Evidence-Based Pharmacotherapy for Pediatric Obsessive-Compulsive Disorder and Chronic Tic Disorders

Alessandro S. De Nadai¹, Eric A. Storch¹,²,³, Joseph F. McGuire¹, Adam B. Levin²,³ and Tanya K. Murphy²,³

¹Department of Psychology, University of South Florida, Tampa, FL, USA. ²Department of Pediatrics, University of South Florida College of Medicine, Tampa, FL, USA. ³Department of Psychiatry and Behavioral Sciences, University of South Florida College of Medicine, Tampa, FL, USA. Corresponding author email: denadai@mail.usf.edu

Abstract: In recent years, much progress has been made in pharmacotherapy for pediatric obsessive-compulsive disorder (OCD) and chronic tic disorders (CTDs). What were previously considered relatively intractable conditions now have an array of efficacious medicinal (and psychosocial) interventions available at clinicians’ disposal, including selective serotonin reuptake inhibitors, atypical antipsychotics, and alpha-2 agonists. The purpose of this review is to discuss the evidence base for pharmacotherapy with pediatric OCD and CTDs with regard to efficacy, tolerability, and safety, and to put this evidence in the context of clinical management in integrated behavioral healthcare. While there is no single panacea for these disorders, there are a variety of medications that provide considerable relief for children with these disabling conditions.

Keywords: obsessive-compulsive disorder, tic disorders, Tourette disorder, psychopharmacology
Introduction

Obsessive-compulsive disorder (OCD) and chronic tic disorders (CTDs) can be highly impairing conditions which affect a wide range of youth. Multiple prevalence estimates for children and adolescents indicate that approximately 1%-2% of children experience OCD, 0.5%-1.0% experience Tourette Disorder, 1.0%-2.0% experience chronic tic disorders and approximately 5% experience transient tic disorders.1-7

Obsessive-compulsive disorder is characterized by unwanted intrusive cognitions that persist against the patient’s wishes (obsessions) followed by repetitive behaviors intended to reduce associated distress (compulsions), which can be variably expressed.8-10 The content of obsessions often includes perceived contamination, uncertainty about completing an action (eg, checking locks), taboo thoughts (ie, sexual, religious, aggressive), and symmetry and ordering obsessions. Common compulsions include excessive hand washing, repetitive touching of objects, covert rituals (eg, counting, praying), reassurance seeking, unnecessary checking to ensure tasks have been completed, and ordering of objects in a certain configuration until they are perceived as “in order”. Tic disorders are characterized by both simple and complex tics, which are often manifest themselves through motor actions (eg, eye-blinking, shoulder shrugging, or detailed facial gestures) and verbal expressions (eg, groaning, cursing in public despite no intention of doing so). Tic disorders encompass chronic tic disorder (CTD), transient tic disorder (TTD), and Tourette Disorder (TD); CTDs (motor or verbal) are often grouped with TD in treatment trials and in conceptualization of pathology, whereas transient tic disorder has received less focus in clinical research. Thus, this review will address CTD and TD under the umbrella of CTDs. Obsessive-compulsive disorder and CTDs share similarities in phenotypes and neurobiology and are commonly comorbid: a modest amount of children with a principal diagnosis of OCD experience comorbid tics (20%-40%), while a higher percentage of youth with tics experience comorbid OCD (20%-60%).11-17

Comorbid tics are more frequent in younger OCD patients, and both disorder classes are more prevalent in younger boys.18

Obsessive-compulsive disorder and CTDs interfere with the child’s functioning in the school, interpersonal, emotional, and home domains.19-28 In clinical samples, over half of patients with both conditions have been observed to experience functional difficulty due to symptoms of both conditions,21,24 with many patients having two or more problem areas in functioning. This is particularly problematic given that these conditions can occur during critical periods of social and academic development for youth, where interference from these conditions can lead to missing out on critical experiences which may affect optimal functioning in adulthood (eg, reduced access to social and academic opportunities can lead to difficulty in vocational and social functioning as adults due reduced experiences of age appropriate norms). For example, a child with OCD may have compulsions getting in the way of completing school assignments, or a child with vocal tics may have difficulty practicing reading aloud before the class or speaking to the teacher, and children with both conditions may experience distraction due to obsessions or premonitory urges that can interfere with concentration inside and outside of the classroom.

Neurobiological research of OCD has focused on the orbitofrontal cortex (along with the amygdala) in a fear learning model. Although its etiology is multidetermined, OCD has a genetic component, with increased risk of familial transmission and some observed genetic loci of interest that merit further investigation.29-36 Additionally, alterations in glutamatergic functioning may also be associated with OCD.37 Other research foci in the development of OCD have implicated fear learning,38 operant theory,39 cognitive theory,40 and sensitivity to negative affect.41 Tic disorders are associated with dysfunction of the prefrontal cortex and the basal ganglia along with the limbic system.42,43 Androgens have been implicated in the childhood development of OCD and CTDs, with empirical support provided by the elevated morbidity rate of both conditions in early youth as well as the study of androgen roles in CTDs. Tic disorders also have a genetic basis, with increased risk observed in family members of probands who experience tics.44,45 Research on genetic inheritance for both conditions indicate polygenic influences with some overlap.46 Environmental risks for OCD/CTDs have also been identified such as perinatal difficulties,47 traumatic experiences,48,49 and immune related risks.50-54
A variety of orally administered pharmacotherapies have demonstrated efficacy for youth with OCD and CTDs, each with specific benefits and risks. The purpose of this review is to delineate medication options based on clinical research, with randomized clinical trial (RCT) evidence being weighted most highly followed by open trial evidence, with case reports and other uncontrolled research holding less influence. Controlled evidence is particularly pertinent for tic disorders, as tic severity may fluctuate over relatively brief periods of time. An appropriate control group is necessary to separate medication effect from a naturalistic course. Emphasis is placed on the efficacy, safety, tolerability, and relative place in evidence based support of these agents. Empirical work was included if the predominant focus of the research was on children; exceptions were made only in the case of lack of pediatric research for a particular agent, and such research with an adult focus has been specifically identified. While there is little evidence to indicate that OCD and CTDs present with substantial differences between children and adults that affect treatment decision making, the evidence base for pharmacotherapy is more robust for adults. The majority of medications indicated for children have also been shown efficacious with adults, and any substantial discrepancies are explicitly noted.

Pharmacotherapy Options for the Treatment of Pediatric OCD

Selective reuptake inhibitor (SRI) medications have received the majority of research with pediatric OCD, which encompass the selective serotonin reuptake inhibitors (SSRIs) and a specific tricyclic antidepressant (clomipramine), and over 1,000 patients are now available for comparison in meta-analysis. Meta-analysis of RCTs have indicated that these medications have a significant effect relative to placebo, with overall effect size estimates ranging from 0.46–0.48, and with clomipramine showing a significant advantage over SSRIs in efficacy relative to placebo. However, head to head comparisons between clomipramine and SSRIs in a single trial are unavailable, and variables in study design and subject selection can influence effect sizes. Additionally, other factors (such as tolerability) have implications for treatment selection.

