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Tardive Dyskinesia: *Minimizing Risk and Improving Outcomes in Schizophrenia and Other Disorders*

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THE USE OF ANTIPSYCHOTIC AGENTS FOR PSYCHIATRIC DISORDERS

In the United States, antipsychotic drugs are the cornerstone of treatment for schizophrenia,[1] for which about 2 million patients are treated annually.[2] In addition, antipsychotic agents are widely used in the treatment of schizoaffective disorders and mood disorders with psychotic features. They are also sometimes prescribed for diagnoses that do not include a psychotic component.[3] According to the US Department of Health and Human Services, 11 million antipsychotic prescriptions were paid by Medicaid in 1998, 51% of which were for atypical antipsychotics.[4]

Psychosis can have a devastating impact on economic prospects, socialization, and quality of life. Unfortunately, long-term treatment with antipsychotics carries the risk of serious adverse effects, including tardive dyskinesia, which can have a substantial negative life impact.[5] Because for many patients antipsychotics are the only effective treatment, clinicians who prescribe them must be educated about their risks and guard against serious long-term effects. Adverse effect risk can vary with individual patient vulnerabilities, treatment duration, dosage, and drug class (conventional/first-generation antipsychotics [***FGAs***] or atypical/second-generation antipsychotics [***SGAs***]). In schizophrenia, treatment is commonly lifelong; therefore the best treatment uses the antipsychotic agent with the best long-term efficacy-to-risk ratio for the individual patient.[6]

MOTORIC ADVERSE EFFECTS

Acute motoric adverse effects can begin to appear within the first few hours of antipsychotic treatment. All antipsychotics can cause potentially fatal neuroleptic malignant syndrome, characterized by diffuse muscular rigidity, tremors, fever, labile blood pressure, and cognitive and autonomic disturbances.[7] Extrapyramidal symptoms (***EPS***) may develop in 50% to 60% of patients treated with FGAs.[8] ***Dystonias*** appear as disturbances of muscle tone, whereas ***dyskinesias*** are disturbances of movement.[9]

Acute dystonia, involuntary and sometimes painful muscle contractions in neck, face, tongue, or back,[10] can usually be relieved with anticholinergic agents.[10]

Akathisia (motor restlessness) frequently manifests as pacing or inability to sit still.[10] Acute akathisia does not always respond to antiparkinsonian drugs.[11,12] Drug-induced akathisia can be mistaken for psychotic agitation, sometimes leading clinicians to increase the antipsychotic dose.[13] However, akathisia is best treated by reducing the dose or switching antipsychotics.[10,12]

Drug-induced parkinsonism (tremors, rigidity, shuffling gait, extremely slow movement or paralysis)[10] can be alleviated with antiparkinsonian agents including anticholinergics.[10]

Involuntary orofacial movements that seemed associated with neuroleptic treatment were described as early as 1957 and, along with limb and trunk movements described later, were called ***tardive dyskinesia*** (***TD***) in 1964.[13] As the name "tardive" implies, TD was considered to be a result of months or years of exposure to antipsychotic drugs.[13] Early reports consistently emphasized its persistence long after discontinuation of neuroleptics.[13] These criteria remain today.

Training in the assessment of TD has decreased since prescribing practices have come to favor SGAs.[14] Because many clinicians lack training in movement disorders and many patients do not complain of dyskinesias, TD may be underdiagnosed.[15] Whereas acute dystonia, akathisia, and drug-induced parkinsonism may be transient and reversible with treatment, TD can be persistent.[16,17] Persistence is usually defined as sustained TD symptoms >3 months after withdrawal of the offending neuroleptic,[9,18] but in some studies it can mean >3 months whether or not antipsychotic treatment continues.[19] In up to 50% of affected patients, TD becomes chronic and irreversible.[20]

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Some dyskinesias described in the 1960s-1970s first appeared after neuroleptic cessation but disappeared several weeks later.[10,13] These symptoms, called ***withdrawal dyskinesia***, reflect the action of neuroleptics to suppress or mask dyskinesia.[21,22]

When TD first appears *during* antipsychotic use, withdrawal may initially worsen involuntary movements.[21,23] Later (sometimes in 1-2 months) TD can remit spontaneously. Thus, withdrawal of antipsychotics, when possible, is a primary treatment for TD.[23] Dyskinesia that first appears *on withdrawal* may be masked again if antipsychotics are restarted. Then it is important to avoid both FGAs, with their higher associated incidence of TD, and concomitant anticholinergic medications for acute drug-induced movement disorders, with their potential to exacerbate TD.[20,23]

Dystonia that persisted 20 months after discontinuation of phenothiazines—in other words, ***tardive dystonia***—was described in 1962.[13] In a recent study of long-term antipsychotic use, annual incidence of tardive dystonia was 0.7% versus 10.2% incidence of TD.[24] Tardive dystonia is characterized by sometimes painful muscular contractions that may result in slow twisting movements or dystonic postures and abnormal gait.[25] It may affect neck muscles first and present as an abnormal head position.[9] Some authors contend that tardive dystonia can be mistaken for TD, and that TD identified within a year of antipsychotic initiation is usually tardive dystonia.[26] No treatment for tardive dystonia has been proven generally effective. Tetrabenazine, anticholinergics, clozapine, clonazepam, or the combination of clozapine plus clonazepam have been helpful in some cases.[9,25-28] In 1 recent case, antipsychotics were discontinued and schizophrenia and severe tardive dystonia were managed successfully with mood stabilizers and benzodiazepines alone.[29]

