Tourette Syndrome and Tic Disorders: A Decade of Progress

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ABSTRACT

Objective: This is a review of progress made in the understanding of Tourette syndrome (TS) during the past decade including models of pathogenesis, state-of-the-art assessment techniques, and treatment. **Method:** Computerized literature searches were conducted under the key words "Tourette syndrome," "Tourette disorder," and "tics." Only references from 1996–2006 were included. **Results:** Studies have documented the natural history of TS and the finding that tics usually improve by the end of the second decade of life. It has also become clear that TS frequently co-occurs with attention-deficit/hyperactivity disorder), obsessive-compulsive disorder, and a range of other mood and anxiety disorders. These comorbid conditions are often the major source of impairment for the affected child. Advances have also been made in understanding the underlying neurobiology of TS using in vivo neuroimaging and neurophysiology techniques. Progress on the genetic front has been less rapid. Proper diagnosis and education (involving the affected child and his or her parents, teachers, and peers) are essential prerequisites to the successful management of children with TS. When necessary, modestly effective antitic medications are available, although intervening to treat the comorbid attention-deficit/hyperactivity disorder and/or obsessive-compulsive disorder is usually the place to start. **Conclusions:** Prospective longitudinal studies and randomized clinical trials have led to the refinement of several models of pathogenesis and advanced our evidence base regarding treatment options. However, fully explanatory models are needed that would allow for more accurate prognosis and the development of targeted and efficacious treatments. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(8):947–968. **Key Words:** Tourette disorder, Tourette syndrome, tic disorder, review.

Tics have been the subject of medical speculation for hundreds of years (Kushner, 1999). Putative explanations for the occurrence of tics and their high degree of variability have included inherited factors, influence of toxins, and emotional, psychological, or infectious processes. Although major gaps remain in our knowledge of the etiology of tics and the most effective treatment, the past decade has seen significant advances in our understanding of the neurophysiological mechanisms at work. Although no ideal treatment for tics has been established, randomized clinical trials have clarified the short-term benefits of a number of agents. This review summarizes the clinical features of tics, before briefly considering current models of pathogenesis and evidence-based interventions for Tourette syndrome (TS) and related conditions.

PHENOMENOLOGY

TS is a developmental neuropsychiatric disorder with childhood onset. There is no diagnostic test for TS. According to *DSM-IV-TR* (American Psychiatric Association, 2000), it is characterized by brief, stereotypical, but nonrhythmic movements and vocalizations

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called tics. Common tics include eye blinking, grimacing, jaw, neck, shoulder or limb movements, sniffing, grunting, chirping, or throat clearing. In the natural history of TS, motor tics often begin between the ages of 3 and 8, several years before the appearance of vocal tics. Tics typically follow a waxing and waning pattern of severity, intensity, and frequency (Leckman et al., 1998; Lin et al., 2002; Robertson et al., 1999). Tic severity usually peaks early during the second decade of life with many patients showing a marked reduction in severity by the end of adolescence (Bloch et al., 2006a; Coffey et al., 2004; Leckman et al., 1998; Pappert et al., 2003). Only 20% or fewer of children with TS continue to experience a moderate level of impairment of global functioning by the age of 20 years (Bloch et al., 2006a). However, tic disorders that persist into adulthood can be associated with the most severe symptoms including violent episodes of self-injurious motor tics (secondary to hitting or biting) or socially stigmatizing coprolalic utterances or gestures (e.g., shouting obscenities or racial slurs).

The description of tics as simply intermittent trains of involuntary motor discharge is incomplete. Many tics are often under partial voluntary control, evidenced by patients' capacity to suppress them for brief periods of time. A related feature of tics is that they are frequently associated with antecedent sensory phenomena, including a general sense of inner tension or focal "premonitory urges." These urges can be experienced as nearly irresistible. They can be a major source of impairment. An ineffable and fleeting feeling of relief often follows performance of a tic or series of tics (Banaschewski et al., 2003; Kwak et al., 2003a).

Tics often occur in discrete bouts over time scales of days to years (Peterson and Leckman, 1998). The bouts are characterized by brief periods of stable intertic intervals of short duration, typically 0.5 to 1.0 seconds. These bouts of tics have been shown to occur in bouts and interbout intervals that may last from minutes to several hours to even longer periods. It is possible that the waxing and waning of tic severity (over the course of months) and the peaking of worst-ever tic severity early in the second decade of life may reflect the same multiplicative processes that govern the timing of tic expression. A deeper understanding of these events may occur as we begin to understand the neural events involved in tic generation (at the millisecond time scale) (Leckman et al., 2006).

Tics are also sensitive to a number of factors including everyday psychosocial stress, anxiety, emotional excitement, and fatigue (Findley et al., 2003; Hoekstra et al., 2004a). Interestingly, activities that require focused attention and fine motor control, such as reading aloud, playing a musical instrument, engaging in certain sports (and even performing surgery) are commonly associated with the transient disappearance of tics.

Although much diminished, tics can occur during sleep. Polysomnographic studies indicate that sleep disturbance is frequently part of the TS picture with a decreased quality of sleep and increased arousal phenomena (Cohrs et al., 2001; Kostanecka-Endress et al., 2003). Associated comorbidities, particularly attention-deficit/hyperactivity disorder (ADHD) are also likely to contribute to sleeping difficulties (Ivanenko et al., 2004).

COMORBIDITY

Simple and transient tics in the absence of comorbid conditions are common and occur in at least 5% of children (Khalifa and von Knorring, 2003). In clinical samples TS alone is the exception rather than the rule (Scahill et al., 2005). ADHD is frequently diagnosed in children with TS, with a prevalence as high as 60% to 70% (Coffey et al., 2000; Eapen et al., 2004; Spencer et al., 1998). A high frequency of comorbid ADHD has also been observed in community samples (Khalifa and von Knorring, 2005; Kurlan et al., 2002; Scahill, 2005). This co-occurrence of TS and ADHD can be associated with disruptive behaviors such as aggression, explosive behavior, low frustration tolerance, and noncompliance (Budman et al., 2000; Kurlan et al., 2002; Snider et al., 2002). When comorbid ADHD is present, it is frequently associated with academic difficulties, peer rejection, and family conflict (Carter et al., 2000; Hoekstra et al., 2004c; Peterson et al., 2001a; Spencer et al., 2001; Sukhodolsky et al., 2003). The relationship of aggressive and explosive behavior ("rage attacks") with TS is unclear and controversial (Budman et al., 2000).

In clinical samples about 50% of patients with TS have prominent obsessive-compulsive (OC) symptoms. OC disorder (OCD) is far more common in children and adults with TS than without TS (Amercian Psychiatric Association, 2000). Analysis of vertical

transmission patterns in families suggests that OCD and TS may share some of the same underlying genetic vulnerability (Pauls, 2003). Of note, ''tic-related'' OCD is emerging as a specific subtype of OCD (Miguel et al., 2005). Several clinical series have documented that individuals with a tic-related form of OCD are more likely to report obsessions of symmetry and exactness and a need to do and redo activities to achieve a sense of completion or a sense of things looking, feeling, or sounding ''just right'' (Kwak 2003a; Woods et al., 2005). Children and adolescents with OCD are impaired in multiple domains of adaptive and emotional functioning. When comorbid OCD is present along with ADHD, there is an additional burden on social, school, and family functioning (Sukhodolsky et al., 2005).

The co-occurrence of depression and anxiety symptoms with TS may reflect the cumulative psychosocial burden of having tics or shared biological diatheses (Coffey et al., 2000; Kurlan et al., 2002; Lin et al., 2006). The fourfold increase in the frequency of migraines in patients with TS (Kwak et al., 2003b) suggests a possible shared etiology (Barbanti and Fabbrini, 2004; Breslau et al., 2003). Co-occurrence with autism has also been reported. Indeed, among autistic subjects, the prevalence of TS has been reported to be 6.2%, about 10 times the prevalence of the general population (Baron-Cohen et al., 1999; Kadesjo and Gillberg, 2000).

