Psychiatric Treatment and Management of Psychiatric Comorbidities of Movement Disorders

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Abstract

Pediatric movement disorders may present with psychiatric symptoms at many points during the course of the disease. For the relatively common pediatric movement disorder, Tourette syndrome, psychiatric comorbidities are well-described and treatment is well-studied. Treating these comorbidities may be more effective than treating the movements themselves. For more uncommon movement disorders, such as juvenile-onset Huntington disease, treatment of psychiatric comorbidities is not well-characterized, and best practice recommendations are not available. For the least common movement disorders, such as childhood neurodegeneration with brain iron accumulation, psychiatric features may be nonspecific, so that underlying diagnosis may be apparent only after recognition of other symptoms. However, psychiatric medication, psychotherapy, and psychosocial support for these disorders may prove helpful to many children and adolescents.
Introduction

Pediatric movement disorders vary widely in their presentation, and psychiatric features may appear at many points in the course of the disease. In some movement disorders, psychiatric symptoms may present first, as is often seen in Huntington disease (HD), where mood symptoms may predominate, or in Tourette syndrome (TS), in which tics are often preceded by attention-deficit symptoms and followed by obsessive-compulsive behaviors. In some cases, what appears to be a pediatric psychiatric disorder eventually declares itself to be a movement disorder with a deteriorating course, clearly different than the expected course of a primary psychiatric condition.

In this review, six pediatric movement disorders with psychiatric features will be discussed: TS, Sydenham chorea (SC), juvenile-onset HD, pantothenate kinase-associated neurodegeneration (PKAN), phospholipase A2 group 6-associated neurodegeneration, and stereotypic movement disorders. For TS, good evidence is available for best-practice treatment of tics and psychiatric comorbidities. For two of these disorders, TS and stereotypic movement disorder, direct psychotherapy of the movement itself may be a useful treatment approach. What is known about comorbidities, published treatment, and the emotional experience of the other, less common and less well-studied disorders will be reviewed in this article.

Tourette syndrome (TS)

The psychiatric comorbidities of TS are numerous, well-studied, and often more distressing to patients than the tics themselves. In fact, comorbidity is the rule for TS. The Tourette Syndrome International Database Consortium (TIC database) is the largest source of comorbidity data for TS. This consortium of clinicians from 27 countries has collected data about patients with TS since 1996. Diagnoses are ascertained using Diagnostic and Statistical Manual (DSM) criteria. In the TIC database sample of 5060 5- to 17-year-olds, 74.7% of patients had at least one psychiatric comorbidity, with attention-deficit hyperactivity disorder (ADHD) by far the most common comorbidity, followed by obsessive-compulsive disorder (OCD) (see Table 1). In a somewhat larger TIC database sample that included adults, other significant comorbidities included self-injurious behavior (14%) and poorly controlled/explosive angry outbursts (37%). Many patients with TS have multiple psychiatric
comorbidities. ADHD appears to be a key driver of complex comorbidity in TS: in the child/adult TIC database study, the presence of ADHD was associated with increased comorbidity of all studied conditions except anxiety disorders. This distribution of comorbidity mirrors that reported in smaller studies.

The often complex psychiatric comorbidity experienced by patients with TS poses diagnostic and treatment challenges. Patients ultimately developing the “triad” of TS + ADHD + OCD typically present with ADHD as preschoolers, soon followed by tics (modal onset 6-8 years), and later by OCD (12 years) or obsessive-compulsive behaviors (OCBs), as demonstrated in a longitudinal study of 976 children followed over 15 years. This progression of symptoms can be confusing and upsetting to children and their families, sometimes triggering concern that treatment of an earlier condition caused later symptoms, for instance, that medications for ADHD led to tics.

The following sections will review key aspects of recognition and treatment of psychiatric comorbidities of TS, closing with a review of behavioral treatments of tics. Medication treatment of tic disorders is reviewed elsewhere in this journal.

TS: psychoeducation

Both the American Academy of Child and Adolescent Psychiatry (AACAP) and the European Society for the Study of Tourette Syndrome recommend psychoeducation and monitoring of symptoms as first-line interventions for patients with TS. Good psychoeducation for patients and families includes review of symptoms, comorbid conditions, and treatment options versus watchful waiting of tics. The natural history of tic disorders should be reviewed. The news that many patients do not take medication for their tics and that most will find that their tics diminish with age is greatly reassuring to children and their families. Patients and families should be taught to observe the natural waxing and waning of tics, watching for tic triggers and stressors that could be modified.

For many children with TS, school is the most challenging aspect of daily life. Classroom accommodations such as tic breaks, extended time on tests, and no-tolerance policies for bullying can reduce stress and possibly tics at school. Having an “elevator speech” prepared to explain tics to peers and teachers can be quite helpful. In addition, psychoeducation of teachers and peers may reduce bullying and ridicule in the classroom. College students who watched a TS education video reported
improved attitudes towards people with tics compared to their peers who watched a generic video. However, grade school children shown a similar video did not improve ratings of peers presented with TS.

Excellent support groups for patients with TS are active in many countries, including the Tourette Association of America. These groups provide educational materials for patients, families and teachers, as well as support groups and summer camps for youth. Many children with TS have never met a peer with TS, and find interacting with peers who also have TS a great support.

Some patients with TS will require more than psychoeducation. Treatments for comorbid conditions such as ADHD and OCD are often more effective than directly treating tics, and better control of these conditions can secondarily reduce stress and tics. Thus, following psychoeducation, the next steps in the TS treatment algorithm would be evidence-based treatment of comorbid conditions, followed by non-pharmacologic treatment of tics, and finally by medication treatment of tics.

