Tic Suppression: The Medical Model

Steve W. Wu, M.D.,1 Elana Harris, M.D., Ph.D.,2 and Donald L. Gilbert, M.D., M.S.1

Abstract

Tics are intermittent, repetitive, patterned but usually nonrhythmic motor movements or sounds performed in response to urges or involuntarily. They are the cardinal symptom required for a DSM-IV-TR diagnosis of Tourette’s disorder (TD). Many children with TD present with mild tics that cause no significant impairment. However, when tics cause pain or interference, medical treatment is reasonable. This article reviews current evidence for treatment of tics in TD with medications as well as deep brain stimulation and transcranial magnetic stimulation. It concludes with some context for understanding this literature, relevant to treatment decisions and future treatment research in TD.

Introduction

Practical evaluation of the recent literature on medical tic treatment is the focus of this review. Tics are intermittent, repetitive, patterned but usually nonrhythmic motor movements or sounds performed in response to urges or involuntarily. Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) uses numbers, types, frequency, duration of tics, and age of onset to classify primary tic disorders into (1) transient tic disorder, (2) chronic motor or vocal tic disorder, (3) tic disorder not otherwise specified, and (4) Tourette’s disorder (TD) (American Psychiatric Association 2000). The many different treatments that have been used to suppress tics are broadly inhibitory of the motor system or its inputs. Historic tic treatments include dramatic interventions such as arsenic and electrotherapy (Meige and Feindel 1907). More recent efforts include pharmacologic agents of many classes, none of which was designed or marketed specifically for tic suppression (Robertson 2000; Leckman 2002; Scahill et al. 2006). In extreme cases, stereotactic ablative surgery (Temel and Visser-Vandewalle 2004) and deep brain stimulation (DBS) (Mink 2009; Porta et al. 2009) have been employed.

Although different strategies exist to treat tics medically, these options are all partially effective in tic reduction. Given the potential adverse effects of each approach, it is prudent to evaluate whether each individual’s tics need to be treated. Many patients have mild infrequent tics for which prolonged daily medications may not be justified. However, those who have moderate to severe tics that may cause pain, social or functional interference may benefit from tic reduction with pharmacologic agents (Gilbert 2006). At present, clinicians treating tics pharmacologically may use a two- or three-tiered approach (Gilbert 2006). A two-tiered approach is to begin with alpha adrenergic agonists, clonidine or guanfacine, and, if necessary, consider dopamine 2 (D2) receptor blocking agents—the typical and atypical neuroleptics. The three-tiered approach inserts a middle tier of possibly efficacious medications, largely to avoid or postpone the risks of neuroleptics. There are currently few promising medical options for suppression of severe tics. Surgical or electrophysiological approaches are not in wide use but will be reviewed here. Behavioral treatments lie outside the scope of this review.

Before 2000, most publications on tic treatment in TD involved small samples. A review of these studies described 17 agents in 12 medication classes, including alpha2 adrenergic agonists, psychostimulants, dopamine agonists, typical and atypical neuroleptics, selective serotonin reuptake inhibitors, opiates, benzodiazepines, and nicotinic agents (Robertson 2000). The total number of studied patients numbered fewer than 600, approximately equivalent to the number in the Multimodal Treatment of ADHD study (Arnold et al. 1997; The MTA Cooperative Group 1999). Since 2000 there have been just a few large, rigorous studies capable of generating reasonable estimates of treatment effects on tics.

Neuroleptics

In 2004, the Tourette Syndrome Association–sponsored Tourette Syndrome Practice Parameter Work Group produced a comprehensive review of pharmacotherapy for symptoms of TD (Scahill et al. 2006). At that time, there were three neuroleptics judged to have class A evidence for tic suppression: haloperidol, pimozide, and risperidone. Currently, only haloperidol and pimozide are approved by the U.S. Food and Drug Administration for treatment of tics.

Once the decision has been made to pharmacologically intervene with a neuroleptic, the treating physician has to make an important choice between the typical neuroleptics, which are primarily dopamine receptor blockers, versus the atypical neuroleptics, which
have more variable dopamine receptor effects plus other effects on serotonin 5-hydroxytryptamine (5-HT) receptor subtypes.

**High potency D2 receptor blocking agents: typical neuroleptics**

There is a long tradition, dating back over 40 years, of using dopamine receptor antagonists to control tics. The Tourette Syndrome Practice Parameter Work Group rated two typical neuroleptics (haloperidol and pimozide) and risperidone as having class A evidence of efficacy, with 35%-65% tic score reduction in placebo-controlled studies (Scahill et al. 2006). Efficacy overall is probably fairly similar for pimozide and haloperidol (Pringsheim and Marras 2009) as well as for risperidone (Bruggeman et al. 2001).

There are several other high potency neuroleptics with similar reported treatment effects. There is less published support for the typical neuroleptic fluphenazine, but some clinicians prefer it based on drug interaction and cardiac profiles. Risperidone is considered an atypical neuroleptic due to its 5-HT2A receptor antagonism, but it still has fairly high D2 receptor affinity and can induce tardive movement disorders in children (Correll and Kane 2007; Wonodi et al. 2007). Metoclopramide up to 40 mg daily showed a positive effect in a small, 8-week, double-blind, randomized, placebo-controlled trial (Nicolson et al. 2005).

**Aripiprazole**

Aripiprazole is unusual in that it blocks D2 receptors but also has high affinity for the presynaptic D2 receptor as an agonist. Aripiprazole is a partial agonist at 5-HT1A receptors and a strong antagonist at 5-HT2A receptors (Inoue et al. 1996; Jordan et al. 2002). Of all the atypical neuroleptics, aripiprazole also has the lowest affinity for adrenergic, muscarinic, and histamine receptors (Shapiro et al. 2003). Numerous case reports have reported tic reduction at doses of 2.5 to 30 mg daily. A retrospective assessment of 37 children showed both reduction of tic scores and reduction in tantrums (Budman et al. 2008).

