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Chapter 8

Tourette disorder and other tic disorders

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Abstract

A combination of motor and phonic tics is the hallmark of Tourette syndrome (TS). This complex neuropsychiatric disorder is often associated with psychiatric comorbidities such as attention-deficit hyperactivity disorder and obsessive–compulsive disorder. The first step in management is to establish the diagnosis of TS, avoiding potential diagnostic confounders (such as compulsions, stereotypies, or habits). Once a diagnosis of TS is made, a discussion with the patient and family about the level of impairment and presence or absence of comorbidities will guide the decision and choice of treatment. Not every patient with TS will need active treatment. When needed, active treatment falls into one of the following three categories: behavioral, pharmacologic, and nonpharmacologic. This chapter summarizes and reviews the evidence base supporting these treatments. It also discusses the evidence base and approach to the treatment of common psychiatric comorbidities. A treatment algorithm based on published data and expert consensus is proposed.

INTRODUCTION

Tourette syndrome (TS) is a childhood-onset complex neuropsychiatric disorder characterized by the presence of multiple motor tics and at least one phonic tic occurring for a period of at least 1 year (Bloch and Leckman, 2009; Serajee and Mahbubul Huq, 2015). TS is relatively common, affecting 4–6 in every 1000 children (Bloch and Leckman, 2009). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines a tic as "a sudden, rapid, recurrent, nonrhythmic movement or vocalization" (American Psychiatric Association, 2013). DSM-5 establishes the following criteria to diagnose TS: (1) the presence of both motor and phonic tics (not necessarily concurrently), (2) beginning before age 18 years, (3) persisting for more than 1 year despite fluctuations, and (4) not explained by the effects of a substance or another medical condition (American Psychiatric Association, 2013). Related tic disorders listed in the DSM-5 include provisional tic disorder, which consists of multiple motor and/or phonic tics that have a duration of less than 1 year, and persistent or chronic tic disorder, which is defined as either motor or phonic tics (but not both) that last for at least a year (Bloch and Leckman, 2009).

Developmentally, tics typically begin between ages 5 and 7, with motor tics generally appearing earlier than phonic tics (Serajee and Mahbubul Huq, 2015). The most common tics at onset are simple motor tics such as facial grimacing, eye blinking (eye tics occur in over 95% of individuals clinically diagnosed with TS (Martino et al., 2012)), and nose twitching (Leckman et al., 1998). Simple vocal tics include coughing, grunting, sniffing, and squeaking and often occur several years after the onset of motor tics (Leckman, 2003). The appearance of additional tics typically progresses in a rostral–caudal pattern, with facial and head tics appearing first, followed by trunk and limb tics, and subsequently by vocal tics (Leckman et al., 1998). With age, both motor and phonic tics tend to be more complex (i.e., involve multiple muscle groups or consist of multisyllabic words or phrases), although not

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all individuals with TS will develop complex tics (Leckman et al., 1998; Bloch and Leckman, 2009; Serajee and Mahbubul Huq, 2015). Coprolalia and copropraxia (socially unacceptable words and gestures), although often associated with TS in popular culture, are in fact uncommon, occurring in fewer than one in five individuals. Individuals with coprolalia and/or copropraxia often have more severe tics and are more likely to have comorbid conditions such as OCD and ADHD (Freeman et al., 2009).

Although the diagnosis of a tic disorder is usually straightforward, other abnormal movements can be at times mistaken for tics. Blinking tics may raise the question of seizures, and sniffing tics, for instance, may be mistaken for allergies. Coughing tics may be misattributed to gastric reflux or allergies. The differential diagnosis for tics should include stereotypies, compulsions, habitual behaviors, myoclonus, dystonia, akathisia, athetosis, choreas (other involuntary hyperkinetic disorders), and tremors (Fig. 8.1). The following guidelines can be used to distinguish tics from other types of movements.

Tics are *variable* (an individual will have different tics over time), *fluctuating* (the presence and severity of any particular tic or cluster of tics waxes and wanes),

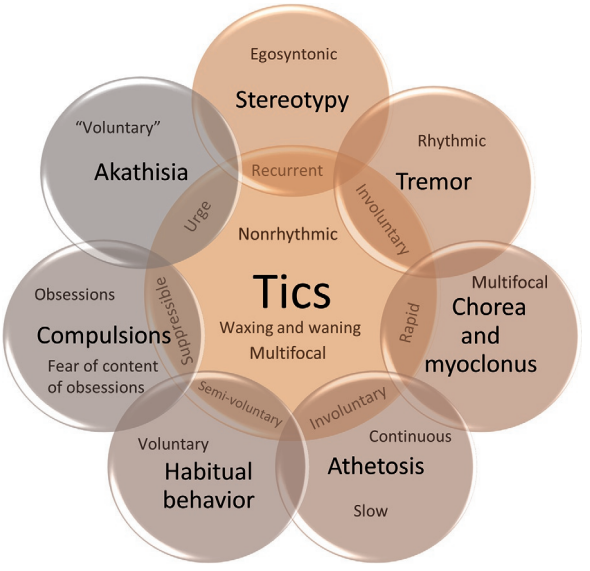

Fig. 8.1. Venn diagram representing some of the features of tics in comparison to common differential diagnoses. Adapted from Swain JE, Leckman JF. (2005). Tourette syndrome and Tic disorders: overview and practical guide to diagnosis and treatment. Psychiatry (Edgmont) 2(7): 26–36. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000195/; Tagwerker Gloor F, Walitza S. (2016). Tic disorders and Tourette syndrome: current concepts of etiology and treatment in children and adolescents. Neuropediatrics 47(2): 084–096. doi: 10.1055/s-0035-1570492; and Jankovic J, Fahn S. (1986). The phenomenology of tics. Mov Disord 1(1): 17–26. https://doi.org/10.1002/mds.870010103.

distractible (tics often decrease while doing activities requiring heightened concentration such as playing video games), and often *suggestible* (discussing tics or seeing someone else tic can result in exacerbation) (Leckman, 2003). In many individuals, although often not in young children, tics are *suppressible* (at least partially, for a short period), and associated with a *premonitory urge.* A premonitory urge is a sensory feeling or urge to move that is frequently uncomfortable and is relieved by tic execution. The awareness of the presence of premonitory urges increases with age (Bloch and Leckman, 2009; Tagwerker Gloor and Walitza, 2016). Premonitory urges are usually classified as either sensory tic, just-right experiences, or urges (without obsessions) (Cavanna and Nani, 2013). A sensory tic is a bodily sensation, mainly musculoskeletal, that occurs immediately before or accompanying a tic. The sensation drives the individual to perform a movement (tic) until a sensation of relief is achieved. A just-right experience, as implied by its name, is driven by a need to have objects, sounds, people, actions, or movements be or feel a certain "just right" way. To note, the just-right experience can also be classified as a compulsion (Tagwerker Gloor and Walitza, 2016), though it is more closely related to TS biologically than to OCD (Darrow et al., 2017). Finally, an urge is a drive to do a "repetitive action" (either tics or compulsions) that is not associated with sensory phenomena, obsessions, or fears.

Tics are have been hypothesized to be "unvoluntary" movements as opposed to either voluntary or involuntary movements (Jankovic, 1997). Unvoluntary movements have been defined by Cavanna and Nani as "an action [that] is perceived as a voluntary response to an uncontrolled and involuntary urge to move," much as a cough or sneeze might be (Cavanna and Nani, 2013).

Tics usually reach their maximum severity by early adolescence, and most individuals with TS will see their symptoms improve by late adolescence or early adulthood (Ong et al., 2016). While up to two-thirds of individuals will continue to have tics in adulthood, only 10%–20% will continue to have significant symptoms, while the remainder will have mild, often barely noticeable tics (Bloch and Leckman, 2009; Gunduz and Okun, 2016; Groth et al., 2017). Factors predicting progression or prognosis of tics are not well established, although tic severity in adolescence may be loosely associated with tic severity in adulthood in some individuals (Bloch and Leckman, 2009; Serajee and Mahbubul Huq, 2015). Despite this natural history, the impact of TS can be substantial, particularly in children and adolescents, affecting quality of life, social development, school performance, and academic achievement (Conelea et al., 2011).

In addition to tics, most patients with TS will have at least one additional neuropsychiatric disorder, most

commonly attention-deficit hyperactivity disorder (ADHD), which occurs in up to 60% of individuals, or obsessive–compulsive disorder (OCD) (which occurs in 30%–60%) (Conelea et al., 2011; Hirschtritt et al., 2015; Serajee and Mahbubul Huq, 2015). Less common, but still more frequent than the general population, are autism spectrum disorders, depression, anxiety, and behavioral disorders (Hallett, 2015; Serajee and Mahbubul Huq, 2015). Of the patients with TS who present for clinical care 85.7% have at least one comorbid psychiatric disorder, and 57.7% will have two (Hirschtritt et al., 2015). These comorbidities are a major source of psychosocial distress and impairment to the quality of life (Conelea et al., 2011). The higher the burden of comorbidities, the lower the response to treatment (for both tics and comorbid conditions); indeed, both TS + ADHD and TS + OCD have a worse prognosis than TS alone (Tagwerker Gloor and Walitza, 2016). ADHD usually presents concurrent with or just preceding the onset of tics, while OCD typically begins a bit later, between ages 8 and 12 (Bloch and Leckman, 2009).

Although the pathophysiology of TS has not been completely elucidated, TS is thought to be caused by "microscopical and macroscopical abnormalities within the cortico-striatal-thalamo-cortical" (CSTC) loops and, rather than being a disorder of any particular brain region, arises from dysregulation in the CSTC circuitry (Ganos, 2016). The CSTC loops are generally divided into five overlapping functional circuits: sensorimotor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate (limbic) circuits (Ganos et al., 2013). An imbalance of inhibitory–excitatory signals in these circuits is thought to favor the production of tics and related symptoms (Kataoka et al., 2010; Ganos et al., 2013). While tics arise from dysregulation of the sensorimotor and oculomotor loops, OCD symptoms arise from dysregulation of the anterior cingulate and lateral orbitofrontal loops (Wood and Ahmari, 2015; Parmar and Sarkar, 2016) and ADHD symptoms from dysregulation of the dorsolateral prefrontal loops (Posner et al., 2014). Multiple neurochemical and neurotransmitter abnormalities, most notably dopaminergic, adrenergic, GABAergic, and glutamatergic have been reported in TS (Tagwerker Gloor and Walitza, 2016). More recently, other neurochemical pathways have been implicated, including histamine pathways (Rapanelli and Pittenger, 2016), and endogenous cannabinoid pathways (Müller-Vahl, 2013).

However, despite evolving understanding of the underlying circuitry and neurotransmitters involved in the development and maintenance of TS and its comorbidities, treatment for TS remains primarily symptomatic. For most individuals, the goals of treatment are (1) a reduction in tics, (2) improvement or remission of comorbid disorders, and (3) improvement of quality of life, not necessarily in that order. Multiple TS treatment guidelines have been published in the United States, Canada, and Europe (Roessner et al., 2011; Pringsheim et al., 2012; Steeves et al., 2012), all of which recommend beginning with psychoeducation, followed by behavioral therapy such as comprehensive behavioral intervention for tics (CBIT), exposure therapy, and habit reversal therapy (HRT). Although multiple pharmacologic agents have been used to treat TS, only three are FDA approved for the treatment of TS in the United States: haloperidol, pimozide, and aripiprazole (the last one for children only). Thus, many of the most commonly used agents, including some with the strongest evidence base, are used off label. In addition to the standard classes of medications typically used to treat TS (α-adrenergic agents, typical, and atypical neuroleptics), innovative pharmacologic agents are also being investigated for use in TS.