TS and ADHD

The medications used most commonly in the management of comorbid tic disorders and ADHD are stimulants, alpha-2 agonists, and atomoxetine. Rizzo et al. suggested the following algorithm for medication treatment of comorbid ADHD and tic disorders: 1) alpha-2 agonist; 2) psychostimulant; 3) alpha-2 agonist plus psychostimulant, and 4) atomoxetine “or other medications”. A limited number of other studies also suggest the potential benefit of off-label combination therapy for ADHD with both stimulants and atomoxetine, although further studies are needed to confirm its benefit. Tachycardia may be more problematic with this combination therapy than with stimulants or atomoxetine alone.

TS and ADHD: Alpha-2 agonists

Clonidine has been shown to be effective (level A evidence) in two controlled studies. Clonidine reduced both ADHD symptoms (hyperactivity and impulsivity) and TS symptoms (motor tic severity and tic counts) in a study of 41 adults and children with TS. In the multicenter double-blind randomized trial by the Tourette Syndrome Study Group, clonidine, methylphenidate, and their combination were compared to placebo. 136 children with ADHD and chronic tic disorders participated in the study.
Clonidine was particularly helpful for hyperactivity and impulsivity, and methylphenidate for inattention. Combination therapy was most effective in reducing tic and ADHD severity. Despite concerns that stimulants could exacerbate tics, tic exacerbation rates were similar in all arms of the study at 20-25%. In fact, tics improved with all active medications (see Stimulants below).

Guanfacine, another alpha-2 agonist, has demonstrated efficacy in TS +/- ADHD in one 8-week controlled study. Teacher ratings of ADHD were significantly better for subjects on guanfacine, but parent ratings of hyperactivity were not significantly improved versus placebo.\textsuperscript{15}

Alpha-2 agonists can cause sedation, sleep disturbance, fatigue, dizziness, irritability, and hypotension. Blood pressure monitoring is necessary. One tic clinic has reported syncope in 4 of approximately 200 normotensive patients on guanfacine, but none in approximately 450 clonidine-treated patients.\textsuperscript{16} Both clonidine and guanfacine are available as immediate-release and extended-release forms, the latter of which may lead to fewer or milder side effects.\textsuperscript{11,13} The above studies were completed with immediate-release versions. A recent open-label study of clonidine transdermal patch lacked controls and is difficult to interpret, as patients began patch treatment only one week after discontinuing previous tic medications, including neuroleptics, and baseline movements may have included withdrawal dyskinesias.\textsuperscript{17}

TS and ADHD: Stimulants

Stimulants such as methylphenidate are highly effective for ADHD (level A evidence). For many years, there has been significant concern about using stimulants to treat ADHD in patients with comorbid tic disorders, as some patients report tic exacerbations on those agents. In fact, stimulant package inserts list tic disorders or family history of tic disorders as contraindications to use of stimulants. These contraindications have posed a significant clinical dilemma in the treatment of children with tic disorders whose ADHD was significantly impairing.
Multiple meta-analyses have reported that stimulants neither trigger nor exacerbate tics in children. A recent meta-analysis demonstrated that many children with ADHD and comorbid tic disorders benefit significantly from stimulants with minimal tic exacerbation. This analysis of 22 studies of 2,385 children found that tic onset/exacerbation was reported at similar rates for stimulant- (6.5%) and placebo-treated youth. The authors advised, “Clinicians may want to consider re-challenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.” In fact, a two-week study assessing two cohorts of children with ADHD and Tourette syndrome or chronic motor tic disorder found that classroom tic severity and frequency improved in those who received a stimulant compared to placebo, according to teacher ratings. Aggression and oppositional defiance showed improvement on methylphenidate (immediate release) as well.

Tics tend to manifest in early school age, when children often start stimulant treatment of ADHD. This makes it challenging initially to distinguish the etiology of tics, and whether stimulants have played a role. Additionally, tics typically wax and wane in frequency and severity when untreated. It may be difficult to assess the effect of a given medication on these symptoms without a trial lasting several months.

Adverse effects of stimulants that should be monitored include decreased appetite, weight loss, sleep disturbance, headaches and dizziness, change in heart rate and diastolic blood pressure, and worsening obsessive-compulsive symptoms. If adverse effects are reported after starting a stimulant, it is reasonable to switch stimulant families (e.g., change from a methylphenidate agent to an amphetamine agent).

TS and ADHD: Atomoxetine

Atomoxetine, a non-stimulant selective norepinephrine reuptake inhibitor, increases noradrenaline and dopamine in the synaptic cleft, similar to stimulants, and is approved for use in ADHD. Although limited evidence exists for tic efficacy, one double-blind placebo-controlled industry-funded study showed an effect size of 0.40 for reduction in Yale Global Tic Severity Scale total scores.
Atomoxetine side effects include decreased appetite, weight loss, nausea, and tachycardia; blood pressure and pulse monitoring is recommended. Atomoxetine, unlike stimulants, is sedating, and carries two black-box warnings for suicidal thinking in patients younger than 25 years of age and for rare jaundice with associated liver enzyme elevations.

