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Tourette noted a syndrome in several patients that included multiple motor tics, coprolalia, and echolalia. Tics often consist of motions that are used in volitional movements. One half to two thirds of children with Tourette’s disorder exhibit a reduction in or complete

remission of tic symptoms during adolescence. There are many common comorbid psychiatric disorders and behavioral problems likely to emerge along with Tourette’s disorder. For example, the relationship between Tourette’s disorder, attentiondeficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) has not been clearly delineated. Epidemiological surveys indicate that more than half of children with Tourette’s disorder also meet criteria for ADHD. There appears to be a bidirectional relationship between Tourette’s disorder and OCD, with 20 to 40 percent of Tourette’s disorder patients meeting full criteria for OCD. First-degree relatives of patients with OCD have been shown to have higher rates of tic disorders compared to the general population. There have been a few small reports suggesting that the obsessivecompulsive symptoms most likely to occur in Tourette’s disorder are characteristically related to ordering and symmetry, counting, and repetitive touching, whereas OCD symptoms in the absence of tic disorders are more often associated with fears of contamination and fears of doing harm. Motor and vocal tics are divided into simple and complex types. Simple motor tics are those composed of repetitive, rapid contractions of functionally similar muscle groups—for example, eye-blinking, neck-jerking, shoulder-shrugging, and facial-grimacing. Common simple vocal tics include coughing, throat-clearing, grunting, sniffing, snorting, and barking. Complex motor tics appear to be more purposeful and ritualistic than simple tics. Common complex motor tics include grooming behaviors, the smelling of objects, jumping, touching behaviors, echopraxia (imitation of observed behavior), and copropraxia (display of obscene gestures). Complex vocal tics include repeating words or phrases out of context, coprolalia (use of obscene words or phrases), palilalia (a person’s repeating his or her words), and echolalia (repetition of the last-heard words of others). Although older children and adolescents with tic disorders may be able to suppress their tics for minutes or hours, young children are often not cognizant of their tics or experience their urges to perform their tics as irresistible. Tics may be attenuated by sleep, relaxation, or absorption in an activity. Tics often disappear during sleep.

EPIDEMIOLOGY The estimated prevalence of Tourette’s disorder ranges from 3 to 8 per 1,000 school-age children. Males are affected between 2 and 4 times more often than females. The unique features of Tourette’s disorder in which tics wax and wane and may change in character, frequency, and severity over relatively short periods of time, has made ascertainment of its prevalence challenging. Furthermore, remission of tics is particularly age-dependent in that tics tend to emerge and increase from ages 5 to 10 years of age, and in many cases, decrease in frequency and severity after the age of 10 to 12 years. At age 13 years, however, using stringent criteria, the prevalence rate for Tourette’s disorder drops to 0.3 percent. The lifetime prevalence of Tourette’s disorder is estimated to be approximately 1 percent. ETIOLOGY Genetic Factors Twin studies, adoption studies, and segregation analysis studies all support a genetic basis, albeit a complex one, for Tourette’s disorder. Twin studies indicate that concordance for the disorder in monozygotic twins is significantly greater than that in dizygotic twins. Tourette’s disorder and chronic motor or vocal tic disorder are likely to occur in the same families; this lends support to the view that the disorders are part of a genetically determined spectrum. The sons of mothers with Tourette’s disorder seem to be at the highest risk for the disorder. Evidence in some families indicates that Tourette’s disorder is transmitted in an autosomal dominant fashion. Studies of a

long family pedigree suggest that Tourette’s disorder may be transmitted in a bilinear mode; that is, Tourette’s disorder appears to be inherited through an autosomal pattern in some families, intermediate between dominant and recessive. A study of 174 unrelated probands with Tourette’s disorder identified a greater than chance occurrence of a rare sequence variant in SLITRK1, believed to be a candidate gene on chromosome 13q31. Up to half of all patients with Tourette’s disorder also have ADHD, and up to 40 percent of those with Tourette’s disorder also have OCD. These frequent comorbidities with Tourette’s disorder can lead to a plethora of overlapping symptoms. Family studies have provided compelling evidence for the association between tic disorders and OCD. First-degree relatives of persons with Tourette’s disorder are at high risk for the development of Tourette’s disorder, chronic motor or vocal tic disorder, and OCD. Current understanding of the genetic bases of Tourette’s disorder implicates multiple vulnerability genes that may serve to mediate the type and severity of tics. Candidate genes associated with Tourette’s disorder include dopamine receptor genes, dopamine transporter genes, several noradrenergic genes, and serotonergic genes. Neuroimaging Studies A functional magnetic resonance imaging (fMRI) study of brain activity two seconds

