Contemporary Assessment and Pharmacotherapy of Tourette Syndrome*

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THE TOURETTE SYNDROME PRACTICE PARAMETER WORK GROUP

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INTRODUCTION

Tourette syndrome (TS) is a movement disorder of childhood onset defined by the presence of motor and phonic tics. In addition to tics, TS is frequently associated with obsessive-compulsive symptoms, inattention, impulsive behavior and motor restlessness (Jankovic, 2001a; Leckman, 2002). The tics of TS show a wide spectrum from mild to severe. Impaired adaptive functioning in TS may be related to tics or the presence of associated conditions such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), learning disabilities (LD), and other behavioral difficulties. In many cases, these co-occurring conditions may be of greater clinical importance than the tic symptoms. The impact of TS on family members, educational progress, occupational performance, or peer relationships can be substantial. Thus, clinical management of TS requires attention to severity of tics, associated features, response to coping with a chronic illness and overall functioning.

Accurate diagnosis, including identification of comorbid conditions, is an essential step toward appropriate treatment for patients with TS. Clinical care involves education of the patient and family, advocacy in school and occupational environments, as well as symptom management. In many patients with TS, symptom management requires pharmacotherapy for tics or coexisting conditions. The clinical evidence supporting efficacy and safety for medications used in patients with TS varies. But this evidence offers the best guide to clinical practice and identifies areas for future research. In addition to medication interventions for patients with TS, OCD, and TS accompanied by ADHD, there are behavior treatments with different levels of empirical support (for reviews, see Piacentini and Chang, 2001; Craighead and Craighead, 2001; Foa, Franklin & Moser, 2002; Wells et al., 2000). Other non-pharmacological interventions include psychosurgery and deep brain stimulation (Temel Y, Visser-Vandewalle, 2004). These interventions will not be included in this report.

Description of the Process

This guide to clinical assessment and pharmacotherapy for TS was developed by consensus of the TS Practice Parameter Work Group. Published studies were identified through a Medline search for articles in English between 1983 and 2002 using the key words: Tourette syndrome, Tourette's disorder, Gilles de la Tourette syndrome, and tics. Following the initial literature search in 2002, newly published papers have been reviewed and incorporated into this review as appropriate. To ensure that important studies were not missed, the literature search also included a survey of reviews, including book chapters on the assessment and pharmacological treatment of Tourette syndrome, ADHD and OCD.

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Diagnosis of TS and Assessment of Tics

The initial assessment of a patient referred to the medical setting for a tic disorder includes a review of the early developmental history, medical history, onset and course of tics, and associated problems. A thorough evaluation of how the symptoms affect family, friends, school and workplace is essential for gauging the impact of having TS on the patient. Given the high likelihood of a genetic contribution, a thorough family history of tics, ADHD, obsessive-compulsive symptoms, and chronic medical, psychiatric or neurological conditions is also warranted.

Diagnosis of a tic disorder relies on the history as well as on direct clinical observation (Table 1). The clinical interview should include assessment of:

- Onset and course of symptoms,
- Current severity of motor and phonic tics,
- Presence of premonitory sensations and capacity for tic suppression,
- Overall burden caused by the tics, and
- Treatment approaches implemented to date.

TABLE 1

CLASSIFICATION OF TIC DISORDERS*

TRANSIENT TIC DISORDER, CHRONIC TIC DISORDER, TOURETTE SYNDROME: COMMON FEATURES

- Onset before age 18
- Can not be explained by another medical condition (e.g., substance abuse, Huntington's disease).
- Definite diagnosis: Motor and/or phonic tics must be witnessed by a reliable examiner directly at some point in the illness or viewed on a video recording.
- Diagnosis by history: Tics not witnessed by a reliable examiner, but tics were witnessed by a reliable family member or close friend, and the description of tics is accepted by a reliable examiner.

TOURETTE SYNDROME: DEFINING FEATURES

Both multiple motor and one or more phonic tics have been present at some time during the illness (concurrent motor and phonic tics not required).

- Tics occur many times a day, nearly every day or intermittently throughout a period of more than a year.
- The anatomic location, number, frequency, complexity, type, severity of tics change over time.

CHRONIC MULTIPLE MOTOR TIC OR PHONIC TIC DISORDER: DEFINING FEATURES

Either multiple motor or phonic tics, but not both, have been present at some time during the illness.

- The tics occur many times a day, nearly every day, or intermittently throughout a period of more than a year.
- The anatomic location, number, frequency, complexity, or severity of tics change over time.

TRANSIENT TIC DISORDER: DEFINING FEATURES

Multiple motor and/or phonic tics.

- The tics occur many times a day, nearly every day for at least 2 weeks, but not for longer than 12 consecutive months.

* (Modified from The Tourette Syndrome Classification Group, "Definitions and Classifications of Tic Disorders" *Arch Neurol* 1993; 50:1013-1016 and American Psychiatric Association, *Diagnostic and Statistical Manual,* Fourth Edition-Treatment Revision, 2000.)

One challenge in the assessment of tic disorders is establishing the distinction between tics and behavioral symptoms. Clinician-family dialogue can establish a common vocabulary about the tics, promote a clear description of the symptoms and tease apart tics from compulsions and impulsive behavior. Other diagnostic considerations include:

- There is no laboratory test for the diagnosis of a tic disorder. The diagnosis is based on the enduring presence of motor and vocal tics and exclusion of other explanations. Selective laboratory tests can rule out other medical problems (see Table 2).
- In addition, except for the presence of tics, the standard neurological examination is usually normal.
- Further diagnostic and severity assessments may include: Symptom checklists completed by the patient, parent and/or teacher (Goetz and Kompoliti, 2001; Scahill et al., 1999) and/or clinician-based measures (Leckman et al., 1989; Scahill et al., 1997).
- Analysis of videotaped material (Goetz et al., 1987; Chappell et al., 1994).

