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Tourette's Disorder

Gholson J. Lyon, MD, PhD
David Shprecher, DO
Barbara Coffey, MD, MS
Roger Kurlan, MD[*]

Address
*Atlantic Neuroscience Institute, Overlook Hospital, 99 Beauvoir Avenue, Summit, NJ 07902, USA
Email: Roger.Kurlan@atlantichealth.org

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Opinion statement

Tourette's disorder (TD) is a common childhood-onset neuropsychiatric disorder characterized by chronic motor and vocal tics. TD frequently occurs with other neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), and may contribute to reduced quality of life and disability. Currently available treatments to reduce tics are limited by variable clinical response and frequent adverse effects. They include alpha-2 agonists, antipsychotics (first and second generation), tetrabenazine, benzodiazepines, and habit reversal therapy. Some new and emerging (but unproven) treatments are also discussed, including topiramate and dopamine agonists. In addition, there is increasing interest in deep brain stimulation, but this is not yet ready for general use.

Introduction

In the 1800s, the French neurologist Georges Gilles de la Tourette described the first nine cases of Tourette's syndrome, characterized by childhood onset of multiple motor and vocal tics. In our current nomenclature in the DSM-IV, the name has changed to Tourette's disorder (TD), which includes specific diagnostic criteria: the presence of multiple motor tics and at least one vocal tic for greater than 1 year; onset prior to age 18 years; and frequent tics, often occurring in bouts, which cause marked distress or impairment and are not secondary to another condition. The most recent iteration of the DSM-IV-TR has eliminated the impairment criterion.

Clinical manifestations of tics can be very diverse and can be classified as either simple or complex movements and vocalizations. *Simple motor tics* are characterized by quick jerks of typically single muscle groups. More complex, purposeful, or coordinated movements are termed *complex motor tics*. Some motor tics have a slow, twisting, or sustained quality that may resemble dystonia, and thus they are described as *dystonic tics*. *Simple vocal tics* are inarticulate noises or sounds, whereas *complex vocal tics* are syllables, words, or phrases that have linguistic meaning. Virtually any movement or sound can be the manifestation of a tic if it is involuntary. Despite the notoriety of the complex vocal tic coprolalia (involuntary uttering of obscenities), only a small minority of patients experience this symptom. Tics have a number of other characteristic features that are fairly specific. They are suppressible, tend to wax and wane, and also tend to change location over time. Patients often will describe an inner tension or urge that is transiently relieved by the tic itself.

Although the diagnosis of TD formally requires the presence of both motor and vocal tics, it has been pointed out that because the production of vocalizations involves the contraction of muscles (typically pharyngeal, laryngeal, and respiratory), the historic phenomenologic distinction between motor and vocal tics is artificial and does not reflect underlying neurobiology. Treatment considerations are therefore similar for the conditions *Chronic Motor Tic Disorder* (CMTD) or *Chronic Vocal Tic Disorder* (CVTD), in which only one of the tic types occurs [1]. Most expert clinicians now view TD, CMTD, CVTD, and transient tic disorder as variants of the same primary disorder. These are viewed as primary tic disorders because they are thought to derive from mostly hereditary factors (although environment may contribute) and do not reflect brain dysfunction secondary to other causes, including drugs (most notably neuroleptics).

Tics may be associated with a variety of other conditions. Considered to be *secondary tic disorders*, these include common neurodevelopmental disorders (eg, autism), pervasive developmental disorder (PDD), Asperger's syndrome, mental retardation, and developmental stuttering. Psychiatric disorders, such as attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), are also frequently comorbid with tics in clinically referred samples. Our own work demonstrated that about one third of children diagnosed with ADHD have tics [2]. TD, ADHD, and OCD occur comorbidly so often in clinical samples that they are collectively referred to as the "clinical triad" of the TD neuropsychiatric spectrum and may be challenging to treat.