TS and OCD

Like TS, OCD is characterized by unwanted repetitive behaviors. However, in OCD, repetitive behaviors, or compulsions, are triggered by intrusive thoughts (obsessions) rather than the sensory urges that often precede tics. Obsessive thoughts precede compulsions, and sensory urges precede tics. However, TS and OCD symptoms overlap in some patients. Patients with tics and OCD may report experiencing some repetitive behaviors which cannot be clearly classified, or which seem intermediate between compulsions and tics.

Tic-related OCD tends to present in childhood, particularly in boys, while non-tic-related OCD tends to present later in life. The obsessions and compulsions reported by patients with OCD + TS differ from those reported by patients with OCD – TS. Patients with OCD + TS are more likely to report compulsions to blurt obscenities, count, or self-harm, while patients with OCD only are more likely to endorse compulsions to order, clean, or arrange.

TS and OCD Treatment: the Pediatric Obsessive-Compulsive Disorder Treatment Study (POTS)

Psychotherapy and medication management have both demonstrated efficacy in pediatric OCD. The Pediatric Obsessive-Compulsive Disorder Treatment Study (POTS) is a key study in the treatment of pediatric OCD. While selective serotonin reuptake inhibitors (SSRIs) and exposure and ritual prevention therapy (ERP), a form of cognitive-behavioral therapy (CBT) specific to OCD, were well-established in adults, this large-scale study answered several important pediatric questions, including relative efficacy of therapy versus SSRI medication, and the impact of tics on treatment response.
POTS is a multisite randomized controlled trial of 112 youth (7-17 years old) with OCD. The study compared ERP, sertraline (titrated to a maximum dose of 200 mg daily), combined ERP and sertraline, and placebo. All active treatments outperformed placebo on the Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the primary outcome measure. ERP combined with sertraline (53.6%, 95% CI 36-70%) produced similar outcomes to ERP alone (39.3%, 95% CI 24-58%), but better than sertraline alone (21.4%, 95% CI 10-40%). ERP alone led to significantly greater remission rates than did placebo. ERP continuation studies have shown up to 9-month durability of this improvement, with two-thirds of patients maintaining improvement even after medication discontinuation.

The POTS II randomized controlled trial then studied augmentation management in children already on an SSRI, comparing full ERP (as provided in POTS I) to briefer ERP instructions given by prescribers in medication management clinics. Full ERP, but not the abbreviated ERP instruction, augmented medication effects significantly as measured by CY-BOCS.

In the POTS studies, ERP worked just as well for patients with tic-related OCD as it did for patients with OCD only. However, the comorbidity of tics with OCD appeared to alter treatment response to sertraline treatment. Patients with comorbid tics responded no better to sertraline than to placebo, as measured by CY-BOCS score at 12 weeks. Thus, ERP is an essential component of therapy for patients with tic-related OCD.

The following two sections further address psychotherapy and medication protocols for pediatric OCD. Typically, these protocols have been developed for OCD alone, rather than directly addressing treatment strategies for OCD + TS.

Best-Practice OCD Treatment: ERP Efficacy and Techniques

Evidence-based treatment guidelines and the American Academy of Child and Adolescent Psychiatry practice parameters recommend ERP therapy as first-line treatment of mild to moderate OCD, and ERP combined with an SSRI for moderate to severe OCD in young people. Multiple studies, including the POTS trials, and meta-analyses suggest that ERP leads to equal or better outcomes compared to pharmacotherapy alone and has more enduring effects. Like medications for OCD,
ERP has been shown to alter brain function, decreasing caudate nucleus glucose metabolism in patients with OCD\textsuperscript{44} and increasing neurotransmitter levels, including glutamate/glutamine, and N-acetyl-aspartate/N-acetyl-aspartyl-glutamate.\textsuperscript{45}

ERP is focused on extinction: repeated exposure to the anxiety-provoking stimulus without engagement in ritualized response reduces distress. Exposure is gradual, moving from least to most severe anxiety-provoking stimuli, using a symptom hierarchy that ranks predicted distress for each item or task.\textsuperscript{46} For instance, a child with contamination fear might start therapy by touching doorknobs (exposure) without immediately washing her hands (ritual prevention), and gradually work up to touching the most-feared items on the child’s symptom hierarchy, such as public toilets. Other components of ERP include psychoeducation about OCD and cognitive strategies such as externalizing the disease, constructive self-talk, and restructuring. For children, parental involvement in therapy sessions and coaching between therapy visits strengthens therapeutic success.\textsuperscript{43} ERP can be delivered in weekly outpatient sessions, or in more intensive programs. Modifications have also been published for group and family sessions, as well as treatment of very young children with their parents.\textsuperscript{43,47-49}

Unfortunately, many barriers prevent wider implementation of ERP.\textsuperscript{50,51} Access to ERP-trained therapists is limited, particularly therapists trained to work with children.\textsuperscript{52} Patients with OCD of all ages may be anxious about confronting their fears and so may not follow through with ERP. Local therapist skills in ERP may not be optimal due to low OCD case volume. Some families find it is cheaper to obtain medication management than ERP, and some practices may steer their providers towards providing shorter medication management visits rather than longer therapy visits.\textsuperscript{31,53,54}

Best-Practice OCD Treatment: Pharmacologic Therapy

It is not uncommon for patients with OCD to start with medication treatment only due to limited access to ERP. However, as noted in the section on the POTS trials, efficacy of these medications for children with OCD + TS may be less robust than for patients with OCD only.
The most studied and recommended pharmacologic agents for OCD are SSRIs. Based on the available evidence, the following algorithm for pharmacologic management of pediatric OCD is suggested: 1) Food and Drug Administration (FDA)-approved SSRI monotherapy; 2) second SSRI; 3) partially-effective SSRI augmented with an atypical antipsychotic; 4) clomipramine; 5) combination of SSRI and clomipramine.

