Tourette Syndrome and Other Tic Disorders

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Synonyms, Key Words, and Related Terms

Tourette's syndrome, TS, Gilles de la Tourette's syndrome, GTS, Tourette's disorder, DSM-IV-TR 307.23, Tourette disorder, Gilles de la Tourette syndrome, motor tics, vocal tics, coprolalia, coprophrasia, stereotypic movement disorder, chronic motor or vocal tic disorder, DSM-IV-TR 307.22, stereotyped motor movement, stereotyped vocalization, transient tic disorder, DSM-IV-TR 307.21, tic disorder not otherwise specified, DSM-IV-TR 307.20, Tourette Syndrome Study Group criteria, TSSG criteria, phonic tic disorder

Introduction

Background

Definition

Tourette syndrome (TS) is defined as a chronic idiopathic syndrome with both motor and vocal tics beginning before adulthood (APA, 2000; TSCS Group, 1993) (see

). Tics are repetitive, stereotyped movements or vocalizations, such as blinking, sniffing, touching the ground, or tensing the abdomen. However, this definition is remarkably sterile compared with patients' actual experience of TS. Furthermore, although TS is diagnosed on the basis of tics, these are not always the most important symptom for a patient with TS.

Brief history

A historical example of TS is provided by Samuel Johnson (1709-1784), the author of the first good English dictionary and the subject of Boswell's biography (McHenry, 1967; Murray, 1979). Many of those who met him were surprised by his repetitive "nervous movements," and he voiced repeated word fragments or other sounds. All these were suppressible with an effort of will, yet they were clearly not voluntary in the usual sense, as they were present even in situations that embarrassed him.

On one occasion, Johnson called his movement "involuntary," yet on another occasion, he called them a "bad habit." He touched objects in a stereotyped fashion, went through a complex ritual on passing through a doorway, and had excessive worries about his religious status and health. Additionally, he suffered from episodes of depression and ate, even in polite company, "like a wild animal." However, he was one of the great minds of his day, and he demonstrated remarkable persistence and clever wit in the face of repeated adversity.

Some of Johnson's contemporaries believed his odd behavior was a psychological disturbance, while others believed it was a variant of rheumatic chorea. Now, we would consider his symptoms reasonably typical of TS, though without further examination, the diagnosis obviously cannot be determined with certainty.

Current understanding

Originally, TS was believed to be a rare and severe disorder, whereas now TS is understood to be less rare and often mild. TS is widely misunderstood by the lay public, and many people are still unaware that cursing tics affect only a minority of people with TS. To some extent, this confusion reflects the medical community's historical ambivalence about the nature of tic disorders.

One of the first descriptions of tics in the medical literature appeared in 1825, when the French physician Jean Itard described 10 people with repetitive behaviors, including complex movements and inappropriate words. (For historical references, see Kushner, 1999.) However, the current conception of TS can be traced to later in the century. The influential physician Jean-Martin Charcot had made a career of neurological nosology, trying to separate illnesses by means of long-term clinical observation. When he turned his attention to tics, he assigned his resident, George Gilles de la Tourette, to report on a few patients they had treated at the Salpêtrière Hospital, supplemented by cases he found in the literature. The goal was to define an illness distinct from hysteria and from chorea.

Gilles de la Tourette had previously shown interest in other complex movements, including reports from other countries of unusual culture-bound movement disorders. In his 1885 paper, *Study of a Nervous Affliction,* he concluded that a new clinical category should be defined (Gilles de la Tourette, 1885; Kushner, 1999). For Charcot and his resident, "convulsive tic illness" differed from other choreiform disorders and

from hysteria in several ways: Mainly, they thought it was untreatable, chronic, progressive, and hereditary. Although Charcot persisted in his efforts to distinguish "Gilles de la Tourette's tic disease" from other illnesses, his contemporaries generally did not agree.

Over the next century, little real progress was made, yet many argued vigorously for one theory or another to explain and treat patients with tics. One popular theme was that tics resulted from a brain lesion, similar to those underlying postinfectious abnormal movements of rheumatic chorea or encephalitis lethargica. Another idea was that tics, like signs of hysteria or the obsessions often observed in people with tics, could be understood and treated best by using Freud's psychoanalytic theories. Some believed that tics reflected normal mechanisms of habit formation gone somewhat awry. The problem shared by all these arguments was that they were based on limited and uncontrolled clinical experience. Generally, 1 or 2 patients, which often representing an author's entire clinical experience with TS, were discussed only to support the author's preconceived notions of causation and treatment. Most writers confused treatment response with etiology.

In the US, the psychoanalytic view prevailed for much of the 20th century. Unfortunately, psychoanalysis does not substantially help tics, and it rests on an untestable theory. In the 1970s, a coalition of clinicians and patient families determinedly assailed the psychoanalytic view of tic disorders. Drs Arthur and Elaine Shapiro, with Bill and Eleanor Pearl of the fledgling Tourette Syndrome Association (TSA), used the efficacy of haloperidol, compelling self-reports from patients, and well-chosen publicity as weapons with which to bludgeon the psychodynamic approach in the public eye. In a fervent rebellion against anything that the public might connect with psychoanalysis, publicity consistently emphasized that TS is a "physical, not a mental or emotional problem" and that TS "is a neurological disorder" (Kushner, 1999).

While these comments made good publicity, they simplistically identify medical specialty with etiology. They also oversimplify the condition; after all, tics are often complex phenomena with sensory, emotional, and volitional components, and patients with tics have high rates of obsessions and impulsivity.

Some hope now exists that a more scientifically oriented, neutral position is emerging between these polemical extremes. In the last few decades, the research effort spurred by the TSA has grown in volume and sophistication. Research has used reliable case definitions and has included randomized controlled treatment (RCT) trials in addition to studies of pathophysiology and etiology. The TSA even has funded controlled studies of a psychological treatment of tics (ie, habit reversal therapy, a form of behavior therapy).

Questions

This brief summary of TS reveals several themes that are revisited in the rest of this article. Naturally, TS is of interest to people with tics, as well as their families and physicians. However, observations of TS also suggest questions about related neuroscientific, medical, and philosophical issues, such as the following:

- What is volition?
- What defines an illness?

- How does movement relate to intention?
- How are neurology and psychiatry defined?

Pathophysiology

The pathophysiology underlying tics and other symptoms of TS is not understood completely, but substantial relevant scientific information is available.

Until recently, the main information on the functional neuroanatomy of tics derived from uncommon cases of tics after known lesions or from analogy to animal models. Similarly, because movements are the most externally obvious signs of TS, attention has focused on the basal ganglia and on dopamine.

Research has been slowed by the lack of a compelling animal model, although several have been described recently. Limitations include the circumscribed behavioral repertoire of many animals, especially rodents, and their inability to report on mental phenomena that in humans help to distinguish tics from other disorders. The results of several different approaches to studying pathophysiology in tic disorders are summarized here. They include biochemical, functional imaging, neuroanatomical, electrophysiological, and other pathophysiologic studies.

Also presented below are the timing of tics and a model for tic generation.

Biochemical studies

Studies have probed the function of several neurotransmitter systems in patients with tics (Anderson, 1999).

Acetylcholine is an important transmitter in the basal ganglia. Case reports or small series in TS have described use of cholinesterase inhibitors, indirect agonists, nicotine, a muscarinic antagonist, and a nicotinic antagonist. Overall, the evidence for a treatment response with any of these is meager, and limited postmortem data appear normal. A peripheral measure of acetylcholine function (red blood cell choline) may be elevated in TS (Anderson, 1999). Nicotine also corrects an abnormal response to TMS in patients with TS (Orth, *Brain,* 2005).

Noradrenergic pathways have been studied in part because tics improve with the centrally acting alpha2-noradrenergic agonist clonidine (Kurlan, 2002). A number of studies showed no abnormalities in plasma or CSF concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite). Urinary excretion of MHPG is decreased. Plasma concentrations of norepinephrine and another metabolite, dopamine-beta-hydroxylase, are also normal.

In an interesting study from Yale, CSF levels of norepinephrine and MHPG were examined (Chappell, 1994). Patients with TS had increased CSF concentrations of norepinephrine and corticotropin-releasing factor, with blood and urine showing similar changes (Chappell, 1996). However, the data can be interpreted as showing primarily that volunteers with TS had a higher stress response to the study protocol, which included lumbar puncture, than that of others (Leckman, 1995).

Serotonin function has also been assessed in TS, and patients have lower plasma tryptophan levels than normal (Comings, 1990). Preliminary postmortem studies also show reduced brain tryptophan concentrations. Unconfirmed results suggest a possible genetic link between TS and a serotonin metabolic enzyme (Comings, 1996). A [^{123}I]b-CIT SPECT study suggests lower serotonin transporter binding in patients with TS, with binding correlating inversely with severity (Muller-Vahl, 2005). However, the relevance of all these findings to pathophysiology awaits further study. Serotonin-3 receptor genes showed no clear abnormalities in TS (Niesler, 2005). Most treatments that modify serotonin function (eg, fluoxetine therapy, tryptophan depletion therapy) have not produced consistent responses (Black, in press). However, a double-blind RCT of the serotonin-3 receptor antagonist drug ondansetron did suggest efficacy (Toren, 2005).

Other transmitter systems that may provide insights into tic production include cannabinoid/anandamide receptors, which are located densely in internal globus pallidus (among other areas). Evidence supports the efficacy of cannabinoids in reducing tic severity in some patients (Muller-Vahl, 2003).

Gamma-aminobutyric acid (GABA) is the most common inhibitory transmitter in the brain; several studies have shown no abnormalities in patients with TS relative to control subjects.

The role of glutamate, the brain's predominant excitatory transmitter, needs further study. One postmortem report showed markedly different glutamate levels in the internal segment of globus pallidus (GPi), but this requires replication because of the number of simultaneous measurements reported.

A transgenic mouse model has shown increased stereotypic activity at rest, which was worsened by administration of a noncompetitive glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801, similar to phencyclidine (McGrath, 2000).

The GABA-ergic striatal medium spiny neurons use enkephalin and dynorphin as cotransmitters. Although occasional patients seem to benefit from opioid agonists or antagonists, the data remain sparse. CSF dynorphin concentrations are normal in individuals with TS (van Wattum, 1999).

One small positron emission tomographic (PET) study was performed to assess opioid receptor binding in TS; this remains an interesting area for research (Weeks, 1994).

Substantial research has focused on the possible role of dopamine in tic production, and that transmitter is discussed in more detail below.

Dopamine - Clinical observations

Substantial evidence indicates that neuroleptic and atypical antipsychotic agents reduce tic severity (Black, in press). Presynaptic dopamine-depleting agents also improve tics, and in some patients, tics may be worsened by neuroleptic withdrawal or, controversially, stimulant use. However, other data do not support a simple hypothesis that dopamine function is hyperactive in individuals with TS.

Tics are not abated with the subsequent development of Parkinson disease (Kumar, 1997). However, in Parkinson disease, dopamine loss is most evident in posterior putamen (Damier, 1999), whereas caudate and ventral striatum are more implicated in TS.

Furthermore, dopamine receptor agonists have also been used to successfully treat tics, and patients whose tics improved with an agonist had evidence of prolactin inhibition, consistent with a postsynaptic effect (Anca, 2001; Black, 2000; Gilbert and Sallee, 2000; Gilbert, 2003). With adequate carbidopa pretreatment, a single dose of levodopa was followed by diminished, not worsened, tic severity (Black, 2000).

In summary, clinical evidence suggests that dopaminergic function is abnormal in TS but leads to more questions than answers about the exact nature of such an abnormality.

Dopamine - Specific genes

Several studies have examined dopamine-related candidate genes for association with a diagnosis of TS. Recent studies suggest a possible association with the dopamine D2 or D4 receptors (Diaz-Anzaldua, 2004; Lee, 2005). However, several prior studies found no association with D2-like receptor genes. The study by Diaz-Anzaldua and colleagues also found possible linkage to the monoamine oxidase A gene (MAO-A) but to an allele with supposedly higher MAO function, whereas tics have also been reported in families with inherited deficiency of MAO-A; clearly confirmation of this intriguing finding is needed.