EPIDEMIOLOGY

Chronic motor and phonic tics and TS have been observed the world over, suggesting that it is not culture bound. Prevalence rates of TS and related conditions vary according to the source, age, and sex of the sample; the ascertainment procedures; and diagnostic system. Once considered an extremely rare disorder, current estimates of the prevalence of TS are approximately 4 to 6/1,000 children in European and Asian populations (Jin et al., 2005; Khalifa and von Knorring, 2003, 2005; Wang and Kuo, 2003). By contrast, simple and transient tics are quite common, affecting up to 6% to 20% of all children (Khalifa and von Knorring, 2003; Kurlan et al., 2002; Robertson, 2003).

Epidemiological studies involving direct observation indicate a highest prevalence of tics in the general population peak at 3 to 5 years of age (the typical age at onset for TS) and at 9 to 12 years of age (when the tics of TS usually reach their worst-ever point) (Gadow et al., 2002).

DIFFERENTIAL DIAGNOSIS

A number of conditions produce symptoms resembling the tics of TS, including myoclonus, tremors, chorea, athetosis, dystonias, akathisic movements, paroxysmal dyskinesias, and ballistic movements (Kompoliti and Goetz, 1998; Krauss and Jankovic, 2002; Saunders-Pullman et al., 1999). The differential diagnosis of TS includes genetic conditions such as Huntington's chorea, metabolic diseases such as Wilson's disease, structural diseases as in hemiballismus associated with insult to the subthalamic nucleus, post-infectious autoimmune processes such as Sydenham's chorea (SC), neuroacanthocytosis, and side effects of antipsychotic medications such as the dystonias and akathisia.

Complex motor tics may appear identical to other purposive movements (you know they are tics because they reappear repeatedly in bouts). In appearance complex tics may also be indistinguishable from some compulsive rituals, but they can be distinguished based on the antecedent presence of either premonitory urges or obsessional thoughts. The diagnosis of TS should be in doubt in the absence of simple tics. Vocal tics can be helpful in ruling out other diagnoses because they are rare in other neurological conditions. Exceptions include Huntington's disease and SC (Mercadante et al., 1997).

ETIOLOGY

A stress diathesis model involving the interaction of genetic and environmental risk factors is frequently invoked to explain the variable expression of tic disorders. The observed association between TS symptoms and stressful life events has been noted since the initial description by Gilles de la Tourette. Such contributing problems may find a common final pathway in the hypothalamic-pituitary-adrenal axis and the associated stress-related neurotransmitters and hormones and their targets. In support of this, data suggest that TS patients may have a heightened reactivity of the hypothalamic-pituitary-adrenal and noradrenergic sympathetic systems as compared with

healthy control subjects (Chappell et al., 1996; Findley et al., 2003).

Genetics

Genetic vulnerability factors have been implicated in the vertical transmission of TS and related disorders (Pauls, 2003). The pattern of hereditary transmission, in which twin studies revealed high concordance rates in monozygotic but not dizygotic twins, initially suggested major gene effects. Indeed, the results of segregation analyses are consistent with models of autosomal transmission set against a polygenic background. Family genetic studies have also reinforced the view that TS and some forms of OCD and ADHD are etiologically related to one another (Leckman et al., 2003; McMahon et al., 2003; Miguel et al., 2005; Nestadt et al., 2002).

Linkage strategies have suggested the importance of several chromosomal regions, including 11q23 (Merette et al., 2000), 4q, and 8p (Tourette Syndrome Association International Consortium for Genetics, 1999). However, a recent effort to confirm and extend the findings from the Tourette Syndrome Association International Consortium for Genetics has led to the identification of new regions and a failure to replicate the original findings (David Pauls, personal communication, 2005).

Identity-by-descent approaches, a technique that assumes that a few founder individuals contributed the vulnerability genes that are now distributed within a much larger population, have been used to study TS populations in South Africa, Costa Rica, and French-speaking Canada (Mathews et al., 2004). They implicate regions near the centromere of chromosome 2 as well as 6p, 8q, 11q, 14 q, 20q, 21q (Simonic et al., 1998), and X (Diaz-Anzaldua et al., 2004). Another large pedigree study in the United Kingdom involving linkage analysis of TS patients is suggestive of linkage at loci on chromosomes 5, 10, and 13 (Curtis et al., 2004).

In addition, a number of cytogenetic abnormalities have been reported in TS families (3 [3p21.3], 7 [7q35–36], 8 [8q21.4], 9 [9pter], and 18 [18q22.3]; Cuker et al., 2004; State et al., 2003). Among the more recent findings, Verkerk et al. (2003) reported the disruption of the contactin-associated protein 2 gene on chromosome 7. This gene encodes a membrane protein located at nodes of Ranvier of axons that may be important for the distribution of the K^+ channels, which would affect signal conduction along myelinated neurons. Most recently, Abelson et al. (2005) identified and mapped a de novo chromosome 13 inversion in a patient with TS. The gene *SLITRK1* was identified as a brain-expressed candidate gene mapping approximately 350 kb from the 13q31 breakpoint. Mutation screening of 174 patients with TS was undertaken with the resulting identification of a truncating frame-shift mutation in a second family affected with TS. In addition, two examples of a rare variant were identified in a highly conserved region of the 3′ untranslated region of the gene corresponding to a brain-expressed micro-RNA binding domain. In vitro studies showed that both the frame shift and the micro-RNA binding site variant had functional potential and were consistent with a loss-of-function mechanism. Studies of both *SLITRK1* and the micro-RNA predicted to bind in the variant-containing 3′ region showed expression in basal ganglia and deep layers of cortex (in both mouse and human). Future research is needed to confirm and expand on the initial findings. For example, if the candidate gene *Slit* and Trk-like family member 1 (*SLITRK1*) is confirmed as a gene of major effect, valid animal models of TS should be forthcoming.

With rare exceptions, such as *SLITRK1*, it is likely that multiple vulnerability genes play a role in the expression of TS and related disorders (Leckman et al., 2003; Zhang et al., 2002). Based on current theories of the pathogenesis of TS, several candidate genes have been assessed in people with TS, including various dopamine receptors (*DRD1*, *DRD2*, *DRD4*, and *DRD5*), the dopamine transporter, various noradrenergic genes (*ADRA2a*, *ADRA2C*, *DBH,* and *MAO-A*), and a few serotonergic genes (*5HTT*; Cheon et al., 2004; Comings, 2001; Lee et al., 2005). Genetic variation at any one of these loci is unlikely to be a major source of vulnerability to the disorder, but in concert these alleles could have cumulative effects and contribute to phenotypic variability.

Ultimately, to explain complex disorders with complex comorbidities such as TS, many techniques will be needed. More work is needed to explore other genetic and epigenetic mechanisms at work that could mimic the expression patterns seen in TS. A variety of genomic and proteomic approaches should also be undertaken to understand the genetics of TS (Hong et al., 2004; Tang et al., 2005).

Epigenetic Factors: Perinatal Events, Psychosocial Stress, Infection, and Immune Response

A number of epigenetic factors have been implicated in the pathogenesis of TS in addition to psychosocial stress, including gestational and perinatal insults, exposure to androgens, heat, and fatigue as well as postinfectious autoimmune mechanisms. For example, perinatal hypoxic/ischemic events appear to increase the risk of developing TS (Burd et al., 1999; Khalifa and von Knorring, 2005; Whitaker et al., 1997). One recent retrospective study added prenatal maternal smoking as a risk factor for TS (Mathews et al., 2006). Altering dopamine signaling may be a key mediator of episodic ischemic effects (Decker et al., 2003).

Male sex is a risk factor for TS. Although this could be understood by genetic mechanisms, frequent male-to-male transmissions within families appear to rule out the presence of an X-linked vulnerability gene. The increased prevalence of TS in males has led to the hypothesis that the presence of androgenic steroids during critical periods in fetal development may play a role in the later development of the illness (Peterson et al., 1998b). Observation of gender-related behaviors (consistent with elevated prenatal androgens) correlated with tic severity supports this notion (Alexander and Peterson, 2004). Although these effects may be due to androgenic steroids expressed early in development, it is likely that there are sex-specific patterns of gene expression in male versus female brains that influence their differentiation and function (Dewing et al., 2006).