A 12-week open-label trial of aripiprazole with 15 pediatric subjects demonstrated significant improvement in all Yale Global Tic Severity Scale (YGTSS) subscales at low doses, early in treatment with a persistent improvement for all subjects (Seo et al. 2008). Murphy et al. (2009) enrolled 16 subjects between the ages of 8–17 to assess safety of aripiprazole in an open-label flexible-dose study. Laboratory measures, extrapyramidal symptoms, electrocardiograms, height, and weight were monitored. They found significant improvement in YGTSS motor, phonic, and total subscales, as well as improvement in obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and depressive symptoms, but the benefits were tempered by an associated significant weight gain (>2.5 kg) in half of the subjects. No other significant side effects were reported. Similarly, Lyon et al. (2009) included 11 subjects with TD between the ages of 9–19 in a 10-week prospective open-label study to test the safety and tolerability of aripiprazole. The mean daily dose of aripiprazole was 4.5 ± 3.0 mg, which was found to reduce YGTSS global severity and tic scores, inattentiveness, hyperactivity, and obsession scores (Lyon et al. 2009). They reported that the most common adverse effects included appetite increase, weight gain, headaches, fatigue, and mild extrapyramidal effects. One subject developed akathisia and muscle cramps.

**Ziprasidone**

Ziprasidone is a potent antagonist of serotonin 5-HT2A and D2 receptors. Its affinity for 5-HT2A receptors is >10-fold higher than its affinity for D2 receptors, and it is an agonist at the 5-HT1A receptor (Seeger et al. 1995; Newman-Tancredi et al. 2001). In an 8-week double-blind trial in 28 children, 20–40 mg daily of ziprasidone showed greater effect than placebo in reducing total tic scores in children, without any significant risks of extrapyramidal side effects in children (Salle et al. 2000).

**Sulpiride and tiapride**

Atypical neuroleptics sulpiride and tiapride have been shown in controlled and open-label studies to reduce tics (Robertson et al. 1990; Muller-Vahl 2007). In the most recently published study, open-label sulpiride in 189 children aged 3 to 15 years was reported as showing benefit (Ho et al. 2009). Given that over half of the patients studied were under age 10 years, a fair proportion of the treatment response in this 6-week study may have been natural tic-waning. Moreover, many clinicians would be reluctant to prescribe neuroleptics for tics at these young ages, when there is little impairment. These two medications are not available in North America.

**Olanzapine**

Olanzapine is a D2 receptor antagonist as well as serotonin 5-HT2A and 5-HT2C receptor antagonist (Bymaster et al. 1996). It has been shown in three brief, open-label studies to reduce tic scores (Budman et al. 2001; Stephens et al. 2004; McCracken et al. 2008). Weight gain is often reported.

**Quetiapine**

Quetiapine blocks D1 and D2 receptors and has high affinity to serotonergic 5-HT2A, histaminergic H1, and dopaminergic D1 and D2 receptors; moderate affinity to alpha1 and alpha2 adrenergic receptors; and minor affinity to muscarinic M1 receptors (Kufferle et al. 1997; Richelson and Souder 2000). Little evidence supports its use for tics. There are a few case reports. A retrospective study of 12 children treated with mean doses of ~200 mg daily suggested benefit in tic reduction at 8 weeks (Mukaddes and Abali 2003).

**Clozapine**

Clozapine is a weak D1-4 receptor antagonist, with a particularly high affinity for the D4 receptor (Meltzer 1994). It is not believed to be efficacious for tic reduction (Caine et al. 1979; Scahill et al. 2006; Bastiaampillai et al. 2008) and is not used due to its side effect profile.

**Adverse Effects of Neuroleptics**

Concern regarding the development of drug-induced movement disorders has limited the use of the typical neuroleptics. The principal neurological adverse reactions associated with pimozide and haloperidol are similar and include acute dystonic reactions, akathisia, drowsiness, cognitive impairment, depression, anxiety, and school phobia. Chronic, tardive, and withdrawal emergent movement disorders may also occur.

General medical effects are also a risk. There is special concern on pimozide for cardiac arrhythmias. As the use of atypical neuroleptics has increased, there has been increasing clinical awareness and concern regarding the potential for serious adverse effects, including weight gain, insulin resistance, and altered lipid metabolism. The metabolic syndrome is of clinical concern due to the association between obesity, diabetes, and dyslipidemia with
cardiovascular disease and other potential long-term, life-altering sequelae.

**Nonneuroleptic Medications in Treatment of Tics**

There were no nonneuroleptic medications judged to have class A evidence for tic suppression in the Tourette Syndrome Practice Parameter (Scahill et al. 2006). Four agents had class B evidence: clonidine, guanfacine, pergolide (now off the U.S. market), and botulinum toxin. Recent studies of these agents plus a few others will be reviewed in this section.

Clonidine and guanfacine are alpha2 adrenergic agonists that have class B evidence for tic suppression. These are generally considered as first-line agents for tic treatment as they have lower side effect profiles. Therefore, these two medications will be discussed first, followed by atomoxetine, all of which are important in the treatment of a very frequent comorbid condition: ADHD.

### Clonidine

Two of the largest TD studies published in the last 10 years have involved clonidine. The first, performed in the United States and funded by the National Institutes of Health, was termed the Treatment of ADHD in Children with Tics (TACT) Study (Tourette Syndrome Study Group 2002). Clonidine, in 2–3 daily doses up to a maximum of 0.6 mg daily, was studied in a double-blind, randomized, placebo-controlled clinical trial by the Tourette Syndrome Study Group. This study involved 136 children, aged 7 to 14 years, with tics and ADHD, randomized to receive clonidine, methylphenidate, placebo, or both, treated over 16 weeks. The primary ADHD outcome measure, a teacher-rated scale, showed symptom severity ratings decreased up to 60% among treated groups. Tic outcomes appeared less robust. Treated groups (not placebo) experienced about a 25% reduction in the tic rating scales by week 16.

This was a landmark clinical trial that influenced clinical practice as well as subsequent studies. It provided firm evidence that many children with tics will tolerate stimulants without a tic exacerbation. It also provided good estimates of treatment effects in ADHD and tics in a complex group of children with both tics and ADHD. Finally, it demonstrated that one of the most widely used tic-suppressing medications is at best modestly beneficial for tics. Sedation was a very common side effect in the clonidine-only group. Limitations of the TACT study include a nonrepresentative ADHD patient sample, where 75% of children were predominantly inattentive, which is not typical of the TD-plus-ADHD clinic population. In addition, since both medications were already marketed, many eligible children would already have tried these medications, and so there may have been some selection bias (Gilbert and Buncher 2005). A recently published meta-analysis evaluated the TACT study as well as 8 other studies of medication treatments for ADHD in children with tics (Bloch et al. 2009). The authors concluded that psychostimulants were most beneficial for ADHD and that clonidine and guanfacine provided the most effective combined ADHD and tic treatment.