Although tics are very common in the school-age population and are most often mild, tics may be more severe and contribute to disability in a variety of ways. They can be embarrassing to individual patients, leading to social isolation, low self-esteem, anxiety, and depression. Some tics are painful. Tics may interfere with critical school and work activities such as reading and writing and may make public speaking difficult. The mental energy expended to suppress tics in school or in other public settings may interfere with attention and concentration that should be more productively directed elsewhere. Obscene or insulting tics may lead to fights. Frequent tics may interfere with activities of daily living such as eating or dressing. In both primary and secondary disorders, tics are appropriate targets of therapy because they often contribute to functional disability.

Treatment

- The first step in deciding upon treatment is comprehensive evaluation of the patient, including assessment of psychiatric comorbid disorders, if any, and of the relative contribution of the tics and the comorbid disorders to the clinical picture. Assessment of the educational, family, and social resources and of the patient's strengths, competencies, and coping skills is essential. Psychoeducation regarding the nature of tics, their expected course, and their involuntary nature is a crucial component.
- Quantitative assessment of tic frequency, intensity, and interference is helpful; standardized rating instruments such as the Yale Global Tic Severity Scale (YGTSS) are available.
- Not all tics need to be treated. Tics are targets for intervention when they cause distress or functional impairment to the individual.
- If it is determined that tics merit treatment, the recommended first-line tic- suppressing medications are the alpha-2 agonists clonidine and guanfacine. As antihypertensive agents, these are not labeled for tic treatment, but in clinical trials they have reduced tics by about 30% to 35%. Although there are few long-term adverse effects, sedation, dizziness, dysphoria, and headaches may occur.
- Second-line medications are the antipsychotic agents, including classic neuroleptics and the newer atypical agents. Although these medications are

reported to result in 40% to 60% reduction in tics in clinical trials, their adverse effects are problematic, including sedation, dysphoria, cognitive dullness, and extrapyramidal effects such as akathisia or parkinsonism. The most feared side effects of these agents, tardive dyskinesia and neuroleptic malignant syndrome, are rarely seen in the treatment of TD. The frequently associated substantial weight gain leading to obesity and glucose intolerance (metabolic syndrome) is a particularly disturbing problem for children and adolescents.

- Efficacy was recently demonstrated for a type of cognitive behavioral therapy known as *habit reversal therapy* (HRT). Such therapy can be used in conjunction with or independent of medications. Other therapies, both established and emerging, are highlighted below.
- With regard to comorbid ADHD, alpha agonists can be considered for first-line dual therapy when the severity of both symptoms is moderate. Atomoxetine and methylphenidate are effective for comorbid ADHD and generally do not lead to sustained tic exacerbations [3,4]. Other stimulants with known efficacy for ADHD can also be considered, but they may need to be withdrawn if tic exacerbations occur and are sustained. Although the tricyclic antidepressant desipramine can be effective for both symptoms, its rare but established risk of sudden cardiac death in children is unacceptable.
- Comorbid OCD or anxiety disorders can lead to secondary tic exacerbations and may be the primary source of disability in individuals with TD. Effective treatments may include serotonin reuptake inhibitors, cognitive behavioral therapy, or both.

Diet and lifestyle

- A recent study found that approximately 60% of patients with TD are using complementary and alternative medicines, and about 80% of these individuals initiate such therapies without informing their doctor [5]. Unfortunately, no published trials have yet confirmed the efficacy of any such treatments. One group has begun a trial of magnesium and vitamin B_6 [6].

Pharmacologic treatment

Alpha-2 adrenergic agonists

Drugs in this class have demonstrated efficacy for both tics and ADHD in randomized clinical trials, so this class is a good first-line choice for patients with both conditions.

Clonidine binds to the three subtypes of alpha-2 receptors (A, B, and C), whereas guanfacine binds more selectively to alpha-2A receptors, which appear to enhance prefrontal function.

