

Tics and Tourette's disorder

Which therapies, and when to use them



First-line medications have changed; a new 6-step approach considers clinical experience and insights into tic causes and comorbidities.

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When managing pediatric tics and Tourette's disorder, we do not seek to eliminate tic symptoms. Instead—based on evidence and our experience—we use a six-step approach to increase tic control, decrease our patients' embarrassment and discomfort, and help them function more normally.

Drug therapy is not appropriate for all children and adolescents with tic disorders. Mild transient tics and Tourette's disorder usually do not require treatment, and medications should not be given to patients whose tics do not impair their quality of life. Treatment is warranted, however, when tics interfere with peer relations, social interactions, academic performance, or activities of daily living.

Standard treatment of pediatric tic disorders is changing. Instead of using typical antipsychotics,



Table 1

Diagnostic criteria for tic disorders

Shared characteristics

- **Tics defined** as sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- **Onset** before age 18
- **Not caused by** direct physiologic effects of a substance (such as stimulants) or general medical condition (such as Huntington's disease or postviral encephalitis)

Transient tic disorder

- **Single or multiple** motor and/or vocal tics occurring many times a day nearly every day for at least 4 weeks but no longer than 12 consecutive months
- **Criteria** for Tourette's disorder or chronic motor or vocal tic disorder have never been met

Chronic motor or vocal tic disorder

- **Single or multiple** motor or vocal tics, but not both, have been present at some time during the illness
- **Tics occur** many times a day nearly every day or intermittently for more than 1 year, without a tic-free period of more than 3 consecutive months
- **Criteria** for Tourette's disorder or chronic motor or vocal tic disorder have never been met

Tourette's disorder

- **Both** multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently
- **Tics occur** many times a day (usually in bouts) nearly every day or intermittently for more than 1 year, without a tic-free period of more than 3 consecutive months

Source: Adapted from DSM-IV-TR

many experienced clinicians are using other medications that are safer and more effective, particularly for children and adolescents with psychiatric comorbidities such as attention-deficit/hyperactivity disorder (ADHD). In these patients, it is difficult to avoid drug interactions and exacerbation of non-targeted conditions when you attempt to control the tics.

TICS' FLUCTUATING COURSE

Tics and Tourette's disorder are characterized by a fluctuating course. Tic activity tends to occur in bursts over hours to weeks, followed by relative quiescence—spontaneously varying from one extreme to the other. Tics:

- are often preceded by mounting tension
- occur most frequently without volition, although they can be consciously suppressed
- are influenced by emotional state and tend to worsen during increased stress, excitement, or fatigue.

This variable natural history limits the value of uncontrolled studies, as symptom changes are not necessarily treatment-related.

DSM-IV-TR lists three types of childhood tic disorders (*Table 1*). Transient tics are seen in up to 10% of children, chronic tics are less common, and Tourette's disorder has a community prevalence of 0.1 to 0.8%.¹ Tic disorders usually present by age 11² and are three times more common in boys than in girls. One-half of cases remit spontaneously by late adolescence or adulthood, with important treatment implications.²

Causes. Neurophysiologic studies suggest disinhibition and dysfunction of dopamine and related serotonergic

pathways in the cortico-striatal-thalamic-cortical circuit.³ Corollary neuroimaging studies have found decreased metabolism and blood flow in the basal ganglia—specifically the caudate nucleus, thalamus, globus pallidus, and putamen—and increased activity in the frontotemporal cortex—specifically the prefrontal and supplementary motor areas.^{4,5}

Comorbidities. Tics and Tourette’s disorder rarely occur in isolation. The most common comorbidities and the frequencies with which they occur with tic disorders and Tourette’s disorder are:

- ADHD (50% and 90%)⁶
- obsessive-compulsive disorder (OCD)(11% and 80%)⁶
- major depressive disorder (40% and 44%).^{1,6}

Additional comorbid problems include rage attacks, poor impulse control, and learning disorders. Many children with Tourette’s disorder display explosive rage.⁷

GUIDE TO WORKUP

During initial assessment, clearly delineate the onset, severity, complexity, and course of tics. Use empirically validated instruments—such as the Yale Global Tic Severity Scale⁸—at baseline and follow-up visits to monitor the natural history and clinical course, including treatment response. Determine predominant sources of distress and domains of impaired function.

