareness, distress, and impact of movement on functioning and QoL		-	-	-		43	3.3 (2.9, 3.7)	1.1/0.2	-	-

AFFECTED BODY AREAS											
How much do you agree with that the following criterion is useful in the clinical diagnosis of TD? (R1) **To what extent do you agree with the following statements? (R2)**											
- TD is most often evident in orofacial musculature, although other body areas may be affected and should not be neglected	Likert scale	-	-	-	Likert scale	93	4.7 (4.5, 4.9)	0.6/0.1	-	-
- A patient having 1 rating of mild (≥2 on AIMS) affecting 1 body area should be considered as having possible TD		62	3.7 (3.3, 4.1)	1.0/0.2		89	4.4 (4.2, 4.7)	0.7/0.1	+27*	Yes
- A patient needs to have at least moderate dyskinetic movements in 1 body area (≥3 on AIMS) or at least mild dyskinetic movements in 2 body areas (≥2 on AIMS)		48	3.1 (2.6, 3.6)	1.3/0.2		43	3.3 (2.8, 3.8)	1.3/0.3	-5	No
- The number or distribution of affected body areas should be considered in diagnosis of TD		38	3.0 (2.6, 3.4)	1.2/0.2		-	-	-	-	-
MINIMUM DURATION OF ANTIPSYCHOTIC EXPOSURE (FOR DIAGNOSTIC PURPOSES)											
To what extent would you agree that diagnostic criteria for TD should include the following minimum durations of cumulative exposure to antipsychotics or other drugs with DRB properties for patients of any age? (R2)											
- There is no lower limit on the duration of exposure					Likert	54	3.7 (3.2, 4.2)	1.3/0.2		
- At least 1 month	-	-	-	-	scale	50	3.5 (3.0, 4.0)	1.3/0.3	-	-
- At least 3 months						46	3.3 (2.8, 3.8)	1.4/0.3		
PHENOMENOLOGICAL MOVEMENT SUBTYPES											
To what degree are the following phenomenological movement subtypes important in determining the diagnosis and severity of TD? (R1) **To what extent do you agree that the following phenomenological movement subtypes are important in determining the diagnosis and severity of TD? (R2)**											
- Choreoathetoid	Likert	93	4.7 (4.4, 5.0)	0.9/0.2	Likert	100	4.8 (4.8, 5.1)	0.4/0.1	+7	No
- Dystonic	scale	52	3.6 (3.1, 4.1)	1.3/0.2	scale	64	3.8 (3.4, 4.2)	1.1/0.2	+12	No
- Stereotypy		48	3.3 (2.7, 3.9)	1.6/0.3		57	3.6 (3.2, 4.0)	1.1/0.2	+9	No
- Akathisia		55	3.5 (3.1, 3.9)	1.2/0.2		39	3.1 (2.6, 3.6)	1.4/0.3	-16	No
- Tremor		38	2.9 (2.4, 3.4)	1.4/0.3		18	2.4 (2.0, 2.8)	1.2/0.2	-20	No
- Tics		38	3.1 (2.6, 3.6)	1.5/0.3		14	2.8 (2.5, 3.3)	1.1/0.2	-24*	No
- Myoclonus		34	2.9 (2.5, 3.3)	1.2/0.2		7	2.3 (1.9, 2.7)	1.0/0.2	-27*	No
- Other		75	4.5 (4.1, 4.9)	1.0/0.5		-	-	-	-	-
NEUROLOGICAL CONSULTATION											
Under which of the following circumstances should a psychiatrist order a neurological consultation to clarify the differential diagnosis in the evaluation of a patient with possible TD? (R1)											
- Atypical presentation or course of a movement disorder	MC	93								
- Presence of other neurological/systemic medical signs and symptoms	(select any)	90								
- Patient has a family history of other movement or neurodegenerative disorders (e.g., Huntington's disease)		90								
- Unexpected treatment response, intolerability, or resistance of the movement disorder		86	-	-	-	-	-	-	-	-
- Psychiatrist is unsure of whether TD diagnosis is present		86								
- Lack of knowledge about specific treatments for TD		62								
- Severity of movement disorder		55								
- Other		7								

Supplementary Table 3. Survey Responses and Statistical Comparisons – Treatment of TD

***** indicates significant difference (R2-R1) at the 95% CL. [a]Questions are worded exactly as they were worded in the survey and are presented by topic (actual order of survey questions varied from R1 to R2). Responses are listed in order of agreement in Round 2 (or in Round 1 if question was not asked in Round 2), with the highest percentage of agreement first. [b]For Likert scale questions, percent of respondents with score ≥4 ("agree completely" or "agree very much"); for rank order questions, percent of respondents with top-3 ranking. [c]At the 95% confidence level.