There is class I evidence for efficacy of oral clonidine [3, Class I]. Guanfacine is used in clinical practice with similar efficacy, a more favorable side effect profile, and more convenient (daily or twice-daily) dosing.

One recent open-label, prospective 8-week study of guanfacine (at an average dose of 2.0±0.6 mg/d) enrolling 25 medication-free participants (23 males and two females), ages 7–16 years, showed a mean improvement of

	27% on the Hyperactivity Index, 32% on the total score of the teacher-rated ADHD Scale, and 39% on the total tic severity scale [7]. One class I study has now demonstrated the efficacy of the clonidine transdermal system (patch) for tic disorders [8]. Syncope or mania, rare side effects that can lead to discontinuation of guanfacine, do not necessarily recur upon switching to clonidine or another agent [9,10].
Standard dosage	Guanfacine (1 mg tablets) can be started at one half tablet at bedtime and increased by half a tablet every 3–7 days until the maximum dose of 4 mg per day is reached. Extended-release guanfacine is now available in nongeneric formulation. For those who fail to tolerate guanfacine, treatment with clonidine in adults can begin with one half of a 0.1-mg tablet at bedtime, increasing the dose by half a tablet every 3–7 days until the target dose of one half to one tablet two to three times a day is reached. The maximum dose is typically 0.4 mg daily in divided doses. Starting doses for clonidine and guanfacine in children can be half of adult doses.
Contraindications	Known hypersensitivity to the product.
Main drug interactions	Many medications can cause drug–drug interactions, including beta blockers, digoxin, anticoagulant or antiplatelet drugs, and certain calcium channel blockers. These medications can increase the risk of low blood pressure and slow heart rate.
Main side effects	Both clonidine and guanfacine are associated with sedation, fatigue, and somnolence. Reductions in heart rate and blood pressure are modest and rarely lead to discontinuation of treatment.
Special points	Abrupt withdrawal can cause rebound hypertension (including posterior reversible encephalopathy syndrome), headache, and tic exacerbations.
Cost	Thirty 0.1-mg tablets of clonidine cost about $13. Thirty 1-mg tablets of guanfacine cost about $20. We estimate the cost of a 30-day supply of clonidine HCl patches (0.1 mg/24 h) to be about $700. Extended-release guanfacine XR (Intuniv Shire US Wayne, PA) costs about $157.50 for 30 tablets.

Atypical neuroleptics

	Data from experimental and neuroimaging studies and therapeutic response to dopamine blocking agents in patients with TD suggest a central dopamine dysfunction in the etiology of TD. The positive class I evidence in favor of the use of risperidone for TD has been previously reviewed [11]. Several open-label studies have emerged that support the efficacy of olanzapine [12,13], although substantial risk of weight gain has been documented. One small double-blind, randomized trial in 28 children and adolescents demonstrated efficacy of ziprasidone [14, Class II]. However, reports of electrocardiographic changes in children and adolescents and one sudden death with ziprasidone have limited the use and further investigation of this medication [15,16]. There is some evidence from open-label studies and case reports for the efficacy of quetiapine for TD [17,18; Class III and IV]. There is emerging evidence for the efficacy of aripiprazole with unique action as a dopamine partial agonist in TD [19,20,21; Class III and IV].
Standard dosage	Risperidone dosing in children and adolescents can be started at 0.25–0.5 mg daily, administered as a single daily dose in either the morning or evening.

	Dosage adjustments, if indicated, should occur at intervals of not less than 24 h, and more typically every 5–7 days, in increments of 0.25–0.5 mg per day as tolerated, to a recommended dose of 1–3 mg per day. The lowest satisfactory dosage is always sought.
Contraindications	Known hypersensitivity.
Main drug interactions	Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone.
Main side effects	As with all antipsychotics, there is variable risk of extrapyramidal symptoms including parkinsonism and akathisia, tardive dyskinesia, weight gain, or sedation.
Special points	None of the atypical antipsychotics have been approved by the US Food and Drug Administration (FDA) for TD, so all use is off-label.
Cost	All atypical antipsychotics are generally more expensive than the classical neuroleptics, owing to their more recent introduction to the market. For example, 30 tablets of 0.5 mg risperidone costs about $90.