Identify comorbid psychiatric illnesses (*Box*). Often, tics are not impairing⁹ and take on less clinical importance than the associated disorders. Prioritize target symptoms after considering the youth’s and family’s wishes. Follow a multidisciplinary approach, including behavioral, psychotherapeutic, and drug treatment as needed. Involve patients’ parents, schools, and teachers to help monitor functional impairment and treatment impact.

Use follow-up visits as needed to monitor treatment effectiveness. Follow-up frequency may decrease after tics are controlled to an acceptable level, although comorbid disorders may require continued attention.

PANDAS. Consider a diagnosis of pediatric autoimmune neuropsychiatric disorders associ-

Box

Keys to managing childhood tic disorders

- **Assess** for comorbid illnesses, then prioritize and treat the most troublesome symptoms
- **Aim** to decrease rather than eliminate tic-related discomfort
- **Medicate** only if tics cause distress and dysfunction
- **Use one agent** when needed at the lowest effective dosage to minimize side effects and drug interactions
- **Involve** the family and school to monitor progress
- **Reassess** treatment efficacy often

ated with Streptococcus (PANDAS) when tics present abruptly with upper respiratory tract illness.¹⁰ In this context, throat culture and antibody titers for group A beta hemolytic streptococcal infection may be warranted. Treat aggressively with antibiotics such as penicillin V when tests are positive.

6-STEP TREATMENT APPROACH

A six-step approach—based on our experience and available evidence—can guide treatment. Tics coexisting with ADHD/disruptive disorders, OCD/anxiety disorders, or major depressive disorder call for specialized strategies (*Algorithm*).

Step 1: Nondrug therapies. Psychoeducation, supportive therapy, and behavioral therapy are appro-

Use empirically validated instruments such as the Yale Global Tic Severity Scale to monitor tics’ clinical course

priate for all patients with burdensome tics. The unusual behaviors associated with tic disorders may have a far-reaching impact on a child’s functioning, self-esteem, and confidence. These effects can be moderated when children and their families understand tics’ fluctuating nature, including their:



- increase with stress and fatigue
- capacity for brief inhibition
- and high rate of spontaneous remission.

Because of this fluctuating pattern, observe the patient for a few weeks before starting medical treatment, unless dysfunction is severe. Observation is especially useful for initial presentations, in which symptom peaks tend to precede quiescence. Carefully weigh the benefits and potential risks of medical treatment for each patient.

Behavioral options include habit reversal, relaxation training, and self-monitoring. One of the few studies of behavioral therapy found tic symptoms

Approximately one-fourth of patients with Tourette's disorder respond well to clonidine

decreased 55% with habit reversal, 44% with self-monitoring, and 32% with relaxation training.¹¹

Step 2: Adrenergic alpha-2 agonists. If medication seems appropriate for moderate to severe tics, we recommend clonidine or guanfacine (*Table 2*) as first-line therapy. These agents decrease the release of norepinephrine, dopamine, and glutamate, and norepinephrine turnover.¹² They are commonly used to treat Tourette's disorder because they are better tolerated than antipsychotics, although controlled studies supporting their use are limited and the FDA has not approved this indication.

Approximately one-fourth of Tourette's disorder patients respond well to clonidine.⁶ Pulse and blood pressure need to be monitored when using these medications, which in rare cases cause hypotension, bradycardia, and cardiac conduction delay. Because of its sedating properties, clonidine is frequently given at bedtime to promote sleep. Use caution when giving clonidine with medications that have potential cardiovascular effects—such as propranolol or tricyclic antidepressants.

Guanfacine is similar to clonidine except that it binds alpha-2a receptors more selectively and has a longer half-life. As such, it is associated with lower rates of sedation and hypotension than clonidine.