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; CL, confidence limits; QoL, quality of life; MC, multiple choice; MSD, mean significant difference; R1, Round 1; R2, Round 2; SD, standard deviation; SE, standard error of the mean; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

	Round 1 (N=29)				Round 2 (N=28)				Difference (R2-R1)	
Question[a]	Question Type	Respondents, %[b]	Likert score, mean (95% CL)	SD/SE	Question Type	Respondents, %[b]	Likert score, mean (95% CL)	SD/SE	%	MSD[c] (Likert score)
OVERALL CONSIDERATIONS										
After a patient is diagnosed with TD, which of the following do you consider as part of your treatment approach? (R1)										
- Discussion of options with patient and caregivers	MC (select any)	100	-	-	-	-	-	-	-	-
- Review and consider modifying antipsychotic regimen		100								
- Treatment of TD with VMAT2		100								
- Review and consider modifying anticholinergic regimen		86								
- Treatment of TD with other medication		45								
- Other		3								
How important are the following criteria in deciding on the treatment and management approach for patients with TD? (R1)										
- Severity of TD symptoms	Likert scale	97	4.8 (4.6, 5.0)	0.5/0.1	-	-	-	-	-	-
- Severity of underlying disorder		97	4.6 (4.4, 4.8)	0.6/0.1						
- Phenomenology of TD symptoms (e.g., dystonia)		90	4.3 (4.0, 4.6)	0.8/0.1						
- Psychiatric stability on current treatment regimen		90	4.6 (4.3, 4.9)	0.7/0.1						
- Current antipsychotic medication		86	4.6 (4.3, 4.9)	0.8/0.2						
- Current acute extrapyramidal side effects		79	4.3 (4.0, 4.6)	0.8/0.2						
- Patient psychiatric history (e.g., suicide attempts, hospitalizations, severe psychosis, etc.)		79	4.4 (4.1, 4.7)	0.9/0.2						
- Current anticholinergic medication		76	4.2 (3.8, 4.6)	1.0 /0.2						
- Patient-reported subjective awareness, distress, and impact of movements on functioning and QoL		76	4.3 (4.0, 4.6)	0.9/0.2						
- Medication history		72	4.2 (3.8, 4.6)	1.0/0.2						
- Duration of TD symptoms		69	4.0 (3.6, 4.4)	1.0/0.2						
- Patient medical history		66	3.9 (3.5, 4.3)	1.0/0.2						

MANAGEMENT OF ANTIPSYCHOTICS										
How much do you agree with each of the following statements? (R1)										
- In considering whether to modify antipsychotic regimens as part of the management of TD, the severity, stability, and risk of relapse of the underlying psychiatric disorder must be considered	Likert scale	100	4.8 (4.7, 5.0)	0.4/0.1						
- In considering whether to modify antipsychotic regimens as part of the management of TD, the availability of alternative treatments for the underlying psychiatric disorder is an important factor		97	4.6 (4.4, 4.8)	0.6/0.1						
- For patients who can be safely withdrawn from antipsychotic therapy (i.e., for whom alternative therapies are approved and available [antidepressants, etc.]), providers should consider tapering the antipsychotic agent as part of the management of TD		93	4.6 (4.3, 4.9)	0.7/0.1	-	-	-	-	-	-
- For patients who cannot be safely withdrawn from antipsychotics, (i.e., for whom alternative therapies are not approved nor available), providers should consider modifying (eg, maintain treatment, change dose, switch antipsychotic) the antipsychotic agent as part of the management of TD		93	4.6 (4.3, 4.9)	0.9/0.2						
Which of the following should be considered as possible options or modifications to antipsychotic treatment for patients with TD who are unable to be withdrawn from antipsychotic therapy? (R1) **To what extent do you agree that each of the following should be considered as a possible option or modification to antipsychotic treatment for patients with TD who are unable to be withdrawn from antipsychotic therapy? (R2)**										
- Switch to clozapine	MC (select any)	83			Likert scale	79	4.0 (3.6, 4.4)	1.0/0.2	-4	
- Switch from 1st to 2nd/3rd generation antipsychotic		76				78	4.1 (3.7, 4.5)	1.0/0.2	+2	
- Reduce dose		86				60	3.9 (3.5, 4.3)	1.2/0.2	-26*	
- Switch from more potent to less potent antipsychotic		59				54	3.5 (3.1, 3.9)	1.0/0.2	-5	
- Switch from 2nd/3rd to another 2nd/3rd generation antipsychotic		52	-	-		25	2.9 (2.5, 3.3)	1.0/0.2	-27*	-
- Maintain current treatment		69				14	2.6 (2.2, 3.0)	1.2/0.2	-55*	
- Increase dose		17				-	-	-	-	
- Switch from a 1st generation to another 1st generation antipsychotic		10				-	-	-	-	
- Switch from less potent to more potent antipsychotic		10				-	-	-	-	
- Other		3				-	-	-	-	
MANAGEMENT OF ANTICHOLINERGICS										
How much do you agree with each of the following statements? (R1)										
- As part of management of TD, providers should consider whether to modify anticholinergic agents (e.g., reduce dose, taper-off therapy)	Likert scale	97	4.6 (4.4, 4.8)	0.6/0.1						
- In considering whether to modify anticholinergic regimens as part of the management of TD, the presence of acute extrapyramidal side effects and dystonia must be considered		90	4.4 (4.2, 4.7)	0.7/0.1	-	-	-	-	-	-
Which of the following should be considered in defining modifications to treatment with an anticholinergic agent for patients with TD? (R1) **To what extent do you agree that each of the following steps should be considered in modifications to treatment with an anticholinergic agent for patients with TD? (R2)**										
- Reduce dose	MC (select any)	76			Likert scale	71	3.9 (3.5, 4.3)	1.1/0.2	-5	
- Discontinue therapy by tapering		93				68	4.0 (3.6, 4.4)	1.0/0.2	-25*	
- Switch to alternative anticholinergic agent (R1)/amantadine (R2)		24	-	-		54	3.6 (3.2, 4.0)	1.2/0.2	+30*	-
- Other		17				-	-	-	-	
- Initiate therapy		10				-	-	-	-	