Classic neuroleptics

	This class of dopamine blocking agents has long been used in the treatment of TD. Haloperidol and pimozide remain the only two medications with FDA approval for the treatment of TD. The class I evidence in support of the efficacy of haloperidol and pimozide for TD has been previously reviewed [11,22,23]. In general, fluphenazine is the preferred drug of this type, because of its better tolerability [24].
Standard dosage	The patient's age, tic severity, previous response to other medications, and concomitant medications or disease state should be considered when deciding upon initial dosage and titration. Fluphenazine can be titrated gradually to 1–4 mg per day. (Higher doses, up to 20 mg per day, may be considered in adults.) Treatment with pimozide should be initiated at a dose of 0.05 mg/kg per day, preferably taken once at bedtime. The dose may be increased every 3–7 days to a maximum of 0.2 mg/kg, not to exceed 10 mg per day. An initial starting dose of 0.5 mg for haloperidol is typical for children and adolescents, the maximum dose (rarely attained because of side effects) is 20 mg per day.
Contraindications	Haloperidol is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or who have Parkinson's disease. There are several contraindications with the use of pimozide, so referring to the drug label is strongly recommended before initiating this medication. Most important are congenital long QT syndrome, a history of cardiac arrhythmias, the use of other drugs that prolong the QT interval, severe toxic central nervous system depression, or comatose states from any cause.
Main drug interactions	Because pimozide can prolong the QTc interval on the ECG, an additive effect would be anticipated if administered with other drugs (eg, phenothiazines, tricyclic antidepressants or antiarrhythmic agents) that also can prolong the QTc interval. Accordingly, pimozide should not be given with dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, tacrolimus, ziprasidone, or other drugs that have demonstrated QTc prolongation as one of their pharmacodynamic effects. Also, the use of

	macrolide antibiotics in patients with prolonged QTc intervals has been rarely associated with ventricular arrhythmias.
Main side effects	As with all neuroleptics, there is variable risk of extrapyramidal symptoms including parkinsonism and akathisia, tardive dyskinesia, weight gain, or sedation.
Special points	An ECG should be done at baseline for pimozide, and periodically thereafter, especially during the period of dose adjustment.
Cost	30 tablets of 1 mg pimozide cost about $36, and 30 tablets of 1 mg haloperidol cost about $7.

Tetrabenazine

	Tetrabenazine depletes presynaptic dopamine and serotonin stores and blocks postsynaptic dopamine receptors. In clinical studies, tetrabenazine has been found to be effective in a wide range of hyperkinetic movement disorders, including three large TD clinic populations (class IV). One group reported their experience with add-on therapy for 33 pediatric patients (mean age, 11 years) with hyperkinetic movement disorder, including 10 with TD. Dosages in TD patients ranged from 37.5 mg to 200 mg per day, divided three times daily. Of the 90% of patients with at least one follow-up visit, 77% were rated as "improved" [25]. Long-term efficacy was suggested by the experience of another group. Results of a retrospective chart review (Class IV) of 77 TD patients (mean age, 15) showed moderate or marked improvement in global function that was sustained in more than 80% of the patients over a 2-year period [26]. In a separate analysis of pediatric TD patients, weight gain was significantly lower with tetrabenazine, and two thirds of the patients who switched from neuroleptics to tetrabenazine lost weight [27]. An Italian collaboration also reported long-term experience with 120 TD patients (mean age, 21), primarily as add-on therapy. After a mean of 19 months of treatment, 76% maintained a Clinical Global Impression of "improved" [28••]. Recently, clinical trials investigating tetrabenazine for the treatment of chorea associated with Huntington's disease found the drug to be safe and efficacious, leading to approval by the FDA for this indication. Its use for TD is considered off-label.
Standard dosage	It is generally recommended to begin with one 12.5-mg tablet at night and to titrate upwards in 12.5-mg increments to three times per day. Typical doses used in treatment of adult hyperkinetic movement disorders are 50–75 mg per day, divided three times per day [29]. Children may require (and tolerate) higher doses, the mean total dose in children is 107 mg (3.7 mg/kg) per day [25]. The FDA recommends cytochrome CYP2D6 genetic testing (for slow metabolizer status) before reaching 75 mg per day, but in the reported clinical practice series, careful titration alone was used without any serious or life-threatening events.
Contraindications	Tetrabenazine is contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated depression. Tetrabenazine is also contraindicated in patients who have impaired hepatic function or who are taking monoamine oxidase inhibitors or reserpine. At least 20 days should elapse after stopping reserpine before starting tetrabenazine.