The first-line pharmacotherapy, SSRIs, have been shown to be effective for OCD, with a tolerable adverse effect profile, in multiple trials. Interestingly, studies of brain morphometry show that fluoxetine improves OCD grey matter volume deficits. A matched CBT group also clinically improved but did not show these grey matter changes, suggesting that CBT affects the brain in a different way than fluoxetine.

This effect does not vary significantly between specific SSRIs. Three SSRIs, fluoxetine, fluvoxamine, and sertraline, and the serotonergic tricyclic antidepressant (TCA) clomipramine have been FDA-approved for pediatric OCD. Paroxetine is not recommended for pediatric patients due to concerns about agitation related to short half-life, and possible increased risk of suicidal ideation. See Table 2 for FDA-approved antidepressants for pediatric use, indicating approved diagnoses, age range, and recommended initial and target dosing per manufacturer’s label, based on available clinical trials.

While it is typically advised that an adequate SSRI trial for OCD takes 8-12 weeks, a recent meta-analysis of nine OCD medication trials demonstrated that the greatest benefit was seen within two weeks of medication initiation. As in other meta-analyses, clomipramine was more effective versus placebo than SSRIs. This may reflect the earlier release of clomipramine, when study patients were more likely to be serotonin reuptake inhibitor-naïve.

While multiple controlled clinical trials have demonstrated that clomipramine is effective for pediatric OCD, arguably more so than SSRIs, SSRIs are the safer, preferred initial treatment. Clomipramine’s side effects significantly limit its use, and regular monitoring of blood levels and electrocardiograms is required as TCAs can delay cardiac conduction, leading to torsades des pointes and sudden cardiac death. Patients on clomipramine also report anticholinergic adverse effects...
typical of TCAs including sedation, fatigue, orthostatic hypotension, dizziness, dry mouth, constipation, and urinary retention.

For patients whose OCD is not adequately treated with an SSRI plus ERP, augmentation with a low-dose atypical antipsychotic, either risperidone or aripiprazole, is recommended. The antipsychotics olanzapine and quetiapine did not prove effective compared to placebo. However, if SSRI monotherapy is insufficient, studies suggest that adding ERP is more effective than adding risperidone.

TS: Behavioral therapy/ Comprehensive Behavioral Intervention for Tics (CBIT)

As with OCD, behavior therapy has consistently been shown through randomized controlled trials (RCTs) to be effective in the treatment of TS and tic disorders. Habit reversal training (HRT) has emerged as the leading behavioral intervention, demonstrating medium to large effect sizes. HRT is the primary component of Comprehensive Behavioral Intervention for Tics, an empirically supported treatment for tics. Manualized CBIT is an 11-session treatment for both children and adults in which the goal is increased management and control over tics. CBIT training for therapists is available through the Tourette Association of America, which was instrumental in the development of CBIT.

CBIT focuses on building tic awareness, which is necessary prior to the development and use of a competing response. During awareness training, individuals with tics learn to recognize when tics are experienced in addition to detecting the initial urge to tic (i.e., premonitory urge or “tic signal”). Once individuals are able to identify the signal for a tic and are highly aware of tic onset, a competing response can be designed. Competing responses are actions that are physically incompatible with the tic. A child with a mouth-opening tic, for instance, could develop competing response of pressing his/her lips together until the urge to open the mouth fades. Use of the competing response in the moment is maintained until the urge to tic dissipates.
CBIT also utilizes other behavioral interventions alongside HRT, including functional analysis and relaxation training. Functional analysis is the identification of situational factors contributing to tic occurrence (antecedents) as well as environmental responses to the tics (consequences) that increase tic frequency or intensity. For example, monitoring of tics may indicate a child demonstrates more tics at school and when completing homework. This suggests that school stress is a likely antecedent. Encouraging the child to practice competing responses and relaxation strategies regularly at school and while doing homework can reduce stress, thereby, reducing tics. Finally, relaxation training is provided to reduce anxiety, often an internal antecedent state exacerbating tics.

It should be noted that other behavioral interventions have been developed to address tics including ERP (see TS and OCD:ERP) modified for tics, which has demonstrated efficacy, and less-studied techniques such as contingency management training, relaxation training alone, and urge reduction. Few RCTs have compared the effects of pharmacological interventions to behavioral interventions for tics.

Stereotypic movement disorders (SMD)

Patients with stereotypic movement disorders (SMD) have involuntary, repetitive movements with no obvious function. These movements, or stereotypies, are patterned, rhythmic, purposeless and often result from internal stimulation. Severe stereotypies interrupt daily functioning or result in self-injury. There is no clear consensus about how to classify stereotypical movement disorders, and how severe they must be to constitute a disorder. Common stereotypies in SMD include head banging, body rocking, complex hand and arm movements, and self-biting. To meet criteria for SMD, the DSM (5th Edition) requires that the movements cause significant impairment, occur early in development and are not better explained by another neurodevelopmental or mental disorder or result from substance related or other neurological conditions. However, SMD may occur in the presence of genetic or neurodevelopmental disorders such as intellectual disability (ID). Stereotypies occurring outside of the presence of a behavioral or neurological disorder are considered primary, while those occurring within the presence of these other disorders are deemed secondary.
frequently observed in autism spectrum disorder (ASD) as well as other developmental disorders, other psychogenic conditions, neurodegenerative disorders, metabolic disorders, traumatic brain injury, and substance-induced disorders.  