Akathisia was also noted in several of the first reports of TD.[13] Unlike acute akathisia, ***tardive akathisia*** can worsen when the antipsychotic dose is lowered and can present with emergent TD.[12] In a study of chronic schizophrenia, discontinuation of antipsychotics resulted in akathisia and withdrawal TD in a third of patients.[12] When antipsychotics were restarted, the patients who had exhibited akathisia at withdrawal persisted in exhibiting TD for up to 6 weeks, suggesting a relationship between TD and late-onset akathisia.[12] Tardive akathisia may be a preliminary stage of TD in some patients receiving long-term antipsychotic treatment.[12]

INCIDENCE AND PREVALENCE OF TD

In an analysis of studies totaling nearly 35000 patients treated with antipsychotics, the mean corrected prevalence of TD was 18.5%.[30] The incidence of TD in young adults is 4% to 5% annually, but the risk increases with age and duration of neuroleptic treatment.[31]

In the Hillside study, the first long-term prospective study of TD incidence,[15] patients with no baseline TD had a TD incidence of 14% after 4 years of cumulative FGA exposure.[32] The Hillside data on TD persistence suggest an FGA-related annual incidence of 3% for persistent TD (≥3 months) and 2% for transient TD (<3 months).[15] Other prospective studies have similarly shown annual incidence of 4% to 8% with spontaneous remission up to 2.5%.[15]

The incidence of TD is higher in the elderly. In the Hillside study 23% of a subgroup of patients older than 55 years developed TD within 2.2 years.[15] Another prospective study of elderly patients found incidence of 59.8% after 3 years with FGAs.[15]

The incidence of TD is higher in the elderly.

Incidence of TD is also higher in mood disorders, sometimes even higher than in schizophrenia.[32,33] TD incidence may increase in the future as the use of antipsychotics increases for affective disorders and other nonschizophrenic indications.[15]

Incidence and prevalence studies that include outpatients may not control for nonadherence. Up to 50% of outpatients fail to adhere to medication schedules.[2,18] In the context of nonadherence, patients may be developing TD with less total exposure to antipsychotics than is reported.

Another way to look at TD is in risk related to years of neuroleptic exposure. The risk of TD is approximately 5% per year of FGA exposure up to about 40 years of age.[34] After age 40 years, the risk increases.[34] In elderly patients, the risk in the first year of FGA exposure may be as high as 25%.[14] However, the risk per year of SGA exposure has not been firmly established. A recent systematic review of current literature suggests annual TD incidence of about 1% per year with SGAs versus 5% per year with FGAs.[35]

CHARACTERISTICS AND PATHOPHYSIOLOGY OF TD

TD is characterized by movements that are involuntary, repetitive, and purposeless.[8] The movements may be of 3 possible types: chorea (variable, rapid, jerky or fidgety), athetoses (slow, writhing, irregular), or ballismus (sudden, fast, flinging [eg, of arms]).[36] TD may present orofacially or affect the limbs or trunk.

Orofacial:

- Mouthing movements, chewing, sucking, licking[11,20]
- Lip smacking[11,16,20]
- Grimacing, tongue protrusion, lip puckering and pursing[11,16,20]
- Rapid eye blinking, brow wrinkling[5,20]

• Likelihood of oral-lingual movements increasing with age[10]

Limbs:
• Rapid movements of arms, legs, or trunk[11]
• Flexion-extension movements in fingers, toes, ankles, or wrists[20]
• Finger movements evoking guitar or piano playing[20]
• Symptoms in extremities more common in younger patients[10]

Trunk:
• Shoulder shrugging[11,36]
• Pelvic rocking (if abdominal involvement)[16]
• Grunting or other sounds with each breath (if diaphragmatic involvement)[11,16,36]

TD carries secondary physical and psychiatric risks. Orofacial TD can impair chewing and swallowing. Dental problems can develop and progress to mouth infections. Nutritional intake, especially in the elderly, may become insufficient.[16,31] Orofacial and truncal TD are associated with unintelligible speech.[11,31] Severe limb or truncal dyskinesia alters gait and can result in falls.[16,31] When the diaphragm is involved, respiratory distress can result.[11,37] Unintelligible speech, altered appearance, and falls can lead to shame and eventual depression.[37]

Severe TD can add considerably to the stigma and social and employment obstacles faced by persons with schizophrenia. According to a 2002 consensus conference assembled to develop recommendations for physical health monitoring of patients with schizophrenia, "Movement disorders…add to the stigmata associated with schizophrenia and can provide unnecessary obstacles to optimum social and vocational adjustment."[17] In short, TD is associated with increased morbidity and poor quality of life.[38]

The etiology and pathophysiology of TD have not been conclusively proved. Several theories of underlying mechanisms make sense given response to antipsychotic drugs, but animal-model and clinical data both support and refute the theories.

Dopaminergic system: Antipsychotics block dopamine D_2 receptors. This may cause upregulation, an increase in the number of D_2 receptors in the brain striatum, and resulting spontaneous, random muscle contractions or movements, the hallmarks of TD.[8,39] Over time the dopamine receptor blockade may increase the sensitivity to dopamine in the nigrostriatal dopamine receptor system.[10,40] Animal models have demonstrated this hypersensitivity and have shown decreased dopamine turnover long after cessation of neuroleptics, but do not account for all aspects of human TD.[40] Human studies have not supported the hypersensitivity hypothesis; they have not shown measurable differences in dopamine turnover in cerebral spinal fluid or number of postmortem D_2 receptors in patients with and without TD.[40]

GABA insufficiency in the anatomical loop that controls motor function has also been proposed as a cause of TD.[40] Some animal and human studies support altered GABA function or decreased GABA-synthesizing enzymes with neuroleptic treatment and TD, but others do not.[40]

Metabolic problems may also contribute to TD. This is supported by increased risk of TD in diabetes and some treatment success with branched-chain amino acids (see ***page 9***).[40]