In this chapter, we summarize the evidence for the currently available treatments for TS and review the ongoing studies of new agents. We discuss, briefly, the implications of comorbid psychiatric disorders on TS management. We finish with a discussion of treatment-refractory TS and the proposed treatment paradigms, including deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tCDS).

APPROACH TO THE TREATMENT OF TS

Not all patients with tics or TS require treatment; in fact, based on the epidemiologic estimates of TS prevalence in the general population and those based on clinical studies, many individuals with TS will never come to clinical attention (Scharf et al., 2015). The major determining factor underlying the decision to treat lies with the patient's assessment regarding how much the tics or comorbid conditions interfere with daily life (Roessner et al., 2011; Gunduz and Okun, 2016). It is important to recognize the presence and effect of comorbid disorders such as OCD and ADHD when formulating a treatment plan, as psychiatric conditions often contribute more to functional impairment and disability than do either motor or phonic tics (Neri and Cardona, 2013).

The first step when evaluating a patient with TS is to perform a thorough history and physical examination, including a psychiatric evaluation (Swain and Leckman, 2005). Psychoeducation is a critical next step. Providers should discuss the characteristic variability of tics, the associated comorbidities, and the natural course (Roessner et al., 2011). This discussion and psychoeducation usually results in a reduction of stress associated with the diagnosis and improves the sense of agency

Table 8.1

Indications for initiating treatment in TS

Indication	Examples	Rationale
Subjective discomfort	Musculoskeletal pain from the performance of tics, injuries, from severe tics (Krauss and Jankovic, 1996; Cheung et al., 2007), pain associated with the urges	Treatments of tics would decrease the need for pain medications or other therapies
Social impairment	Social isolation, bullying, discharge from the classroom due to tics	If social impairment detected, treatment can help in reducing the social stigma and improving quality of life
Emotional difficulties	Depression, anxiety, low self-esteem	Treatment to improve quality of life; it is usually hard to distinguish between a reactive and a primary mood disorder
Functional disability	Poor school performance, sleep disruption, speech interruption by phonic tics, decreased attention due to tics	Treatment by reducing tics can improve functional state

Adapted from the European guidelines for initiating pharmacologic or behavioral treatment for tics: Roessner V et al. (2011). European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry 20(4): 173–196. https://doi.org/10.1007/s00787-011-0163-7.

of the patient. Many patients with TS, particularly those with mild symptoms, prefer a "Watch and Wait" initial approach, as treatment is symptomatic in nature, and disease-modifying therapies (e.g., those that alter the outcomes or natural course of illness) are not available (Roessner et al., 2011).

There is no clear consensus on what constitutes an indication to start treatment in TS. However, the European guidelines published in 2011 (Roessner et al., 2011) recommend starting treatment in the situations summarized in Table 8.1.

When the patient with TS reaches a decision to start treatment, two initial treatment approaches are available: behavioral and pharmacologic. These two strategies are not exclusionary and in many cases are complementary. It is important to educate the patients and their families that the goal of treatment is not complete tic suppression but improved control and reduction of tic severity. The currently available treatments decrease tics by around 25%–50% (Roessner et al., 2011). Although there is no "correct" order of treatment, behavioral interventions, if available, are usually first-line, followed by adrenergic agents, atypical neuroleptics, and subsequently by typical neuroleptics and other agents (Fig. 8.2). These forms of treatment and the evidence for each are described in detail in the following text. Table 8.2 summarizes a number of the randomized, controlled studies behind the evidence base of the different treatments.

Behavioral therapy

Multiple behavioral interventions have been developed for the treatment of TS and its associated comorbidities. Of these, HRT (Azrin and Peterson, 1990) and CBIT (Azrin and Nunn, 1973), two closely related approaches, have the highest level of evidence. Other interventions, such as anger control training, parent training, and relaxation techniques, have been less well-studied, and their efficacy is less clear (Whittington et al., 2016). The theoretic basis for HRT/CBIT is that tics can be triggered by internal (cognitive or emotional) stimuli, often described as premonitory urges, as well as by external stimuli (e.g., tics can become conditioned to occur more frequently in some locations/situations than in others) (Verdellen et al., 2004; Hwang et al., 2012). Thus, the role of these behavioral interventions is to break the "stimulus–response sequence" (Verdellen et al., 2004). The core features of HRT/CBIT include increasing awareness of tic triggers and premonitory urges, modifying triggering situations/patterns, and competing response training (Azrin and Nunn, 1973). A competing response is defined as a motor behavior that opposes (competes with) the tic, can be sustained for few minutes, can be easily camouflaged into daily movements, and increases the strength of the antagonistic muscles (Azrin and Nunn, 1973; Piacentini et al., 2010). It is initiated at the onset of the premonitory urge, during the tic, or even soon after (Hwang et al., 2012).

Many single center studies and a few multicenter randomized controlled trials indicate that HRT/CBIT can improve tic control and perform better than supportive therapy in both children (effect size 0.68) and adults (effect size 0.57) (Azrin and Peterson, 1990; Wilhelm et al., 2003, 2012; Verdellen et al., 2004; Deckersbach et al., 2006; Piacentini et al., 2010). Improvement in tic severity is typically between 25% and 30% after 8–10 weeks of treatment. Attrition rates are approximately 10%, suggesting that behavioral therapy is in general well tolerated. Although the data do not support the

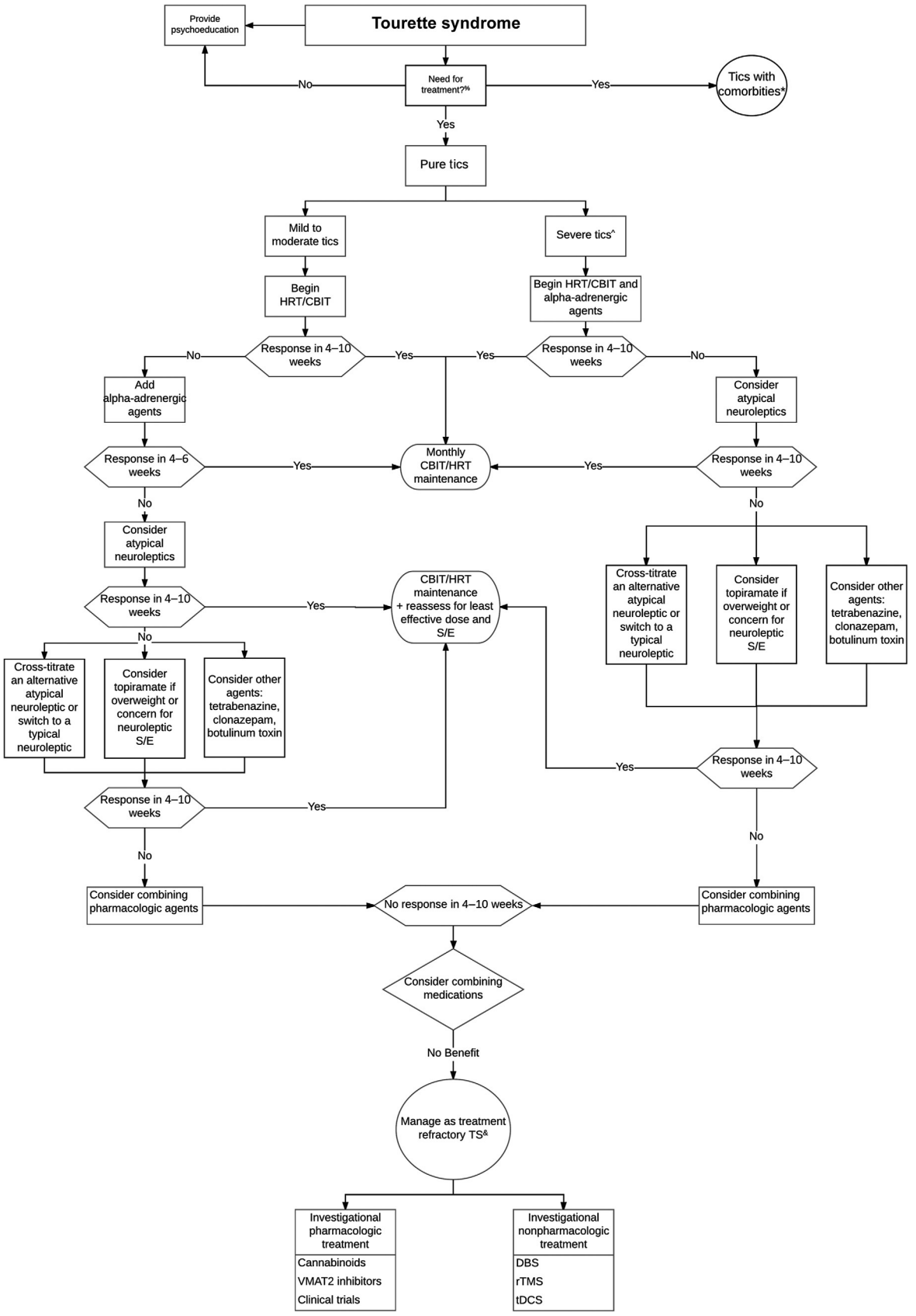

Fig. 8.2. See figure legend on next page.

efficacy of HRT/CBIT in one type of tic over another, tics that are preceded by an easily identifiable urge and those that a simple competing response can counter are most likely to improve (Hwang et al., 2012; McGuire et al., 2013).

However, behavioral interventions are resource intensive and require the presence of highly skilled clinicians, typically psychologists, occupational therapists, or physicians. Geographical access, coverage by payer sources, and time commitment can limit feasibility. Group treatment, videoconferencing, and other telehealth delivery methods, as well as internet-based, structured, self-guided approaches have been tested in small samples, and show promise. If demonstrated to be effective, these adaptations may increase access to care (Himle et al., 2012). "Tic Helper" is an online tool that is available for youth with TS. It is based on the same principles of CBIT using an interactive interface with videos, rating scales, and exercises (Conelea and Wellen, 2017). The results of the phase-2 study (NCT02413216, 2015) have not been published yet. There are also ongoing studies evaluating additional telehealth-type approaches (NCT02605902, 2015; NCT02900144, 2016; NCT03019731, 2017).

Pharmacologic agents

Pharmacologic agents can also be used to treat tics, as either an alternative or a complement to behavioral therapies or when behavioral approaches fail or are not available. These agents are described in the order in which they are commonly used in the United States, based on their side effect profiles, their evidence base, and their relative efficacies. Published European guidelines suggest a slightly different order of use (Roessner et al., 2011), and individual healthcare providers may have unique preferences. The evidence for each of the agents commonly used to treat TS is outlined in the following text. Table 8.3 summarizes the usual treatment doses, side effects, and level of evidence for the different pharmacologic agents.

Adrenergic agents

The first-line pharmacologic treatment for TS according to the published US guidelines are the adrenergic agents, clonidine and guanfacine, primarily because they have a lower burden of side effects, despite a potentially lower potency in reducing tic severity compared to neuroleptics (Roessner et al., 2011). The mechanism of action of the adrenergic agents is thought to be a decrease in the noradrenergic tone at the level of the locus coeruleus (Jiao et al., 2015).