Dopamine - Monoamine metabolite measurements

Findings from early studies suggested that TS may be associated with a decrease in dopamine metabolism, as measured by homovanillic acid (HVA) levels in CSF. However, other studies demonstrated different results. For instance, a larger, later study showed no overall difference between TS patients with or without obsessive-compulsive disorder (OCD) and control subjects without these conditions (Leckman, 1995). Other investigators measured plasma or urine HVA values or examined dopamine, HVA, or tyrosine hydroxylase levels in postmortem brain tissue and found no consistent abnormalities.

Dopamine - Receptor-binding neuroimaging studies

Several groups have studied D2-like dopamine receptor binding in TS by using PET or single-photon emission CT (SPECT).

Four studies showed no meaningful differences between TS and control groups with the use of carbon-11 raclopride, [iodine-123]iodo-6-methoxybenzamide (IBZM), [^{123}I]iodo-2[beta]-carbomethoxy-3[beta]-(4-iodophenyl)tropane (beta-CIT), or ^{11}C 3-*N*-methylspiperone (Heinz, 1998; Singer, 1992; Turjanski, 1994; Wong, 1997). (However, a preliminary report from 1 of these studies did describe positive findings.)

One other study with a clever design compared more ill monozygotic (MZ) twins with TS to their less ill co-twins by using IBZM SPECT and found a correlation of symptomatic severity with binding in the caudate but not in the putamen (Wolf, 1996). This finding may help identify the caudate as more important than the putamen, yet interpretation of the results is difficult owing to presumably different neuroleptic exposure between groups (Robertson, 1996).

The present author and colleagues compared patients with TS and control subjects by using a newer D2 ligand, [^{18}F]*N*-methylbenperidol. Results of preliminary analysis suggest no substantive group difference (Black, unpublished data). Although one could quibble about details of each of these studies, such as sample size, treatment status, or pharmacology of the ligand used, the most likely conclusion from the available data is that D2-like receptor binding is normal in TS.

On the other hand, there are compelling suggestions that presynaptic markers of dopamine innervation may be abnormal in TS. Several of these studies have shown significant group differences, most consistently higher concentrations of presynaptic markers or activity in ventral striatum (Albin, 2003; Ben-Dor, 2007; Ernst, 1999; Heinz, 1998; Malison, 1995; Meyer, 1999; Peterson, 2001; Serra-Mestres, 2004; Singer, 2002; Stamenkovic, 2001; Wong, 1994). Increased presynaptic dopamine transporter markers appear to begin in childhood before treatment (Cheon, 2004). In TS, abnormal dopamine production—or abnormal regulation of dopamine production—leads to dopamine-influenced abnormal movement and other behavior.

The results of Singer et al in 2002 suggest normal dopamine release at baseline in TS but altered dopamine release in response to a pure pharmacologic challenge (amphetamine). This observation may correspond to the essentially normal neurological function seen in people with TS when their tics are not apparent.

Dopamine - Pharmacologic activation neuroimaging

The author and his colleagues have studied volunteers with chronic tic syndromes and control subjects in a pharmacologic-cognitive interaction fMRI study. Subjects performed a working memory ("2-back") task or a response inhibition ("go/no-go") task before and again during infusion of levodopa (with carbidopa). Some but not all other studies of patients with TS have shown higher than normal commission errors on response inhibition tasks (Channon, 2004; Goudriaan, 2005; Serrien, 2005). In this study, no differences between groups were observed with the response inhibition task (Hershey, *Cogn Brain Res,* 2004).

However, activation in the TS group was abnormal with the working memory task (Hershey, Biol Psychiatry, 2004). Several brain regions (including parietal cortex and thalamus) showed higher activity during the memory task in TS, but during the levodopa infusion the same task produced normal levels of activation. Since task performance was similar in the 2 groups, the results are best explained by a true difference in brain response between the 2 groups: The TS group apparently requires more activation of several working memory–related regions to sustain normal task performance. These exciting results, if confirmed, suggest that TS patients may have a dopamine-responsive abnormality of brain function in nonmotor as well as motor brain circuits.

Functional imaging studies

The activity of the brain, at rest or in relation to symptoms or specific cognitive or motion tasks, has been studied in TS and recently reviewed (Silbersweig, 2004).

- Resting cerebral blood flow or metabolism
  - Several groups compared TS patients with control subjects in terms of regional resting brain function, as indexed by blood flow or metabolism (Peterson, 2001). The results suggested no alteration in average whole-brain activity, but some relatively consistent regional differences were found. Increased activity was observed in primary sensorimotor cortex, which may be a nonspecific reflection of excessive movement. All groups found decreased activity in the basal ganglia, perhaps best localized to ventral striatum (Braun, 1993; Diler, 2002; George, 1992; Hall, 1990; Klieger, 1997; Moriarty, 1995; Riddle, 1992).
  - Some investigators found increased activity in the orbital frontal cortex (Braun, 1995; Crespo-Facorro, 1999), but another found decreased orbital activity (Braun, 1993).
  - Two groups examined the correlation of metabolism among specific brain regions and showed differences between TS and controls, some of which related specifically to tic severity (Eidelberg, 1997; Eidelberg, 2002).
- Correlations with tic severity or tic suppression
  - In an fMRI study, self-rated intensity of the current urge to tic was correlated with right caudate BOLD signal intensity (Peterson, 1998).
  - Findings also implicated the cingulate cortex, as did a PET study in which regional cerebral blood flow was correlated with tic frequency in individuals with TS (Stern, 2000). In the PET study in which atlas-normalized blood flow was searched voxel by voxel for within-subject correlations with the number of tics observed during each of several blood flow scans; tics were associated not only with the expected increased activity in primary motor cortex but also with altered activity in more sensory or volitional brain regions, such as anterior cingulate.
  - In a [^{18}F]fluorodeoxyglucose (FDG) PET study, caudate and thalamus metabolism was inversely correlated with clinical severity (Jeffries, 2002).
  - A case report described fMRI correlates of coprolalia in 1 subject with TS (Gates, 2004).
  - In ongoing fMRI studies, Stuart Mostofsky at the Kennedy Krieger Institute uses the important control of intentional tic-like movements in people with TS.
- Functional imaging with intentional motor activation
  - In an fMRI study, volunteers with TS performing a simple finger-tapping task had a larger activation of sensorimotor and supplementary motor area than that of control subjects (Biswal, 1998).
  - By contrast, an fMRI study of precision movement showed decreased activity of supplementary motor area in tic patients versus control subjects (Serrien, 2002).
- Functional imaging with behavioral or cognitive activation
  - In 2001, Rauch and colleagues reported findings from a pilot study in which TS patients (like patients with OCD) showed deficient activation of striatum during implicit learning.

In the same year, Swerdlow and colleagues developed a method for imaging brain function during prepulse inhibition of the startle reflex, a well-studied phenomenon that requires striatal activation.

Neuroanatomic studies

Lesion studies

Several cases of tics beginning after a focal brain lesion have been reported. These suffer the difficulties of all case reports, yet in general one may say that prefrontal, basal ganglia, and thalamic lesions are especially common. One interesting series described 6 patients who suddenly developed tics, obsessions, or compulsions after anaphylactic reaction to wasp stings produced bilateral globus pallidus lesions (Laplane, 1981; Laplane, 1994).

Evaluation of tics secondary to encephalitis or degenerative illnesses

Motor and vocal tics and compulsions frequently were reported in patients who survived the encephalitis lethargica epidemic in the 1910s and 1920s. Similar symptoms also occur in some patients with Huntington disease, Wilson disease, neuroacanthocytosis, or frontal lobe degeneration (Jankovic, 2004). None of these illnesses cause pure, circumscribed lesions. Still, together these observations confirm the impression that the basal ganglia and frontal cortex may be involved in the tics of idiopathic TS.

Autopsy studies

As TS is (fortunately) rarely fatal, only a handful of autopsied cases have been reported. Most abnormalities were in the basal ganglia, yet this was also the region most carefully scrutinized because of a priori hypotheses (Swerdlow, 1994). A recent report discusses altered distribution within the lenticular nuclei of parvalbumin-positive interneurons (Kalanithi, 2005). The results are intriguing but require replication, as they result from study of only 3 TS brains.

In vivo volumetry

The largest study of regional brain volumes to date involved more than 150 individuals with TS and a similar number of comparison children and adults (Peterson, 2001; Peterson, 2003). Subjects with TS had large dorsal prefrontal and parieto-occipital regions and smaller inferior occipital volumes. Symptom severity was best correlated with volume in orbitofrontal, midtemporal, and parieto-occipital cortex. TS patients were found to have significantly reduced caudate volumes (Peterson, 2003). The importance of this finding is highlighted by the fact that, on prospective follow-up of patients who had MRI volumetry, smaller caudate volume in childhood correlated significantly with severity of tics, obsessions, and compulsions an average of 7.5 years later (Bloch, 2005).

Another study showed that patients with TS had small right frontal lobes, large left frontal lobes, and more frontal lobe white matter compared with healthy control

subjects (Fredericksen, 2002). Other investigators also found increased frontal white matter (Hong, 2002).

Two prior studies had selectively examined basal ganglia volumes and had found slightly smaller left putamen volume and a diminution of the normal asymmetry of basal ganglia volume (Peterson, 2001). These findings were not replicated when more- and less-affected twins with TS were compared (Hyde, 1995).

One MRI study revealed abnormal T2 relaxation time in the putamen and caudate nuclei (Peterson, 1994). One case report described a child with a sudden onset of stereotyped behaviors after a streptococcal infection; this child had basal ganglia volumes larger than those of age-matched controls during the acute illness and smaller volumes months later (Giedd, 1996).

Some consistencies arise from these studies. These include decreased caudate volume and, possibly, increased prefrontal white matter and dorsolateral prefrontal gray matter volumes. In one volumetric study, abnormal basal ganglia volumes in a group of patients with TS were entirely attributable to comorbid attention deficit hyperactivity disorder (ADHD) (Castellanos, 1996). Similar results were reported from a study of regional brain volumes in relation to streptococcal antibody titers in TS (Peterson, 2000). In other studies, however, the effects of OCD or ADHD were examined and did not explain all of the imaging findings.

The implication is that at a minimum, careful clinical assessment, including information about OCD or ADHD symptoms, is required when the results of any new neuroimaging study are interpreted in individuals with TS.

Electrophysiologic studies

In 2001, Hallett summarized results of traditional electrophysiologic studies in TS. Event-related potentials that indicate motor preparation, inhibition of prepotent motor responses, or unexpected events have been variably abnormal in TS patients (Hallett, 2001; Johannes, 2002; Johannes, 2003; O'Connor, 2001).

Several laboratories have used short-interval transcranial magnetic stimulation (TMS) to investigate cortical inhibition in TS. In 1997, Ziemann et al showed abnormal cortical inhibition in tic patients. However, in 2001 Moll et al suggested that this was not specific to a TS diagnosis but was accounted for by a comorbid diagnosis of ADHD. Findings from a follow-up study in 2003 suggested that an OCD diagnosis might also account for the original results.

In 2004, Gilbert et al focused on current symptom severity and could account for 50% of the variance in short-interval cortical inhibition across a group of TS subjects with simple measures of current (recent) severity of tics and hyperactivity. ADHD symptoms, specifically hyperactivity, best accounted for the findings. Repeat studies in the same children replicated these findings and demonstrated their temporal stability (Gilbert, 2005). The results have been independently replicated (Orth, *Brain,* 2005).

Other pathophysiologic studies

Neuropsychological studies have been conducted to study specific areas of cognitive function. Among other goals, this approach may inform our understanding of the genesis of tics. (The interested reader can consult an excellent review by Como in 2001.) Since that review, independent studies found patients with TS performed worse than controls on a weather-prediction task that involved habit learning. In this task, cues predict outcomes at probabilities between 0 and 100%; the subject gradually learns to predict outcomes correctly even though feedback to the subject appears to be inconsistent. Worse performance on this task correlates with more severe illness (Keri, 2002; Marsh, 2004). In animal and human studies, habit learning tasks require a healthy striatum. Other forms of memory, including other kinds of procedural learning, are generally normal in TS (Marsh, 2005).

Intentional and reflexive eye movements were studied in TS; the results are summarized being as consistent with the hypothesis that "the ability to inhibit or delay planned motor programs is significantly impaired in Tourette's syndrome. Altered cortical-basal ganglia circuitry may lead to reduced cortical inhibition making it harder for Tourette's syndrome subjects to withhold the execution of planned motor programs" (LeVasseur, 2001).