The second study, which employed the clonidine patch, was performed in China and funded by a pharmaceutical company (Du et al. 2008). The 1- or 2-mg-per-week patch was compared with a placebo patch in a randomized, 3:1 allocation, double-blind, 4-week study of 437 children ages 6 to 18 years with tic disorders but no other diagnosed disorders (Du et al. 2008). The treatment effects in the two groups were similar through week 3, at which point nonresponders (41 clonidine and 10 placebo) were withdrawn from the study. Week-4 outcomes were reported as significantly better in the clonidine group, which had a 69% tic scale reduction, than the placebo group, which had a 47% tic scale reduction. Limitations of this enormous study include a nonrepresentative TD sample of tic-only children, and a failure to use Intention-To-Treat Analysis. The effects attributed to clonidine are more likely due to time plus attrition at the 3-week mark.

### Guanfacine

Guanfacine, another alpha2 adrenergic agonist, may be more commonly used now than clonidine for tic suppression, as well as for ADHD (Biederman et al. 2008; Bloch et al. 2009). Placebo-controlled trials had previously been reviewed (Scahill et al. 2006). Briefly, placebo-controlled studies showed about a 30% tic score reduction (Scahill et al. 2001; Cummings et al. 2002). Findings were similar in an open-label study (Boon-yasidhi et al. 2005).

### Atomoxetine

A randomized, double-blind, placebo-controlled, 18-week study of atomoxetine was initiated before its marketing for ADHD treatment in the United States. One hundred forty-eight children aged 7–17 years with both ADHD and tics were eligible. The aim of the study was to see whether this ADHD treatment would not exacerbate tics, while reducing ADHD symptoms. Doses were 1.0 to 1.8 mg/kg daily. ADHD symptom reduction was modest. Tics did not worsen but rather, on average, improved, ~25% in the atomoxetine group versus 15% in the placebo group, which was significant at the trend level (Allen et al. 2005). An unusual study design feature allowed for early withdrawal but continued eligibility to receive medication in an open-label extension, creating an incentive for blinded investigators to withdraw nonresponders early and treat them openly. Baseline tic severity was somewhat milder than in other studies. A re-analysis of the 117 children from this study who met TD criteria showed somewhat stronger tic reduction effects (Spencer et al. 2008).

### Levetiracetam

Four studies of levetiracetam have been reported recently and are informative about the medications as well as about study designs. The open-label studies of up to 2,000 mg levetiracetam daily, one a 12-month study of 60 children (Awaad et al. 2005) and another a 12-week study of 29 children (Fernandez-Jaen et al. 2009), reported significant effects on tic symptoms as well as on a variety of other measures. Adverse behavioral effects led to drop-outs in a few cases. A possible advantage to open-label studies may be that more severely affected children and families might be willing to participate, knowing that they are guaranteed to receive medication. However, a disadvantage includes inability to be sure about type I error—falsey attributing effects to treatment that are really the effects of time or placebo effects. This concern about type I error appears to have been validated, as in the two controlled studies, one with a placebo arm (Smith-Hicks et al. 2007) and the other with an active comparator, clonidine (Hedderick et al. 2009); levetiracetam showed no tic-suppressing effect. The controlled trials were much smaller, but should have been powered to detect a signal of a large difference, if present.

### Topiramate

Topiramate at a mean dose of 100 to 125 mg daily was reported efficacious in a recent double-blind, placebo-controlled study in 29
children and adults with TD. Treatment of comorbid disorders with up to one additional medication was allowed. Nine subjects dropped out; however, 20 reached the 10-week end point, with an ~50% tic score improvement reported in the treated group, versus ~20% in the placebo group (Jankovic et al. 2010). Despite its small size, this was an important study, because topiramate, at approximately this dose, has been used for both migraines (Winner et al. 2005) and tics (Abuzzahab and Brown 2001; Kuo and Jimenez-Shahed 2010), but tic effects had not been rigorously assessed.

**Dopamine agonists**

Pro-dopaminergic medications to treat TD may first have been suggested 30 years ago (Feinberg and Carroll 1979). Subsequently, a number of small open-label and randomized, controlled trials have suggested that dopamine agonists may have a modest effect in reducing tic scores (Lipinski et al. 1997; Black and Mink 2000; Gilbert et al. 2003; Anca et al. 2004) similar to benefit in restless leg syndrome (Earley et al. 1998).

**Donepezil**

Donepezil, an acetyl-cholinesterase inhibitor approved for treatment of Alzheimer’s disease, was studied at a dose of 5 to 10 mg, open-label, for 14 weeks in 20 boys ages 8–14 years with TD and ADHD. Half of subjects dropped out, but a 30% to 40% reduction in tic scores occurred in completers. There was no benefit for ADHD (Cubo et al. 2008).

**Ondansetron**

Ondansetron, a 5-HT3 receptor antagonist usually prescribed as short-term anti-emetic, was used in a 3-week, randomized, double-blind, placebo-controlled study in 30 TD patients aged 12 to 46 years. No significant reduction was seen at week 3 at a dose of 24 mg daily in the total tic score, although statistically significant improvement was seen on a global scale (Toren et al. 2005). There was a large placebo effect in this study. As the cost for this medication is extremely high and the effect small, there does not appear to have been much further enthusiasm for a larger study the authors advocated.

**Cannabinoids**

The effects of a daily 10-mg dose of delta-9-tetrahydrocannabinol have been studied in a randomized, double-blind, placebo-controlled, 6-week study in 24 adults. Seven subjects dropped out of the study. The authors reported statistically modest benefits over placebo (Muller-Vahl et al. 2003).

