

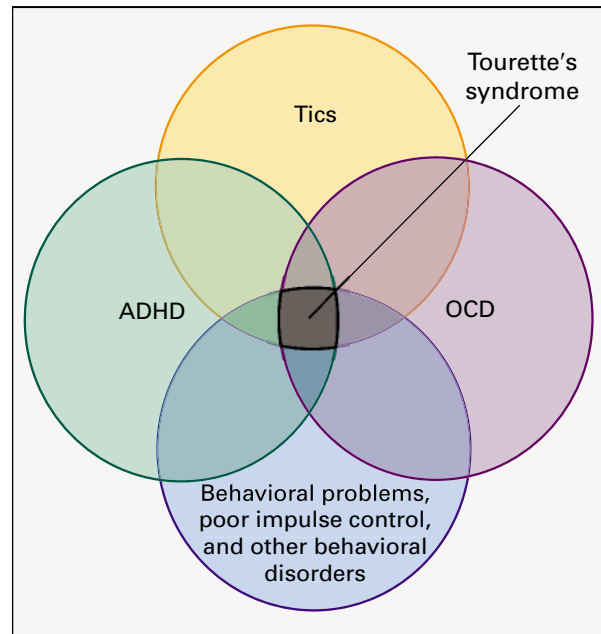
*Medical Progress***TOURETTE'S SYNDROME**

JOSEPH JANKOVIC, M.D.

**T**OURETTE'S syndrome is a neurologic disorder named after the French neurologist Georges Gilles de la Tourette, who, in 1885, described nine patients with childhood-onset tics, accompanied in some by uncontrollable noises and utterances, as well as features that are now associated with attention-deficit-hyperactivity disorder, obsessive-compulsive disorder, poor impulse control, and other coexisting behavioral problems.<sup>1-3</sup> Although Tourette considered the disorder he described to be hereditary, it was ascribed to psychogenic causes for nearly a century after the original report. The perception of Tourette's syndrome as a rare, bizarre psychological disorder began to change in the 1960s, when the beneficial effects of neuroleptic drugs on the symptoms of the syndrome began to be recognized.<sup>4</sup> This observation helped to stimulate research into the neurobiologic mechanisms of Tourette's syndrome, as a result of which it is now recognized as a relatively common, biologic, genetic disorder with a spectrum of neurobehavioral manifestations that wax and wane during its natural course. The marked fluctuations in the severity and frequency of symptoms, coupled with the striking variation in manifestations from one patient to another, however, contribute to frequent misdiagnosis.<sup>5</sup> Despite greater awareness of Tourette's syndrome as a result of increased educational efforts directed at physicians and other health care providers, psychologists, educators, and the general public, many cases still remain undiagnosed, or patients' symptoms are wrongly attributed to hyperactivity, nervousness, habits, allergies, asthma, dermatitis, and other conditions.<sup>6,7</sup>

**DIAGNOSIS**

The diagnosis of Tourette's syndrome (Fig. 1) is based on a history and observation of tics, often supported by the presence of coexisting behavioral disorders, particularly attention-deficit-hyperactivity disorder and obsessive-compulsive disorder, and a family history of similar symptoms. Tics, the clinical hallmark of Tourette's syndrome, are sudden, brief, intermittent, involuntary or semivoluntary movements



**Figure 1.** Clinical Hallmarks of Tourette's Syndrome.

The diagnosis is based on the occurrence of tics along with behavioral disorders, including attention-deficit-hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Other behavioral disorders include anxiety and mood disorders, learning disorders, sleep disorders, conduct and oppositional behavior, and self-injurious behavior.

(motor tics) or sounds (phonic or vocal tics). They typically consist of simple or coordinated, repetitive or sequential movements, gestures, and utterances that mimic fragments of normal behavior.<sup>3,8</sup> Simple motor tics involve only a single muscle or a group of muscles, and often cause a brief, jerking movement (clonic tics); they may also be slower, causing a briefly sustained abnormal posture (dystonic tics) or an isometric contraction (tonic tics).<sup>8</sup> Examples of simple clonic motor tics include blinking, nose twitching, and head and limb jerking.

Dystonic tics include sustained eye closure (blepharospasm), ocular deviations, bruxism, mouth opening, torticollis, and shoulder rotation. Tonic tics are typically manifested by tensing of abdominal or limb muscles. Examples of complex motor tics include head shaking, trunk bending or gyrating, brushing hair, touching, throwing, hitting, jumping, kicking, making rude gestures, grabbing one's genitalia and making other lewd or obscene gestures (copropraxia), and imitating others' gestures (echopraxia). Burping, vomiting, and retching have also been described as part of the clinical picture of Tourette's syndrome. Some complex, repetitive movements and sounds may be considered a compulsion when they are preceded by or associated with a feeling of anxiety or a fear that if

From the Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, 6550 Fannin, Suite 1801, Houston, TX 77030, where reprint requests should be addressed to Dr. Jankovic.

they are not promptly or properly executed, “something bad” will happen.

Simple phonic tics typically consist of sniffing, throat clearing, grunting, squeaking, screaming, coughing, barking, blowing, and making sucking sounds. Complex phonic tics include linguistically meaningful utterances and verbalizations, such as the shouting of obscenities, profanities, or otherwise socially inappropriate words or phrases (coprolalia), the repetition of someone else’s words or phrases (echolalia), and the repetition of one’s own utterances, particularly the last syllable, word, or phrase in a sentence (palilalia). Coprolalia, perhaps the most recognizable and certainly one of the most distressing symptoms of Tourette’s syndrome, is actually present in less than half of patients with Tourette’s syndrome. The true frequency of coprolalia, however, is unknown, because some patients are able to modify the utterances by using only fragments of the word, such as “sh” or “f,” and others have only “mental” coprolalia and do not actually utter the word.