Neurotoxicity and neuronal cell loss could result from chronic antipsychotic treatment and cause TD. Some brain imaging studies have shown differences between patients with and without TD, but others have not.[40]

Spontaneous dyskinesias, which can occur without the use of antipsychotics, sometimes appear in the elderly[10,15,16,19] and in patients with schizophrenia.[34,41] Before the advent of the FGAs, abnormal involuntary movements similar to TD were described in some psychotic patients.[40] Spontaneous dyskinesias have been documented in up to 40% of neuroleptic-naïve patients with schizophrenia[34] and may manifest the underlying cerebral pathology of schizophrenia.[34,41] The schizophrenia disease process may increase vulnerability to TD from antipsychotic drugs.[14,41] In psychotic patients who do not experience spontaneous dyskinesias, chronic antipsychotic treatment may be the "final straw" that induces TD.[40]

A combination of factors and mechanisms are most likely involved in TD, with the highest risk in patients who have psychosis, advanced age, and long-term use of antipsychotics.[40]

RISK FACTORS FOR TD

TD occurs at higher rates in older patients,[9,18,42-46] patients with affective disorders,[5,9,19,32,46,47] and patients with a history of FGA use.[44-46] Other identified risk factors have included diabetes, ethnicity, negative symptoms of psychosis, cognitive dysfunction, substance abuse, early EPS, and use of antiparkinsonian agents.[42,46] Individual patients will present with varying risk factors for TD, some controllable and some not.

Age: Advancing age is the most accepted risk factor for development of TD.[9,18,30,33,42-46] An analysis of 8 studies showed weighted mean prevalence 3 times higher in patients older versus younger than 40 years of age.[18] In a prospective study of neuroleptic-treated outpatients ages >45 years, the incidence of TD at 1-, 2-, and 3-year follow-up was 26%, 52%, and 60%, respectively. The corresponding incidence in a study of younger adults was 5%, 19%, and 26%.[43] Prevalence in patients ages >65 years has been reported as 5 times greater than that in younger patients.[15] Age can also be considered a prognostic factor in TD; as age advances, rates of spontaneous remission decrease.[15,46,48]

Sex: Female sex has long been identified as a risk factor for TD.[9,15,39,46] The increase with advancing age may be far greater in women than men.[49,50] An analysis of 19 studies before 1981 showed weighted mean prevalence 41% higher in women than in men. However, in some of the studies, the women received longer and/or higher-dose treatment than the men.[18] Some incidence[42] and prevalence studies[6,23] have not supported an increased risk of TD in women. The higher numbers of affected women in other studies may relate to methodology and age/sex demographics.[6] The evidence is inconclusive.

Ethnicity: Some data suggest a higher risk for patients of African de-

scent.[24,31] One study found a cumulative annual TD incidence of 46.5% in African Americans and 27.2% in whites.[31] In another study, nonwhite patients (mostly African Americans) were almost twice as likely to develop TD.[48] African descent has also predicted poorer TD outcomes.[46]

The schizophrenia disease process may increase vulnerability to TD from antipsychotic drugs.

Affective disorders: Bipolar and other affective disorders may carry a higher risk for TD than other psychiatric diagnoses, including schizophrenia.[5,9,19,32,33,46,47] Four studies of antipsychotic-treated patients with mood disorders found TD prevalence of 26% to 64%.[32,47] In the 2 studies with schizophrenia comparator groups, the prevalence was 18% and 25% in schizophrenia versus 26% and 42% in affective disorders.[32,47] The appearance of TD has been shown to relate to depression rather than mania in bipolar disorder.[47] In patients with schizophrenia, comorbid depression and even a family history of affective disorders can increase TD risk.[47] The presence of an affective disorder can also predict poorer outcomes, with less chance of reversal of TD.[46]

Diabetes mellitus has also long been considered a risk factor for TD.[16,42,46] Several studies over the past 15 years have demonstrated an association between pre-existing diabetes or insulin resistance and the development of TD in antipsychotic-treated patients.[51-54] However, in other recent studies, diabetes did not predict TD.[44,55]

Alcoholism and substance abuse may increase risk of TD.[31,33,39,44,46] In 1 study of older patients, a history of alcohol abuse increased TD risk by a factor of 1.7.[43] The schizophrenia study Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found that substance abuse significantly predicted TD.[44]

Concomitant medications: Medications other than neuroleptics (eg, amphetamines, antihistamines, and tricyclic antidepressants) have been associated with dyskinesias over the long term.[9] Anticholinergic agents used to treat drug-induced parkinsonism can worsen TD.[5,23,44] If the antipsychotic masks the emergence of TD symptoms, the anticholinergic may be continued for the long term and exacerbate the latent TD. The TD might not be detected until it is advanced and difficult to reverse. In the CATIE study, patients who had TD at baseline were more likely to be receiving anticholinergics.[44]

Antipsychotic use: Genetic vulnerability to movement disorders and the use of antipsychotic medications combine to create a high genetic risk of TD.[37] Although it is generally accepted that a lower FGA dose will carry a lower TD risk, the evidence that high dosing increases risk has been mixed.[9,23] There is little evidence comparing the incidence of TD with low- versus high-potency FGAs.[42] Because TD appears to be related to duration of treatment,[18,23,44,45] clinicians should become more vigilant about TD over time with antipsychotic use. The Curacao Extrapyramidal Syndromes Study demonstrated that patients without TD after many years on antipsychotics still were at risk for TD.[24] Newly diagnosed TD occurred at an annual rate of 10.2% over 9 study years.[24] The mean antipsychotic use duration of the patients with new-incident TD was 18 years.[24]

TD takes from months to many years to appear. The wide variation in onset may relate in part to variations in ***cumulative antipsychotic exposure*** because of dosing variations and intermittent versus continuous treatment. One study found duration of prior neuroleptic use at baseline and cumulative amount of high-potency neuroleptics increased risk of TD by factors of 2.4 and 1.7, respectively.[43] Nomenclature in tobacco research presents an example of disease risks related to cumulative exposure. In the "pack years" measurement, 3 pack years is the exposure produced by smoking 3 packs of cigarettes per day for 1 year, 1 pack per day for 3 years, 1/2 pack per day for 6 years, etc.[56] Similarly, it is possible that high-dose neuroleptics taken for a short time may cause TD as easily as lower doses over longer periods. To allow for this possibility, clinicians should keep doses as low as possible.