before and after a tic, found that paralimbic and sensory association areas were involved. Furthermore, evidence suggests that voluntary tic suppression involves deactivation of the putamen and globus pallidus, along with partial activation of regions of the prefrontal cortex and caudate nucleus. Compelling, but indirect, evidence of dopamine system involvement in tic disorders includes the observations that pharmacological agents that antagonize dopamine (haloperidol [Haldol], pimozide [Orap], and fluphenazine [Prolixin]) suppress tics and that agents that increase central dopaminergic activity (methylphenidate [Ritalin], amphetamines, and cocaine) tend to exacerbate tics. The relation of tics to neurotransmitter systems is complex and not yet well understood; for example, in some cases, antipsychotic medications, such as haloperidol, are not effective in reducing tics, and the effect of stimulants on tic disorders reportedly varies. In some cases, Tourette’s disorder has emerged during treatment with antipsychotic medications. More direct analyses of the neurochemistry of Tourette’s disorder have been possible utilizing brain proton magnetic resonance spectroscopy (MRS). Neuroimaging studies using cerebral blood flow in positron emission tomography (PET) and single photon emission tomography (SPECT) suggest that alterations of activity may occur in various brain regions in patients with Tourette’s disorder compared to controls, including the frontal and orbital cortex, striatum, and putamen. An investigation examining the cellular neurochemistry of patients with Tourette’s disorder utilizing MRS of the frontal cortex, caudate nucleus, putamen, and thalamus demonstrated that these patients had a reduced amount of choline and N-acetylaspartate in the left putamen along with reduced levels bilaterally in the putamen. In the frontal cortex, patients with Tourette’s disorder were found to have lower concentrations of N-acetylaspartate bilaterally, lower levels of creatine on the right side, and reduced myoinositol on the left side. These results suggest that deficits in the density of neuronal and nonneuronal cells are present in patients with the disorder. Abnormalities in the noradrenergic system have been implicated in some cases by the reduction of tics with clonidine (Catapres). This adrenergic agonist reduces the release of norepinephrine in the central nervous system and, thus, may reduce activity in the dopaminergic system. Abnormalities in the basal ganglia are known to result in various movement disorders, such as Huntington’s disease, and are also implicated as likely sites of disturbance in Tourette’s disorder. Immunological Factors and Post Infection An autoimmune process and, in particular, one that is secondary to group A betahemolytic streptococcal infections was hypothesized as a

potential mechanism for the development of tics and obsessive-compulsive symptoms in some case. Data have been conflicting and controversial, and this mechanism appears to be unlikely as an etiology of Tourette's disorder in most cases. One case-control study found little evidence of the development or exacerbation of tics, or obsessions or compulsions, in children with welldocumented and treated group A beta-hemolytic streptococcal infections.

DIAGNOSIS AND CLINICAL FEATURES A diagnosis of Tourette's disorder depends on a history of multiple motor tics that generally emerge over a period of months or years, and the emergence of at least one vocal tic at some point. According to the American Psychiatric Association's Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), tics may wax and wane in frequency, but must have persisted for more than a year since the first tic emerged to meet the diagnosis. The average age of onset of tics is between 4 years and 6 years of age, although in some cases, tics may occur as early as 2 years of age. The peak age for severity of tics is between 10 and 12 years. To meet diagnostic criteria for Tourette's disorder, the onset must occur before the age of 18 years. In Tourette's disorder, typically the initial tics are in the face and neck. Over time, the tics tend to occur in a downward progression. The most commonly described tics are those affecting the face and head, the arms and hands, the body and lower extremities, and the respiratory and alimentary systems. In these areas, the tics take the form of grimacing; forehead puckering; eyebrow-raising; eyelid-blinking; winking; nosewrinkling; nostril-trembling; mouth-twitching; displaying the teeth; biting the lips and other parts; tongue-extruding; protracting the lower jaw; nodding, jerking, or shaking the head; twisting the neck; looking sideways; head-rolling; hand-jerking; arm-jerking; plucking fingers; writhing fingers; fist-clenching; shoulder-shrugging; foot, knee, or toe shaking; walking peculiarly; body writhing; jumping; hiccupping; sighing; yawning; snuffing; blowing through the nostrils; whistling; belching; sucking or smacking sounds; and clearing the throat. Several assessment instruments are currently available that are useful in making diagnoses of tic disorders, including comprehensive self-report assessment tools, such as the Tic Symptom Self Report and the Yale Global Tic Severity Scale, administered by a clinician (Table 31.8c-1). Table 31.8c-1 Clinical Assessment Tools in Tic Disorders