Motor and phonic tics are often preceded by premonitory sensations, which consist of localizable paresthesia or discomfort; these sensations are temporarily relieved after the execution of the tic. Examples include a burning feeling in the eye before an eye blink, tension or a crick in the neck that is relieved by stretching the neck or jerking the head, a feeling of tightness or constriction that is relieved by extension of the arm or leg, nasal stuffiness before a sniff, dry or sore throat before throat clearing or grunting, and itching before a rotatory movement of the scapula.<sup>8</sup> Besides such local or regional premonitory sensations, there may be nonlocalizable and less specific premonitory phenomena, such as urges, anxiety, anger, or other psychic symptoms. Many patients report that in order to relieve the uncomfortable urge they have to repeat a particular movement until “it feels good” or “it feels just right.”<sup>9</sup>

The ability of patients to suppress their tics helps to differentiate tics from other hyperkinetic movement disorders such as chorea, dystonia, athetosis, myoclonus, and paroxysmal dyskinesias.<sup>10</sup> Many patients with Tourette’s syndrome note a reduction in the frequency and severity of their tics when they are concentrating on mental or physical tasks or sensations (such as playing a video game or having an orgasm). In addition to their temporary suppressibility, tics are also characterized by suggestibility, and by exacerbation with stress, excitement, boredom, fatigue, and exposure to heat. The frequency of tics may also increase during relaxation after a period of stress — thus, children often “release” their tics when they come home from school. Although the tics have traditionally been thought to disappear during sleep, a variety of sleep studies have demonstrated that motor and phonic tics may persist during all stages of sleep.<sup>11,12</sup> Tics can be troublesome for patients with

Tourette’s syndrome, because they cause embarrassment, interfere with social interactions, and can, at times, be quite painful or uncomfortable. In rare instances, they can cause secondary neurologic deficits, such as compressive cervical myelopathy as a result of violent head and neck tics.<sup>13</sup>

Tourette’s syndrome, the most common cause of tics, is manifested in a broad spectrum of motor and behavioral disturbances and affects males approximately three times as frequently as females. To aid in the diagnosis of Tourette’s syndrome, the Tourette Syndrome Classification Study Group<sup>14</sup> has formulated the following criteria for a definite diagnosis of Tourette’s syndrome: both multiple motor tics and one or more phonic tics must be present at some time during the illness, although not necessarily concurrently; tics must occur many times a day, nearly every day, or intermittently throughout a period of more than one year; the anatomical location, number, frequency, type, complexity, or severity of tics must change over time; the onset must occur before the age of 21 years; involuntary movements and noises must not be explainable by other medical conditions; and motor tics, phonic tics, or both must be witnessed directly by a reliable examiner at some point during the illness or be recorded by videotape or cinematography. These and other diagnostic criteria<sup>15,16</sup> are designed to assist in accurate diagnosis, in genetic-linkage studies, and in differentiating Tourette’s syndrome from other tic disorders (Table 1).<sup>17,18</sup>

Although these diagnostic criteria require that the onset occur before the age of 21 years, in 96 percent of patients the disorder is manifested by 11 years of age, typically beginning between 3 and 8 years of age.<sup>19</sup> According to one study, the average age at the onset of tics is 5.6 years, and tics usually become most severe at 10 years of age; by 18 years of age, half of patients with Tourette’s syndrome are free of tics.<sup>20</sup> Tics may persist into adulthood, although their severity is usually gradually diminished (Fig. 2). In the majority of cases, tics in adults represent the persistence or recurrence of childhood-onset tics,<sup>21</sup> but in rare instances, patients may have their first occurrence of tics during adulthood.<sup>22</sup> In these adults with new-onset tics, it is important to search for secondary causes such as infection, trauma, use of illicit drugs, exposure to neuroleptic drugs, and neuroacanthocytosis (Table 1).<sup>17,22</sup>

In addition to involuntary noises, some patients have speech dysfluencies that resemble developmental stuttering, and as many as half of all patients with developmental stuttering may have undiagnosed Tourette’s syndrome.<sup>23</sup> Except for tics, increased rates of blinking,<sup>24</sup> subtle oculomotor disturbances related to saccadic eye movements,<sup>25</sup> and other evidence of mild impairment of motor control (e.g., poor penmanship), the results of neurologic examination in patients with Tourette’s syndrome are normal.

**TABLE 1.** ETIOLOGIC CLASSIFICATION OF TICS.

<b>Primary causes</b>
Sporadic tics
Transient motor or phonic tics (for <1 yr)
Chronic motor or phonic tics (for >1 yr)
Adult-onset (recurrent) tics
Tourette's syndrome
Primary dystonia
Inherited tic disorders
Tourette's syndrome
Huntington's disease
Primary dystonia
Neuroacanthocytosis
Hallervorden-Spatz disease or neurodegeneration with brain iron accumulation type 1
Tuberous sclerosis
Wilson's disease
<b>Secondary causes</b>
Infections (e.g., encephalitis, Creutzfeldt-Jakob disease, neurosyphilis, Sydenham's chorea)
Drugs causing tardive tics (e.g., amphetamines, methylphenidate, pemoline, levodopa, cocaine, carbamazepine, phenytoin, phenobarbital, lamotrigine, antipsychotics, and other dopamine-receptor-blocking drugs)
Toxins (e.g., carbon monoxide)
Developmental problems (e.g., static encephalopathy, mental-retardation syndromes, chromosomal abnormalities, autistic-spectrum disorders [Asperger's syndrome])
Chromosomal disorders (e.g., Down's syndrome, Klinefelter's syndrome, XYY karyotype, fragile X syndrome, triple X syndrome, 9p mosaicism, partial trisomy 16, monosomy 9p, citrullinemia, Beckwith-Wiedemann syndrome)
Other (e.g., head trauma, stroke, neurocutaneous syndromes, schizophrenia, neurodegenerative diseases)
<b>Related manifestations and disorders</b>
Stereotypes, habits, and mannerisms
Self-injurious behavior
Motor restlessness
Akathisia
Compulsions
Excessive startle
Jumping Frenchmen of Maine syndrome

