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REVIEW ARTICLE

The Role of Atypical Antipsychotics for Treatment of Tourette's Syndrome: An Overview

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Abstract Tourette's syndrome (TS) is a neuropsychiatric disorder of childhood onset characterized by multiple motor and phonic tics that fluctuate over time. Tic symptoms often improve by late adolescence, but some children and adults with TS may experience significant tic-related morbidity, including social and family problems, academic difficulties, and pain. When more conservative interventions are not successful, and when certain psychiatric comorbidities further complicate the clinical profile, treating TS with an atypical antipsychotic medication may be a reasonable second-tier approach. However, the evidence supporting efficacy and safety of the atypical antipsychotics for treatment of tics is still very limited. The objective of this paper is to provide an updated overview of the role of atypical antipsychotics for treatment of TS, with evidence-based guidance on their use. Evidence for efficacy of different typical and atypical antipsychotics for treatment of tics was examined by conducting a systematic, keyword-related search of 'atypical antipsychotics' and 'Tourette's syndrome' in PubMed (National Library of Medicine, Washington, DC, USA). Four recent treatment consensus publications were also reviewed. This review focused on literature published from 2000 to 2013 and on available randomized controlled trials in TS. Evidence supporting the use of atypical antipsychotics for treatment of TS is limited. There are few randomized medication treatment trials in TS (i.e. risperidone, aripiprazole, ziprasidone), which employed varying methodologies, thereby restricting meaningful comparisons among studies. Future collaborations among clinical sites with TS expertise employing high-quality study design may better elucidate the role of atypical antipsychotics for treatment of TS.

Key Points

Non-pharmacological behavioral therapies are first-tier treatments for impairing tics of moderate severity in patients with Tourette's syndrome (TS).

Atypical antipsychotics are second-tier treatments for impairing tics of moderate severity and may be helpful for treating TS-associated psychiatric comorbidities.

The evidence for use of atypical antipsychotics in TS is limited, and current guidelines also rely on experience and regional practices.

1 Background

Tourette's syndrome (TS) is a neuropsychiatric disorder of childhood onset, characterized by bouts of multiple motor and phonic tics that persist for at least 1 year [1]. The highly related condition chronic tic disorder shares similar demographic and phenomenological features with TS but is distinguished by the presence of *only* chronic motor or *only* chronic vocal tics but *not both* [1]. Tics are defined as sudden, rapid, recurrent non-rhythmic motor movements or

This manuscript is a review article and does not contain clinical studies or patient data.

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vocalizations. Some tics may be very brief, simple movements or phonations involving only one or a few proximally related muscle groups (e.g. eye blinking, throat clearing). Other tic symptoms comprise more complex motor or phonic repertoires involving multiple muscle groups (e.g. twisting, utterances of words or phrases). Premonitory urges are sensory phenomena (e.g. a localized tickling or an itchy sensation) that precede and are alleviated by executing the tic. Sometimes described as a feeling of being 'not just right', the premonitory urges provoke repetition of the tic and may be more distracting than the tics [2]. Tics may intensify during periods of stress, anxiety, excitement, and fatigue and may be more prominent in a particular setting [3]. Suppressible for varying periods of time, particularly in novel or social settings, tics often diminish during intense focus on a particular activity or task [4].

1.1 Epidemiology of Tourette's Syndrome (TS)

TS occurs worldwide, and estimates of its prevalence vary depending upon the diagnostic criteria and assessment methodology employed. The overall international prevalence of TS has been estimated to be 1 %, and up to 3–4 % for chronic motor or chronic vocal tic disorders [5]. The prevalence of TS in youth between the ages of 5 and 18 years has been reported to be between 0.4 and 3.8 % [6]. The first estimate of the national prevalence of diagnosed TS in the USA was obtained by the National Survey of Children's Health (NSCH) in 2007, which included questions and collected complete data about TS from 64,034 youths aged 6–17 years. Data concerning a child in the family who was diagnosed with TS were obtained by using random-digit dialed telephone surveys and interviews of parents or guardians [7]. This population-based national survey found that boys were three times as likely to be diagnosed with TS than were girls, and that non-Hispanic White youth were two times more likely to be diagnosed with TS than Hispanic and non-Hispanic Black youth, with an overall estimated prevalence of a lifetime diagnosis of TS to be 3.0 per 1,000. The NSCH data also indicated that 79 % of children diagnosed with TS had a co-occurring neurodevelopment condition [7]. A population-based study using prospective data obtained from the Longitudinal Study of Parents and Children (ALSPAC) in England examined prevalence of tic disorders in 6,768 children aged 13 and 14 years [8]. By applying three levels of diagnostic stringency (i.e. narrow, intermediate, and broad), the investigators found a prevalence of 0.3–0.8 % for TS and of 1–3 % for chronic tic disorder. Using this data set, the prevalence of co-morbid psychiatric disorders was significantly lower [8]. A recent meta-analysis of 13 studies in children determined a TS prevalence of 0.77 %, with rates in males four times higher than in females [9]. Less information is known about the incidence of TS. A population-based study that identified all children born in Denmark from 1990 to 1999, and obtained diagnoses reported by psychiatrists through 2004 by linkage with the Danish National Psychiatric Registry, reported a TS incidence of 65/100,000 [10].

1.2 Genetic and Epigenetic Influences on TS

Both genetic and epigenetic influences have been associated with TS. Family and twin studies have highlighted the importance of genetic risk factors in the development of TS. Concordance rates for chronic tic disorder between monozygotic twins are 77–94 % compared with 23 % for dizygotic twins [11, 12]. First-degree relatives have a risk for TS ranging between 9.8 and 15 % and a risk for other tic disorders ranging between 15 and 20 % [13]. However, investigations of TS inheritance by using candidate-gene association, nonparametric linkage studies, and results from the first genome-wide association study (GWAS) that included 1,285 TS cases and 4,964 matched controls have not yet identified definitive TS susceptibility genes [14, 15]. The previously favored genetic models that posited patterns of simple autosomal dominant Mendelian inheritance in TS have yielded to a growing appreciation of the complex polygenetic architecture of this disorder. Furthermore, it appears likely that both additive and multifactorial influences, in combination with genetic factors, play a role in TS [16]. Results from an investigation using genome wide complex trait analysis (GCTA), a strategy employed in the study of a number of complex neuropsychiatric disorders including schizophrenia and autism, suggest that multiple rare genetic changes (including variants significantly associated with gene expression in the parietal cortex and cerebellum) may account for a significant proportion of the genetic risk in TS [17]. Recent identification of a rare mutation in the histidine decarboxylase (Hdc) gene, first discovered in a two-generation kindred with multiply affected family members, and also studied using Hdc transgenic mice animal models, has provided evidence implicating the involvement of the Hdc gene and histadinergic neural pathways in the etiology of TS [18–20].