Evidence for the use of SRIs in pediatric OCD has been most conclusively demonstrated through RCTs, which have demonstrated efficacy for clomipramine, sertraline, fluoxetine, fluvoxamine and paroxetine (with pooled RCT effect sizes for each medication observed to be 0.85, 0.47, 0.51, 0.31, and 0.44, respectively). With regard to prescriptive use for children, the United States Food and Drug Administration (FDA) has provided approval for pediatric OCD treatment for clomipramine (ages 10 and above), sertraline (ages 6 and above), fluoxetine (ages 7 and above), and fluvoxamine (ages 8 and above). For each of these medications, dosing titration using the lowest recommended dose with incremental increases every 2–4 weeks based on efficacy and tolerability is recommended. Frequent visits at treatment initiation are also recommended, followed by less frequent monitoring after the medication regimen is stabilized.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Among FDA approved SSRIs for pediatric OCD, no significant efficacy differences have been observed, and no direct comparisons have been made in the context of a single trial. Thus, choice of agent usage is relegated to preferred half-life, observed patient response, and idiographic tolerability of an individual agent, as the SSRIs do differ from one another in pharmacodynamics and drug interactions. In pediatric OCD trials, more commonly reported side effects of SSRIs include abdominal discomfort, decreased appetite, sleep interference in the form of either insomnia or somnolence, and fatigue. While these side effects are not commonly prohibitive, significant patient dropout (22%) attributable to side effects has been observed in pediatric OCD trials.
The FDA Black Box warning for suicidality for SSRIs has addressed concern regarding the administration of SSRI medications, which was based on a compilation analysis of data from RCTs in children with depression and anxiety disorders as well as on lay testimony of perceived risks. The risk for suicidal behaviors are theorized to occur in the context of behavioral activation, a phenomenon which can involve agitation, hostility, restlessness, impulsivity, emotional lability, and insomnia. These symptoms most often seen 1–9 days after a dose change, when younger children may be at higher risk from activation syndrome (with particular focus placed on mood and irritability). When considering SSRI suicide risk by diagnosis, Bridge et al found no statistically significant increase in risk of suicidal thinking or behavior when considering pediatric OCD SSRI trials, where they found an increased risk difference between SSRIs and placebo to be 0.5 and a number needed to harm of 200. Nevertheless, while such risk may have been higher in trials for depression relative to those for OCD, providers must carefully monitor for increased suicidal ideation when administering SSRIs to children with OCD, especially considering the high comorbidity rate with depression, which sometimes may go undetected given the difficulties in diagnosing pediatric internalizing disorders. Managing activation can be accomplished by titrating and adjusting doses slowly, using the minimum therapeutic dose, and/or changing to a different medication. Additionally, practice parameters recommend the use of CBT alone in mild and moderate severity cases, and together with a SSRI in more severe cases. The combination approach should be considered given its efficacy and tolerability with the additional benefit of reduced suicidal symptoms reported in those receiving CBT + SSRI versus those receiving only SSRI treatment.

Clomipramine

Clomipramine was the first antidepressant to demonstrate efficacy in RCTs for pediatric OCD and is FDA approved in treating youth with OCD ages 10 and older. It has demonstrated relatively stronger effects in reducing obsessive-compulsive symptoms than the SSRIs, with an estimated effect size of 0.85 relative to placebo. Clomipramine is a tricyclic antidepressant which exerts effects on serotonin and norepinephrine, which may partially account for its increased efficacy relative to the selective agents. When using clomipramine, a baseline electrocardiogram (EKG) is indicated to observe for cardiac arrhythmia, and further EKG monitoring along with blood level monitoring of medication levels is indicated. Other side effects associated with clomipramine include dry mouth, somnolence, dizziness, fatigue, tremor, weight gain, and constipation. Thus, while clomipramine has the strongest demonstrated efficacy among medications for pediatric OCD, it is often not indicated as a first-line agent due to its side effects, with particular concern given to its relationship with cardiac arrhythmia.

Other Agents

Atypical antipsychotics have drawn the majority of attention among other agents in treatment for OCD, with particular attention given to their role in augmenting non- or partial-response to SSRIs. Some data support this practice among adults; one recent meta-analysis suggests such use to be considered after 12 weeks of incomplete response to two adequate trials of SRI therapy. However, despite its frequent use in youth, no methodologically rigorous data exist regarding antipsychotic augmentation of SRI therapy in youth with OCD beyond case reports. Additionally, there are concerning metabolic and cardiac effects associated with antipsychotic use among youth. Given the lack of RCT data and the risks of associated adverse effects, this option should only be considered after failure of appropriate CBT (of sufficient duration by a professional with expertise) and when symptoms are severely impairing functioning. Further evidence beyond uncontrolled reports is required to justify its use in youngsters with OCD.

A new direction in augmenting agents involves the glutamate modulators memantine and riluzole, which have had open trial support for treatment resistant OCD in youth, with promising results. While preliminary, these medications provide an alternative to the traditional serotonin hypothesis in pharmacotherapy for pediatric OCD. Other glutamate modulators such as n-acetylcysteine and glycine have been theorized to be of pharmaceutical use, but no evidence currently exists to support their efficacy in pediatric OCD.
Pharmacotherapy Options for the Treatment of Pediatric Chronic Tic Disorders

The two major classes of medication that have been indicated as efficacious with pediatric chronic tic disorders are dopamine antagonists (typical and atypical), and alpha-2 agonists. While no meta-analytic estimates exist with regard to the efficacy of these agents, the effect sizes of antipsychotics relative to placebo are larger than those for alpha-2 agonists. Given the unique pharmacodynamic and pharmacokinetic characteristics of these medications, treatment choice is guided by weighing risks of adverse effect profile versus expectancy of treatment response.

Typical Antipsychotics

Typical antipsychotics were the first medications to display efficacy in controlled research for pediatric tic disorders, and thus have the broadest evidence base. The only medication with FDA approval for pediatric CTDs is pimozide (ages 12 and older). Haloperidol has a long history in the treatment of CTDs, with evidence stretching back 50 years. While RCTs have demonstrated the efficacy of haloperidol in adults, controlled evidence in youth is lacking; one crossover trial failed to find efficacy relative to placebo on the primary outcome measure, though secondary outcome measures of global functioning detected overall improvement. Side effects that are frequently reported include extrapyramidal symptoms, sedation/drowsiness, weight gain, and increased prolactin secretion. Dosage reduction can be used to manage these side effects. Side effects from typical antipsychotics that can be serious include tardive dyskinesia and neuroleptic malignant syndrome. For CTDs, much lower doses are used than those used for psychotic disorders. For this reason and perhaps because of neurobiological differences, those with CTDs appear to have low risk for tardive dyskinesia. Estimates of the risk of tardive dyskinesia in children and adolescents treated for TD range from 1%–4.8%. However, the risk of such effects increases with greater treatment duration and dosage, may persist after treatment discontinuation. Pimozide, which is a less powerful antagonist of norepinephrine than haloperidol, has been employed in treatment for pediatric CTDs. Its efficacy has been established in RCTs with fewer adverse effects than haloperidol. However, it still presents with a substantial side effect profile including weight gain, akathisia, acute dystonia, QTc prolongation, tardive dyskinesia, and extrapyramidal effects. Given its QTc effects, electrocardiograms at baseline, during titration, and at regular intervals throughout treatment are indicated. Additionally, interactions with antidepressant medications (which are commonly employed with OCD, such as fluvoxamine) have been observed, which presents substantial concern when working with comorbid conditions.

Fluphenazine, which has antagonistic properties for both D1 and D2 receptors, is better tolerated than haloperidol with regard to sedation and extrapyramidal effects while showing similar efficacy to haloperidol in adults. However, controlled data in youth are lacking. Despite its relatively more desirable side effect profile, fluphenazine still presents the risks of traditional neuroleptic adverse effects including akathisia, tardive dyskinesia, and extrapyramidal effects.

Atypical Antipsychotics (Second Generation Antipsychotics)

The more recently introduced atypical antipsychotics have now garnered a substantial evidence base with regard to efficacy for pediatric CTDs. The major advantage of atypical antipsychotics is the reduced risk of tardive dyskinesia and extrapyramidal symptoms associated with classic neuroleptics. However, there are concerns about the safety and tolerability of these medications, especially with regard to increased levels of prolactin (with the exceptions of aripiprazole, quetiapine, and clozapine), sedation, and metabolic effects which can lead to elevated glucose levels, increased appetite, and weight gain.