For diagnostic and treatment purposes, it is essential to differentiate stereotypies from behaviors or movements resulting from other disorders (e.g., OCD, TS, and dyskinesia). Compared to tics, movements attributable to SMD typically have an earlier age of onset (< 3 years old) and occur in a more fixed and lengthier pattern.  

Stereotypies lack the premonitory urge or “tic signal” associated with many tics.  

Movements associated with SMD are less likely to be perceived by the child as distressing and more likely to occur during periods of excitement.  

Unlike compulsions in OCD, stereotypic movements are not used as a means of reducing distress from a specific, intrusive thought or to comply rigidly with rules, but rather appear purposeless. As discussed above, stereotypies are commonly found in individuals with ASD; the DSM-5 notes that a diagnosis of SMD in addition to ASD is warranted only when the stereotypies are self-injurious in nature or severe enough to be a primary target of treatment.  

Stereotypies that are easily stopped by distraction and are not experienced as interfering or distressing are better understood as typically occurring repetitive movements or stereotypies not warranting diagnosis of SMD.  

Although SMD must be distinguished from movement/behaviors resulting from other psychiatric conditions, SMD may be comorbid with neuropsychiatric diagnoses such as ADHD, tic disorders, developmental coordination disorder, and to a lesser degree, OCD.  

It is important to note that self-injurious stereotypies may not indicate depressive mood.  

SMD: Behavioral strategies  

Multiple behavioral interventions have been developed to target and reduce stereotypic movements. Research into the efficacy of these methods has been sparse but is growing.  

Interventions have developed from various interpretations of stereotypies and are not necessarily specific to stereotypies resulting solely from SMD.  

As such, behavioral interventions for stereotypies in general will be reviewed below. Many argue that stereotypies persist as a result of continued reinforcement (internal and/or external). Therefore, functional analysis may be beneficial in reducing stereotypies or
related impairment by identifying antecedents and consequences, as in CBIT (described above). With regard to consequences, functional analysis is particularly helpful in understanding the means by which the movement is reinforced and potentially perceived as functional.\textsuperscript{90,92,93}

Antecedent-based strategies have been developed to prevent the stereotypical movement from occurring by altering the environment.\textsuperscript{90,92} One major antecedent-based strategy is environmental enrichment, also understood as noncontingent reinforcement or alternative stimulation.\textsuperscript{92,94} This involves providing access to other reinforcing or competing sensory stimuli for individuals with stereotypies, thus reducing occurrence of the stereotypy and its inherent reinforcement. Environmental enrichment requires the presence of various other forms of stimulation to be available in the environment that are equally, if not more, reinforcing than engaging in the stereotypic movement. It is particularly beneficial to have alternative stimuli that are “matched” to the resulting sensory experiences of the stereotypic movement.\textsuperscript{92,95} For example, for a child with mouth stereotypic movement, the family would give the child multiple toys that could provide oral stimulation and does not give the child any social consequence if the child does engage in the stereotypy.

Consequence-based strategies intervene in response to the target behavior. They may focus on sensory extinction, displacement of reinforcement, differential reinforcement, punishment (as understood in operant conditioning) or inhibitory stimulus control, or a combination of reinforcement and sensory extinction or punishment (i.e., response interruption and redirection).\textsuperscript{92,96,97} A combination of antecedent and consequence based strategies can also be used.\textsuperscript{90,96,97} Additionally, there is evidence to suggest that behavior therapy with HRT has efficacy in treating stereotypic movements in individuals without ASD.\textsuperscript{98,99} See Table 3 for an overview of behavioral intervention techniques.

For self-injurious stereotypies, which warrant their own specifier within the SMD diagnosis, special considerations may apply. When prevention of harm to self or others is necessary, intervention becomes a greater priority. Response blocking and more consequence-based approaches may therefore be more appropriate in immediately preventing further harm to self.\textsuperscript{101,102} Response-blocking and
consequence-based approaches are the most frequently studied interventions for self-injurious behavior in children with developmental disabilities.\textsuperscript{101}

Sydenham chorea

Like TS, Sydenham chorea (SC) is a movement disorder with significant psychiatric comorbidity. SC is triggered by group A beta-hemolytic streptococcal infection, as is rheumatic fever (RF). Neuropsychiatric comorbidity is common in both RF and SC, but more common with SC. Common SC comorbidities include anxiety, depression, and ADHD, in addition to new-onset OCD.\textsuperscript{103-106} Additional symptoms of SC include obsessive-compulsive spectrum disorders, hypotonia, involuntary movement, decreased coordination, fine motor impairment, weakness, and involuntary relaxation. Phonemic verbal fluency may be reduced (words with a given letter), but not semantic verbal fluency (words in a particular category) after controlling for age and education.\textsuperscript{105,107-110} The development of comorbidities is also influenced by genetic predisposition, developmental level, and gender.\textsuperscript{111} Children with premorbid ADHD have been shown to be at increased risk of developing SC.\textsuperscript{104} SC movement and psychiatric symptoms can be quite persistent, with over 72\% reporting persistent symptoms after 2.7 years.\textsuperscript{111}

Interestingly, SC and TS typically present in childhood and affect the basal ganglia and related cortical and thalamic areas.\textsuperscript{112} Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) are likely related to SC.\textsuperscript{113-115}

SC: Management of comorbidities

Management of the neuropsychiatric comorbidities of SC focuses on eliminating the streptococcal infection and preventing recurrence.\textsuperscript{107} To date, no guidelines or standardized recommendations exist due to lack of sufficient quality research of the various management strategies.