In addition to motor and phonic tics, patients with Tourette's syndrome often have a variety of behavioral symptoms, particularly those associated with attention-deficit-hyperactivity disorder and obsessive-compulsive disorder. A thorough discussion of the pathogenesis of these coexisting disorders is beyond the scope of this review.<sup>26,27</sup> These coexisting behavioral conditions often interfere more than tics do with overall functioning and with academic and work performance; if these disorders are left untreated, they may lead to social and emotional maladjustment. Although only 3 to 6 percent of school-aged children have attention-deficit-hyperactivity disorder,<sup>27</sup> a majority of patients with Tourette's syndrome have symptoms of attention-deficit-hyperactivity disorder, obsessive-compulsive disorder, or both at some time during the course of their illness (Fig. 1).<sup>28</sup> In many patients, the inability to pay attention is the result not only of coexisting attention-deficit-hyperactivi-

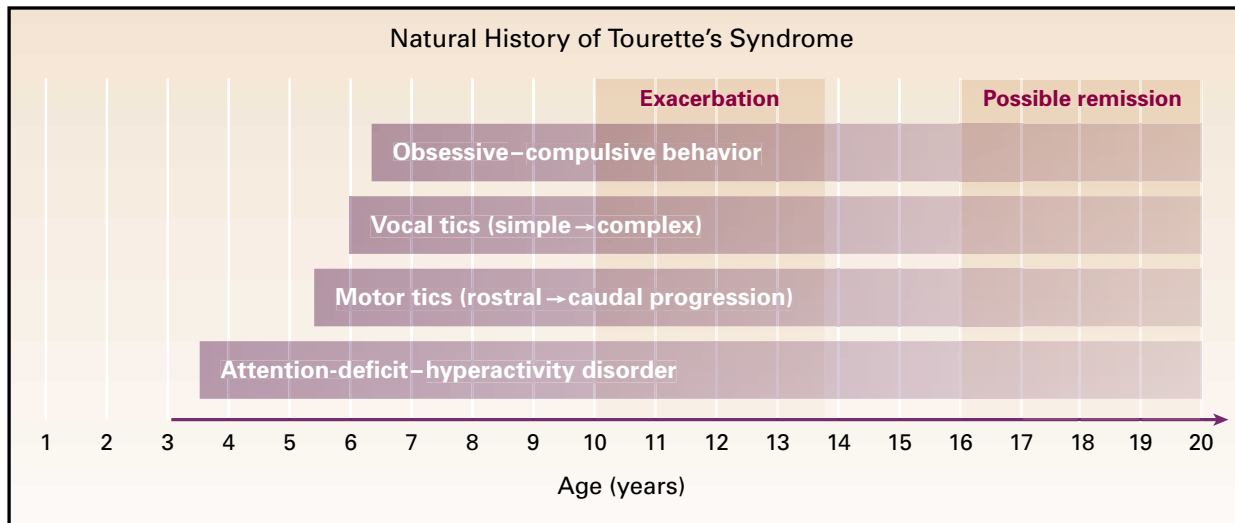
ty disorder but also of uncontrollable intrusions of thoughts or obsessive fixation of attention on irrelevant objects or topics, of the mental concentration that is exerted in an effort to suppress tics and premonitory urges, and of the sedative effects of the medications used to treat Tourette's syndrome.

That obsessive-compulsive disorder is a part of the spectrum of neurobehavioral manifestations of Tourette's syndrome has been well accepted for a long time.<sup>19</sup> Obsessions — characterized by intense, intrusive thoughts (such as worries about bodily waste and secretions); unfounded fears; a need for exactness, symmetry, evenness, and neatness; an excessive concern with matters of religion; perverse sexual thoughts; and intrusions of words, phrases, or music — can lead to the slowing of cognitive function.<sup>29</sup> Compulsions consist of subjective urges to perform meaningless and irrational rituals, such as checking, counting, cleaning, washing, touching, smelling, hoarding, and rearranging. Obsessive-compulsive disorder is now considered to be a multidimensional condition that can occur alone as a primary (idiopathic or familial) disorder, as a coexisting disorder in patients with Tourette's syndrome, or as a result of a variety of lesions in the frontal-limbic-subcortical circuits.<sup>30</sup>

Other behavioral problems associated with Tourette's syndrome include poor impulse control and an inability to control anger, as a result of which some patients may have outbursts of temper, episodic attacks of rage, emotional storms, inappropriate sexual aggressiveness, antisocial or oppositional behavior, and symptoms of anxiety and depression. One of the most distressing symptoms of Tourette's syndrome is self-injurious behavior.<sup>2,6</sup> Commonly, such behavior involves the compulsive, repetitive inflicting of damage to the skin by biting, scratching, cutting, engraving,<sup>6</sup> or hitting (particularly in the eye and throat), often accompanied by an irresistible urge (obsession). It has also been reported that Tourette's syndrome is frequently associated with migraine headaches, which were present in 26.6 percent of patients in one study.<sup>31</sup>

## PATHOGENESIS

Various biochemical, imaging, neurophysiological, and genetic studies support the notion that Tourette's syndrome is an inherited, developmental disorder of synaptic neurotransmission resulting in the disinhibition of the cortico-striatal-thalamic-cortical circuitry.<sup>1</sup> Although postmortem neuropathological examinations of the brains of patients with Tourette's syndrome have not revealed any specific pathologic changes,<sup>32</sup> the basal ganglia, particularly the caudate nucleus and the inferior prefrontal cortex, have been implicated in the pathogenesis of Tourette's syndrome, as well as in that of obsessive-compulsive disorder and attention-deficit-hyperactivity disorder.<sup>33</sup> There are no animal models of Tourette's syndrome,



**Figure 2.** The Natural History of Tourette's Syndrome.

but several families of horses with equine self-mutilation syndrome have been described that have features resembling human Tourette's syndrome.<sup>34</sup>