Because Tourette's disorder is frequently comorbid with attentional, obsessional, and oppositional behaviors, these symptoms often emerge prior to the tics. In some studies, more than 25 percent of children with Tourette's disorder received stimulants for a diagnosis of ADHD before receiving a diagnosis of Tourette's disorder. The most frequent initial symptom is an eye-blink tic, followed by a head tic or a facial grimace. Most complex motor and vocal symptoms emerge several years after the initial symptoms. Coprolalia, a very unusual symptom involving shouting or speaking socially unacceptable or obscene words, occurs in less than 10 percent of patients and rarely in the absence of comorbid psychiatric disturbance. Mental coprolalia—in which a patient experiences a sudden, intrusive, socially unacceptable thought or obscene word—occurs more often than coprolalia. In severe cases, physical self-injury has occurred due to tic behaviors. Jake, age 10 years, came to the Tourette Disorder Clinic for an evaluation of motor tics in the head and neck, occasional coughing and grunting, and a new symptom of throat clearing many times per day. Jake had a past history of ADHD, which included significant hyperactivity, and impulsive and oppositional behavior He is a fifth-grade student in a regular class at the local public school. Before the consultation, parent and teacher ratings, including the Child Behavior Checklist (CBCL), Swanson, Nolan, and Pelham-IV (SNAP-IV), Conners' Parent and Teacher Questionnaires, Tic Symptom SelfReport (TSSR), and medical history survey, were sent to his family. His mother and

the classroom teacher rated him well above the norm for hyperactivity, inattention, and impulsiveness. He was failing several subjects in school, often argued with adults, was occasionally aggressive, and had few friends. His tics were rated as moderate. Jake’s mother recalls difficulties with overactivity, oppositional and defiant

behaviors and behavior since preschool. At age 5, due to his activity level and argumentative and aggressive behavior, his kindergarten teacher encouraged the family to obtain a psychiatric consultation. Jake’s pediatrician made a diagnosis of ADHD and recommended a trial of Concerta (methylphenidate extended-release tablets) at 36 mg per day, which was started at the beginning of the first grade. Within a week of starting medication, Jake’s overly active and impulsive behavior showed a dramatic improvement; however, he remained argumentative and oppositional. However, when on his Concerta, Jake was able to stay in his seat and complete his work and was better able to wait his turn on the playground. The next few months went well, however, by early spring, Jake seemed to be returning back to some of his old ways. He was talking out of turn in class, and getting out of his seat, which was disruptive to the class. After an increase in Concerta to 54 mg per day, in the spring of his first-grade year, however, he began showing motor and phonic tics consisting of head-jerking, facial movements, coughing, and grunting. The Concerta was discontinued to see if this made a difference and was immediately stopped and, although the tics transiently decreased, they came back in full force within a month. In hindsight, Jake’s mother recalled that Jake had exhibited eye blinking and grunting prior to starting the Concerta, but she had dismissed these events as unimportant and they did not seem to disrupt Jake’s daily life. While Jake was off Concerta during a period when he began middle school in the 6th grade, Jake was disruptive to his classes and he began to be severely teased by several classmates for his impulsivity, frequent motor tics, and loud grunting and throat clearing. Jake became despondent and began to refuse to go to school. At this point, it was decided to place Jake in a special education class. However, after several months of this placement, Jake felt worse about himself, despised school, and begged to be returned to regular classes. At this point Jake’s pediatrician made the referral to a child and adolescent psychiatrist at a local university Tourette Disorder Clinic. During his evaluation at the Tourette Disorder Clinic, Jake was reported to be a healthy child who was the product of an uncomplicated pregnancy, labor, and delivery, and whose developmental milestones were achieved at appropriate times. Intellectual testing completed by the school psychologist revealed a full scale IQ of 105. Jake’s mother noted that Jake has had long-standing trouble falling asleep but sleeps through the night. Jake has always been described as argumentative and easily frustrated with frequent outbursts of temper; however, when he is not having a tantrum, his mood is generally upbeat. Jake was noted by the child and adolescent psychiatrist to be of average height and weight with no dysmorphic features. His speech was rapid in tempo but normal in tone and volume. His speech is coherent and developmentally appropriate, without evidence of thought disorder; however, vocal tics including grunting, coughing, and obvious throat clearing were observed. Jake denied depressed mood or suicidal ideation, although he reported distress about everyday issues such as being teased by peers, not having enough friends, and his poor school performance. Jake also denied recurring worries about contamination or harm coming to him or family members, or