Symptom checklists completed by the adolescent or adult patient or by a parent of a younger child may be useful to document the frequency, intensity, and interference of tics or behavior problem. However, these assessments are vulnerable to patient or parent biases regarding symptom classification and completeness. Therefore, tic ratings based on direct interview and observation by an experienced clinician is usually considered the gold standard for diagnosis and measure of tic severity. Although not unique to TS, most patients with TS describe premonitory sensations that precede tics, and report some capacity to suppress their tics for brief periods of time (Kwak, Dat Vuong, & Jankovic, 2003; Leckman, 2002).

Analysis of videotaped material is reliable, but more applicable for research purposes than for clinical use due to the time required to evaluate recorded material (Goetz et al., 1987; Chappell et al., 1994). Even in research settings, a threat to the validity of videotaped ratings is that patients may suppress their tics when they know that they are being observed or videotaped. The use of trained observers in naturalistic settings has been proposed as a way to document tics that often are suppressed during a clinical interview (Nolan, Gadow, and Sverd, 1994). When compared to a clinician rating, however, classroom observation study revealed only a modest correlation (Nolan, Gadow, and Sverd, 1994). This suggests that observers may miss simple motor and low volume vocal tics. The expense of direct classroom observation is another limitation of this strategy for evaluating tic severity.

Rarely are medical tests used to detect or evaluate the severity of tics. However, in rare cases, neurophysiological investigation may be helpful in differentiating tics from seizures, myoclonus and psychogenic movement disorders (Jankovic, 2001b). Electroencephalography (EEG) is not needed unless the patient manifests episodic, paroxysmal alteration of consciousness or other features suggestive of a seizure disorder. Videotelemetry with combined EEG and electromyographic (EMG) recording is not indicated in the evaluation of TS except when attempting to evaluate a sleep disorder (Glaze et al., 1983; Hanna & Jankovic, 2003; Kostanecka-Endress et al., 2003). Although differences in brain volumes and dopamine function between patients with TS and normal controls have been demonstrated in neuroimaging studies (Moriarty et al., 1997; Singer et al., 1997; Peterson et al., 2001; Singer et al., 2002; Peterson et al., 2003), computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission tomography (SPECT) have no current role in the diagnostic evaluation of TS.

Tics can occur in disorders other than TS, and specific diagnostic tests may be required to confirm these other conditions (see Table 2). Examples include: Neuroacanthocytosis, Huntington's disease, Wilson's disease, Sydenham's chorea, head trauma, effects of certain drugs, and developmental disorders (Kumar and Lang, 1997; Jankovic, 2001b).

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a more recently proposed postinfectious, immune-mediated form of TS and OCD. As in Sydenham's chorea, some investigators suggest that tics and obsessive-compulsive symptoms follow Group A b-hemolytic streptococcal infection. Current criteria for PANDAS include presence of tic disorder or OCD, onset of tics prior to puberty, episodic course of tics and obsessive-compulsive symptoms, documented evidence of a recent streptococcal infection, and temporal association between symptom exacerbation and streptococcal pharyngitis (Murphy et al., 2004; Swedo, 2002). Elevated antistreptococcal antibody (ASO) and antideoxyribonuclease B (anti-DNase B) titers are not formally part of the definition and are not sufficient evidence to initiate antibiotic treatment.

Support for the PANDAS concept is mixed. Higher levels of serum antineuronal antibodies (Hallett and Kiessling, 1997; Singer et al., 1998; Morshed et al., 2001) have been observed in TS samples compared to

controls. Several labs have induced tic-like movements in laboratory animals following brain infusion of sera from TS patients with high levels of autoantibodies (Loiselle et al., 2003; Hallett et al., 2000; Morshed et al., 2001;Taylor et al., 2002; Church et al., 2003) but this finding was not replicated in another study (Loiselle et al., 2004). In addition, a placebo-controlled study failed to show the effectiveness of prophylactic penicillin in preventing exacerbations of tic and obsessive-compulsive symptoms (Garvey et al., 1999). Plasma exchange, in which offending autoantibodies are presumably removed, was effective in one study in children with TS and OCD, but it has not been replicated (Perlmutter et al., 1999). Thus, while intriguing, the clinical implications of the autoimmune hypothesis are not yet clear. Throat cultures may be considered in patients with acute onset or significant exacerbations of TS symptoms or in patients complaining of pharyngitis. Treatment with antibiotics should not be initiated without clinical evidence of infection and a positive throat culture. Experimental treatments based on the autoimmune theory, such as plasma exchange, immunoglobulin therapy, or prophylactic antibiotic treatment, should not be undertaken outside of formal clinical trials.

Evaluation and Diagnosis of OCD, ADHD and Learning Disability

OCD

Obsessive-Compulsive Disorder is defined by the presence of recurrent, unwanted worries, thoughts, images or impulses that are difficult to dislodge and/or the presence of repetitive behavior that the person feels compelled to perform. The diagnosis is appropriate when the patient or a close family reports that the obsessions or compulsions involve an average of an hour per day and interfere with daily living to some degree. In most cases, patients agree that the obsessive worries are greater than necessary and that the repetitive habits are excessive, but this awareness may not be present in younger children.