#### Neuroimaging

Although standard anatomical neuroimaging studies in patients with Tourette's syndrome are unremarkable, volumetric magnetic resonance imaging (MRI) studies have suggested that the normal asymmetry of the basal ganglia, with the volume normally larger on the right than the left, is lost in Tourette's syndrome, supporting the notion that there is a developmental abnormality.<sup>33</sup> Functional MRI studies in patients with Tourette's syndrome have shown decreased neuronal activity during periods of suppression in the ventral globus pallidus, putamen, and thalamus and increased activity in the prefrontal, parietal, temporal, and cingulate cortical areas normally involved in the inhibition of unwanted impulses.<sup>33</sup> In one study, positron-emission tomography (PET) with <sup>18</sup>F-fluorodeoxyglucose showed two patterns: evidence of increased metabolic activity in the lateral premotor and supplementary motor cortexes and in the midbrain (pattern 1) and decreased metabolic activity in the caudate and thalamic areas (limbic basal-ganglia-thalamocortical projection system) (pattern 2).<sup>35</sup> Using PET with [<sup>15</sup>O]water, Stern et al.<sup>36</sup> found increased activity in the areas responsible for sensorimotor, language, executive, and paralimbic function and in the frontal subcortical area that was temporally related to the motor and phonic tics and the irresistible urge that precedes these behaviors.

#### Neurophysiology

Studies using back-averaging electroencephalographic techniques have found that the premovement

potential (Bereitschaftspotential) is absent in some patients before the execution of motor tics. This finding suggests that the movements are truly involuntary, but this potential may be present in other patients, providing evidence of a voluntary component to some tics.<sup>37</sup> Furthermore, studies using transcranial magnetic stimulation have demonstrated that the cortical silent period is shortened and intracortical inhibition is defective in patients with Tourette's syndrome and in patients with obsessive-compulsive disorder and tics. This provides a possible explanation for the decreased motor inhibition and intrusive phenomena in Tourette's syndrome and obsessive-compulsive disorder.

#### Neurochemistry

An alteration in the central neurotransmitters has been suggested as a cause of Tourette's syndrome, chiefly because there have been relatively consistent responses to the modulation of the dopaminergic system. The few brains that have been studied post mortem have had low levels of serotonin in the brain stem, low levels of glutamate in the globus pallidus, and low levels of cyclic AMP in the cortex.<sup>3,32</sup> The observed increase in the rate of binding of 3H-mazindol to the presynaptic dopamine-uptake-carrier sites suggests that Tourette's syndrome represents a developmental disorder resulting in dopaminergic hyperinnervation of the ventral striatum and the associated limbic system.<sup>3</sup> With the use of single-photon-emission computed tomography or PET, some studies,<sup>39</sup> but not all,<sup>40</sup> have demonstrated increased density of the presynaptic dopamine transporter and the postsynaptic D2 dopamine receptor and have suggested that there is abnormal regulation of dopamine release and uptake in Tourette's syndrome.<sup>41</sup>

### Genetics

Finding a genetic marker, and ultimately the gene that may be responsible for the disorder, has been the highest priority in research on Tourette's syndrome during the past decade. Unfortunately, despite a concerted effort by many investigators, Tourette's syndrome genes have thus far remained elusive. A systematic genome scan involving 76 affected families with a total of 110 pairs of siblings showed two regions, 4q and 8p, with increased lod scores, suggesting that these loci may contain Tourette's syndrome-related genes.<sup>42</sup> Other genetic studies have found possible associations with various candidate genes, but their relevance to the pathogenesis of Tourette's syndrome has been questioned. Future genetic studies must consider the common observation that both parents of a child with Tourette's syndrome often have Tourette's syndrome or a forme fruste of it. Such bilineal transmission is present in 25 to 41 percent of families with Tourette's syndrome.<sup>43,44</sup> Twin studies, which have found 89 to 94 percent concordance for Tourette's syndrome, also provide strong evidence of a genetic cause.<sup>45</sup> In one study involving 16 pairs of monozygotic twins, low birth weight was a strong predictor of more severe tics.<sup>45</sup> Other factors that may influence the expression of a Tourette's syndrome gene include maternal life stress and nausea and vomiting during the first trimester of pregnancy.<sup>46</sup>

### Immunology

The potential role of antecedent infection with group A beta-hemolytic streptococcus and the consequent presence of antineuronal antibodies have been explored in patients with a variety of neurologic disorders, including Sydenham's chorea and Tourette's syndrome.<sup>47-49</sup> Evidence cited in support of the immunologic theory of Tourette's syndrome includes elevated titers of antistreptococcal antibodies in some patients,<sup>50</sup> the frequent presence of B lymphocyte antigen D8/17,<sup>51</sup> and increased levels of antineuronal antibodies against putamen in patients with Tourette's syndrome.<sup>52</sup> There is, however, no relation between the presence of the antineuronal antibodies and the age at onset, the severity of tics, or the presence of coexisting disorders.<sup>52</sup> Although streptococcal infection may trigger the onset of symptoms in a small subgroup of patients with Tourette's syndrome, the relation among group A beta-hemolytic streptococcus, antineuronal antibodies, and Tourette's syndrome has yet to be resolved, and further studies are needed.<sup>53</sup> Because of uncertainties about the possible causal relation between streptococcal infection and Tourette's syndrome and because of potential risks, immunologic therapies — such as plasmapheresis, the use of intravenous immune globulin,<sup>54</sup> and the administration of antibiotics for acute exacerbations of the symptoms of Tourette's syndrome — are currently considered to be unwarranted.<sup>55</sup>

### Epidemiology

The epidemiology of Tourette's syndrome is not precisely defined.<sup>43,56</sup> Observational studies in public schools have suggested that the prevalence of Tourette's syndrome is about 0.7 percent,<sup>43,57</sup> but estimates of its prevalence have varied markedly, with some estimates as high as 4.2 percent when all types of tic disorders are included.<sup>58,59</sup> There are many reasons for this wide variation, the most important of which are different methods of ascertainment of cases, different study populations, and different clinical criteria.

