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TOURETTE SYNDROME AND OBSESSIVE-COMPULSIVE DISORDER

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Abstract

Tourette syndrome and obsessive-compulsive disorder are neuropsychiatric disorders that have sparked considerable interest over the decades. They are the focus of research for a remarkable diversity of disciplines, ranging from neuroimagers and prenatal epidemiologists to experts in the neural circuits that connect the cortex with the basal ganglia, as well as neuroimmunologists focusing on brain-based autoimmune phenomena. Several hypotheses have been put forward to explain the onset and exacerbation of these illnesses. Here we discuss the clinical phenomenology and treatment options that are currently available. New psychopharmacological agents are being used that are based on a greater understanding of the neurobiology and are being used in combination with behavioral interventions. Longitudinal clinical investigations into clinical symptoms and the natural course are providing additional clues on the underlying pathophysiology. Recent advances in research models are also reviewed in an attempt to clarify some of the molecular etiologies that lead to these disorders.

Keywords

Tourette syndrome; obsessive-compulsive disorder; basal ganglia; autoimmune disorders; streptococcal infections; neuroleptic treatment

Tourette syndrome (TS) and obsessive-compulsive disorder (OCD) are model neuropsychiatric disorders that have been the subject of medical interest for centuries [1]. Many explanations have been suggested for the etiology of tics and OCD symptoms and have included genetic factors, the influence of toxins, psychological, and infectious processes. There have been significant advances of our understanding of the neurobiological mechanisms at work in these disorders, as well as improvements in the treatments available. Several reviews on more specialized aspect of TS, OCD and related disorders have appeared over the last several years [2–4]. Here we concentrate on the clinical features of tic disorders and OCD and discuss evidence-based interventions for these disorders.

Tourette syndrome

Tourette syndrome is one of several tic disorders that are classified either by their type (motor or phonic tic) or their duration (transient or chronic). The diagnosis of a transient tic is made if the tics are present for less than 12 months. If the tics persist for more than 12 months, they

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are classified as chronic tic disorder. If both vocal and motor tics are present for longer than one year, the diagnosis of Tourette syndrome is appropriate.

Tic disorders commonly begin in childhood, with the typical age of onset between 5 and 7 years. Most cases begin with simple tics such as eye blinking, or facial movements, and may progress in a caudal fashion to include tics of the head, neck, shoulders, arms, legs, and abdomen. More complex tics may develop over time, and might include hopping or turning, touching or tapping, or multiple tics occurring in rapid succession, such as arm thrusting, head jerk and loud vocalization. The variety of complex tics is myriad and can consist of any movement that an individual might normally make. Vocal tics usually begin one or two years after the onset of the motor tics and often consist of throat clearing, humming or grunting. More complex vocal tics include the repetition of words or parts of words, swearing (coprolalia), or the repetition of what others around are saying (echolalia). These more complex vocal tics occur in only the minority of cases (approximately 20%). Transient tics are quite common in childhood and can affect up to 10% of school age children. The prevalence of chronic tic disorders, including TS, is between 2 and 4%. Once presumed to be rare, the prevalence of Tourette syndrome is now estimated to range between 1 to 10 per 1000 in school age children [5].

Individuals with a chronic tic disorder often describe a premonitory sensation prior to the tic. They may report an itch or sensation in a specific muscle group, or they may describe an urge that builds in intensity immediately prior to the tic. These sensations may build in intensity as the individual attempts to suppress the tic. The performance of the tic is associated with momentary relief from the sensation [6]. Tics tend to occur in bouts – both in the short-term and over longer periods of observation [7]. Indeed, this waxing and waning of the intensity and frequency of tics is expected, with approximately 3 significant exacerbations of symptoms over the course of a year [8]. Tics also occur in bouts, with several groups of tics occurring together. Moreover, tics tend to increase as an individual becomes stressed or tired, and many patients report that their tics worsen toward the end of the day. This observation may also be true because many individuals feel more comfortable and no longer suppress their tics in the privacy of their homes. Other environmental events can influence tic severity and may include exposure to stimulant medications, infections, or exposure to steroids. Overall tic severity may be influenced by perinatal events, which may exert a negative affect brain development. In twin studies, for example, two separate studies showed that the more severely affected monozygotic twin was the twin with lower birth weight [6].