**Botulinum toxin**

Botulinum toxin blocks acetylcholine release at the neuromuscular junction and can be used to reduce muscle spasms in spasticity or dystonia. Its efficacy in treating localized tics were initially reported in early 1990s (Lang 1992; Jankovic 1994). Since then, several case reports and open-label studies have documented the tic-suppressing efficacy of botulinum toxin injected directly into muscles where an aggravating tic is being performed. Different doses of botulinum toxin type A have been used to treat motor tics, with reports of up to 300 IU per session (Jankovic 1994; Aguirrigomozcorta et al. 2008). The benefit of motor tics from botulinum toxin injection has been reported to range from moderate to near complete resolution (Jankovic 1994; Kwak et al. 2000; Aguirrigomozcorta et al. 2008; Rath et al. 2009). In addition, several investigators also found improvement in quality of life and lessening of disability (Salloway et al. 1996; Kwak et al. 2000; Porta et al. 2004; Aguirregomozcorta et al. 2008; Vincent 2008). The only randomized, double-blinded, controlled study yielded a median of 39% reduction in simple motor tics, but the patients did not report global benefit (Marras et al. 2001). The reason for the failure in this study to identify global patient benefit, despite evidence of tic reduction, is unclear (Marras et al. 2001). It is possible that the global improvement scale is not sensitive to effects of treating one or a few tics, or that the overall tic interference in the study participants was low at baseline.

Electromyography-guided botulinum toxin injections of vocal cords have been shown to reduce vocal tics. The largest open-label study for vocal tics had 30 subjects and they received 2.5 IU of botulinum toxin type A into each vocal cord (Porta et al. 2004). Twenty-eight of 30 subjects in this study had improvement in vocal tics, with 15 subjects reported tic-free after treatment. In other case reports, botulinum toxin type A doses for vocal tics range from 0.625 to 30 IU per session with similar efficacy (Salloway et al. 1996; Scott et al. 1996; Trimble et al. 1998; Vincent 2008). The duration of benefit for motor and vocal tics generally is up to 3 to 4 months. Interestingly, many publications have reported that botulinum toxin injection also decreases premonitory urges (Jankovic 1994; Scott et al. 1996; Kwak et al. 2000; Marras et al. 2001; Porta et al. 2004; Vincent 2008; Rath et al. 2009).

Reported adverse events from botulinum toxin injections include weakness, motor restlessness, discomfort, blurry vision, ptosis, hypophonia, hoarseness, dysphagia, and aspiration. Although botulinum toxin is an effective option for treating patients with tic disorders, it should not be used as a first-line agent given that the procedure is invasive and costly and that the toxin has potential adverse effects. However, for severe self-injurious tics for which other treatments have failed, botulinum toxin injection is worth a try.

**Deep Brain Stimulation**

DBS for treating TD was first published in 1999 (Visser-Vandewalle et al. 1999). Since then, nearly 20 articles have been published about DBS for the treatment of tics. These are mainly case reports or small case series. Although published recommendation for DBS in TD suggests that patients should be at least 25 years old (Mink et al. 2006; Visser-Vandewalle et al. 2006), many reports have included younger patients (Maciunas et al. 2007; Shahed et al. 2007; Servello et al. 2008). Several studies utilized blinded stimulator on/off evaluations (Houeto et al. 2005; Ackermans et al. 2006; Maciuñas et al. 2007; Servello et al. 2008; Welter et al. 2008; Zabek et al. 2008; Martínez-Torres et al. 2009). Targeted regions have included centromedian nucleus of thalamus, globus pallidus interna, subthalamic nucleus, anterior limb of internal capsule, and nucleus accumbens (Table 1). Timing of initial response and tic reduction has been reported in all of these targets, although at widely variable rates. Programming setting has also ranged from monopolar to bipolar stimulation, low versus high voltage stimulation, with frequency from 65 Hz (Visser-Vandewalle et al. 2003) to 185 Hz (Diederich et al. 2005; Flaherty et al. 2005; Shields et al. 2008), and pulse width of 60–600 μs (Houeto et al. 2005; Maciuñas et al. 2007; Servello et al. 2008; Welter et al. 2008) to 450 μs (Visser-Vandewalle et al. 1999).