Main drug interactions Caution should be used when giving any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of tetrabenazine, and the daily dose of tetrabenazine should be halved. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated.

Main side effects Depression is a common side effect. Neuroleptic malignant syndrome (NMS), akathisia, agitation, parkinsonism, dysphagia, and arrhythmias involving QT prolongation have been reported with use of tetrabenazine. It should not be used in combination with drugs known to prolong QTc (which in certain circumstances can lead to torsades de pointes and/or sudden death), in patients with congenital long QT syndrome, or in patients with a history of cardiac arrhythmias. Adverse reactions associated with tetrabenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by the concomitant use of dopamine antagonists.

Special points Tetrabenazine is available only through specialty pharmacies because of factors that relate to its orphan drug status and the need to provide appropriate education on the Risk Evaluation & Mitigation Strategy (REMS) program.

Cost Tetrabenazine can be quite expensive, and an assistance program is available for eligible patients. The average wholesale price in the United States for brand-name Xenazine (Lundbeck, Deerfield IL) is $34.25 for each 12.5-mg tablet and $68.50 for each 25-mg tablet.

Benzodiazepines

There is an older literature, based mainly on case reports, regarding the efficacy of clonazepam and possibly other benzodiazepines in the treatment of TD [30, 31, 32, 33, Class IV]. No large-scale trials have been conducted to date. Nonetheless, selective use of benzodiazepines during acute or severe tic exacerbations is often quite helpful. Response to individual drugs may vary.

Standard dosage In the absence of solid evidence, it is reasonable to begin with clonazepam. The starting dose is 0.25–0.5 mg, which can be increased to twice daily after 3–7 days. In severe cases, the titration schedule can be increased by increments of 0.25–0.5 mg daily until the desired effect is reached.

Contraindications Clonazepam should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with significant liver disease. It is contraindicated in acute narrow-angle glaucoma.

Main drug interactions Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine, or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Main side effects Sedation and imbalance may occur but usually improve over time. Dysphoria or disinhibition also may occur.

Cost Thirty 0.5-mg clonazepam tablets costs about $11.

Interventional procedures

Botulinum toxin

Evidence for the use of botulinum toxin types A and B injections (including one class II trial for simple motor tics and one class IV study for phonic

tics), is reviewed in an American Academy of Neurology Practice Parameter [34••]. Botulinum toxin has been reported to reduce the associated premonitory sensations in some subjects [35].

Standard dosage Dosing for treatment of tics is not standardized. Per-muscle titration guidelines for treatment of cervical dystonia and blepharospasm are provided in the package insert.

Contraindications Presence of infection at proposed injection sites, hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation, or any motor neuron, myopathic, or neuromuscular junction disorder.

Complications Local muscle atrophy can occur with chronic use. Dry mouth or dysphagia can occur with injections in cervical or facial muscles. Patients should also be advised of the (very rare) risk of diffuse muscle weakness, even with focal injections.

Special points Local intramuscular injections of botulinum toxin can be useful, but this approach is limited because of expense, short duration of benefit, and use restricted to only one or two disabling types of tics (eg, eye blinking, neck jerks).