A number of studies have examined the natural history and course of TS. The typical course is for a fluctuating though gradually increasing severity of tics from their onset until early adolescence. This pattern is followed by a gradual decrease in tic symptomatology toward the end of the second decade of life [9]. Most affected individuals report that the period of worst ever tics is between the ages of 10 and 12 years. Nonetheless, some patients have persistent tics in adulthood, while others may have continued disability due to co-occurring conditions such as Attention Deficit Hyperactivity Disorder (ADHD) or obsessive-compulsive disorder (OCD) [9].

As noted above, TS is often associated with other disorders. In clinic populations, approximately 65% of children with TS meet the diagnostic criteria for Attention Deficit with Hyperactivity Disorder [10]. In addition, over half also have significant obsessive-compulsive symptoms, and approximately 30% meet the diagnostic criteria for obsessive-compulsive disorder (OCD). Finally, some reports from clinically ascertained cases have shown an increase in aggressiveness, anxiety disorders, depression and learning difficulties in TS patients. Whether these co-occurring conditions reflect ascertainment bias is not completely clear. More

recently, however, community-based surveys have found that ADHD and disruptive behavior do occur with higher than expected frequency in children with TS [5].

Obsessive-compulsive disorder

Obsessions are recurrent and intrusive thoughts or images that may be followed by repetitive compulsive behaviors. The compulsions are often performed to reduce perceived harm, relieve the anxiety that is associated with the intrusive thoughts, or to achieve a sense of completion [11]. The diagnosis of OCD requires that the obsessions and/or compulsions are time consuming and cause distress or impairment. The prevalence of OCD appears to be influenced by age with estimates of less than 1% in children, rising to 2 to 3% in older adolescents and adults [12][13].

Recent studies have used factor analysis analyses to identify subgroups of patients with similar symptom clusters or dimensions [14][15]. The factors that have emerged are (1) aggression and checking, (2) symmetry and ordering/arranging, (3) contamination and cleaning, and (4) hoarding. This method of subtyping offers new opportunities for geneticists to reanalyze heterogeneous samples and evaluate whether these subtypes breed true, or if there are associations between specific subtypes and susceptibility genes.

The term “tic-like” compulsion refers to touching, tapping, rubbing, and repeating routine activities such as opening and closing a door, setting down an object and picking it back up again and again. Tic-like compulsions are more often found in OCD patients with a history of tics and may be difficult at times to distinguish from more complex tics. In other cases, it is clear that the repetitive habits are performed to relieve anxiety caused by an obsession. The emergence of these “tic-like” activities often starts during childhood and may continue into adulthood [16][17].

PANDAS

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) is an acronym first coined by Swedo (1998)[18]. It was proposed to capture those cases of TS/OCD that are the result of an immunological response to a prior group A beta hemolytic streptococcal (GABHS) infection. Presumptive evidence for a link between GABHS infection emerged in the early 1990s. Kiessling and colleagues (1993)[19] noticed an increase in tic disorders in a pediatric clinic after a wave of streptococcal infections swept through Providence, Rhodes Island. Five diagnostic criteria were proposed for PANDAS: (1) the presence of a tic disorder and/or OCD consistent with DSM-IV; (2) prepubertal onset of neuropsychiatric symptoms; (3) a history of a sudden onset of symptoms and/or an episodic course with abrupt symptom exacerbation interspersed with periods of partial or complete remission; (4) evidence of a temporal association between onset or exacerbation of symptoms and a prior streptococcal infection; and (5) adventitious movements (e.g., motoric hyperactivity and choreiform movements) during symptom exacerbation [18].

The diagnosis of PANDAS remains a controversial area of on-going research. However, a recent epidemiological study lends support to its conceptualization [20]. Over 100,000 records were screened and 144 children between 4 and 13 years were part of the case-control study. These cases were matched with five controls by birth, gender, primary physician, and frequency of seeking health care. Children with a tic disorder or OCD were approximately 2 times more likely than controls to have had a streptococcal infection in the prior 3 months. Moreover, the odds ratio increased in children who had several infections over the previous 12 months compared to control cases (odds ratio of 14; 95% CI: 1.93,51.0). The investigators concluded that approximately 10% of all TS cases could be related to an earlier streptococcal infection.