Clonidine

Clonidine, an α2-adrenergic receptor agonist that is typically used for blood pressure control, is available in three major forms: immediate-release tablets, slow-release tablets, and a patch. The initial interest in clonidine for tics emerged as an alternative to the FDA-approved antidopaminergic medications (e.g., haloperidol and pimozide), and has been used in the treatment of TS since 1978 (Ross and Moldofsky, 1978). Most, but not all (Shapiro et al., 1983), published studies, including those comparing clonidine to placebo and those comparing clonidine to typical neuroleptics, suggest that it is effective, although it appears to have a lower efficacy than the neuroleptic agents (Leckman et al., 1985, 1991). In addition to improvement in both motor and phonic tics, treatment with clonidine has also been shown to improve behavioral problems, most notably impulsivity and hyperactivity; in fact, it is used in

Fig. 8.2. Proposed treatment algorithm for Tourette syndrome—focusing on tic management (continue in Fig. 8.3). %: not every patient with TS requires treatment, the decision is individualized. Refer to the approach to the treatment of TS section for details. *: refer to Fig. 8.3. ˆ: severe tics defined as Yale Global Tic Severity Scale (YGTSS) tic severity score > 35. &: when considering a diagnosis of treatment refractory tics, evaluate the following: reassess the diagnosis of TS (rule out mimics); confirm proper medication trials (most notably evaluate the maximum dose reached and duration of trial); confirm proper medication titration as a titration done too fast can result in preventable side effects; ensure control of psychiatric comorbidities. Abbreviations: *CBIT*, comprehensive behavioral intervention for tics; *DBS*, deep brain stimulation; *D/C*, discontinue; *H3R*, histamine-3 receptor; *HRT*, habit reversal therapy; *rTMS*, repetitive transcranial magnetic stimulation; *S/E*, side effects; *tDCS*, transcranial direct current stimulation; *VMAT2*, vesicular monoamine transporter type 2. Adapted from Jankovic J, Kurlan R. (2011). Tourette syndrome: evolving concepts. Mov Disord 26(6): 1149–1156. https://doi.org/10.1002/mds.23618; Roessner V et al. (2011). European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry 20(4): 173–196. https://doi.org/10.1007/s00787-011-0163-7; Rizzo R et al. (2013). Tourette syndrome and comorbid ADHD: current pharmacological treatment options. Eur J Paediatr Neurol 17(5): 421–428. https://doi.org/10.1016/j.ejpn.2013.01.005; Hirschtritt ME et al. (2015). Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry 72(4): 325. https://doi.org/10.1001/jamapsychiatry.2014.2650; Kious BM, Jimenez-Shahed J, Shprecher DR. (2016). Treatment-refractory Tourette syndrome. Prog Neuropsychopharmacol Biol Psychiatry 70: 227–236. https://doi.org/10.1016/j.pnpbp.2016.02.003; Ong MT, Mordekar SR, Seal A. (2016). Fifteen minute consultation: tics and Tourette syndrome. Arch Dis Child Educ Pract Ed 101(2): 87–94. https://doi.org/10.1136/archdischild-2015-309138 supplemented by expert consensus.

Table 8.2

Summary of multiple randomized, controlled studies of the pharmacologic and behavioral treatments in TS

Study	Study Design	Age range (years)	Number of subjects	Arms of the study	Mean medication doses (SD) in mg/day	Primary tic outcome measure	Results, mean (SD)	Effect size (to comparator group)	Observations
Shapiro and Shapiro (1984)	Randomized, double-blind crossover	11–53	20	Pimozide Placebo	6.88 (1.26) 17.42 (1.45)	TSSS	1.52 4.42	— —	A significant improvement of tic severity using pimozide compared to placebo
Shapiro et al. (1989)	Randomized, placebo-controlled, parallel group crossover	8–46	57	Haloperidol Pimozide Placebo	4.5 10.6 —	TSSS	1.2 (1.2) 2.5 (3) 2.9 (2.5)	0.87 0.14 —	Haloperidol was effective compared to placebo using the TSSS (pimozide achieved a significant difference only when using CGI scale). QTc is noted to be longer in the pimozide group though not in the abnormal range
Leckman et al. (1991)	Randomized, double blind	7–48 7–37	21 19	Clonidine Placebo	4.4 μg/kg —	TSGS	27 (11.1) 31.5 (9.6)	0.43 —	Subjects in clonidine total TSGS improved by 26% compared to 11% for subjects receiving placebo with the greatest benefit noted for motor tics
Singer et al. (1995)	Randomized double-blind, placebo-controlled	7–13	37	Clonidine Desipramine Placebo	0.2 100 —	YGTSS TSSS HTSS	No significant change	—	Neither clonidine nor desipramine improved the tic scales. Desipramine improved ADHD symptoms and did not worsen tics
Feigin et al. (1996)	Multicenter, double-blind, placebo-controlled, crossover	7–16	24	Deprenyl Placebo	10 —	YGTSS	Decrease by 9.3 points on total YGTSS compared to placebo	—	A trend toward a statistically significant improvement of total YGTSS was noted. No improvement in ADHD scores noted in the overall assessment by significant in the first period of the study
Sallee et al. (1997)	Double-blind, placebo-controlled, double crossover	7–16	22	Haloperidol Pimozide Placebo	3.5 (2.2) 3.4 (1.6) —	TSGS	20.7 (17.3) 17.1 (14.1) 26.8 (15.9)	0.37 0.65 —	64% of subjects when receiving either active treatment achieved 70% reduction in the TSGS compared to only 23% when on placebo. Side effects were a main cause for halting further dose increases with haloperidol having a higher rate of side effects
Scahill et al. (1997)	Double-blind, placebo-controlled, crossover	8–33	14	Fluoxetine Placebo	20 —	YGTSS	26.9 (10.65) 21.6 (9.06)	0.54 —	There was no significant improvement in the tic scores using Fluoxetine compared to placebo. There was a trend toward improvement of the OCD scales.

Continued

Table 8.2

Continued

Study	Study Design	Age range (years)	Number of subjects	Arms of the study	Mean medication doses (SD) in mg/day	Primary tic outcome measure	Results, mean (SD)	Effect size (to comparator group)	Observations
Sallee et al. (2000)	Randomized, placebo-controlled, double-blind	7–17	16 11	Ziprasidone Placebo	28.2 (9.6) —	YGTSS (change)	−8.6 (6.7) −1.7 (5)	1.13 —	Ziprasidone significantly reduced the YGTSS scores compared to placebo. Somnolence is the most common side effect. EPS were not statistically different between the 2 groups
Bruggeman et al. (2001)	Randomized, double-blind, parallel group	11–45 11–50	24 26	Pimozide Risperidone Baseline	2.9 3.8 —	TSSS	2 1.9 4.3	— — —	41 patients completed the study. A higher proportion of the pimozide group had OCD. Risperidone and pimozide have similar efficacy in decreasing TSSS. No significant difference in side effects
Marras et al. (2001)	Randomized, double-blind, placebo-controlled, crossover	15–55	20	Botulinum toxin Placebo	Variable per muscle guidelines	Number of tics	Median −39.7% Median 5.8%	—	In addition to the decrease in the number of tics, the mean urge score decreased. Interestingly, there was no improvement on the patient's global impression scale
Scahill et al. (2001)	Randomized, double-blind, placebo-controlled	7–15	17 17	Guanfacine Placebo	1.5–3 3	YGTSS	10.7 (7) 15.4 (5.5)	0.74 —	Guanfacine improved the ADHD teacher-rated score by 37% (compared to 8% for placebo). It also decreased the total tic score significantly by 31% (compared to 0% in the placebo group). Side effects included insignificant decrease in blood pressure and pulse rate
Singer et al. (2001)	Randomized sequence, double-blind, placebo-controlled, crossover	8–14	10	Baclofen —	60 —	YGTSS	48.3 (19.4) 52.7 (20)	0.22 —	There was a statistically significant reduction in total YGTSS (due to impairment scale improvement rather than tic scale improvement)
Cummings et al. (2002)	Randomized, double-blind, placebo-controlled	6–16	12 12	Guanfacine Placebo	2 —	YGTSS	32.25 (15.7) 28.92 (19.9)	0.17 —	This study did not show a significant improvement in tic scores or ADHD symptoms
Dion et al. (2002)	Randomized, double-blind, placebo-controlled	14–49	23 23	Risperidone Placebo	2.5 (Median) —	TSSS	3.39 (2.18) 4.59 (2.17)	0.55 —	9 subjects withdrew from the study early (6 in treatment group and 3 in the placebo group). 61% of the risperidone group compared to 26% of the placebo group had a 1-point drop on TSSS. More EPS and depression side effects in the treatment group

Gaffney et al. (2002)	Randomized, double-blind, followed by a single-blind period	7–17	12 9	Clonidine Risperidone	0.175 (0.075) 1.5 (0.9)	YGTSS	38.5 (16.9) 40.9 (11.7)	— 0.16	There was no significant difference in tic reduction between clonidine and risperidone on YGTSS (21% reduction for risperidone compared to 26% reduction for clonidine). Most common side effect noted in either group is sedation
Kulan (2002)	Multicenter, randomized, double-blind, placebo-controlled, parallel group (2 × 2)	7–14	34 37 33 32	Clonidine MPH Clonidine +MPH Placebo	0.25 25.7 26.1 —	YGTSS		0.64 0.75 0.75 —	19 subjects withdrew from the study, and most for inadequate treatment. This study identified that clonidine improved tics compared to placebo and improved impulsivity and hyperactivity. Methylphenidate helped with attention with a lesser improvement on tics when alone. The combination treatment was most effective. No worsening of tics was noted with the use of methylphenidate
Müller-Vahl et al. (2002)	Randomized, double-blind, placebo-controlled, crossover	18–66	12	THC Placebo	5–10 mg/day —	TSSL	−14 (10.97) −4.92 (6.69)	0.83 —	Only TSSL data showed a statistically significant improvement, while the other tic scales such as YGTSS did not reach statistical significance
Spencer et al. (2002)	Randomized, double-blind, placebo-controlled	5–17	21 20	Desipramine Placebo	154 (63) 150 (48)	YGTSS	43 (23) 61 (15)	1.2 —	There was a significant reduction in the YGTSS (58% compared to 5% for placebo) with equal response from motor and phonic tics. Similar significant improvements were noted in ADHD symptoms (inattentive and hyperactive)
Müller-Vahl et al. (2003)	Randomized, double-blind, placebo-controlled	18–68	12 12	THC Placebo	5–10 mg/day —	Multiple	—	—	There was evidence of statistically significant improvement in multiple tic scales such as TSSL, YGTSS and TS-CGI. Only an as-treated analysis was done, no intention to treat analysis was presented
Scahill et al. (2003)	Randomized, double-blind, placebo-controlled, parallel group	6–62	16 18	Risperidone Placebo	2.5 (0.85) 3.5 (0.94)	YGTSS	17.6 (4.75) 25.4 (8.75)	0.89 —	2 patients withdrew from the study (1 in each group). There was a significant improvement of YGTSS total score (32% decrease in risperidone group compared to 7% decrease in the placebo group). Major side effect is weight gain of 2.8 kg in the risperidone group (none in the placebo)