However, clearly, genetic risks do not account entirely for TS and there are numerous reported associations in the literature between TS and various prenatal factors, including increased maternal nausea and vomiting during the first trimester, maternal life stress, complications during pregnancy, and maternal smoking during pregnancy [21–23]. The largest prospective study to date of non-genetic risk factors and TS included data derived from 6,090 children (including 122 with either TS or chronic tic

disorder at age 13 or 14 years) from the ALSPAC [24]. This study showed that maternal use of alcohol during the last 2 months of pregnancy; and maternal smoking, caffeine, or alcohol use in the last trimester; cannabis use during pregnancy (independent of maternal alcohol and tobacco use); parity and inadequate maternal weight gain during pregnancy were all significantly associated with TS/chronic tic disorder [24–26].

Postnatal environmental factors have also been proposed to play a role in TS, including possible infectious and autoimmune triggers [27–29]. The PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) hypothesis proposes a causal relationship between group A β-hemolytic streptococcal infections and the subsequent development of tics and/or other neuropsychiatric symptoms. However, the clinical and scientific evidence supporting the PANDAS hypothesis is mixed, and its existence as a distinct clinical entity remains highly controversial [30–33]. At this time, there appears to be insufficient evidence to support routine testing for group A streptococcus in youth with tics, nor are there consistent findings to justify routine treatment with antibiotics for putative PANDAS cases in the absence of acute infection. Similarly, there is insufficient evidence at this time to support treatment with immune-modifying agents in most children with TS outside research settings.

1.3 The Natural History of TS

The natural history of TS is characterized by the appearance of tics around ages 5–6 years. Tics typically follow a waxing/waning course over the ensuing years, peaking around ages 9–12 years, with a gradual diminution of symptoms during adolescence and significant if not complete remission of tics by early adulthood in the majority of cases [34]. While longitudinal data derived from a patient cohort followed from childhood to adulthood revealed that only 10 % experienced complete tic remission, it has been estimated that no more than 20 % of individuals with TS will continue to experience lifelong moderate to severe tics [35, 36]. Although there are no population-based studies of TS in adults, a meta-analysis of two studies evaluating TS in adults reported a prevalence of 0.05 %, indicative of the significant decline observed in TS prevalence with maturation [9]. Tic characteristics also appear to change during the lifespan. A study of 43 adult patients with TS followed at a specialty neurology program suggests that adult patients with TS have more facial and truncal tics and fewer phonic tics than youth with TS. Moreover, only about 20 % of the adults with TS in this cohort reported developing 'new' tics; most adults appear to experience episodic re-emergences or exacerbations of prior childhood tics [37].

Suggested predictors of tic severity in adulthood include smaller caudate volumes, poorer fine motor control, greater tic severity in childhood, and the presence of untreated psychiatric co-morbid conditions such as attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) [38, 39]. Long-term effects and impacts of various treatment interventions on the natural course of TS are not known. At this time, there is no known prophylaxis or cure for TS and therefore management remains largely aimed at reducing current symptom severity and decreasing functional burden.

1.4 The Neurobiology of TS

Proposed neural mechanisms underlying TS have implicated dysfunctional sensorimotor gating and disturbances of the cortico-basal ganglia circuits [40, 41]. Neuroimaging studies support the role of specific brain regions (including the ventral prefrontal cortex, orbital frontal cortex, anterior circulate cortex, parietal cortex, and the somatosensory cortex) along with the striatum and the thalamus in the pathophysiology of TS [42, 43]. The basal ganglia encompass a network of interconnected subcortical structures including the striatum, globus pallidus, substantia nigra, and subthalamic nucleus. Input from the cortex, thalamus, hippocampus, midbrain, and other structures is first conveyed to the striatum, which then relays processed information to the globus pallidus and substantia nigra. These latter structures in turn project to the thalamus and then back again to the cortex. This important circuitry known as the 'cortical–striatal–thalamic–cortical circuit' (CSTC) makes possible coordination of motor and cognitive processes, including action selection, performance monitoring, response inhibition, and goal-directed behaviors that may become habitualized [44]. Disturbances of various neurotransmitter systems involved in this important circuitry have been hypothesized to play a role in the pathophysiology of TS, including abnormalities in the dopamine, glutamate, gamma-aminobutyric acid, and serotonin and histamine neurotransmitter systems [19, 45].

Abnormalities in the CSTC are also implicated in a number of psychiatric disorders, including those that occur commonly with TS such as OCD, ADHD, non-OCD anxiety disorders, and mood disorders [46, 47]. Rates of these particular psychiatric comorbidities are elevated among clinically referred populations of both children and adults with TS although the reported frequencies of co-occurring OCD and ADHD appear to be markedly lower in TS cases derived from population-based samples [8, 48, 49]. When present, such co-morbid psychiatric conditions often cause greater morbidity than tics and may take priority as the primary target for treatment [50].

1.5 Treatment Considerations in TS

Once the TS diagnosis and identification of co-morbid conditions is made, therapeutic intervention begins with comprehensive psycho-education (i.e. educating affected individual, family, and in some cases school staff, peers, or employers) about TS, its natural course and prognosis, and about the impact of co-morbid psychiatric symptoms. A systematic exploration of specific sources of stress and of meaningful types of support for the affected individual is necessary. In cases characterized by mild, non-disruptive tics uncomplicated by psychiatric co-morbidity, psycho-education alone may be adequate. However, if tics are of mild to moderate severity and are adversely impacting daily functioning and quality of life (QOL), a trial of behavioral intervention is recommended for tic treatment.