The medication with the most research evidence in treatment for CTDs is risperidone, with efficacy demonstrated through four RCTs (effect sizes = 0.55–1.0). However, risperidone has been associated with weight gain, increased prolactin levels, and sedation/fatigue as common side effects. Nevertheless, the tolerability of risperidone has been considered preferable to that of traditional neuroleptics such as haloperidol. Ziprasidone has 5HT-2 and D2 antagonistic properties along with norepinephrine and 5HT reuptake inhibition. It has RCT evidence to demonstrate
efficacy relative to placebo (effect size = 0.76), but merits EKG monitoring due to effects on QTc. Additionally, mild sedation has been observed. Thus, while it has been demonstrated as efficacious, particular concern with regard to its effect on cardiac conduction raises caution when considering its use. Additionally, while mild sedation has been observed, It is perhaps the atypical antipsychotic with the lowest weight gain profile.

Olanzapine has displayed efficacy in children with CTDs in several open trials\textsuperscript{124–126} and one small crossover trial.\textsuperscript{127} However, it has increased risk from weight gain and metabolic effects relative to other atypical antipsychotics.\textsuperscript{121,124,128} Thus, given its other associated side effects such as sedation and increased prolactin levels, consideration for its use in CTDs should be made in the context of other available medicinal and behavioral treatment options.

Aripiprazole is a D2 regulator (partial agonist/antagonist), addressing hyperdopaminergic conditions in the limbic system and hypodopaminergic condition in the frontal and prefrontal cortices.\textsuperscript{129} Multiple open trials have indicated improvement in CTD symptoms,\textsuperscript{130–133} but controlled evidence in children is currently lacking, although RCTs are underway. Sedation, nausea, headache, agitation, and insomnia have been observed as side effects; some weight gain has been observed, but to a lesser degree than other comparable agents.\textsuperscript{121,134}

Quetiapine has empirical support from one open label trial,\textsuperscript{135} but lacks RCT evidence to support its use. It is a weaker D2 antagonist than comparable medications, and thus its theoretical efficacy for CTDs is questioned. Abdominal discomfort, gastrointestinal upset, somnolence, and weight gain have been observed as common side effects.

Given the observed side effects of atypical antipsychotics, careful observation of adverse effects is recommended. With regard to metabolic effects, the American Diabetes Association has published monitoring guidelines for these agents.\textsuperscript{136} While these criteria have not been empirically validated, they provide a starting point in evaluating metabolic side effects with patients. Correll\textsuperscript{92} has recommended detailed monitoring schedules that include testing for glucose, lipids, and liver function at three months after treatment initiation and then every six months thereafter, and to evaluate for sedation and weight gain at each visit. Additionally, symptoms of elevated prolactin can include menstrual interruption in females and breast tenderness in males and females, and merit further inquiry upon observation. Proactive management of such effects is recommended including adjusting dosing, changing medications, and monitoring of lifestyle habits (eg, appropriate diet and exercise).

**Alpha-2 Agonists**

The alpha-2 agonists clonidine and guanfacine have demonstrated efficacy in treating pediatric CTDs. While observed effect sizes in treating CTDs have been lower than those for antipsychotics, the major benefits of the alpha-2 agonists relative to antipsychotics is their reduced side effect profile (which does not include metabolic interference or extrapyramidal symptoms) and their efficacy for comorbid ADHD.\textsuperscript{137}

Clonidine has demonstrated efficacy in RCTs for CTDs (effect sizes = 0.26–0.57),\textsuperscript{101,118,138} with fewer side effects than neuroleptic and atypical antipsychotic medication. Common side effects reported with clonidine use include sedation, irritability, headaches, and dry mouth. However, given its short half-life, withdrawal symptoms such as temporary increases in blood pressure and heart rate have been reported.\textsuperscript{139,140} Thus, blood pressure and pulse should be monitored at baseline and during titration, with some recommendations for baseline and follow up ECGs.\textsuperscript{141}

Guanfacine is more highly selective for the alpha-2-adrenergic receptors, which is hypothesized to be the reason for its improved side effect profile relative to clonidine (with particular regard to sedation). It also has a longer half-life than clonidine, reducing the risk of withdrawal effects and permitting for more convenient dosing (which can be limited to twice per day). Efficacy of treatment for CTDs has been demonstrated for guanfacine through RCTs (effect sizes = 0.67–0.84), with one including comorbid ADHD.\textsuperscript{102} Although one study did not detect improvement over placebo,\textsuperscript{142} it was limited by a small sample size, short duration, and a floor effect due to mild baseline tic severity.

**Other Agents**

The efficacy of the anticonvulsant topiramate was recently supported through an RCT by Jankovic.
et al. (ES = 1.01),\textsuperscript{99} and has further support from retrospective chart reviews.\textsuperscript{143} Like the alpha-2 agonists, topiramate has the advantage of no risk of extrapyramidal side effects or weight gain relative to typical or atypical antipsychotics. Common observed side effects include somnolence, weight loss, and cognitive slowing. The anticonvulsant levetiracetam has shown open-label evidence for improving tics;\textsuperscript{144,145} however, two small randomized crossover trials did not detect a tic-reducing effect.\textsuperscript{101,146} Commonly reported side effects include somnolence, headache, dizziness, and asthenia. Significant agitation has also been associated with levetiracetam use and suicidal ideation has been observed in 1% of patients,\textsuperscript{147,148} which merits close monitoring for psychiatric adverse events during administration.\textsuperscript{149}

Mecamylamine is a nicotine receptor agonist which has conflicting research support, where a retrospective case report series indicated some efficacy,\textsuperscript{150} but it did not demonstrate superiority to placebo in a well-designed RCT.\textsuperscript{151} Nicotine (via gum or transdermal patch) as an augmentation strategy with haloperidol has been investigated, with open trial evidence showing minor effects for CTDs,\textsuperscript{152} but an RCT did not support its efficacy.\textsuperscript{151} Baclofen is an agent that interacts with GABA to inhibit the release of various neurotransmitters (including glutamate), which has support in a large open label trial,\textsuperscript{153} and a small RCT indicated significant difference from placebo on the CGI–Severity,\textsuperscript{154} but only near-significance on the Yale Global Tic Severity Scale (YGTSS).\textsuperscript{155,156} For very localized tics, botulinum toxin has been studied, with some evidence from open trials.\textsuperscript{157,158} In an RCT, botulinum toxin reduced number of tics per minute as recorded on videotape, but patients did not report perceived benefit.\textsuperscript{159} Additionally, although botulinum toxin may display some effectiveness in addressing a very localized tic (eg, facial grimacing), it does not address the underlying psychopathology as tics may simply be reassigned to different body parts,\textsuperscript{159} and thus it should not be considered a common treatment for a wide variety of tics.

Other agents that interact with the dopaminergic system include metoclopramide, tetrabenazine, tiapride, sulpiride, and pergolide. Metoclopramide is a D2 antagonist which has traditionally been used for gastroesophageal reflux disease and as an anti-nausea agent, with side effects that can include sedation, increased appetite, and increased levels of prolactin, along with a risk of tardive dyskinesia and extrapyramidal symptoms.\textsuperscript{160} Though it has a limited evidence base for CTDs, in a small RCT it demonstrated efficacy compared to placebo (effect size = 0.95).\textsuperscript{161} Tetrabenazine is a dopamine agonist that intercedes in dopamine reuptake, which has case series and open trial support.\textsuperscript{162–164} Side effects include sedation, depression, nausea, insomnia, akathisia, and parkinsonism, and insomnia. Tiapride is a benzamide that has some support through an RCT to improve tics compared to placebo,\textsuperscript{165} with hyperprolactinemia, somnolence, and weight gain as side effects of note. Sulpiride is similar to tiapride, and has some support through retrospective studies to improve tics in adults.\textsuperscript{166} The most common side effects reported were sedation and depression, although tardive dyskinesia was reported in a case report.\textsuperscript{167} Both sulpiride and tiapride are available in Europe but not in the United States. Pergolide interferes with dopamine release and has been investigated for use in Parkinson’s disease. While efficacy compared to placebo has been reported,\textsuperscript{168,169} pergolide has been associated with cardiac valve pathology in treatment for Parkinson’s disease and has been withdrawn from the United States market.\textsuperscript{170,171}