However, evidence for cumulative exposure as a risk factor for TD is mixed.[19,23] At least 1 study found the amount of drug administered in any one year was more predictive than the cumulative amount over many years.[23] Some authors have noted that with doubtful completeness and accuracy of records in chronic patients, it can be difficult to establish total exposure anyway.[19] However, in the clinical setting, a new middle-aged or elderly patient with a longstanding diagnosis of schizophrenia and history of antipsychotic use most likely has significant antipsychotic exposure and risk of TD.

Early EPS: The risk of TD may be higher in patients with EPS or a history of early EPS.[8,15,31,33,38,46,57] In the European Schizophrenia Outpatient Health Outcomes study, baseline EPS predicted later TD. In approximately half of patients who had TD after 1 year of the study, it was preceded by EPS.[58] The CATIE study found that severity of EPS at baseline was significantly related to TD prevalence.[44] However, the risk of TD posed by EPS has not been proved conclusively.[9] It has not been determined whether EPS or its treatment with anticholinergics constitutes the greater risk.[42]

Other reported risk factors for TD include baseline preclinical movement disorder or tremor,[31] brain damage (eg, from head trauma),[37] mental retardation,[39] and history of electroconvulsive therapy.[15,16]

DIFFERENTIAL RATES OF TD WITH FGAs VERSUS SGAs

Although SGAs have fewer motor side effects than FGAs, all antipsychotics carry some risk of development of movement disorders.[16] It is generally accepted that long-term FGA use bears a high risk of TD. With FGAs, TD incidence has been approximately 5% per year in adults and 25% to 30% per year in elderly patients.[38] Up to 25% of patients with chronic psychosis who have been treated with FGAs may now have TD.[46] After 20 years of FGA use, almost 70% of patients may have TD.[8]

The Mount Sinai Conference on the Pharmacotherapy of Schizophrenia

issued the consensus opinion, "There is sufficient evidence to conclude that SGAs are less likely to cause TD than FGAs are."[57] This opinion is widely supported.[6,8,45,59] Trials of SGA efficacy and safety have suggested an incidence of approximately 1% per year with SGAs versus approximately 5% per year with FGAs.[35] In a prospective study of patients with borderline dyskinesia at baseline, those treated with FGAs were approximately twice as likely as those treated with SGAs to develop definitive TD within 6 months.[60] A review of 11 controlled studies found that in nongeriatric adults, TD incidence was 0.8% with SGAs versus 5.4% with an FGA.[38] The CATIE study showed a significantly higher prevalence of TD in patients receiving an FGA at baseline than in patients receiving an SGA alone.[44]

Additional comparisons on rates of TD have been conducted between FGAs and SGAs, including in younger and older patients.[38,61-72] The review of the individual studies is beyond the scope of this article.

The first SGAs were called "atypical" because they reduced the risk of EPS that typically occurred with FGAs.[15] All are associated with a lower incidence of EPS than FGAs.[3,17] SGAs also have multiple receptor binding characteristics, with a lower affinity for dopamine D_2 receptors and greater affinities for other neuroreceptors.[1,37] SGAs, via their $5HT_{2A}$ antagonism, can reduce dopamine D_2 blockade activity in the nigrostriatal pathway.[73]

Meta-analyses have shown that all SGAs at recommended doses have significantly lower rates of EPS and levels of antiparkinsonian medication use.[17] Because SGAs have a lower risk of EPS,[15] it may follow that SGAs carry a lower risk of TD.[31] That was the conclusion of a meta-analysis of 11 prospective studies of SGAs,[38] but it has not been proved unequivocally.[15] Most evidence of lower risk with SGAs is based on studies not specifically designed to assess TD risk. Comparative treatment with FGAs and SGAs was not always blinded or randomized and diagnosis of TD was rarely by neurologic assessment.[15] Although multiyear well-controlled studies are necessary to quantify long-term incidence, ethical concerns have dictated that TD incidence studies of ≥5 years have been naturalistic, with less reliable data.[74] Naturalistic studies may not control for nonadherent patients or physicians who switch SGAs or combine 2 antipsychotics. Many studies used very high doses of FGAs, and if the risk of TD is associated with cumulative exposure, then it may be dose-related.[35] A meta-analysis of 31 randomized controlled trials comparing SGAs with low-potency FGAs found that "optimum" doses of these FGAs were no more likely to induce EPS than SGAs were; the risk was significantly lower only with clozapine.[15,75]

SGAs have not existed long enough for the kinds of long-term studies that have shown FGAs cause TD eventually in most patients. Because many SGAs have faster dissociation from the D_2 receptor than do FGAs,[15,35] they might be expected to take longer to cause any dopamine-related adverse effect. Most SGA studies have run for <2 years, not long enough to conclude definitively that the risk of TD is low with long-term SGA treatment.