Habit reversal therapy (HRT) and the more encompassing comprehensive behavioral intervention for tics (CBIT) are safe, non-pharmacological treatments with demonstrated efficacy in double-blind, randomized, controlled trials [51–53]. CBIT includes psycho-education, relaxation training, functional behavioral assessment, and HRT, with an effect size that approximates or exceeds that of conventional tic pharmacotherapy in double-blind, randomized controlled trials with enduring effects in both children and in adults [52, 53]. Different tic types or tic symptom profiles ascertained by cluster analysis in children and adults with TS appear to respond equally well to CBIT and it is now recommended as a first-line treatment for TS [54, 55]. However, to whom and how CBIT is optimally delivered is still not clear. Also, the comparative efficacy of CBIT versus medication (alone or in combination with CBIT) for treatment of tics requires investigation through randomized controlled trials.

In cases of moderate to severe, highly impairing tics that are refractory to CBIT, or in circumstances where the affected individual is unable to engage in CBIT, medication management may be necessary. The decision to embark on a medication trial is made only after a careful assessment of the potential benefits and risks, and needs to be coordinated with other necessary psychosocial interventions and environmental modifications. Medication treatment may be appropriate when tics cause sustained social or emotional problems; when tics result in pain, injury or other subjective discomfort; or when tics impair academic or occupational performance [56]. Moderate to severe tics that occur in the presence of certain psychiatric co-morbid conditions also known to be responsive to medication is another indication for pharmacological intervention.

Different tiers of evidence-based pharmacotherapy for tics have been well described and recommended [49, 57–60]. However, the quantity and quality of data supporting pharmacotherapy for TS is limited. Even well designed clinical trials in TS have been characterized by varying and relatively small sample sizes, with inclusion of study subjects with diverse TS clinical phenotypes whose ages span different periods of neurodevelopment and prior medication exposures. There are neither substantial data about the longitudinal impact on tics of different treatments for TS nor significant evidence to guide treatment selection among medications of the same tier. As a result, medication management of tics still remains a somewhat frustrating process of trial and error until more patient-specific algorithms become available. The highly subjective nature of tic impairment, which does not always correspond with objective ratings of tic severity, also underscores the frequent need for individualized treatment strategies [60]. Due to concerns about the potentially adverse consequences of medications on the developing brain, most clinicians hold off pharmacological treatment in children until tics are of persistently significant severity and disruption, but there is little evidence yet to guide intervention optimization in terms of timing, length of treatment, and long-term outcomes. There is an even greater dearth of information concerning age-related, racial, ethnic, and gender influences on appropriate dosing and treatment selection.

The alpha-2-adrenergic agents clonidine and guanfacine are preferred by some prescribers as first-line medication interventions due to their relatively benign side effect profile. Alpha-2-adrenergic agonists activate presynaptic auto-receptors and reduce norepinephrine levels. These agents have demonstrated efficacy in a number of double-blind/placebo-controlled studies and are considered a preferred, evidence-based treatment for tics with ADHD [60–62]. While alpha-2-adrenergic agonists have a medium-to-large effect size (i.e. 0.5–0.68) for treatment of tics with co-morbid ADHD, effects on tics without co-morbid ADHD appear minimal (i.e. 0.15) and may be associated with sedation, headache, orthostatic hypotension, irritability, and dizziness [61–64]. Nonetheless, clonidine and guanfacine are the *only* two medications for treatment of tics in children that received "strong recommendations" by the Canadian guidelines for evidence-based treatment of tic disorders [57].

Yet, in cases where more conservative treatments have not proved helpful, the benefits of using stronger tic suppressants (i.e. 'second-line' tic medications) may outweigh their considerably higher risks and side effects. The burden of tics, particularly when complicated by psychiatric co-morbidities, is significant for many individuals with TS, and multiple studies have now demonstrated the negative impact on QOL, including social rejection, bullying and isolation, emotional problems, job discrimination, and functional impairment [65, 66]. Therefore, the decision to proceed to treatment with second-tier tic medications for

TS may be appropriate following careful consideration of current and enduring circumstances, social support, academic and/or occupational functioning, non-tic medical risk factors, and potentially modifiable environmental influences.

To provide the clinician with relevant background and perspective, this paper briefly reviews the existing evidence base for using typical antipsychotics to treat TS. Upon considering the limitations of this evidence base, this paper then reviews and examines the role of a particular class of second-tier tic medications, the atypical antipsychotics, for treatment of tics in TS.

2 Methods

The objective of this paper is to provide an updated overview of the evidence-based treatments using atypical antipsychotics for TS. First, a systematic literature search using the keyword-related terms 'atypical antipsychotics' and 'Tourette's syndrome' for all studies that documented the pharmacological effects of atypical antipsychotics for treatment of TS was performed using the PubMed (National Library of Medicine, Washing, DC, USA) database for the period 1 January 2000–31 December 2013. The rationale for this search strategy was to focus on more contemporary clinical investigations of higher methodological rigor.

We identified 231 articles published in English. All titles and abstracts were screened for relevance to the main topic. The review focused on clinical studies with >20 experimental subjects although, in several instances, smaller or older studies, case reports, and further relevant literature were also examined by searching through the references of each article.

Randomized trials or non-randomized studies evaluating second-generation antipsychotic medications for treatment of TS were identified. Full texts were evaluated to identify salient information and to ascertain standards of methodological rigor. A total of 154 articles were excluded from the search; 77 articles were used in the current paper by applying the research procedures above.

To establish the hierarchy of evidence-based treatments, the following criteria, derived from the International Psychopharmacology Algorithm Project and also used by the 2006 Tourette's Syndrome Association Medical Advisory Board: Practice Committee, to categorize strength of empirical evidence were applied: (1) category A refers to treatments with 'good' supportive evidence for short-term safety and efficacy based on 'at least two or more' randomized, placebo-controlled trials with statistically significant positive results; (2) category B refers to treatments with 'fair' supportive evidence based on 'at least one' randomized, placebo-controlled study with positive results; (3) category C refers to treatments with only 'minimal' supportive evidence based on retrospective case series, open-label studies, case reports, and accumulated clinical experience [60, 67].

Four existing consensuses for pharmacological treatment of TS were also reviewed: *Contemporary Assessment and Pharmacotherapy of Tourette Syndrome* by the Tourette Syndrome Association Medical Advisory Board: Practice Committee [60]; the *European Clinical Guidelines for Tourette Syndrome and Other Tic Disorders* [58]; the *Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders* [57]; and the American Academy of Child and Adolescent Psychiatry *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Tic Disorders* [68].