The most commonly proposed mechanism for PANDAS is the molecular mimicry hypothesis. Most individuals produce antibodies to fight a streptococcal infection. In vulnerable patients, those antibodies cross-react with the individual's tissues and presumably compromise their function. One model for this pathological process is rheumatic fever, in which antibodies generated against an earlier streptococcal infection lead to symptoms of the illness. If these autoantibodies attack heart tissue, the result is carditis; and if antibodies cross-react with joints, the result is arthritis. Finally, if the autoantibodies pass through the blood-brain barrier, they are believed to compromise the normal activity of the basal ganglia and a movement disorder appears, termed Sydenham's chorea.

In TS/OCD, a single study was conducted to treat TS/OCD patients with plasmapheresis in an effort to remove potential autoantibodies [21]. There were improvements of symptoms in patients that persisted in some cases for over 1 year. However, this study and its important findings have yet to be replicated. A number of laboratories have examined serum from affected individuals and found evidence for autoantibodies [22–25]. Recent studies have also found evidence for the involvement of cytokines and regulatory T cells [26][27].

Another approach to the study of PANDAS has been to infuse the serum of affected individuals directly into the basal ganglia (ventrolateral striatum) of rats in an attempt to develop an animal model of the disorder. The prediction is that infusion of sera with autoantibodies (as determined by immunocytochemical screening) may lead to the development of stereotypies, compared to infusion of sera that lack autoantibodies. The results here have been mixed as well, with several laboratories finding significant production of stereotypies [28][29], while others have not [30][31]. Additional research is necessary to determine whether autoantibodies are produced in vulnerable individuals and whether these are etiologically related to the symptoms observed in PANDAS cases.

Treatment

The treatment of children with TS begins with a determination of the target symptoms such as tics, ADHD, OCD, or disruptive and explosive behavior. Specific treatments may include behavioral interventions, medications or both. Despite the frequency of disruptive behavior problems in children with TS, there is surprisingly little information on the use of behavioral interventions in children or adults. Two recent studies show promising results for parent training in school age children and anger control training in adolescents. In the parent training study, 24 children (age range 6 to 11 years; 18 boys and 6 girls) with TS or chronic motor tic disorder accompanied by disruptive behavior were randomly assigned to parent training or treatment as usual [32]. Nearly all of the children met criteria for Oppositional Defiant Disorder; 10 were diagnosed with ADHD and on stable medication. After 10 weeks of the parent-training program, parent ratings of disruptive behavior showed a significant decrease of 51% compared to 19% in the treatment-as-usual group. Seven of 11 children in the parent training intervention were rated as Much Improved or Very Much Improved by a clinician blind to treatment assignment compared to 2 of 12 in the control group, which was statistically significant. Our group also completed a study of anger control training in adolescents with TS. This report is in preparation, although the preliminary results are encouraging (Sukhodolsky and Scahill, unpublished data). These pilot studies suggest that these interventions are similarly effective in children and adolescents with TS as in youngsters with disruptive behavior that do not have TS. Additional large-scale trials are warranted to confirm the efficacy of behavioral interventions in child and adolescents with TS.

There is also growing interest in habit reversal training, which is a behavioral intervention for tics [33–36]. Habit reversal training involves several components such as increasing the patient's awareness of tics prior to their expression, self-monitoring, relaxation training, and competing responses. The awareness training component is based in part on the premonitory

urges described earlier. The momentary relief from the premonitory urge immediately following the execution of a tic reported by many individuals with TS may actually reinforce the performance of tics. Habit reversal training attempts to increase the person's awareness of tics and to initiate a voluntary, competing movement rather than the tic. Patients are taught to maintain the competing response for several minutes until the urge to tic subsides. Preliminary studies are positive and there are two ongoing multisite trials (one in children and one in adults) that should provide important new information on the efficacy of habit reversal training in TS. Although the increased interest and research into behavioral interventions in TS is an important development future research is needed on the integration of medication and behavioral treatments.