TD can arise from years of FGA treatment even after discontinuation of the drugs; this has been called a "legacy of treatment."[41] Thus, if a patient has been switched from FGAs to an SGA, it is unclear whether emergence of TD indicates harm from the SGA or "legacy" harm from the FGAs.[74] Although it implicates FGAs, legacy harm can nevertheless confound the results and conclusions of SGA studies

Table 1

Summary of Clinical Evidence Related to Atypical Antipsychotics and Risk of TD

Therapeutic Dimension	Current Evidence
Atypical antipsychotic with no risk of TD	No
Decreased TD in atypical compared with typical agents	Yes (~1%/y vs ~5%/y)
Mechanism(s) of action understood	Unclear
Evident when compared with low-dose typical agents	Yes
True for nonschizophrenic diagnoses	Unknown
True for specific subpopulations (eg, children, elderly)	Yes
Difference between atypical agents	No
Decrease maintained with atypical-typical combinations	Unlikely
Decrease maintained with atypical-atypical combinations	Unknown
Difference according to formulation (eg, oral compared with depot)	No (limited data)
Antidyskinetic properties	Yes
Mechanism(s) of action understood	Unclear
Difference between atypical agents	No
Treatment (suppression) compared with cure	Unclear

TD indicates tardive dyskinesia.
Adapted with permission from Reference 35.

Figure 1

Abnormal Involuntary Movement Scale (AIMS)

(A) Examination Procedure: Either before or after the examination procedure, observe the patient unobtrusively, at rest (eg, in waiting room). The chair to be used in this examination should be a hard, firm one without arms.

1. Ask the patient to remove shoes and socks.
2. Ask the patient if there is anything in his or her mouth (eg, gum, candy); if there is, remove it.
3. Ask the patient about the *current* condition of his or her teeth. Ask the patient if he or she wears dentures. Do teeth or dentures bother the patient *now*?
4. Ask the patient whether he or she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they *currently* bother the patient or interfere with his or her activities.
5. Have the patient sit in a chair with hands on knees, legs slightly apart and feet flat on floor. (Look at entire body for movements while in this position.)
6. Ask the patient to sit with hands hanging unsupported. If male, between legs; if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)
7. Ask the patient to open mouth. (Observe tongue at rest in mouth.) Do this twice.
8. Ask the patient to protrude the tongue. (Observe abnormalities of tongue movement.) Do this twice.
9. Ask the patient to tap thumb, with each finger, as rapidly as possible for 10 to 15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements.)
10. Flex and extend patient's left and right arms (one at a time). (Note any rigidity.)
11. Ask the patient to stand up. (Observe in profile. Observe all body areas again, hips included.)
12. Ask the patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)
13. Have the patient walk a few paces, turn and walk back to chair. (Observe hands and gait.) Do this twice.

(B) Rating sheet

Patient Name _____ Rater Name _____

Patient # _____ Data Group: AIMS _____ Evaluation Date_____

Instructions: Complete the above examination procedure before making ratings.
For movement ratings, circle the highest severity observed.

Code: 0: None 1: Minimal, may be extreme normal 2: Mild 3: Moderate 4: Severe

Facial and Oral Movements	**1. Muscles of Facial Expression** • eg, movements of forehead, eyebrows, periorbital area, cheeks • Include frowning, blinking, smiling, and grimacing	0	1	2	3	4
	2. Lips and Perioral Area eg, puckering, pouting, smacking	0	1	2	3	4
	3. Jaw eg, biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
	4. Tongue Rate only increase in movements both in and out of mouth, NOT the inability to sustain movement	0	1	2	3	4
Extremity Movements	**5. Upper** *(arms, wrists, hands, fingers)* • Include choreic movements (ie, rapid, objectively purposeless, irregular, spontaneous), athetoid movements (ie, slow, irregular, complex, serpentine) • Do NOT include tremor (ie, repetitive, regular, rhythmic)	0	1	2	3	4
	6. Lower *(legs, knees, ankles, toes)* eg, lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of the foot	0	1	2	3	4
Trunk Movements	**7. Neck, shoulders, hips** eg, rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4
Global Judgments	**8. Severity of Abnormal Movements**	0	1	2	3	4
	9. Incapacitation Due to Abnormal Movements	0	1	2	3	4
	10. Patient's Awareness of Abnormal Movements Rate only patient's report.	0	1	2	3	4
Dental Status	**11. Current Problems with Teeth and/or Dentures**	0: No		1: Yes		
	12. Does Patient Usually Wear Dentures?	0: No		1: Yes		

Adapted from Reference 50.

that include patients treated previously with FGAs.[15,74] Longitudinal studies of patients who never received FGAs would be necessary to determine the true risk of TD with SGAs.[15]

Study results can also be confounded by mistaking spontaneous dyskinesia for TD, especially in the elderly, and by the masking of TD symptoms by antipsychotics.[15] The risks of EPS and the neuropharmacologic properties of the different SGAs vary, therefore the risks of TD may also vary.[15]

Not all SGA study results support the idea of lower TD risk. In a naturalistic study of >20 000 elderly patients with dementia, no significant difference was found between FGAs and SGAs in inducing a movement disorder within 1 year of treatment initiation.[76] An 18-month schizophrenia study found no significant differences in EPS or movement disorders among groups receiving an FGA and various SGAs.[1] In a cross-sectional study of nongeriatric patients who had received only SGAs, FGAs for <5 years, or FGAs for at least 5 years, the TD prevalences were 19%, 19%, and 42%, respectively; in other words, there was no difference between use of FGAs for <5 years and use of SGAs.[74]

In summary, the preponderance of evidence suggests that SGAs have a low risk for TD relative to high-dose FGAs, but the data are not entirely conclusive (**Table 1**).[35] Some authors would classify use of FGAs versus SGAs as a risk factor for TD.[35]