3 Typical Antipsychotics

Historically, the hypothesis that abnormal dopamine neurotransmission underlies TS has been most widely pursued, using neurophysiological, post-mortem brain tissue, neuroimaging, and clinical investigations [42, 69]. Increased numbers of striatal and cortical dopamine receptors in affected individuals, and abnormalities of dopamine receptor-binding properties in the basal ganglia, have been reported [70–73]. Significant tic suppression has been consistently demonstrated using pharmacological strategies that emphasize high-potency D2 receptor antagonism using typical antipsychotic medications [74].

The typical antipsychotics haloperidol and pimozide are currently the only two US FDA-approved medications for the treatment of TS. While there are no recent randomized, double-blind, controlled studies of fluphenazine, this typical antipsychotic has also been used by the medical community (particularly among neurologists) for treating tics.

Acting primarily as D2 dopamine-receptor antagonists, these agents may achieve up to 60–80 % reduction in tic frequency and severity in most individuals with TS, based on findings reported in a number of older randomized controlled trials [75, 76]. However, the usefulness of typical antipsychotics for treatment of tics is significantly limited by their common adverse effects, including parkinsonism, acute dystonia, akathisia, tardive dyskinesia, cognitive dulling, sedation, and neuroendocrine disturbances, including hyperprolactinemia, temperature dysregulation, sexual dysfunction, and weight gain [59]. Behavioral side effects, including increased aggression, depression, anxiety, school phobia, and agitation, are also relatively common and must be distinguished from underlying psychiatric co-morbid conditions [77].

3.1 Haloperidol

Haloperidol is a butyrophenone derivative with high potency for D2-receptor blockade. It was the first typical antipsychotic to demonstrate tic suppression in 1961 [78] and 'category A/good' evidence for its use in TS is based on efficacy demonstrated in early clinical trials. Haloperidol was reported to be superior to both pimozide and placebo in a parallel cross-over study of 57 subjects aged 8–46 years; inferior to both pimozide and placebo in a double-blind randomized cross-over study in 22 children aged 7–16 years; superior to placebo and of comparable efficacy to pimozide in a small placebo-controlled double-blind randomized cross-over study of nine patients aged 8–28 years; and superior to placebo and of comparable efficacy to pimozide but with poorer tolerability, higher rates of discontinuation (47 % haloperidol vs. 8 % pimozide), and greater side effects, including acute dystonias and dyskinesias in a long-term follow-up (1–15 years) study of 33 patients [75, 76, 79–81].

Due to considerable side effects and lack of contemporary evidence supporting its use, haloperidol is not currently viewed as a preferred treatment for tics and instead is recommended only when better alternatives have been unsuccessful.

When used, haloperidol is usually started at 0.5 mg/day and carefully titrated upwards in 0.25- to 0.5-mg increments every 5–7 days until optimal tic control is achieved. The typical dose range for treatment of tics with haloperidol is 2–10 mg daily.

3.2 Fluphenazine

Fluphenazine is among the oldest typical antipsychotics, a phenothiazine derivative that acts on both D1 and D2 receptors. An older placebo-controlled, double-blind trial reportedly showed fluphenazine and trifluoperazine to be as effective as haloperidol but with fewer side effects for tic suppression [82]. Open-label studies, including a recent retrospective chart review of 268 patients with TS treated with fluphenazine for 0–16.8 years over a 26-year period that indicated marked to moderate improvement in 80.5 %, suggest that it is better tolerated than haloperidol [83–86].

While current evidence supporting the use of fluphenazine for treatment of tics is only 'category B/fair', it may be considered when treating moderate to severe tics that are refractory to preferred treatments. Fluphenazine is started at 0.5–1.0 mg daily and slowly increased by 0.5–1.0-mg increments every 5–7 days to approximately 0.5–12.0 mg daily.

3.3 Pimozide

Pimozide is a diphenylbutylpiperidine with potent postsynaptic dopamine receptor blockade and also blocks calcium channels. In addition to the aforementioned studies, pimozide has been investigated and shown to improve tics in two retrospective studies [87, 88]. Pimozide has been shown to be effective in both short-term and long-term suppression of tics in a prospective and blinded clinical trial of ten children aged 7–13 years who continued to receive or were withdrawn from active treatment [89]. In a larger clinical trial of 50 subjects aged 10–65 years that used a double-blind parallel-group design, pimozide and the atypical antipsychotic risperidone were shown to be of comparable efficacy [90]. A randomized, double-blind cross-over study in 19 children aged 7–17 years comparing risperidone with pimozide also showed tic reduction with both agents [91].

The 2009 Cochrane review of the six randomized trials evaluating pimozide for treatment of tics in 162 patients aged 7–53 years concluded that there *is* significant evidence to support the use of pimozide for treatment of tics [92]. However, along with typical albeit possibly milder antipsychotic side effects, pimozide is also associated with an elevated risk for QTc prolongation, and with sudden death at high doses [59].

The FDA recommends cytochrome P450 (CYP)2D6 genotyping before exceeding 4 mg of pimozide daily in adults or 0.05 mg/kg/day in children and that dosages should not be increased any faster than every 14 days in poor/slow metabolizers [93]. A baseline electrocardiogram (ECG) with periodic follow-up ECGs after dosage increases and during treatment is recommended.

Given such concerns, while pimozide has 'category A/good' evidence to support its use and appears to be better tolerated than haloperidol, like fluphenazine, it is usually reserved for treatment of moderate–severe tics when safer alternatives have been exhausted. When used, pimozide is started at 0.5 mg/day and titrated every 7–14 days by 0.5 mg. The typical dose range is 1–8 mg daily.

3.4 Benzamides

Substituted benzamides (i.e. tiapride, sulpiride, amisulpride) are selective D2-receptor antagonists and are believed to have fewer extrapyramidal side effects than the typical antipsychotics. These agents are not currently available in the USA but are still used widely in other countries for treatment of TS [58, 94, 95].

3.4.1 Tiapride

Tiapride is a moderately potent D2- and D3-receptor antagonist with relatively high regional selectivity for limbic areas [94–96]. An older randomized, double-blind, placebo-controlled, cross-over study of tiapride in 17 children demonstrated efficacy, and current information is otherwise based on widespread clinical experience overseas and from case reports [96–99]. The evidence supporting tiapride for tics is 'category B/fair' (i.e. less robust than for haloperidol or pimozide). Side effects resemble those of other typical antipsychotics but are believed to be milder, although no head-to-head comparison studies are available.