Startle reflexes can be studied in a repeatable way and are abnormal in TS, as in OCD. Recent advances allow the study of such reflexes in the functional MRI environment (Swerdlow, 2001) and in preclinical models that offer hope for rapid screening of potential treatments (Swerdlow, 2004).

Immune studies related to group A streptococcal infections are discussed below. In addition, a recent large longitudinal study suggests that 2 cytokines, interleukin-12 and tumor necrosis factor-alpha, are associated with recrudescences of symptoms in patients with TS (Leckman, 2005). Whether these are markers specifically for TS symptoms remains to be determined. Although a pilot microarray study of gene expression in TS peripheral blood did not find a statistically different pattern of expression, the 6 genes with increased expression in TS were all related to immune function (Tang, 2005). However, none of these same genes were detected in a microarray study of postmortem putamen tissue, suggesting that further study is required in this area (Hong, 2004).

One potential clue to the pathophysiology of TS is the high male-to-female ratio (up to 10:1 in some prevalence studies). One attempt to follow up on whether this reflects an androgen-mediated effect, perhaps during prenatal development, examined gender-related behavioral and neuropsychological variables in male and female patients with TS, with some support for this hypothesis (Alexander and Peterson, 2004).

Timing of tics

Peterson and Leckman (1998) have drawn attention to the timing of tics. In the course of an office visit, tics tend to occur in bouts rather than being distributed evenly. Similarly, viewed over the course of several months, days with worse tics also tend to cluster together. A consistent temporal pattern when viewed at any of various time scales is a fractal pattern, a typical feature of a chaotic mathematical system. This suggests the possibility of searching for neuronal firing patterns or other physiologic processes that replicate on even smaller time scales the timing of tics as observed over minutes or months.

Several clinical syndromes are distinct from TS but have overlapping features. These include the repetitive, intrusive thoughts or suppressible but eventually irresistible rituals in OCD, and echophenomena or utilization behavior in patients with catatonia or frontal lobe injury. Conceivably, progress in any of these conditions may yield further insights into the pathophysiology of tic disorders.

Additional insights into tics may be gathered by reference to other illnesses with overlapping features. Tics may be classified as a stereotypic movement disorder; ie, the movements are often complex and are repetitive rather than random.

Stereotypies are observed in a number of human and animal situations and may bear some relevance to the anatomy and pathophysiology of TS. Animal models include stallions with inherited repetitive movements, grooming rituals, and self-injury; tethered sows or other animals confined to small quarters; Labrador dogs who repeatedly lick their paws to the point of abrasions; rodents given apomorphine or stimulants; and more recently, rodents injected with plasma from patients with TS. The relevance of these animal models has been reviewed by Swerdlow (2004).

In people, a spectrum of stereotyped movement severity ranging from normal to problematic may occur (Jankovic, 1994). Simple stereotypies are common in infancy and early childhood. Habits and mannerisms are nearly ubiquitous. However, stereotypies become clearly pathologic in autism or Rett syndrome. Determining why tics chronically persist in a few individuals but briefly appear and then wane in others is important.

A model of tic production

Knowledge about primate basal ganglia anatomy and physiology has been summarized (see Image 1) (Mink, 2001; Mink, 1996). In this view, motor patterns are generated in the cerebral cortex and brain stem. Performance of a specific intended movement includes not only selection of the desired movement but also inhibition of antagonistic movements and of similar movements of neighboring body parts.

The basal ganglia are organized so as to inhibit, or apply a "brake" to these undesired motor programs. Normally, the basal ganglia allow selective release of the brake from the desired action. Tics may result from a defect in this braking function. This may be caused by an episode of overactivity in a focal subset of striatal neurons, perhaps in the striatal matrisomes identified by Graybiel and colleagues (Flaherty, 1994). The episodic focal overactivity may result from any of various mechanisms acting at any of various locations from cortex to thalamus.

Dopaminergic innervation of striatum has several characteristics that would allow generation of such abnormal epochs of striatal activity; these include dopamine's modulation of the resting membrane potential set point and the influence of dopamine on long-term potentiation or long-term depression (relatively long lasting changes in neuronal excitability based on the prior neuronal inputs).

Finally, this theory is largely derived from studies of the motor circuit involving motor cortex, striatum, internal pallidum, subthalamic nucleus, and ventral thalamus. However, parallel neuronal circuits influence other regions of frontal cortex, including orbitofrontal, medial prefrontal, and dorsolateral prefrontal cortex.

These pathways are relatively separated in cortex, yet they physically course closer together in the basal ganglia, thalamus, and midbrain.

Lesion and neuroimaging data in individuals with OCD or ADHD implicate abnormalities in nonmotor regions of frontal cortex. Possibly the frequent, but not uniform, occurrence of these symptom complexes in patients with tics represents processes of similar pathology but overlapping anatomy (see Image 2).

Frequency

United States

The frequency of TS depends on the definition of the phenotype. Some authors (Comings, 1995; Comings, 1987) have argued for diagnosing a TS-related illness with psychological manifestations even in the absence of tics; this would inflate the apparent prevalence.

The frequency of TS also depends on the ascertainment source. Rates of tic disorders estimated from physicians or medical records are lower than rates from population samples. This difference suggests that many people with tics do not seek medical attention (though this may be less true in some cultures [Khalifa and von Knorring, 2005]). Experience with family members and with volunteers in research studies, who often have typical tics and tic histories but who never sought medical attention, also support this conclusion.

Medical care is a surrogate—and imperfect—measure of the impairment or distress required for a diagnosis of a tic disorder according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, (DSM-IV) criteria. (The 2000 text revision known as DSM-IV-TR removed this criterion.)

Until recently, the best general population study of TS prevalence came from Apter et al in 1993. In this study, trained physicians screened more than 28,000 adolescents entering military service in Israel and concluded that prevalence was about 0.05%.

Careful epidemiologic studies have occasioned a dramatic change in perspective. A consensus has developed that definite TS occurs an order of magnitude more commonly, ie, in about 0.5% of school-age children. When all chronic tic disorders (including motor-only or vocal-only chronic tics) are taken together, the prevalence increases to about 2% (Comings, 1990; Hornse, 2001; Khalifa, 2003; Kurlan, 1994; Lanzi, 2004; Mason, 1998; Wang, 2003; Jin et al, 2005; Khalifa and von Knorring, 2005).

Grouping chronic tic disorders with TS is defensible for several reasons, most notably because TS is overrepresented in relatives of probands with chronic tic disorder, and vice versa. However, in many of these individuals, *chronic* may mean only 2-3 years. In addition to family studies, phenomenological studies also suggest that chronic motor or vocal tic disorder and TS are similar, except possibly for severity (Diniz, 2005; Saccomani, 2005). Transient tic disorders are even more common in children (3-15% in different studies).

International

Mortality/Morbidity

Little or no excess mortality is associated with TS.

Many people with tics lead a fairly normal life. However, even mild tics can be distressing. For example, a patient of one of the present authors is a man with mild TS has a successful professional career and a good family life. He is used to his tics and does not prefer any treatment with noticeable adverse effects. However, he finds his symptoms annoying and would rather be free of them if given the choice. He states, "It is like I am on stage 16 hours a day. Every waking moment I am trying not to tic when people are watching." Other people with TS have more severe symptoms. Occasionally, the symptoms can be disabling.

- The most common disability is social in nature (Carter, 2000; Martinez, 2003). Patients with loud vocalizations or large movements either endure substantial criticism, or they withdraw from many activities. Prejudice in work and school settings is common.
- Tics also interrupt the individual's behavior and thought. Most patients find that they sometimes lose track of a conversation or that they are slow to complete a task because of incessant interruptions by their tics.
- Self-injurious behavior is not uncommon. Occasionally, self-injury is intentional and due to a comorbid problem (eg, suicide during an episode of major depression). At times self-injury is pseudointentional; an example is repeatedly hitting one's face as a complex tic.
- Perhaps more common than self-injuries are inadvertent injuries (Cath, 2001; Robertson, 1990; Wang, 2003). Sometimes, these injuries are due to complex tics or compulsions, such as a need to touch high-voltage wires. Other times, they are due to inattentiveness or impulsivity. (In one of the author's cases, the father of a man with TS does not allow him to use power tools because he had had several near catastrophes.) Inadvertent injuries such as broken bones, cervical arthritis, or shin splints can also occur after simple yet repetitive and/or intense tics.
- In clinical samples, most morbidity is due to inattention, impulsivity, obsessions, compulsions, or complex behavioral symptoms such as inappropriate social behavior, rage attacks, or insistence on sameness.
- A minority of people with chronic tic syndromes receive disability compensation.

Race

- TS has been described in people of many ethnic origins.
  - In the US, most patients with TS who are examined at research centers or who are affiliated with lay organizations are white. This observation may be due to differences in their seeking healthcare rather than in actual symptomatic prevalence.
  - Most likely, this disorder is distributed similarly among all races, but data to address this issue more definitively are limited, as most studies enroll subjects from patient populations.

- Only a few community-based epidemiologic studies have provided data on tics, and most are from racially homogeneous populations. Some useful data come from the Great Smoky Mountains Study of Youth, a psychiatric epidemiologic study conducted in western North Carolina (Costello, 1996; Costello, 1999).
    - Children aged 9, 11, or 13 years were examined on the basis of a stratified statistical sample in a defined catchment area, except that a 100% sample was obtained for American Indian children.
    - Too few children with TS (0.10%) were included to permit conclusions about prevalence by race. However, the 3-month prevalence of "any tic disorder" was 3.53% iÀ 0.94%, and prevalence by race was as follows: white, 2.1%; African American, 5%; American Indian, 1.5%.
    - Caveats to interpreting this data include a low total number of African American children and, more importantly, the diagnoses were based on only the observations of parents and lay interviewers.

Sex

Boys are more likely than girls to have chronic tics. The male-to-female ratio in TS and in chronic motor tic disorder is approximately 5:1 (between 2:1 and 10:1 in different studies).

Age

- By definition, TS has onset in childhood, when the individual is younger than 21 years (DSM-IV) or 18 years (Tourette Syndrome Study Group [TSSG]).
    -
    - A multicenter study of German families (Hebebrand, 1997) showed that this definition is arbitrary but reasonable. In relatives of TS probands who also had tics, the tics usually started when the individual was younger than 18 years, but 5 relatives had otherwise typical histories for TS with onset after the age of 21 years.
    - One study of a birth cohort with TS showed that the most common age for tic onset was 9-14 years (Leckman, 2003).
    - Generally, simple motor tics (eg, blinking) are first noticed when the individual is approximately 5-10 years old, with vocal tics starting at 8-15 years.
    - The modal age of symptom onset increases roughly with complexity: Simple tics are reported earliest in life, while complex tics, compulsions, obsessions, and sensory tics, and/or premonitory sensations tend to develop somewhat later.
- TS almost always persists throughout life. Fortunately, tic severity on average peaks in adolescence and wanes thereafter. This average is deceptive, however, because fluctuation of severity throughout life is typical, and patients can first seek medical attention for lifelong tics in late life after a worsening of tic severity.

Clinical

History

Tics tend to fluctuate in severity, distribution, and character over intervals that are usually of weeks to years. A typical example is as follows: A boy starts blinking excessively when aged 5 years and develops a repetitive nonrhythmic palatal click several months later. By age 7 years, the blinking persists, while forceful nasal exhalations and shoulder shrugging have replaced the click. As a teenager, he has all the old tics present together with violent head shaking. In college, subtle head shaking and hardly visible abdominal tensing may be the only remaining tics, with exacerbations during examination week.

Two case definitions for TS are accepted widely: the DSM-IV-TR definition, which is widely used in the US for clinical purposes (see the DSM-IV-TR criteria for tic disorders below), and the TSSG definition (see TSSG criteria for tic disorders below). Experts identify similar groups of patients by using either set of criteria.