Several quantitative ratings are available for assessment of OCD in patients with TS, including clinician ratings, self-reports, and parent reports. The most commonly used clinician rating is the Yale-Brown Obsessive-Compulsive Scales (YBOCS) (Goodman et al., 1989a; Goodman et al., 1989b) for adults and the companion (CYBOCS) for children and adolescents (Scahill et al., 1997). Among the commonly used self-reports

TABLE 2

SELECTED CONDITIONS WITH SHARED FEATURES OF TS AND LABORATORY TESTS USED FOR THE DIAGNOSIS

DISORDER	SHARED SYMPTOM PICTURE	LABORATORY TEST
Huntington's disease	Chorea, clonic & dystonic tics	> 30 CAG repeat on DNA analysis
Neuroacanthocytosis	Mouth movements, lip biting, dystonias, motor and phonic tics	> 15% red blood cells as acanthocytes, elevated serum creatine kinase
Wilson's disease	Dystonia and dystonic tics	Reduced blood ceruloplasmin, Kayser-Fleisher rings on ophthalmologic examination
Sydenham's chorea	Chorea, tic-like movements	Evidence of a Group A beta-hemolytic streptococcal infection (preceding 2-6 months)
Drug-induced	Motor and phonic tics, mouth movements	Recent history of stimulant drug use, may be positive toxicology screen
Developmental Disorders	Stereotypic movements, Tic-like mannerisms	History of multiple delays in language, socialization, cognition
Head trauma	Motor and phonic tics	Recent history of head trauma (preceding 2 weeks to 6 months)

for obsessive-compulsive symptoms, only the Leyton Obsessional Inventory (Cooper, 1970; Berg et al., 1986; Berg et al., 1988) has population and clinic-based data supporting its reliability and validity. Detailed self-report versions of the YBOCS have also been introduced for evaluating the presence and severity of obsessive-compulsive symptoms (Leckman et al., 1995; Rosenfeld et al., 1992).

ADHD

Attention Deficit Hyperactivity Disorder is characterized by the early childhood onset of an enduring pattern of inattention and/or hyperactivity and impulsive behavior (American Psychiatric Association, 2000). Diagnosis and assessment of ADHD symptom severity in children and adolescents requires information from multiple informants including parents, teachers, and the child. This includes attention to the impact of the child's behavior on family members, peers and school achievement. Clinic observation of the child's activity level, discourse, and ability to maintain focus is also essential; however, some children are able to restrain their behavioral expressions of ADHD during a clinic visit. Thus, the use of parent and teacher rating scales is the most practical way to collect information about the child's behavior across different settings (home and school). Examples of parent and teacher rating scales that have demonstrated reliability and validity for assessing ADHD and measurement of change with treatment include the Parent and Teacher Questionnaires developed by Conners (Goyette et al., 1978); the ADHD Rating Scales (DuPaul et al., 1998); and the SNAP-IV (Swanson et al., 1999). Developed by Swanson and Pelham, the SNAP-IV was used as the primary outcome measure in a large multi-site treatment trial in children with ADHD (MTA Cooperative Group, 1999).

One limitation of these ADHD rating scales is that the scores may be influenced by the parental reading ability or cultural background. A source of measurement error from teachers occurs when the rating of inattention and hyperactivity is confounded by the presence of behavioral problems. Consequently, while these scales are useful in the clinical evaluation of ADHD in children with TS, they should not be used as the only means of making the diagnosis.

One additional method for assessing ADHD is through direct observational methods, either in a simulated or actual classroom setting (Abikoff, Gittelman, and Klein, 1980; Gadow et al., 1995; Swanson, 1998). These observational methods are becoming increasingly common in research settings, but may not be feasible for clinical practice given cost and time constraints.

LEARNING DISABILITIES

Children and adolescents with TS who are failing academically should be considered for psychoeducational testing—especially if the child also has ADHD (Schultz et al., 1998 Como, 2001). A carefully conducted psychoeducational assessment can document the presence of a learning disability or more fine-grained difficulties with planning, organization, visual motor integration and even impulse control. Importantly, even in the absence of a documented learning disability, the presence of tics, obsessive-compulsive symptoms or ADHD may interfere with academic progress. If these symptoms do hinder academic performance, the presence of TS can qualify a student for special educational assistance under current legislation which addresses educational benefits for handicapped citizens.

PHARMACOTHERAPY

General considerations

The decision to use pharmacotherapy in TS begins with identification of target symptoms, which typically fall into one of three categories: tics, attention deficit hyperactivity disorder, or obsessive-compulsive symptoms. This section describes the current evidence for medication treatment for each of these symptom domains. In order to guide clinical practice, the medications used in TS are classified according to their level of empirical support. The following criteria from the International Psychopharmacology Algorithm Project were selected:

CATEGORY A reflects treatments with *Good* supportive evidence for short-term safety and efficacy derived from at least two randomized placebo-controlled trials with positive results;

CATEGORY B corresponds to treatments with *Fair* supportive data as evidenced by at least one positive placebo-controlled study; and

CATEGORY C reflects treatments with *Minimal* supportive evidence such as open-label studies and accumulated clinical experience (Jobson and Potter, 1995).