Surgical complications included bleeding near tip of stimulator lead, poor scar healing, abdominal hematoma, and lead infection.
<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Age/gender</th>
<th>Onset of tics</th>
<th>Target(s)</th>
<th>DBS settinga</th>
<th>Initial onset of tic reduction</th>
<th>Tic reduction</th>
<th>Other symptom reduction</th>
<th>Adverse effects</th>
<th>Follow-up duration</th>
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</thead>
<tbody>
<tr>
<td>Ackermans et al. (2007)</td>
<td>1</td>
<td>39 years/M</td>
<td>6 years</td>
<td>Thalamus (cm, vo, spv)</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>Vertical gaze palsy, Reduced energy and sexual functions</td>
<td>6 months</td>
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<td>Ackermans et al. (2006)</td>
<td>2</td>
<td>45 years/M</td>
<td>7 years</td>
<td>Thalamus (cm, vo, spv)</td>
<td>6.4 V, 130 Hz, 120 μs, monopolar</td>
<td>NR</td>
<td>Tics/min reduction: 85%</td>
<td>Compulsion resolved</td>
<td>1 year</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>27 years/M</td>
<td>7 years</td>
<td>Bilateral thalamus (cm, vo, spv) + GPi</td>
<td>3.1 V, 170 Hz, 210 μs, monopolar</td>
<td>93%</td>
<td>Compulsion resolved</td>
<td>Reduced energy and a sudden short dystonic jerk of the whole body</td>
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<td>50 years/M</td>
<td>3 years</td>
<td>Thalamus (cm, vo, spv)</td>
<td>2 V, 130 Hz, 90 μs, bipolar</td>
<td>First 2 postoperative weeks</td>
<td>YGTSS score reduction: 66%</td>
<td>OCD and mood improved</td>
<td>2 years</td>
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<td>Dehning et al. (2008)</td>
<td>1</td>
<td>44 years/F</td>
<td>5 years</td>
<td>GPi</td>
<td>4.2 V, 145 Hz, 210 μs, monopolar</td>
<td>First week of stimulation</td>
<td>Tic free at 12 months of follow-up</td>
<td>NR</td>
<td>Depressed mood, vertigo, stomach</td>
<td>12 months</td>
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<td>Diederich et al. (2005)</td>
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<td>27 years/M</td>
<td>8 years</td>
<td>GPi</td>
<td>2 V, 185 Hz, 150 μs in one lead and 120 μs in the other, bipolar</td>
<td>Several weeks</td>
<td>Tics/min reduction: 73%</td>
<td>Depressive and anxiety symptoms reduced</td>
<td>Hematoma near tip of the right electrode</td>
<td>Mild fatigue, “Woozy” feeling</td>
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<td>Flaherty et al. (2005)</td>
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<td>37 years/F</td>
<td>10 years</td>
<td>ALIC</td>
<td>4.1 V, 185 Hz, 210 μs, bipolar</td>
<td>Tic frequency decreased with intraoperative stimulation</td>
<td>YGTSS score reduction: 20%</td>
<td>NR</td>
<td>Apathy, depression, hypomania</td>
<td>18 months</td>
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<td>26 years/M</td>
<td>NR</td>
<td>GPi</td>
<td>NR</td>
<td>NR</td>
<td>Vocal tic resolution; “marked” improvement in motor tics</td>
<td>NR</td>
<td>Left stimulator lead infection</td>
<td>NR</td>
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<td>43 years/M</td>
<td>5 years</td>
<td>Thalamus (cm, vo, spv)</td>
<td>NR</td>
<td>NR</td>
<td>“Partial” relief of tics</td>
<td>Dissociative behavior</td>
<td>12 months</td>
<td>(continued)</td>
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<tr>
<td>Reference</td>
<td>n</td>
<td>Age/gender</td>
<td>Onset of tics</td>
<td>Target(s)</td>
<td>DBS setting⁸</td>
<td>Initial onset of tic reduction</td>
<td>YGTSS score reduction:</td>
<td>Tic reduction</td>
<td>Other symptom reduction</td>
<td>Adverse effects</td>
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<td>Houeto et al. (2005)</td>
<td>1</td>
<td>36 years/F</td>
<td>7 years</td>
<td>Thalamus (cm, pf) + GPi</td>
<td>1.5 V, 130 Hz, 60 µs, monopolar</td>
<td>Immediately after surgery</td>
<td>65%b</td>
<td>70%c</td>
<td>Reduced self-injurious behavior</td>
<td>Weight loss, anxiety, nausea, hypotonia</td>
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<td>Kuhn et al. (2007)</td>
<td>1</td>
<td>26 years/M</td>
<td>“Puberty”</td>
<td>NA</td>
<td>7 V, 130 Hz, 90 µs, monopolar</td>
<td>“Gradually” over the course of 1 year</td>
<td>YGTSS score reduction: 41%</td>
<td>Motor tics: 67%d</td>
<td>Improved psychosocial functions</td>
<td>Improved quality of life</td>
</tr>
<tr>
<td>Maciunas et al. (2007)</td>
<td>5</td>
<td>18–34 years/M</td>
<td>3–12 years</td>
<td>Thalamus (cm, pf)</td>
<td>130 Hz, 60 µs</td>
<td>NR</td>
<td>YGTSS score reduction: 64%</td>
<td>Decreased obsessions, compulsions, self-injurious behaviors, anxiety, premonitory sensations</td>
<td>Decreased</td>
<td>Vertigo, blurry vision, abdominal discomfort, upward eye deviation, poor scar healing, abdominal hematoma</td>
</tr>
<tr>
<td>Martinez-Torres et al. (2009)</td>
<td>1</td>
<td>38 years/M</td>
<td>7 years</td>
<td>Subthalamic nucleus</td>
<td>130 Hz, 60 µs</td>
<td>Initiation of stimulation</td>
<td>Vocal tics: 70%d</td>
<td>Tics/10 minutes reduction: 97%</td>
<td>Decreased compulsions</td>
<td>NR</td>
</tr>
<tr>
<td>Servello et al. (2008)</td>
<td>18</td>
<td>17–47 years/ M (n = 15)</td>
<td>4–12 years</td>
<td>Thalamus (cm, pf, vo)</td>
<td>2.5–4 V, 130 Hz, 60–120 µs</td>
<td>NR</td>
<td>YGTSS score reduction: 64%</td>
<td>Decreased</td>
<td>OCD/depression improvement</td>
<td>Mild OCD improvement</td>
</tr>
<tr>
<td>Servello et al. (2009)</td>
<td>4</td>
<td>25 years/M</td>
<td>12 years</td>
<td>ALIC/NA</td>
<td>4.5–5 V, 130–160 Hz, 150–180 µs</td>
<td>NR</td>
<td>Mild</td>
<td>Mildly improved OCD/depression scores</td>
<td>NR</td>
<td>10 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31 years/F</td>
<td>6 years</td>
<td>ALIC/NA</td>
<td></td>
<td></td>
<td></td>
<td>Mild OCD improvement</td>
<td>OCD/depression improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>37 years/M</td>
<td>Before 10 years</td>
<td>Thalamus (cm, pf, vo) + ALIC/NA</td>
<td></td>
<td></td>
<td></td>
<td>OCD and impulsivity improvement</td>
<td></td>
<td>19 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47 years/M</td>
<td>18 years</td>
<td>ALIC/NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Age</td>
<td>Duration</td>
<td>Target</td>
<td>Parameters</td>
<td>YGTSS Score Reduction</td>
<td>OCD Improvement</td>
<td>Complications</td>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shahed et al. (2007)</td>
<td>16 years/M</td>
<td>3 years</td>
<td>GPi</td>
<td>5 V, 160 Hz on right, 145 Hz on left, 90 µs, monopolar</td>
<td>NR</td>
<td>YGTSS score reduction: 84%</td>
<td>Compulsively pushed on the IPG</td>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shields et al. (2008)</td>
<td>40 years/F</td>
<td>10 years</td>
<td>ALIC</td>
<td>4.1 V, 185 Hz, 210 µs</td>
<td>NR</td>
<td>YGTSS score reduction: 23% 46%</td>
<td>Self-injurious behavior resolved, mood improved</td>
<td>21 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visser-Vandewalle et al. (1999)</td>
<td>42 years/M</td>
<td>NR</td>
<td>Thalamus (median, rostral intralaminar nuclei, vo)</td>
<td>1.5 V, 130 Hz, 450 µs</td>
<td>Postoperative period</td>
<td>Tics/min reduction: 79%</td>
<td>NR</td>
<td>1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visser-Vandewalle et al. (2003)</td>
<td>28, 42, 45 years/M</td>
<td>5–8 years</td>
<td>Thalamus (cm, vo, spv)</td>
<td>2-3 V, 65–100 Hz, 210 µs</td>
<td>Within first postoperative week</td>
<td>Tics/10 minutes reduction: 72.2%–90.1%</td>
<td>Self-injurious behavior, compulsions decreased</td>
<td>Dizziness</td>
<td>8 months–5 years</td>
<td></td>
</tr>
<tr>
<td>Welter et al. (2008)</td>
<td>30 years/M</td>
<td>6–13 years</td>
<td>Thalamus (cm, pf) + GPi</td>
<td>130 Hz, 60 µs</td>
<td>Within days postoperatively</td>
<td>YGTSS score reduction: 65%–96%²</td>
<td>Self-injurious behavior, depression anxiety, impulsivity improved</td>
<td>Nausea, vertigo, anxiety, lethargy, paraesthesia, decreased libido</td>
<td>20–60 months</td>
<td></td>
</tr>
<tr>
<td>Zabek et al. (2008)</td>
<td>31 years/M</td>
<td>7 years</td>
<td>Right NA</td>
<td>3 V, 130 Hz, 210 µs, bipolar</td>
<td>NR</td>
<td>Tics/15 minutes reduction: 60%</td>
<td>Compulsion, self-injurious behavior decreased</td>
<td>IPG malfunction</td>
<td>28 months</td>
<td></td>
</tr>
</tbody>
</table>