USE OF VMAT2 INHIBITORS										
As part of the management of TD, when should the prescription of VMAT2 inhibitors be considered? (R1) **To what extent do you agree that the following should be considered in the prescription of VMAT2 inhibitors as part of the management of TD? (R2)**										
- As part of overall and integrated, pharmacologic treatment plan	MC	86			Likert	97	4.9 (4.8, 5.1)	0.4/0.1	+11	
- Depends on a patient's condition and needs	(select	76			scale	97	4.6 (4.4, 4.8)	0.6/0.1	+21*	
- If a patient and caregiver request, prefer, or agree with this treatment option	any)	55				86	4.3 (4.0, 4.6)	0.8/0.2	+31*	
- After the response to antipsychotic maintenance/modifications is determined		55				75	4.0 (3.6, 4.4)	1.0/0.2	+20	
- After the response to anticholinergic maintenance/modifications is determined		48	-	-		36	3.2 (2.8, 3.6)	1.1/0.2	-12	-
- At same time as decisions on antipsychotic/anticholinergic modifications are determined		28				32	3.3 (2.9, 3.7)	1.0/0.2	+4	
- Before the response to antipsychotic/anticholinergic modifications is determined		7				-	-	-	-	
Which of the following patient- or drug-specific factors impact selection of a specific VMAT2 inhibitor? (R1)										
- Tolerability	MC	93								
- Efficacy	(select	86								
- Safety	any)	86								
- Ease of use		79	-	-	-	-	-	-	-	-
- Cost		69								
- Previous treatment with VMAT2 inhibitors		69								
- Patient or caregiver preference		66								
- Label indication		55								
If a VMAT2 inhibitor is ineffective, not tolerated, or declined by a patient, what is the priority for the possible next steps with other agents that are not approved but reasonably could be used off-label based on limited evidence? (R1) **If a VMAT2 inhibitor is ineffective, not tolerated, or declined by a patient, to what extent do you agree that the following next steps are important to consider based on available evidence and your clinical experience? (R2)**										
- Switch to another VMAT2 inhibitor before using other agents	Rank	83			Likert	82	4.4 (4.1, 4.7)	0.9/0.2	-1	
- Botulinum toxin A for dystonic symptoms	order	45			scale	54	3.5 (3.1, 3.9)	1.1/0.2	+9	
- Amantadine		62				29	3.1 (2.8, 3.4)	0.9/0.2	-32*	
- Benzodiazepines (clonazepam)		45				14	2.6 (2.2, 3.0)	1.0/0.2	-31*	
- Antioxidants (vitamins, herbal products)		45	-	-		11	2.3 (1.9, 2.7)	1.2/0.2	-34*	-
- Branched-chain amino acids		28				8	2.3 (1.9, 2.7)	1.1/0.2	-19*	
- Levetiracetam		7				7	2.3 (2.0, 2.6)	0.8/0.2	0	
- Cholinesterase inhibitors (donepezil)		10				4	2.0 (1.7, 2.3)	0.9/0.2	-6	
- None of the above		3				-	-	-	-	
- Other		14				-	-	-	-	