Tic Symptoms

TRADITIONAL ANTIPSYCHOTICS

The mainstay of treatment for tics has been the potent dopamine (D2) post-synaptic blockers. Several placebo-controlled trials have established the efficacy of the traditional antipsychotics, haloperidol and pimozide,

for the treatment of tics (Ross et al, 1978; Shapiro et al., 1984; Shapiro et al, 1989). Randomized clinical trials comparing pimozide to haloperidol favored haloperidol in one study (Shapiro et al., 1989), but showed equal efficacy in another (Sallee et al., 1997). This study also showed that pimozide was better tolerated at equivalent doses. The dosages used in these studies ranged from 2 to 20 mg per day for haloperidol and from 2 to 48 mg per day for pimozide, with more recent studies at the low end of the range. In contemporary TS clinical practice, doses range from 1 to 5 mg for haloperidol and 2 to 8 for pimozide (Kurlan, 1997; Riddle & Carlson, 2001; Scahill et al., 2000). Though it has not been well studied, fluphenazine is another traditional antipsychotic of the phenothiazine class that is used in clinical practice. A small controlled study of haloperidol, fluphenazine and trifluoperazine found similar benefit for tics. Haloperidol was associated with more sedation and extrapyramidal side effects; fluphenazine was the best tolerated (Borison et al., 1982). At doses ranging from 2 to 15 mg per day in two divided doses, fluphenazine was also effective in 17 of 21 patients in an open-label study that included both children and adults (Goetz et al., 1987). In a naturalistic follow-up of 41 patients treated for at least one year, fluphenazine was reported to be safe and effective without a single occurrence of tardive dyskinesia (Silay, Vuong, & Jankovic, in press).

ATYPICAL ANTIPSYCHOTICS

The atypical antipsychotics include the more selective D2 blocking drugs (tiapride and sulpiride) and drugs with serotonin blocking effects but variable D2 blocking properties such as risperidone, olanzapine, ziprasidone, quetiapine and clozapine. The differences in efficacy of the atypical antipsychotics for the treatment of tics appears to be related to the relative potency of dopamine blockade. For example, clozapine, which is a weak D2 blocker, does not appear to be effective for the treatment of tics (Caine et al., 1979). Since the introduction of the newer atypical antipsychotics, there has been increased interest in them as alternatives to the traditional medications in this class. Following promising results from initial open-label reports, risperidone has been shown to be superior to placebo in two trials (Dion et al., 2002; Scahill et al., 2003) and equally effective to pimozide (Bruggeman et al., 2001) and clonidine (Gaffney et al., 2001). Two open-label trials of olanzapine in a total of 30 adult patients have shown encouraging results for the treatment of tics (Budman et al., 2001; Stamenkovic et al., 2000). The atypical antipsychotic, ziprasidone, has been evaluated in a pilot controlled study in 28 children with TS and was found to be superior to placebo in reducing tics (Sallee et al., 2000).

The specific D2 receptor blocking agents, tiapride and sulpiride, are commonly used for the treatment of tics in Europe, but they are not available in the United States (Eggers et al. 1986; Roberston et al., 1990). In doses ranging from 5 to 6 mg/kg of body weight per day, tiapride was superior to placebo in decreasing tics after six weeks of treatment in 27 children with TS (Eggers et al., 1988). A retrospective study of sulpiride in 63 patients with TS (ages10 to 68 years) reported a positive response in more than 50% of the sample (Robertson et al., 1990). The daily dose of sulpiride ranged from 200 to 1000 mg but several patients were also receiving other medications for tics making it difficult to assess the benefits of sulpiride in reducing tics. Table 3 summarizes the evidence-based category for each antipsychotic medication used in the treatment of tics as well as the typical starting and maintenance doses.

ADVERSE EFFECTS WITH THE ANTIPSYCHOTICS

The traditional antipsychotic drugs are associated with a range of possible neurological side effects including parkinsonism, dystonia, dyskinesia, and akathisia in the short-term, and tardive dyskinesia in the long-term. Other side effects may include cognitive blunting, depression, weight gain, and school phobia (Bruun et al., 1988). The newer antipsychotics appear to have a lower percentage of neurological side effects in the short-term. The relative risk of tardive dyskinesia is presumably lower, but more person-years of exposure to the atypical antipsychotics is required to confirm this speculation. Social phobia was observed in 2 of 12 risperidone treated children with TS in a placebo-controlled study by Scahill and colleagues (Scahill et al., 2003).

An emerging concern with the atypical antipsychotics across several clinical populations is weight gain and related metabolic abnormalities (Allison & Casey, 2001; Martin et al., 2004; Meyer & Koro, 2004). Based on reports from non-TS clinical populations, clozapine appears to associated with highest risk of weight gain followed in order by olanzapine, quetiapine, risperidone and ziprasidone (Allison & Casey, 2001). Another important clinical consideration is the potential for some psychotropic drugs to prolong cardiac conduction times—especially prolonged QTc. Among currently available antipsychotics used in the treatment of tics, pimozide appears to be mostly likely to induce a prolonged QTc, though the occurrence is presumed to be rare in the dose ranges used in the treatment of tics. However, the risk for cardiac conduction abnormalities may increase when pimozide is combined with drugs that inhibit of Cytochrome P450 3A4 isoenzyme