Behavioral treatment for OCD is well-established in adults. This body of research shows that exposure to feared stimuli and response prevention (blocking the conditioned response) are the active ingredients in reducing the primary symptoms of OCD. The use of exposure and response prevention in children and adolescents with OCD does not have the same impressive body of evidence. Nonetheless, there is growing evidence that these interventions are effective for children [37]. In addition, it will be important to examine the possibility of age effects on the efficacy of exposure and response prevention for the treatment of OCD, and determine whether this approach will be effective for the so-called *tic-related* form of OCD. As noted above, studies in both children and adults indicate that patients with tic-related forms of OCD are less likely to identify triggers for obsessive worries and more likely to perform compulsive behavior to achieve a sense of completion [16][17]. Thus, it is not clear whether the exposure-response prevention paradigm applies without some adaptation.

Medications for TS

The first consideration when planning pharmacological treatment of individuals with TS is the target symptoms: tics, ADHD, or OCD. In each case, the goal of treatment is to reach a balance between adequate symptom control and adverse effects.

Over the past thirty years, a number of medications have been used for the treatment of tic disorders, but only a few of these have been tested in adequate placebo-controlled studies [38]. The most effective treatment of tics is antipsychotics with postsynaptic blocking properties including haloperidol, pimozide and risperidone. Haloperidol and pimozide are older antipsychotic medications that are associated with a range of adverse effects such as dyskinesia, dystonia, akathisia, Parkinsonism, cognitive dulling, weight gain, sedation, dysphoria, and social phobia. The usual dose of haloperidol ranges from 1 to 4 mg per day in two divided doses. Pimozide typically ranges from 2 to 6 mg per day in a single dose. QT prolongation is unlikely at this lower dose range. However, patients that are placed on pimozide should have an initial cardiogram, as well as one after dose adjustments, and periodically during the course of treatment [38]. Pimozide is also vulnerable to drug interaction. For example, drugs that inhibit the hepatic cytochrome isoenzyme 3A4 such as erythromycin is likely to cause a dramatic rise in the pimozide level and increase the potential for QT prolongation [39].

More recently, clinicians have been moving to the atypical antipsychotics for the treatment of tic disorders based on the presumption that this class of medications will be less likely to cause the neurological side effects associated with haloperidol and pimozide. Risperidone, which has both D2 and 5HT2 blocking properties, has demonstrated superiority to placebo in two randomized trials and appears equally effective to pimozide [38]. These trials showed that at doses ranging between 1.0 to 3.0 mg per day given in two divided doses, risperidone did indeed show few neurological side effects. The most common side effects were sedation and weight gain. Another atypical antipsychotic, ziprasidone, has also been studied in a placebo-controlled

investigation [40] and was superior to placebo. Approval of ziprasidone was initially delayed in the US market due to FDA concerns about the potential for QT prolongation and vulnerability to drug-drug interaction in a manner similar to that noted for pimozide. Additional investigation showed only a modest impact of ziprasidone on QT interval and it does not appear to be vulnerable to drug interaction. Nonetheless, recent treatment guidelines suggest that cardiac monitoring is warranted prior to the start of treatment, during the dose adjustment phase and periodically during the course of treatment [38].

Alpha-2 agonists have often been used to treat tics as well as ADHD. Clonidine is typically given at dosages of 0.15 to 0.3 mg per day, in three or four divided doses. Clonidine is not as effective as the antipsychotic medications described above for reducing the frequency and intensity of tics. However, given its lower side effect profile, it is often the first medication tried in the treatment of children with tic disorders. Another alpha-2 agonist, guanfacine, was studied in a randomized clinical trial with 34 children with ADHD and chronic tic disorder. At doses ranging from 1.5 to 3 mg per day given in three divided doses, guanfacine was superior to placebo for ADHD symptoms and tics [41].

A frequently asked question is whether stimulant medications can be used in the treatment of tic disorders. This persistent question is based on numerous case reports showing that exposure to stimulants aggravates tics in children with TS. However, there have been several placebo-controlled trials that have shown that stimulants do not invariably cause an increase in tic symptom in children with TS [38]. Indeed, it may be a minority of children with TS and ADHD who show an exacerbation of tics in response to stimulant medications. The results of these studies indicate that clinicians should try stimulants with children with ADHD, as these medications remain the most effective treatment for ADHD. However, children with tics and ADHD treated with stimulants should be monitored closely. In addition, a conservative approach to dosing of the stimulant as well as combined use of an alpha-2 agonist may reduce the likelihood of tic worsening. Nonstimulant medications such as guanfacine or atomoxetine should be considered for children with ADHD who cannot tolerate stimulant medications [41][42].

