Current PSYCHIATRY

Tardive dyskinesia: How to prevent and treat a lingering nemesis

Make informed therapeutic choices as you weigh antipsychotics' benefits against the risk of triggering TD

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Atypical antipsychotics seldom cause tardive dyskinesia (TD), but we cannot let our guard down when prescribing them. Although they pose a much lower risk of TD than do conventional antipsychotics, atypicals can cause TD in vulnerable patients.

Less worrisome than in the past, TD's associated problems linger, including insidious onset, tendency for persistence, and lack of reliably effective treatment. It is important, therefore, for psychiatrists to:

- identify patients at risk for developing TD
- recognize extrapyramidal symptoms (EPS) when they occur
- and manage these side effects appropriately.

A CHANGING CLINICAL PICTURE

The term "dyskinesias" covers a variety of abnormal involuntary movements (*Box*). The incidence and prevalence of TD have dropped markedly in the last 10 years, as:

Box

TD's worrisome orofacial signs

Tardive dyskinesia (TD) tends to develop in patients receiving long-term antipsychotic treatment. Its typical movements are choreiform (jerky) or athetoid (writhing), irregular, and purposeless.

TD onset is usually insidious and may occur during drug therapy or weeks after antipsychotics are discontined. Its signs are usually observed in the face or mouth, and typical orofacial dyskinetic movements are:

Lips: puckering, pouting, smacking

Jaw: chewing, biting, side-to-side movements, jaw openings

Tongue: twisting, rolling, undulations, protrusion, darting ("fly-catching")

Face: blinking, frowning, grimacing.

The trunk and extremities are involved less often. Choreiform finger and wrist movements, flexion and rotation of the ankle, toe movements, foot tapping, and rocking or twisting of the neck, hip, and trunk may be seen. Patients are often oblivious to these movements, which may be only intermittently present and are absent during sleep. Anxiety and arousal states may aggravate TD.

- more and more older, chronically ill patients are switched from conventional to atypical agents
- younger psychotic patients are usually treated with atypicals as first-line therapy and are never exposed to conventional antipsychotics.

TD prevalence of about 20%—as shown by earlier studies of long-term conventional agents[1]—is declining. Newer studies comparing atypicals with conventional antipsychotics demonstrate much lower prevalence rates.[2,3]

TD incidence—estimated by new cases of TD per year of drug treatment—may have declined 10-fold, from 5% with conventional antipsychotics to 0.5% with atypicals. Likewise, incidence in the elderly may have fallen from 25% to 2.5%.[4]

Risk factors. Despite these improvements, case reports[5-7] demonstrate that TD is possible in patients treated with atypicals, even without previous exposure to a conventional antipsychotic. Besides antipsychotic use, risk factors for developing TD include:

- older age
- negative symptoms of schizophrenia
- affective disorders
- acute EPS
- and diabetes mellitus.[8]

RECOGNIZING TD SYMPTOMS

Recognizing TD may be complicated by the presence of other EPS, particularly drug-induced parkinsonism (DIP). DIP typically develops early and often when treating patients with conventional antipsychotics (*Table 1*). TD and DIP may occur simultaneously in the same patient, making accurate diagnosis even more difficult.

Other dyskinesias may complicate the diagnosis. Three common TD variants, which may be acute or tardive (occurring after long-term antipsychotic therapy), are:

- **akathisia,** a distressing and at times irresistible urge to move the legs or other parts of the body
- **dystonia,** abnormal muscle tone and posture and muscle spasms
- **tics,** brief muscle contractions, usually in the face, including vocal tics.

AIMS testing. Defining a "case of TD" by dyskinetic movement severity is somewhat arbitrary. A commonly accepted definition is two area scores of "mild" or one rating of "moderate" using the Abnormal Involuntary Movement Scale (AIMS).[9] The AIMS has been widely used in epidemiologic and treatment studies of TD and is easy to administer in a clinical setting (*see Related Resources, page 62*).