Step 3: Atypical antipsychotics. If symptoms do not respond adequately to an adrenergic alpha-2 agonist, try an atypical antipsychotic. Atypicals block dopamine (D2) receptors and—as a result of serotonergic-2 blockade—are less likely to cause extrapyramidal symptoms than are older antipsychotics.

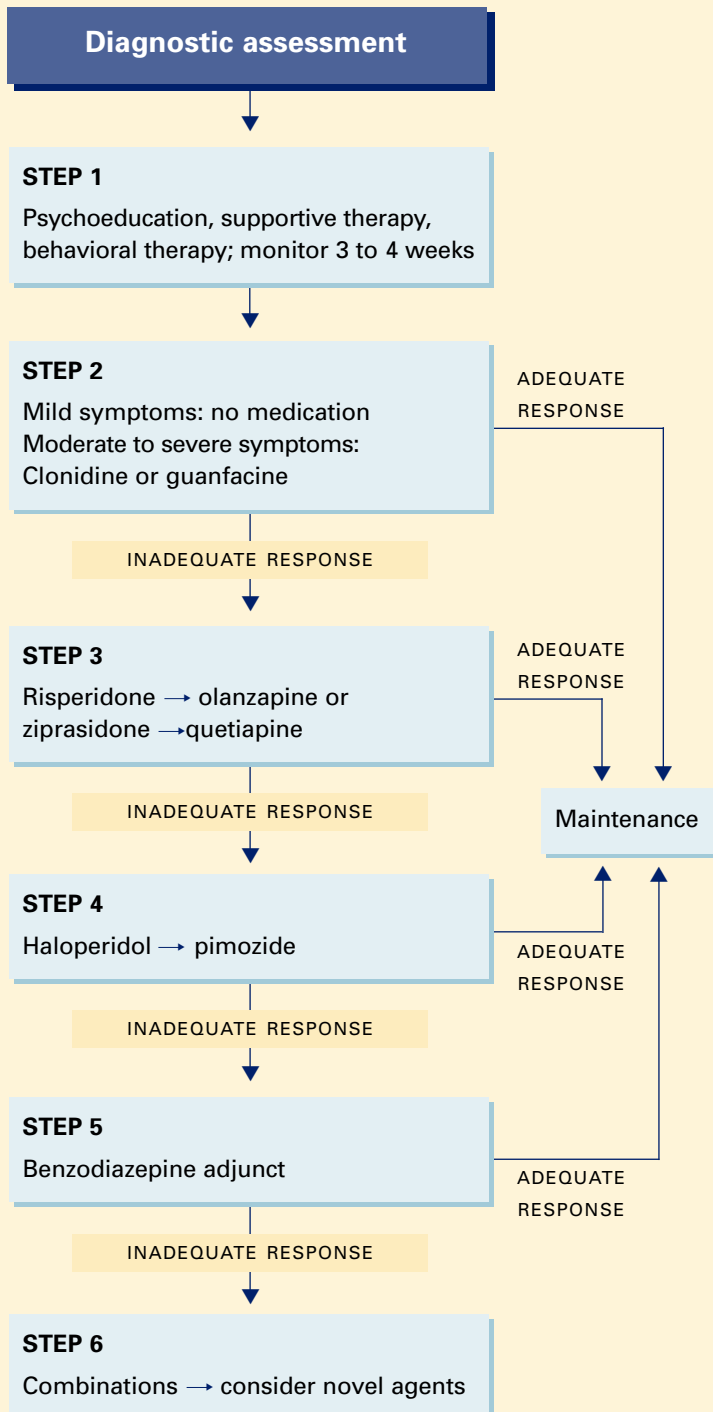
Risperidone, the most studied atypical in Tourette's disorder, has been shown to reduce symptoms by 21 to 61%—an effect significantly greater than placebo¹³ and similar to that of pimozide¹⁴ and clonidine. Because it is also relatively well-tolerated, a risperidone trial is warranted before using typical antipsychotics. Tics may worsen during withdrawal while switching a patient from a typical to an atypical antipsychotic.