Medications for OCD

Clomipramine, a tricyclic antidepressant medication with serotonin reuptake inhibiting properties, was the first effective medication used for the treatment of OCD. Several early trials in both children and adults demonstrated that clomipramine was not only more effective than placebo, but was superior to desipramine, which is a related drug that lacks serotonin reuptake properties [38]. More selective serotonin reuptake inhibitors (SSRIs) were then introduced, and these have proven to be the main pharmacological treatment for OCD.

The most commonly used SSRIs are fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram, and all of these except citalopram and escitalopram have been studied in placebo-controlled investigations in children with OCD. A few common treatment guidelines can be offered as these medications have several features in common. First, although there is some variation, these drugs have relatively long half-lives. Therefore, the dose should start low and be increased slowly to avoid over-shooting the optimal medication dose. Second, the SSRIs have a high likelihood of interacting with other drugs. Specifically, each of the SSRIs inhibits one or more of the hepatic cytochrome enzymatic pathways. For example, fluoxetine and paroxetine are potent inhibitors of the 2D6 pathway. The antipsychotic medication, risperidone, relies on this metabolic pathway. In the presence of 2D6 inhibitor, the level of risperidone will rise and increase the risk of risperidone-related adverse effects. Third, parents and children may need to be reminded that SSRI treatment of OCD may take several weeks to show benefit. Furthermore, it is unrealistic to expect that the SSRI will take away all OCD symptoms.

It appears that each of the SSRIs is equally effective for the treatment of OCD. Fluoxetine remains the best-studied SSRI in pediatric populations. Although effective, clomipramine is associated with more adverse effects, as well as the need for drug level and cardiac monitoring. As noted above, it is also vulnerable to drug interaction that may increase the likelihood of clomipramine-associated side effects. The dose for clomipramine starts at 25–50 mg/day, with increases to a maximum of 200 mg/day in children and 300 mg/day in adults, while single doses should not exceed 150 mg. The SSRIs do not require routine cardiograms or serum drug levels. The most common side effects are gastrointestinal complaints, sexual dysfunction, sedation, and behavioral activation. The latter problem is especially common in children [43].

Despite their effectiveness in approximately 60–70% of patients, there still remain a significant number of individuals who do not respond to SSRI treatment. For these individuals, it is possible that augmentation strategies may be tried. To date, the addition of an antipsychotic medication is the most effective class of medications for augmentation [44]. In addition, cognitive-behavioral therapies deserve consideration either as an adjunct or as a first line treatment for children and adolescents with OCD.

Future Directions

The next decade of research on TS, OCD and related disorders will continue to build on advances in neuroimaging and genetics. Although these disorders are not likely to be caused by single genes, it is likely that progress will be made in discovering specific mutations and brain circuits that underlie their pathophysiology. These advances may well inform pharmacotherapy as well as behavioral interventions that improve the quality of life for affected individuals. As research progresses, animal models will be an important aspect of the work that will allow investigators to test specific hypotheses and novel therapeutics. Thus, TS and OCD are model neuropsychiatric disorders for evaluating the link between brain function and behavior and have benefited from investigations from multiple disciplines. It is through these types of translational programs that clinicians may expect a better understanding of the underlying molecular basis for these disorders, and better treatments for their patients and families.

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References

1. Kushner H. Freud and the diagnosis of Gilles de la Tourette's illness. *Hist Psychiatry* 1998;9:1–25. [PubMed: 11620004]
2. Scahill, L.; Vaccarino, F.; Mercadante, M.; Lombroso, P. Obsessive-compulsive disorder and Tourette's syndrome. In: Rosenberg, R.; Prusiner, S.; DiMauro, S.; Barchi, R.; Nestler, E., editors. *The Molecular and Genetic Basis of Neurologic and Psychiatric Disease*. Woburn, MA: Butterworth-Heinemann; 2007.
3. Harris K, Singer H. Tic disorders: neural circuits, neurochemistry, and neuroimmunology. *J Child Neurol* 2006;21:678–689. [PubMed: 16970869]
4. Frey K, Albin R. Neuroimaging of Tourette syndrome. *J Child Neurol* 2006;21:672–677. [PubMed: 16970868]
5. Scahill L, Sukhodolsky D, Williams S, Leckman J. The public health importance of tics and tic disorders. *Adv Neurology* 2005;96:240–248.