- DSM-IV-TR criteria for tic disorders from the American Psychiatric Association, 2000
    -
        - Diagnostic criteria for TS (DSM-IV-TR 307.23)
            -
                - Both multiple motor and 1 or more vocal tics have been present at some time during the illness, though not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)
                - The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.
                - The onset is before age 18 years.
                - The disturbance is not due to the direct physiologic effects of a substance (eg, stimulants) or a general medical condition (eg, Huntington disease or postviral encephalitis).
    -
        - Diagnostic criteria for chronic motor or vocal tic disorder (DSM-IV-TR 307.22)
            -
                - Single or multiple motor or vocal tics (eg, sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalizations), but not both, have been present at some time during the illness.
                - The tics occur many times a day nearly every day or intermittently throughout a period of more than 1 year; and during this period there was never a tic-free period of more than 3 consecutive months.
                - The onset is before age 18 years.
                - The disturbance is not due to the direct physiologic effects of a substance (eg, stimulants) or a general medical condition (eg, Huntington disease or postviral encephalitis).
                - Criteria have never been met for TS.
        - Diagnostic criteria for transient tic disorder (DSM-IV-TR 307.21)
            -

- Single or multiple motor and/or vocal tics (eg, sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalizations) are present.
- The tics occur many times a day, nearly every day for at least 4 weeks, but for no longer than 12 consecutive months.
- The onset is before age 18 years.
- The disturbance is not due to the direct physiologic effects of a substance (eg, stimulants) or a general medical condition (eg, Huntington disease or postviral encephalitis).
- Criteria have never been met for TS or chronic motor or vocal tic disorder.
- Specify if this is a single or recurrent episode.
  - Tic disorder not otherwise specified (DSM-IV-TR 307.20): This category is for disorders characterized by tics that do not meet criteria for a specific tic disorder. Examples include tics lasting less than 4 weeks or tics with an onset after age 18 years.
- TSSG criteria for tic disorders, 1993
  -
  - Diagnostic criteria for TS (coded as A-1 or A-2 depending on source of information)
    -
    - Both multiple motor and one or more vocal tics have been present at some time during the illness, though not necessarily concurrently.
    - The tics occur many times a day, nearly every day, or intermittently throughout a period of more than 1 year.
    - The anatomic location, number, frequency, complexity, type, or severity of tics changes over time.
    - Tics have their onset before age 21 years.
    - Involuntary movements and noises cannot be explained by other medical conditions.
    - Motor and/or vocal tics must be witnessed by a reliable examiner directly at some point in the illness or be recorded by videotape or cinematography (for definite TS, A-1) or (for tics not witnessed by a reliable examiner) tics must be witnessed by a reliable family member or close friend, and description of tics as demonstrated must be accepted by reliable examiner (for TS by history, A-2).
  - Diagnostic criteria for chronic multiple motor tic or phonic tic disorder (B-1 and B-2)
    -
    - Either multiple motor or vocal tics, but not both, have been present at some time during the illness.
    - The tics occur many times a day, nearly every day, or intermittently throughout a period of more than 1 year.
    - The anatomic location, number, frequency, complexity, or severity of tics changes over time.
    - Tics have their onset before age 21 years.
    - Involuntary movements and noises cannot be explained by other medical conditions.
    - Motor and/or vocal tics must be witnessed by a reliable examiner directly at some point in the illness or be recorded by videotape or cinematography (for definite chronic multiple

motor tic or phonic tic disorder, B-1) or (for tics not witnessed by a reliable examiner) tics must be witnessed by a reliable family member or close friend, and description of tics as demonstrated must be accepted by a reliable examiner (for chronic multiple motor tic or phonic tic disorder by history, B-2).

- o Diagnostic criteria for chronic single tic disorder (C-1 and C-2): This disorder is the same as in the previous category (B-1 and B-2), but with a single motor or vocal tic.
- o Diagnostic criteria for transient tic disorder (D-1 and D-2)
  - o
    - ▪ This disorder is characterized by single or multiple motor and/or vocal tics.
    - ▪ The tics occur many times a day, nearly every day, for at least 2 weeks, but for no longer than 12 consecutive months, although the disorder began over 1 year ago.
    - ▪ The anatomic location, number, frequency, complexity, or severity of tics changes over time.
    - ▪ Patient has no history of TS or chronic motor or vocal tic disorders.
    - ▪ Tics have their onset before age 21 years.
    - ▪ Motor and/or vocal tics must be witnessed by a reliable examiner directly at some point in the illness or be recorded by videotape or cinematography (definite transient tic disorder, D-1) or (for tics not witnessed by a reliable examiner) tics must be witnessed by a reliable family member or close friend, and description of tics as demonstrated must be accepted by a reliable examiner (for transient tic disorder by history, D-2).
- o Diagnostic criteria for nonspecific tic disorder (E-1 and E-2)
  - o
    - ▪ Tics that do not meet the criteria for a specific tic disorder fall into this category; an example would be a tic disorder with tics lasting less than 1 year and without any change over that period of time.
    - ▪ Motor and/or vocal tics must be witnessed by a reliable examiner directly at some point in the illness or by videotape or cinematography (for definite nonspecific tic disorder, E-1) or (for tics not witnessed by a reliable examiner) tics must be witnessed by a reliable family member or close friend, and description of tics as demonstrated must be accepted by a reliable examiner (for nonspecific tic disorder by history, E-2).
- o Diagnostic criteria for definite tic disorder, diagnosis deferred F: This disorder meets all criteria for definite TS (first definition, A1), but duration of illness has not yet extended to 1 year.
- o Diagnostic criteria for probable TS type G
  - o
    - ▪ Type 1 fulfills all criteria for definite TS (first definition, A1) except for the third and fourth criteria.
    - ▪ Type 2 fulfills all criteria for definite TS (first definition, A1) except for the first criterion; this type can be either a single motor tic with vocal tics, or multiple motor tics with possible vocal tic(s).

- Diagnostic criteria for probable multiple tic disorder, or motor and/or vocal tics H: This disorder fulfills all criteria for definite chronic multiple tic disorder (second definition) completely, except for the third and/or fourth criteria.

Physical

An important caveat is that many patients with tics may not demonstrate them on their first office visit, especially when one is looking directly at the patient. In such cases, important aids to diagnosis can include obtaining the patient's history from several sources; scheduling follow-up office visits; and, most importantly, assigning the patient (or his or her parents) to bring a home video to show their behavior. Learning to watch the patient out of the corner of one's eye while speaking with a family member or writing in the chart is also helpful.

The remainder of the physical examination is important primarily for differential diagnosis. Special attention should be paid to the patient's mental status, cornea (Kayser-Fleischer rings), eye movements, abnormal movements, muscle tone, gait, postural stability, and bradykinesia or tremor if any. General neurological and psychiatric examinations are also important.

A number of non-tic symptoms are relatively common in patients with TS and are described briefly in the Table.

Symptoms of TS

Symptom	Description/Comment
Sensory hypersensitivity	Cannot stand to have wrinkly socks, cuts the tags off his or her shirts, refuses all but bland food, or agitated in a visually complex environment
Learning disability	Approximately 20% in clinical samples, more closely associated with comorbid ADHD than with tics; also associated with male sex, earlier onset, severity, perinatal problems, and lower rates in family members (Burd, 2005)
School phobia	Can be an adverse effect of neuroleptic treatment
Complex socially inappropriate behavior	Insults, racial slurs, and paraphilias (or, more commonly, suppressed urges) are present in a large minority of patients with TS, associated with comorbid ADHD
Rage attacks	Sudden outbursts lasting approximately 5-30 min, usually in children or teenagers; inconsolable, unremitting violent frustration, commonly after being denied an unreasonable request; often followed by apparently sincere contrition and remorse
Insistence on sameness	Refusal to take another way home or omit a step in a routine, even when hurried; often without a clear obsession or other obsessive-compulsive symptoms
Anxiety and depression	Common in patient samples but not clearly more common in the general TS population

TS with both OCD and episodes of mania	Surprisingly high rates of mania in patients with TS and OCD shown in at least 2 studies, management frequently difficult

Described below are the classification of tics, their general features, and the signs and symptoms of specific tics (sensory tics, dystonic tics, and coprolalia) and of related conditions such as OCD and ADHD.

- Classification of tics
  -
    - Tics are traditionally (if arbitrarily) classified by their distribution and complexity.
    - Tics most often occur in the face, neck, pharynx, shoulders, and midline torso but can affect nearly any body part (see Image 3).
    - Albin has pointed out that stimulation of the ventral basal ganglia can reproduce some socially meaningful complex gestures (eg, stereotyped fear or pleasure displays in rodents), and that socially meaningful gestures predominantly involve these same body regions (Albin, 2004).
    - However, some tics do not readily fit traditional classifications
- General features of tics
  -
    - Most tics are simple, meaningless movements, yet tics are not entirely random, often involving elements of experience, practice, and social convention.
    - Echolalia or echopraxia (ie, imitation of another's speech or movements) occurs in as many as one third of patients.
    - Seeing another person with tics with excessive blinking may induce a bout of blinking in someone who has not had that tic for years. Similarly, hearing about tics increases their severity (Woods, 2001).
    - Tics sometimes appear to recapitulate a new, voluntary behavior; one example is "air typing" as a complex tic after learning to touch type (observed in 2 unrelated individuals by one of the authors). A man whose self-history was published in 1902 described his tics as often involving an urge to do just what was forbidden, such as "clucking" when told to be quiet in school. He compared his motor and vocal tics to a "desire for forbidden fruit" Kushner, 1999).
    - As with most movement disorders, tics are worse at times of emotional stress and are diminished dramatically during sleep.
- Tics are distinguished from other movement disorders by several typical characteristics.
  -
    - Tics are most commonly brief movements, yet not so brief as the movements of myoclonus.
    - Myoclonus is not suppressible, whereas tics (and chorea) are suppressible. Often, after prolonged forced suppression, a rebound of tic severity occurs, though this is hard to demonstrate in controlled settings (Meidinger, 2005).
    - Similarly, tics tend to improve somewhat when the individual is absorbed in an enjoyable or demanding activity.
    - Individual tics may resemble the individual movements of chorea, yet tics are repeated stereotyped movements, while chorea consists of

movements that are unpredictably distributed through the body. For example, a man with tics may be "the guy who shakes his head," while someone with chorea may be simply "the guy that twitches a lot." However, in distinction to tremor or most stereotypies, including typical tardive dyskinesia, tics are not rhythmic.

- Tics are nearly unique compared with other movement disorders in the perceived degree of volition. Although tics are clearly not voluntary in the usual sense (no one decides to have tics), the term *involuntary* is not strictly accurate.
  -
    o Often in children and occasionally in adults, tics appear to be truly involuntary: The person tics without awareness or without a sense of voluntary movement. However, when pressed for details, adults describe most tics as a volitional response to an irresistible impulse, rather than an involuntary movement (Kwak, 2003). For example, patients often say, "I shake my head" rather than "my head shakes."
    o One of the authors' patients tried to describe his tics to people who have not experienced them: "Think of the last time you were at the symphony or at church and you had a tickle in your throat. Maybe you could hold it back until the end of the quiet movement or the end of the prayer, but then you just had to cough or clear your throat. This is something like what it feels like to have a tic, but with TS it is happening throughout the day, every day."
    o Tic syndromes can nearly always be differentiated from uncomplicated OCD. Simple tics or pure obsessions are easily identified, and essentially all patients with chronic tics have simple tics at some point. However, because the definitions overlap, individual complex actions cannot always be labeled clearly as a tic rather than a compulsion. Complex tics generally preceded by sensory phenomena or occur without warning, whereas compulsions generally involve obsessive worries and themes of contamination or guilt. However, both can be associated with symmetry concerns or a need to repeat something until an ineffable sense of "getting is just right" is achieved (Coffey, 1998; Leckman, 1994).
- Sensory tics
  -
    o Sensory tics refer to repeated, unwanted, uncomfortable sensations, often in the absence of a verifiable stimulus (Miguel, 2000; Scahill, 1995).
    o Common examples are "something in the throat," or a hard-to-describe local discomfort in the shoulders.
    o Sensory tics often precede motor or vocal tics but can occur independent of externally apparent tics. In the former case, they also are called premonitory sensations, and often the actual movement or vocalization is perceived as relieving the uncomfortable sensation, akin to "scratching the itch." Blinking after an uncomfortable sensation in the eye is one example.
    o At other times, patients report a more generalized discomfort or restlessness, sometimes reminiscent of the subjective component of akathisia.
    o Some published self-descriptions of tics identify these sensory phenomena as the core symptoms of TS (Bliss, 1980). However,

developmentally, children have motor tics several years (on average) before they first report premonitory sensations.