Patients with TS report higher levels of psychosocial stress, and latent class modeling of prospective longitudinal data indicate that antecedent stresses can increase future tic and OC symptom severity (Findley et al., 2003; Lin et al., 2006). The TS patients also have significantly higher levels of CSF corticotrophin-releasing factor than either normal controls or non–tic-related OCD patients. Although the functional significance of this finding remains to be elucidated, these results are consistent with the hypothesis that stress-related neurobiological mechanisms may play a role in the pathobiology of TS.

Temperature dysregulation involving some change in hypothalamic function has also been proposed as a factor in the pathobiology of some individuals with TS (Kessler, 2002, 2004). In a case series (Scahill et al., 2001b) an increase in ambient temperature, as well as core body temperature, was associated with a transient increase in tics in some patients. This increase in tics was correlated with their local sweat rate via a dopamine-mediated pathway in the hypothalamus.

Speculation concerning a postinfectious etiology for TS and OCD dates from the late 1800s (Kushner, 1999) and has recently become an intense and controversial area of research (Hoekstra et al., 2004a). It is well established that group A β-hemolytic streptococci (GABHS) can trigger immune-mediated disease in genetically predisposed individuals. Rheumatic fever is a delayed sequela of GABHS, occurring approximately 3 weeks following an upper respiratory tract infection. Inflammatory lesions involving the joints, heart, and/or CNS characterize rheumatic fever. The CNS manifestations are referred to as SC. In addition to chorea, some SC patients display motor and phonic tics as well as OC and ADHD symptoms, suggesting the possibility that, at least in some instances, these disorders share a common etiology (Maia et al., 1999). Case reports have also implicated other infectious processes in TS etiology including Lyme disease (Riedel et al., 1998) and *Mycoplasma* pneumonia (Muller 2004; Muller et al., 2000).

Swedo et al. (1998) proposed that pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) represents a distinct clinical entity and includes some cases of TS and OCD. In PANDAS it is postulated that although GABHS is the initial autoimmunity-inciting event, viruses, other bacteria, or even noninfectious immunological responses are capable of triggering subsequent symptom exacerbations via molecular mimicry, such that antibodies directed against GABHS attack (because of a similar structure) cells in the brain (Snider and Swedo, 2004).

The strongest evidence that GABHS may be involved in the onset of TS and OCD comes from the recent report by Mell et al. (2005). This is a case-control study of 144 children 4 to 13 years old who received their first diagnosis of OCD, TS, or tic disorder between January 1992 and December 1999. Cases were matched to controls by birth date, sex, primary physician, and propensity to seek health care. Patients with OCD, TS, or tic disorder were more likely than controls to have had streptococcal infection in the 3 months before onset date. The risk was higher among children with multiple streptococcal infections within 12 months. Indeed, having multiple infections

with group A β-hemolytic streptococcus within a 12-month period was associated with an increased risk of TS with an odds ratio of 13.6 (95% confidence interval 1.93–51.0).

In contrast, unselected TS cases followed longitudinally for 1 year (Luo et al., 2004) indicated no more than a chance association between newly acquired GABHS infections and tic symptom exacerbations. Similarly, in a case-control study Perrin et al. (2004) found little evidence of increased tic or OC symptoms in the aftermath of well-documented (and treated) GABHS infections, casting some doubt on the hypothesis. To date, treatments based on the molecular mimicry hypothesis have been nonspecific, the results have been inconsistent (Hoekstra et al., 2004b; Perlmutter et al., 1999) and the data concerning antibiotic prophylaxis have not been particularly compelling (Garvey et al., 1999; Snider et al., 2005).

The exact immunological mechanisms involved in TS remain in doubt. Molecular mimicry, altered cytokine production, and altered immune suppression have been implicated. With regard to molecular mimicry, several groups have reported increased titers of antistreptococcal antibodies (Cardona and Orefici, 2001; Church et al., 2003; Muller et al., 2001; Wendlandt et al., 2001), whereas others have not (Luo et al., 2004; Morshed et al., 2001; Singer et al., 1998). There have also been a number of studies reporting the presence of antineural antibodies in the serum of TS and OCD patients (Morshed et al., 2001; Singer et al., 1998; Wendlandt et al., 2001).

Basic research to develop an animal model and study the molecular mechanisms of PANDAS using antineural antibodies have, however, yielded only mixed results (Hallett et al., 2000; Hoffman et al., 2004; Loiselle et al., 2003; Singer et al., 2005; Taylor et al., 2002). In the most promising study to date, Kirvan et al. (2003) demonstrated that antibodies produced by a 14-year-old girl with SC specifically recognized a number of neuronal ligands including lysoganglioside and *N*-acetyl-β-D-glucosamine. More important, these antibodies were found to bind to the surface of human neuronal cells and trigger the calcium/calmodulin-dependent protein kinase II cascade, suggesting that SC may be due in part to alterations in intracellular signaling pathways. This finding has now been replicated in PANDAS cases (Kirvan et al., 2006). Other promising candidates for mechanistic involvement in TS are α- and γ-enolase, aldolase C, and pyruvate kinase M1 (Dale et al., 2005), although these findings are controversial (Singer et al., 2005).

Recently, investigators have begun to look beyond B cell mechanisms. For example, we recently reported that certain proinflammatory cytokines (tumor necrosis factor-α and interleukin-12) were elevated in TS patients compared with controls at baseline and during symptom exacerbation (Leckman et al., 2005). Preliminary data also indicate that some TS subjects may have decreased numbers of regulatory T cells (Kawikova et al., 2007). Additional prospective longitudinal studies are needed to examine the relationships between an array of immune modulators and T cell mechanisms.

NEURAL SUBSTRATES OF HABIT FORMATION, MOTOR CONTROL, AND TICS

Habits are assembled routines that link sensory cues with motor action through a form of procedural learning. Understanding the neural substrates of habit formation and procedural learning may lead to a better understanding of TS (Canales and Graybiel, 2000; Leckman and Riddle, 2000; Leckman et al., 2006; Mink, 2001). Although no direct causal link between tics and habits has been established, recent studies are showing deficits in procedural learning. In a study of 20 children with TS compared with 20 healthy controls, Keri et al. (2002) showed a deficit in the probabilistic classification task that was more severe in a subset with more severe tic symptoms. In a larger study of more than 50 children and adults with TS, Marsh et al. (2004) found that TS patients had impaired habit learning relative to normal controls. Furthermore, their acquisition rate of the task actually correlated inversely with the severity of tic symptoms. A follow-up report (Marsh et al., 2005) confirmed the deficit in probabilistic learning and also found that a test for another subtype of procedural learning, perceptual motor skill learning, was not different in TS subjects. This suggests that different forms of procedural learning may be dissociable according to TS pathology and severity of symptoms. In addition to difficulties with procedural learning, patients with TS have consistently shown difficulties with fine motor control, motor inhibition, and visual motor integration (Crawford et al., 2005; Muller et al., 2003, Schultz et al., 1998). Perhaps the most striking observation is the recent finding that

poorer performance with the dominant hand on the Purdue Pegboard test during childhood is associated with worse adulthood tic severity (Bloch et al., 2006b).

Neural Circuitry

To make advances in understanding of the clinical aspects of TS, investigators have been studying the basic brain circuits that underlie procedural learning, habit formation, and internally and externally guided motor control. Progress has been particularly remarkable in studying the multisynaptic neural circuits or loops that link the cerebral cortex with several subcortical regions (Graybiel and Canales, 2001; Haber, 2003; Haber et al., 2000; Jog et al., 1999; Middleton and Strick, 2000). Key aspects of our understanding of these neurons and circuits are outlined below.

Basic Circuitry. Cortical neurons projecting to the striatum outnumber striatal medium spiny neurons by about a factor of 10 (Zheng and Wilson, 2002). These convergent cortical efferent neurons project to the dendrites of medium spiny neurons within two structurally similar but neurochemically distinct compartments in the striatum: striosomes and matrix. These two compartments differ by their cortical inputs, with the striosomal medium spiny projection neurons mainly receiving convergent limbic and prelimbic inputs and neurons in the matrix mainly receiving convergent input from ipsilateral primary motor and sensory motor cortices and contralateral primary motor cortices (Leckman, 2002; Mink, 2006). The response of particular medium spiny projection neurons in the striatum is partly dependent on perceptual cues that are judged salient, so rewarding and aversive stimuli can both serve as cues (Canales and Graybiel, 2000).