Which of the following are the most useful measures of a minimal clinically important difference(s) in response to treatment for TD in a given patient? (R1) **To what extent do you agree that each of the following are useful measures of a minimal clinically important difference in response of TD to treatment in a given patient? (R2)**										
- Subjective clinician impression of "much improved"	MC	69			Likert	82	4.4 (4.1, 4.7)	0.8/0.2	+13	
- Subjective patient report of improvement in distress, functioning, or QoL	(select any)	72			scale	82	4.3 (4.0, 4.6)	0.9/0.2	+10	
- Subjective patient impression of "much improved"		76				78	4.3 (4.0, 4.6)	0.9/0.2	+2	
- At least 30% decrease in total AIMS		52				68	4.0 (3.7, 4.3)	0.8/0.2	+16	
- At least 2-point decrease in total AIMS		38	-	-		39	3.5 (3.2, 3.8)	0.8/0.2	+1	-
- At least 3-point decrease in total AIMS		17				-	-	-	-	
- At least 50% decrease in total AIMS		21				-	-	-	-	
- Nearly 100% decrease in total AIMS		3				-	-	-	-	
- Subjective patient impression of "very much improved"		14				-	-	-	-	
- Subjective clinician impression of "very much improved"		10				-	-	-	-	

Supplementary Table 4. Glossary of Terms

Phenomenological movement subtypes[51,52]	Categories of abnormal or involuntary movements. Subtypes most commonly associated with TD are: • Choreoathetoid: irregular contracting, writhing movements of finger/hand piano-playing movements, foot tapping, truncal rocking, or pelvic thrusting • Stereotypy: repetitive, rhythmic movements, such as the "classic" oral-buccal-lingual movements of chewing/opening of jaw/mouth, tongue protrusion, lip smacking/pursing, and grimacing • Dystonia: sustained or intermittent spasms or twisting movements or postures • Akathisia: motor restlessness, urge to move, shifting in place, inability to sit still, pacing
VMAT2 inhibitors	Vesicular monoamine transporter-2 inhibitors include tetrabenazine, valbenazine, and deutetrabenazine. Valbenazine and deutetrabenazine are FDA approved for TD in adults.
DRBA properties	Prolonged exposure to a drug with dopamine receptor blocking agent (DRBA) properties, such as first- and second-generation antipsychotics and anti-emetics (e.g., metoclopramide) is associated with the development of TD
Extrapyramidal symptoms (EPS)	A traditional term used to describe treatment-emergent abnormal movements (e.g., akathisia, dystonia, parkinsonism, NMS, TD). This term is considered by movement disorders specialists as lacking in clinical precision and clarity but has been widely accepted in psychiatric practice to refer to drug-induced movement disorders
TD screening	Method of assessing whether an individual meets diagnostic criteria for TD, usually with a standard instrument (e.g., AIMS)
Structured TD assessment	Method of assessment for TD in which an established, standardized process is followed with a specific set of questions and/or observations (e.g., the AIMS)
Semi-structured assessment	Modified method of assessment for TD in which part of a structured assessment may be utilized along with observations obtained through standard clinical history and examination procedures
AIMS[38]	12-item rating scale used in contemporary clinical trials to assess TD severity and treatment effects
Schooler-Kane AIMS[43]	TD diagnostic criteria developed for research purposes • ≥3 months of cumulative antipsychotic exposure • Score ≥3 (moderate or severe) in ≥1 AIMS item or score ≥2 (mild or worse) in ≥2 AIMS items • Absence of other conditions that might produce abnormal involuntary conditions
Glazer et al AIMS[53]	TD diagnostic criteria developed for research purposes • AIMS total score ≥3 (moderate or severe) with score ≥2 (mild or worse) in ≥1 AIMS item
APA practice guidelines[39]	TD diagnostic criteria suggested in APA practice guidelines for schizophrenia management • Abnormal movements present continuously for ≥4 weeks • History or ≥3 months cumulative antipsychotic exposure (may be shorter in patients ≥60 years) • Dyskinesia onset occurs while patient is on antipsychotics or within a few weeks of discontinuing antipsychotics