- o Not surprisingly, the distribution of sensory tics mimics that of motor and vocal tics.
- Dystonic tics
  -
    - o Dystonic tics refer to repeated movements that resemble fragments of childhood-onset generalized dystonia.
    - o An example is one of the authors' patients, a man with lifelong mild motor and vocal tics who when aged 45 years developed typical blepharospasm (involuntary squeezing of the eyelids). After 2 years, the blepharospasm remitted while other tics predominated, only to recur after a year or so.
    - o This name also has been used to describe simpler nonclonic tics that alternatively, perhaps more aptly, have been called tonic tics. These are common, and examples include 1- to 5-second isometric contractions at the shoulders or repeated tensing of the abdominal muscles.
- Coprolalia
  -
    - o Coprolalia refers to unprovoked, unwanted outbursts of obscenities and occurs in 10-40% of patients with TS, depending on the method of ascertainment.
    - o Complex tics can include touching a hot iron or a stranger's breasts.
    - o A well-known case history describes a woman with coprolalia, among other tics, who became deaf in childhood (Chappell, 1996). She learned sign language and could communicate without tics until becoming fluent, whereupon she developed signing tics, including socially unacceptable signs.
    - o Signing tics also occur in prelingually deaf individuals (Morris, 2000).
- Obsessive-compulsive symptoms
  -
    - o Obsessions are unwanted repetitive thoughts, fears, or mental images, eg, "I better do that over again until it looks right."
    - o Compulsions are actions, generally perceived as volitional but irresistible, performed repeatedly to reduce obsessive worries or according to rigid rules. Common compulsions are counting, checking, straightening, hoarding, or grooming.
    - o Phenomenologically, obsessions and compulsions share many features with tics, and historically, some authors have referred to them as mental tics or psychic tics.
    - o Obsessions and compulsions occur in tic patients about 20 times more commonly than in the general population. In many cases, symptoms meet DSM-IV criteria for OCD. Relatives also have markedly elevated rates of obsessions and compulsions, with or without tics. Conversely, relatives of children with OCD have high rates of TS whether or not the proband has TS (Chabane, 2005; do Rosario-Campos, 2005). These facts support the view that OC symptoms, like tics, are part of the natural TS phenotype rather than a comorbid second illness (Miguel, 2004; Pauls, 2004).
    - o Findings such as those just described may suggest useful avenues for research into the treatment of tics. On the other hand, the observation that purely symptomatic therapies may treat 1 symptom but not the

other makes sense if one accepts that they may be generated by different, but similarly affected, areas of the brain.

- ADHD symptoms
  -
    - o ADHD refers to a clinically defined syndrome beginning in childhood and characterized by inattention and distractibility, behavioral hyperactivity, or marked impulsivity.
    - o In recent years, several important findings have emerged from studies of (nontic) ADHD.
      - o
        - ▪ The reliability of ADHD diagnosis by experts compares well with that of most other medical illnesses.
        - ▪ Findings suggest that, like essential hypertension, ADHD as currently defined represents a clinically convenient threshold imposed on a unimodal population distribution of symptom severity.
        - ▪ The syndrome is highly heritable whether the phenotype is defined by clinician diagnoses or parents' reports of symptoms.
        - ▪ Finally, safe treatments of proven efficacy are available.
- Clearly, ADHD is common (>25%) in patients with TS seen by physicians. To some extent, the prevalence may represent primarily referral bias; patients with uncomplicated tics are less likely to seek medical attention. However, ADHD is common even in epidemiologic samples of TS and in TS-affected relatives of pure-TS probands.
- The genetic relationship of TS with ADHD is less clear than its relationship with OCD (Pauls, 2004).
- The clinical picture is similar to that observed in populations without tics.

Causes

Causes of TS may be genetic, nongenetic, related to streptococcal infection, or other.

- Genetic causes
  -
    - o TS is known to be familial; prevalence of TS in first-degree relatives is 5-15%, or at least 10 times the prevalence in the general population. Chronic motor tics (without vocal tics) are also common in relatives. This is not surprising, since vocal tics are essentially motor tics of the muscles used in speech. In the rest of this article, chronic motor or vocal tic disorder is not distinguished from TS.
    - o Genetic factors are implicated in twin studies, which show that the ratio of concordance in MZ versus dizygotic twin pairs is approximately 5:1 (Price, 1985). By the early 1990s, available data supported a single major autosomal dominant gene with pleiotropic expression (ie, chronic motor tics, TS, or OCD) and incomplete penetrance (about 70% in women, 99% in men) (Devor, 1990; Pauls, 1992). However, family linkage methods excluded a single dominant gene in most of the genome, and more recent results suggest alternative models. These models include the involvement of several genes rather than one, intermediate penetrance in heterozygotes compared to either homozygote, or mixed genetic-environmental causes (State, 2001).

- o A sibling-pair approach, which may be more sensitive under these conditions, now is being employed to search for TS genes. The TSA and the National Institutes of Health have supported an international collaborative genetic study that is using linkage and sibling methods to analyze 500 markers in over 2200 individuals from 269 families (Pauls, 2004).
  - o As of 2005, no chromosomal region had been definitely associated with TS, although some regions showed possible involvement and were identified by independent groups. Complete results are expected soon.
  - o Other approaches to identifying specific genes related to TS include examination of families with visible chromosomal abnormalities or a high degree of consanguinity (State, 2003). One such association has been reported (Abelson, 2005) but affects at most a small minority of people with tics.
- Nongenetic causes
  - •
  - o Nongenetic causes also must exist, because discordant MZ twin pairs are known.
  - o Additional evidence for environmental or epigenetic causes includes differences in severity between affected MZ twins, with greater severity in the twin with perinatal complications than in the co-twin and cases of secondary (symptomatic) tics with vascular, degenerative, toxic, or autoimmune causes (Hyde, 1992).
  - o The possibility that some, or perhaps many, cases of TS may be caused by an abnormal immune response to streptococcal infection has generated substantial interest.
- Streptococcal infections
  - •
  - o In the late 1800s and early 1900s, chorea was widely assumed to be usually due to rheumatic fever. The link of chorea to prior streptococcal illness first was proven in the 1950s. The delay occurred partly because chorea often follows streptococcal recurrence by several months and often occurs without coeval arthritis, carditis, or serologic abnormality.
  - o In the 1970s, patients with Sydenham chorea were demonstrated to have high levels of antibodies that react to human brain. These antibodies have since been shown to cross-react to certain proteins on group A beta-hemolytic streptococci (GABHS) (Kirvan, 2003).
  - o Although tics and chorea can be differentiated clinically, the definitions were less clear in the 19th century. For instance, Charcot and Gilles de la Tourette distinguished tics and chorea primarily on grounds of course and presumed cause rather than phenomenology.
  - o In recent years, interest has been growing in the possibility that streptococcal illness may produce not only chorea but also tics, obsessions, or compulsions. In several cases tics began suddenly after a streptococcal infection, and investigators proposed a research case definition for poststreptococcal autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) (Snider, 2003).
  - o Some observations support a connection between GABHS and tics (Swedo, 2004).
    - o

- Children with Sydenham chorea have frequent OCD compared with healthy controls or those who have rheumatic fever without chorea (Asbahr, 1999). In a large case-control study, children with OCD or a chronic tic disorder were more than twice as likely as controls to have had a documented GABHS infection in the 3 months prior to the neuropsychiatric diagnosis, and children with multiple GABHS infections in a 12-month period were 13.6 times more likely to later be diagnosed with TS (Mell, 2005).
  - Several times, patients with either tics or OCD have been found to have high levels of antistreptococcal or anti-DNase antibodies (Snider, 2003). This is not a nonspecific indicator of distress, since other patient populations do not have these findings. Patients with tics or OCD also have high levels of a B-cell marker (D8/17) that similarly is elevated in Sydenham chorea (Murphy, 2001). Finally, children with TS may have increased levels of circulating antineuronal antibodies (see Image 4) (Church, 2003; Kiessling, 1993; Pavone, 2004; Wendlandt, 2001).
  - The results above must be tempered by several considerations (Kurlan, 2004).
    -
      - First, almost all humans have a GABHS infection at some time, whereas more than 95% never develop OCD or chronic tics, suggesting a substantial role for host factors.
      - Second, any stressor—including an acute infectious illness—can exacerbate tics. Even without a direct causal link, patients or their parents first may notice tics at a time of stress. The association of TS with immune response is not specific to GABHS (see Pathophysiology (Muller, 2004).
      - Third, a positive laboratory result for streptococcal infection can occur without current illness. Additionally, most people with tics simply do not meet a case definition of sudden onset with infection and dramatic subsequent remission. For instance, a nationwide search for such cases for a treatment study sponsored by the National Institute of Mental Health, resulted in only approximately 50 referrals (Perlmutter, 1999).
      - Fourth, some laboratory reports contradict the aforementioned results (Loiselle, 2004; Singer, 2004). A large study recently found no evidence for abnormal serum antineuronal antibodies in patients diagnosed either with PANDAS or with TS (Singer, 2005).
  - Streptococcal involvement represents a promising lead that may result in breakthroughs in the understanding of tic pathogenesis. However, treatment based on this hypothesis is not standard care at present. A controlled study showed that, in highly selected patients, OCD can improve after intravenous immunoglobulin (IVIG) therapy (Perlmutter, 1999). However, achieving true blinding for IVIG administration is difficult, and a placebo effect cannot be excluded. Tics were not affected by treatment in the blinded condition.
  - Whether antibody-mediated poststreptococcal illness causes most, a few, or no cases of TS is still unknown. In the meantime, a reasonable approach in these cases is to treat acute GABHS infections or

rheumatic fever with antibiotics to prevent cardiac sequelae but to avoid invasive immune therapies. A possible exception may be highly select cases of OCD that fit stringent criteria for PANDAS, which might be treated in a research protocol.

- Other causes
  -
    o See Neuroanatomic studies in [Pathophysiology](#).
    o See also [Differentials](#).

Differentials

[Chorea Gravidarum](#)
[Chorea in Adults](#)
[Chorea in Children](#)
[Cocaine](#)
[Complex Partial Seizures](#)
[Frontal Lobe Syndromes](#)
[Hallervorden-Spatz Disease](#)
[Hemifacial Spasm](#)
[Huntington Disease](#)
[Inherited Metabolic Disorders](#)
[Mental Retardation](#)
[Movement Disorders in Individuals with Developmental Disabilities](#)
[Neuroacanthocytosis](#)
[Neuroacanthocytosis Syndromes](#)
[Neuronal Ceroid Lipofuscinoses](#)
[Neurosyphilis](#)
[Periodic Limb Movement Disorder](#)
[Restless Legs Syndrome](#)
[Tardive Dyskinesia](#)
[Tuberous Sclerosis](#)
[Wilson Disease](#)

Other Problems to be Considered

Akathisia
Autism
Carbon monoxide
Dystonia
Encephalitis lethargica
Hyperekplexia and other startle syndromes
Mannerisms
Monoamine oxidase A deficiency
Myoclonus
Obsessive-compulsive disorder
Paroxysmal dyskinesias
Rett syndrome

Stimulants
Stroke

Workup

Lab Studies

- When an appropriately experienced physician finds typical indications of TS in the patient's history and examination, no further workup is generally necessary.
- Further workup may be needed if unusual features are present in the history or physical examination or if other abnormalities are found on neurological examination.
    -
        - o Unusual findings may include rigidity, bradykinesia, spasticity, myoclonus, chorea, dementia, or psychosis.
        - o Further workup may include corroboration of the patient's history with that of another source, with clinical follow-up, or with laboratory testing.
- Serum ceruloplasmin or slit lamp examination for Kayser-Fleischer rings might be considered.
    -
        - o This examination is not always necessary.
        - o However, if unusual features are present, these tests may lead to lifesaving measures.

Imaging Studies

- Structural imaging studies are not routinely needed in the evaluation of patients with a typical history and examination findings. These studies are indicated only to exclude specific illnesses suggested by abnormal history or examination findings.
- At present, functional imaging studies have no proven clinical utility in the evaluation of tic disorders.
- Data from unpublished reports suggest possible future clinical benefits of neuroimaging. For example, caudate volume in childhood is inversely associated with illness severity in adulthood (Block, 2004).

Other Tests

- Neuropsychological testing may be useful: Patients with difficulties in the school or work setting may benefit from an evaluation for learning disorders so that adaptive strategies can be identified.