Choosing Among Pharmacotherapy Options for Pediatric OCD and CTDs

Clinical management of pediatric obsessive compulsive disorder

The main choices among pharmacotherapy options for pediatric OCD include SSRIs and clomipramine. While clomipramine has demonstrated modestly superior outcomes relative to SSRIs, its side effects (especially its cardiovascular effects) limit its frontline use. Thus, SSRIs are most often used as first-line agents, with clomipramine used only after unsuccessful SSRI trials.\textsuperscript{87,88} Table 1 provides a visual comparison of medications with RCT evidence for pediatric OCD. Although pharmacotherapy has demonstrated modest efficacy in the treatment of pediatric OCD, CBT with exposure and response prevention (E/RP) has demonstrated strong efficacy in pediatric OCD treatment, with meta-analytic results suggesting greater efficacy than pharmacological monotherapy.\textsuperscript{60,61} Exposure with response prevention has a more favorable side effect profile than pharmacotherapy and directly addresses
## Table 1. Controlled evidence for pharmacotherapy options in the treatment of pediatric OCD.

| Medication class               | Advantages                                                                 | Disadvantages                                                                 | Medication       | Supporting research | Dose ranges employed | Duration of intervention | Outcomes*                                                                                     |
|-------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------|---------------------|----------------------|-------------------------|---------------------------------------------------------------------------------------------|
| Selective Serotonin Reuptake Inhibitors | Demonstrated efficacy compared to placebo and fewer side effects compared to clomipramine | Not as efficacious as clomipramine for pediatric OCD | Fluoxetine       | Liebowitz et al64  Geller et al18 Riddle et al66 | 10–80 mg/day          | 8–16 weeks               | 49%–57% treatment response for medication, 25%–27% treatment response for placebo  |
|                               |                                                                             |                                 | Fluvoxamine      | Riddle et al65     | 50–200 mg            | 10 weeks                | 42% treatment response for medication, 26% treatment response for placebo  |
|                               |                                                                             |                                 | Paroxetine       | Geller et al60 Geller et al63 | 10–60 mg            | 10–16 weeks             | 47%–71% treatment response for medication, 33%–41% treatment response for placebo |
|                               |                                                                             |                                 | Sertraline       | POTS72 March et al70 | 25–200 mg            | 12 weeks                | 42%–53% treatment response for medication, 26%–37% treatment response for placebo |
| Tricyclic Antidepressants     | Most efficacious medication for pediatric OCD                               | Increased side effect profile, need for EKG and blood level monitoring        | Clomipramine     | DeVeauh-Geiss et al67 Flament et al87 Leonard et al17 | 50–200 mg            | 5–8 weeks                | 58%–75% treatment response for medication, 10%–17% response for placebo |

Notes: *Response rates calculated from multiple outcomes (eg, CY-BOCS,197 CGI-I154).
the behavioral nature of obsessions and compulsions; CBT alone is considered the first line therapy for mild and moderate cases while CBT with an SSRI is recommended for severe cases.72 Cognitive behavioral therapy has been perceived as credible and effective by parents of children seeking anxiety treatment,172 and there are some indications that parents may prefer psychotherapy to SSRI use.173 However, a subset of children/families may be unwilling to participate in CBT, adhere to CBT principles, or may have poor insight into their symptoms, and pharmacotherapy may be particularly indicated for these populations. Another innovative treatment for pediatric OCD which combines CBT and biological treatments involves the use of D-cycloserine (DCS), a partial NMDA agonist which is proposed to enhance CBT outcome through facilitating fear extinction. While this is a relatively new approach to combining biological and behavioral approaches to OCD, DCS augmentation of CBT has displayed efficacy relative to CBT augmentation with pill placebo in children with OCD as well as other adult anxiety disorders, including OCD,38,40,174–176 Generally, obsessive-compulsive symptoms remain chronic without appropriate treatment,177,178 and thus an intervention is recommended (in contrast to the option of no treatment) which considers the functional impairment experienced in proportion to the risk of adverse effects of the selected treatment.

Clinical management of pediatric chronic tic disorders

The main choices among pharmacotherapy options for pediatric CTDs include neuroleptics, atypical antipsychotics, and alpha-2 agonists. While neuroleptics have the most robust evidence base with regard to efficacy for pediatric CTDs, they also have a significant side effect profile. Thus, atypical antipsychotics and alpha-2 agonists have emerged as first-line pharmacotherapy options for pediatric CTDs,103,179 with neuroleptics reserved for treatment refractory cases with marked impairment. Like with medications for pediatric OCD, it is important to balance side effects with efficacy and it is recommended to increase dosages conservatively. Table 2 provides a visual comparison of medications with RCT evidence for pediatric CTDs.

For youth with CTDs, tics generally run a waxing and waning course, with many youth experiencing remission of tics by age 18.55,89 The majority of remaining youth will continue to exhibit tics, albeit with reduced severity compared to those experienced in childhood and adolescence, and a minority will continue to experience sustained tic symptoms. Given these observations, the option of no treatment or behavioral therapy should be considered in the context of presenting severity versus the side effects of the medication employed, with particular consideration given to habit reversal training (HRT). The central components of HRT involve creating awareness of premonitory urges in context and then implementing incompatible competing behaviors, such as contracting the muscle opposite of the tic. For example, a child may learn to identify that he has an eye-blinking tic when sitting in class, become able to identify it each time it happens, and then invoke a response where he consciously uses his eye muscles to hold his eyes open when feeling such an urge. Habit reversal training was the central component of the multi-site RCT for the Comprehensive Intervention for Tics (CBIT), along with functional analysis and relaxation training. In this large (N = 126), multi-site RCT, the CBIT intervention displayed an effect size of 0.68 relative to the control arm, with a reduction in tic severity comparable to contemporary medical interventions.58 Additionally, at 6 month follow up 87% of treatment responders contacted experienced continued benefit from the CBIT intervention. However, most patients were on medications during the trial and a head to head comparison of therapy to medication, similar to the Pediatric OCD Treatment Study (POTS)72 is needed. While CBIT is a promising intervention, it may not be appropriate for younger children and those with limited insight/motivation, and outcomes may be affected by certain comorbidities that would impact self-monitoring (eg, ADHD).

Clinical management of common comorbid conditions

Comorbid conditions in children present complexity in the context of therapeutic management for clinicians. Unfortunately, comorbidity is the rule rather than the exception in the clinical presentation of children with OCD and CTDs, and may be associated with attenuated response and remission rates.180–183 It has also been observed that with CTDs, more impairment may be caused by the comorbid
Table 2. Controlled evidence for pharmacotherapy options in the treatment of pediatric tic disorders.