Cost Very expensive (>$1000 per injection).

Surgery

Deep brain stimulation

Limitations of pharmacologic treatments have led to the recent use of surgical deep brain stimulation (DBS) to treat disabling tics in patients with TD. Data from two class II trials (double-blind cross-over with stimulation "on" and "off") of bilateral thalamic DBS suggest that some patients can benefit [36,37]. However, the exact location of leads is not standardized across centers, and influence on comorbidities and other psychosocial factors underlying tic exacerbations must also be carefully considered. There is limited evidence for the efficacy of DBS, and further research is warranted [38].

Standard procedure DBS for TD should be performed only as part of a clinical trial or as part of an International Registry. (Contact Kevin McNaught, Scientific Adviser for the Tourette Syndrome Association, www.tsa-usa.org, for details.)

Contraindications Medical conditions preventing general anesthesia and neurosurgery.

Complications Perioperative complications related to surgery and anesthesia (mortality rates <1% in recent publications).

Cost Very expensive (>$100,000) and may not be covered by medical insurance.

Behavioral therapy

- The behavioral treatment with the most empirical support for tics is known as habit reversal training (HRT). HRT involves helping patients to become more aware of their tics by identifying pre-tic warning signs (eg, premonitory urges) and engaging in a tic-incompatible competing response, thereby disrupting the tic.
- Some small published trials have investigated the efficacy of HRT [39,40]; Class II for small numbers). The results of a large class I randomized trial of

HRT, known as the Comprehensive Behavioral Intervention for Tics/Habit Reversal Training (CBIT/HRT) trial, have not yet been published. Preliminary reported results indicate a statistically significant superiority over a comparative treatment (supportive therapy), with effect size comparable to that of medication [41••, Class I].

Standard procedure Habit reversal training.

Contraindications None.

Complications Not sufficiently tested with severe, treatment-refractory cases.

Special points Results from the CBIT trial are eagerly awaited. To date, HRT has not been directly compared with medications in any trial. Active focusing on premonitory sensations and active mental attempts to carry out tic-competing actions could detract from more appropriately directing attention elsewhere (eg, in a school classroom).

Cost Weekly therapy sessions may yield costs higher than for medication.

Emerging therapies

- Some emerging therapies have some positive evidence in the literature; for other therapies, the preponderance of evidence weighs against their use, or no patient data have yet been published.
- Despite case reports and series highlighting the potential efficacy of **levetiracetam** for TD [42, Class IV], two randomized trials have thus far shown no efficacy [43,44; Class III).
- To date, there is no convincing evidence base for the role for **intravenous immune globulin (IVIG)/plasmapheresis** in the management of TD, nor is there a role for antibiotics outside of standard-of-care treatment for acute streptococcal infection.
- A small class III study (ten subjects per group) of the GABA-B agonist **baclofen** showed benefit relative to placebo. Improvement was due primarily to reduced tic impairment (perception of impact on social/academic function), not tic severity [45].
- There is increasing evidence that **glutamate-modulating agents** may be useful in the treatment of OCD, thus leading some investigators to hypothesize that such agents may also be useful in TD [46, Class IV]. This is based on glutamate's major role in cortico-striatal-thalamo-cortical circuits (CSTC), the recognized extensive interaction between glutamate and dopamine systems, results of familial genetic studies, and data from neurochemical analyses of postmortem brain samples. However, insufficient data are available to determine whether TD is definitively associated with a hyperglutamatergic or hypoglutamatergic state, so potential treatment options may use either glutamate antagonists or agonists.
- There is some interest in **repetitive transcranial magnetic stimulation** (r-TMS) for research and possible treatment of TD. However, data from published open-label trials have conflicted; a class I trial is under way.