Procedures

Histologic Findings

Staging

Treatment

Medical Care

General principles

Some general principles must be kept in mind. First, all present treatments of TS are purely symptomatic. No curative or preventive treatments are known. Second, tics often are not the worst problem. Third, this is a chronic disorder, and usually the goal is long-term benefit rather than quick improvement at any cost. Fourth, symptoms frequently improve or worsen over any period of time, even in untreated TS. Corollaries of these principles include the following: Treatment is not always needed; treatment should be directed first at the most troublesome symptom; apparent success or failure of any treatment may be coincidental; and beginning with reasonable trials of single agents is usually better than rushing to high doses or polypharmacy.

TS has been described as either a neurological or a psychiatric disorder. These labels have nothing to do with the cause or treatment of TS but simply relate to the fact that neurologists and psychiatrists have been the main medical experts who have researched and treated TS. These specialists have been well represented on the medical and scientific advisory boards to the TSA. A parent of a child with TS gave the author the following advice on choosing a physician: "We don't care if it's a psychiatrist or a neurologist, but we do care that it is someone who has experience treating Tourette's syndrome and who will treat all the symptoms."

Chronic motor (or vocal) tic disorder is managed similarly to TS and not discussed separately.

Discussed below are proven treatments for tics from replicated controlled studies, other treatments for tics, treatment for obsessive-compulsive symptoms in patients with tics, treatment for ADHD in patients with tics, and treatment for other symptoms in patients with tics.

- Proven treatments for tics from replicated controlled studies
    -
        - o Dopamine D2 receptor antagonists: In 1959, soon after its introduction, chlorpromazine was reported to dramatically improve tic severity (Bockner, 1959). Since then, several allocation RCTs with various neuroleptics (eg, haloperidol, fluphenazine, pimozide) have confirmed these initial results (Kurlan, 1995). On average, tic severity declines by approximately 50-80% with neuroleptic treatment.
            - o
                - ▪ Neuroleptic drugs are the current standard in terms of efficacy in the treatment of tics. They can be effective at doses far below the usual treatment dose for psychosis, and most

adverse effects are manageable with pharmacologic manipulations. Unfortunately, many patients do not tolerate acute adverse effects (most commonly sedation, weight gain, depression, lethargy, and akathisia), and prolonged treatment poses a small risk of tardive dyskinesia. Therefore, other treatments have been investigated.
- Risperidone, olanzapine, and ziprasidone produced at least as much clinical effect as a classic neuroleptic comparator, with fewer adverse effects (Bruggeman, 2001; Onofrj, 2000; Sallee, 2000). A small study of clozapine suggested little effect (Caine, 1979). Some physicians have found the dopamine D2R partial agonist aripiprazole effective for tic suppression (Murphy, 2005), but RCT data are not yet available.
- Metoclopramide is a D2 receptor antagonist that is usually used for nausea. A case series (Acosta, 2004) and a RCT (Nicolson, 2005) suggest it treats tics with good short-term tolerability.
- o Dopamine agonists: Paradoxically, several mixed dopamine agonists have also been proven effective in reducing tic frequency (Anca, 2001; Black, 2000; Gilbert, 2000; Gilbert, 2003). To date, they have been tested exclusively in relatively low doses, partly because of a theory that, at these doses, they must antagonize dopamine function by selective action at presynaptic receptors. However, accumulating evidence suggests that this rationale is faulty, and trials with higher doses may be expected. Similarly, the present author and colleagues currently are conducting a placebo-controlled double-blind study of levodopa as a treatment for tics (Black, 2002).
- o Habit reversal therapy: Five RCTs have demonstrated the efficacy of a specific form of behavior therapy for tics (Azrin, 1980; Azrin, 1990; O'Connor, 2001; Wilhelm, 2003; Deckersbach, 2005). The originally tested treatment consisted of a package of interventions called habit reversal therapy (Black, 2003): monitoring, relaxation, and other nonspecific elements of behavior therapy. The most important element is application of a competing response whenever the patient notices either a tic or the urge to tic.
  - o
    - Initially, heavy effort on the part of the patient may be needed. However, in all 4 reported studies, at long-term follow-up at least one half of treated patients had greater than 75% reduction in overall tic severity, whether based on self-report of home tic counts or on blind review of a videotape filmed in the clinic.
    - The effort expended by patients decreased dramatically as tic frequency declined, usually within the first few weeks of treatment. No substitution of other tics was noted, which commonly occurs when patients substitute a volitional action on a haphazard basis (see Image 5).
    - Anecdotally, others have not found such impressive results, which may relate to patient selection or therapeutic technique. Further replication studies are being supported by the TSA.
    - Interestingly, several elements of this treatment are reminiscent of treatments used by Brissaud in 1902 (though with a radically different theoretical background) (Kushner, 1999). Some data now explain why his treatments may not

have been as effective. If the competing response is not paired with tic urges or tics, no benefit is observed (Miltenberger, 1998). Similarly, other behavior therapies used in the last several decades (eg, massed practice) are relatively ineffective.

- Since the realization of the failures of psychoanalysis in treating tic disorders in the 1970s, patients and physicians have looked askance at psychological treatment, including behavior therapy. The available data no longer justify this view. In fact, the plausibility of behavior therapy makes some sense on an intuitive level. Since tics respond briefly even to random environmental influences, it is not surprising that a well-designed behavioral intervention may produce more satisfactory results. Note that this is very different to simply telling the patient not to tic, or "trying harder," neither of which tends to be effective over the long run (Woods and Himle, 2004).
- A parallel is present with obsessions and compulsions, which share many phenomenologic characteristics with tics. OCD symptoms do not respond well to psychodynamic treatment but are effectively treated with behavior therapy. Such treatment has biologic effects, such as normalization of abnormally high baseline metabolism in orbitofrontal cortex. Case series have shown a reduction in tics by using the same behavior therapy method proven to benefit patients with OCD (Jenkins, 2001; Woods, 2000).

- Other treatments for tics
  -
    - Guanfacine: This agent was tested in an RCT in children with both ADHD and chronic tic disorders (Scahill, 2001). The drug was clearly superior to placebo in the reduction of both ADHD and tic symptoms (31% on average), with few adverse effects. It also has been shown to be efficacious in adults with nontic ADHD.
    - Clonidine: This drug has frequently been used to treat tics. A large RCT confirmed its efficacy for both ADHD symptoms and tics in patients with TS (TSSG, 2002). Clonidine or guanfacine maybe appropriate as a first agent in many patients.
    - Norepinephrine reuptake inhibitors: Both desipramine and atomoxetine have shown definite though modest benefit for tics in tic patients being treated for ADHD (Spencer, 2002; Allen, 2005).
    - Botulinum toxin injections and oral baclofen: After enthusiastic retrospective reports, blinded trials of these 2 agents have revealed statistically significant but clinically modest benefit compared to placebo (Marras, 2001). Botulinum toxin injections may improve urges or sensory tics, as well as observable tics, and it may be the treatment of choice for patients with a single, especially problematic, dystonic tic.
    - Tetrabenazine: This is a presynaptic dopamine-depleting agent with the advantage that it has not been reported to cause tardive movement disorders. A retrospective report noted marked clinical improvement in 57% of 47 patients with TS (Jankovic, 1997). Its acute adverse effects are similar to those of neuroleptics. Tetrabenazine is an orphan drug in the US. However, it is available to patients from the manufacturer in England via the named patient use exception of the US Food and Drug Administration (FDA).

- o Baclofen: This drug has little effect on average, but it also has relatively few adverse effects and may be appropriate in select patients (Singer, 2001).
- o Benzodiazepines: Retrospective reports suggest that benzodiazepines, such as clonazepam, reduce tic severity in some patients (Truong, 1988). The effect is less than that of neuroleptics and probably nonspecific. Adverse effects are fairly common. However, clonazepam is tolerated better than haloperidol on average, and when no clinical pressure exists for urgent treatment, it is a reasonable option.
- o Levetiracetam: An open series of 60 children and adolescents with doses titrated to 1000 to 2000 mg/d suggests this medication is well tolerated and may prove effective (Awaad, 2005).
- o SSRIs: These agents (eg, clomipramine, fluoxetine) improve tics in some patients, worsen them in others, and have no effect on tics in yet others (Bruun, 1998; Iancu, 1995; Kurlan, 1993; Scahill, 1997). SSRIs may be reasonable first agents in patients with significant depression or OCD symptoms.
- o Ondansetron: A double-blind RCT in patients aged 12-46 years with TS of ondansetron 8-24 mg/d showed efficacy for a self-report but not an observer-rated measure of clinical improvement (Toren, 2005).
- o Naltrexone/naloxone: These have been reported helpful in a few patients, but other studies have shown transient worsening of tics with opioid antagonists (Chappell, 1992; Erenberg, 1992). An RCT of naloxone showed some benefit at low doses, but worsening of tics at higher doses (van Wattum, 2000). Case reports also have described benefit with opioid agonists (Chappell, 1993; McConville, 1994).
- o Cannabinoids: Two RCTs support the efficacy of cannabinoids in reducing tic severity in some patients (Muller-Vahl, 2003).
- o Nicotine: Both nicotine and a nicotine antagonist, mecamylamine, have been touted as treatments for tics. The antagonist has few adverse effects at the doses recommended, but 1 RCT found no statistically significant effect versus placebo (Silver, 2001). A small blind study did show some benefit (Orth, *Brain,* 2005). However, given that nicotine is not a safe drug, its therapeutic use should await more compelling proof of efficacy.
- o Repetitive transcranial magnetic stimulation (rTMS) has not been effective in TS (Orth, *Clin Neurophysiol,* 2005).
- o Surgical treatments are described in Surgical Care.
- Treatment for obsessive-compulsive symptoms in patients with tics
  - •
  - o Initial treatment of OCD in patients with tics usually consists of a selective serotonin reuptake inhibitor, generally at 3-4 times the antidepressant dose. More recently, risperidone monotherapy has been advocated as a first treatment, especially in patients with significant impairment from tics and from OC symptoms.
  - o Behavior therapy for OCD (eg, exposure and response prevention) is clearly proven to be effective (Hembree, 2003). A trial of behavior therapy is indicated for every patient with clinically significant OCD symptoms unless the symptoms are substantially remitted by another intervention.
  - o In patients with tics (and perhaps in their relatives), obsessions respond better to fluoxetine plus haloperidol than to fluoxetine plus placebo (McDougle, 1994). Therefore, even if tics are well-controlled,

addition of a D2 antagonist is indicated if bothersome OCD symptoms do not respond adequately to conventional initial treatment.

- o In a highly select group of patients who fit research criteria for sudden onset of tics or OCD associated with a proven recent streptococcal infection, OCD responded dramatically to intravenous immunoglobulin G (IVIG) or plasmapheresis (Perlmutter, 1999).
- o See the eMedicine article on [Obsessive-Compulsive Disorder](#) or the 2003 review by Miguel and colleagues for further details of OCD treatment.

- Treatment for ADHD in patients with tics
  - o ADHD can be significant in patients referred for treatment of TS.
  - o Stimulants such as methylphenidate or dextroamphetamine represent the oldest class of psychotropic drugs still in common use, and have known safety profiles. They are the most effective treatments of ADHD. Their labeling includes warnings that they may cause tics (Castellanos, 1997), but several recent prospective studies show that their effect on tics is at worst temporary, even with continued use (Gadow, 1992; Gadow, 1999; Sverd, 1989; TSSG, 2002).
  - o Stimulant use in people with ADHD does not cause future drug abuse and may even prevent it (Biederman, 1999).
  - o A comorbid tic disorder should not be considered a serious contraindication to the use of stimulants for treatment of ADHD (Kurlan, 2003). Several studies have shown that stimulants do not cause lasting worsening of tics.
  - o Methylphenidate may be better tolerated than dextroamphetamine in people with TS (Castellanos, 1997).
  - o Clonidine has also been proven useful for ADHD in people with TS. The benefits of clonidine and methylphenidate are additive (TSSG, 2002). Guanfacine most likely has similar effects.
  - o RCTs have also shown that desipramine and atomoxetine help with ADHD symptoms in people with TS (Spencer, 2002; Allen, 2005); tics also improve slightly.
  - o A double-blind RCT showed possible benefit for selegiline on ADHD symptoms and tics (Feigin, 1996).
  - o Bupropion may benefit ADHD but may temporarily worsen tics (Spencer, 1993).
  - o See the eMedicine article on [Attention Deficit/Hyperactivity Disorder](#) for further details on the conventional pharmacologic and behavioral treatment of ADHD.