A careful drug history is required before TD can be diagnosed definitively. Spontaneous dys

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Table 1

Features that differentiate two common extrapyramidal symptoms

	Tardive dyskinesia (TD)	Drug-induced parkinsonism (DIP)
Onset	Late	Early
Type of movement	Choreoathetoid	Tremor
Amount of movement	Increased	Decreased
Muscle tone	Decreased	Increased
Most common site	Orofacial	Extremities
Response to anticholinergics	Tends to worsen	Tends to improve

kinesias—usually orofacial—are sometimes seen in older patients who are not taking neuroleptics.[8] Antidepressants, mood stabilizers, or antihistamines may infrequently trigger neurologic side effects—including dyskinesias, akathisia, and tremor—which are almost invariably reversible after the causative agent is withdrawn.[8,10]

MANAGING MILD TD

Atypical antipsychotics have radically altered the clinical outlook for patients with TD and improved our ability to manage their symptoms. The clinician treating a TD patient today rarely faces the dilemma that exists with conventional antipsychotics: discontinue treatment and risk psychotic relapse, or continue treatment and risk persistent TD.

Using atypicals. Today, patients who need antipsychotic therapy for TD are usually already taking atypicals, which may ameliorate TD and control psychotic symptoms. Case reports and some studies have shown therapeutic effects in patients with TD taking olanzapine,[3] risperidone,[2] quetiapine,[11] ziprasidone,[12] aripiprazole,[13] or the substituted benzamides (such as sulpiride), which are not marketed in the United States.[14]

Interestingly, TD triggered by taking one atypical may respond to treatment with another. Suzuki et al[15] reported that three patients who had developed early-onset TD while taking risperidone showed TD remission after risperidone was replaced by olanzapine in one patient and by quetiapine in the other two.

The atypicals are well tolerated but not without side effects. Weight gain is the most common problem and one with potentially serious health consequences.[16]

Using conventional agents. Even though atypicals are available, the clinician may consider continuing therapy with conventional antipsychotics in patients with TD when:

- the patient's mental status has been satisfactory while taking conventional agents
- TD has been mild and stable over an extended time
- the patient has no side effects other than TD.