²Optimal stimulation parameters.
³Bilateral thalamic stimulation alone, bilateral pallidal stimulation alone.
⁴Bilateral simultaneous thalamic and pallidal stimulation.
⁵Maximal tic reduction reported.
⁶This man also had Parkinson disease secondary to exon 5 deletion in Parkin gene.
⁷These subjects had previous bilateral thalamic DBS (cm, pf, and vo nuclei).
⁸Thalamic leads were placed after the ALIC leads broke from retrocollic neck jerks.
⁹Best improvement occurred with GPi stimulation alone.

Abbreviations: ALIC = anterior limb of internal capsule; Cm = centromedian nucleus; DBS = deep brain stimulation; F = female; GPi = globus pallidus interna; IPG = internal pulse generator; M = male; NA = nucleus accumbens; NR = not reported; OCD = obsessive-compulsive disorder; Pf = parafascicular nucleus; Spv = substantia periventricularis; vo = ventralis oralis complex; YGTSS = Yale Global Tic Severity Scale.
Noninvasive Transcranial Stimulation

Transcranial magnetic stimulation is a noninvasive technique in which a hand-sized magnetic coil is placed over the scalp and focal magnetic pulses are administered. These magnetic pulses depolarize neurons within the spatial field of the coil, resulting in action potentials. Single or paired pulses can be used to measure brain physiology or briefly interrupt brain function. Repetitive transcranial magnetic stimulation (rTMS) can entrain inhibitory or excitatory neuronal connections, resulting in transient or sometimes lasting functional changes. rTMS treatment protocols aimed at changing brain function for weeks or months typically involve multiple daily rTMS treatment sessions over 2 or more weeks. rTMS of dorsolateral prefrontal cortex is Food and Drug Administration cleared for treating medication-refractory depression. rTMS has been used experimentally to treat other psychiatric and neurologic disorders (Ridding and Rothwell 2007). Several rTMS studies to treat tics have been published since it was first shown to reduce tics with 1 Hz rTMS over primary motor area and vertex (Karp et al. 1997). Two were single-blinded, sham-controlled, cross-over studies (Munchau et al. 2002; Orth et al. 2005). These studies consisted of 1 Hz repetitive stimulation, which is an inhibitory paradigm, administered over 2 consecutive days using a figure-of-eight coil with intensity set at 80% of the subjects’ active motor thresholds. Neither 1,200 pulses per day and targeting the left premotor and left motor areas, nor 1,800 pulses per day targeting premotor sites reduced tic scores significantly. Another pilot study published in 2004 was blinded and sham-controlled, which recruited 8 TD subjects (Chae et al. 2004). These subjects received randomized stimulations of 1 or 15 Hz rTMS over the left motor cortex or left prefrontal cortex. Each subject received 2,400 stimuli per day over 5 days. The subjects showed a decreased trend in YGTSS scores from baseline to day 5. These were essentially pilot and safety studies looking for signal of treatment benefit. Possible explanations of these negative studies, besides actual lack of potential efficacy, included improper target selection or pulse intensity, insufficient number of treatment sessions, and lack of precise and consistent stimulation without neuronavigation systems.

Two other pilot studies with supplementary motor area as target, higher pulse intensities, and higher number of treatment sessions yielded more promising results. In one, the standard figure-of-eight coil was used for 10 sessions over 2 weeks at 1 Hz repetitive stimulation (1,200 pulses per day) over bilateral supplementary motor area at an intensity of 100% of resting motor threshold (Mantovani et al. 2006). In this study, two of three TD subjects were tic-free by the end of the stimulation protocol. The subsequent study also used similar settings and targets, with the exception of the intensity at 110% of resting motor threshold and the use of a double cone stimulation coil (Mantovani et al. 2007). The two subjects in this study had 36% and 68% in tic reduction. Limitations of these studies include no sham control, no blinding, small sample size, and short follow-up. Adverse side effects in these studies include mild headache and fatigue.

To date, there is one published study using transcranial direct-current stimulation, a 5-day 2-mA cathodal stimulation (15 minutes per day) over the left motor cortex (Mrakic-Sposta et al. 2008). Both subjects reported some decrease in tics.

In summary, although noninvasive transcranial stimulation has therapeutic potential for treating tics, more studies are needed to determine efficacy and safety.

Discussion

The implications of this body of literature for decisions about treatment are not a simple matter of consulting a comprehensive practice parameter. The unfortunate reality is that none of the medications currently prescribed is highly effective for moderate or severe tics. Rather, there are many medications that may help to a small degree (Table 2). Meta-analyses and careful calculations of effect sizes across a series of small studies will not change this. Other interventions, like behavioral therapy or transcranial magnetic stimulation, are quite time intensive. DBS is invasive, expensive, and risky, and needs to be considered with extreme care when the patient is young and has many years of life ahead (Gilbert 2007).