Continued

Table 8.2

Continued

Study	Study Design	Age range (years)	Number of subjects	Arms of the study	Mean medication doses (SD) in mg/day	Primary tic outcome measure	Results, mean (SD)	Effect size (to comparator group)	Observations
Gilbert et al. (2004)	Randomized double-blind crossover	7–17	19	Pimozide	2.4	YGTSS	34.2 (14.2)	—	Risperidone resulted in a significantly ($P = 0.05$) lower YGTSS score compared to pimozide. Risperidone had a higher weight gain (mean 1.9 kg with risperidone compared to 1 kg with pimozide)
				Risperidone	2.5		25.2 (13.6)	0.65	
Stephens et al. (2004)	Single-blind, placebo run-in	7–13	10	Olanzapine	14.5	YGTSS	6 (4.94)	2.42	Significant reduction in tic score with olanzapine. Main side effect noted with olanzapine was weight gain (mean increase 12 lbs ± 5.71), and this was statistically significant
				Baseline	—		20.3 (6.72)	—	
Allen et al. (2005)	Randomized, double-blind, placebo-controlled	7–17	76	Atomoxetine	1.33 mg/kg/day	YGTSS	16.2 (6.9)	0.38	Almost significant reduction in total tic score. Significant improvement in ADHD scales. Side effects notable for increase in heart rate and decrease in body weight
			72	Placebo	—		19.2 (8.7)	—	
Nicolson et al. (2005)	Randomized, double-blind, placebo-controlled	7–18	27	Metoclopramide	32.9	YGTSS	13.9 (3.7)	1	There was a significant reduction in the total tic score (39% reduction in the metoclopramide group compared to 15% in the placebo group). There was no change in obsessive and ADHD scales. Intention to treat analysis was not conducted
				Placebo	—		19.4 (5.8)	—	
Toren et al. (2005)	Randomized, double-blind, placebo-controlled	12–46	15	Ondansetron	24	YGTSS	17.5 (9.48)	0.9	There was a significant improvement on the TSGS score in the ondansetron group compared to the placebo group. The YGTSS improvement failed to reach significance
			—	—	—	TSGS	20.58 (12.82)	1.06	
			15	Placebo	—	YGTSS	27.28 (12.12)	—	
			—	—	—	TSGS	40.78 (23.72)	—	
Smith-Hicks et al. (2007)	Randomized, double-blind, placebo-controlled, crossover	8–16	22	Levetiracetam	1563	YGTSS	16.8 (6.25)	0.32	This study did not show a significant decrease in tics using levetiracetam as compared to placebo
				Placebo	—		18.95 (7.28)	—	
Du et al. (2008)	Randomized, placebo-controlled	6–18	326	Clonidine patch	1–2 mg daily	YGTSS	9.83 (7.77)	0.26	Significant drop-off rate noted as nonresponders were switched to tiapride by 3 weeks. Clonidine patch resulted in a significant decrease in tics compared to placebo with a 69% response rate. No significant difference in side effects between the groups
			111	Placebo	—		11.84 (8.01)	—	

Hedderick et al. (2009)	Randomized, double-blind, flexible crossover	8–27	12	Clonidine Levetiracetam	0.2 1150	YGTSS	21.8 (4.4) 23.6 (10.6)	0.22 (vs levetiracetam) and 0.57 vs baseline	2 subjects withdrew from the study. Clonidine showed a modest improvement of total tic score compared to baseline, this is not noted for levetiracetam (to note the baseline score for each evaluation is different)
Jankovic et al. (2010)	Randomized, double-blind, placebo-controlled	7–65	15 14	Topiramate Placebo	118 —	YGTSS	12.36 (12.04) 23.1 (8.99)	1 —	Significant drop-off rate noted. Topiramate resulted in a significant improvement of YGTSS score (decrease by 14 points compared to 5 points for placebo). No significant difference in side effects
Piacentini et al. (2010)	Randomized, observer-blind, controlled trial	9–17	61 65	CBIT Supportive therapy	— —	YGTSS	17.1 (7.97) 21.1 (7.71)	0.51 —	Effect size listed is the effect compared to supportive treatment. Effect size compared to background is 0.68. CBIT is comprehensive behavioral intervention for tics. Patients who were randomized to CBIT received 8 sessions over 10 weeks, and responders received 3 monthly treatment boosters
Liu et al. (2011)	Multicenter, controlled	5–17	98 97	Aripiprazole Tiapride	— —	YGTSS	24.36 (16.38) 23.26 (15.31)	0.07 —	There was a significant decrease in YGTSS by 60.21% in the aripiprazole group and 63.92% in the tiapride group compared to baseline. There was no significant difference in effect size (compared to baseline) or side effects between the two groups
Kurlan et al. (2012)	Multicenter, double-blind, placebo-controlled	6–17	42 20	Pramipexole Placebo	0.43 —	YGTSS (change from baseline)	−7.16 (1.4) −7.17 (2)	0.01 —	No significant difference in tics between pramipexole and placebo groups
Wilhelm et al. (2012)	Randomized, observer-blind, controlled trial	16–69	63 59	CBIT Supportive therapy	— —	YGTSS	17.8 (7.32) 19.3 (7.4)	0.2 —	Effect size listed is the effect compared to supportive treatment. Effect size compared to background is 0.57. The supportive therapy group had a lower tic score at baseline. CBIT is comprehensive behavioral intervention for tics. Patients who were randomized to CBIT received eight sessions over 10 weeks, and responders received 3 monthly treatment boosters

Continued

Table 8.2

Continued

Study	Study Design	Age range (years)	Number of subjects	Arms of the study	Mean medication doses (SD) in mg/day	Primary tic outcome measure	Results, mean (SD)	Effect size (to comparator group)	Observations
Yoo et al. (2013)	Multicenter, randomized, double-blind, placebo-controlled	6–18	32 29	Aripiprazole Placebo	11 (6.1) —	YGTSS	13.6 (9.1) 19.9 (9.5)	0.68 —	17 subjects withdrew from the study (8 from placebo and 9 from treatment). Significant improvement in tic score compared to placebo. Significant weight gain in aripiprazole compared to placebo
Ghanizadeh and Haghighi (2014)	Randomized parallel group	6–18	31 29	Aripiprazole Risperidone	4 (2.4) 0.7 (0.2)	YGTSS	12.8 (12) 19.3 (12.5)	0.53 —	17 subjects in the aripiprazole and 18 subjects in the risperidone group continued the study (large proportion due to resolution of tic symptoms). No significant difference in tic reduction. No significant difference in side effects
Jiao et al. (2015)	Randomized	5–12 5–12	128 116	Clonidine patch Haloperidol	1–2 mg daily 0.5–1 mg BID	YGTSS	26.3 (20.8) 36.28 (25.2)	0.43 —	Both groups had improvement in their YGTSS with a higher drop in tic score in the clonidine patch group. No significant side effects noted
Sallee et al. (2017)	Multicenter, randomized, double-blind, placebo-controlled	7–17 7–17 7–17	44 45 44	Aripiprazole low Aripiprazole high Placebo	6.8 13.3 —	YGTSS	−13.4 (1.6) −16.9 (1.6) −7.1 (1.6)		There was a statistically significant improvement on the YGTSS total score in both the low dose and high dose groups as compared to placebo (values in results are the least square mean difference). Main side effects include sedation, somnolence, and fatigue

Gray highlighted rows indicate a study with an adult or mixed population.

Table 8.3

Medication doses, side effects, and level of evidence

Medication	Starting dose (daily)	Usual therapeutic dose (daily)	Notable side effects	Level of evidence	FDA approval for TS	Other relevant FDA approvals
Clonidine	0.05–0.1 mg	0.1–0.4 mg	Sedation, dizziness, hypotension	A	No	—
Guanfacine	0.5–1 mg	1–4 mg	Sedation, dizziness, hypotension	B	No	ADHD (pediatric)
Atomoxetine	40 mg	40–60 mg	Tachycardia, weight loss, nausea, decreased appetite, headache, dry mouth, insomnia, fatigue	B	No	ADHD
Haloperidol	0.25 mg	0.75–5 mg	Extrapyramidal symptoms, increased appetite, sedation, cardiovascular side effects, hyperprolactinemia	A	Yes	Nonpsychotic behavior disorders (pediatric)
Pimozide	0.5 mg	2–4 mg	Extrapyramidal symptoms, increased appetite, sedation, QT prolongation, hyperprolactinemia	A	Yes	—
Fluphenazine	0.5–1 mg	2–5 mg	Drowsiness, fatigue, QT prolongation, worsening of narrow angle glaucoma, extrapyramidal side effects, hyperprolactinemia	C	No	—
Risperidone	0.5 mg	2–4 mg	Extrapyramidal symptoms, increased appetite, orthostatic hypotension, sedation, QT prolongation, hyperprolactinemia	A	No	Irritability in autism spectrum disorders (pediatric)
Aripiprazole	2.5–5 mg	5–10 mg	Extrapyramidal symptoms, increased appetite, orthostatic hypotension, sedation, QT prolongation, akathisia	B	Yes (pediatric)	Irritability in autism spectrum disorders (pediatric)
Olanzapine	2.5–5 mg	5–10 mg	Extrapyramidal symptoms, sedation, increased appetite, orthostatic hypotension, QT prolongation	B	No	—
Ziprasidone	5 mg	5–40 mg	Extrapyramidal symptoms, sedation, increased appetite, orthostatic hypotension, QT prolongation	B	No	—
Quetiapine	25–50 mg	100–400 mg	Extrapyramidal symptoms, sedation, increased appetite, orthostatic hypotension, QT prolongation	C	No	—
Topiramate	25 mg	50–200 mg	Somnolence, cognitive problems, weight loss	B	No	—
Valproate	250–500 mg	700–1000 mg	Gastrointestinal side effects, drowsiness, headache, CBC changes	C (poor quality RCT)	No	—
Tetrabenazine	12.5–37.5 mg	50–100 mg	Drowsiness, fatigue, nausea, depression, insomnia, parkinsonism	C	No (Canadian label for TS)	—
Clonazepam	0.25–0.5 mg	0.5–4 mg	Sedation, ataxia, paradoxical reactions, short-term memory impairment	C	No	—
Baclofen	5–15 mg	10–60 mg	Drowsiness, sedation, withdrawal seizures or psychosis, constipation	B	No	—
Tetrahydrocannabinol	2.5 mg	5–10 mg	Headache, fatigue, dry mouth, dizziness, anxiety, depression, long-term cognitive complication in the pediatric population	A	No	—
Botulinum toxin	Variable	Variable	Variable by dose and injection site	B	No	—
Metoclopramide	5 mg	10–30 mg	Extrapyramidal side effects, cardiovascular side effects	B	No	—
Ondansetron	8 mg	8–24 mg	Transient abdominal pain	B	No	—
Pramipexole	0.125 mg	0.25–0.5 mg	Headache, nausea, vomiting, myalgia, fatigue	B	No	—

Level of evidence: *A*, two or more randomized placebo-controlled clinical trials; *B*, one randomized placebo-controlled clinical trial; *C*, case series or open-label studies.
Summary of the doses, side effects, and level of evidence of commonly used pharmacologic agents in TS.

pediatric ADHD (off-label). Dosing of clonidine in studies ranged between 3 mcg/kg/day and 5 mcg/kg/day (0.1–0.3 mg/day). Side effects, the most common of which include sedation, dizziness, and orthostatic hypotension, typically appeared at doses above 6–7 mcg/kg/day (Leckman et al., 1991). Clonidine patches, which provide a more controlled release of clonidine into the bloodstream, are also effective, although local skin reactions can limit tolerance and adherence (Jiao et al., 2015).

Based on the current literature, clonidine appears to have a medium effect size in tic reduction and to be generally well tolerated, although the small number of studies and the small number of patients enrolled limit the quality of the evidence. Reported effect sizes, as compared to placebo, range from 0.43 to 0.64 for tablets and 0.26 for the clonidine patch (Table 8.2). Dosing the clonidine tablet starts at 0.05–0.1 mg, and the typical therapeutic dose is between 0.1 mg/day and 0.4 mg/day. Dosing for the clonidine patch varies between 1 mg and 2 mg daily. The major side effects that can limit long-term adherence are sedation, dizziness, and hypotension (Malaty and Akbar, 2014).

Guanfacine

Guanfacine is another α2-adrenergic receptor agonist that has more recently been used for treatment of tics. Guanfacine has certain advantages over clonidine, particularly for children, as it is less sedating and has a longer duration of action (Scahill et al., 2001). Only two double-blind placebo-controlled studies have assessed the efficacy of guanfacine in TS. The first, published in 2001, showed a significant (large) improvement in tic severity (Scahill et al., 2001), while the second, published in 2002, showed no improvement in tics over that seen for placebo (Cummings et al., 2002). No significant side effects were reported in either study. Possible side effects are similar to those of clonidine (sedation, bradycardia, hypotension, and dizziness); although in many cases, they are milder (Malaty and Akbar, 2014).