Several other less abundant striatal cell types probably have a key role in modulating habit learning, including cholinergic tonically active neurons (TANs) and fast-spiking GABAergic interneurons (Gonzalez-Burgos et al., 2005; Jog et al., 1999). TANs are sensitive to salient perceptual cues because they signal the networks within the corticobasal ganglia learning circuits when these cues arise. Specifically, they are responsive to dopaminergic inputs from the substantia nigra, and these signals probably participate in the calculation of perceived salience (reward value) of perceptual cues along with excitatory inputs from midline thalamic nuclei. Although the dopamine neurons' response reflects mismatch between expectation and outcome, the TANs are invariant to reward predictability (Morris et al., 2004). In addition, TAN pairs are typically synchronized compared to a minority of dopamine neuron pairs. It appears that the striatal cholinergic and dopaminergic systems carry distinct messages by different means that can be integrated differently to shape the basal ganglia responses to reward-related events (Morris et al., 2004).

The fast-spiking spiny interneurons of the striatum receive direct cortical inputs predominantly from lateral cortical regions, including the primary motor and somatosensory cortex, and they are highly sensitive to cortical activity in these regions. They are also known to be electrically coupled via gap junctions that connect adjacent dendrites. Once activated, these fast-spiking neurons can inhibit many nearby striatal projection neurons synchronously via synapses on cell bodies and proximal dendrites (Koos and Tepper, 1999). The characteristic electrophysiological properties of the striatal fast-spiking neurons (i.e., irregular bursting with stable intraburst frequencies) are reminiscent of temporal patterning of tics (Peterson and Leckman, 1998).

Neuropathological Findings. Although neuropathological studies of postmortem TS brains are few, a recent stereological study indicates that there is a marked alteration in the number and density of GABAergic parvalbumin-positive cells in basal ganglia structures (Kalanithi et al., 2005). In the caudate there was a greater than 50% reduction in the GABAergic fast-spiking interneurons and a 30% to 40% reduction of these same cells in the putamen. This same study found a reduction of the GABAergic parvalbumin-positive projection neurons in the external segment globus pallidus as well as a dramatic increase (>120%) in the number and proportion of GABAergic projection neurons of the internal segment of the globus pallidus (GPi). These alterations are consistent with a developmental defect in tangential migration of some GABAergic neurons. Further studies are needed to confirm and extend these findings, such as toward a more complete understanding of how the different striatal interneurons are affected, and determine how alterations in GABAergic interneurons and GPi projection neurons could lead to a form of thalamocortical dysrhythmia (Leckman et al., 2006; Llinás et al., 2005).

Volumetric Magnetic Resonance Imaging (MRI). Volumetric MRI studies of basal ganglia in individuals with TS are largely consistent with these postmortem

results. In the largest study of basal ganglia volume involving a total of 154 subjects with TS and 130 healthy controls, Peterson et al. (2003) found a significant decrease in the volume of the caudate nucleus in both the child and adult age groups. However, they did not find a difference in striatum or a correlation between symptom severity and caudate volumes in this cross-sectional study, possibly because their sample consisted of a combination of children and adults. Bloch et al. (2005) found an inverse correlation between caudate volume in childhood and tic severity in early adulthood. In addition, Bloch et al. found that the caudate volume in childhood could account for approximately one fifth of the variance in tic severity in early adulthood.

In the same group of subjects, the cerebrums and ventricles were isolated and then parcellated into subregions using standard anatomical landmarks. Individuals with TS were found to have larger volumes in dorsal prefrontal regions, larger volumes in parieto-occipital regions, and smaller inferior occipital volumes (Peterson et al., 2001b). Regional cerebral volumes were significantly associated with the severity of tic symptoms in orbitofrontal, midtemporal, and parieto-occipital regions. There also appears to be age-dependent alterations in the cross-sectional area of the corpus callosum. Specifically, Plessen et al. (2004) reported a decrease in corpus callosum size in children as well as an increase in size in adults with TS, indicating that changes in white matter tracks in this disorder.

In addition, Lee et al. (2005) using volumetric MRI methods to compare thalamic volumes in 18 treatment-naïve boys versus 16 healthy control subjects found that the TS subjects had significantly larger left thalamic volumes in comparison with those of healthy subjects. In another preliminary report, Ludolph et al. (2006) recently showed locally increased gray-matter volumes bilaterally in the ventral putamen. There were also regional decreases in gray matter in the left hippocampal gyrus. These findings confirm an association between striatal abnormalities and TS and the involvement of temporolimbic pathways of the corticostriatothalamocortical circuits, but these findings await confirmation in a larger series.

A recent study showed that a childhood diagnosis of TS, OCD, or ADHD significantly increased the likelihood of detecting cerebral hyperintensities, particularly in the subcortex (Amat et al., 2006). This supports the notion that subcortical injury, perhaps due to autoimmune processes, may play a role in the pathophysiology of these conditions. Clearly, more volumetric studies using comparable methods across all implicated brain regions are needed to clarify the brain morphology of TS and related disorders, as well as the role of imaging in diagnosis and treatment.

Functional Brain Imaging. Thus far, there have only been a few published studies of TS using functional MRI (fMRI), which takes advantage of state-dependent blood oxygenation as a measure of brain activity. In adults with TS, Peterson et al. (1998a) compared brain activity during blocks of time, during which tics were voluntarily suppressed or not suppressed. During tic suppression, prefrontal cortical, thalamic and basal ganglia areas were activated. These activations were inversely correlated with tic severity (i.e., less activation was associated with higher tic severity). This finding suggests that a greater ability of basal ganglia to suppress cortical activity may be linked with decreased tic severity and is in agreement with positron emission tomography and single-photon emission computed tomography studies that suggest involvement of the basal ganglia in TS (Gerard and Peterson, 2003). Some investigators have sought to alter the activity of the prefrontal areas with magnetic fields in an effort to enhance the voluntary control of tics, with mixed results (George et al., 2001). In another fMRI study Serrien et al. (2002) mapped brain activity during motor tasks compared to baseline in three control and three TS patients. TS subjects had considerably reduced activations in premotor and parietal cortices as well as the basal ganglia and thalamus. In contrast to these studies, Biswal et al. (1998) found an increase in brain activity in cortical motor areas during voluntary bimanual motor tapping movements, but this study used low resolution and different analyses for patients versus controls. In a pilot study using a working memory task during fMRI, Hershey et al. (2004) compared TS patients to control subjects both with and without levodopa infusion. They observed increased brain activity in parietal, frontal cortical, and thalamic areas of TS patients, and the increased activity was normalized by levodopa. Most recently, Bohlhalter et al. (2006) studied the neural correlates of tics and associated urges using an event-related fMRI protocol. On the basis of synchronized video/audio recordings,

fMRI activities were analyzed 2 seconds before and at tic onset. A brain network of paralimbic areas including the anterior cingulate and insular cortex, supplementary motor area, and parietal operculum was found to be activated before tic onset. In contrast, at the beginning of tic action, significant fMRI activity was found in sensorimotor areas including the superior parietal lobule bilaterally and the cerebellum. The results of this study indicate that paralimbic and sensory association areas are critically implicated in tic generation.

Investigators have also examined the correlation of metabolic activity across various brain regions and found that changes in the coupling of the putamen and ventral striatum with a number of other brain regions differentiated TS patients from controls. For example, in position emission tomography studies, Jeffries et al. (2002) noted a reversal in the pattern of corticostriatothalamocortical circuit interactions in the motor and lateral orbitofrontal cortices. Similarly, Stern et al. (2000) found that increased activity in a set of neocortical, paralimbic, and subcortical regions (including the supplementary motor, premotor, anterior cingulate, dorsolateral-rostral prefrontal, and primary motor cortices; Broca's area; insula; claustrum; putamen; and caudate) were highly correlated with tic behavior. Perhaps not surprising, in the one patient with prominent coprolalia, the vocal tics were associated with increased activity in the prerolandic and postrolandic language regions, insula, caudate, thalamus, and cerebellum.