6. Leckman J. Tourette's syndrome. *Lancet* 2002;360:1577–1586. [PubMed: 12443611]
7. Peterson B, Leckman J. The temporal dynamics of tics in Gilles de la Tourette syndrome. *Biol Psychiatry* 1998;44:1337–1348. [PubMed: 9861477]
8. Lin H, Katsoyich L, Ghebremichael M, Findley D, Grantz H, Lombroso P, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. *J Child Psychol Psychiatry* 2007;48:157–166. [PubMed: 17300554]
9. Bloch M, Peterson B, Scahill L, Otko J, Katsoyich L, Zhang H, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Peds Adolesc Med* 2006;160:65–69.
10. Sukhodolsky D, Scahill L, Zhang H, Peterson B, King R, Lombroso P, et al. Disruptive behavior in children with Tourette's syndrome: association with ADHD comorbidity, tic severity, and functional impairment. *J Am Acad Child Adolesc Psychiatry* 2003;42:98–105. [PubMed: 12500082]
11. Miguel E, do Rosario-Campos M, Prado H, do Valle R, Rauch S, Coffey B, et al. Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder. *J Clin Psychiatry* 2000;61:150–156. [PubMed: 10732667]
12. Karno M, Golding J, Sorenson S, Burnam M. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry* 1988;45:1094–1098. [PubMed: 3264144]
13. Valleni-Basile L, Garrison C, Jackson K, Waller J, McKeown R, Addy C, et al. Frequency of obsessive-compulsive disorder in a community sample of young adolescents. *J Am Acad Child Adolesc Psychiatry* 1994;33:782–791. [PubMed: 8083134]
14. Nestadt G, Addington A, Samuels J, Liang K, Bienvenu O, Riddle M, et al. The identification of OCD-related subgroups based on comorbidity. *Biol Psychiatry* 2003;53:914–920. [PubMed: 12742679]
15. Mataix-Cols D, Rosario-Campos M, Leckman J. A multidimensional model of obsessive-compulsive disorder. *Am J Psychiatry* 2005;162:228–238. [PubMed: 15677583]
16. Scahill L, Kano Y, King R, Carlson A, Peller A, LeBrun U, et al. Influence of age and tic disorders on obsessive-compulsive disorder in a pediatric sample. *J Child Adolescent Psychopharmacology* 2003;13:7–18.
17. Leckman J, Grice D, Barr L, de Vries A, Martin C, Cohen D, McDougle C, Goodman W, Rasmussen S. Tic-related vs. non-tic-related obsessive compulsive disorder. *Anxiety* 1995;1:208–215. [PubMed: 9160576]
18. Swedo S, Leonard H, Garvey M, Mittleman B, Allen A, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264–271. [PubMed: 9464208]
19. Kiessling L, Marcotte A, Culpepper L. Antineuronal antibodies in movement disorders. *Pediatrics* 1993;92:39–43. [PubMed: 8516083]
20. Mell L, Davis R, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. *Pediatrics* 2005;116:56–60. [PubMed: 15995031]
21. Perlmutter S, Leitman S, Garvey M, Hamburger S, Feldman E, Leonard H, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999;354:1153–1158. [PubMed: 10513708]
22. Church A, Dale R, Lees A, Giovannoni G, Robertson M. Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis. *J Neurol Neurosurg Psychiatry* 2003;74:602–607. [PubMed: 12700302]
23. Loiselle C, Wendlandt J, Rohde C, Singer H. Antistreptococcal, neuronal, and nuclear antibodies in Tourette syndrome. *Pediatr Neurol* 2003;28:119–125. [PubMed: 12699862]
24. Morshed S, Parveen S, Leckman J, Mercadante M, Bittencourt Kiss M, Miguel E, et al. Antibodies against neural, nuclear, cytoskeletal, and streptococcal epitopes in children and adults with Tourette's syndrome, Sydenham's chorea, and autoimmune disorders. *Biol Psychiatry* 2001;50:566–577. [PubMed: 11690591]
25. Pavone P, Parano E, Rizzo R, Trifiletti R. Autoimmune neuropsychiatric disorders associated with streptococcal infection: Sydenham chorea, PANDAS, and PANDAS variants. *J Child Neurol* 2006;21:727–736. [PubMed: 16970875]