TABLE 3

ANTIPSYCHOTIC DRUGS USED IN THE TREATMENT OF TICS: EMPIRICAL SUPPORT AND DOSING GUIDELINES

MEDICATION	EMPIRICAL SUPPORT	STARTING DOSE (mg)	USUAL DOSE RANGE (mg/day)
Haloperidol	A	0.25 to 0.5	1 to 4
Pimozide	A	0.5 to 1.0	2 to 8
Risperidone	A	0.25 to 0.5	1 to 3
Fluphenazine	B	0.5 to 1.0	1.5 to 10
Tiapride	B	50 to 150	150 to 500
Ziprasidone	B	5 to 10	10 to 80
Olanzapine	C	2.5 to 5.0	2.5 to 12.5
Sulpiride	C	100 to 200	200 to 1000

TABLE 4

NON-ANTIPSYCHOTIC DRUGS USED IN THE TREATMENT OF TICS: EMPIRICAL SUPPORT AND DOSING GUIDELINES

MEDICATION	EMPIRICAL SUPPORT	STARTING DOSE (mg)	USUAL DOSE RANGE (mg/day)
Clonidine	B	0.025 to .05	0.10 to 0.30
Guanfacine	B	0.5 to 1.0	1.0 to 3.0
Pergolide**	B	0.025	0.10 to 0.25
Botulinum toxin	B	30 to 300 units in one or more focal sites	
Tetrabenazine	C	25	37.5 to 150
Baclofen	C	10	40 to 60
Nicotine Patch	C	7	7 to 21
Mecamylamine	C	2.5	2.5 to 7.5
Flutamide	C	250	750***

* doses in mg unless otherwise specified
** second controlled study was superior to placebo only when tic-related impairment was included in the analysis
*** only one controlled study, minimal dose information provided

(e.g., clarithromycin) (Desta et al., 1999). The association of prolonged QTc and risperidone, quetiapine or olanzapine appears to be lower than pimozide (Zareba & Lin, 2003). Approval of ziprasidone by the federal Food and Drug Administration (FDA) was delayed due to the Agency's concerns about QTc prolongation. Detailed examination of the cardiac effects of ziprasidone persuaded the FDA to approve the drug without specific warning about cardiac arrhythmia or recommendations for ECG monitoring (http://www.fda.gov/cder/foi/label). For pimozide, a cardiogram is recommended at baseline, during the dose adjustment phase of pimozide and annually during ongoing treatment (Kurlan, 1997; Scahill et al., 2000; Singer, 2001). Patients and families should be urged to check with treating clinicians before starting a concomitant medication.

NON-ANTIPSYCHOTIC MEDICATIONS

Several non-antipsychotic medications have been tried for the treatment of tics, though most have not been carefully studied (see Table 4). Clonidine is an alpha adrenergic agonist, antihypertensive agent that has been used in the treatment of TS for over 20 years (Cohen, Young, Nathanson, & Shaywitz, 1979). Despite its frequent use, controlled studies with clonidine are few in number and results inconsistent. Side effects include sedation, dry mouth, headache, irritability, and mid-sleep awakening. Blood pressure and pulse should be measured at baseline and monitored during dose adjustment. Specific guidelines for blood pressure monitoring during follow up have not been established. Baseline and follow up electrocardiograms have been recommended in some practice guidelines (American Academy of Child and Adolescent Psychiatry, 1997), but not others (Gutgesell et al., 1999). Although blood pressure is generally not a problem with clonidine, patients and families should be educated about abrupt discontinuation and the potential for rebound increases in blood pressure, tics and anxiety (Leckman et al., 1986). Guanfacine is another alpha-adrenergic antihypertensive that has entered into clinical practice. To date there are two placebo-controlled trials of guanfacine in TS populations (Scahill et al., 2001; Cummings et al., 2002). In these trials, the tic severity of the study subjects was generally mild. Nonetheless, in both studies guanfacine was associated with a 30% decrease in tics from baseline. This level of improvement was significantly better than placebo in one study (Scahill et al., 2001). Perhaps due to the small sample size, guanfacine was not superior to placebo in the other study (Cummings et al., 2002). Whether guanfacine would be effective for the treatment of moderate to severe tics remains unstudied.

Two small controlled studies have evaluated the efficacy of fluoxetine for tics (Kurlan et al., 1993; Scahill et al., 1997). Both found little or no benefit on tic symptoms. Tetrabenazine is a dopamine-depleting drug which acts by inhibiting central vesicular monoamine transporter type 2 (VMAT2). It is not on the market in the United States, and only two open-label studies have been published (Jankovic & Orman, 1988; Jankovic and Beach, 1997). Taken together, these two studies treated 64 patients with TS. Of these, approximately two thirds (n=44) showed a moderate to marked reduction in tics on a clinician-rated global severity measure. Side effects included drowsiness, parkinsonism, depressed mood, insomnia, akathisia, and a few reports of dystonia.

Pergolide is a mixed dopamine agonist with action at both D1 and D2 receptors that is used to enhance dopamine function in Parkinson's disease. Given the putative heightened dopaminergic tone in TS, pergolide is hypothesized to turn off presynaptic synthesis of dopamine and bring about an improvement in tics. In the first open-label study, 24 of 32 subjects reportedly had a positive response (Lipinski et al., 1997). Two double-blind, placebo-controlled studies with pergolide showed superiority to placebo (Gilbert et al., 2000; Gilbert et al., 2002). Interpretion of the results of these studies is hindered by the confounding effects of the crossover design in the first study, and equivocal benefits on tics in the second study. In the crossover study, the observed benefit between active and placebo was dramatically different in the first and second arm of the study. In the second, which used a parallel design, pergolide was no better than placebo on the clinician-rated measure of tic severity. Superiority to placebo was demonstrated only when tic-related impairment was included in the analysis. Case reports of ergot-induced pleural, retroperitoneal or pericardial fibrosis, vasospasm, and cardiotoxicity may limit the use of pergolide in Parkinson's disease and TS. There are no data on non-ergoline dopamine agonists such as pramipexole and ropinirole. Finally, a placebo-controlled study with the partial dopamine agonist, talipexole, showed no positive effect on tics and several subjects complained of dizziness and nausea (Goetz et al., 1994).