### TREATMENT

The first step in the treatment of a patient with Tourette's syndrome is the proper education of the patient, family members, teachers, and other persons who interact with the patient. Parents, educators, and physicians must work as partners in advocating the best possible school environment for children with Tourette's syndrome. National and local support groups, such as the Tourette Syndrome Association (<http://www.tsa-usa.org>), can provide additional information and can serve as a valuable resource for patients and their families. Given the time and effort that various behavioral therapies require on the part of the patient, the family members, and the therapist, it is not surprising that even if they are effective, the benefits of such therapies are usually only temporary. These therapies, however, may be useful ancillary techniques for patients in whom the response to other therapies, including pharmacotherapy, is not entirely satisfactory.<sup>60</sup> Medications are usually considered when symptoms begin to interfere with peer relationships, social interactions, academic or job performance, or activities of daily living. Because of the broad range of neurologic and behavioral manifestations and their varying severity, therapy for Tourette's syndrome must be individualized and tailored specifically to the needs of the patient, and the most troublesome symptoms should be targeted first (Table 2).<sup>61</sup> To avoid unnecessary changes that might be made in response to normal variations in symptoms during the natural course of the disease, each medication and each dosage regimen should be given an adequate trial.

### Treatment of Tics

In treating tics, the goal should not be to eliminate all the tics completely but to relieve tic-related discomfort or embarrassment and to achieve a degree of control of tics that allows the patient to function as normally as possible. A number of rating scales for tics have been used in various studies of treatments for tics.<sup>62</sup> Although there have been only a limited number of double-blind, placebo-controlled trials, the dopamine-receptor-blocking drugs (neuroleptics) are considered the most effective anti-tic agents (Table 2). Haloperidol and pimozide are the

only neuroleptic drugs currently approved by the Food and Drug Administration for the treatment of Tourette's syndrome. In one randomized, double-blind, controlled study, pimozide was found to be superior to haloperidol with respect to efficacy and side effects.<sup>63</sup> Some clinicians, however, prefer risperidone,<sup>64</sup> fluphenazine, thioridazine, trifluoperazine, molindone, thiothixene, or tiapride. It is not clear whether the atypical neuroleptics, such as clozapine, olanzapine, or quetiapine, will be effective in the treatment of tics and other manifestations of Tourette's syndrome, but ziprasidone was found in one study to diminish the severity of tics by 35 percent.<sup>65</sup> Tetrabenazine, a drug that depletes monoamine and blocks the dopamine receptors (but is not yet available in the United States), is a powerful anti-tic drug, and it has an advantage over the conventional neuroleptics in that it does not cause tardive dyskinesia.<sup>66</sup>

Other side effects that may be associated with neuroleptics include sedation, depression, weight gain, school phobia, and hepatotoxicity. In addition, pimozide may prolong the QT interval, and it is therefore recommended that electrocardiography be performed before a patient starts taking pimozide, three months after it is begun, and at least once a year thereafter.

Other drugs found to be useful in the treatment of tics include clonazepam, pergolide, cannabinoids, nicotine gum, and transdermal nicotine patches, but none of these drugs have been studied in well-designed, placebo-controlled trials.<sup>67</sup> Focal motor and vocal tics have also been treated successfully with injections of botulinum toxin in the affected muscles.<sup>68-70</sup> Such local chemical denervation not only ameliorates involuntary movements but may also eliminate the premonitory sensory component. The benefits last three to four months, on average, and no serious complications have been reported. Although stereotactic surgery has not generally been found to be useful in the treatment of tics, a preliminary report of the case of a 42-year-old man whose severe motor and phonic tics have been controlled by high-frequency deep-brain stimulation of the thalamus is encouraging.<sup>71</sup>

#### Treatment of Coexisting Behavioral Symptoms

Behavioral modification and adjustments in the school and classroom environments play an important part in the treatment of patients with Tourette's syndrome and are helpful in raising self-esteem and improving motivation.<sup>72</sup> It is beyond the scope of this review to provide a comprehensive description of drug treatment for behavioral disturbances.<sup>26,73,74</sup>

#### Attention-Deficit-Hyperactivity Disorder

Central nervous system stimulants, such as methylphenidate, controlled-release methylphenidate, dextroamphetamine, a mixture of amphetamine salts (Adderall), and pemoline, are clearly the most effective

**TABLE 2. DRUG TREATMENT OF TOURETTE'S SYNDROME.\***

DRUG	INITIAL DOSE†
	mg/day
Dopamine-receptor blockers for tics	
Fluphenazine	1.0
Pimozide	2.0
Haloperidol	0.5
Risperidone	0.5
Ziprasidone	20.0
Thiothixene	1.0
Trifluoperazine	1.0
Molindone	5.0
Dopamine deplete for tics	
Tetrabenazine	25.0
CNS stimulants for ADHD	
Methylphenidate	5.0
Pemoline	18.7
Dextroamphetamine	5.0
Noradrenergic drugs for impulse control and ADHD	
Clonidine	0.1
Guanfacine	1.0
Serotonergic drugs for OCD	
Fluoxetine	20.0
Clomipramine	25.0
Sertraline	50.0
Paroxetine	20.0
Fluvoxamine	50.0
Venlafaxine	25.0

\*CNS denotes central nervous system, ADHD attention-deficit-hyperactivity disorder, and OCD obsessive-compulsive disorder.

†Adult dosages are given; they must be adjusted for children.

agents in the treatment of attention-deficit-hyperactivity disorder.<sup>75</sup> These agents have also been found useful as a short-term therapy for conduct disorders.<sup>76</sup> In addition to the possible development of tolerance, there are other potential adverse effects of these stimulant drugs, such as nervousness, irritability, insomnia, anorexia, abdominal pain, and headaches.<sup>77</sup> Pemoline can produce hepatotoxic effects in rare instances. Although central nervous system stimulants may initially increase the frequency and intensity of tics, with continued use these drugs can be well tolerated without sustained exacerbation of tics.<sup>78,79</sup> The antidopaminergic drugs can be combined with the central nervous system stimulants if the latter produce an unacceptable exacerbation of tics.