Clinically referred patients with tic disorders often have other comorbid psychiatric conditions. Epidemiologic studies have found associations between tics and ADHD, OCD, learning disabilities, anxiety, and other psychiatric disorders (Freeman et al. 2000; Kurlan et al. 2001, 2002; Peterson et al. 2001; Snider et al. 2002). The treatment of comorbid conditions frequently takes precedence over treatment of the tics, due to the impairment generated by the comorbid condition (Brand et al. 2002; Sukhodolsky et al. 2003; Bernard et al. 2009). Therefore, it may be necessary for patients and/or family members to rank the severity of each neuropsychiatric symptom before embarking on a treatment strategy. Detailed managements of ADHD and OCD are beyond the scope of this review, but treatment of ADHD and OCD in youth without tics may be applicable (The MTA Cooperative Group 1999; The Pediatric OCD Treatment Study Team 2004).

Therefore, given the complexity of TD, treatment decision optimally involves a broader understanding of our patients, their tics, the relationship between tics and other impairing symptoms, and challenges and limitations of clinical trials in TD.

Tic diagnostic nosology as a basis for diagnosis and treatment

In the medical literature, tics have been described since 1825 (Itard 1825). Despite this long history, and the high heritability of tendencies to tic, the biological basis for primary tic disorders remains obscure. The clinical diagnosis is based on history and observation (Dooley et al. 2003), not any testing. In the DSM-IV-TR, primary tic disorders are classified as transient or chronic (American Psychiatric Association 2000). These categories are problematic, and change is anticipated for Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V).
For Transient Tic Disorder, the diagnosis cannot be confirmed while the child is still having tics, because there is no way to know if the tics will be transient. This is not just a nosology issue. Some children with what we may initially diagnose as transient tic disorder will go on eventually to have a severe case of TD. Fortunately, most will not. Today, we cannot predict very well, when tics are new, whether symptoms will persist. If biological or psychosocial mechanisms contributing to persistence of tics could be identified, tic treatments could perhaps be designed to preempt or modify the course of TD in childhood or prevent impairing tics from persisting into adulthood.

For the primary chronic tic disorder, TD, 1-year or more duration is established at the time of diagnosis. However, the cardinal symptoms for DSM-IV-TR diagnosis, tics, occur in a variety of other idiopathic developmental and psychiatric conditions (Kurlan et al. 2002) as well as in a number of neurological conditions. In practice, tics are often seen in children with ADHD (Gadow et al. 2009), obsessive compulsive and anxiety disorder (Nestadt et al. 2003; Nestadt et al. 2009), and autistic spectrum disorder (Canitano and Vivanti 2007; Gadow et al. 2009), and mental retardation (Searcy et al. 2000), including Fragile X disorder (Schneider et al. 2008). Less commonly, tics can occur secondarily as part of a conversion disorder (psychogenic tics) (Kurlan et al. 1992; Dooley et al. 1994; Isaacs et al. 2009) or as an acute, chronic, tardive, or withdrawal drug-induced movement disorder (Singer et al. 2010). Finally and much more rarely, tics can occur as part of a variety of neurological conditions, including Sydenham’s Chorea (Mercadante et al. 1997; Hounie et al. 2004), and neurodegenerative disorders such as neuroacanthocytosis (Yamamoto et al. 1982) and neurodegeneration with brain iron accumulation (Nardocci et al. 1994). Tics secondary to infection or trauma have also been described (Chouinard and Ford 2000; Jankovic and Mejia 2006). Although tic disorders are usually relatively easy to diagnose by history and observation, misdiagnoses may occur (Kompoliti and Goetz 1998), particularly when clinicians are not familiar with the differential diagnosis or with clinical features distinguishing tics and another common patterned movement, stereotypies (Harris et al. 2008).

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### Table 2. Summary of Medications Used for Tourette’s Disorder

<table>
<thead>
<tr>
<th>Medication</th>
<th>Grade</th>
<th>Dose per day</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>A</td>
<td>1–4 mg</td>
<td>Sedation, weight gain, metabolic syndrome, extrapyramidal symptoms, galactorrhea, withdrawal dyskinesias</td>
</tr>
<tr>
<td>Pimozide</td>
<td>A</td>
<td>2–8 mg</td>
<td>Sedation, weight gain, extrapyramidal symptoms, QT interval prolongation</td>
</tr>
<tr>
<td>Risperidone</td>
<td>A</td>
<td>1–3 mg</td>
<td>Sedation, weight gain, metabolic symptoms, extrapyramidal symptoms, hyperprolactinemia</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>B</td>
<td>1.5–10 mg</td>
<td>Sedation, irritability, dysphoria, dystonia, akathisia</td>
</tr>
<tr>
<td>Tiapride</td>
<td>B</td>
<td>150–500 mg</td>
<td>Sedation, weight gain, dizziness</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>B</td>
<td>10–80 mg</td>
<td>QT interval prolongation, sedation, weight gain, metabolic symptoms</td>
</tr>
<tr>
<td>Clonidine</td>
<td>B</td>
<td>0.1–0.3 mg</td>
<td>Sedation, dizziness, hypotension, rebound hypertension</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>B</td>
<td>1–3 mg</td>
<td>Sedation, dizziness, hypotension, rebound hypertension</td>
</tr>
<tr>
<td>Pergolide</td>
<td>B</td>
<td>0.1–0.25 mg</td>
<td>Sedation, hallucination, dyskinesias, retroperitoneal fibrosis</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>B</td>
<td>30–300 units in one or more focal sites</td>
<td>Weakness, dysphagia, ptosis, hypophonia</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>B</td>
<td>1–1.8 mg/kg</td>
<td>Nausea, decreased appetite, abdominal discomfort</td>
</tr>
<tr>
<td>Topiramate</td>
<td>B</td>
<td>50–200 mg</td>
<td>Paresthesia, decreased appetite, cognitive slowing, renal stones, acute glaucoma</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>B</td>
<td>24 mg</td>
<td>Abdominal discomfort, extrapyramidal symptoms, QT interval change</td>
</tr>
<tr>
<td>Delta</td>
<td>B</td>
<td>10 mg</td>
<td>Sedation, dizziness, dry mouth, increased appetite</td>
</tr>
<tr>
<td>9-tetrahydrocannabinol</td>
<td>B</td>
<td>5–40 mg</td>
<td>Sedation, increased appetite, dysphoria, extrapyramidal symptoms</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>B</td>
<td>2.5–12.5 mg</td>
<td>Sedation, weight gain, metabolic symptoms</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>C</td>
<td>200–1,000 mg</td>
<td>Sedation, extrapyramidal symptoms</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>C</td>
<td>2–30 mg</td>
<td>Sedation, weight gain, metabolic symptoms</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>C</td>
<td>25–250 mg</td>
<td>Sedation, weight gain, metabolic symptoms, dizziness, dysphoria</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>C</td>
<td>37.5–150 mg</td>
<td>Sedation, extrapyramidal symptoms, depression, QT interval prolongation</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>C</td>
<td>40–60 mg</td>
<td>Sedation, ataxia, withdrawal reaction</td>
</tr>
<tr>
<td>Baclofen</td>
<td>C</td>
<td>7–21 mg</td>
<td>Skin reaction, palpitation, hypertension</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>C</td>
<td>2.5–7.5 mg</td>
<td>Dry mouth, urinary retention, constipation, hypotension</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>C</td>
<td>750 mg</td>
<td>Gynecomastia, elevated liver enzymes, abnormal blood counts</td>
</tr>
<tr>
<td>Flutamide</td>
<td>C</td>
<td>10 mg</td>
<td>Abdominal discomfort, irritability, nightmare, headache, sedation, dizziness, urinary dysfunction, arrhythmia</td>
</tr>
</tbody>
</table>