- Treatment for other symptoms in patients with tics
  - o In carefully selected, tic-free adolescents with affect-laden episodes of aggression, replicated results from controlled trials show substantial efficacy of divalproex (Donovan, 2000).
  - o Whether these results can be confirmed for rage attacks in TS remains to be proven.
  - o Selective serotonin reuptake inhibitors (SSRIs) may also be useful (Bruun, 1998).
  - o Research on the management of (other) conduct disorder symptoms in TS is sorely needed.

Surgical Care

Stereotactic neurosurgery, either to place deep brain stimulators or to ablate tissue, is indicated only rarely for the treatment of obsessions, compulsions, and possibly tics. Recent case reports suggest deep brain stimulation (DBS) in various sites may be helpful. However, this approach is limited to patients with exceptionally debilitating symptoms and those in whom prior, thorough trials of less dramatic interventions were ineffective. Such surgery should be carried out only in referral centers experienced with these procedures and after multispecialty evaluation of the patient.

Consultations

- Patients should be evaluated at least once by someone with experience treating patients with TS, and they should be informed about how to contact a local support group or the national TSA office.
- Additional referrals may be needed for the following measures based on the needs of the patient and the skills of the primary physician evaluating the patient's TS:
    -
        - Botulinum injections
        - Habit reversal therapy for tics; behavior therapy for OCD, ADHD, or conduct disorder; or psychiatric care of OCD, ADHD, or comorbid anxiety or depressive illness
        - Neuropsychological testing and educational interventions to address learning disabilities or to help formulate an individualized education program
        - Education of teachers, classmates, or work colleagues may be helpful (Woods and Marcks, 2005).
        - Legal assistance (eg, to protect a child's educational rights under the federal Individuals with Disabilities Education Act or for protection under the Americans with Disabilities Act)
        - Family counseling

Diet

- Ordinary diet is not known to have an effect on tics.
- Some concentrated dietary supplements used as drugs (also called nutraceuticals) may affect tic severity.
    -
        - For example, one of the author's patients had a marked increase in tic severity while taking an herbal product marketed for weight loss and containing ephedrine, ginkgo, caffeine, guaraná, and other ingredients.
        - Some nutraceuticals may possibly improve tic symptoms, but no adequate evidence exists at present.
        - Furthermore, because these products do not undergo the meticulous scrutiny required of other drugs by the FDA, their safety in general is not well established. This is important since a large majority of patients with TS have used these drugs (Mantel, 2004).
        - However, both the National Institutes of Health and the TSA have expressed interest in supporting properly designed research on such

treatments, and adequately tested products may be hoped for in the future.

Activity

Activity may be undertaken as the patient wishes.

Medication

Choice of initial treatment depends largely on the following factors: (1) which symptoms (eg, tics, obsessions, impulsivity) are most problematic at presentation, (2) the severity of presenting symptoms, (3) the patient's sense of urgency for treatment, and (4) the patient's aversion to risk of likely or unlikely adverse effects.

For many patients the most reasonable option is to forgo treatment altogether. Education of patient and family (and teacher or employer) may suffice. If a single dystonic tic predominates, especially in the face, neck, or larynx, botulinum toxin injection is a reasonable first treatment.

If ADHD symptoms predominate the presentation, they can be addressed first. Guanfacine or clonidine has the best evidence for also improving tics; stimulants have the best efficacy for ADHD symptoms. Other options are noted in the treatment section above.

If OCD symptoms predominate the presentation, they can be addressed first, most likely with a serotonin reuptake inhibitor and/or risperidone.

If severe tics are the presenting symptom, a newer antipsychotic agent may be the best initial treatment. The dose used is substantially lower than the dose used to treat psychosis.

If tics are mild to moderate in severity or if they occur in risk-averse patients, any of the non-antipsychotic treatments described in Medical Care can be tried sequentially. Clonidine may be the most widely used, while habit reversal therapy likely has the lowest risk of serious adverse effect.

The combination of dopamine antagonists with stimulants is used sometimes, yet it makes little enough sense pharmacologically that other options should be explored thoroughly.

Drug Category: *Antipsychotic agents*

These agents affect dopamine receptors but also affect serotonin receptors involved with frontal lobe functions.

Drug Name	Risperidone (Risperdal)

Description	Mixed dopamine-serotonin antagonist. Compared with other antipsychotics, may produce less sedation. Theoretically has a lower risk of tardive dyskinesia than haloperidol; clearly produces fewer acute adverse effects.
Adult Dose	0.25-3 mg PO bid or equivalent dose qhs (mean final daily dose in 1 multicenter study was 3.8 mg)
Pediatric Dose	Not established; 0.25-2 mg PO bid or equivalent dose qhs
Contraindications	Documented hypersensitivity
Interactions	Carbamazepine may decrease effects; may inhibit effects of levodopa; clozapine may increase levels
Precautions	Adverse effects of all antipsychotics may include sedation, akathisia, dystonia, parkinsonism, hyperprolactinemia, dysregulation of body temperature, and neuroleptic malignant syndrome; small risk of tardive dyskinesia at doses used to treat TS
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Drug Name	Olanzapine (Zyprexa)
Description	Atypical antipsychotic that produces fewer acute parkinsonian, akathitic, or dystonic adverse effects than haloperidol. In schizophrenia, has approximately 33%-50% the risk of tardive dyskinesia compared with haloperidol.
Adult Dose	2.5-20 mg PO qhs
Pediatric Dose	Not established; 2.5-5 mg PO qhs
Contraindications	Documented hypersensitivity
Interactions	Fluvoxamine may increase effects; antihypertensives may increase risk of hypotension and orthostatic hypotension; levodopa, pergolide, bromocriptine, charcoal, carbamazepine, omeprazole, rifampin, and cigarette smoking may decrease effects
Precautions	Adverse effects of all antipsychotics may include sedation, akathisia, dystonia, parkinsonism, hyperprolactinemia, dysregulation of body temperature, and neuroleptic malignant syndrome; small risk of tardive dyskinesia at doses used to treat TS; causes significant weight gain in many, though relative risk versus other antipsychotics controversial
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Drug Name	Ziprasidone (Geodon)
Description	Atypical antipsychotic. In a head-to-head study, caused less weight gain than olanzapine in schizophrenia.
Adult Dose	Not established; 10-40 mg PO qhs

Pediatric Dose	5-40 mg PO qhs (mean final daily dose in 1 study was 28.2 mg)
Contraindications	Documented hypersensitivity; patients with clinical or ECG evidence of long QT syndrome or those taking drugs that cause torsades de pointes or prolong QT interval (see CARE Foundation)
Interactions	CYP-450-3A4 inhibitors (eg, erythromycin, ketoconazole) may increase serum levels; CYP-450-3A4 inducers (eg, carbamazepine, rifampin) may decrease serum levels; drugs that increase QT/QTc interval (eg, amiodarone, fluoroquinolones) increase risk of life-threatening arrhythmias
Precautions	Adverse effects of all antipsychotics may include sedation, akathisia, dystonia, parkinsonism, hyperprolactinemia, dysregulation of body temperature, and neuroleptic malignant syndrome; small risk of tardive dyskinesia at doses used to treat TS; causes prolongation of QT interval more so than risperidone, olanzapine, or haloperidol, though less than thioridazine (Mellaril); for other drugs, ECG effect is associated with serious cardiac arrhythmias
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Drug Name	Haloperidol (Haldol)
Description	Anti-tic efficacy of haloperidol has been known for 40 y.
Adult Dose	0.25-5 mg PO qhs
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; narrow-angle glaucoma; bone marrow suppression; severe cardiac or liver disease; severe hypotension
Interactions	May increase serum concentrations of TCAs and hypotensive action of antihypertensive agents; phenobarbital or carbamazepine may decrease effects; anticholinergics may increase intraocular pressure; lithium may cause encephalopathy-like syndrome
Precautions	Adverse effects of all antipsychotics may include sedation, akathisia, dystonia, parkinsonism, hyperprolactinemia, dysregulation of body temperature, and neuroleptic malignant syndrome; small risk of tardive dyskinesia at doses used to treat TS; possible dysphoria, sometimes of significant intensity; several cases of school phobia apparently related to haloperidol have been reported
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Drug Name	Fluphenazine (Prolixin)

Description	High-potency typical antipsychotic with pharmacology similar to that of haloperidol. Proven to diminish tic severity.
Adult Dose	0.25-5 mg PO qhs
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; narrow-angle glaucoma
Interactions	May potentiate effects of narcotics, including respiratory depression; lithium increases CNS effects; barbiturates may decrease effects
Precautions	Besides extrapyramidal symptoms as with haloperidol, mild leukocytosis, leukopenia, and eosinophilia occasionally occur; dermatologic reactions common; watch for urinary retention, blurred vision, dry mouth, and constipation due to anticholinergic effects
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Drug Name	Pimozide (Orap)
Description	Atypical neuroleptic approved by FDA for treatment of tics. Rarely indicated in current practice: offers no substantial advantage over other high-potency neuroleptics (risperidone and olanzapine better tolerated), has significant drug interactions, and slight but serious risk of cardiac arrhythmia.
Adult Dose	1-6 mg PO qhs; manufacturer recommends maximum total daily dosage of 10 mg
Pediatric Dose	0.0 5 mg/kg or 1 mg PO qhs initially; not to exceed 0.2 mg/kg or 10 mg PO qhs
Contraindications	Documented hypersensitivity; history of cardiac arrhythmias or long-QT syndrome; concurrent macrolide antibiotics
Interactions	Increases toxicity of MAOIs, alfentanil, CNS depressants, guanabenz
Precautions	ECG recommended at initiation of therapy and at regular intervals thereafter; careful observation for extrapyramidal symptoms especially needed in geriatric patients
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Drug Category: *Presynaptic dopamine-depleting agents*

These agents suppress tics. Presynaptic depleters have acute adverse effects similar to neuroleptics but theoretically may avoid risk of tardive dyskinesia.

Drug Name	Tetrabenazine
Description	Investigational drug not approved by US FDA. May be obtained from manufacturer via named patient protocol (see Tetrabenazine).
Adult Dose	25-100 mg PO qhs
Pediatric Dose	Not recommended
Contraindications	Documented hypersensitivity
Interactions	Not established
Precautions	Investigational drug
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Drug Category: *Dopamine agonist*

These agents suppress tics. Dopamine agonists have few adverse effects and modest but proven efficacy.

Drug Name	Pergolide (Permax)
Description	**Pergolide was withdrawn from the US market** March 29, 2007, because of heart valve damage resulting in cardiac valve regurgitation. It is important not to abruptly stop pergolide. Health care professionals should assess patients' need for dopamine agonist (DA) therapy and consider alternative treatment. If continued treatment with a DA is needed, another DA should be substituted for pergolide. For more information, see FDA MedWatch Product Safety Alert and Medscape Alerts: Pergolide Withdrawn From US Market. Mixed ergot derivative dopamine agonist. Proven effective for tic suppression.
Adult Dose	Not established; 0.05-1 mg PO qhs to tid
Pediatric Dose	0.05 mg PO qhs to 0.1 mg PO tid
Contraindications	Documented hypersensitivity
Interactions	Dopamine antagonists such as neuroleptics (eg, phenothiazines, butyrophenones, thioxanthenes) or metoclopramide may diminish effectiveness; because pergolide is >90% bound to plasma proteins, caution when administered with other drugs known to affect protein binding
Precautions	May cause valvular heart disease (yearly echocardiograms recommended for patients on chronic therapy); inhibits secretion of prolactin; causes transient rise in serum concentrations of growth hormone and decrease in serum

	concentrations of luteinizing hormone; adverse effects include nausea, hypotension, hallucinations, and somnolence; use caution in patients who have been treated for cardiac dysrhythmias; may cause or exacerbate preexisting states of confusion and hallucinations or dyskinesia
Pregnancy	B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Drug Category: *Alpha2-adrenergic agonists*

These agents are used for tic suppression or for treatment of ADHD.