Thus, although the data are mixed, there is some evidence from one study that guanfacine may be effective in reducing tic severity, with an effect-size estimate of 0.74 (Table 8.2). Guanfacine is typically preferred over clonidine because of a milder side effect profile. The usual starting dose for guanfacine in TS is 0.5–1 mg/day, and the typical therapeutic dose is 1–4 mg a day (Malaty and Akbar, 2014). Long-acting forms are also available.

Atomoxetine

Atomoxetine is another adrenergic agent, although it acts as a norepinephrine reuptake inhibitor. Only one randomized double-blind, placebo-controlled study has been conducted for atomoxetine in TS, although, with over 140 participants, it is one of the largest pharmacologic studies of TS published to date (Allen et al., 2005). Initial analyses showed that tic severity did not worsen in comparison to placebo, and that ADHD symptoms substantially improved among those taking atomoxetine. A subsequent reanalysis showed a significant decrease in tics (effect size of 0.4) by the first week (Spencer et al., 2008). However, substantial dropouts in both the treatment and placebo groups limited the interpretation of the results of this study. Notable side effects included tachycardia, decrease in body weight, nausea, and decreased appetite. Other reported side effects include headache, dry mouth, insomnia, and fatigue. Thus, although this study provides some evidence that atomoxetine may improve tics, in the context of treating comorbid ADHD (for which it has an FDA indication), the benefit observed in tic control may have been secondary to improvement in ADHD control. Further, atomoxetine's side effect profile may limit its functional utility. The typical treatment dose varies between 40 mg and 60 mg daily (Ong et al., 2016).

Neuroleptic agents

Neuroleptic agents consist of a heterogeneous group of drugs with varying degrees of antagonism to the dopamine D2 receptor systems. First-generation (and typically higher potency D2 receptor blocking) agents are termed "typical" neuroleptics (e.g., haloperidol and pimozide), while second-generation and variable D2 receptor blocking agents are termed "atypical" neuroleptics (e.g., risperidone and aripiprazole). The neuroleptic agents remain the cornerstone of treatment of tics in TS in much of the world, including the United States. Indeed, all three of the currently FDA-approved treatments for TS belong to this group (haloperidol, pimozide, and aripiprazole). Up to 70% of patients treated with neuroleptics have a marked decrease (varies between 75% and 91%) in their tics (Roessner et al., 2011). Although most studies indicate similar effects on tic reduction between the neuroleptic agents, there are important differences in their side effect profiles. For example, there is increased concern for extrapyramidal side effects with the typical neuroleptics (Pringsheim and Marras, 2009), compared with increased concern for weight gain and metabolic syndrome with the use of the atypical neuroleptics (Fedorowicz and Fombonne, 2005). Recommended monitoring for all neuroleptics includes routine neurologic exams, weight assessments, liver transaminase levels, blood count, electrocardiograms, and prolactin levels (the latter if there is evidence of gynecomastia or menstrual changes) (Ong et al., 2016).

Typical neuroleptics

Although less commonly used in recent years, haloperidol, pimozide, and fluphenazine are historically the most widely used typical neuroleptics in the treatment of TS. The most common side effects associated with this class of medications include somnolence, hyperprolactinemia, obesity, metabolic syndrome, and temperature dysregulation (Malaty and Akbar, 2014). Extrapyramidal side effects, including acute reactions such as akathisia and dystonic reactions, are common, while tardive dyskinesia (and tardive tic-like symptoms), though reported (Thenganatt and Jankovic, 2016), appear to be rare in patients with TS (Müller-Vahl et al., 2011). Large retrospective studies fail to detect any cases of tardive dyskinesia (Müller-Vahl et al., 2011), though limited by their retrospective design. Other potentially serious side effects are cardiovascular in nature and include arrhythmias, QT interval prolongation, and hypotension (Fulop et al., 1987). Haloperidol appears to have the narrowest therapeutic window with regard to extrapyramidal side effects (Sallee et al., 1997), while pimozide is associated with a higher potential for QT prolongation.

Haloperidol. Haloperidol is a butyrophenone (Dion et al., 2002) and is the longest used medication in the treatment of TS (Malaty and Akbar, 2014). Multiple studies dating back to 1978 have examined the efficacy of haloperidol in TS, most often in comparison to placebo and/or to pimozide (Ross and Moldofsky, 1978; Shapiro et al., 1989; Sallee et al., 1997). Most (but not all) of these studies indicate that haloperidol is moderately effective in reducing tics in comparison to placebo, with an effect size between 0.37 and 0.87 (Table 8.2). Although effective, treatment is frequently limited by significant side effects. The usual daily dosage starts at 0.25 mg daily and increases up to 2 mg three times a day (e.g., up to 6 mg/day). The typical therapeutic dose varies between 0.75 mg and 5 mg daily, customarily in divided doses (e.g., two or three times a day) (Malaty and Akbar, 2014). The major side effects to consider include extrapyramidal symptoms, increased appetite, and sedation, and the major adverse effects are primarily cardiovascular in nature. Other important side effects include the possibility of hepatic insufficiency and blood dyscrasias (such as leukopenia). Individuals on haloperidol should be monitored regularly for these and other neuroleptic related adverse effects (Ong et al., 2016).

Pimozide. Pimozide is a dimethylbutylpiperidine and is the most studied neuroleptic for the treatment of TS, with six independent crossover or parallel-group design studies (Pringsheim and Marras, 2009). Most of these studies indicate that pimozide treatment results in improvement in tic severity, with some evidence of increased benefit over that seen with haloperidol, and with an overall better side effect profile (Shapiro and Shapiro, 1984; Shapiro et al., 1989; Sallee et al., 1997; Bruggeman et al., 2001; Gilbert et al., 2004).

The effect size as compared with placebo varies between 0.14 and 0.65 (Table 8.2). The usual starting dose for pimozide is 0.5 mg, increasing up to 2–10 mg daily. The typical therapeutic dose varies from 2 mg to 4 mg daily (Malaty and Akbar, 2014). The major side effects to consider include extrapyramidal symptoms, increased appetite, and sedation. Prolongation of QT interval is possible, especially when paired with other QT-prolonging agents. As with haloperidol, regular monitoring is essential (Ong et al., 2016).

Fluphenazine. Although fluphenazine is clinically used to treat TS, no prospective, placebo-controlled, double-blind studies of fluphenazine have yet been conducted (Malaty and Akbar, 2014). Instead, open-label and retrospective studies form the basis of the evidence. One large retrospective study indicated that fluphenazine treatment could result in up to 80% improvement in tic symptoms in some individuals (Wijemanne et al., 2014). The usual starting dose is 0.5–1 mg daily, and the typical therapeutic dose varies from 2 mg to 5 mg daily. The most common side effects include drowsiness and fatigue. QT prolongation is less common than with haloperidol or pimozide, but can occur, particularly if paired with other QT-prolonging agents. As fluphenazine treatment can worsen glaucoma, this medication is contraindicated in patients with known or suspected narrow-angle glaucoma (Malaty and Akbar, 2014).

Atypical neuroleptics

Atypical neuroleptics have variably potent D2 receptor blocking activity as well as serotonin 5-HT2 receptor blocking effects. The lower affinity for dopamine D2 receptors and the effects on serotonin receptors appear to be the mechanism behind lower reported rates of neurologic side effects, most notably extrapyramidal symptoms (Scahill et al., 2003). All of the tested agents in this class, with the notable exception of clozapine, have shown possible benefit in the control of tics in TS, although there is a significant variation in the quality and number of studies for the different agents. Risperidone and aripiprazole have the best evidence base.

Risperidone. Risperidone is a benzisoxazole with high antagonism to serotonin 5-HT2 receptors at low doses and to dopamine D2 receptors at higher doses (Dion et al., 2002). There are at least six randomized, blinded studies of risperidone in TS. Two of these were placebo-controlled trials (Dion et al., 2002; Scahill et al., 2003), while others have compared risperidone

to other agents, including pimozide (Bruggeman et al., 2001; Gilbert et al., 2004), clonidine (Gaffney et al., 2002), and aripiprazole (Ghanizadeh and Haghighi, 2014). All of these studies showed a significant reduction in tics with risperidone, with an effect size of 0.55–0.89 compared to placebo (Table 8.2).

The daily dosage starts at 0.5 mg and increases up to 6 mg daily. The usual therapeutic dose varies from 2 mg to 4 mg daily (Malaty and Akbar, 2014). The major side effects to consider include extrapyramidal symptoms, increased appetite, weight gain (average reported between 1.9 and 2.8 kg), orthostatic hypotension, depression, and sedation. Prolongation of QT interval is possible especially when paired with other QT-prolonging agents. Other neuroleptic specific adverse effects should be monitored (Ong et al., 2016).

Aripiprazole. Aripiprazole is a quinolinone with a partial agonist activity on the dopamine D2 and serotonin 5-HT1A receptors with antagonism to the serotonin 5-HT2A receptors (de Bartolomeis et al., 2015). It received FDA approval for the treatment of TS in the pediatric population in 2014.

There are at least four randomized, controlled studies of aripiprazole in TS. Two studies are placebo-controlled (Yoo et al., 2013; Sallee et al., 2017) and the other two compared aripiprazole to other neuroleptic agents, including risperidone (Ghanizadeh and Haghighi, 2014) and tiapride (Liu et al., 2011). The latter study, with 195 participants, is one of the largest pharmacologic studies of TS published to date. All of these studies showed a significant reduction of tics with aripiprazole treatment, with an average effect size of 0.68 compared to placebo (Table 8.2).

The usual daily dosage of aripiprazole starts at 2.5–5 mg and increases up to 25 mg daily. The usual therapeutic dose varies between 5 mg and 10 mg daily. The major side effects to consider include extrapyramidal symptoms, increased appetite, weight gain of around 3.5 pounds over a 10-week period (Yoo et al., 2013), orthostatic hypotension, and sedation. Prolongation of QT interval is possible, especially when paired with other QT-prolonging agents. It is recommended to monitor the neurologic exam, weight, liver transaminase levels, blood count, electrocardiogram, blood lipids, glucose, and prolactin (if there is suspicion for gynecomastia or menstrual changes) (Yoo et al., 2013). Other neuroleptic specific adverse effects should be monitored (Ong et al., 2016).

Other neuroleptics

Other neuroleptics considered for use in treating TS include olanzapine, ziprasidone, clozapine, and quetiapine. Of these, olanzapine has the most evidence base, while the others have little or no evidence to support their use in treating tics.

Olanzapine has a higher serotonin 5-HT2 receptor activity compared with the effect of dopamine D2 receptors resulting in a lower incidence of extrapyramidal side effects and hyperprolactinemia (Roessner et al., 2011), but higher rates of weight gain and metabolic syndrome. In addition to multiple case reports and open-label studies, there are two blinded studies that assessed the effect of olanzapine on TS control. One single-blind, placebo run-in study (Stephens et al., 2004) and one double-blind crossover study (Onofrj et al., 2000) reported a statistically significant decrease in tics with olanzapine. The effect size as compared with placebo was 2.42 (Table 8.2). The most notable side effect was weight gain ranging between 2 and 20 pounds (Stephens et al., 2004). Other noted side effects include elevated liver alkaline phosphatase, nausea, fatigue, and headaches.

Only one randomized, placebo-controlled, double-blind study assessed the effect of *ziprasidone* in decreasing tics in a pediatric sample (Sallee et al., 2000). Sixteen TS subjects received ziprasidone and 11 received placebo. Ziprasidone resulted in a significant reduction on the tic scale score compared with placebo with an effect size of 1.13 (Table 8.2). Interestingly, the most common side effect was somnolence and there was no difference in the incidence of extrapyramidal side effects between the two groups over the relatively short period of study (56 days).