| Medication class | Advantages | Disadvantages | Medication | Supporting research | Dose range employed | Duration | Outcomes |
|------------------|------------|---------------|------------|---------------------|---------------------|----------|----------|
| Neuroleptics     | Most robust evidence base in demonstrating efficacy for tics | Potential side effects include tardive dyskinesia and extrapyramidal symptoms | Pimozide | Sallee et al\textsuperscript{106} Bruggeman et al\textsuperscript{119} Gilbert et al\textsuperscript{113} | 0.5–4 mg | 4–8 weeks | Shown to reduce tic severity compared to placebo, mixed results when compared against risperidone |
| Atypical antipsychotics | Indicated to be as effective as neuroleptics, with little risk of tardive dyskinesia and extrapyramidal symptoms | Side effect profile includes metabolic effects, sedation, and prolactin interference | Risperidone | Bruggeman et al\textsuperscript{106} Dion et al\textsuperscript{20} Gaffney et al\textsuperscript{118} Gilbert et al\textsuperscript{113} Scahill et al\textsuperscript{98} | 0.5–6 mg | 4–8 weeks | 44%–63% treatment response for medication, 6%–26% treatment response for placebo |
|                    |            |               | Ziprasidone | Sallee et al\textsuperscript{100} | 5–40 mg | 6 weeks | 39% reduction in tic symptoms for medication, 16% symptom reduction for placebo |
| Alpha-2 Agonists  | Demonstrated as efficacious compared to placebo, reduced side effect profile relative to neuroleptics and atypical antipsychotics | Reduced efficacy compared to neuroleptics and atypical antipsychotics | Clonidine | Gaffney et al\textsuperscript{118} Du et al\textsuperscript{138} Hedderick et al\textsuperscript{101} | 0.1–4 mg | 4–8 weeks | 50%–69% treatment response for medication, 47% treatment response for placebo |
|                    |            |               | Guanfacine | Scahill et al\textsuperscript{102} | 1.5–3 mg | 8 weeks | Significant reduction of tics compared to placebo |
| Anticonvulsants   | Recently demonstrated efficacy at a level comparable | Less robust evidence base with regard to efficacy and side effects | Topiramate | Jankovic et al\textsuperscript{99} | 25–200 mg | 10 weeks | Significant reduction of tics compared to placebo |
| Drug                  | Efficacy Details                                                                 | Dose/Delivery          | Duration | Notes                                                                 |
|-----------------------|----------------------------------------------------------------------------------|------------------------|----------|-----------------------------------------------------------------------|
| Botulinum toxin       | Avoids adverse events associated with continued medication administration          | Varied dose, 1 injection | 2 weeks  | 39% reduction in number of tics observed for intervention group, 6% increase in number of tics observed for placebo groups |
| Other dopamine        | Preliminary indications of efficacy, provides alternatives to conventional pharmacological approaches | 5–6 mg/kg body wt      | 10 weeks | Reduction of tics observed as assessed by behavioral evaluation in a RCT |
| antagonists            | Limited evidence base, undesirable side effect profiles, tiapride unavailable in the United States | 5–40 mg               | 8 weeks  | 64% treatment response for medication, 15% for placebo group         |
| Baclofen               | Significant improvement in overall impairment, but no significant reduction in motor or vocal tics | 3 mg–60 mg             | 4 weeks  |                                                                       |
| Botulinum toxin       | Limited evidence for efficacy, does not address underlying psychopathology, tics may reassigned to different parts of body |                                                                       |          |                                                                       |
| Tiapride              | Reduction of tics observed as assessed by behavioral evaluation in a RCT          | 5–6 mg/kg body wt      | 10 weeks |                                                                       |
| Metoclopride          | 64% treatment response for medication, 15% for placebo group                      | 5–40 mg               | 8 weeks  |                                                                       |

Notes: *Response rates calculated from multiple outcomes (e.g., YGTSS, CGH).*
conditions than the tics themselves. In the context of pharmacotherapy, the presence of CTDs in children may substantially attenuate response to SSRIs for children with OCD, where one study found a 75% response rate for children with OCD only in comparison to a 53% rate for those children with OCD who also present with tics, and another found non-significance relative to placebo in post-hoc analyses for sertraline monotherapy in children with OCD and comorbid tics. Moreover, this comorbidity has been associated with a greater OCD relapse rate following paroxetine treatment. Further complicating matters is the fact that OCD is often comorbid with CTDs and depression, and CTDs are frequently comorbid with OCD and ADHD. Given the high comorbidity rate found between OCD and CTDs (as well as with other conditions), clinicians often are faced with multiple decisions in treatment planning for these comorbid conditions. In general, the state of current psychopharmacological practice when presented with comorbidity for children with OCD and tics is to use the agent that is appropriate for each condition if pharmacotherapy is needed, while considering the possible negative or positive effects that the agent may have on comorbid conditions.

The situation is simplified in pharmacotherapy for OCD, where SSRIs can affect both OCD and depression/anxiety, and while they have not been observed to help with CTDs, they have not been associated with worsening of comorbid tics. On the other hand, with regard to comorbid ADHD and CTDs, while there is some evidence that stimulants may exacerbate tics and anxiety in children with CTDs, a meta-analysis by Bloch et al indicates that this effect may be dependent on the specific agent and dosing, and one multisite RCT found roughly equal tic increases when using methylphenidate, clonidine, or placebo. Although the issue of stimulants and CTDs presents with some contrasting evidence, using clonidine or guanfacine to address comorbid CTDs and ADHD simultaneously is a consideration when choosing among pharmacotherapy options for these conditions. Additionally, there is some evidence that risperidone and aripiprazole may have positive effects on anxiety symptoms, which is hypothesized to be a consequence of their action on 5HT receptors, and is a further consideration when treating comorbid CTDs and OCD.

Conclusion

The goal of this review has been to discuss the current state of research on pharmacotherapy for pediatric OCD and CTDs, to provide an overview for clinical practice, and to demarcate current limitations in the literature to identify future research directions. While gains have been made in developing effective and safe/tolerable pharmacotherapy options for pediatric OCD and CTDs, much progress remains to be made. While pharmacotherapy is associated with generally positive treatment response, no current medication consistently achieves the more stringent criterion of symptom remission. Even with CBT for pediatric OCD (the most efficacious intervention reviewed), a significant proportion of children remain symptomatic following treatment. With regard to pediatric OCD, moving beyond the serotonin hypothesis into other domains such as ascertaining the role of glutamate may provide fertile ground for efficacy gains. For CTDs, identifying and evaluating safe and effective alternatives to neuroleptics and atypical antipsychotics are indicated, with the use of alpha-2 agonists and topiramate as a starting point. Across disorders, identifying moderators and mediators of response and side effects is of critical importance to facilitate treatment individualization. Identifying which populations respond better to a certain medicine or which patient groups are less likely to experience side effects from a particular agent could assist in improved idiographic care.

With regard to contemporary agents, more comparative work between medications in a randomized fashion could allow for direct comparisons of efficacy and adverse event rates. Many medications have demonstrated efficacy relative to placebo, and for a new medication to be of incremental value, it must be more efficacious or have better safety/tolerability than currently available agents, which is a hypothesis that may be best tested in a RCT with medications compared against one another. The evidence base is robust enough to move beyond the “nil hypothesis” that pharmacotherapy is better than no intervention at all, and to make further progress, the benchmark in many cases may be efficacious contemporary agents.

One further consideration is that that these medications are not prescribed in a vacuum, but are administered in the context of integrated behavioral
healthcare. Careful weighing of the benefits and risks relative to the degree of impairment is of foremost importance when employing medications is needed, with particular regard given to available behavioral interventions. Moreover, given side effects of some agents, establishing a therapeutic relationship is of substantial consequence in promoting adherence to the intervention and comfort in reporting adverse events, and can also serve to empower a patient’s decision making in treatment and provide a source of support to the patient in the face of functional interference. Such a relationship, often defined as the “therapeutic alliance”, has been indicated for further exploration with pediatric psychopharmacology, and explains a portion of outcome variance in pharmacotherapy for adult depression as well as a variety of pediatric psychotherapies. It is also important to consider the family role with these conditions, with a particular focus on how the family may interact with the child’s symptom presentation. For example, a family may overly accommodate a child’s OCD symptoms or be overly critical of a child’s CTD symptoms, which can serve to worsen symptoms. In the presence of heterogeneity among family reactions to the pathology, clinicians can foster a supportive but disciplined approach towards implementing the chosen intervention.

Compared to only 25 years ago, a marked increase in pharmacotherapy interventions have become available for children with OCD and CTDs to intervene for these debilitating conditions. This has provided an array of efficacious interventions for youth with markedly reduced side effect profiles, although much progress still remains to be made. Given this expansion of treatment options, the major decisions in clinical pharmacotherapy come down to a balance of efficacy and adverse effects in the context of functional impairment and available psychosocial interventions. Managing these variables in the context of the evidence base for each approach will foster improved child outcomes.

Disclosures
This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors confirm that they have permission to reproduce any copyrighted material.