In one comparative, crossover study in adults with severe Tourette's disorder, olanzapine was more effective at 5 and 10 mg/d than pimozide at 2 and 4 mg/d, respectively.¹⁵ Weight gain and abnormal glucose tolerance associated with olanzapine may be troublesome side effects. Ziprasidone has demonstrated a 35% decrease in tic symptoms in placebo-controlled studies.¹⁶ Its use has been associated with increased risk of QTc interval prolongation, requiring ECG monitoring.

Two case series have reported positive effects when quetiapine was used for tics and Tourette's disorder.¹⁷ Like clozapine (which is ineffective for tics), quetiapine has relatively low D2 antagonist potency, suggesting its efficacy in treating tics may be limited. Unlike clozapine, however, quetiapine has few anticholinergic effects. Aripiprazole's pharmacodynamic profile suggests similar efficacy, but its use in tic disorders has not been validated.

Algorithm

6-step treatment approach to tics and Tourette's disorder



WITH COMORBID DISORDERS

Arrows (→) indicate sequence of recommended therapies

ADHD/disruptive disorders

Clonidine or guanfacine → TCA → stimulants → atypical antipsychotics → typical antipsychotics → clonidine or guanfacine + TCA → clonidine or guanfacine + stimulants → clonidine or guanfacine + neuroleptics → TCA + neuroleptics → neuroleptics + stimulants

OCD/anxiety disorders

Behavioral therapy → SSRIs (three trials) + clonidine or guanfacine → +/- benzodiazepine → clomipramine → atypical antipsychotic or clomipramine + SSRI → typical antipsychotic + SSRI

Major depressive disorder

CBT → SSRIs (three trials) +/- clonidine or guanfacine → TCA → SSRI + atypical antipsychotic → SSRI + typical antipsychotic

TCA: tricyclic antidepressant

OCD: obsessive-compulsive disorder
SSRI: selective serotonin reuptake inhibitor

CBT: cognitive-behavioral therapy

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Further controlled trials of atypical antipsychotics in children and adolescents with tic disorders are needed. ECGs are recommended to monitor QTc intervals when using these medications.

Step 4: Typical antipsychotics. Haloperidol is the most commonly used medication for treating pediatric Tourette's disorder¹³ and one of two drugs (pimozide is the other) approved by the FDA for this indication. These postsynaptic D2 antagonists are the most-studied and most-potent medications for treating tics and Tourette's disorder. Many other typical antipsychotics such as fluphenazine, thioridazine, trifluoperazine, molindone, and thiothixene also have been used.

In controlled trials, haloperidol improved symptoms by 43 to 66%,¹⁸ which was greater than placebo and equal to the effect of fluphenazine and trifluoperazine. Haloperidol, however, demonstrated a higher rate of EPS.

Pimozide's indication for pediatric Tourette's disorder applies only to treatment-refractory cases. In controlled studies, pimozide was at least as effective as haloperidol,¹⁸ equal to risperidone¹⁴ and less effective than olanzapine.¹⁵ Pimozide caused fewer side effects than haloperidol but more than atypical antipsychotics. Pimozide may cause QTc prolongation, and regular ECG monitoring is required.

Despite their efficacy, typical antipsychotics are associated with common and occasionally severe side effects that limit their long-term tolerability.⁶ Fear of tardive dyskinesia generally limits their use to only severe and treatment-resistant cases.

Step 5: Benzodiazepines. Although controlled trials of tic disorders have not evaluated benzodiazepines, these drugs were effective adjuncts in one case series using haloperidol.⁶ Anecdotal reports suggest they may reduce tics indirectly by lessening anxiety. Many experienced clinicians use

clonazepam, 0.5 to 3 mg/d, or lorazepam, 0.5 to 4 mg/d, to treat Tourette's disorder. Aside from its anxiolytic effects, clonazepam is also considered a minor mood stabilizer.