Recommended doses are between 100 and 900 mg daily starting with 50 mg daily and gradually titrating to tic suppression using divided doses at higher ranges. Maximum doses should not exceed 2–10 mg/kg [56].

3.4.2 Sulpiride

Sulpiride is a highly selective D2 antagonist with additional antidepressant and anxiolytic effects at lower doses [99, 100]. A single, small, randomized, double-blind, placebo-controlled, cross-over study comparing fluvoxamine with sulpiride in children with comorbid TS and OCD reported improvement but did not demonstrate statistically significant effects on tics [98]. Reported improvement in tics has been described in a large case series by Robertson et al. [101, 102] and in a recent open-label study of 189 children aged 3–15 years [101, 102].

Sedation and drowsiness occur relatively commonly. Other side effects include insomnia, agitation, increased appetite, drowsiness, sedation, depression, and endocrine disturbances.

The initial dosage of sulpiride is usually 50–100 mg/day and increased to tic suppression, without exceeding 2–10 mg/kg delivered in divided doses [56].

3.4.3 Amisulpride

There is no significant evidence supporting the efficacy of amisulpride in tic suppression, apart from case reports [103, 104]. Side effects are similar to although possibly milder than those of typical antipsychotics and, because alternative evidence-based treatments are available, its role if any in the treatment of tics remains to be determined.

4 Atypical Antipsychotics

The atypical antipsychotics, also called 'second-generation antipsychotics' were developed in an attempt to circumvent some of the significant side effects associated with the typical antipsychotics, particularly the observed higher rates of drug-induced parkinsonism, acute dystonias, akathisia, and tardive dyskinesia that occur in certain populations treated with these medications. Despite having distinct pharmacological profiles, atypical antipsychotics are all characterized by a relatively greater affinity for 5-HT2 receptors than for D2 receptors. Ten atypical antipsychotics are currently approved by the FDA in the USA: risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole, asenapine, iloperidone, lurasidone, paliperidone, and clozapine. In addition to their primary indications for treating schizophrenia, some have also received FDA approval as augmentation therapy for major depression (aripiprazole, quetiapine, olanzapine/fluoxetine combination), for bipolar depression (quetiapine, olanzapine/fluoxetine combination), for mania (olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone), and for irritability associated with autistic spectrum disorder (risperidone, aripiprazole) [105]. These diverse clinical effects that characterize this class of medications have been explored for their potential benefits in targeting both tics and psychiatric co-morbidities in TS.

The expectation of greater efficacy with fewer side effects has led the atypical antipsychotics to supplant the typical antipsychotics for treatment of a range of indications that are not yet approved by pertinent regulatory agencies, including other forms of psychoses, mood disorders, and autistic spectrum disorders. Treatment of TS is among the most common off-label uses of the atypical antipsychotics [106].

An online questionnaire that solicited information about the use of medications for treatment of TS by members of the European Society for the Study of Tourette Syndrome found that the atypical antipsychotic risperidone was reported as the most commonly prescribed medication for tics, replacing the typical antipsychotics haloperidol and pimozide that were previously the most favored [107]. The atypical antipsychotics are also frequently used off label for treatment of OCD, ADHD, impulse control disorders, and conduct disorders, conditions that are common psychiatric co-morbidities in clinically referred TS [107–109]. Evidence from a review that examined the use of second-generation antipsychotics for non-psychotic disorders in children and adolescents suggests that while these agents share similar efficacy for treatment of mania, extreme mood variability, irritability, aggression, and disruptive behaviors, their individual safety profiles differ significantly, which is a point of particular relevance when selecting among these medications for off-label treatment of TS [106].

It is at least partly the perception of an enhanced safety profile and of potentially broader clinical applications that

has contributed to the sixfold increase between 1993 and 2002 of antipsychotic prescriptions in children and adolescents in the USA, including more prolonged use and more frequent prescription for non-psychotic disorders [110]. Use of atypical antipsychotics in children aged <18 years accounted for 15 % of all antipsychotic usage in the USA in 2004–2005 as compared with only 7 % in 1996–1997 [111, 112]. Similar trends have also been reported in several European countries.

While these agents appear to have reduced risks for extrapyramidal side effects in comparison with the typical antipsychotics, their proclivity for weight gain, sedation, orthostatic hypotension, and adverse metabolic effects associated with type II diabetes and cardiovascular disease raises different but serious concerns [113–115]. Children appear to be at even higher risk than adults for adverse effects associated with atypical antipsychotics, including increased extrapyramidal symptoms and metabolic and endocrine abnormalities [114]. A large retrospective cohort study of youth aged 6–24 years enrolled in the Tennessee Medicaid program in the USA between 1996 and 2007 comparing 28,858 recent antipsychotic initiators with 14,429 matched controls showed a threefold increase risk for new-onset type 2 diabetes apparent within the first year of follow-up and that remained elevated for up to 1 year following discontinuation of atypical antipsychotic use [115]. These risks and others, combined with the absence of strongly compelling data supporting the efficacy of most atypical antipsychotics for treatment of tics underscores their current second-tier designation [57, 59, 116].

Prior to initiating treatment with an atypical antipsychotic, potential risk factors such as a family history of diabetes or cardiovascular disorder, baseline obesity and elevated body mass index (BMI) must be considered. The atypical antipsychotics vary considerably in terms of their risks for weight gain (clozapine, olanzapine > risperidone, quetiapine > paliperidone > aripiprazole, ziprasidone), for hyperprolactinemia (risperidone/paliperidone > haloperidol > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole; risperidone > paliperidone > haloperidol > olanzapine; no significant serum prolactin elevation with aripiprazole, quetiapine, and clozapine), for parkinsonism symptoms (risperidone/paliperidone > olanzapine, aripiprazole, ziprasidone), for orthostasis (clozapine > olanzapine, quetiapine > risperidone), or for sedation (clozapine > olanzapine, quetiapine) [117].

Periodic measurement of weight, BMI, waist circumference, blood pressure, liver function tests, fasting serum lipids and glucose (and serum prolactin when using certain agents such as risperidone, paliperidone, haloperidol, and olanzapine) should be regularly undertaken during treatment with atypical antipsychotics. In cases with persistently elevated serum prolactin that appear otherwise asymptomatic, one must carefully evaluate potential risks versus benefits, and seeking an endocrinology consultation may be appropriate.