fears of acting on unwanted impulses. Other than mild touching habits involving the need to touch objects with each hand three times or in combinations of three, Jake denies repetitive rituals. Several motor tics were also observed during the evaluation session, including blinking, head-

jerking, and shoulder tics. Jake was restless and easily distracted throughout the session and often needed assistance with entertaining himself when not directly involved in conversation. Given the history of enduring motor and phonic tics, confirmed by direct observation, the diagnosis of Tourette's disorder and ADHD, as well as oppositional defiant disorder were confirmed. Jake and his family attended several sessions with the child and adolescent psychiatrist to learn about the waxing and waning nature of tic symptoms and the natural history of Tourette's Disorder, as well as ADHD. Jake and his family were heartened to hear that, in general, tics tend to be at their maximum around his age, and it was somewhat likely that Jake's tics would lessen over time or possibly fully remit. Jake was referred to a behavioral psychologist specializing in habit reversal training. In this treatment Jake was taught to engage in a behavior physically incompatible with his tic (a competing response) each time he experienced the urge to perform this tic. The competing response for Jake's shoulder tic, which consisted of raising his shoulders up as far as he could, was to gently press his shoulders down and extend his neck each time he felt the urge to engage in this tic. With repeated practice of his competing response, Jake's urge to engage in this tic greatly diminished to the point where he was able to manage the urge without performing the tic. Jake was referred to a child and adolescent psychiatrist who decided to re-start the Concerta at 36 mg per day and titrated it back up to 54 mg per day without worsening of the tics. Jake responded well to his behavioral therapy, and over a period of 8 weeks, he had learned how to become aware of the urges that occurred prior to his tics and to voluntarily replace his usual tics with less-distressing and less-disruptive behaviors. However, when Jake entered the 7th grade, he had an exacerbation of his motor and vocal tics, and was also touching objects repeatedly throughout the day. Jake again became despondent, not wanting to go to school. It was decided by his psychologist to add relaxation training to his behavioral treatment, and his child and adolescent psychiatrist another medication to his pharmacological regimen. Jake was prescribed risperidone, 0.5 mg per day, which was titrated up to 1 mg twice daily. With the addition of these psychological and pharmacological interventions, Jake became stabilized within a month, and was able to continue in his school and even went to some parties. Jake and his parents understood the waxing and waning nature of his tics, and were hopeful that they would begin to see some decrease in his tic symptoms within the next few years. At follow-up, when Jake was 15 years of age, Jake had minimal tic symptoms; an occasional eye blink and rare throat clearing was all that was observable. Jake was not currently in behavioral treatment, however, over the years, he had, on a few occasions received some booster therapy sessions to brush up on his habit reversal training when he had a minor exacerbation of tics. Jake had been taken off his risperidone a 2 years before without an exacerbation of tics.