Mr. De Nadai and Mr. McGuire report no financial relationships with commercial interests. Dr. Storch has received grant funding from the All Children’s Hospital Research Foundation, the Centers for Disease Control and Prevention, the International OCD Foundation, Janssen Pharmaceuticals, the National Alliance for Research on Schizophrenia and Affective Disorders, the National Institute of Mental Health, the National Institute of Child Health and Human Development, the Australian Rotary Health Research Fund, Transcept Pharmaceuticals, Biovail Technologies, and the Tourette Syndrome Association. Dr. Storch has received consultancy fees from Prophase Inc. and Otsuka Pharmaceuticals, receives textbook honoraria from Lawrence Erlbaum and Springer publishers, has been an educational consultant for Rogers Memorial Hospital, and receives research support from the All Children’s Hospital Guild Endowed Chair and the University of South Florida. Dr. Lewin has received research support from the International OCD Foundation, the National Alliance for Research on Schizophrenia and Affective Disorders, and Otsuka Pharmaceuticals. Dr. Lewin has received consultancy fees from Prophase Inc. and Otsuka Pharmaceuticals. Dr. Murphy has received research support from the National Institute of Mental Health, the National Institute of Child Health and Human Development, Forest Laboratories, Janssen Pharmaceuticals, Endo, the International OCD Foundation, Transcept Pharmaceuticals, Biovail Technologies, the Tourette Syndrome Association, the All Children’s Hospital Research Foundation, the Centers for Disease Control, and the National Alliance for Research on Schizophrenia and Affective Disorders. Dr. Murphy is on the Medical Advisory Board for Tourette Syndrome Association. She receives textbook honorarium from Lawrence Erlbaum.

References
1. Robertson MM, Eapen V, Cavanna AE. The international prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross-cultural perspective. J Psychosom Res. Dec 2009;67(6): 475–83.
2. Apter A, Fallon TJ Jr, King RA, et al. Obsessive-compulsive characteristics: from symptoms to syndrome. J Am Acad Child Adolesc Psychiatry. Jul 1996; 35(7):907–12.
3. Flament MF, Whitaker A, Rapoport JL, et al. Obsessive compulsive disorder in adolescence: an epidemiological study. J Am Acad Child Adolesc Psychiatry. Nov 1988;27(6):764–71.
4. Khalifa N, von Knorring AL. Tourette syndrome and other tic disorders in a total population of children: clinical assessment and background. Acta Paediatr. Nov 2005;94(11):1608–14.

5. Findley DB. Characteristics of tic disorders. In: Woods DW, Miltenberger RG, editors. Tic Disorders, Trichotillomania, and Other Repetitive Behavior Disorders. New York, NY: Springer; 2001: 53–71.

6. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: a community-based study. Neurology. Aug 2002;59(3):414–20.

7. Murphy TK, Snider LA, Mutch PJ, et al. Relationship of movements and behaviors to Group A Streptococcus infections in elementary school children. Biol Psychiatry. Feb 2007;61(3):279–84.

8. Storch EA, McNamara J, Jordan C, et al. Associations between polymorphisms in GRIK2 Gene and Obsessive-Compulsive Disorder: A Family-Based Study. CNS Neurosci Ther. Mar 2010.

9. Storch EA, Larson MJ, Aldea MA, et al. Multiple pathways to functional impairment in obsessive-compulsive disorder. Clin Psychol Rev. Feb 2010; 30(1):78–88.

10. McKay D, Piacentini J, Greisberg S, Graie F, Jaffer M, Miller J. The structure of childhood obsessions and compulsions: dimensions in an outpatient sample. Behav Res Ther. Jun 2006;44(1):137–46.

11. Cavanna AE, Servo S, Monaco F, Robertson MM. The behavioral spectrum of Gilles de la Tourette syndrome. J Neuropsychiatry Clin Neurosci. Winter 2009;21(1):13–23.

12. Coffey BJ, Biederman J, Smoller JW, et al. Anxiety disorders and tic severity in juveniles with Tourette’s disorder. J Am Acad Child Adolesc Psychiatry. May 2000;39(5):562–8.

13. Eichstedt JA, Arnold SL. Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? Clin Psychol Rev. Feb 2001;21(1): 137–57.

14. Hanna GL. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry. Jan 1995;34(1):19–27.

15. Iverson T, Melin K, Wallin L. Categorical and dimensional aspects of comorbidity in obsessive-compulsive disorder (OCD). Eur Child Adolesc Psychiatry. Feb 2008;17(1):20–31.

16. Riddle MA, Hardin MT, King R, Scahill L, Woolston JL. Fluoxetine treatment of children and adolescents with Tourette’s and obsessive compulsive disorders: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry. Jan 1990;29(1):45–8.

17. Swedo SE, Rapoport JL, Leonard H, Lenane M, Cheslow D. Obsessive-compulsive disorder in children and adolescents. Clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry. Apr 1989;46(4):335–41.

18. Geller DA, Biederman J, Faraone SV, et al. Disentangling chronological age from onset of age in children and adolescents with obsessive—compulsive disorder. Int J Neuropsychopharmacol. Jun 2001;4(2):169–78.

19. Packer LE. Tic-related school problems: impact on functioning, accommodations, and interventions. Behav Modif. Nov 2005;29(6):876–99.

20. Cutler D, Murphy T, Gilmore J, Heyman I. The quality of life of young people with Tourette syndrome. Child Care Health Dev. Jul 2009;35(4): 496–504.

21. Piacentini J, Bergman RL, Keller M, McCracken J. Functional impairment in children and adolescents with obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2003;13 Suppl 1:S61–9.

22. Storch EA, Abramowitz JS, Keeley M. Correlates and mediators of functional impairment in pediatric obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. Aug 2009;19(4):237–47.

23. Dehning S, Muller N, Matz J, et al. A genetic variant of HTR2C may play a role in the manifestation of Tourette syndrome. Psychiatr Genet. Feb 2010; 20(1):35–8.

27. Hyde TM, Aaronson BA, Randolph C, Rickler KC, Weinberger DR. Relationship of birth weight to the phenotypic expression of Gilles de la Tourette’s syndrome in monozygotic twins. Neurology. Mar 1992;42(3 Pt 1):652–6.

28. O’Rourke JA, Scharf JM, Yu D, Pauls DL. The genetics of Tourette syndrome: a review. J Psychosom Res. Dec 2009;67(6):533–45.

29. Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF. A twin study of Tourette syndrome. Arch Gen Psychiatry. Aug 1985;42(8):815–20.

30. Scahill L, Sukhodolsky DG, Williams SK, Leckman JF. Public health significance of tic disorders in children and adolescents. Adv Neurol. 1995; 96:240–8.

31. Storch EA, Platto J, Fagerness J, et al. A genetic family-based association study of OLIG2 in obsessive-compulsive disorder. Arch Gen Psychiatry. Feb 2007;64(2):209–14.

32. Sampaio AS, Fagerness J, Crane J, et al. Association Between Polymorphisms in GRIK2 Gene and Obsessive-Compulsive Disorder: A Family-Based Study. CNS Neurosci Ther. Mar 2010.

33. Cavanna AE, Servo S, Monaco F, Robertson MM. The behavioral spectrum of Gilles de la Tourette syndrome. J Neuropsychiatry Clin Neurosci. Winter 2009;21(1):13–23.

34. Geller DA, Himle JA, Curtis GC, Gillespie BW. A family study of obsessive-compulsive disorder with pediatric probands. Am J Med Genet B Neuropsychiatr Genet. Apr 2005;134B(1):13–9.

35. Mundo E, Richter MA, Zai G, et al. 5HT1Dbeta Receptor gene implicated in the pathogenesis of Obsessive-Compulsive Disorder: further evidence from a family-based association study. Mol Psychiatry. 2002;7(7):805–9.

36. Nestadt G, Samuels J, Riddle M, et al. A family study of obsessive-compulsive disorder. Arch Gen Psychiatry. Apr 2000;57(4):358–63.

37. Pittenger C, Krystal JH, Coric V. Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. NeuroRx. Jan 2006;3(1):69–81.

38. Storch EA, Murphy TK, Goodman WK, et al. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. Dec 2010;68(11):1073–6.

39. Fernandez MA, Storch EA, Lewin AB, Murphy TK, Gefken GR. The Principles of Extinction and Differential Reinforcement of Other Behaviors in the Intensive Cognitive-Behavioral Treatment of Primarily Obsessional Pediatric OCD. Clinical Case Studies. 2006;5(6):511.