4.1 Risperidone

Risperidone is a 5-HT2 receptor antagonist at low doses and functions as a D2 antagonist at high doses. It also has moderate to high affinity for alpha-2 adrenergic, D3, D4, and H1 histamine receptors. Risperidone is considered weakly atypical due to its high incidence of hyperprolactinemia and, at higher doses, its significant extrapyramidal side effects. Among the atypical antipsychotics, only risperidone has 'category A/good' evidence for tic suppression. The use of risperidone for treatment of TS was described in a number of earlier case reports and in open-label studies [118–123]. To date, five randomized, double-blind clinical trials have demonstrated the efficacy of risperidone for the treatment of tics [90, 91, 124–126]. However, because the overall strength of this evidence is not high, and long-term side effects may be significant, risperidone, like the typical antipsychotics haloperidol and pimozide received only 'weak recommendations' in the *Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders* [57].

The first multi-center double-blind trial of risperidone for the treatment of TS used 50 study subjects with TS aged 10–65 years in a 12-week parallel-group study that compared 26 patients treated with risperidone using a mean daily dosage of 3.8 mg with 24 patients treated with pimozide using a mean daily dose of 2.9 mg [90]. Using the Tourette's Symptom Severity Scale (TSSS), the Global Assessment of Functioning (GAF), and the Clinical Global Impressions (CGI) scale as outcome measures, it was found that both active treatments led to significant improvement in global severity ratings of tics, and both agents were well tolerated. Depression, sedation, and fatigue were the most commonly reported side effects in both groups, but fewer subjects in the risperidone group reported extrapyramidal side effects.

An 8-week double-blind, placebo-controlled trial using 48 adolescents and adults compared 24 subjects assigned to risperidone at doses flexibly titrated ranging from 0.5 to 6 mg daily (average daily dose 2.5 mg) with 24 subjects assigned to placebo [124]. Using the global severity score for TSSS, 60.8 % experienced at least a one-point improvement on the seven-point TSSS global scale while on risperidone, compared with only 26.1 % while on placebo. Fatigue and somnolence were the most commonly reported side effects, along with increased tremor and hypokinesia on the ratings of extrapyramidal symptoms, but no differences in reported acute dystonic reactions,

other dyskinesia, parkinsonism, or akathisia were found between risperidone and placebo.

A single-blind placebo lead-in followed by an 8-week randomized double-blind parallel-treatment study compared clonidine (mean dose 0.175 mg daily) with risperidone (mean dose 1.5 mg daily) in 21 youth with TS aged 7–17 years using both the Yale Global Tic Severity Score (YGTSS) total tic and global severity scores as primary outcome measures [125]. Results suggested comparable efficacy with no statistically significant difference between risperidone and clonidine; risperidone produced a reduction of 21 %, while clonidine produced a 26 % reduction in total tic scores. Clinically significant side effects occurred in 33 % of subjects taking risperidone and 58 % of subjects taking clonidine. Sedation was the most common side effect in both groups. Sedation was the most common side effect in study subjects taking clonidine (5.42 %). Stiffness was also a side effect reported among study subjects receiving risperidone (2.2 %).

An 8-week randomized, double-blind, placebo-controlled trial in 34 subjects aged 6–62 years, including 26 children and eight adults demonstrated superiority of risperidone versus placebo for treatment of tics using the total tic score from the YGTSS as a primary outcome measure [127]. Subjects receiving risperidone (mean dose 2.5 mg daily) showed a 32 % YGTSS total tic score reduction compared with a 7 % reduction in the placebo group. Separate analysis of the pediatric group alone showed an effect size of 0.8 for risperidone. Mean weight gain over the 8-week period was 2.8 kg. Generally, risperidone appeared well tolerated, with a low frequency of extrapyramidal side effects.

A randomized, double-blind, cross-over trial in 19 children aged 7–17 years assigned study subjects to treatment with either pimozide (1–4 mg daily) or risperidone (1–4 mg daily) for 4 weeks, followed by a 2-week washout and then active alternate treatment for 4 weeks, and revealed superiority of risperidone (mean dose 2.5 mg daily) versus pimozide (mean dose 2.4 mg daily) assessed by the YGTSS global tic severity scores. However, YGTSS total tic scores were not significantly different between treatment groups [91]. CGI and Tic Symptom Self-Report (TSSR) scores showed a trend towards superiority of risperidone but did not reach statistical significance. Six study subjects failed to complete the trial, including two study subjects from each active treatment who reported worsening of tics. Weight gain that occurred in both groups did not differ statistically between pimozide and risperidone.

Due to its diverse effects on neurotransmission, risperidone may be useful for treating co-morbid symptoms such as aggression or obsessive–compulsive symptoms in children with TS [127]. However, while such strategies appear to be widely employed in the community, strong evidence for treating psychiatric co-morbidities in TS with risperidone is still inadequate and requires additional investigations.

Risperidone behaves more like a typical antipsychotic at higher doses, with side effects that may include sedation, acute dystonic reactions, parkinsonism, akathisia, orthostatic hypotension, hyperprolactinemia with gynecomastia, and significant weight gain.

Doses are initiated at 0.25 mg daily and increased every 5–7 days as indicated to approximately 0.25–4.0 mg daily.

4.2 Aripiprazole

Aripiprazole has a unique mechanism of action among the atypical antipsychotics; it acts as a partial D2-receptor agonist, a partial 5-HT1A agonist, and a partial 5-HT2C agonist. It is also a partial agonist at D3 and D4 receptors. It acts as a D2 antagonist at higher doses and is a high-affinity 5-HT2A receptor antagonist. It is has moderate affinity for histamine and alpha-adrenergic receptors, with negligible activity at cholinergic muscarinic receptors [128, 129].

The use of aripiprazole for treatment of TS has been described in a number of case reports, in case series, in a number of open-label clinical studies, and in retrospective studies [130–144]. During the literature review period, there was a single published multicenter, randomized, double-blind, placebo-controlled 10-week study of aripiprazole in children and adolescents with TS that included 61 children aged 6–18 years. Children were randomized to aripiprazole or placebo; aripiprazole was started at 2.0 mg daily and increased by 5 mg increments every 2 weeks to a maximum of 20 mg daily. Mean dose of aripiprazole was 11 mg daily (range 2–20). Using the change from baseline in YGTSS total tic score as a primary outcome measure, a statistically significant improvement in phonic tics was demonstrated. The effect size was medium (0.62). Nausea, headache, sedation, somnolence, and nasopharyngitis were the most commonly reported side effects. Weight gain (mean 1.6 kg), increased BMI, and increase in waist circumference (mean 1.7 cm) were also significant adverse effects associated with aripiprazole treatment [145].