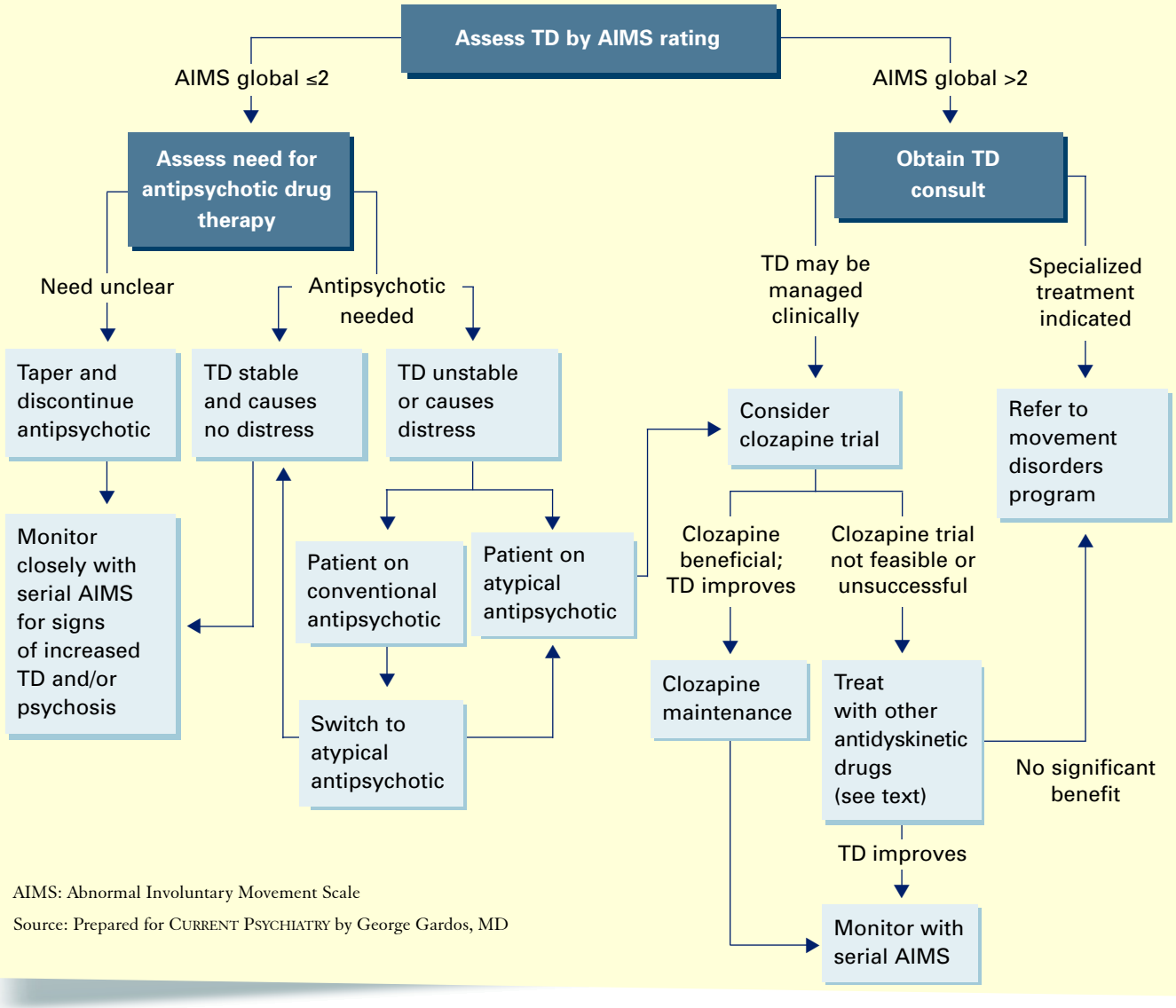
The literature supports the clinical experience that mild TD rarely worsens with continued antipsychotic therapy. Studies of 5 years or more tend to show TD stability with continued conventional antipsychotic therapy.[17] It is prudent to maintain stable chronic psychotic patients with mild TD on the lowest effective dosages of conventional antipsychotics and to monitor them regularly for changes in dyskinesia and psychiatric status.

MANAGING COMPLICATED TD

Managing severe TD or patients showing dystonia, tics, marked akathisia, or DIP coexisting

Algorithm

Clinical management of tardive dyskinesia (TD)



AIMS: Abnormal Involuntary Movement Scale

Source: Prepared for CURRENT PSYCHIATRY by George Gardos, MD

with TD usually calls for more-aggressive interventions (*Algorithm*).

Clozapine remains the first-line treatment for difficult TD; it has a very low propensity for inducing DIP and very rarely causes TD.[18] Controlled studies,[18,19] case reports, and open trials demonstrate its efficacy for reducing TD of all types and severity at a usual dosage of 300 to 500 mg/d. Clozapine's antidyskinetic effects may be attributed to the absence of rebound after withdrawal and its greater efficacy in more-severe cases.[18]

Long-term clozapine therapy is recommended for TD, as symptoms remit slowly. Because weight gain, sedation, and other side effects—as well as mandatory blood monitoring—make clozapine less-than-ideal in clinical practice,

researchers are seeking other effective therapies for TD.

Other atypicals. The obvious place to look is the other atypicals, which are simpler than clozapine to administer long-term. To date, however, these drugs have not proven to be as reliably effective as clozapine for TD. A recent review concluded that among the atypicals only clozapine induces less EPS than low-potency conventional antipsychotics.[20]

Nonantipsychotic agents. Other antidyskinetic drugs have come and gone; none has stood the test of time or proven effective in controlled trials. These agents may benefit some TD patients, but improvement is usually not dramatic.