40. Wilhelm S, Buhlmann U, Tolin DF, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. Am J Psychiatry. Mar 2008;165(3):335–41.

41. Yorulmaz O, Gencoz T, Woody S. Vulnerability factors in OCD symptoms: cross-cultural comparisons between Turkish and Canadian samples. Clin Psychol Psychother. Mar-Apr 2010;17(2):110–21.

42. Leckman JF, Bloch MH, Smith ME, Larabi D, Hampson M. Neurobiological substrates of Tourette’s disorder. J Child Adolesc Psychopharmacol. Aug 2010;20(4):237–47.

43. Dehning S, Muller N, Matz J, et al. A genetic variant of HTR2C may play a role in the manifestation of Tourette syndrome. Psychiatr Genet. Feb 2010; 20(1):35–8.

44. Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF. A twin study of Tourette syndrome. Arch Gen Psychiatry. Aug 1985;42(8):815–20.

45. Hyde TM, Aaronson BA, Randolph C, Rickler KC, Weinberger DR. Relationship of birth weight to the phenotypic expression of Gilles de la Tourette’s syndrome in monozygotic twins. Neurology. Mar 1992;42(3 Pt 1):652–6.

46. Dehning S, Muller N, Matz J, et al. A genetic variant of HTR2C may play a role in the manifestation of Tourette syndrome. Psychiatr Genet. Feb 2010; 20(1):35–8.

47. Scahill L, Sukhodolsky DG, Williams SK, Leckman JF. Public health significance of tic disorders in children and adolescents. Adv Neurol. 1995; 96:240–8.

48. Sampaio AS, Fagerness J, Crane J, et al. Association Between Polymorphisms in GRIK2 Gene and Obsessive-Compulsive Disorder: A Family-Based Study. CNS Neurosci Ther. Mar 2010.

49. Storch EA, Platto J, Fagerness J, et al. A genetic family-based association study of OLIG2 in obsessive-compulsive disorder. Arch Gen Psychiatry. Feb 2007;64(2):209–14.

50. Scahill L, Sukhodolsky DG, Williams SK, Leckman JF. Public health significance of tic disorders in children and adolescents. Adv Neurol. 1995; 96:240–8.

51. Sampaio AS, Fagerness J, Crane J, et al. Association Between Polymorphisms in GRIK2 Gene and Obsessive-Compulsive Disorder: A Family-Based Study. CNS Neurosci Ther. Mar 2010.
54. Murphy TK, Sajid M, Soto O, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. Feb 1998;155(2):264–71.

56. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette syndrome. J Child Neuropsychiatry. Nov 2003;13 Suppl 1:S24–6.

58. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette syndrome. J Pediatr. Oct 1998;133(4 Pt 1):14–9.

59. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. Oct 2004;292(16):1969–76.

60. Storch EA, Larson M, Adkins J, Geffken GR, Murphy TK, Goodman WK. Evidence-Based Treatment of Pediatric Obsessive-Compulsive Disorder. In: Steele RG, Elkin TD, Roberts MC, editors. Handbook of Evidence-Based Therapies for Children and Adolescents: Springer US; 2008:103–20.

61. Watson HJ, Rees CS. Meta-analysis of randomized, controlled treatment trials for pediatric obsessive-compulsive disorder. J Child Psychol Psychiatry. May 2008;49(5):489–98.

62. Geller DA, Biederman J, Stewart SE, et al. Which SSRI? A meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder. J Am Acad Child Psychiatry. Nov 2003;42(11):1919–28.

63. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with obsessive-compulsive disorder: a multicenter, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. Nov 2004;43(11):1387–96.

64. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with obsessive-compulsive disorder: a placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. Dec 2002;41(12):1431–8.

65. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. J Am Acad Child Adolesc Psychiatry. Feb 2001;40(2):222–9.

66. Riddle MA, Scailli L, King RA, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. Nov 1992;31(6):1062–9.

67. The Pediatric OCD Treatment Study Team. 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. Oct 2004;292(16):1969–76.

68. Storch EA, Piacentini J, Obsessive-compulsive disorder in children. In: Sadock BJ, Sadock VA, Ruiz P, Kaplan HI, editors. Kaplan & Sadock’s Comprehensive textbook of Psychiatry. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2009:3671–8.

69. Piacentini J, Frazier S, Kim SJ. Obsessive–Compulsive Disorder. The Medical Basis of Psychiatry. 2008:161–80.

70. Murphy TK, Segarra A, Storch EA, Goodman WK. SSRI adverse events: How to monitor and manage. Int Rev Psychiatry. Apr 2008;20(2):203–8.

71. Moller HJ, Baldwin DS, Goodwin G, et al. Do SSRIs or antidepressants in general increase suicidality? WPA Section on Pharmacopsychiatry: Consensus statement. Eur Arch Psychiatry Clin Neurosci. Aug 2008;258 Suppl 3:3–23.

72. Geller DA, Hoog SL, Heiligenstein JH, et al. Fluoxetine treatment for obsessive-compulsive disorder. J Clin Psychiatry. Feb 2010;71(2):163–69.

73. Murphy TK, Sajid M, Soto O, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in children with obsessive-compulsive disorder and tics. Biol Psychiatry. Jan 2004;55(1):61–8.

74. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. J Psychosom Res. Dec 2009;67(6):497–501.

75. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette syndrome: the first two decades. Pediatrics. Jul 1998;102(1 Pt 1):14–9.

76. Leckman JF. Phenomenology of tics and natural history of tic disorders. Brain Dev. Dec 2003;25 Suppl 1:S24–8.

77. Piacentini J, Woods DW, Scailli L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. May 2010;303(19):1929–37.

78. Murphy TK, Kurlan R, Leckman JF. The immunobiology of Tourette’s disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, and related disorders: a way forward. J Child Adolesc Psychopharmacol. Aug 2010;20(4):317–31.

79. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. Feb 1998;155(2):264–71.

80. Symonds PE,矢田和, Watanabe K, et al. Obsessive-compulsive disorder: is there an association with childhood streptococcal infections and altered immune function? Semin Clin Neuropsychiatry. Oct 2001;6(4):266–76.

81. Murphy TK, Sajid M, Soto O, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in children with obsessive-compulsive disorder and tics. Biol Psychiatry. Jan 2004;55(1):61–8.
Pharmacotherapy for OCD and CTDs

140. Cantwell DP, Swanson J, Connor DF. Case study: adverse response to clonidine. J Am Acad Child Adolesc Psychiatry. Apr 1997;36(4):539–44.

141. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry. Oct 1997;36(10 Suppl):855–121S.

142. Cummings DD, Singer HS, Krieger M, Miller TL, Mahone EM. Neuropsychiatric effects of guanfacine in children with mild tourette syndrome: a pilot study. Clin Neuropharmacol. Nov–Dec 2002;25(6):325–32.

143. Kuo SH, Jimenez–Shahed J. Topiramate in treatment of tourette syndrome. Clin Neuropharmacol. May 1993;16(3):299–305.

144. Cummings DD, Singer HS, Krieger M, Giuliano J. Baclofen treatment in children and adolescents with Tourette syndrome. Eur J Paediatr Neurol. Nov 2009;13(6):541–5.

145. Awaad Y, Michon AM, Minarik S. Use of levetiracetam to treat tics in children and adolescents with Tourette syndrome. Mov Disord. Jun 2005;20(6):714–8.

146. Smith-Hicks CL, Bridges DD, Paynter NP, Singer HS. A double blind randomized placebo control trial of levetiracetam in Tourette syndrome. Mov Disord. Sep 2007;22(12):1764–70.

147. Mula M, Sander JW. Suicidal ideation in epilepsy and levetiracetam therapy. Epilepsy Behav. Aug 2007;11(1):130–2.

148. Kossoff EH, Bergey GK, Freeman JM, Vining EP. Levetiracetam psychosis in children with epilepsy. Epilepsia. Dec 2001;42(12):1611–3.