At this time, while there have been a number of uncontrolled studies exploring aripiprazole for treatment of tics in children and in adults, there is 'category B/fair' evidence to support the efficacy of aripiprazole for the short-term treatment of tics in children only. However, based on regional practices, this agent is highly popular and often selected as a first choice among atypical antipsychotics for treatment of tics. Similar to risperidone, there may be a rationale for using aripiprazole for treatment of combined tics and psychiatric co-morbidities such as ADHD, but the evidence base remains to be established

[139, 145]. There is some evidence that aripiprazole may be safer than pimozide in terms of lower frequency of QTc prolongation, but such studies require further replication [146].

When used for treatment of tics, aripiprazole may be initiated at 1.0 mg and is usually increased in 2.5- to 5-mg increments every 7–14 days. Typical dose ranges from 2 to 30 mg daily.

4.3 Ziprasidone

Ziprasidone, like other atypical antipsychotics, binds 5-HT2A receptors with high affinity and to a relatively less extent also binds D2 receptors. Ziprasidone also binds 5-HT1A and 5-HT2C receptors, is an antagonist of 5-HT2C receptors, and has only moderate affinity for adrenergic alpha and histaminergic H1 receptors, with negligible effects at muscarinic M1 receptors [147]. Ziprasidone showed moderate tic suppression in a single flexibly dosed, double-blind, randomized, placebo-controlled parallel-group study of 28 children aged 7–17 years with TS and chronic tic disorder in doses of 5–40 mg daily. Mean change from baseline to last visit in total tic scores was 34.8 versus 6.9 % in the placebo group [148]. Efficacy was also reported in an open-label study of 24 youths aged 7–16 years with TS [149]. Treatment-emergent effects include somnolence, sedation, and akathisia, but ziprasidone seems not to be associated with any appreciable weight gain. There seems to be higher risk for QT-interval prolongation with ziprasidone than with olanzapine, risperidone, or haloperidol [59, 150, 151].

While there is only 'category B/fair' evidence to support its use, it may be reasonable to consider ziprasidone for TS patients with baseline obesity or who have other risk factors for metabolic syndrome/diabetes. Ziprasidone is started at 5–10 mg daily and gradually increased every week to 10–40 mg daily.

4.4 Olanzapine

Olanzapine is characterized by its high-affinity antagonism at D1, D2, D3, D4, 5-HT2A and 5-HT2C, and muscarinic and histamine H1 receptors. Olanzapine has been reported to decrease tics in case reports and in a few open-label studies in TS, including a 6-week open-label trial in 14 adults; an 8-week flexible-dosing open-label study of ten adults (that included follow-up at 6 months of three study subjects who continued to receive olanzapine); a 6-week, flexible-dosing open-label trial in 12 children with tics; a single-blind, 2-week placebo lead-in 8-week treatment study in ten children; and a very small 52-week double-blind cross-over study in four adults aged 19–40 years with severe tics that compared olanzapine (5–10 mg) and low-dose pimozide (2–4 mg) [152–161].

Although some of these small studies suggest that olanzapine may also be beneficial for addressing co-morbid aggression, there is only 'category C/minimal' current evidence for using olanzapine to treat tics. While there are some encouraging data from uncontrolled studies, clearly more rigorous controlled trials using larger samples are required. Olanzapine too may possibly target both tics and some symptoms of psychiatric co-morbidities, but the current data supporting such efficacy are very scant. Furthermore, the significant weight gain and excessive sedation that are commonly reported adverse effects with olanzapine may limit widespread enthusiasm for treating tics with this medication [157, 158, 161].

Olanzapine is started at 2.5–5.0 mg daily and increased every 5–7 days up to a maximum of 30 mg daily.

4.5 Quetiapine

Quetiapine is a dibenzothiazepine with moderate to low antagonist at 5-HT1A, 5-HT2, D1, D2, and histamine H1 and has low affinity for alpha-1 and alpha-2 adrenergic receptors. Evidence that exists for its effectiveness in TS is based on case reports, a retrospective study of 12 children aged 8–18 years, an open-label study of 12 children aged 8–18 years, an open-label study of 12 children aged 8–16 years, and an open-label study of 12 adults aged 20–52 years [162–168]. Sedation and weight gain are the most common side effects. While this agent merits further study, current evidence to support the efficacy of quetiapine for treatment of tics is 'category C/minimal'.

When used, quetiapine can be initiated at 12.5–25.0 mg daily and increased as tolerated and indicated up to 300–400 mg daily.

4.6 Metoclopromide

Metoclopromide is a robust D2 receptor antagonist and also a mixed 5-HT3 receptor antagonist/5-HT4 receptor agonist that is ineffective for psychosis [169]. It is most commonly used as an antiemetic for a number of medical conditions and is also the most common cause of drug-induced movement disorders, including tardive dyskinesia [170]. Metoclopromide was evaluated in one randomized, double-blind, placebo-controlled trial for treatment of TS in 27 medication-free youths; they showed a 30 % reduction in total tic score compared with 13 % in the placebo arm [171]. Its efficacy was also reported in a small open-label study and case series, including nine children and one adult who were also taking a variety of other tic suppressants [172].

While currently the very limited evidence for using metoclopromide is 'category B/fair', it shares many of the extrapyramidal side effects associated with the typical antipsychotics and therefore has not been extensively used for treatment of tics.

4.7 Clozapine

Clozapine is a dibenzodiazepine with 5-HT2A, 5-HT2C, 5-HT3, and D1 antagonism. Based exclusively on several case reports, clozapine is not believed to be helpful and is thought to actually worsen tics [173, 174]. Given the lack of evidence to support clozapine for treatment of tics, combined with concerns about its significant adverse side effects, including agranulocytosis and metabolic syndrome, clozapine is not currently recommended for treatment of TS [176].

5 Newer Atypical Antipsychotics

Our search did not reveal any significant treatment evidence for tics using the most recently FDA-approved four atypical antipsychotics (i.e. iloperidone, asenapine, lurasidone, paliperidone). Therefore it remains to be determined whether these newer agents offer any significant advantages over the aforementioned atypical antipsychotics. Apart from paliperidone, which may be potentially beneficial to patients who have responded to risperidone but could not tolerate its extrapyramidal side effect, there is no obvious benefit for using these latest agents for tic suppression and there may be possible ill consequences [174].