Although attention-deficit-hyperactivity disorder was initially considered to be a noradrenergic disorder,<sup>80</sup> recent studies have provided evidence that the beneficial effects of methylphenidate on the disorder are mediated by the serotonin system.<sup>81</sup> The  $\alpha_2$ -adrenergic agonists are also useful in the treatment of attention-deficit-hyperactivity disorder, particularly if

central nervous system stimulants are not well tolerated or are contraindicated. Clonidine, a presynaptic  $\alpha_2$ -adrenergic agonist that is used as an antihypertensive drug because it decreases plasma norepinephrine levels, reduces the symptoms of attention-deficit-hyperactivity disorder and impulse-control problems, and may also ameliorate tics. The drug is also available in the form of a transdermal patch. Guanfacine is pharmacologically similar to clonidine and may be effective in patients in whom clonidine fails to control behavioral symptoms.<sup>82</sup> Guanfacine may have some advantages over clonidine in that it has a longer half-life, appears to be less sedating, and produces less hypotension. Although less effective than methylphenidate in controlling attention-deficit-hyperactivity disorder, the drugs have an advantage over methylphenidate in that they do not increase the frequency or severity of tics.<sup>83</sup> The most frequently encountered side effects of clonidine and guanfacine include sedation, dry mouth, itchy eyes, dizziness, headaches, fatigability, and postural hypotension. Selegiline, a monoamine oxidase B inhibitor used primarily in the treatment of Parkinson's disease, has also been found to be effective in controlling the symptoms of attention-deficit-hyperactivity disorder without exacerbating tics.<sup>84</sup> Other drugs occasionally used in the treatment of mild cases of attention-deficit-hyperactivity disorder include tricyclic antidepressants, such as imipramine, nortriptyline, and desipramine. Because of potential cardiotoxicity, an electrocardiographic or cardiac evaluation is recommended before the initiation of desipramine therapy, and follow-up electrocardiography should be performed every three to six months.

#### **Obsessive-Compulsive Disorder**

The selective serotonin-reuptake inhibitors are clearly the most effective drugs in the treatment of obsessive-compulsive disorder.<sup>85,86</sup> These include fluoxetine, fluvoxamine, clomipramine, paroxetine, sertraline, venlafaxine, and citalopram. Although there have been no comparative trials, long-term clinical trials indicate that fluoxetine, sertraline, and fluvoxamine are among the best tolerated of the selective serotonin-reuptake inhibitors.<sup>85,87</sup> In some cases that are refractory to treatment, selective serotonin-reuptake inhibitors may need to be combined with buspirone, clonazepam, lithium, and even neuroleptics.<sup>88</sup> When a combination of drugs is used, it is prudent practice to discuss with the patients potential adverse reactions, including the so-called serotonin syndrome (characterized by confusion, hypomania, agitation, myoclonus, hyperreflexia, sweating, tremor, diarrhea, and fever), withdrawal phenomena, and possible extrapyramidal side effects.<sup>89</sup> The selective serotonin-reuptake inhibitors are effective not only in the treatment of obsessive-compulsive disorder associated with Tourette's syndrome but also in the management of associated

anxiety and social phobias.<sup>90</sup> In patients with extremely severe and disabling obsessive-compulsive disorder in whom optimal pharmacologic therapy has failed, psychosurgery — either limbic leucotomy or cingulotomy — may be considered as a last resort.<sup>91,92</sup>

### CONCLUSIONS

The progress in research on Tourette's syndrome has been extraordinary.<sup>93</sup> Coupled with a growing recognition of the richness of the clinical phenomenology of Tourette's syndrome and related disorders and fueled by remarkable advances in the neurosciences, research promises to provide new insights into this complex neurobehavioral disorder. Since Tourette's syndrome is considered a model disorder for the study of the interaction among the developmental, neurobiologic, and behavioral systems, it is likely that these findings will enhance our understanding not only of Tourette's syndrome but of many other neurologic and behavioral disorders as well.

### REFERENCES

1. Leckman JF, Cohen DJ, Goetz CG, Jankovic J. Tourette syndrome: pieces of the puzzle. In: Cohen DJ, Jankovic J, Goetz CG, eds. Tourette syndrome. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:369-90.
2. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 2000;123:425-62.
3. Singer HS. Current issues in Tourette syndrome. *Mov Disord* 2000;15:1051-63.
4. Kushner HI. From Gilles de la Tourette's disease to Tourette syndrome: a history. *CNS Spectrum* 1999;4(2):24-35.
5. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev Med Child Neurol* 2000;42:436-47.
6. Jankovic J, Sekula SL. Dermatological manifestations of Tourette syndrome and obsessive-compulsive disorder. *Arch Dermatol* 1998;134:113-4.
7. Hogan MB, Wilson NW. Tourette's syndrome mimicking asthma. *J Asthma* 1999;36:253-6.
8. Jankovic J. Phenomenology and classification of tics. *Neurol Clin* 1997;15:267-75.
9. Leckman JF, Walker DE, Goodman WK, Pauls DL, Cohen DJ. "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. *Am J Psychiatry* 1994;151:675-80.
10. Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. *Ann Neurol* 1995;38:571-9.
11. Rothenberger A, Kostanecka T, Kinkelbur J, Cohrs S, Woerner W, Hajak G. Sleep and Tourette syndrome. In: Cohen DJ, Jankovic J, Goetz CG, eds. Tourette syndrome. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:245-59.
12. Hanna PA, Jankovic J. Sleep and tic disorders. In: Chokroverty S, Hening Walters A, eds. *Sleep and movement disorders*. Woburn, Mass.: Butterworth-Heinemann (in press).
13. Krauss JK, Jankovic J. Severe motor tics causing cervical myelopathy in Tourette's syndrome. *Mov Disord* 1996;11:563-6.
14. The Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. *Arch Neurol* 1993;50:1013-6.
15. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM-IV. Washington, D.C.: American Psychiatric Association, 1994:100-5.
16. Robertson MM, Banerjee S, Kurlan R, et al. The Tourette Syndrome Diagnostic Confidence Index: development and clinical associations. *Neurology* 1999;53:2108-12.
17. Jankovic J. Differential diagnosis and etiology of tics. In: Cohen DJ, Jankovic J, Goetz CG, eds. Tourette syndrome. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:15-29.
18. Kurlan R, Behr J, Medved L, Como P. Transient tic disorder and the clinical spectrum of Tourette's syndrome. *Arch Neurol* 1988;45:1200-1.