Jake continued on Concerta 54 mg per day and was well controlled on that dose, was doing well in school, and had become more popular since he had joined the soccer team. (Adapted from L. Scahill M.S.N., Ph.D. and J.F. Leckman, M.D.) PATHOLOGY AND LABORATORY EXAMINATION No specific laboratory diagnostic test exists for Tourette's disorder, but many patients with Tourette's disorder have nonspecific abnormal electroencephalographic findings. Computed tomography (CT) and magnetic resonance imaging (MRI) scans have revealed no specific structural lesions, although about 10 percent of all patients with Tourette's disorder show some nonspecific abnormality on CT scans. DIFFERENTIAL DIAGNOSIS Tics must be differentiated from other movements and movement disorders (e.g., dystonic, choreiform, athetoid, myoclonic, and hemiballismic movements) and the neurological diseases that they may characterize (e.g., Huntington's disease, parkinsonism, Sydenham's chorea, and Wilson's disease), as listed in Table 31.8c-2. Tremors, mannerisms, and stereotypic movement disorder (e.g., head-banging or bodyrocking) must also be distinguished

from tic disorders. Stereotypic movement disorders, including movements such as rocking, hand-gazing, and other self-stimulatory behaviors, seem to be voluntary and often produce a sense of comfort, in contrast to tic disorders. Although tics in children and adolescents may or may not feel controllable, they rarely produce a sense of well-being. Compulsions are sometimes difficult to distinguish from complex tics and may be on the same continuum biologically. Tic disorders may also occur comorbidly with mood disturbances. In a recent survey, the greater the severity of tics, the higher the probability of both aggressive and depressive symptoms in children. When a child experiences an exacerbation of tic symptoms, behavior and mood also seem to deteriorate. Table 31.8c-2 Differential Diagnosis of Tic Disorders

COURSE AND PROGNOSIS Tourette's disorder is a childhood-onset neuropsychiatric disorder characterized by both motor and vocal tics, which usually emerge in early childhood, with a natural history leading to reduction or complete resolution of tics symptoms in most cases by adolescence or early adulthood. During childhood, individual tic symptoms may decrease, persist, or increase, and old symptoms may be replaced by new ones. Severely afflicted persons may have serious emotional problems, including major depressive disorder. Impairment may also be associated with the motor and vocal tic symptoms of Tourette's disorder; however, in many cases, interference in function is exacerbated by comorbid ADHD and OCD, both of which frequently coexist with the disorder. When the above three disorders are comorbid, severe social, academic, and occupational problems may ensue. Although most children with Tourette's disorder will experience a decline in the frequency and severity of tic symptoms during adolescence, at present, no clinical measures exist to predict which children may have persistent symptoms into adulthood. Children with mild forms of Tourette's disorder often have satisfactory peer relationships, function well in school, and develop adequate self-esteem, and may not require treatment. TREATMENT Once a diagnosis of Tourette's disorder is made, psychoeducation is a useful intervention in order for families to gain an understanding of the variability of tics, the natural history of the disorder, and ways to support reduction of stress. It is particularly important for families to be well-informed advocates for their children, since tics may be misinterpreted by an uneducated observer as a child's purposeful misbehavior, rather than a response to an irresistible urge. The need for treatment is based on subjective distress of a child with respect to tics as well as observable disruptions in functioning. In mild cases, children with tic disorders who are functioning well socially and academically may not seek, nor require treatment. In more severe cases, children with tic disorders may be ostracized by peers and have academic work compromised by the disruptive nature of tics, and a variety of interventions including psychosocial,

pharmacological, and school based may be considered. A scale to measure tic severity, the Premonitory Urge for Tics Scale (PUTS), was examined psychometrically, and found to be internally consistent and correlated with overall tic severity in youth over 10 years of age. The European clinical guidelines for Tourette's syndrome and other tic disorders summarized and reviewed the evidence-based treatments for Tourette's disorder and developed a consensus for psychosocial and pharmacological treatments. This guideline recommends that both behavioral and pharmacological interventions be considered in more severe cases, with behavioral interventions typically the first line of treatment. Indications for treatment include, but are not limited to, the following clinical presentations. Tics require treatment when they cause social and emotional problems, depression, or isolation. Children who are prone to severe persistent complex motor tics or loud vocal tics may be the objects of bullying and social rejection. In these cases, depressive symptoms commonly