Step 6: Other options. Numerous novel medications have been studied in trials of tics and Tourette's, although most—including the mixed D1/D2 agonist pergolide—have not been proven effective. In an uncontrolled study, the parenteral opioid antagonist naloxone decreased tics at low doses and increased them at higher doses. Botulinum toxin, nicotine, mecamlamine (a nicotine antagonist),

Fear of tardive dyskinesia generally limits the use of typical antipsychotics to only severe, treatment-resistant cases

baclofen, and flutamide have not proven efficacy in placebo-controlled trials.

Transcranial magnetic stimulation and neurosurgery have been used in patients with severe refractory tics and Tourette's disorder but are not well-established treatments.

TICS AND COMORBIDITIES

ADHD. When it presents with tics, ADHD is frequently an independent target—or even the main target—of management. Because stimulants may exacerbate tics, nonstimulant medications such as clonidine, guanfacine, or desipramine could be tried first.¹⁹ Clonidine has been shown to ameliorate aggression, hyperactivity, and impulsivity but has sedating side effects. Atomoxetine—a nonstimulant ADHD medication—is another option for youth with comorbid tics and ADHD.

In our experience, carefully monitored stimulant trials may also be tried. A recent controlled trial showed that methylphenidate and clonidine, separately and combined, are effective for ADHD and comorbid Tourette's disorder.²⁰ Stimulants of potential benefit include methylphenidate and amphetamine (not just dextroamphetamine), including their long-acting formulations.

continued



Table 2

Recommended drugs and dosages for pediatric tics and Tourette's disorder*

Class/drug	Starting dosage (mg/d)	Dosage increase interval	Dosage range (mg/d)	Dosing regime	Potency/ CYP-450 pathway	Delay to onset
Alpha2 agonists						
Clonidine	0.025-0.05	5 to 7 days	0.1-0.3	bid or tid (patch every 5 to 7 days)	N/A	2 to 8 wks
Guanfacine	0.5	5 to 7 days	0.5-4	bid to tid	N/A	2 to 8 wks
Side effects	Common: dry mouth, drowsiness, dizziness, sedation, weakness, skin rashes (patch) Rare: hypotension, bradycardia, conduction delay, rebound symptoms					
Atypical antipsychotics						
Risperidone	0.25-1	7 to 21 days	0.5-6	qd to bid	high/ 2D6, 3A4	2 to 4 wks
Olanzapine	2.5-5	7 to 21 days	2.5-10	qd to bid	medium/ 1A2, 2D6	2 to 4 wks
Ziprasidone	20	7 to 21 days	40-160	qd to bid	medium/ 3A4	2 to 4 wks
Quetiapine	12.5-25	7 to 21 days	100-600	qd to bid	low/ 3A4	2 to 4 wks
Side effects	Common: weight gain (especially in youth), sedation Rare: hepatic enzyme elevation, extrapyramidal symptoms (EPS), increased QTc interval (ziprasidone)					
Typical antipsychotics						
Haloperidol	0.25-0.5	7 to 21 days	2-10 mg	qd to tid	high/ 2D6, 3A4	2 to 4 wks
Pimozide	0.5	7 to 21 days	1-8 mg	qd to tid	high/ 1A2, 2D6, 3A4	2 to 4 wks
Side effects	Common: EPS (acute dystonia, akathisia, parkinsonism), sedation, weight gain, dysphoria, cognitive dulling, increased plasma prolactin Rare: neuroleptic malignant syndrome (potentially fatal: autonomic instability, hyperthermia and muscular rigidity); tardive dyskinesia; increased QTc interval (pimozide)					
Tricyclic antidepressants						
Desipramine	25	5 to 7 days	2.5-5 /kg/d	qd to bid	2D6	3 to 6 wks
Nortriptyline	10	5 to 7 days	0.5-3 /kg/d	qd to bid	2D6	3 to 6 wks
Imipramine	25	5 to 7 days	2.5-5 /kg/d	qd to bid	2C19, 2D6, 3A4	3 to 6 wks
Clomipramine	25	5 to 7 days	3 /kg/d	qd to bid	2C19, 2D6, 3A4	3 to 6 wks
Side effects	Common: anticholinergic (dry mouth, blurred vision, constipation); antihistaminic (sedation, weight gain); and antialpha adrenergic (dizziness) Rare: heart palpitations, seizures, hepatic enzyme elevations, increased QTc interval					

* Benzodiazepines (clonazepam or lorazepam) may be useful adjuncts; see text for side effects and dosages.