19. Robertson MM. The Gilles de la Tourette syndrome: the current status. *Br J Psychiatry* 1989;154:147-69.
20. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics* 1998;102:14-9.
21. Goetz CG, Tanner CM, Stebbins GT, Leipzig G, Carr WC. Adult tics in Gilles de la Tourette's syndrome: description and risk factors. *Neurology* 1992;42:784-8.
22. Chouinard S, Ford B. Adult onset tic disorders. *J Neurol Neurosurg Psychiatry* 2000;68:738-43.
23. Abwender DA, Trinidad KS, Jones KR, Como PG, Hymes E, Kurlan R. Features resembling Tourette's syndrome in developmental stutterers. *Brain Lang* 1998;62:455-64.
24. Tullen JHM, Azzolini M, de Vries JA, Groeneveld WH, Passchier J, van De Wetering BJ. Quantitative study of spontaneous eye blinks and eye tics in Gilles de la Tourette's syndrome. *J Neurol Neurosurg Psychiatry* 1999;67:800-2.
25. Farber RH, Swerdlow NR, Clementz BA. Saccadic performance characteristics and the behavioural neurology of Tourette's syndrome. *J Neurol Neurosurg Psychiatry* 1999;66:305-12.
26. Elia J, Ambrosini PJ, Rapoport JL. Treatment of attention-deficit-hyperactivity disorder. *N Engl J Med* 1999;340:780-8.
27. Goldman LS, Genel M, Bezman RJ, Slanetz PJ. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *JAMA* 1998;279:1100-7.
28. Coffey BJ, Park KS. Behavioral and emotional aspects of Tourette syndrome. *Neurol Clin* 1997;15:277-89.
29. Singer HS, Schuerholz LJ, Denckla MB. Learning difficulties in children with Tourette syndrome. *J Child Neurol* 1995;10:Suppl 1:S58-S61.
30. Berthier ML, Kulisevsky J, Gironell A, Heras JA. Obsessive-compulsive disorder associated with brain lesions: clinical phenomenology, cognitive function, and anatomic correlates. *Neurology* 1996;47:353-61.
31. Barabas G, Matthews WS, Ferrari M. Tourette's syndrome and migraine. *Arch Neurol* 1984;41:871-2.
32. Swerdlow NR, Young AB. Neuropathology in Tourette syndrome: an update. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:151-61.
33. Peterson BS. Neuroimaging studies of Tourette syndrome: a decade of progress. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:179-96.
34. Dodman NH, Normile JA, Shuster L, Rand W. Equine self-mutilation syndrome (57 cases). *J Am Vet Med Assoc* 1994;204:1219-23. [Erratum, *J Am Vet Med Assoc* 1994;205:1179.]
35. Eidelberg D, Moeller JR, Antonini A, et al. The metabolic anatomy of Tourette's syndrome. *Neurology* 1997;48:927-34.
36. Stern E, Silbersweig DA, Chee K-Y, et al. A functional neuroanatomy of tics in Tourette syndrome. *Arch Gen Psychiatry* 2000;57:741-8.
37. Hallett M. Neurophysiology of tics. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:237-44.
38. Greenberg BD, Ziemann U, Cora-Locatelli G, et al. Altered cortical excitability in obsessive-compulsive disorder. *Neurology* 2000;54:142-7.
39. Wolf SS, Jones DW, Knable MB, et al. Tourette syndrome: prediction of phenotypic variation in monozygotic twins by caudate nucleus D2 receptor binding. *Science* 1996;273:1225-7.
40. Meyer P, Bohnen NI, Minoshima S, et al. Striatal presynaptic monoaminergic vesicles are not increased in Tourette's syndrome. *Neurology* 1999;53:371-4.
41. Ernst M, Zametkin AJ, Jons PH, Matochik JA, Pascualvaca D, Cohen RM. High presynaptic dopamine activity in children with Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 1999;38:86-94.
42. The Tourette Syndrome Association International Consortium for Genetics. A complete genome screen in sib pairs affected by Gilles de la Tourette syndrome. *Am J Hum Genet* 1999;65:1428-36.
43. Hanna PA, Janjua FN, Contant CF, Jankovic J. Bilineal transmission in Tourette syndrome. *Neurology* 1999;53:813-8.
44. Lichter DG, Dmochowski J, Jackson LA, Trinidad KS. Influence of family history on clinical expression of Tourette's syndrome. *Neurology* 1999;52:308-16.
45. Hyde TM, Aaronson BA, Randolph C, Rickler KC, Weinberger DR. Relationship of birth weight to the phenotypic expression of Gilles de la Tourette's syndrome in monozygotic twins. *Neurology* 1992;42:652-8.
46. Leckman JF, Dolnansky ES, Hardin MT, et al. Perinatal factors in the expression of Tourette's syndrome: an exploratory study. *J Am Acad Child Adolesc Psychiatry* 1990;29:220-6.
47. Allen AJ. Group A streptococcal infections and childhood neuropsychiatric disorders: relationships and therapeutic implications. *CNS Drugs* 1997;8:267-75.
48. Hallett JJ, Harling-Berg CJ, Knopf PM, Stopa EG, Kiessling LS. Antistriatal antibodies in Tourette syndrome cause neuronal dysfunction. *J Neuroimmunol* 2000;111:195-202.
49. Cardona F, Orefici G. Group A streptococcal infections and tic disorders in an Italian pediatric population. *J Pediatr* 2001;138:71-5.
50. Swedo SE, Leonard HL, Mittleman BB, et al. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. *Am J Psychiatry* 1997;154:110-2.
51. Murphy TK, Goodman WK, Fudge MW, et al. B lymphocyte antigen D8/17: a peripheral marker for childhood-onset obsessive-compulsive disorder and Tourette's syndrome? *Am J Psychiatry* 1997;154:402-7.
52. Singer HS, Giuliano JD, Hansen BH, et al. Antibodies against human putamen in children with Tourette syndrome. *Neurology* 1998;50:1618-24.
53. Kurlan R. Tourette's syndrome and "PANDAS": will the relation bear out? Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Neurology* 1998;50:1530-4.
54. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999;354:1153-8.
55. Hamilton CS, Garvey MA, Swedo SE. Therapeutic implications of immunology for tics and obsessive-compulsive disorder. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:311-8.
56. Scahill L, Tanner C, Dure L. The epidemiology of tics and Tourette syndrome in children and adolescents. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:261-71.
57. Comings DE, Himes JA, Comings BG. An epidemiologic study of Tourette's syndrome in a single school district. *J Clin Psychiatry* 1990;51:463-9.
58. Costello EJ, Angold A, Burns BJ, et al. The Great Smoky Mountains Study of Youth: goals, design, methods, and the prevalence of DSM-III-R disorders. *Arch Gen Psychiatry* 1996;53:1129-36.
59. Mason A, Banerjee S, Eapen V, Zeitlin H, Robertson MM. The prevalence of Tourette syndrome in a mainstream school population. *Dev Med Child Neurol* 1998;40:292-6.
60. Piacentini J, Chang S. Behavioral treatments for Tourette syndrome and tic disorders: state of the art. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:319-31.
61. Jankovic J. Gilles de la Tourette syndrome. *Curr Ther* 1999;51:915-9.
62. Goetz CG, Kampoliti K. Rating scales and quantitative assessment of tics. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:31-42.
63. Sallee FR, Nesbitt L, Jackson C, Sine L, Sethuraman G. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997;154:1057-62.
64. Bruun RD, Budman CL. Risperidone as a treatment for Tourette's syndrome. *J Clin Psychiatry* 1996;57:29-31.
65. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000;39:292-9.
66. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 1997;48:358-62.
67. Lang AE. Update on the treatment of tics. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:355-62.
68. Kwak CH, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. *Arch Neurol* 2000;57:1190-3.
69. Scott BL, Jankovic J, Donovan DT. Botulinum toxin injection into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. *Mov Disord* 1996;11:431-3.
70. Marras C, Andrews D, Sime EA, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001;56:605-10.
71. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet* 1999;353:724.
72. Peterson BS, Cohen DJ. The treatment of Tourette's syndrome: multimodal, developmental intervention. *J Clin Psychiatry* 1998;59:Suppl 1:62-72.
73. Zametkin AJ, Ernst M. Problems in the management of attention-deficit-hyperactivity disorder. *N Engl J Med* 1999;340:40-6.
74. Riddle MA, Carlson J. Clinical psychopharmacology for Tourette syndrome and associated disorders. In: Cohen DJ, Jankovic J, Goetz CG, eds. *Tourette syndrome*. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001:343-54.
75. Manos MJ, Short EJ, Findling RL. Differential effectiveness of meth-