26. Leckman J, Katsoyich L, Kawikova I, Lin H, Zhang H, Kronig S H, et al. Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome. *Biol Psychiatry* 2005;57:667–673. [PubMed: 15780855]
27. Kawikova I, Leckman J, Kronig H, Katsoyich L, Bessen D, Ghebremichael M, et al. Decreased numbers of regulatory T cells suggest impaired immune tolerance in children with Tourette syndrome: a preliminary study. *Biol Psychiatry* 2007;61:273–278. [PubMed: 16996487]
28. Hallett J, Harling-Berg C, Knopf P, Stopa E, Kiessling L. Anti-telencephalic antibodies in Tourette syndrome cause neuronal dysfunction. *J Neuroimmunol* 2000;111:195–202. [PubMed: 11063838]
29. Taylor J, Morshed S, Parveen S, Mercadante M, Scahill L, Peterson B, et al. An animal model of Tourette's syndrome. *Amer J Psychiatry* 2002;159:657–660. [PubMed: 11925307]
30. Loiselle C, Lee O, Moran T, Singer H. Striatal microinfusion of Tourette syndrome and PANDAS sera: failure to induce behavioral changes. *Mov Disord* 2004;19:390–396. [PubMed: 15077236]
31. Singer H, Mink J, Loiselle C, Burke K, Ruchkina I, Morshed S, Parveen S, Leckman J, Hallett J, Lombroso P. Microinfusion of antineuronal antibodies into rodent striatum: Failure to differentiate between elevated and low titers. *J Neuroimmunol* 2005;163:8–14. [PubMed: 15885303]
32. Scahill L, Sukhodolsky D, Bearss K, Findley D, Hamrin V, Rains A. A randomized trial of parent management training in children with tic disorders and disruptive behavior. *J Child Neurol* 2006;21:50–656.
33. Piacentini J, Chang S. Behavioral treatments for Tourette syndrome and tic disorders: State of the art. *Adv Neurology* 2001;85:319–331.
34. Piacentini J, Chang S. Behavioral treatments for tic suppression: habit reversal training. *Adv Neurology* 2006;99:227–233.
35. Wilhelm S, Deckersbach T, Coffey B, Bohne A, Peterson A, Baer L. Habit reversal versus supportive psychotherapy for Tourette's disorder: a randomized controlled trial. *Am J Psychiatry* 2003;160:1175–1177. [PubMed: 12777279]
36. Woods D, Twohig M, Flessner C, Roloff T. Treatment of vocal tics in children with Tourette syndrome: investigating the efficacy of habit reversal. *J Applied Behav Analysis* 2003;36:109–112.
37. Team POTS. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA* 2004;292:1969–1976. [PubMed: 15507582]
38. Scahill L, Erenberg G, Berlin C, Budman C, Coffey B, Jankovic J, et al. Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRx* 2006;3:192–206. [PubMed: 16554257]
39. Desta Z, Kerbusch T, Flockhart D. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimoziide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999;65:10–20. [PubMed: 9951426]
40. Sallee F, Kurlan R, Goetz C, Singer H, Scahill L, Law G, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000;39:292–299. [PubMed: 10714048]
41. Scahill L, Chappell P, Kim Y, Schultz R, Katsoyich L, Shepherd E, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry* 2001;158:1067–1074. [PubMed: 11431228]
42. Allen A, Kurlan R, Gilbert D, Coffey B, Linder S, Lewis P D, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurolog* 2005;65:1941–1949.
43. Scahill L, Kim Y, Lettinga J. Assessment and pharmacological treatment of children with Obsessive-Compulsive Disorder. *J Clin Psychopharm.* in press
44. Bloch M, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken M, Leckman J. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Molec Psychiatry* 2006;11:622–632. [PubMed: 16585942]