The first-line intervention for SC is acute treatment of the streptococcal infection.\textsuperscript{116,117} The American Academy of Pediatrics Red Book also recommends long-term continuous prophylaxis to prevent disease recurrence and for cardiac protection. This secondary prophylaxis significantly decreases both disease recurrence and neuropsychiatric exacerbations, and is recommended for a minimum of 5
years or until age 21 years (whichever is longer), and potentially for life in those with rheumatic heart disease. Penicillin G prophylaxis may reduce SC recurrence and neuropsychiatric exacerbations in children.

Symptomatic management is also important. Symptoms tend to improve with rest and sleep. In contrast, intentional movement, excitement, and stress tend to aggravate symptoms.

Insufficient evidence exists regarding symptomatic medication use. "Off-label" medication use must be slowly titrated since the risk of adverse effects is greater in those with SC compared to healthy controls. Sodium valproate, which raises brain GABA levels, has the potential to improve hyperactivity, aggression, irritability and impulsivity. Low-dose risperidone, haloperidol, and pimozide may also improve symptoms. SSRIs have not been studied in SC.

Immunological interventions that target the humorally-mediated autoimmune response have also been studied, including intravenous immunoglobulin (IVIG), corticosteroids, and plasma exchange. These studies have been small and level of evidence is not high. In a cross-sectional study, 17 children with SC were treated with IVIG, compared to a standard treatment SC group (n=9) and non-SC group (n=17). Six months after treatment, the IVIG group showed fewer behavior difficulties, less impulsivity, and better cooperation and executive functioning compared to the standard treatment group. Studies of IVIG treatment of the streptococcal-related autoimmune disease, PANDAS, have been mixed. One small study reported improvement in neuropsychiatric symptoms including anxiety, depression, obsession, compulsion, impairment, and overall severity after IVIG (n=9) or plasmapheresis (n=10). Recently, a randomized controlled study of IVIG for PANDAS in 35 children failed to demonstrate that IVIG was more effective than placebo. Gadian et al. reviewed the literature, which suggested that IVIG may speed recovery in SC, and recommended that IVIG be considered in severe cases of SC (grade C evidence).
The management of neuropsychiatric symptoms in SC requires communication between a multidisciplinary team including patient, family, clinicians, and teachers. Psychoeducation and cognitive behavioral therapy is appropriate.107

Juvenile-onset Huntington’s disease

Unlike SC, HD is not post-infectious, and typically manifests in adulthood. Approximately 5-7% of patients with HD have onset before the age of 21 years, 80% of whom received the gene through paternal transmission.126 In Ribai et al.’s127 large series of 1452 Huntington’s patients, 2% had symptom onset before the age of 20.

Family history positive for HD is a key diagnostic feature in pediatric patients. However, children occasionally present with symptoms before their affected parents manifest symptoms, family history is not known, or the history is not revealed to the treatment team.127

Psychiatric manifestations of juvenile HD appear to vary with age of onset and may precede clear motor symptoms such as chorea. In a series of 12 juvenile patients with HD, symptoms upon first presentation were assessed.128 Patients under 10 years of age presented with cognitive dysfunction as the first symptom in 71% and behavioral symptoms in 58%. Most of these young patients were symptomatic by 5 years of age. Two of the 12 children in the series were initially diagnosed with ADHD and one with motor tics.

Adolescent-onset (10 years of age and older) HD patients are more likely than younger patients to present with oropharyngeal dysfunction as the first sign of disease. Cognitive symptoms were reported at initial presentation in 40% of cases, and behavioral symptoms in 17% of the above patient series. Testing revealed serial declines in Wechsler verbal, performance, and full-scale intellectual quotients.128 Letort et al.129 described heterogeneous symptoms in adolescent-onset HD, including substance misuse, recurrent suicidality, hyperactivity, and personality disorder. Other severe behaviors requiring “medical or legal intervention” in HD-affected teenagers include arson and sexual misconduct.126
In Ribai's series of 29 patients with juvenile-onset HC, behavioral disturbance was reported in 79% of patients, and cognitive decline in 100%. Many of these young patients had quite severe psychiatric symptoms, sometimes for many years before they manifested chorea. Severe developmental delays and substance use disorders were each reported in 10.3% of patients in this series. Other serious symptoms included psychosis, recurrent suicide attempts, and anorexia. Ribai's group suggested that HD "be considered as a diagnostic hypothesis in a child or young adult with an atypical movement disorder and severe, progressive psychiatric or cognitive disturbances, even in the absence of an HD-positive family history." Atypical behavioral presentations should spur inquiry into the reason for non-custodial parents' absence (e.g., institutionalization, imprisonment, death) that might suggest an HD diagnosis.