Clozapine, a potent serotonin receptor antagonist and a weak dopamine D1 receptor blocker, does not appear to be effective in tic control (Caine et al., 1979; Roessner et al., 2011). In addition, it is associated with significant side effects, including a black box warning of neutropenia, and is subject to tight monitoring as a result (Kar et al., 2016). Further warnings including orthostatic hypotension, syncope, and cardiotoxicity, as well as more recent reports that clozapine can induce or worsen tics make it a poor choice (Begum, 2005; Bastiampillai et al., 2008).

There are no prospective, blinded studies published for the use of *quetiapine* in the treatment of TS. However, open-label and retrospective studies suggest that quetiapine has a possible effect in reducing tics (de Jonge et al., 2007).

Anticonvulsant agents

The anticonvulsant agents evaluated in the treatment of TS all have at least some GABAergic mechanism of action. They include topiramate, levetiracetam, and valproate.

Topiramate

Multiple studies have examined the effect of topiramate in reducing tics, the best designed of which was a 6-week randomized, double-blind, placebo-controlled study conducted by Jankovic et al. (2010). This study showed

a significant improvement in tic severity in the topiramate group compared to the placebo group, with an effect size of 1 (Table 8.2). The study was limited by a relatively high dropout rate in the treatment and placebo groups. The most commonly noted side effects (seen equally frequently in both the treatment and placebo groups) included gastrointestinal symptoms (abdominal pain, diarrhea), drowsiness, and headache. There was a mean decrease in body weight of around 2.1 kg in the treatment group.

A meta-analysis published in 2013 reviewed 14 trials that assessed the use of topiramate in children with TS. A total of 1003 subjects were included in the analysis with an age range of 2–17 (Yang et al., 2013). Most of the studies included were of poor quality and had variable follow-up times, tic scales used, and primary outcomes. Only three of the trials reviewed in this meta-analysis showed a significant reduction of tics with the use of topiramate. The most commonly reported side effects included drowsiness, loss of appetite, cognitive dysfunction, and weight loss (Yang et al., 2013).

In summary, there is some evidence that topiramate can improve tic control in TS subjects, although the quality of the evidence is variable at best. The common side effect of weight loss can be considered beneficial in some subjects, especially those who have experienced significant weight gain from treatment with neuroleptic class agents. Other notable side effects include kidney stones, glaucoma, paresthesias, and cognitive dysfunction (Malaty and Akbar, 2014).

Levetiracetam

Two randomized double-blind studies have evaluated the use of levetiracetam in the management of TS. One was placebo-controlled (Smith-Hicks et al., 2007) and the other compared levetiracetam with clonidine (Hedderick et al., 2009). Neither study showed levetiracetam as effective on tic control. Thus, based on the current evidence, levetiracetam does not appear to be an effective pharmacologic agent in the treatment of tics.

Valproate

A meta-analysis by Yang et al. (2015) identified five randomized controlled studies and five case series that have evaluated the use of valproate in the treatment of TS. One of the randomized trials showed a benefit of valproate when compared to placebo and another trial showed benefit when compared to haloperidol. Unfortunately, the interpretation of these studies was limited due to concerns about methodology (allocation concealment, blinding, randomization, reporting loss to follow-up, and concern for selective reporting). Accordingly, evidence for the use of valproate in TS is still lacking and additional well-designed studies are needed.

Dopamine-depleting agents

The presynaptic dopamine-depleting agents are a cornerstone in the treatment of hyperkinetic disorders. These agents do not appear to carry the risk of tardive dyskinesia (a major concern of postsynaptic dopamine receptor agents such as neuroleptics) (Vijayakumar and Jankovic, 2016). The first agent used in this class for the treatment of hyperkinetic disorders was reserpine, though only one case report has been published for TS (Rojas and Davies, 1999). Reserpine is no longer available in the US market due to concerns about side effects, most notably orthostatic hypotension and gastrointestinal complications (Jankovic, 2016).

Currently, the most commonly available presynaptic dopamine-depleting agents belong to a class of medications called the vesicular monoamine transporter (VMAT) inhibitors. These agents work by decreasing monoamine uptake into vesicles and depleting stores of monoamines including dopamine. Three agents are available in the US market: tetrabenazine (approved for the management of Huntington's disease), valbenazine (approved for the management of tardive dyskinesia), and deutetrabenazine (approved for the management of Huntington disease and tardive dyskinesia). None of these agents has an FDA approval for use in TS, though tetrabenazine is commonly used off-label. Valbenazine and deutetrabenazine are closely related to tetrabenazine. Valbenazine is a prodrug to a tetrabenazine isomer and deutetrabenazine incorporates deuterium into the tetrabenazine molecule (Jankovic, 2016). The hope is that those molecular modifications could improve pharmacodynamics.

One retrospective open-label study by Kenney et al. (2007) assessed the effect of tetrabenazine use in 77 TS subjects. The mean duration of tetrabenazine use was 2 years and the mean dose was 50.4 mg (±27 mg) usually divided three times a day. A large majority of subjects (83%) had moderate to marked improvement in TS symptoms. The most common side effects included drowsiness/fatigue, nausea, depression, insomnia, and parkinsonism.

Ongoing studies are investigating the use of the newer agents (valbenazine and deutetrabenazine) for TS. There is great enthusiasm for the two newer VMAT inhibitors as they are more specific to VMAT2, have a longer half-life, and have a lower side effect profile than tetrabenazine, making them potentially more effective and better tolerated (Jankovic, 2016). A phase-1 study of deutetrabenazine (SD-809) (Jankovic et al., 2016) in 23 adolescent TS subjects indicated a significant reduction of tics at week 8 on 36 mg given daily. Treatment side effects were frequent (65% of subjects reported at least one) although mostly mild–moderate: fatigue, headache, irritability, somnolence, hyperhidrosis, diarrhea, and

nasopharyngitis. One patient reported suicidal ideation, although this was thought to be related to the patient's baseline psychiatric state. There are three ongoing studies evaluating deutetrabenazine in TS (NCT03452943, 2018; NCT03567291, 2018; NCT23571256, 2018). Of the two phase-2 randomized, placebo-controlled studies for valbenazine (NBI-98854) (NCT03325010, 2017; NCT03530293, 2018), one is still ongoing, and one, a pediatric trial, was discontinued because of lack of efficacy late in 2018.

GABAergic agents

The two most commonly employed GABAergic agents in the management of TS include clonazepam and baclofen, neither of which currently has a strong evidence base.

Of these, clonazepam has the longest tradition of use, though only expert recommendation and open-label studies support the treatment (Gonce and Barbeau, 1977; Kaim, 1983; Merikangas et al., 1985). The usual starting dose is 0.25–0.5 mg daily and can increase up to 6 mg daily (Roessner et al., 2011; Malaty and Akbar, 2014). The typical therapeutic dose varies from 0.5 to 4 mg daily divided two or three times a day (Singer, 2010). This agent may be a consideration when there is a significant component of anxiety, or when impairment due to tics is infrequent and tic control is needed only in certain situations. The development of tolerance, common with the use of all benzodiazepines, is a concern with clonazepam use (Roessner et al., 2011). The therapy limiting side effects include sedation, paradoxic reactions, ataxia, and short-term memory complaints (Roessner et al., 2011).

Baclofen is a GABA-B receptor agonist. A small double-blind, placebo-controlled, crossover study evaluated baclofen (daily dose of 60 mg) over a 4-week period in 10 pediatric TS subjects. The clinical global impression severity score significantly improved, but the tic severity improvement did not reach statistical significance (effect size 0.22) (Singer et al., 2001). Larger open-label studies show significant improvement in motor and phonic tics even at lower doses (Awaad, 1999). The usual starting dose is 5–10 mg three times a day with a typical daily therapeutic dose from 10 mg to 60 mg (Malaty and Akbar, 2014). The most common side effects include drowsiness and sedation, which can be significant (Roessner et al., 2011) and limit baclofen's utility in TS. Dizziness and hypotension may also occur. Abrupt cessation can precipitate seizures or psychosis (Malaty and Akbar, 2014). Baclofen is rarely used in clinical practice except in the context of chronic painful dystonic tics.

Botulinum toxins

Botulinum toxins (BoNT) induce a relative muscle weakness by cleaving components of the presynaptic soluble NSF attachment protein receptor (SNARE) complex (essential for vesicular fusion), resulting in a significant reduction of acetylcholine release in the synaptic cleft (Malaty and Akbar, 2014). Multiple case reports and open-label studies have shown improvement in both motor (Kwak et al., 2000) and phonic tics with BoNT injections (Porta et al., 2004). Only one randomized, double-blind, placebo-controlled, crossover study evaluated the use of BoNT in the management of simple motor tics in TS (Marras et al., 2001). This study evaluated BoNT in 20 TS subjects, comparing the number of tics and tic scale scores at baseline to those 2 weeks after BoNT injection. There was a significant improvement in the simple motor tics. The side effects were consistent with the BoNT side effects observed in other indications and were dependent on the injection sites.

In summary, BoNT can be considered for the treatment of focal dystonic tics refractory to the usual pharmacotherapy. BoNT may also be considered in cases of coprolalia, where injections into the vocal cords can be used to reduce the impact of intrusive vocal tics, though hypophonia may be a trade-off. Identifying the most troublesome, focal, and typically simple tics is important prior to the use of BoNT (Thenganatt and Jankovic, 2016).

Other agents

Multiple additional agents have been studied for possible efficacy in TS, including glutamatergic agents, D-serine, riluzole (Lemmon et al., 2015), and *N*-acetylcysteine (Bloch et al., 2016a), nicotinic agents nicotine (McConville et al., 1992; Silver et al., 2001b; Howson et al., 2004), mecamylamine (Silver et al., 2001a), metoclopraminde (Nicolson et al., 2005), ondansetron (Toren et al., 2005), lithium (Kerbeshian and Burd, 1988), dopamine agonists, such as pramipexole (Kurlan et al., 2012) and talipexole (Goetz et al., 1994), naloxone (van Wattum et al., 2000), buspirone (Dursun et al., 1995), SSRIs (Scahill et al., 1997), vigabatrin (Catalyst Pharmaceutical Partners Inc., 2015), omega-3 fatty acid (Gabbay et al., 2012), physostigmine (Stahl and Berger, 1980), and spiradoline mesylate (Chappell et al., 1993). Some of these are based on hypotheses of the mechanism of TS development and treatment, e.g., glutamatergic agents (Lemmon et al., 2015); some have been effective in related disorders, e.g., SSRIs (Scahill et al., 1997); and some have been tried for other reasons. To date, the evidence base for these agents is weak or nonexistent, and for some, the potential side effect profiles are serious

enough to outweigh any potential efficacy. Thus, these agents are not currently recommended for use in TS.

Pharmacologic Agents in the Pipeline

Most of the TS medications that are currently under investigation are based on the newly described neurochemical changes at the basis of TS pathophysiology (e.g., histamine, glutamate, endocannabinoids) or are examining new agents that have an effect on previously described pathways (dopamine agonists or dopamine depletors). For some of these agents, multiple studies are underway, while for others, studies are in the initial exploratory phases examining safety and preliminary efficacy.

Histaminergic

Based on genetic (Castellan Baldan et al., 2014) and pathophysiologic (Hartmann et al., 2012; Xu et al., 2015) studies indicating that histaminergic signaling may be abnormal in a subset of patients with TS, histamine H3 receptor (H3R) modulators have been studied as potential TS treatments. Of the two phase-2 clinical trials examining histaminergic agents, the first studied an H3R antagonist, PF-03654746 (NCT01475383, 2011). This study was terminated in 2012 and no results are publicly available, suggesting that it was not effective. Preliminary results, published on clinicaltrials.gov, from the second, a randomized, double-blind, placebo-controlled study of an H3R inverse agonist (AZD5213) (NCT01904773, 2013) showed that the higher of the two doses studied (0.5 mg and 2 mg) resulted in a statistically significant reduction in tic severity (AstraZeneca, 2016), although the final result from this study has not yet been published.