RECOGNITION AND DIAGNOSIS

Although persistent TD usually takes several years of antipsychotic treatment to appear, some cases have been documented in only 2 months with FGAs.[37] Whereas advanced TD is largely untreatable, early detection can enable possible reversal by discontinuing or reducing the dose of the antipsychotic in some patients.[22] A panel of experts (see Mount Sinai consensus statement) reviewed the quality and quantity of data regarding the development of TD and recommended the following regarding the management of TD risk[17,57]:

• Before initiating FGA or SGA treatment, examine all patients for baseline neurologic status, including parkinsonian signs and involuntary movements.
• When initiating treatment or increasing dose, monitor for EPS weekly until the dose has been stabilized for 2 weeks.
• With FGAs, examine for TD at least every 6 months.
• With SGAs and no concomitant FGAs, examine for TD annually.
• With patients at high risk for EPS (eg, older age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs.

Although some involuntary movements seem obvious, TD can be frustratingly difficult to diagnose accurately. No clinical or laboratory test can diagnose or rule it out. Volitional or psychotic mannerisms, tics, and drug-induced parkinsonism must be distinguished from TD and can coexist with TD in the same patients.[10] The nature and severity of abnormal movements may vary considerably over time.[42] Clinicians should be vigilant because patients may not complain of TD symptoms; many are unaware of their own dyskinesias.[25] Studies have found a marked increase in identification of probable TD by the use of routine, formal examinations with rating scales such as the Abnormal Involuntary Movement Scale (AIMS)[77] or the Simpson Abbreviated Dyskinesia Rating Scale.[49,78,79] Besides detecting emergent TD, periodic formal examinations can also help to evaluate its course.[22] Repeat instrumental assessments a few months after a TD diagnosis can track the progress of treatment or identify persistent TD.[25]

Even with routine, careful examination, TD can be difficult to detect early, because the antipsychotic agents that cause the underlying pathology can also mask the emergence of symptoms. Some authors refer to an "induction period" of exposure to antipsychotics, followed by a "latent period" when the pathology has begun, and finally a "clinical period" when TD becomes detectable.[42] During long-term treatment with FGAs, clinicians have increased the dose to maintain efficacy. Dose increases might raise the risk of TD development,[35,42] but the TD could remain latent, its symptoms masked by the FGAs.[21]

The National Institute of Mental Health developed the AIMS examination as a research tool.[22] Because AIMS can identify the presence and severity of choreoathetoid and other movements typical of TD, it is widely recommended for clinical screening for TD and follow-up of patients diag-

Table 2

Conditions That May Resemble TD

Spontaneous dyskinesias occurring in the elderly[19,37] and in schizophrenia[10,34,40]*
Oral movements from ill-fitting dentures and other dental problems[10,25]
Drug-induced dyskinesias from antiparkinsonian drugs or stimulants[10,11,16]
Autism[16]
Chronic motor tic disorder[37]
Huntington's disease[11,16,37]
Meige's syndrome[37]
Restless legs syndrome[16]
Rett's syndrome[16]
Senile chorea[37]
Sydenham's chorea[37]
Tourette syndrome[37]
Wilson's disease[11,37]

TD indicates tardive dyskinesia.
*If documented to have begun after initiation of antipsychotic treatment, spontaneous dyskinesias are more likely TD.[13]

nosed with TD (**Figure 1**).[22]

By itself, AIMS does not diagnose TD.[22] In 1982 Schooler and Kane developed 3 diagnostic criteria for TD[22,25,80]:

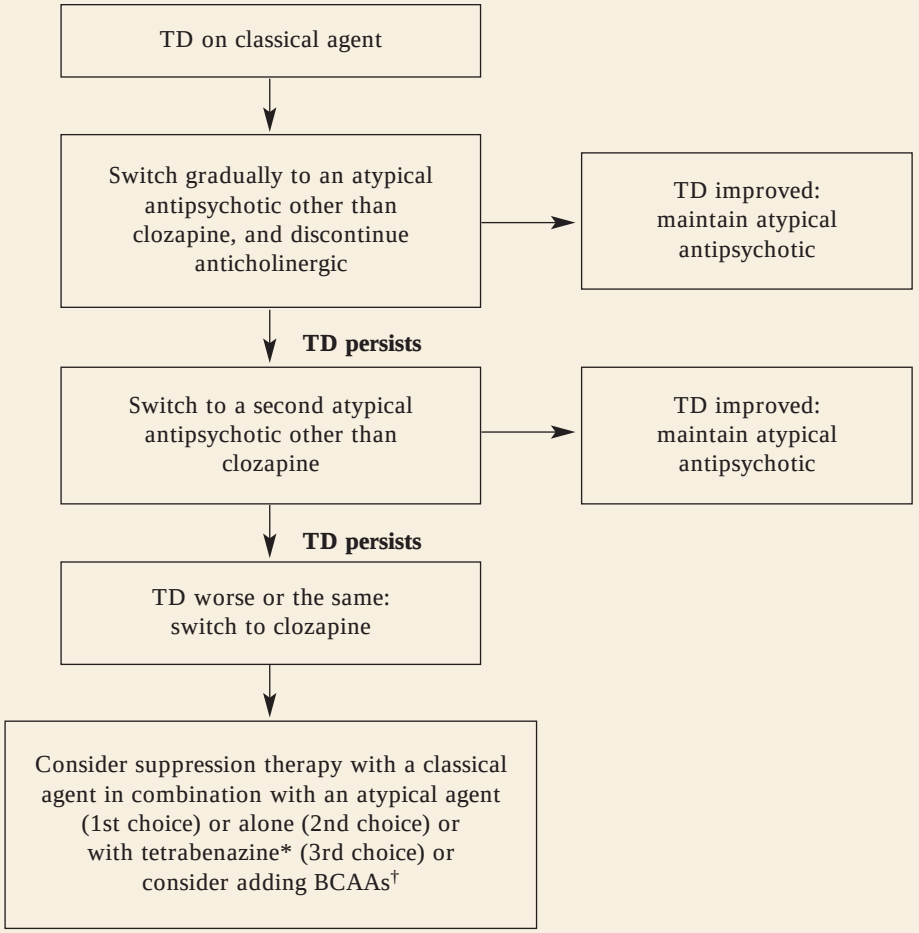
- At least 3 months cumulative exposure to neuroleptics
- Presence of at least moderate abnormal involuntary movements in 1 or more body area(s) or mild movements in 2 or more body areas
- Absence of other conditions that might produce involuntary movements.