Injection of botulinum toxin, which is a standard treatment for dystonia, has been evaluated in 3 open studies and one placebo-controlled trial in TS (Awaad, 1999; Jankovic, 1994; Kwak, Hanna and Jankovic, 2000). The placebo-controlled study showed roughly a 40% difference between active drug and placebo (Marras et al, 2001). Botulinum toxin is injected directly into the selected muscle group involved in the motor

or vocal tic. The frequency and injection repetition rate has not been standardized, but a range of every three to nine months has been employed across most studies. Benefit is generally limited to the anatomical area of the injection. In open-label studies, the presence of premonitory urges predicted a higher likelihood of positive response (Jankovic, 1994; Kwak, Hanna and Jankovic, 2000). The botulinum injections may in fact reduce the premonitory sensations at the injection site (Marras et al., 2001). Adverse effects include transient soreness at the injection site, weakness of the injected muscle and loss of voice volume when the vocal cords are the target of treatment.

Open-label studies of the long-acting benzodiazepine, clonazepam, have been carried out in adults (Gonce and Barbeau, 1977) and adolescents with TS (Steingard et al., 1994), but there are no controlled trials in TS. Clonazepam is unlikely to be effective as a single medication for tics, but it may be useful as an adjunctive treatment. The dose ranges from 0.5 to 4 mg per day given in two or three divided doses. Side effects include sedation, short-term memory problems, ataxia, and disinhibition. These adverse events, especially disinhibition, often limit its use in children (Graae et al., 1994).

Nicotine, administered as a transdermal patch or chewing gum, has been evaluated in open-label studies and one controlled study. These studies provide unconvincing evidence that nicotine can provide an adjunctive benefit for tic suppression when added to ongoing treatment with an antipsychotic (Sanberg, et al., 1989; McConville et al., 1992; Silver et al., 2001). Mecamylamine, a nicotinic receptor antagonist, was no better than placebo in reducing tics (Shytle et al., 2001). The antiandrogen, flutamide, which has theoretical appeal for the treatment of tics, showed little clinical benefit in the only placebo-controlled study (Peterson et al., 1998).

PHARMACOTHERAPY FOR TICS – SUMMARY

Table 5 compares the percent improvement in tics from drugs evaluated in placebo-controlled trials. At first glance, haloperidol appears to be the most effective for reducing tics. However, due to the side effect burden of haloperidol, many clinicians do not use it as a first line for the treatment of tics. When tics are mild, suppressing medication is not usually indicated. For tics of moderate or greater severity, guanfacine or clonidine may be considered as the first line treatment because of the favorable safety margin of these medications. In patients with moderate tics, the 30% decrease in tic severity associated with these medications may be sufficient. Botulinum toxin may be considered in patients with a single but interfering tic. However, treatment guidelines on dose and frequency of injection remain somewhat uncertain. Therefore, for tics in the marked or severe range, more potent medications may be required. Experienced clinicians may vary in their preferences with some favoring the atypical antipsychotics such as risperidone or ziprasidone (Kurlan, 1997; Scahill et al., 2000, Singer, 2001). Others may select pimozide or fluphenazine. Although fluphenazine has not been evaluated in a placebo-controlled trial, in one open study subjects reported a preference to fluphenazine over haloperidol (Goetz et al., 1987).

Treatment of Obsessive-Compulsive Disorder (OCD)

The tricyclic antidepressant, clomipramine, was the first effective drug treatment for OCD. Early studies showed that clompramine was more effective in treating OCD than its close chemical relative, desipramine (Leonard et al., 1989). Unlike desipramine, which is a selective norepinephrine reuptake blocker, clomipramine also has serotonin reuptake blocking properties. Clomipramine

TABLE 5

PERCENT IMPROVEMENT FOR MEDICATIONS SHOWING SUPERIORITY TO PLACEBO FOR THE TREATMENT OF TICS

DRUG	IMPROVEMENT*	DRUG	IMPROVEMENT*
Clonidine	35%	Risperidone	35% to 50%
Guanfacine	30% to 37%	Haloperidol	66%
Pergolide	35%	Pimozide	39% to 58%
Botulinum toxin	40%	Tiapride	44%
Ziprasidone	35%		

*Without adjustment for placebo

has been studied in both adult and pediatric populations and has demonstrated superiority to placebo in several controlled trials (DeVeaugh-Geiss et al., 1990; DeVeaugh-Geiss et al., 1992). These observations led to the evaluation of more selective serotonin reuptake inhibitors (SSRIs). Currently, there are six SSRIs on the market: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram. All but escitalopram have demonstrated efficacy in the treatment of OCD in adults (Tollefson et al., 1994; Griest et al., 1992; Griest et al., 1995; Wheadon et al., 1993; Koponen et al., 1997; Jenike, 2004). Of these, all but citalopram and escitaolpram have also been evaluated in controlled studies in pediatric populations (March et al., 1998; Geller et al., 2001; Riddle et al., 2001; Geller et al., 2003).