Timing of psychiatric symptoms in juvenile-onset HD may also be atypical versus usual presentation of primary psychiatric disorders. For instance, selective mutism classically presents by the time of school entrance, around age 4-6 years of age, but has been reported to present later, in the context of mood symptoms, in children who developed HD with oropharyngeal dysfunction. When teens from HD-affected families develop mood or behavioral problems, it is important to assess the home environment. HD-unaffected adolescents living with HD-affected relatives face significant stressors not impacting typical teenagers. If a teen is living with an older, more severely affected relative, the teen may experience stress from caring for the affected relative and living in a disrupted home environment. This stress may trigger depression, with resultant mood and behavior symptoms not due to HD. In one study, teens from HD families who completed home interviews described struggling to provide home care for affected relatives. Some of them missed a significant amount of school until the family was able to obtain paid caregivers. Many teens reported frequent worry about their own health and HD status. Some reported abuse by affected parents. Most teens interviewed in HD focus groups had not met other teens from affected families and reported feeling isolated from affected and non-affected parents and from their peers.
Treatment of psychiatric symptoms in HD is not well-established in any age group, and the pediatric literature consists of case reports. In the absence of clear guidance from the research literature, some authors have advised treating isolated psychiatric symptoms in children and teenagers from HD families "as though the primary inciting factors are social or environmental, and then reassessing neurological and cognitive function in 6-12 months. Progression of neurologic symptoms, despite optimal psychological and social management, helps to support a formal diagnosis of HD".126

Antipsychotics, antidepressants, mood stabilizers and anticonvulsants have been reported as symptomatic agents for psychiatric symptoms in HD.129 Two agents are approved for HD movements in adults, tetrabenazine and deutetrabenazine. Both agents carry black box warnings for depression and suicidality, but rate of these symptoms is significantly lower with deutetrabenazine.129,135 One case report cited successful treatment of psychotic depression in a 12-year-old who was refusing to eat, suffering delusions of being poisoned with amitriptyline plus tetrabenazine. This combination would require close monitoring, as both the antidepressant and tetrabenazine prolong the corrected QT interval.132 In another case report, an 8-year-old with HD initially diagnosed with ADHD did not fare so well on methylphenidate. The child demonstrated a rapid decline in fine motor skills, and developed dysarthria, hypertonia and motor impersistence within 4 weeks of starting the stimulant. After these adverse effects appeared, the family disclosed a previously-unreported paternal history of HD, triggering concerns that "stimulant-induced hyperdopaminergic toxicity accelerated the rate of neurodegeneration".136

Dopamine-depleting or -blocking agents may exacerbate dystonia and rigidity in HD.126 However, second-generation antipsychotics have proven helpful for severe aggression and agitation in HD. A risperidone study of 5 HD patients included one juvenile patient, a 17-year-old with previous diagnoses of conduct disorder and learning disability. He had a significant decline in aggression on long-acting injectable risperidone, which was started due to noncompliance with oral medication.130
Neurodegeneration with brain iron accumulation

Psychiatric symptoms are prevalent in several childhood disorders of neurodegeneration with brain iron accumulation (NBIA)s. These disorders are much rarer than TS, SC, and HD. One such disorder, pantothenate kinase-associated neurodegeneration (PKAN) can present with symptoms of psychiatric disorders with known basal ganglia dysfunction, such as OCD and tic disorders. Children who lose the ability to speak due to an NBIA are occasionally diagnosed with selective mutism or severe depression, although the motor signs of NBIA are not features of psychiatric mutism or depression. Brain magnetic resonance imaging (MRI) demonstrates iron accumulation and is a key tool for diagnosis of NBIA.137

PKAN, previously known as Hallervorden-Spatz syndrome, is a rare autosomal recessive disorder of basal ganglia iron deposition caused by mutations in the pantothenate kinase 2 (PANK2) gene.138,139 Classic and atypical subtypes of PKAN have been reported, as well as patients who appear intermediate in type.140 Classic PKAN presents in the first decade of life. PKAN rapidly progresses to loss of ambulation and premature death. Psychiatric symptoms are not typically reported. Atypical PKAN presents later, in the second or third decade, with less severe neurologic symptoms, slower symptom progression, and more frequent psychiatric symptoms or comorbidity.141 Patients with atypical PKAN exhibit dystonia, choreoathetosis, a range of speech symptoms including ultimate loss of speech, and gradual gait disturbance, with loss of ambulation 15-40 years after presentation.137

Structured psychiatric assessment of children with NBIA, screening systematically for a range of disorders, has not been reported. While two case series provide some details of psychiatric manifestations of PKAN, methods of ascertainment are unclear. In one series of 16 juvenile patients with PKAN, eight had psychiatric symptoms, including OCD (5 patients), behavior problems (4), hyperactivity (3), tics (2) and depression (1).140 OCD and tics were not reported in another case series of 22 patients from ten families, although it is not clear these symptoms were investigated. Six of these patients were reported to have psychiatric issues, including emotional lability, impulsivity, and inattention.142
PKAN can prove a diagnostic challenge and may masquerade as an atypical presentation of many psychiatric disorders. Two case reports illustrate patients with PKAN-related loss of speech, initially diagnosed as a conversion disorder in one case\(^\text{143}\) and selective mutism in another.\(^\text{144}\) Each of the latter two patients presented with mutism (at ages 11 years and 16 years, respectively) many years after the typical onset of functional selective mutism (before 5 years).\(^\text{145}\) Children with functional selective mutism almost always retain their typical speech with first-degree relatives in their homes, and do not exhibit a decline in speech skills.