Dopamine Modulation

As with habits and stereotypies, ascending dopaminergic pathways likely play a role in the consolidation and performance of tics. Evidence of abnormal dopamine neurotransmission in TS is inferred from two clinical observations. First, blockade of dopamine receptors by neuroleptic drugs suppresses tics in a majority of patients. In addition, dopamine-releasing drugs precipitate or exacerbate tics (Scahill et al., 2006). Indeed, it has been shown that TS patients release more dopamine in response to amphetamine compared to normal controls at dopaminergic synapses (Singer et al., 2002). Second, the importance of dopamine in TS is supported by brain imaging using single-photon emission computed tomography. Several investigators report increased levels of dopaminergic innervation of the striatum in TS subjects compared with controls (Albin et al., 2003; Cheon et al., 2004; Müller-Vahl et al., 2000; Serra-Mestres et al., 2004). In one twin study involving five pairs, tic severity was related to dopamine D2 receptor binding in the head of the caudate (Wolf et al., 1996).

Neurophysiology

Noninvasive in vivo neurophysiological research in TS has led to several areas of significant progress. The first concerns the use of a startle paradigm to measure inhibitory deficits by monitoring the reduction in startle reflex magnitude. Swerdlow et al. (2001) have recently confirmed and extended earlier findings indicating that TS patients have deficits in sensory gating across a number of sensory modalities. Although prepulse inhibition abnormalities have been observed across a variety of neuropsychiatric populations including schizophrenia, OCD, Huntington's disease, nocturnal enuresis, attention-deficit disorder, Asperger's syndrome, and TS, perhaps some final common pathways mediate abnormal prepulse inhibition in all of these diseases. With respect to TS, these deficits in inhibitory gating are consistent with the idea that there is some diminished ability to appropriately manage or ''gate'' sensory inputs to motor programs, which are released as tics (Swerdlow et al., 2000). A second advance has been the investigation of motor system excitability by means of single and paired pulse transcranial magnetic stimulation. Studies to date in groups of patients with TS have indicated that the cortical silent period (a period of decreased excitability following stimulation) is shortened in TS. This intracortical excitability is seen frequently in children with ADHD comorbid with a tic disorder (Moll et al., 1999; Ziemann et al., 1997). This heightened level of cortical excitability may be related to the possible reduction in the number of GABAergic interneurons in the cortex (Kalanithi et al., 2005). This may even fit with recent genetic findings in sequence variants involved in the genes that regulates axonal-dendritic development (Abelson et al., 2005).

Third, Serrien et al. (2005) recently identified similar sensorimotor-frontal connections involved in the acute suppression of involuntary tics as evidenced by increased EEG coherence in the alpha frequency band (8–12 Hz) range during suppression of voluntary movements in individuals with TS compared with

healthy subjects during a Go-No Go task. This finding taken with the findings from the Peterson et al. (1998b) report suggest fairly clearly that the frontal lobes may play an important compensatory role in tic suppression and coherence in the alpha band may be part of this process.

Finally, the preliminary findings that ablation (or high-frequency stimulation using deep brain electrodes) in regions of the GPi and/or the midline thalamic nuclei can ameliorate tics in severe, persistent cases of TS (Vandewalle et al., 1999) powerfully support the view that electrophysiological studies and interventions hold promise just as they do for disorders such as Parkinson's disease.

Prospective longitudinal studies with higher resolution will be needed to examine fully the developmental processes, sexual dimorphisms, and possible effects of medication on critical cell compartments. It will also be important to determine whether any of these volumetric and functional findings are predictive of later clinical outcomes. The combination of imaging techniques with real-time neurophysiological techniques, such as electroencephalography and magnetoencephalography, may help to determine whether any brain imaging findings in TS contribute to the production of tics or whether they constitute a compensatory response (Albin and Mink, 2006; Llinas et al., 2005; Segawa, 2003).

ASSESSMENT

Accumulated clinical experience during the past 10 years confirms the adage that clinical evaluation of the child or adolescent with TS properly considers the "whole person," possessed of a rich personal and interpersonal life, not just a collection of abnormal motor symptoms (Cohen and Leckman, 1999; Scahill et al., 2006). In the process of a comprehensive evaluation, the full range of difficulties and competencies should be charted. A critical question is the degree to which tics interfere with the child's emotional, social, familial, and school experiences. To determine this, it is often useful to monitor symptoms over a few months to assess their severity and fluctuation, impact on the family, and the child's and family's adaptation. This monitoring can often be accomplished with the family's keeping records or using standard forms (Leckman et al., 1999b).

Although the distressed family may focus on the annoying and socially stigmatizing tics, it is the clinician's responsibility to place the tics into the proper context of the child's overall development. By the time of evaluation, the child may be upset by his or her inability to control the tics and by criticism from parents, teachers, and peers who exhort him or her to control his or her strange behavior, which they may believe he or she can control. Central tasks of evaluation include the clarifying and addressing of family issues, such as parental guilt and misconceptions. Indeed, diagnostic evaluation is closely connected with the first steps of treatment.

Children with TS tend to have difficulties with attention and persistence as well as planning, organization, and social problem solving (Channon et al., 2003; Crawford et al., 2005; Mahone et al., 2001; Ozonoff and Jensen, 1999; Yuen et al., 2005). Many have poor penmanship (Schultz et al., 1998). School work may also be impaired by a variety of compulsions, such as the need to scratch out words or return to the beginning of a sentence (Bloch et al., 2006b). Psychological testing is useful if a learning disability is suspected. Indeed, in database of 5,450 patients with TS, 1,235 (22.7%) had learning disabilities (Burd et al., 2005).

Tics are sudden, habit-like movements or utterances that typically mimic some fragment of normal behavior and involve discrete muscle groups. The neurological examination of a child with TS is thus of considerable value. Tics may be mistaken for akathisia, tardive dyskinesia, chorea, or other hyperkinetic movement disorders (Jankovic, 2001). Cases with unusual histories, co-occurring changes in mental status, or evidence of seizures should be considered for referral.

Diagnostic criteria in common use include the International Classification of Disease and Related Health Problems, 10th revision (World Health Organization, 1998) and the *DSM-IV-TR*. Although there are some clear discrepancies, these manuals are broadly congruent with each other. Finally, to minimize error in case ascertainment and produce an instrument measuring the likelihood of having TS, an international team of experts has recently published a TS Diagnostic Confidence Index (Robertson et al., 1999). Scores on this Diagnostic Confidence Index are highly correlated with current tic severity, as measured by a psychometrically sound and widely used clinician-rating scale, the Yale Global Tic Severity Scale (Storch et al., 2005).

A comprehensive assessment also includes a thorough perinatal, medical, developmental family, and psychosocial history along with screening for ADHD, OCD, and learning difficulties. Exploration of the child's strengths and abilities is worthwhile because they are often overlooked in the throes of the diagnosis and over focus on the tics. Children with TS are often anecdotally observed to be particularly attuned to the concerns and well-being of others, possibly because of their own experience of illness (Cohen and Leckman, 1999). As with all pediatric psychiatric care, evaluation and documentation of medical care are necessary, including the date of the last physical examination and consideration of laboratory tests to rule out any medical conditions including infections or neurological conditions. This is especially important before starting any medication treatment.

TREATMENT OF TICS

Despite some advances during the past 10 years, ideal antitic treatments are not yet available. The decision to begin treatment is based on symptom severity involving the presence of at least moderately severe tics and evidence that the tics are a significant source of interference with daily life as reflected in self-esteem, interpersonal relationships (family members, peers, and teachers), and ability to perform up to one's potential in school settings (King et al., 2003; Swain and Leckman, 2003). Many cases of TS are more troubling to family members than the affected individual and may be managed successfully without resorting to medications. Additionally, because the symptoms wax and wane in severity, it often best to initiate treatment with educational interventions and lifestyle adjustments before resorting to medications (Leckman et al., 1999b). In patients presenting with comorbid ADHD, OCD, depression, or bipolar disorder, it is advisable to treat the comorbid condition first because treatment of such disorders may diminish tic severity. Although a thorough review of the interventions for each of these disorders is beyond the scope of this review, some of the most recent studies are mentioned in passing, and further details may be found elsewhere (Bloch et al., 2006c; Castellanos et al., 1997; Martin et al., 2003; Scahill et al., 2006; Tourette Syndrome Study Group, 2002).