The AIMS is used to establish the presence of the abnormal movements. The third criterion is the most difficult to satisfy in clinical practice, because it requires a complex differential diagnosis.

TD is a diagnosis of exclusion (**Table 2**); many other syndromes that cause abnormal movements must be ruled out.[42] When TD is mistaken for certain other conditions (eg, resting tremor), the results can be harmful (as in treating the tremor with anticholinergics).[20] A neurologist should be con-

Figure 2

Algorithm for the Management of TD



*Tetrabenazine use for the treatment of TD is considered experimental; tetrabenazine has orphan drug status in the United States.

†BCAAs have been approved by the US Food and Drug Administration as a medical food for the indication of TD in males and had been marketed as Tarvil; the current availability of Tarvil is not known as the manufacturer has ceased its production, but BCAAs may be produced by a compounding pharmacy.

TD indicates tardive dyskinesia; BCAAs, branched-chain amino acids.

Adapted with permission from Reference 64.

sulted if the clinician is unsure that the movements are TD or if signs of dementia are present, especially in a younger person.

Brief interruptions of neuroleptic treatment can unmask latent TD, thereby aiding early detection.[5,81] However, in vulnerable patients, a diagnostic drug-free interval long enough to unmask TD may risk relapse into psychosis.[5,81] Moreover, evidence suggests drug holidays or other drug-free intervals actually increase the risk for TD.[9,16,18] Because antipsychotics are the only effective treatment for schizophrenia, emergence of TD during a drug-free interval would not dictate immediate drug withdrawal, but other steps should be taken (see following section).[5,81]

PREVENTION AND TREATMENT

Advanced TD is usually irreversible and no treatment has been shown to be uniformly effective,[6,8,16,18,26,32,72] therefore the best treatment is prevention.[8,26,45] Prevention of TD is easiest in patients who do not have schizophrenia or other disorders with psychotic features. For these patients, treatment alternatives other than antipsychotics should be sought.[18] In patients who require antipsychotics, SGAs should be first-line therapy because they probably have lower risk for development of TD.[8] Prevention strategy should include using a single antipsychotic at the lowest dose effective for the patient[9,15,23,26,48] for the shortest term possible[23] with regular documented re-evaluations of antipsychotic need, efficacy, and possible dose reduction[16,18,23,48] and regular examination for specific signs of dyskinesia.[15,23] Elderly patients are particularly vulnerable to adverse effects of any medication[16] and therefore require extra caution and lower dosing.[18,30,31] Some authors suggest antiparkinsonian agents should be avoided, if possible, in all patients receiving antipsychotics.[18,23] If signs of TD appear during treatment with antiparkinsonian agents, they should be tapered gradually to the minimum necessary to control parkinsonism, or ideally discontinued.[9,45]

The APA Task Force on Late Neurological Effects of Antipsychotic Drugs called discontinuing antipsychotics the "theoretical treatment of choice" for TD.[10] TD may be mild and reversible by withdrawing antipsychotics in one third of patients, with higher rates in younger patients.[13,18,39] Some studies have shown that when TD was identified early, up to 90% of younger patients achieved remission after discontinuing the antipsychotic.[13] In most cases, remission can be predicted to occur within 3 months of withdrawal or not at all.[13] Unfortunately, discontinuing antipsychotics is not a viable option for most patients with chronic schizophrenia and certain other disorders, who will always need antipsychotic treatment.[18,46]

Thus, for patients receiving FGAs, switching to an SGA is recommended (**Figure 2**).[16,45,64] If TD emerges in a patient receiving an SGA, the clinician can try lowering the dose or switching to another SGA. Decreasing the dose will frequently help if the TD is identified early enough.[10,16,25] Discontinuing any anticholinergics may also help.[50,64] TD has improved in up to 60% of patients after ceasing anticholinergics.[82]

Open trials have sometimes shown promise of particular agents to treat TD, but closer scrutiny in randomized controlled trials show lack of benefit. A systematic review of the TD treatment literature shows no definitive treatment in well-done studies[83]; however, the review did not include all possible interventions, such as branched-chain amino acids (BCAAs). It was hoped that lithium used in combination with neuroleptics would prevent TD, but this was not supported in controlled studies.[9,23] Three studies demonstrated efficacy of tetrabenazine,[9,84] but it is less successful over the long term,[9] the benefits reverse on discontinuation, and adverse effects (anxiety, depression) are common.[64] Because anticholinergics exacerbate TD, it was hoped cholinergic agents (choline, deanol, lecithin) could ameliorate it.[9,23] They helped in uncontrolled studies,[9] but a meta-analysis of randomized controlled trials found that positive results for cholinergic drugs did not reach statistical significance.[85] Evidence is also limited, mixed, or anecdotal regarding benzodiazepines, baclofen, valproic acid, melatonin, vitamin B_6, vitamin E, levodopa, botulinum toxin, reserpine, ondansetron, and gabapentin.[9,50,64,86] Because TD is likely heterogeneous, no single treatment will help all affected patients.[49]