The Vansteenkiste case report described a woman who developed progressive speech problems and involuntary arm movements at 11 years of age. She was correctly diagnosed with PKAN by brain MRI at age 28, “after several evaluations by psychiatrists and neurologists for her alleged conversion disorder”. While she had symptoms of several psychiatric disorders, her presentation was not classic for any of them, likely triggering the conversion disorder diagnosis. At that time of her successful PKAN diagnosis, she was near-mute, relying on her phone for communication. She “showed frequent repetitive stereotypical movements: stretching, touching her nose, waving and squeezing the hands. The movements appeared as complex motor tics, but no tics were seen in her face”.\(^\text{143}\) This movement pattern differentiated her from patients with typical tic disorders, who almost always present with early and persistent motor tics involving the face, especially blinking.\(^\text{146}\) Another adolescent patient with PKAN has been described as demonstrating similar face-touching movements.\(^\text{139}\)

Treatment of the psychiatric manifestations of pediatric PKAN has been reported only rarely. A boy who had been diagnosed with PKAN at 10 years of age presented emergently with prominent auditory hallucinations at 14 years of age. He had no family history of psychosis. He had been severely anxious for the preceding four months, worried about the “forthcoming destruction of the world”. The teen communicated by writing, describing fears that birds would kill him. He responded favorably to the antipsychotic olanzapine.\(^\text{147}\)

The patient diagnosed with selective mutism reported above was initially treated with fluoxetine and weekly psychotherapy for the mutism and severe depression. That treatment proved unsuccessful. His inappropriate affect and the “extreme poverty of content” of his speech were concerning for the development of psychotic depression. He was treated with olanzapine augmentation of the fluoxetine,
then with a second trial of venlafaxine and aripiprazole. On the aripiprazole, the patient developed bilateral lower extremity dystonia which persisted off aripiprazole, and PKAN was ultimately diagnosed following brain MRI. Rigidity and dysphagia improved on a regimen of botulinum toxin, tetrabenazine, clonazepam and biperiden, but mutism persisted.144

CONCLUSION

Providers treating children with movement disorders can best serve them by understanding the complex interplay of psychiatric symptoms and movements in these conditions. Psychotherapy and psychiatric medications may directly improve some movements. However, treatment of comorbid anxiety, depression, ADHD, and obsessive-compulsive symptoms may provide as much or more symptom relief for many young patients. In addition, understanding the stress children and teens face when growing up in families with multigenerational movement disorders can lead to better care for patients with movement disorders. Providers should be vigilant regarding atypical behavioral presentations or unusual motor features that may be early signs of neurodegenerative disorders. Pediatric neurologists and child and adolescent psychiatrists may need to work in consultation to develop the best team approach for many children with movement disorders.

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References


Table 1. Psychiatric comorbidities of juvenile Tourette syndrome in Tourette Syndrome International Database Consortium (TIC) database

<table>
<thead>
<tr>
<th>Psychiatric comorbidity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Tourette syndrome only)</td>
<td>25.3%</td>
</tr>
<tr>
<td>ADHD (+/- OCD)</td>
<td>61.2%</td>
</tr>
<tr>
<td>OCD (+/- ADHD)</td>
<td>19.2%</td>
</tr>
<tr>
<td>OCD + ADHD</td>
<td>13.2%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>15.3%</td>
</tr>
<tr>
<td>Conduct disorder/oppositional defiant disorder</td>
<td>14.5%</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>12.2%</td>
</tr>
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</table>
Table 2. FDA-approved pediatric antidepressants for major depression and obsessive-compulsive disorder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Indication</th>
<th>Age</th>
<th>Initial Dose</th>
<th>Target dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>OCD</td>
<td>7-17 years</td>
<td>10 to 20 mg/day</td>
<td>10-60 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8-18 years</td>
<td>10 mg/day</td>
<td>10 to 60 mg/day</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>SSRI</td>
<td>MDD</td>
<td>12-17 years</td>
<td>10 mg/day</td>
<td>10 to 20 mg/day</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>SSRI</td>
<td>MDD, OCD</td>
<td>6-17 years</td>
<td>25 mg/day</td>
<td>200 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6-12 years),</td>
<td>(13-17 years)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>or 50 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>SSRI</td>
<td>OCD</td>
<td>8-17 years</td>
<td>25 mg at bedtime</td>
<td>200 mg/day</td>
<td>Increase by 25 mg every 4 to 7 days. Divide BID for doses over 50 mg.</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>TCA</td>
<td>OCD</td>
<td>10-17 years</td>
<td>25 mg/day</td>
<td>3 mg/kg: up to 200 mg/day</td>
<td>Do not exceed 100 mg/day in first 2 weeks</td>
</tr>
</tbody>
</table>
Table 3. Behavioral interventions for stereotypical movements.

<table>
<thead>
<tr>
<th>Antecedent-Based</th>
<th>Intervention before target behavior.</th>
<th>Noncontingent reinforcement or environmental enrichment. Provides competing sensory stimuli, preventing stereotypy. 92,94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequence-Based</td>
<td>Intervention in response to stereotypy.</td>
<td>Sensory extinction and punishment. Includes response blocking (physically blocking head-banging) 92, or pairing aversive stimuli with stereotypy (sounding buzzer to decrease movement) 92,94.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reinforcement strategies. Reinforcing other behaviors performed instead of stereotypy, or displacement of reinforcement 92,94.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reinforcement and punishment combination strategies. Response interruption and redirection (RIRD) combines sensory extinction or punishment with differential reinforcement 92,94,96.</td>
</tr>
<tr>
<td>Antecedent and Consequence Combination of noncontingent and contingent strategies.</td>
<td>RIRD. May be combined with contingent reinforcement (see above) or with noncontingent reinforcement 90,96.</td>
<td></td>
</tr>
<tr>
<td>Other Modified behavioral interventions</td>
<td>Modified habit reversal with differential reinforcement. Periods of awareness training and consequence-based reinforcement are provided by parents 98.</td>
<td></td>
</tr>
</tbody>
</table>