Source: Adapted from DSM-IV-TR

Combining stimulants with antipsychotics or clonidine may also be useful.

To control rage attacks, a trial of mood stabilizers or atypical antipsychotics may be combined with standard tic medications.

Tricyclic antidepressants have been used to treat tics—especially in children with comorbid ADHD.²¹ A case series and controlled study by Singer et al of desipramine and clonidine found no significant impact on tics,²² although this trial was limited by a fixed dose design and few assessment points.

More recently, a double-blind, placebo-controlled trial found a 58% decrease in tic symptoms with desipramine (mean dosage 3.4 mg/kg/d) in patients with tics and ADHD.¹⁹ This effect was associated with small increases in heart rate and blood pressure.

Tricyclics' potential toxicity in overdose and anticholinergic side effects require caution and may limit their use. However, they can be considered as adjuncts in treating chronic tic disorders, especially with comorbid ADHD. Serum levels and ECG monitoring every 3 to 6 months are required to rule out prolonged conduction times and tachycardia. Concurrent methylphenidate use may increase serum desipramine levels, and concurrent pimozide use may increase risk for arrhythmias.

OCD and anxiety disorders. Medically treating anxiety can help indirectly to manage tics, which are sensitive to stress.⁹ OCD comorbidity is especially common in youth with a family history of Tourette's disorder.⁶ Screening for OCD is important, as its secretive symptoms frequently go unnoticed and its prognosis may be poorer with a concurrent tic disorder.

Standard treatment for pediatric OCD is cognitive-behavioral therapy, followed when needed by selective serotonin reuptake inhibitors (SSRIs),

then clomipramine. These treatments are added to tic management, with attention to primary and comorbid symptoms. Anecdotal reports suggest that SSRIs occasionally exacerbate tics. Similarly, behavioral side effects are common in younger children treated with SSRIs and may aggravate ADHD symptoms.

Carefully monitored stimulant trials may be effective for ADHD and comorbid Tourette's disorder

Mood disorders. Except for tricyclics, antidepressants have been ineffective at reducing tics/Tourette's disorder. Tricyclics, however, have not been proven effective in depressed youth, in part because of methodologic limitations in controlled trials. Even so, tricyclics may help some children with tics and major depressive disorder. SSRIs combined with usual tic treatment may also be tried, with monitoring for tic worsening.⁹ To control rage attacks, a trial of mood stabilizers or atypical antipsychotics may be combined with standard tic medications.

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Most pediatric tics are transient and do not require medication. For burdensome tics and Tourette's disorder, adrenergic alpha-2 agonists—rather than typical antipsychotics—are recommended as first-line therapy. Although alpha-2 agonists are not FDA-approved for this indication, their side effects are generally more tolerable.

BottomLine



Related resources

- ▶ Leckman JF, Cohen DJ (ed). *Tourette's syndrome. Tics, obsessions, compulsions: developmental psychopathology and clinical care*. New York: John Wiley & Sons, 1999.
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DRUG BRAND NAMES

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|-----------------------------------|-----------------------------|
| Aripiprazole • Abilify | Lorazepam • Ativan |
| Atomoxetine • Strattera | Molindone • Moban |
| Desipramine • Norpramin | Nortriptyline • Pamelor |
| Clomipramine • Anafranil | Olanzapine • Zyprexa |
| Clonazepam • Klonopin | Pimozide • Orap |
| Clonidine • Catapres | Quetiapine • Seroquel |
| Clozapine • Clozaril | Risperidone • Risperdal |
| Desipramine • Norpramin | Thioridazine • Mellaril |
| Fluphenazine • Permitil, Prolixin | Thiothixine • Navane |
| Guanfacine • Tenex | Trifluoperazine • Stelazine |
| Haldoperidol • Haldol | Ziprasidone • Geodon |
| Imipramine • Tofranil | |

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