Cannabinoid

The cannabinoid system's role in TS is receiving increasing attention given the possible response to Δ-9-tetrahydrocannabinol (THC) and the role of endocannabinoid receptors on the dopamine pathways (Müller-Vahl, 2013). There are multiple cannabinoid agents derived from the cannabis plant: marijuana (dried buds), and cannabis extracts (oils, pills, sprays). Synthetically produced cannabinoids are available (Patterson, 2017). The two main active ingredients in cannabis include THC and cannabidiol (CBD). THC containing compounds have been the most studied in TS (Patterson, 2017). Two small randomized, placebo-controlled trials evaluated THC in adults with TS (Müller-Vahl et al., 2002, 2003): one was a single-dose study and the other a 12-week study. Both studies showed significant improvement in self-reported tic symptom lists at some, but not all, visits, with an effect size of 0.83 for those visits (Table 8.2). Only one of the studies showed a significant improvement in additional tic scales at some points (Müller-Vahl et al., 2003). The most common side effects included headache, fatigue, xerostomia, dizziness, anxiety, depression, and other psychologic effects (Müller-Vahl, 2013). Slow titration may mitigate these side effects. Studies of cannabinoids and endocannabinoids have been conducted in adults only, as the pediatric population is at high risk of long-term cognitive complications and has a doubled risk of psychosis with THC exposure (Müller-Vahl, 2013).

Two additional ongoing studies are investigating THC and cannabidiol compounds. The first is an ongoing study of a combination of dronabinol (synthetic THC) and the dietary supplement palmotoylethanol in adult TS subjects (expected completion January 2019) (NCT03066193, 2017). The second, a randomized, placebo-controlled, parallel group trial is assessing Nabiximols (THC and cannabidiol mixture) in adults with TS (expected completion May 2019) (NCT03087201, 2017).

In addition to using cannabis derivatives, investigators are also exploring strategies to increase the availability of endocannabinoids as a potential treatment for tics. One strategy is to inhibit the catabolic pathway of the endocannabinoids. Studies are currently evaluating two agents. One study is a phase-2 clinical trial assessing a fatty acid amide hydrolase (FAAH) inhibitor (NCT02134080, 2014). FAAH is an anandamide-metabolizing enzyme and is an important part of the endocannabinoid catabolism pathway. Inhibiting this enzyme results in an increase in the bioavailability of endocannabinoids (Hartmann et al., 2016). This study is currently suspended and no results are available. The other study is a phase-1 randomized, placebo-controlled, crossover safety and tolerability study evaluating a small molecule called ABX-1431 (NCT03058562, 2017). This is a selective inhibitor of monoacylglycerol lipase (MGLL), a modulator of endogenous cannabinoids. The study was completed in November 2017 but no published results are available. Unpublished data indicate that MGLL might be effective in TS treatment (Szejko et al., 2018). Thus, although potentially promising as a future treatment for TS, use of the cannabinoids is not recommended at present, because of lack of consistent evidence of effect, coupled with increased risk of adverse events, particularly in children.

Postsynaptic dopamine receptor antagonists

Ecopipam is a new selective dopamine D1 receptor antagonist (Malaty and Akbar, 2014; Thenganatt and Jankovic, 2016). Promising data from an open-label study (Gilbert et al., 2014) indicated a significant reduction of tics at 8 weeks. A phase-2 multicenter, randomized,

placebo-controlled, crossover study evaluated Ecopipam in 40 subjects aged 7–17 years with TS (NCT02102698, 2014). They were randomized to either Ecopipam (50 mg or 100 mg depending on weight) or placebo for 30 days and then crossed to the other treatment for another 30 days after a 2-week washout period. There was a significant reduction in tics as measured by the Yale Global Tic Severity Scale total tic score in the Ecopipam group as compared to placebo (at 30 days: mean difference -3.2, $P = 0.033$). Adverse events were mild to moderate and balanced between the groups (Gilbert et al., 2018).

Glutamatergic

Although most of the studies of glutamatergic agents were negative in TS (Lemmon et al., 2015; Bloch et al., 2016a), newer agents affecting the glutamatergic pathways are also under development. For example, acamprosate (SNC-102), usually used in the treatment of alcohol abuse, has been studied in 16 adult TS subjects as part of a phase-2 open-label study. Acamprosate is generally well tolerated in adults with alcohol abuse, and side effects are minimal (Mason and Heyser, 2010). Results for this study, which was completed in January 2016, are not yet available (NCT02217007, 2014).

Antioxidants

Antioxidants have been studied in a variety of disorders, with mixed results, and interest in antioxidants for treating TS and other related disorders continues to be high among patient groups. An antioxidant mitochondrial rescue agent, vatiquinone (EPI-743), has also been evaluated in a phase-1 trial in adults with TS (NCT01719523, 2012). Although the study was completed in 2013, there are no published results. This drug is also being investigated for other movement disorders, including Leigh's disease, Friedreich ataxia, and Parkinson's disease.

Treatment in the setting of comorbidities

Comorbid psychiatric disorders are quite common in TS and are a major source of impairment (Neri and Cardona, 2013; Kious et al., 2016). As noted in the introduction, for individuals presenting for clinical treatment of TS, the presence of at least one psychiatric comorbidity can "be regarded [as] the rule rather than the exception" (Roessner et al., 2011). The most common comorbid disorders are ADHD and OCD, which account for 72.1% of all psychiatric comorbidities and typically cause more impairment than the tics themselves (Denckla, 2006a, b; Hirschtritt et al., 2015). As such, for many individuals with TS, treating the comorbid disorders is a priority and can result in a significant improvement of tics (Hoekstra et al., 2004), decreasing or eliminating the need for tic specific medications. Fig. 8.3 demonstrates a suggested treatment algorithm for patients with TS and concurrent OCD and/or ADHD.

Attention-deficit hyperactivity disorder

In TS patients, ADHD symptoms usually start prior to the onset of tics (between ages 4 and 6) (Bloch and Leckman, 2009; Hirschtritt et al., 2015). Untreated ADHD can worsen academic performance (Abwender et al., 1996), decrease the response to behavioral therapy (Lyon and Coffey, 2009), and induce disruptive behaviors (Sukhodolsky et al., 2003). Nonpharmacologic interventions including psychotherapy are recommended as a first-line treatment when available. The pharmacologic treatments for ADHD in TS usually fall into three classes as supported by controlled clinical trials (Rizzo et al., 2013), listed in the preferred order of use: α-adrenergic medications, clonidine (Leckman et al., 1991; Kulan, 2002) and guanfacine (Scahill et al., 2001); psychostimulants, primarily methylphenidate and its derivatives (Gadow et al., 1995; Castellanos et al., 1997; Kulan, 2002); and atomoxetine (Spencer et al., 2008). Although psychostimulants were once thought to induce or worsen tics, and thus were contraindicated in the treatment of TS, recent evidence suggests that this is not the case (Bloch and Leckman, 2009). Multiple, well-conducted controlled randomized studies failed to show that psychostimulants either induce (Palumbo et al., 2004; Roessner et al., 2006) or worsen tics (Bloch et al., 2009). Indeed, both long-term open-label (Gadow et al., 1999) and double-blind studies (Gadow et al., 1995; Castellanos et al., 1997; Kulan, 2002) show that the use of methylphenidate can actually result in tic improvement, possibly because of improvement in co-occurring ADHD symptoms. Note, however, that individual response can be variable, and that higher than usual doses of psychostimulants (methylphenidate dose more than 45 mg twice a day or dexamphetamine dose more than 22.5 mg twice a day) can result in a temporary worsening of tics (Castellanos et al., 1997); thus titration of psychostimulants should be slow and cautious. There is also evidence that a combination of α-adrenergic agents and psychostimulants can be more effective than either agent alone in the setting of severe or treatment refractory ADHD in TS (Bloch et al., 2009). The effect of psychostimulants is also synergistic with other tic-specific medications (Kulan, 2002). Other agents such as the secondary amine tricyclic antidepressants (e.g., desipramine) can also improve ADHD in the setting of TS, but are of limited use in practice because of their side effect profiles and narrow therapeutic windows (Spencer et al., 2002).

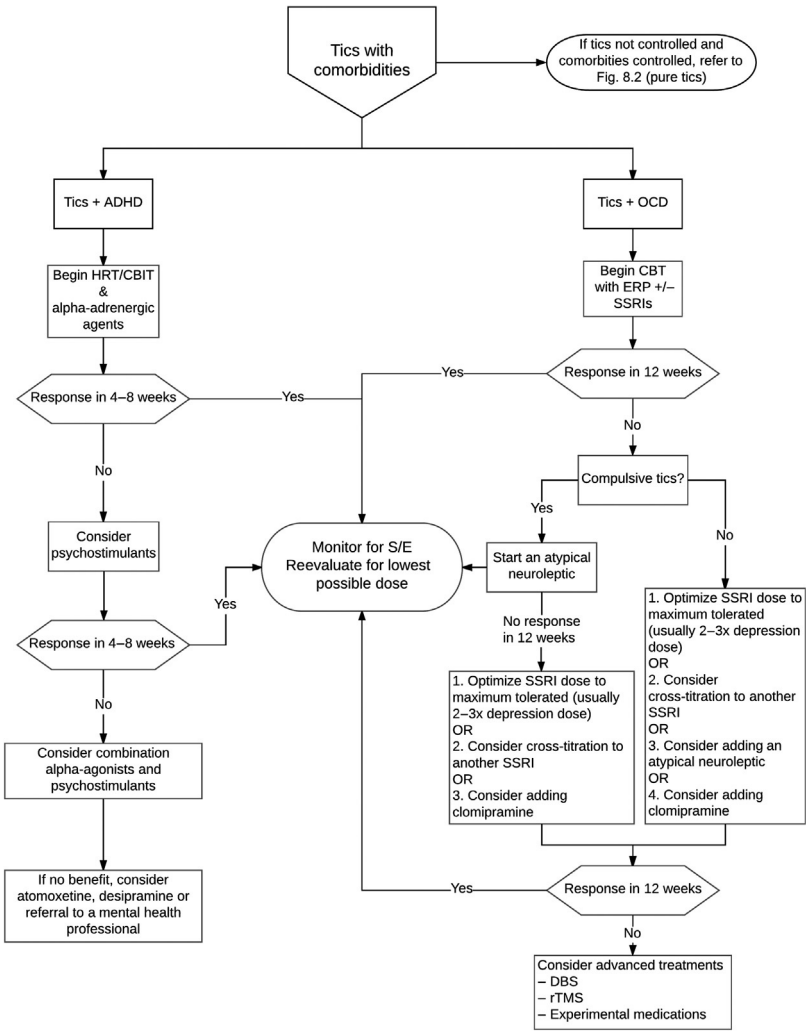

Fig. 8.3. Proposed treatment algorithm for Tourette syndrome—focusing on ADHD and OCD management (accompanies Fig. 8.2). Abbreviations: *ADHD*, attention-deficit hyperactivity disorder; *CBIT*, comprehensive behavioral intervention for tics; *CBT*, cognitive behavioral therapy; *DBS*, deep brain stimulation; *D/C*, discontinue; *ERP*, exposure and response prevention; *HRT*, habit reversal therapy; *OCD*, obsessive–compulsive disorder; *rTMS*, repetitive transcranial magnetic stimulation; *S/E*, side effects; *SSRI*, selective serotonin reuptake inhibitor. Adapted from Jankovic J, Kurlan R (2011). Tourette syndrome: evolving concepts. Mov Disord 26(6): 1149–1156. https://doi.org/10.1002/mds.23618; Roessner V et al. (2011). European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry 20(4): 173–196. https://doi.org/10.1007/s00787-011-0163-7; Rizzo R et al. (2013). Tourette syndrome and comorbid ADHD: current pharmacological treatment options. Eur J Paediatr Neurol 17(5): 421–428. https://doi.org/10.1016/j.ejpn.2013.01.005; Hirschtritt ME et al. (2015). Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry 72(4): 325. https://doi.org/10.1001/jamapsychiatry.2014.2650; Kious BM, Jimenez-Shahed J, Shprecher DR. (2016). Treatment-refractory Tourette syndrome. Prog Neuropsychopharmacol Biol Psychiatry 70: 227–236. https://doi.org/10.1016/j.pnpbp.2016.02.003; Ong MT, Mordekar SR, Seal A. (2016). Fifteen minute consultation: tics and Tourette syndrome. Arch Dis Child Educ Pract Ed 101(2): 87–94. https://doi.org/10.1136/archdischild-2015-309138 supplemented by expert consensus.