result. Tic reduction and psychoeducation to the school may be indicated in order to preserve healthy social relationships, and to diminish depressive and anxiety symptoms. Tics may also lead to impairment in academic achievement, when school functioning is disrupted. School difficulties in children with Tourette's disorder are not uncommon, and reduction in tics may support increased academic success. Tics may also lead to physical discomfort, based on the repetitive musculoskeletal exertion, especially in relation to head and neck tics. In some children with Tourette's disorder, tics can worsen headaches and migraines. Behavioral and pharmacological interventions can both target tic reductions, which can lead to improved quality of life. Evidence-based Behavioral and Psychosocial Treatment The Canadian guidelines for the evidence-based treatment of tic disorders: behavioral therapy, deep brain stimulation and transcranial magnetic stimulation, and a large multi-site randomized controlled trial of "Comprehensive Behavioral Intervention for Tics," (CBIT) both found converging evidence supporting habit-reversal training and exposure and response prevention as efficacious treatments for tic reduction. In a randomized controlled trial of CBIT, 61 children received habit reversal training as their main component of treatment, and they also received relaxation treatment and a functional intervention to identify situations that worsened or sustained tics and strategies to decrease exposure to these situations. The control group of 65 children received supportive psychotherapy and psychoeducation. After 10 weeks of treatment, the Yale Global Tic Severity Scale Total Tic score was significantly reduced in the behavioral intervention group compared with the control group. Habit Reversal. The primary components of habit reversal are awareness training, in which the child uses self-monitoring to enhance awareness of tic behaviors and the premonitory urges or sensations indicating that a tic is about to occur. In competingresponse training, the patient is taught to voluntarily perform a behavior that is

physically incompatible with the tic, contingent on the onset of the premonitory urge or the tic itself, blocking expression of the tic. The competing-response strategy is based on the self-reported observations of patients that tics are performed in response to irresistible premonitory urges in order to diminish the urge. Because performing the tic satisfies or reduces the premonitory urges, the tics are reinforced, and over time, become repeated entrenched behaviors. Competing-response training is different from voluntary tic suppression in that the patient initiates a voluntary behavior to manage the premonitory urge and thus disrupts the reinforcement of the tic, rather than simply trying to suppress the tic. Successful competing-response training results in significant reduction in premonitory urge intensity or complete elimination of the urge altogether so that tics are no longer provoked. For motor tics, a behavior that is less noticeable may be chosen, whereas for vocal tics, slow rhythmic breathing is the most common voluntary competing response. The competing responses are designed to be performed without disrupting usual activities. Exposure and Response Prevention. The rationale for this treatment is based on the notion that tics occur as a conditioned response to unpleasant premonitory urges, and since the tics reduce the urge, they become associated with the premonitory urge. Each time the urge is reduced by the tic, their association is further strengthened. Rather than using competing responses, as in habit-reversal training, exposure and response prevention asks the patient to suppress tics for increasingly prolonged periods in order to break the association between the urges and the tics. Theoretically, if a patient learns to resist performing the tic in response to the urge for long enough periods, the urge may become more tolerable, or attenuate, and the need to perform the tic may diminish. Many other behavioral interventions such as relaxation training, self-monitoring, bio (neuro) feedback, and cognitive-behavioral treatment (CBT), have not been shown to be efficacious in the

reduction of tics on their own; however, some of these strategies may be included in comprehensive treatment programs for children with tic disorders who are receiving habit-reversal training. Habit reversal has been the most extensively researched behavioral treatment for tic disorders; it has been shown to be highly effective, and is currently the first-line behavioral treatment for tic disorders. Evidence-based Pharmacotherapy Several reviews of pharmacological treatments for tics suggest that the following classes of pharmacologic agents have an evidence base for treating tics: typical and atypical antipsychotics; noradrenergic agents; and alternative treatments such as tetrabenazine, topiramate, and tetrahydrocannabinol. Atypical and Typical Antipsychotic Agents. Risperidone, with its high affinity for dopamine D2 and serotonin 5-HT2 receptors, is the most well-studied atypical antipsychotic in the treatment of tics. There is considerable evidence for its efficacy. Multiple randomized, controlled studies in children and adolescents have