5.1 Iloperidone

Iloperidone is a member of the piperidinyl-benzisoxazole derivative class of antipsychotic medications. Similar to most of the other second-generation antipsychotics, is a mixed D2/5-HT2A antagonist, with relatively high alpha-2 antagonism and low anti-histaminergic (H1) effects, which may account for its relatively mild sedation and low weight gain. It appears to have less akathisia than ziprasidone but requires slower titration, is associated with orthostatic hypotension, dizziness, dry mouth and dyspepsia, as well as QT prolongation comparable to that of ziprasidone, with more weight gain [175–178].

5.2 Asenapine

Asenapine belongs to the dibenzo-oxepino pyrrole class of atypical antipsychotic medications and strongly antagonizes D1, D2, D3, D4, 5-HT1A, 5-HT2A, 5-HT2C, alpha 1 and alpha 2 receptors, and H1 receptors. It has moderate antagonism at H2 receptors. It has been found to be less effective for schizophrenia than olanzapine. Side effects include sedation, dizziness, somnolence, fatigue, dry mouth, and weight gain [177].

5.3 Lurasidone

Lurasidone belongs to the benzisothiazol class of atypical antipsychotic agents and acts as a D2, 5-HT2A, and 5-HT7 receptor antagonist and 5-HT1A partial agonist. It has minimal affinity for alpha 1 receptors and no affinity for muscarinic M1 and histamine H1 receptors. It is metabolized by CYP3A4. QTc prolongation risk associated with lurasidone is reportedly minimal. Akathisia, psychotic disorders, dystonia, agitation, nausea, vomiting, dizziness, and agitation are also side effects [177].

5.4 Paliperidone

Paliperidone is a member of the benzisoxazole derivative class of atypical agents and is the major active metabolite of risperidone. It is an antagonist at D2 receptors, alpha 1 and alpha 2 adrenergic receptors, and H1-histaminergic receptors. It also has 5-HT2A agonism but no affinity for muscarinic M1 or beta adrenergic receptors. It is believed to have fewer adverse effects than its parent compound and is available in an extended-release preparation. Headache, akathisia, insomnia, somnolence, orthostatic hypotension, and worsening of psychosis are common side effects [177, 179].

6 Conclusions

At this time, best practice guidelines from the USA, Canada, and Europe recommend HRT and CBIT as first-line treatments for impairing tics of moderate severity and in cases where behavioral-responsive psychiatric co-morbidities are present [68, 179–181]. Medication intervention is used in cases of moderate to severe tics causing severe impairment in QOL or in cases where medication-responsive psychiatric co-morbidities are present. Among the atypical antipsychotics currently available in the USA, risperidone (A) is considered to have the most robust evidence for tic treatment efficacy in TS and is usually considered as a first choice among this class, followed by aripiprazole (B), ziprasidone (B), olanzapine (C), and quetiapine (C) (Table 1). Among members of the European community, risperidone and tiapride have received recommendations as first-line treatments for tics, with aripiprazole and pimozide viewed as agents of second choice [56]. Although presently there is only category B evidence supporting its efficacy for tic suppression, aripiprazole has

Table 1 Evidence-based tic treatments using typical and atypical antipsychotics

Category (A) = two or more randomized controlled studies supporting efficacy OR * strong regional experience and practice

Category (B) = At least one randomized controlled study or large case series

Agent	Starting dose (mg/day)	Typical dose range (mg/day)	Category of evidence
Haloperidol	0.25–0.5	2–10	A
Pimozide	0.5–1.0	1–8	A
Fluphenazine	0.5–1.0	0.5–12.0	B
Risperidone	0.25–0.5	0.5–4.0	A
Aripiprazole	1.0–2.5	2–30	A*/B
Ziprasidone	5–10	10–40	B
Tiapride	50–100	100–900	B

become an increasingly popular treatment for TS and is regarded by many as the antipsychotic with the most advantageous efficacy/side effect ratio [182, 183].

However, the evidence base for using atypical antipsychotics for treatment of TS is compromised by the small sample sizes of existing randomized trials, highly variable study subject populations that in some instances included both children and adults of varying ages and of differing co-morbidity status, variable histories and durations of prior treatment exposures, and the use of different measures for assessing treatment outcomes. During the study period 2000–2013 no significant studies investigated the newer atypical antipsychotics asenapine, iloperidone, lurasidone, or paliperidone for treatment of TS, nor were there any double-blind studies that compared different atypical antipsychotics with each other for treatment of tics. While there appears to be some evidence suggesting that the atypical antipsychotics may be most useful for treating TS complicated by co-morbid psychiatric conditions, this clinical impression needs further validation. These current limitations highlight the urgent need for further investigations using improved methodologies with larger sample sizes in both children and in adults with TS.

With improved surveillance and enhanced understanding of potential long-term adverse effects associated with atypical antipsychotics, clinicians will be better equipped to evaluate treatment costs and benefits on a case-by-case basis. While a retrospective study that examined rates of tardive dyskinesia in 521 patients with TS, treated with both typical and atypical antipsychotics, suggests that tardive dyskinesia is very uncommon in the TS population, given the more widespread and longer-term use of these medications in children, these findings need to be replicated using well controlled, prospective studies [184]. It appears likely that the more commonly occurring metabolic side effects associated with the atypical antipsychotics, particularly in children, pose a more serious risk for morbidity. Such concerns underscore the importance of establishing evidence-based efficacy that can justify potentially more significant risks.

A recent meta-analysis of randomized, placebo-controlled trials using both typical and atypical antipsychotics showed a significant effect of active treatments when compared with placebo, but no significant difference in the efficacy of the four antipsychotic agents (i.e. risperidone, pimozide, haloperidol, and ziprasidone) that were evaluated [64]. Thus, it remains to be determined what role atypical antipsychotics should play in the treatment of tics and whether the atypical antipsychotics confer meaningful therapeutic advantages over the older typical antipsychotic medications for treatment of TS. Advances in pharmacogenomics will increasingly help guide pharmacological management by identifying metabolizer status and genetic predictors for treatment response. Future collaborations among clinical sites with expertise in TS that employ high-quality study designs may provide better clarity of the role of atypical antipsychotics for treatment of TS.

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