Medications for tics must also take into account the natural, idiosyncratic, and sometimes dramatic variations in tic severity. Failure to do so may suggest an effective period of medication action that is purely coincidental or temporarily mask a potentially useful treatment. For example, coincidental remittance of tic severity due to the natural history of the illness with initiation of a medication may convince the clinician and family that a medication was effective. In another case, natural worsening of the symptoms may lead to reactive and unnecessary increases in medication and increased risk of adverse effects. Education, lifestyle adjustments, and watchful waiting with reminders about the waxing and waning course of TS are often the right strategy at first (Leckman et al., 1999b).

Educational Interventions

With the support of advocacy groups such as the Tourette Syndrome Association, enhanced awareness about TS for families, educators, and peers may promote better understanding and tolerance, which can have a positive influence on the overall course of illness (Leckman et al., 1999b). Active collaboration with the school is essential to facilitate appropriate classroom management and optimal curriculum planning. In many cases, advice regarding disruptive behavior warrants limit-setting and tolerance of tic behaviors.

Diet and Lifestyle

Acute and chronic stress can exacerbate tics, so education about the potential role of stress in TS is warranted. Psychotherapy may be useful to improve self-esteem, social coping, family strain, and school adjustment, but it is unclear whether they directly affect tic severity. Regular appointments with the same clinical team who can help the patient deal with the changing manifestations of the disorder through the years is optimal when possible. Regular contact via telephone or e-mail may also be helpful. Participation in regular school and extracurricular activities is encouraged to offset potential overprotection. No specific diet is known to be of particular benefit, although a balanced, healthy diet may contribute to overall well-being and stress reduction (Mantel et al., 2004). Caffeine should be minimized because it may exacerbate tics in some children (Davis and Osorio, 1998). The impact of physical exercise on tic symptoms has not been systematically studied, although a regular program of exercise can be beneficial as a stress-management strategy, to enhance the child's sense

of mastery, and contribute to overall well-being (Hollenbeck, 2001; Leckman and Cohen, 1999).

Behavioral Therapy

A wide range of behavioral interventions has been applied to the treatment of tics with unconvincing results in most instances (King et al., 1999). For example, techniques such as negative practice and mass practice are not effective and have no place in the treatment of tics (Piacentini and Chang, 2001). Single case studies, three pilot randomized clinical trials, one in children (Piacentini and Chang, 2001), two in adults (Deckersbach et al., 2006; Wilhelm et al., 2003), and one spanning ages 7 to 55 (Verdellen et al., 2004), provide promising results for habit-reversal training (HRT). The active ingredients of HRT are presumed to be awareness training and competing response training. Awareness training attempts to identify the situations in which tics occur as well as the beginning of a tic or bout of tics. Once identified, the patient is coached to impose a voluntary competing movement incompatible with the tic. As yet, HRT is not yet a proven and widely practiced treatment. Two large-scale clinical trials are now under way, one in children and one in adults. These trials should provide definitive information on the efficacy of HRT for TS and associated conditions.

Cognitive-behavioral treatments such as exposure and response prevention continue to be a mainstay for the treatment of OCD, especially when there is significant anxiety or phobic avoidance (Pediatric OCD Treatment Study, 2004). Although adding psychosocial therapy to methylphenidate may not improve its effectiveness in stimulant-responsive children with ADHD (Scahill, 2005), parent training (Kazdin, 2003) and anger management (Sukhodolsky et al., 2004) for disruptive behavior in children and adolescents with TS may also be helpful. Although not rigorously supported by controlled research, other formal dynamic interpersonal or supportive psychotherapeutic interventions may facilitate normal developmental tasks of friendship development, improved school adjustment, coherent personality formation, and day-to-day stress management.

Pharmacological Treatment of Tics

Despite the lack of an ideal antitic medication, several medications have demonstrated efficacy (Scahill et al., 2006) and, with due attention to possible side effects, may be part of a treatment plan (Table 1). Pharmacological treatment may be started with low doses of α-adrenergic drugs, which have shown effect sizes >0.5 in double-blind, placebo-controlled studies (Scahill et al., 2001a; Tourette Syndrome Study Group, 2002). Clonidine primarily activates presynaptic autoreceptors in the locus ceruleus to reduce norepinephrine release and turnover in the cerebral cortex. Reduced levels of norepinephrine in the thalamus may be responsible for the commonly reported sedation with these medications. Starting at 0.05 mg/day with gradual increases on a three or four times per day schedule to the target doses of 0.2 to 0.3 mg/day is recommended (Tourette Syndrome Study Group, 2002). Transdermal patches of clonidine are now available but have not been well studied. Another α-adrenergic agonist with less sedation is guanfacine. Animal studies indicate that guanfacine activates postsynaptic prefrontal α-adrenergic cortical receptors, and based on this mechanism, it is believed to improve impulsivity, attention, and working memory (Avery et al., 2000). Guanfacine can be started

TABLE 1
Drugs Used in the Treatment of Tics: Empiric Support and Dosing Guidelines

Medication	Empiric Support	Starting Dose, mg	Usual Dose Range, mg/day
Nonantipsychotics			
Clonidine	B	0.025–0.05	0.2–0.4
Guanficine	B	0.5–1	2–4
Pergolide	B	0.025 every 2 days	0.15–0.45
Botulinum toxin A	B	Motor tics: 50–75 U	75–250
		Vocal tics: 1–2.5 U	1–2.5
Antipsychotics			
Haloperidol	A	0.25–0.5	1.0–4.0
Pimozide	A	0.5–1	2–8
Risperidone	A	0.25–0.5	1–3.5
Fluphenazine	B	0.5–1.0	1.5–10
Tiapride	B	50–150	150–500
Ziprasidone	B	5–10	10–80

Note: To guide clinical practice, the medications used for TS are classified according to the level of empirical support. The above criteria from the International Psychopharmacology Algorithm Project were selected (Scahill et al., 2006): category A reflects treatments with good supportive evidence of short-term safety and efficacy derived from at least two randomized placebo-controlled trials with positive results; category B corresponds to treatments with fair supportive data as evidenced by at least one positive placebo-controlled study.

at 0.5 mg at bedtime, with gradually increasing doses on a twice-daily schedule. The target dose for the longer acting guanfacine is 1.5 to 4 mg/day (Scahill et al., 2001a). Side effects include sedation and mid-sleep waking, which can often be minimized by adjusting the dose schedule. Other side effects include constipation, hypotension, and even syncope in rare cases (King et al., 2006), so blood pressure and pulse should be monitored, especially early in treatment.

Although clonidine and guanfacine have also been shown to be effective in treating ADHD symptoms, which are comorbid with TS, in double-blind placebo-controlled studies (Scahill et al., 2001a; Tourette Syndrome Study Group, 2002), psychostimulants including methylphenidate, *d*-amphetamine, mixtures of *d*- and *l*-amphetamine, and atomoxetine are often more efficacious (Allen et al., 2005; Castellanos et al., 1997; Gadow et al., 1999; Tourette Syndrome Study Group, 2002).