Vitamin E was found to be effective in some TD treatment studies[14] but not more effective than placebo in the largest controlled trial.[21] Long-term treatment with dopamine-blocking antipsychotics is thought to cause oxidative stress-induced neurotoxicity in the nigrostriatal system.[22] Lipid-soluble antioxidants such as vitamin E decrease free-radical formation, and it is possible that vitamin E may yet emerge as a helpful agent in preventing TD.[23]

Melatonin, a stronger antioxidant than vitamin E, was found to reduce TD in a 6-week placebo-controlled study,[22] but the degree of TD improvement was modest. Melatonin's value as a therapeutic agent for TD remains dubious.[23]

Miscellaneous. Case reports and studies with small series of TD patients have advanced numerous compounds as possible therapeutic agents (*Table 2*). Other drugs that occasionally have shown benefit in TD include buspirone, propranolol, pyridoxine (vitamin B6), ondansetron, clonidine, and the neuropeptide ceruletide.

ECT and diet. Suggested nondrug treatments of TD include electroconvulsive therapy (ECT)[14] and a diet of mixed branched-chain amino acids.[24]

Table 2

Compounds that occasionally show benefit in TD

Class	Example
Cholinergics	Lecithin
Catecholamine depletors	Tetrabenazine (investigational orphan drug)
Calcium channel blockers	Verapamil
Gabaergic compounds	Baclofen
Benzodiazepines	Clonazepam

MANAGING TD VARIANTS

TD variants are notoriously difficult to treat but tend to respond to clozapine.[18] In addition:

- **Tardive dystonia** is often treated with reserpine, tetrabenazine, or high doses of anticholinergic drugs.[25] Botulinum toxin A injections into affected muscles may be remarkably effective but must be repeated regularly.[25]
- **Tardive akathisia** may improve slowly with clozapine, propranolol, or benzodiazepines.[25]

Managing severe or atypical TD is usually beyond the expertise of the practicing psychiatrist. Obtaining consultation from a psychopharmacologist or a neurologist experienced in treating movement disorders is highly recommended.

PREVENTING TD

Conventional antipsychotics are still prescribed by psychiatrists, internists, and family physicians and are often given in emergency rooms. Avoiding these drugs whenever possible and using the lowest effective dosages will reduce the risk of TD.[26]

Patients at relatively high risk for TD—the elderly, those who are very sensitive to acute EPS, and those with affective disorders or diabetes mellitus—are rarely candidates for conventional neuroleptics if a suitable alternative exists. Genetic research may further identify individuals susceptible to TD.[27]

continued

Related resources

- Abnormal Involuntary Movement Scale (AIMS). www.dr-bob.org/tips/aims.html
- Bloom FE, Kupfer DJ (eds). *Psychopharmacology: The fourth generation of progress.* New York: Raven Press, 1995.
- Tandon R, Halbreich U (eds). Atypical antipsychotics: Efficacy and tolerability—achieving the optimal balance. *Psychoneuroendocrinology* 2003;28(suppl 1).

DRUG BRAND NAMES

Aripiprazole • Abilify
Baclofen • Lioresal
Buspirone • BuSpar
Clonazepam • Klonopin
Clonidine • Catapres
Clozapine • Clozaril
Olanzapine • Zyprexa
Ondansetron • Zofran
Propranolol • Inderal
Quetiapine • Seroquel
Risperidone • Risperdal
Verapamil • Calan, others
Ziprasidone • Geodon

DISCLOSURE

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Bottom Line

Atypicals are much less likely than conventional antipsychotics to cause TD and are today's first-line treatment. When possible, avoid using conventional agents. However, switching a patient from long-term conventional therapy to an atypical is a judgment call, not an imperative.

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