Topiramate

One small class III study showed benefit over placebo on the primary outcome, total tic score, over an 8-week treatment period [47]. In this trial, 26% of participants receiving topiramate and 29% of those receiving

placebo had comorbid migraine. Topiramate is FDA-approved for prophylactic management of migraine, and may be considered in TD patients for this indication. Open-label data from treatment of 367 TD patients documented sustained benefit during a mean 9 months of follow-up [48, Class IV]. Both studies were conducted at a single academic center and await duplication.

Standard dosage From an initial dose of 12.5–25 mg per day, titrate to 25–100 mg twice daily. The mean effective dose in a class I study was 100 mg daily.

Contraindications Topiramate should not be administered to individuals with history of glaucoma, nephrolithiasis, or known hypersensitivity.

Main side effects The main side effects include sedation, cognitive slowing, weight loss, and dysgeusia.

Complications Rare but potentially serious complications of acute angle closure glaucoma and nephrolithiasis have been reported.

Special points Use caution in renal or hepatic impairment. Avoid abrupt withdrawal.

Cost The average cost of a 1-month supply at 50 mg twice daily is about $40 for the generic drug and about $320 for the brand name drug.

Dopamine agonists

There was some interest in the use of dopamine agonists, namely **pergolide**, for the treatment of TD, perhaps because of its paradoxic reduction of tics in low dosages. This effect may be analogous to the beneficial effects in restless legs syndrome (RLS). A previous review [11, Class I and III] described evidence supporting the efficacy of pergolide in TD. However, pergolide was removed voluntarily from the US market by its manufacturer in March 2007 after findings emerged for significantly increased rates of cardiac valvular dysfunction in patients with Parkinson's disease who took pergolide and another dopamine agonist, cabergoline.

The findings were consistent with abundant clinical and mechanistic evidence that pergolide and **cabergoline** function as dopamine agonists and also activate the serotonin receptor 5-hydroxytryptamine 2B (5-HT2B), causing a histologically distinct form of fibrotic valvulopathy. Cabergoline is approved in the United States for the treatment of hyperprolactinemic disorders at doses much lower and safer than those used in Parkinson's disease; there are no published reports concerning its use in TD.

Ropinirole is an orally administered nonergoline dopamine agonist. There is only one published case report regarding its efficacy in TD [49, Class IV], although it is FDA-approved for the treatment of RLS. Ropinirole does activate the 5-HT2B receptor but is not known to be a valvulopathogen [50].

There is no published evidence for the efficacy of **pramipexole** in the treatment of TD, but its similarity to pergolide as a dopamine agonist led to an industry-sponsored double-blind, randomized controlled trial in TD. To date, results of this study have not been published.

Standard procedure Conservative dosing of ropinirole (0.25–0.5 mg twice daily) has been studied in TD (ages 15–49). Dosing for TD thus may differ from that used in RLS (which is dosed at night) or in Parkinson disease, which uses a much higher dose.

Contraindications Known hypersensitivity to the product.

Complications	Complications of nausea, dizziness, and headache were reported at rates similar to placebo at the low doses used in a class I RLS trial.
Special points	Use with caution, as there is only one published case report in the literature concerning its use in TD.
Cost	Thirty 1.0-mg tablets cost about $95.

Pediatric considerations

- TD is a disorder of childhood onset in which many or most patients experience a reduction in tics by mid to late adolescence. Tics typically have an onset between the ages of 4 years and 6 years and reach their worst-ever severity between the ages of 10 years and 12 years.
- On average, tic severity decreases during adolescence. By early adulthood, half of individuals experience sufficient reduction such that they are no longer aware that they have tics [51]. Even when tics persist, tic-related impairment is reported to improve in most individuals. Lifelong symptoms persist in some patients, however, and it remains difficult to predict those who are at most risk.
- Comorbid disorders, such as OCD and ADHD, are more common during adolescence and early adulthood in individuals with TD than in the general population.
- It is very important to identify TD early on, so that parents and teachers can be educated concerning the symptoms, course and outcome.

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