149. Gambardella A, Labate A, Colosimo E, Ambrosio R, Quattrone A. Mono- therapy for partial epilepsy: focus on levetiracetam. Neuropsychiatr Dis Treat. Feb 2008;4(1):33–8.

150. Silver AA, Shytle RD, Sanberg PR. Mecamylamine in Tourette’s syndrome: a two-year retrospective case study. J Child Adolesc Pharmacol. Summer 2000;10(2):59–68.

151. Silver AA, Shytle RD, Sheehan KH, Sheehan DV, Ramos A, Sanberg PR. Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette’s disorder. J Am Acad Child Adolesc Psychiatry. Sep 2001;40(9):1103–10.

152. Sanberg PR, Fogelson HM, Manderscheid PZ, Parker KW, Norman AB, McConville BJ. Nicotine gum and haloperidol in Tourette’s syndrome. Lancet. Mar 12 1988;1(8585):592.

153. Awaad Y. Tics in Tourette syndrome: New treatment options. J Child Neurol. May 1999;14(5):316–9.

154. Guy W. Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health; 1976.

155. Singer HS, Wendlandt J, Krieger M, Giuliano J. Baclofen treatment in children and adolescents with Tourette syndrome. J Am Acad Child Adolesc Psychiatry. Jul 1989;28(4):566–73.

156. Jankovic J. Botulinum toxin in the treatment of dystonic tics. Mov Disord. May 1994;9(3):347–9.

157. Kwan C, Jankovic J. Tics in Tourette syndrome and botulinum toxin. J Child Neurol. Sep 2000;15(9):631–4.

158. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor movements. Arch Neurol. Mar 2001;58(5):605–10.

159. Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of tardive dyskinesia and acute extrapyramidal movement disorders. Arch Intern Med. Jun 28 1993;153(12):1469–75.

160. Nicolson R, Craven-Thuss B, Smith J, McKinlay BD, Castellanos FX. A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette’s disorder. J Am Acad Child Adolesc Psychiatry. Sep 2005;44(7):640–6.

161. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology. Feb 1997;48(2):358–62.

162. Jankovic J, Glaze DG, Frost JD Jr. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette’s syndrome. Neurology. May 1984;34(5):688–92.

163. Kenney CJ, Hunter CB, Mejia NI, Jankovic J. Tetrabenazine in the treatment of Tourette syndrome. Journal of Pediatric Neurology. 2007;5(1):9–13.

164. Eggers C, Rothenberger A, Berghaus U. Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. Eur Arch Psychiatry Neurol Sci. 1988;237(4):223–9.

165. Robertson MM, Schnieden V, Lees AJ. Management of Gilles de la Tourette syndrome using sulpiride. Clin Neuropharmacol. Jun 1990;13(3):229–35.

166. Haen Y, Katona CLE, Barnes TRE, Robertson MM. Sulpiride-induced tardive dyskinesia in a person with Gilles de la Tourette syndrome. J Psychopharmacol. May 1993;7(3):290–2.

167. Gilbert DL, Dure L, Sethuraman G, Raab D, Lane J, Salleee FR. Tic reduction with pergolide in a randomized controlled trial in children. Neurology. Feb 2003;60(4):606–11.

168. Gilbert DL, Sutherland G, Sine L, Peters S, Salleee FR. Tourette’s syndrome improvement with pergolide in a randomized, double-blind, cross-over trial. Neurology. Mar 2000;54(6):1310–5.

169. Schade R, Andersohn F, Suijsa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med. Jan 2007;356(1):29–38.

170. Zanettini R, Antonini A, Gatto G, Gentile T, Tesesi S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson’s disease. N Engl J Med. 2007;356(1):39–46.

171. Brown AM, Deacon BJ, Abramowitz JS, Dammann J, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson’s disease. N Engl J Med. 2007;356(1):39–46.

172. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. Biol Psychiatry. Jun 2008;63(12):1118–26.

173. Chasson GS, Buhlmann U, Tolin DF, et al. Need for speed: evaluating slopes of OCD recovery in behavior therapy enhanced with D-cycloserine. Behav Res Ther. Jul 2010;48(7):675–9.

174. Kushner MG, Kim SW, Donahue C, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. Biol Psychiatry. Oct 2007;62(8):835–8.

175. Riddle M. Obsessive-compulsive disorder in children and adolescents. Br J Psychiatry Suppl. 1998;35:91–6.

176. Pauls DL, Alsobrook JP, 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. Am J Psychiatry. Jan 1995;152(1):76–84.

177. Jummaru R, Coffey BJ. Tic disorders. In: Sadowh JB, Sadow VA, Ruiz P, Kaplan HI. editors. Kaplan & Sadow’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2009:3609–23.

178. Storch EA, Lack CW, Simons LE, Goodman WK, Murphy TK, Geffen GR. A measure of functional impairment in youth with Tourette’s syndrome. J Pediatr Psychiatr. Sep 2007;32(9):950–9.

179. Storch EA, Merlo LJ, Larson MJ, et al. Impact of comorbidity on cognitive-behavioral therapy response in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. May 2008;47(5):583–92.

180. Marsh JS, Franklin ME, Leonard H, et al. Tics moderate treatment outcome with sertraline but not cognitive-behavior therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. Feb 2007;61(3):344–7.

181. McDougle CJ, Goodman WK, Leckman JF, Barr LC, Heninger GR, Price LH. The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder. J Clin Psychopharmacol. Oct 1993;13(5):354–8.

182. Khalifa N, van Onckring AL. Psychopathology in a Swedish population of school children with tic disorders. J Am Acad Child Adolesc Psychiatry. Nov 2006;45(11):1346–53.

183. Worthington JJ 3rd, Kimura G, Wyant LE, Pollack MH. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. Int Clin Psychopharmacol. Jan 2005;20(1):9–11.

184. Hoge EA, Worthington JJ 3rd, Kaufman RE, Delong HR, Pollack MH. Aripiprazole as augmentation treatment of refractory generalized anxiety disorder and panic disorder. CNS Spectr. Jun 2008;13(6):522–7.

Journal of Central Nervous System Disease 2011:3
De Nadai et al.

187. Sears J, Patel NC. Development of tics in a thirteen-year-old male following atomoxetine use. CNS Spectr. Apr 2008;13(4):301–3.

188. Parraga HC, Parraga MI, Harris DK. Tic exacerbation and precipitation during atomoxetine treatment in two children with attention-deficit hyperactivity disorder. Int J Psychiatry Med. 2007;37(4):415–24.

189. Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: Treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry. Sep 2009;48(9):884–93.

190. Tourette’s Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. Feb 2002;58(4):527–36.

191. McDougle CJ, Epperson CN, Pelton GH, Wasylk S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. Aug 2000;57(8):794–801.

192. Storch EA, Geffken GR, Merlo LJ, et al. Family-based cognitive-behavioral therapy for pediatric obsessive-compulsive disorder: comparison of intensive and weekly approaches. J Am Acad Child Adolesc Psychiatry. Apr 2007;46(4):469–78.

193. Cohen J. The earth is round (P < 0.05). Am Psychol. 1994;49(12):997.

194. Joshi SV. Teamwork: the therapeutic alliance in pediatric pharmacotherapy. Child Adolesc Psychiatr Clin N Am. Jan 2006;15(1):239–62.

195. Storch EA, Geffken GR, Merlo LJ, et al. Family accommodation in pediatric obsessive-compulsive disorder. J Clin Child Adolesc Psychol. Apr–Jun 2007;36(2):207–16.

196. Walkup JT. Tic disorders and Tourette’s syndrome. Practical child and adolescent psychopharmacology. 2002:382–409.

197. Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children’s Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. Jun 1997;36(6):844–52.

Publish with Libertas Academica and every scientist working in your field can read your article

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:
• Available to your entire community free of charge
• Fairly and quickly peer reviewed
• Yours! You retain copyright

http://www.la-press.com