shown favorable results compared to placebo as well as in head-to-head studies with the typical antipsychotic agents haloperidol and pimozide. Risperidone was associated with fewer adverse events compared to typical antipsychotics; however, it was frequently associated with weight gain, metabolic side effects, and hyperprolactinemia. In a randomized, double-blind, parallel group study of Tourette's disorder comparing risperidone to pimozide, risperidone showed superiority in reducing comorbid obsessivecompulsive symptoms as well as reducing tics. In other randomized clinical trials, efficacy of tic reduction was achieved in studies of children, adolescents, and adults with mean daily doses of 2.5 mg daily with a range of 1 to 6 mg daily. Haloperidol (Haldol) and pimozide (Orap) are the two most well-investigated and Food and Drug Administration (FDA)–approved antipsychotic agents in the treatment of Tourette's disorder, although atypical antipsychotics such as risperidone are often chosen as first-line agents due to their safer side-effect profiles. Both haloperidol and pimozide have been shown to be efficacious in multiple randomized clinical trials in the treatment of Tourette's disorder. Both haloperidol and pimozide present significant risks for extrapyramidal side effects; in a long-term naturalistic follow-up study, haloperidol was found to produce more significant acute dyskinesia and dystonia compared to pimozide. A third typical antipsychotic, fluphenazine, has been used in the United States for many years in the treatment of tic disorders, in the absence of robust data supporting its efficacy. A small controlled study of fluphenazine, trifluphenazine, and haloperidol found similar reductions in tics; however, haloperidol was associated with more extrapyramidal side effects and more sedation. The frequency of sedation, dystonia, and akathisia of typical antipsychotics, probably due to their predominant dopaminergic blockade in the nigrostriatal pathways, limits their use and increases the appeal of the atypical antipsychotics. Risperidone and pimozide were found to be of equal efficacy in one study of children, adolescents, and adults with Tourette's disorder. Aripiprazole has become a pharmacological agent of interest in the treatment of tic disorders due to its mode of action; in addition to its D2 receptor antagonistic actions, aripiprazole is also a partial D2 and 5-HT1A receptor agonist and a 5-HT2A antagonist. A multisite double-blind controlled study of aripiprazole in children with Tourette's disorder in China found a reduction in tic behaviors in about 60 percent of the aripiprazole group compared to about 64 percent reduction in a group treated with tiapride, a benzamide with selective D2 receptor antagonism. There was no significant difference between the two groups. Although sedation and sleep disturbance are common side effects with aripiprazole, weight gain is less pronounced than with risperidone. Olanzapine and ziprasidone were shown to be efficacious in the treatment of tic disorders in at least one randomized controlled trial. Sedation and weight gain were prominent side effects with olanzapine,

and potential QT prolongation was an issue with ziprasidone. Quetiapine has been suggested as a potentially useful agent in the treatment of tics, with its greater affinity for 5-HT2 receptors than for D2 receptors, however, randomized clinical trials are needed. Clozapine, contrary to many other

atypical antipsychotics, has not been found to be useful in the treatment of tics. Noradrenergic Agents. Noradrenergic agents including clonidine and guanfacine, as well as atomoxetine, are frequently used in children as primary treatments or adjunctive treatments for comorbid ADHD and tics. Several studies have provided some evidence for the efficacy of clonidine, an alpha 2-adrenergic agent, in the treatment of tics in children, adolescents, and adults with tic disorders. The largest randomized trial with oral clonidine compared to placebo found a modest reduction in tics with clonidine. A multisite randomized double-blind placebo controlled trial using the clonidine patch in the treatment of tic disorders in children found a significant improvement in tic symptoms (about 69 percent) compared to about 47 percent of the children in the control group. Clonidine has generally been used in dosages ranging from 0.05 mg orally three times daily to 0.1 mg four times daily; and guanfacine is usually used in dosages ranging from 1 to 4 mg per day. When used in these dosage ranges, adverse effects of the α-adrenergic agents may include drowsiness, headache, irritability, and occasional hypotension. Guanfacine has been used frequently to treat children with ADHD successfully, although its efficacy regarding reducing tics is controversial. In one randomized clinical trial treating 34 children with ADHD and tics, guanfacine was found to be superior to placebo in the reduction of tics. In another double-blind placebo-controlled trial of 24 children with Tourette's disorder, guanfacine was not superior to placebo. Atomoxetine, a selective noradrenaline reuptake inhibitor, was found to reduce both tics and ADHD symptoms in a multicenter industry trial of 148 children. Atomoxetine also reduced both tics and ADHD in a subgroup of patients in this study who were diagnosed with Tourette's disorder. Additional studies are needed to confirm safety and efficacy of atomoxetine in the treatment of children with Tourette's disorder. In view of the frequent comorbidity of tic behaviors and obsessive-compulsive symptoms or disorders, the SSRIs have been used alone or in combination with antipsychotics in the treatment of Tourette's disorder. Data, thus far, have supported the efficacy of SSRIs in the treatment of OCD, however there have not been controlled trials yet to determine the effect of SSRIs on tic reduction. Although clinicians must weigh the risks and benefits of using stimulants in cases of severe hyperactivity and comorbid tics, data suggest that methylphenidate does not increase the rate or intensity of motor or vocal tics in most children with hyperactivity and tic disorders. Alternative Agents: Tetrabenazine, Topiramate, and Tetrahydrocannabinol TETRABENAZINE. A vesicular monoamine transporter type 2 inhibitor, tetrabenazine depletes presynaptic dopamine and serotonin, and blocks postsynaptic dopamine receptors. There are no randomized clinical trials of this agent in the treatment of Tourette's disorder in children; however, clinical experience suggests that this agent may