Drug Name	Clonidine (Catapres)
Description	Less effective than neuroleptics in suppressing tics and stimulants at treating ADHD symptoms. However, has modest adverse effects and benefits some patients.
Adult Dose	0.05-0.3 mg PO bid/divided tid or by transdermal patch
Pediatric Dose	0.05-0.1 mg bid/qid PO
Contraindications	Documented hypersensitivity
Interactions	TCAs inhibit hypotensive effects; beta-blockers may potentiate bradycardia; TCAs may enhance hypertensive response associated with abrupt withdrawal; hypotensive effects enhanced by narcotic analgesics
Precautions	Sedation is most common limiting adverse effect; hypotension can be problematic; do not discontinue suddenly because of risk of rebound hypertension
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Drug Name	Guanfacine (Tenex)
Description	Proven in RCT to benefit both ADHD and, to lesser extent, tic severity in children with chronic tics and ADHD.
Adult Dose	0.5-2 mg PO tid
Pediatric Dose	0.5-1 mg PO tid
Contraindications	Documented hypersensitivity
Interactions	Increases effect of other hypotensive agents; TCAs may decrease hypotensive effects
Precautions	Caution in hepatic impairment, severe coronary insufficiency, recent myocardial infarction; taper dosage gradually
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Drug Category: *Skeletal Muscle Relaxant*

These agents may suppress the severity of tics.

Drug Name	Baclofen (Lioresal)
Description	Slightly superior to placebo in RCT in children with TS, though primary effect may not be on tics but on other symptoms; adverse effects modest.
Adult Dose	10-20 mg PO tid/qid
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Opiate analgesics, benzodiazepines, alcohol, TCAs, guanabenz, MAOIs, clindamycin, and hypertensive agents may increase effects
Precautions	Caution in patients with history of autonomic dysreflexia and when spasticity utilized to increase function; autonomic dysreflexia can result from withdrawal of this medication
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Drug Category: *Benzodiazepines*

By binding to specific receptor sites, these agents appear to potentiate the effects of GABA and facilitate inhibitory GABA neurotransmission and other inhibitory transmitters.

Drug Name	Clonazepam (Klonopin)
Description	Reduces tics in some patients, although blinded controlled studies are lacking. Half-life >30 h, but clinical effect wanes more rapidly.
Adult Dose	0.5-6 mg (possibly up to 12 mg) PO qhs or divided bid
Pediatric Dose	0.5-6 mg PO qhs or divided bid
Contraindications	Documented hypersensitivity; severe liver disease; acute narrow-angle glaucoma
Interactions	Phenytoin and barbiturates may reduce effects; CNS depressants increase toxicity (clinically significant pharmacokinetic interactions not common)
Precautions	Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy does not affect them adversely; class IV controlled substance; most problematic adverse effects are sedation, cognitive difficulties, ataxia, and disinhibition
Pregnancy	D - Fetal risk shown in humans; use only if benefits

	outweigh risk to fetus

Drug Category: *Neuromuscular blockers*

These agents suppression of tics and possibly premonitory sensations.

Drug Name	Botulinum toxin A (BOTOX®)
Description	Inhibits release of acetylcholine at neuromuscular junction; injected directly into muscle. Most useful for dystonic tics (eg, sustained eye closure) or only 1 or 2 especially problematic tics (eg, repeatedly flinging head to 1 side causing neck pain and broken glasses). Tics and tic urges may improve; effect can be seen in absence of gross weakness. Successful outcomes require substantial specialized experience in the treating physician.
Adult Dose	Varies with affected muscle to be injected, from approximately 1.25 U in orbicularis oculi to approximately 200 U total in neck or extremity muscles
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Aminoglycosides or drugs that interfere with neuromuscular transmission may potentiate effects
Precautions	Do not exceed recommended dosages and frequencies of administration; presence of antibodies to botulinum toxin type A may reduce effects
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Follow-up

Further Inpatient Care

Further Outpatient Care

In/Out Patient Meds

Transfer

Deterrence/Prevention

Complications

- See Mortality/Morbidity.

Prognosis

- See [Age](#).

Patient Education

- The TSA and its local chapters can be a valuable aid in patient education (see the [TSA Web site](#)).

Miscellaneous

Medical/Legal Pitfalls

- No reason exists to suspect that an individual has diminished capacity (eg, the ability to consent to treatment, participate in research, or make a will) because of a diagnosis of TS.
- Parents of children with TS frequently ask whether TS causes diminished responsibility, eg, "When he hits his brother during a rage attack, is that him or is that the Tourette disease?" Occasionally the same question comes up in the legal arena, eg, "Should Mr A be exculpated for a crime he committed because he has TS?"
    -
        - Group studies clearly show that TS can cause complex unwanted behavior. Sometimes, the answer is obvious, and sometimes, all that is needed is education about what is and is not typical of TS. The TSA and its local affiliates produce some excellent education materials addressed to family, friends, or teachers.
        - Convincingly answering what caused a specific complex act in an individual patient often is impossible.
        - The author finds that discussions about whether the child is guilty tend to be fruitless. It is more helpful to focus on interventions and results: Are we likely to fix this problem by writing a prescription, by providing rewards and punishments, by instructing the patient to stop doing it, or by simply ignoring it?
        - The public does not necessarily credit the physician with indisputable authority regarding guilt, forgiveness, or legal culpability. However, physicians speak from a position of strength when they focus on available treatments and likely prognosis. Also, this approach focuses attention away from punishment and toward problem solving.
- Some rights of people with TS are protected by US federal legislation.
    -
        - Examples include the right to public education in the least restrictive educational setting (Individuals with Disabilities Education Act) and the right to reasonable accommodations in public settings or the workplace (Americans with Disabilities Act).
        - Legal advice and discussion with experienced support group members can be helpful in deciding when and how to pursue legal remedies under these laws.

Test Questions

Question 1:

A 20-year-old man reports, "I touch my nose all the time," touching 1 side then the other side about 100 times a day. This seems to relieve an odd, uncomfortable feeling in the nose. He has no concerns that something bad would happen if he stopped touching his nose, though he feels that stopping may be difficult. His behavior is worse at times of stress, and he first noticed it the week before he started college about a year ago. He sings in a choral group and says he never touches his nose on stage, though sometimes after finishing a performance, the nose touching is worse for a few minutes.Evaluations by an otolaryngologist and an allergist have not uncovered any relevant pathology. On examination, he does not touch his nose for several minutes, until the doctor turns away to read his records. Later in the visit, he touches his nose, first the right and then the left side, every minute or two while discussing an upcoming college football game. He stretches his neck repeatedly, but no other unusual movements are observed. Which of the following best describes his nose touching?

A. Bad habit
B. Complex tic
C. Hysterical symptom
D. Somatic obsession
E. Choreiform movement

The correct answer is B: The history and examination describe a complex motor tic; the effects of suppression, distractibility, and stress are typical. A hysterical or conversion symptom refers to simulated illness that is not accounted for by another illness, whereas this movement is entirely typical. He does not describe a bothersome mental image or excessive worry preceding the movement but rather a physical sensation, and the movement itself would be a compulsion rather than an obsession if it were in response to such a concern. Chorea is distributed randomly rather than repetitively and is perceived as involuntary, whereas this patient says, "I touch my nose." The behavior perhaps can be described as a bad habit, but description as a tic is much more informative.

Question 2:

Which of the following treatments is effective for tics, as shown in randomized controlled trials?

A. Treatment with fluoxetine (Prozac)
B. Psychoanalytic psychotherapy

C. Treatment with valerian root extract

D. Habit reversal therapy

E. Treatment with acetaminophen

The correct answer is D: Habit reversal therapy is more effective than either a wait-list condition or a placebo therapy, as shown in 3 studies with blinded outcome assessments.

Question 1 (T/F):

Stimulants (eg, methylphenidate [Ritalin]) are contraindicated in Tourette syndrome.

The correct answer is False: Several studies have shown that stimulants do not cause lasting worsening of tics. A comorbid tic disorder should not be considered a serious contraindication to the use of stimulants for treatment of ADHD.

Question 2 (T/F):

Currently, the most effective medications for treatment of tics are antipsychotic drugs.

The correct answer is True: Neuroleptics and newer antipsychotics are the most effective medications for tics, but they are not usually the best tolerated drugs.

Question 3 (T/F):

The concordance ratio for monozygotic (MZ) versus dizygotic (DZ) twins in Tourette syndrome is about 5:1.

The correct answer is True: Genetic factors are implicated in twin studies, which show that the ratio of concordance in MZ versus DZ twin pairs is approximately 5:1.

Question 4 (T/F):

The presence of chronic motor and vocal tics is diagnostic of Tourette syndrome.

The correct answer is False: Tics can be caused by many other systemic or neurological illnesses, such as Wilson disease, carbon monoxide poisoning, neuroacanthocytosis, or frontal lobe degeneration. Motor and vocal tics and compulsions were also frequently reported in patients who survived the encephalitis lethargica epidemic in the 1910s and 1920s.


Further Reading

MULTIMEDIA

Media file 1: Tourette syndrome and other tic disorders. Schematic of the hypothetical reorganization of the basal ganglia output in tic disorders, with excitatory projections (open arrows) and inhibitory projections (solid arrows). Line thickness represents the relative magnitude of activity. When a discrete set of striatal neurons becomes active inappropriately (right), aberrant inhibition of a discrete set of internal segment of globus pallidus (GPi) neurons occurs. The abnormally inhibited GPi neurons disinhibit thalamocortical mechanisms involved in a specific unwanted competing motor pattern, resulting in a stereotyped involuntary movement.
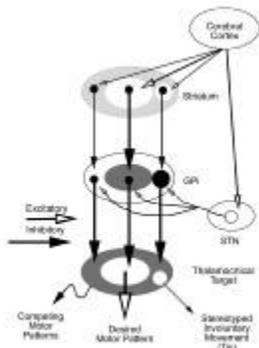
Media type: Image

Media file 2: Tourette syndrome and other tic disorders. Segregated anatomy of the frontal-subcortical circuits: dorsolateral (blue), lateral orbitofrontal (green), and anterior cingulate (red) circuits in the striatum (top), pallidum (center), and mediodorsal thalamus (bottom).
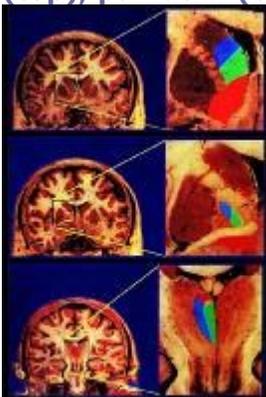
Media type: Image

Media file 3: Tourette syndrome and other tic disorders. Graphic shows the relative likelihood of lifetime sensory tics in a given region, as based on self-report of patients with Tourette syndrome. Overt tics are distributed

similarly.
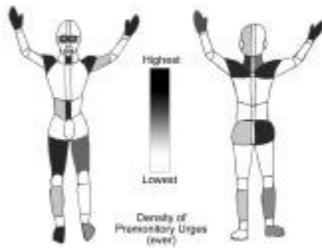
Media type: Image

Media file 4: Tourette syndrome and other tic disorders. Immunologic response found in patients with Sydenham chorea is also found in patients with Tourette syndrome and obsessive-compulsive disorder. Points on the graph represent percent expression of D8/17 antigen on circulating B lymphocytes.
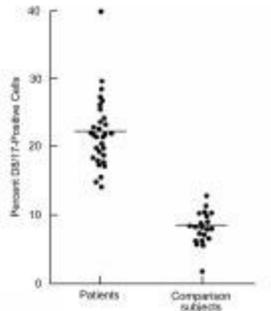
Horizontal line through scatter plot represents the group mean

Media type: Graph

Media file 5: Tourette syndrome and other tic disorders. In a randomized controlled trial of habit reversal therapy (HRT), results differed significantly from those of a control therapy (massed practice; *P* <.001, analysis of variance). The HRT group had a 97% reduction in tics at 18-month follow-up, with 80% of patients tic-free.
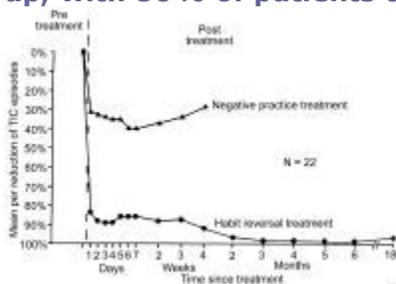
Media type: Graph

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