Antipsychotics have a long history of use against tics with effect sizes for treating tics of at least 0.6 (Swain and Leckman, 2003). They are thought to act primarily by blocking dopamine receptors and thereby decreasing dopaminergic input from the substantia nigra and ventral tegmentum to the basal ganglia. Of the typical antipsychotics, haloperidol and pimozide have been the best studied, with double-blind, controlled studies to support them (Sallee et al., 1997). All of these medications, however, are associated with significant side effects including acute dystonic reactions; oculogyric crises; torticollis; drug-induced parkinsonism; akathisia; social phobia; weight gain; sedation; loss of drive, energy, and personality; dry mouth; blurred vision; galactorrhea; gynecomastia; constipation; urinary retention; and electrocardiographic changes including tachycardia, and tardive dyskinesia (Martin et al., 2003). Thus, if α-adrenergic medications have been tried and found ineffective, the atypical antipsychotics are usually the next class of medications to consider. Atypical antipsychotics block dopamine and serotonin receptors. This dual pharmacological action appears to be protective against the neurological adverse effects associated with typical antipsychotics, such as haloperidol and pimozide, which are primarily dopamine blockers. Following a promising open trial with risperidone for tics (Bruun and Budman, 1996), four randomized controlled trials have showed that risperidone was superior to placebo (Bruggeman et al., 2001; Dion et al., 2002; Gaffney et al., 2002; Scahill et al., 2003). Two of these studies have shown that risperidone was equally as effective as pimozide (Bruggeman et al., 2001; Gaffney et al., 2002). Doses ranging from 1.0 to 3.5 mg/day were effective, and neurological side effects were rare. The most common adverse effects were weight gain, lipid metabolism abnormalities, sedation, and sleep disturbance; social phobia and erectile dysfunction occurred in a few patients. To date, there is only one placebo-controlled trial with ziprasidone (Sallee et al., 2000). This study showed ziprasidone to be virtually identical to risperidone for tic reduction. Although data in pediatric populations are scarce, ziprasidone does not appear to have a lower risk of weight gain (McDougle et al., 2002) compared with risperidone (Scahill et al., 2003) and olanzapine (Malone et al., 2001). Concern about the potential for ziprasidone to alter cardiac conduction, especially QTc prolongation, remains. In a series of pediatric patients with various disorders, Blair et al. (2005) indicate that an electrocardiogram should be obtained at four time points: baseline, during dose adjustment, at maintenance dose, and annually thereafter. Electrocardiograms are not required for atypical antipsychotics unless there is a positive cardiac history in the patient. Recent guidelines suggest that patients should be screened at baseline with a lipid panel and fasting glucose (Martin et al., 2003). These laboratory tests should be repeated at maintenance dose and repeated annually thereafter. Weight and diet should also be monitored.

To date, the use of olanzapine for tics is supported by minimal data: three open-label trials (Budman et al., 2001; Stamenkovic et al., 2000; Stephens et al., 2004) and one controlled study (Onofrj et al., 2000) with only four subjects. However, until more data are available, it should not be considered a first- or second-line treatment option.

Other antipsychotics that have been used in Europe but that are not available in the United States include tiapride and sulpiride. Pergolide is a mixed dopamine agonist used in Parkinson's disease, which in lower doses is thought to have a greater effect on presynaptic autoreceptors and lead to decreased dopamine release. Pergolide has been evaluated in open-label and placebo-controlled trials (Gilbert et al., 2000; 2003; Lipinski et al., 1997). These results suggest that pergolide has a positive but moderate effect on tics. Adverse effects include nausea, syncope, sedation, and dizziness.

This agent may be especially useful if a child presents with comorbid restless legs syndrome.

Only small, open-label pilot studies are available for medications such as aripirazole, tetrabenazine, and benzodiazepines. Ariprazole is a novel antipsychotic with antidopaminergic properties that has been effective and tolerable in a few case series (Bubl et al., 2006; Kastrup et al., 2005; Padala et al., 2005), but controlled studies are needed before recommendations are possible. Tetrabenazine is a nonantipsychotic dopamine antagonist, approved as an investigational drug. Available data suggest that tetrabenazine may be useful, but more study is needed (Sandor, 2003). The benzodiazepines, such as clonazepam, are used as anxiolytics and occasionally used as an adjunctive treatment for tics, although it has not been well studied. Given these drawbacks, especially disinhibition and dependence, clonazepam is not used widely in TS.

A collection of agents has been tested during the past 10 years in largely small, open-label pilot challenge studies with equivocal results for treating TS. Among these agents are such calcium channel antagonists as donepezil (Hoopes, 1999), dopaminergic modulators selegiline (Feigin et al., 1996), levodopa (Black and Mink, 2000), odansetron (Toren et al., 1999, 2005), ropinirole (Anca et al., 2004), and metaclopromide (Nicolson et al., 2005); the hormonal modulators flutamide (Peterson et al., 1998b) and cyproterone (Izmir and Dursun, 1999); the antiepileptic drugs topiramate (Abuzzahab and Brown, 2001) and levetiracetam (Awaad et al., 2005); the anti-inflammatory celecoxib (Muller, 2004); and various nutritional supplements (Mantel et al., 2004). However, data on the safety and efficacy of these agents are limited. Further systematic study is needed, especially in children, before these can be recommended for the treatment of tics.

The GABAergic muscle relaxant baclofen has been shown to improve tics in one large open trial, although it lacked baseline or follow-up scores (Awaad, 1999). In the one small double-blind placebo-controlled crossover study (Singer et al., 2001), baclofen was no better than placebo in reducing tic severity in children. Nicotine chewing gum and patches have also been used to treat tics. In open trials encouraging effects of nicotine on tics were reported (Silver et al., 2001a). However, in the only placebo-controlled trial there was little evidence of beneficial effects on tics (Silver et al., 2001b). In that study the nicotine patch or a placebo patch was added to ongoing treatment with haloperidol. There was no enduring benefit on tics after the addition of the patch. The nicotine antagonist mecamylamine has been tested against tics. A promising initial retrospective case study (Sanberg et al., 1998 was again countered by a double-blind, placebo-controlled study that failed to find significant effects (Silver et al., 2001c. The absence of benefit and the risk of nausea and vomiting limit the usefulness of nicotinic drugs to treat TS.

Botulinum toxin injection into discrete muscle groups has been shown to be effective in open and placebo-controlled trials (Kwak et al., 2000; Marras et al., 2001), including phonic tics (Porta et al., 2004). These data suggest that botulinum toxin may be most useful for single bothersome dystonias. Botulinum toxin blocks acetylcholine release at the neuromuscular junction and produces a reversible and temporary reduction in muscle activity, which may last weeks to months for dystonic tics. Main side effects include soreness at the injection site, muscle weakness, ptosis if injected for eye blinking, and transient dysphagia if injected into the larynx.

Several medications have been shown to be ineffective for the treatment of tic disorders. For example, there is no evidence that selective serotonin reuptake inhibitors are effective in suppressing tics. However, selective serotonin reuptake inhibitor treatment for pediatric OCD is well supported by clinical trials and many TS patients have comorbid OCD (Pediatric OCD Treatment Study Team, 2004). Unfortunately, many patients with OCD and a coexisting tic disorder respond less well to selective serotonin reuptake inhibitors and may require the addition of small doses of a neuroleptic or an atypical neuroleptic such as risperidone, which increases the response to selective serotonin reuptake inhibitors (Bloch et al., 2006c).

Other Emerging/Experimental Therapies

In accordance with the theory that a subtype of TS, characterized by abrupt onset and co-occurring GABHS infection, may be the result of an autoimmune process, immune therapies have been examined with inconsistent results. For example, Perlmutter et al. (1999) found that intravenous gamma globulin was effective in reducing tic and OCD symptoms, although Hoekstra et al. (2004b) reached opposite conclusions

after evaluating their data. At present, the clinician is simply encouraged to be vigilant in assessing children with pharyngitis or those exposed to streptococcus and to vigorously treat with antibiotics if there is a positive throat culture. Plasmapheresis, intravenous immunoglobulin, or corticosteroids are experimental treatments under study, but are of uncertain benefit at this point (Tucker et al., 1996. They should only be undertaken with experts in the context of a formal research study. With certain unambiguous and sudden tic onset associated with streptococcal infection, antibiotic treatment has been occasionally remarkably effective; but again, antibody treatment is only warranted when there is clear evidence of streptococcal infection.

Transcranial magnetic stimulation is a new technology in which a brief, powerful magnetic field is generated by a small coil positioned over the skull and which induces an electrical current in the brain. Such noninvasive brain stimulation may effect long-term changes in cortical excitability, which may be abnormal in TS (George et al., 2001). This is still an experimental therapy the therapeutic stimulation parameters of which are unknown. However, a recent pilot study suggests that the treatment is safe and warrants further study (Chae et al., 2004).