Evidence has suggested an association between TD and impaired clearance of the large neutral amino acid phenylalanine, particularly in men.[49] BCAAs, a "medical food" (designed for oral or enteral administration under physician supervision for a specific condition with nutritional requirements), was approved for TD in males. BCAAs might improve TD by decreasing amine neurotransmitter synthesis. Ingesting BCAAs decreases availability of phenylalanine to the brain. One study gave high-dose BCAAs or placebo to men with long histories of antipsychotic treatment and TD. TD movements decreased 36.5% in the BCAA group but increased 3.4% in the placebo group. One third of the BCAA group had TD movement reductions of ≥60%.[49] In a small uncontrolled trial, the same investigators gave BCAAs to children and adolescents, with resulting decreases of 40% to 65% in TD symptoms.[78] BCAAs were shown to be safe and tolerable in both studies.[49,78] Minor weight gain occurred, but in the placebo-controlled study there was no significant difference in weight gain between the BCAA and placebo groups.[49] BCAA formulations have not been tested in women of childbearing age and are not recommended in patients with diabetes and other metabolic disorders, renal disease, and certain other disorders.[49]

Because no management strategies or treatments have been shown to prevent or reverse all TD, more studies of incidence, risk factors, and potential treatments are urgently needed. Specifically required are long-term incidence studies in different populations,[10,42] for example, in countries with less antipsychotic drug use or different dosing than the United States.[10] Also required are well-designed SGA trials that include more women, minorities, and patients of all ages to reach a better estimate of the true risk of TD with these agents. These studies would provide stronger evidence if they followed uniform standards[38]:

- Randomized, double-blind, and >1 year long
- Examining for TD at 3-month intervals using AIMS

• Including a final reassessment to confirm diagnosis in patients who first met TD criteria at study endpoint
• Comparing SGAs head-to-head to establish differential effects (especially in FGA-naïve patients)
• Using lower potency FGAs in low-to-medium doses
• Including adherence assessments to minimize intermittent treatment effects and withdrawal dyskinesia

ECONOMIC COST OF TD

Managed care programs usually require patients to seek care through primary care providers.[16] As more individuals are covered by managed care plans, more antipsychotic prescriptions will come from primary care physicians.[16] Yet primary care physicians do not receive adequate training in the use of antipsychotics and the need for periodic examination for TD.[16] Clinicians need to be aware of subtleties in prescribing and the potential costs of TD.

Numerous costly studies over many years have failed to establish a universally effective treatment, and research costs continue. TD imposes costs of medical care, disability, and lost productivity. The economic costs of inadequate solutions are accompanied by costs of human suffering for patients and their families. Even if the incidence of TD is lower with SGAs than FGAs, TD and its costs may continue to rise as the rate of utilization of antipsychotics rises.

With the increased use of antipsychotics, including off-label use, the costs and frequency of lawsuits that allege inappropriate prescribing have increased.[5] Clinicians who do not understand TD and fail to detect its early signs, or do not intervene to prevent progression when those signs appear, risk legal action.[5] Since it has been generally accepted that SGAs have a lower risk of TD, the use of an FGA before an SGA may now carry legal risk for the prescriber. First-line treatment with an SGA is now widely considered the standard of care for schizophrenia.[5] In 2 classic malpractice cases involving TD after antipsychotic treatment, the defense lacked 2 elements of good care: informed consent and documentation of valid medical reasons for the antipsychotic treatment decision, including adequate consideration of TD.[87]

Informing family members about signs of TD can also aid in early detection.[5]

ETHICAL CONSIDERATIONS IN RECOMMENDED ANTIPSYCHOTIC TREATMENT

Most long-term incidence studies have focused on FGAs and have clearly linked TD with FGA use. However, the link with SGA use has been neither fully established nor disproved. Thus we are not certain about SGAs, but we know FGAs carry a high risk of TD. SGAs are generally recommended over FGAs except when the SGAs fail in efficacy, tolerability, or patient preference.[45] Clinicians can choose agents from the SGA class with differing risks and benefits according to the clinical needs of a given patient. With the higher TD risk posed by FGAs, using SGAs as first-line treatment for antipsychotic-naïve patients is recommended.[8,45]

Every patient is different and treatment should always be individualized. Further, psychotic symptoms and response to antipsychotics can change over time.[88] Some patients will not respond to an SGA, including clozapine, or will respond initially but then relapse even with a higher dose. If a patient does not respond to trials of at least 2 different SGAs, switching to an FGA may then make sense. After treatment failure with SGAs, the potential benefit of antipsychotic efficacy would outweigh the increased risk of TD.

However, the ultimate decision belongs to the patient, who may remain undisturbed by TD or prefer it to the risk of psychotic relapse inherent in any medication switch.[18,89]

When an antipsychotic is prescribed, **documentation** of the medical reasons is essential. Every time a patient is reassessed, a lack of adverse effects could be considered an opportunity to lower the dose to reduce the adverse effect risk.[81] Therefore, the rationale not to change treatment must be documented, as well as any decision to change it.

The risk of TD with long-term use of antipsychotics, especially FGAs, is a concern for all clinicians who prescribe these powerful drugs. SGAs have been shown to have lower risk for motoric adverse effects than FGAs, and have become the preferred first-line treatment for schizophrenia. Physicians, patients, and families need education on TD risks, symptoms, management, and outcomes. Clinicians must consider TD before prescribing antipsychotics, examine for it periodically, and be prepared to modify the treatment plan if the first signs emerge.

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