have benefit in tic reduction. In a follow-up of 2 years of treatment in 77 children and adolescents, one study reports tic reduction improvement in 80 percent of subjects. Side effects of this agent include sedation, parkinsonism, depression, insomnia, anxiety, and akathisia. TOPIRAMATE. A γ-aminobutyric acid (GABA)ergic drug, used primarily as an anticonvulsant, topiramate was found to be efficacious compared to placebo in reducing tics in a small randomized clinical trial of children and adults with Tourette's disorder. Side effects were minimal. Although this does not confirm its efficacy, GABA-modulating agents require further study in the treatment of tic disorders. TETRAHYDROCANNABINOL. A suggestion that tetrahydrocannabinol (THC) may be safe and efficacious in the treatment of tics, without neuropsychological impairment, is based on a

randomized double-blind placebo-controlled trial with 24 patients treated with THC for 6 weeks at doses of up to 10 mg with significant improvement in tic severity. In this trial, reported adverse effects included dizziness, fatigue, and dry mouth. Potential additional side-effects include anxiety, depressive symptoms, tremor, and insomnia. This small trial does not confirm efficacy for this agent in the treatment of tics, rather it raises questions about the potential improvements in treatment-resistant tic disorders using this agent. In summary, the greatest evidence for the safe and efficacious pharmacological treatment of Tourette's disorder seems to be associated with the atypical antipsychotics, in particular, risperidone. Pharmacological treatment may be combined with and enhanced by a variety of behavioral interventions such as habit reversal and school interventions that may diminish stressful situations in the school environment. REFERENCES Debes NM, Hansen A, Skov L, Larsson H. A functional magnetic resonance imaging study of a large clinical cohort of children with Tourette syndrome. J Child Neurol. 2011;26:560–569. Eddy CM, Rickards HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. Ther Adv Neurol Disord. 2011;4:25–45. Hartmann A, Worbe Y. Pharmacological treatment of Gilles de la Tourette syndrome. Neurosci Biobehav Rev. 2013;37:1157– 1161. Janovic J, Jimenez-Shahed J, Brown L. A randomized, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. J Neurol Neurosurg Psychiatry. 2010;81:70–73. Jummani R, Coffey BJ. Tic disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3609. Knight T, Stevvers T, Day L, Lowerison M, Jette N, Pringsheim T. Prevalence of tic disorders: A systematic review and meta-analysis. Pediatr Neurol. 2012;47:77–90. Kraft JT, Dalsgaard S, Obel C, Thomsen PH, Henriksen TB, Scahill L. Prevalence and clinical correlates of tic disorders in a community sample of school-age children. Eur Child Adolesc Psychiatry. 2012;21:5–13. Liu ZS, Chen YH, Zhong YQ, Zou LP, Wang H, Sun D. A multicentre controlled study on aripiprazole treatment for children with Tourette syndrome in China. Zhonghua Er Ke Za Zhi. 2011;49:572–576. Paschou P. The genetic basis of Gilles de la Tourette Syndrome. Neurosci Biobehav Rev. 201337:1026–1039.

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