The results of neurosurgical procedures reinforce the functional importance of thalamic regions that are part of the cortical-subcortical loops (Ackermans et al., 2006; Vandewalle et al., 1999). In 1999 Vandewalle et al. introduced the use of deep brain stimulation as a new approach for intractable TS. To date, several patients have undergone bilateral thalamic stimulation with promising results on tics and associated behavioral disorders (Ackermans et al., 2006; Mink et al., 2006). In 2002 bilateral stimulation of the posteroventral GPi was performed in a patient with refractory TS (van der Linden et al., 2002). The rationale for the choice of this target was the positive effect of GPi stimulation on hyperkinesias in Parkinson's disease. Most recently, two patients with severe TS had bilateral electrodes placed in the midline thalamic nuclei and in the GPi (Ackermans et al., 2006). In these two patients, both targets were effective in reducing tics. In sum, as in other movement disorders, a deeper understanding of the circuitry involved in TS may lead to specific circuit-based therapies using deep-brain stimulation to treat refractory cases (Visser-Vandewalle et al., 2003, 2004). However, because TS often spontaneously resolves by adolescence, surgical intervention should be viewed as an extraordinary step and only considered in the most severe and refractory cases that interfere with function and persist into adulthood.

FUTURE PERSPECTIVES

Animal and human studies of habits, tics, and stereotypies have advanced in breadth, sophistication, and scope during the past decade. The number of groups engaged in this work has grown to a point where a critical mass of investigators is poised to make significant new contributions to our understanding of these behaviors. Despite enormous progress, the complexity of these systems in primates and humans is formidable (Holt et al., 1997). The key issue is how to disentangle the elaborate interactions between regions of the frontal cortex and the basal ganglia and how these interactions act in concert to learn and set motor, emotive, and cognitive action plans. Joint ventures that combine the efforts of investigators at the leading edge of genetics, neuroimmunology, and the neurosciences (molecular, neural network, developmental, behavioral) with clinical scholars are needed to sustain and accelerate progress in this field.

Most of the available evidence indicates that corticostriatothalamocortical circuits are crucial for the development of habits as well as tics and repetitive movements. Despite this convergence, the precise mechanisms involved remain in doubt. Why do tics appear when they do? Why do they wax and wane? Why do they reach a worst-ever point in early adolescence for the majority and become even more severe in adulthood for an unlucky few? These developmental issues are likely crucial for a full understanding of tic disorders. In our view, a determined effort to explore the electrophysiology of this disorder using EEG and magnetoencephalographic recordings is our next best step (Leckman et al., 2006; Llinas et al., 2005).

The monoaminergic systems continue to be major areas of focus because they have been repeatedly implicated in highly diverse behavioral and cognitive functions including habit formation, the induction of stereotypies, and treatment of tics. Specifically, midbrain dopaminergic neurons play a central role in motor control and attentional processes by means of direct connections to the striatum and prefrontal cortex, respectively. Understanding the timing and

maturation of the dopaminergic system and the role it plays in the growth, differentiation, and plasticity of the CNS may shed light on critical windows of vulnerability in the development and timing of tics (Dewing et al., 2006).

Neural ontogeny of the GABAergic systems is also an intriguing area of study germane to understanding movement disorders and the suspected role of faulty inhibitory circuitry. Many such inhibitory GABAergic interneurons of the cerebral cortex migrate tangentially from the same embryonic regions in the ganglionic eminence that also give rise to the GABAergic fast-spiking interneurons of the striatum (Xu et al., 2003). An appealing hypothesis is that adverse events that arise at specific developmental points impair the appropriate migration and maturation of these cells and their assembly into inhibitory motor control circuits. This could account for the imbalances, deficits, and disorganization of function of cell groups in the striatum and cortex, leading to deficits in movement inhibition hypothesized to occur in some patients with TS. Furthermore, given the multiple afferent systems and integration of sensorimotor and limbic information in the basal ganglia, this promises to be a rich area of study. By understanding molecular switches involved in cell fate, proliferation, migration, and death, it may be possible to design therapeutic interventions to halt or reverse potentially neurotoxic events before the manifestation of any symptoms.

The application of computational neural networks may also greatly confirm or dismantle present theories about the etiology of tic disorders. Dynamic computer simulations of neuroanatomical and neurochemical circuitry may one day lead to a greater understanding of the brain–behavior interface. Such models are already being applied to the study of prefrontal cortical-basal ganglia circuitry as it relates to both motor and cognitive information processing (Frank et al., 2001). For example, modeling of tonic and phasic dopaminergic activity, perhaps as mediated by D1 and D2 receptors in the striatum and prefrontal cortex, respectively, may be promising. These tonic inputs may stabilize representations by increasing the signal-to-noise ratio of background versus evoked prefrontal cortex activity, whereas tonic inputs may signal when new inputs should be encoded or old representations should be updated in response to salient, reward-predicting information (Cohen et al., 2002). As new data regarding different cortical regions are incorporated, future models may provide testable hypotheses of how differences or manipulations of genetics, circuit organization, and pharmacology may lead to a disordered or cured phenotype.

In reviewing the progress during the past decade several caveats must be kept in mind. First, there may be neurobiological consequences of having tics. Second, the act of suppressing tics may affect regional activity in the brain. In other words, the contextual mental state of the individual at the time of a study may affect the measurement of interest. In the future, we can anticipate the deployment of advanced technologies (MR spectroscopy, diffusion tensor imaging, near-infrared optical spectroscopy, and as yet unknown techniques) and the combination of behavioral or neurophysiological stimuli (single or paired pulse transcranial magnetic brain stimulation and studies of prepulse inhibition and startle reflexes) within the confines of brain imaging devices. These maneuvers will likely yield valuable data to identify meaningful endophenotypes for future genetic studies. Longitudinal studies are needed to address questions of risk and resilience, and ideally these would involve subjects at high genetic risk who have yet to display the characteristic symptoms of TS. Likewise, the development of valid animal or neurocomputational models would be a major step forward.

Despite our advances, there is no ideal antitic pharmacotherapy. Results are highly variable and unfortunately often associated with a heavy side-effect burden. However, novel psychotropics are continually appearing, each with a different array of cellular and subcellular targets. It is hoped that converging pharmacological and neuropathological research will find medications that are both highly effective and have minimal side effects. Behavioral interventions under study may provide new approaches to the treatment of tics and adaptive behavior patterns in TS.

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Pediatrician Characteristics Associated With Attention to Spirituality and Religion in Clinical Practice Daniel H. Grossoehme, BCC, MDiv, Judith R. Ragsdale, MDiv, Christine L. McHenry, MD, MATS, Celia Thurston, DMin, Thomas DeWitt, MD, Larry VandeCreek, BCC, DMin

Objective: The literature suggests that a majority of pediatricians believe that spirituality and religion are relevant in clinical practice, but only a minority gives them attention. This project explored this disparity by relating personal/professional characteristics of pediatricians to the frequency with which they give attention to spirituality and religion. *Methods:* Pediatricians ($N = 737$) associated with 3 academic Midwestern pediatric hospitals responded to a survey that requested information concerning the frequency with which they (1) talked with patients/families about their spiritual and religious concerns and (2) participated with them in spiritual or religious practices (eg, prayer). The associations between these data and 10 personal and professional characteristics were examined. *Results:* The results demonstrated the disparity, and the analysis identified 9 pediatrician characteristics that were significantly associated with more frequently talking with patients/families about their spiritual and religious concerns. The characteristics included increased age; a Christian religious heritage; self-description as religious; self-description as spiritual; the importance of one's own spirituality and religion in clinical practice; the belief that the spirituality and religion of patients/families are relevant in clinical practice; formal instruction concerning the role of spirituality and religion in health care; relative comfort asking about beliefs; and relative comfort asking about practices. All of these characteristics except pediatrician age were also significantly associated with the increased frequency of participation in spiritual and religious practices with patients/families. *Conclusions:* Attention to spiritual and religious concerns and practices are associated with a web of personal and professional pediatrician characteristics. Some characteristics pertain to the physician's personal investment in spirituality and religion in their own lives, and others include being uncomfortable with spiritual and religious concerns and practices. These associations shed light on the disparity between acknowledged spirituality and religion relevancy and inattention to it in clinical practice. **Pediatrics** 2007;119:e117–e123.