Obsessive–compulsive disorder

Comorbid OCD, in addition to being impairing in itself, can also induce worsening of the TS phenotype (Kious et al., 2016). Although rare, malignant TS (characterized by tics severe enough to require hospitalization, self-injurious tics, and life-threatening tics) (Cheung et al., 2007), poor quality of life (Kano et al., 2015), and mood disorders (Lebowitz et al., 2012) have all been linked to comorbid OCD. No controlled studies have specifically addressed the treatment of OCD in the setting of TS (Neri and Cardona, 2013), and treatment for OCD in TS is the same as that for OCD without TS. Cognitive-behavioral

therapy (CBT) with an exposure/response prevention (ERP) component has the strongest evidence base and is considered to be first line of treatment for OCD (Hirschtritt et al., 2015). SSRIs are the first-line pharmacologic agents, and the only class of medications to have primary efficacy for OCD. Although evidence is limited, response to SSRIs (as monotherapy) in TS + OCD is not as robust as response in OCD alone (McDougle et al., 1993). The addition of atypical neuroleptics can help in improving symptom control by augmenting the treatment effects of SSRIs (Delgado et al., 1990; Bloch et al., 2006). If these treatment strategies fail, the addition of clomipramine, or in severe, treatment-refractory cases, more advanced treatments such as DBS, can be effective (Hirschtritt et al., 2015).

TREATMENT REFRACTORY TS

Given the variability of tics and the different experiences of patients with TS, there is currently no clear definition of treatment refractory TS. Tic severity, functional impairment, disability from tics, and ability to tolerate tics in daily functioning are clearly relevant factors in this determination (Porta et al., 2011). Additional criteria include treatment failure with behavioral therapy plus more than one standard pharmacologic and/or nonpharmacologic treatments (Kious et al., 2016). However, it is important to assess the following factors to ensure "true refractoriness":

- The adequacy of the therapeutic trials—appropriate dosing, appropriate duration of treatment
- The precision of the TS diagnosis (assess for the presence of functional tics in addition to true tics, assess for other movement disorders that may mimic tics)
- The speed and suitability of the titration schedule—titrate too fast and the medication might be declared unsuitable because of avoidable side effects
- The adequacy of treatment of the psychiatric comorbidities (Kious et al., 2016).

When a diagnosis of treatment-refractory TS is established, consider novel pharmacologic and nonpharmacologic treatment options. The novel pharmacologic agents have been discussed earlier and should be used with caution, given their limited evidence base. The most studied nonpharmacologic intervention for refractory TS is DBS, which has a rapidly growing evidence base. Other possible interventions include rTMS and tDCS.

Deep brain stimulation

DBS involves the implantation of an electrode into a specific brain region (referred to as the target) through a small burr hole in the skull. This electrode is connected to an implantable generator that allows programmable electrical stimulation of the brain target. This stimulation results in modulation of the brain oscillations, disruption of pathologic signals, and inhibition of signal transmission resulting in the improvement of symptoms. DBS is currently approved by the FDA for the management of essential tremor, Parkinson's disease, dystonia (humanitarian device exemption), and OCD (humanitarian device exemption). Its use in TS is still considered to be investigational.

Despite an initial success by Hassler and Dieckmann in using stereotactic lesions of the thalamus (thalamotomy) for the management of treatment refractory TS, neurosurgery for TS was not widely adopted because of concerns related to the invasiveness of the procedure and possible complications (Ackermans et al., 2008). However, in (1999) Vandewalle et al. rekindled interest in brain surgery for the treatment of refractory TS, in the form of DBS, based on its success in Parkinson disease and reported positive results of DBS of the ventro-oralis/centromedian–parafascicular complex of the thalamus in a small series of patients (Vandewalle et al., 1999). Since this initial report, there have been a large number of studies (though many small and uncontrolled) of multiple different brain targets evaluating DBS in TS (Deeb et al., 2016). These studies have generally reported a significant improvement in tic control, although complications, including higher than anticipated rate of explants have been observed.

There is currently no consensus on the optimal target(s) for DBS in TS, and there is no direct comparison of the eight different targets that have been evaluated to date (Deeb et al., 2016). However, the data indicate that following thalamic or pallidal stimulation, approximately 97% of patients developed at least some benefit in their tic control (Kious et al., 2016), suggesting that these two targets, which are the most commonly used, show efficacy in treatment-refractory TS. Results in other targets are less robust, though the sample sizes are small. It is notable that these other targets can influence comorbid conditions (for example, anterior limb of the internal capsule can improve OCD symptoms) (Schrock et al., 2015; Baldermann et al., 2016; Servello et al., 2016). Ultimately, the optimal target of this evolving therapy will need to be elucidated with regard to tics and comorbid conditions.

Although most individuals who receive DBS for treatment-refractory TS are adults, there is no evidence-based consensus on the minimal appropriate age of implantation. On the one hand, concerns have been expressed about implantation in the pediatric population given the observed natural history of TS, and the fact that most children will experience an improvement in their tics with age (Cavanna et al., 2011). On the other hand, it can be argued that delaying surgical treatment until adulthood

in very severe, treatment-refractory cases can result in significant impairment during important formative years, with possible social, personal, and functional repercussions (Poysky and Jimenez-Shahed, 2007). The Tourette Association of America (TAA) DBS Database and Registry Study group has published an expert guideline for TS patient selection that attempts to operationalize inclusion criteria for DBS surgery and addresses these concerns (Schrock et al., 2015):

- DSM-5 diagnosis of TS
- Discussion by the institutions ethics committee for any TS patient under the age of 18
- Tics as major cause of disability
- Yale Global Tic Severity Scale of at least 35
- Video recording of the tic movements
- Trial of CBIT
- Failure of usual treatments of TS (defined as at least three different pharmacologic classes)
- Psychiatric conditions investigated and appropriately treated
- No suicidal or homicidal ideations for 6 months prior to the surgery

Given the small number of patients in the published studies, the TAA DBS Database and Registry was developed to pool the data from all the participating centers (Deeb et al., 2016). The analysis of this data will result in significant insights and help the planning of future pivotal trials (Kious et al., 2016).

Repetitive transcranial magnetic stimulation

rTMS is a noninvasive form of brain stimulation that is delivered through a coil placed over the patient's head. Using electromagnetic induction, the coil produces short electric current pulses that in turn alter the neural activity of the underlying cortex. The frequency of stimulation alters the effect: a high-frequency stimulation (>5 Hz) causes excitation of the cortex, while a low-frequency stimulation (1 Hz) decreases cortical excitability (Rossi et al., 2009; Di Lazzaro et al., 2011; Le et al., 2013; Bloch et al., 2016b).

The supplementary motor area (SMA) appears to be hyperexcitable in patients with TS and is a target of potential interest for rTMS (Bohlhalter et al., 2006; Hampson et al., 2009). Multiple open-label studies have reported that low-frequency rTMS of the SMA can improve tic symptoms (Mantovani et al., 2006; Kwon et al., 2011; Le et al., 2013; Salatino et al., 2014). A more recent study found that although SMA rTMS was safe without significant side effects, there was no improvement in tic severity in the studied group as a whole (Bloch et al., 2016b). Some benefit was noted in a subset of patients with OCD, however (Bloch et al., 2016b). On the other hand, the results of two randomized, double-blind, sham-controlled studies were negative (Wu et al., 2014; Landeros-Weisenberger et al., 2015).

Transcranial direct current stimulation

tDCS is another noninvasive form of brain stimulation that has been of interest in treatment of tics. This technique does not employ electromagnetic induction but instead delivers electrical stimulation directly to the target transcranially (Auvichayapat and Auvichayapat, 2011). It allows for a more focused and deeper area of stimulation. The evidence of its effectiveness in TS is limited to case reports and case series that show positive benefit in tic control (Kious et al., 2016). There is no consensus on target or dose of stimulation (Behler et al., 2018). For example, Carvalho et al. published a case report of a 16-year-old boy with refractory TS who received tDCS as compassionate treatment. He received ten 30-min daily sessions of cathodal tDCS (considered inhibitory) over the preSMA. The total tic severity score decreased by 22% at week 1, 41% at week 2, and were sustained at 3 and 6 months follow up at 39% (Carvalho et al., 2015). A similar study reported on two men with TS (ages 26 and 31 years) who received cathodal tDCS over the preSMA. They received both sham tDCS and real tDCS separated by a 2-week washout. The YGTSS severity scale decreased by 20.3% and 10.6% after 5 days of real tDCS with only minimal improvement after sham tCDS (5.08% and 2%). The authors noted a transient large improvement of their sensation of general wellness (increased by 132% and 450%) that occurred at day 5 of tDCS but waned after 2 weeks to baseline (Mrakic-Sposta et al., 2008). On the other hand, a study investigating twice daily cathodal tDCS sessions over the SMA and preSMA areas over 5 days in three subjects (ages 18, 20, and 55 years) showed a 34.5% improvement in tic severity in one subject only with the other two showing a worsening of their tic severity (Behler et al., 2018). This discrepancy in findings indicates the importance of future work to elucidate effective stimulation site, polarity, and frequency (Behler et al., 2018). A randomized, crossover study (NCT02216474, 2014) assessing multiple movement disorders, including TS, is currently underway. Although results for TS are not yet available, individuals with Huntington disease who received tDCS as part of this study showed improvement in working memory with dorsolateral prefrontal tDCS (Eddy et al., 2017). Another double-blind, crossover, sham-controlled trial of tDCS is underway for subjects with TS, age 12 years and older. Subjects will receive 18 sessions of 1.4 mA cathodal tDCS over the SMA. A preliminary report about two subjects

is published. YGTSS was not collected for those two subjects but will be collected for future subjects. There was a noted reduction in the frequency and severity of tics on the adult tic questionnaire (34.9% and 20.6% after 6 weeks of real tDCS) and a reduction of the premonitory urges on the premonitory urge for tics scale (Eapen et al., 2017).

CONCLUSION

TS is a complex neuropsychiatric disorder characterized by multiple motor tics and at least one phonic tic. It is generally associated with at least one psychiatric comorbidity, most commonly ADHD and/or OCD. The treatment of TS and its associated comorbidities should be individualized and tailored to the patient's phenotype, keeping in mind that many individuals will not need treatment for their tics. Treatments are effective, but are aimed at reducing tic severity and improving quality of life rather than eliminating tics entirely. A poorer quality of life, more severe tics, and decreased functional level are often associated with poorly controlled psychiatric comorbidities, highlighting the importance of recognition and treatment of these conditions. The treatment of tics includes behavioral interventions (such as CBIT), pharmacologic agents, and, in rare cases, more invasive nonpharmacologic treatments (such as DBS). The quality of evidence guiding the treatment algorithms in TS is at best moderate, primarily due to a small number of randomized controlled studies, many of which included a relatively small number of subjects and followed them for short periods. Treatment algorithms presented here represent both the current evidence base for treatment of tics and comorbid conditions and expert opinion.

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