ylphenidate and Adderall in school-age youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1999;38:813-9.

76. Klein RG, Abikoff H, Klass E, Ganeles D, Seese LM, Pollack S. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Arch Gen Psychiatry* 1997;54:1073-80.

77. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997;100:662-6.

78. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Grossman S. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry* 1999;56:330-6.

79. Law SE, Schachar RJ. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry* 1999;38:944-51.

80. Biederman J, Spencer T. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. *Biol Psychiatry* 1999;46:1234-42.

81. Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG. Role of serotonin in the paradoxical calming effect of psychostimulants in hyperactivity. *Science* 1999;283:397-401.

82. Hunt RD, Arnsten AFT, Asbell MD. An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1995;34:50-4.

83. Horrigan JP, Barnhill LJ. Guanfacine for treatment of attention-deficit hyperactivity disorder in boys. *J Child Adolesc Psychopharmacol* 1995;5:215-23.

84. Feigin A, Kurlan R, McDermott MP, et al. A controlled trial of deprenyl in children with Tourette's syndrome and attention deficit hyperactivity disorder. *Neurology* 1996;46:965-8.

85. Flament MF, Bisslerbe J-C. Pharmacologic treatment of obsessive-compulsive disorder: comparative studies. *J Clin Psychiatry* 1997;58:Suppl 12:18-22.

86. Grados M, Scahill L, Riddle MA. Pharmacotherapy in children and adolescents with obsessive-compulsive disorder. *Child Adolesc Psychiatric Clin North Am* 1999;8:617-34.

87. Milanfranchi A, Ravagli S, Lensi P, Marazziti D, Cassano GB. A double-blind study of fluvoxamine and clomipramine in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol* 1997;12:131-6.

88. Goodman WK, Ward HE, Murphy TK. Biologic approaches to treatment-refractory obsessive-compulsive disorder. *Psychiatric Ann* 1998;28:641-9.

89. Kurlan R. Acute parkinsonism induced by the combination of a serotonin reuptake inhibitor and a neuroleptic in adults with Tourette's syndrome. *Mov Disord* 1998;13:178-9.

90. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 2001;344:1279-85.

91. Rauch SL, Baer L, Cosgrove GR, Jenike MA. Neurosurgical treatment of Tourette's syndrome: a critical review. *Compr Psychiatry* 1995;36:141-56.

92. Baer L, Rauch SL, Ballantine HT Jr, et al. Cingulotomy for intractable obsessive-compulsive disorder: prospective long-term follow-up of 18 patients. *Arch Gen Psychiatry* 1995;52:384-92.

93. Cohen DJ, Jankovic J, Goetz CG, eds. Tourette syndrome. Vol. 85 of *Advances in neurology*. Philadelphia: Lippincott Williams & Wilkins, 2001.

Copyright © 2001 Massachusetts Medical Society.

---

#### POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

---

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal's* Editorial Offices.

---