Table 6 shows the level of empirical support and typical dose range for clomipramine and the SSRIs in children and adults. A guiding principle in using these medications in pediatric populations is to start with low doses and increase gradually. This is especially true of fluoxetine and citalopram, which have relatively long half-lives. The side effects of the SSRIs include headache, sedation, insomnia, behavioral activation, akathisia, nausea, vomiting, diarrhea, anorexia, and sexual dysfunction. Children appear to be at a higher risk for activation than adults (Riddle et al., 1991; Grados et al., 1999). If these side effects do not subside with continued treatment, the dosage should be reduced. In some cases, the level of activation is unacceptable and discontinuation is required.

Another issue that has emerged with the SSRIs, particularly when used in children and adolescents, is the concern about suicidal ideation and behavior (http://www.fda.gov/cder/drug/antidpressants/SSRI labeling). Although this is not a new issue (King et al., 1991), it has become a matter of increased concern following the release of data from several pediatric depression studies in Britain. In these placebo-controlled studies of children and adolescents with major depression, youngsters who were treated with paroxetine reported a higher frequency of self-injurious thoughts and behavior than the placebo group. Given that these patients were being treated for depression, it is not clear whether these findings apply to children with OCD who are treated with SSRIs.

The clinical management of patients treated with an SSRI or clomipramine also warrants attention to the potential for drug-drug interaction. For example, erythromycin, which potently inhibits the CYP 3A4 isoenzyme, can raise the level of clomipramine to toxic levels (Osterheld, 1996). Common drugs such as cimetadine may inhibit the activity of several CYP isoenzymes resulting in an increased level of the anti-obsessional medication. The SSRIs can also inhibit the action of these hepatic enzyme systems, which could have a clinically significant impact on the levels of the other drugs. Fluoxetine and paroxetine are potent inhibitors of 2D6, which is a common pathway for several drugs including risperidone and haloperidol. Thus, the addition of fluoxetine or paroxetine to ongoing treatment with risperidone or haloperidol will raise the level of the antipsychotic and increase the likelihood of adverse effects. Fluvoxamine is an inhibitor of 3A4, which will predictably raise the level of pimozide or clomipramine.

Special consideration is warranted when discontinuing the shorter acting SSRIs: sertraline, fluvoxamine,

TABLE 6

MEDICATIONS USED IN THE TREATMENT OF OCD: EMPIRICAL SUPPORT AND DOSING GUIDELINES

	EMPIRICAL SUPPORT		STARTING USUAL DOSE	
MEDICATION	CHILD	ADULT	DOSE (mg)	RANGE (mg/day)
Clomipramine	A	A	25 - 50	100 - 250
Fluoxetine	A	A	5 - 20	10 - 60
Sertraline	A	A	25 - 50	50 - 250
Fluvoxamine	A	A	25 - 50	50 - 350
Paroxetine	B	A	5 - 10	10 - 60
Citalopram	B	A	5 - 10	20 - 40

and paroxetine. Several case reports and one prospective study have shown that abrupt discontinuation of these medications is associated with a withdrawal syndrome characterized by flu-like symptoms and depressed mood (Rosenbaum et al., 1993).

It has been estimated that 30% to 40% of OCD patients will show only partial or no response to one or more adequate trials of clomipramine or an SSRI. This observation has led to various combination medication strategies (see Hollander et al., 2002 for a review and the Combined therapy section below).

PHARMACOTHERAPY FOR OCD – SUMMARY

Based on available evidence, there is no compelling evidence to support the selection of any one SSRI or clomipramine as the first line treatment. Fluoxetine, sertraline and fluvoxamine appear to be equal in efficacy, and each has been studied in pediatric samples for disorders other than OCD. Citalopram and paroxetine have each been shown to be effective in adults with OCD, and have some supportive evidence for the treatment of children with OCD as well. As with the other tricyclics, clomipramine can cause a prolongation of the QT interval (Riddle, Geller and Ryan, 1993; Varley, 2001). Clomipramine is also associated with a range of other side effects such as tachycardia, fatigue, dizziness, dry mouth, sweating, tremor, constipation, urinary retention and weight gain. Thus, clomipramine is generally not the drug of first choice for OCD. On the other hand, in light of its pharmacological differences from the SSRIs, it should be considered when a patient has failed two SSRI trials (Expert Consensus Panel, 1997). Case reports suggest that intravenous administration of clomipramine may be useful in refractory OCD (Warneke et al., 1984; Koran et al., 1998; Sallee et al., 1998).

Treatment of ADHD

The stimulants are the first line agents for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (Greenhill et al., 1996; MTA Cooperative Group, 1999). Stimulants fail in 10% to 20% of ADHD cases (Elia, et al., 1991) either due to lack of efficacy or adverse effects including tics (Erenberg et al., 1985; Golden, 1974; Lowe et al., 1982; Lipkin et al., 1994; Riddle et al., 1995; Varley et al., 2001). The emergence of tics in some children with ADHD has also been documented in two placebo-controlled trials that excluded subjects with tic disorders (Barkley, et al., 1992; Borcherding et al., 1990). The results of these studies indicate that stimulants may induce tics in some children without pre-existing tics and lead to discontinuation.