Grade refers to level of evidence in treatment studies.
A, demonstrated efficacy in more than one randomized, placebo-controlled trial.
B, demonstrated efficacy in one placebo-controlled trial.
C, probable efficacy in open-label, observational studies.
It is unknown whether common mechanisms underlie the presentation of tics in these many different diagnoses or whether treatments, when indicated, should differ.

**Tic scale scores as a treatment outcome**

Tics wax and wane over minutes, hours, days, and the lifetime (Leckman et al. 1998; Peterson and Leckman 1998; Peterson et al. 2001). Thus, although tics can be seen and counted, videotaped tic counts in the clinic (Goetz et al. 1987) are not reasonable as a primary outcome for tic suppression trials. Rating scales, with their own sets of limitations, are more typically used.

The rating scale most often used in clinical trials is the YGTSS (Leckman et al. 1989), but primary treatment outcomes may be either the total YGTSS, which includes an anchored but subjective metric of tic impairment, or the total tic scale only, which is less subjective but does not capture global life effects. The YGTSS tic-only scores capture the broad phenomenology (number, frequency, intensity, complexity, and interference; motor vs. phonic) of the tic symptoms in TD but create some difficulty in clinical trial outcome interpretation despite greater objectivity and reliability. First, a YGTSS total tic score, for example, 20 (out of 50 possible), is often used as a floor for inclusion into a study. However, the total tic score cannot be easily interpreted as a measure of global tic symptom severity. The YGTSS scores motor and phonic tics as distinct phenomena, with scores from 0 to 25 for motor and 0 to 25 for phonic tics. So, an individual with both mild motor and mild phonic tics and not interested in treatment could have a higher score, and qualify for study entry, than a person with a very severe phonic or motor (but not both severe) tics desperate for treatment but, by scoring, ineligible for study (unless the investigator fudge up the baseline rating score). A second problem is that the total score is made up of five equally scored components that are not equally responsive to treatment. More data are needed on this, but one reason that tic scores may seem not to change much with treatment may be that some scale components are less responsive to any intervention than others. For example, it may be more reasonable to expect a short-term intervention to reduce the frequency or severity of tics than to reduce the number or complexity of them.

**TD symptom reduction as a treatment outcome**

Most persons with TD who present to clinics for treatment do not experience much suffering due to the primary symptom on which their diagnosis is based. Rather than tics, most difficulties are due to inattention, impulsivity, worry, or anger (Brand et al. 2002; Sukhodolsky et al. 2003; Bernard et al. 2009). A few studies have addressed treatment of these other problems, for example, ADHD in children with TD. Another recent study evaluated the effect of tics on OCD treatment outcomes (March et al. 2007). More commonly, however, clinical trials in TD emphasize tic suppression and exclude patients with significant or currently treated ADHD, OCD, or anxiety disorders, yielding data on a nonrepresentative subsample of TD patients (Gilbert and Buncher 2005).

An alternate approach would be to conceptualize TD as a condition characterized necessarily by tics but so commonly by other problems that these problems are themselves part of the phenotype and not a distinct problem or comorbidity. Then, a composite symptom or impairment score, along with a global function scale, could be the treatment outcome. There is precedent for this in some molecularly defined neurological diagnoses with heterogeneous domains of symptoms. For example, in Niemann Pick Type C, a very rare disease causing ataxia, eye movement deficits, seizures, dementia, and other problems, a multi-symptom rating scale has been developed for use as a treatment outcome (Wraith et al. 2009; Yanjanin et al. 2010).

A TD composite score might be particularly useful if more basic, upstream neurobiological mechanisms in TD are identified and targeted by novel treatments. At present, such a scale would have little added value over current practice in clinical trials, where symptom domains are rated on separate rating scales. Thus, in interpreting the results of a study for patient care, it is prudent to look at not only the primary outcome but also secondary effects seen in other rating scales. Global measures of function and improvement can also aid in interpreting the usefulness of an agent in a clinical trial. A significant global benefit in a placebo-controlled trial may be important, even if the tic score does not register much change.

In conclusion, a great deal of effort has gone into trials of treatment for tics in TD. In most cases, treatment results are modest. Clinicians need to be frank about this with patients, so that expectations are realistic and risk benefit analyses are rational. Researchers may consider that there is little to be gained from further study of the medications described in this review, or of minor variations on these medications. Future research should be directed toward understanding physiological mechanisms in TD and designing rational, novel interventions that prevent or modify its course.

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**References**


Allen AJ, Kurlan RM, Gilbert DL, Coffey BJ, Linder SL, Lewis DW, Winner PK, Dunn DW, Dure LS, Sallee FR, Milton DR, Mintz...


Gilbert DL, Buncher CR: Assessment of scientific and ethical issues in two randomized clinical trial designs for patients with Tourette’s


Address correspondence to:
Steve W. Wu, M.D.
Division of Neurology
Cincinnati Children’s Hospital Medical Center
3333 Burnet Ave. MLC 2015
Cincinnati, OH 45229
E-mail: steve.wu@cchmc.org