In contrast to these clinical observations, three placebo-controlled studies have evaluated the short-term effects of stimulants on children with ADHD and tic disorders (Castellanos et al., 1997; Gadow et al., 1995; Tourette Syndrome Study Group, 2002). Two naturalistic studies have examined the long-term effects of stimulants in TS (Gadow et al., 1999; Law and Schachar, 1999). The findings of these studies suggest that children with ADHD and tics do not invariably manifest an increase in tics upon exposure to stimulant medication, though an exacerbation in tics may occur in some cases.

Drugs from several classes have been used as alternatives to the stimulants in children or adults with ADHD. These include the alpha-2 agonists, clonidine and guanfacine; the tricyclic antidepressants, desipramine and nortriptyline; the newer antidepressants, bupropion, venlafaxine and atomoxetine; the beta blocker, pindolol; and the selective monoamine oxidase inhibitor, deprenyl. Table 7 shows the level of empirical support for these medications in the treatment of ADHD.

Despite the positive results of three placebo-controlled studies (Biederman et al., 1989; Singer et al., 1995; Spencer et al., 2002), many clinicians are reluctant to use desipramine due to concerns about prolonged cardiac conduction times (Riddle, Geller & Ryan, 1993; Varley, 2001). Nortriptyline, also a tricyclic, has been less-well studied in ADHD. In doses ranging from 50 to 200 mg/day given in divided doses, bupropion was generally well tolerated and equal to methylphenidate in one study (Barrickman et al., 1995) and superior to placebo (Casat, et al., 1987; Casat et al., 1989; Conners et al., 1996). Case reports have suggested that bupropion may accentuate tic symptoms (Spencer et al., 1993). Although presumably rare, bupropion may increase the risk of seizures in vulnerable individuals (Belson & Kellly, 2002).

The beta blocker, pindolol, was evaluated in one controlled study that compared it to placebo and methylphenidate. At a dose of 20 mg twice daily, pindolol effectively reduced ADHD symptoms, but two subjects developed nightmares and hallucinations raising questions about the usefulness of pindolol in ADHD at this dose level.

Deprenyl, which is a selective monoamine oxidase inhibitor that enhances dopaminergic function, is used in the treatment of Parkinson's disease. One open-label study (Jankovic et al., 1994) and one placebo-controlled crossover study (Feigin et al., 1996) suggest that deprenyl may be effective for the treatment of ADHD in children with TS without increasing tics. Clear interpretation of the results from the crossover study is hampered by the apparent order effect. At low doses

TABLE 7

NON-STIMULANTS USED IN THE TREATMENT OF ADHD: EMPIRICAL SUPPORT AND DOSING GUIDELINES

MEDICATION	EMPIRICAL SUPPORT	STARTING DOSE (mg)	USUAL DOSE RANGE (mg/day)
Desipramine	A	10 to 25	50 to 150
Nortriptyline	C	10 to 25	20 to 100
Clonidine	B	0.025 to 0.05	0.15 to 0.25
Guanfacine	B	0.25 to 0.5	1.5 to 3.5
Bupropion	A	25 to 50	75 to150
Deprenyl	B	5.0	5 to15
Venlafaxine	B*	37.5	75 to 200
Atomoxetine	A	10 to 20	40 to 80
Pindolol	B	5-10	15 to 40

*data in pediatric populations are limited

(5 to 10 mg per day), deprenyl does not require dietary restrictions. However, data on drug interaction in non-Parkinson populations are limited.

Although clonidine has been used for over 20 years in the treatment of TS, there are few placebo-controlled studies evaluating the effects on ADHD symptoms. Ten children with tic disorders and ADHD were studied in a blinded, placebo-controlled withdrawal trial and a 37% increase in the core symptoms of ADHD was observed following withdrawal from clonidine (Hunt et al., 1985). In a crossover study of 34 subjects with ADHD and TS, Singer and colleagues (1995) compared clonidine to desipramine and placebo and found that clonidine was no better than placebo after six weeks of treatment. Connor and colleagues randomly assigned 24 subjects to receive clonidine only, clonidine plus methylphenidate or methylphenidate alone (N=8 in each group) in an open-label study. All groups showed improvement in ADHD symptoms after 3 months of treatment (Connor et al., 2000).

The Tourette Syndrome Study Group (2002) conducted a multi-site, randomized trial with four groups including clonidine alone, methylphenidate alone, clonidine and methylphenidate, and placebo. The 136 subjects with a tic disorder and ADHD ranged from 7 to 14 years. The clonidine alone group showed a 40% improvement on the primary teacher rating compared to 38% for the methylphenidate group and 59% for combined treatment. The stimulant doses used were slightly less than most contemporary methylphenidate studies (e.g., MTA Cooperative Group, 1999). This may explain the modest improvement observed in the methylphenidate alone group (Rapport et al., 1994). Approximately a quarter of the subjects in the clonidine and methylphenidate only groups showed an increase in tics, which was only slightly higher than the rate observed in the placebo group. In general, the tics improved across all treatment groups.

Guanfacine has been evaluated in three open-label studies and one randomized controlled trial in children and adolescents with ADHD (Hunt, Arnsten, & Asbell, 1995; Horrigan & Barnhill, 1995; Chappell et al., 1995; Scahill et al., 2001). In the double-blind study involving 34 youngsters with ADHD and a tic disorder, guanfacine was significantly better than placebo on teacher ratings of classroom behavior (Scahill et al., 2001). At doses ranging from 1.5 mg to 4 mg per day in three divided doses (in most cases), guanfacine was well tolerated across these four studies with mild, transient sedation being the most common adverse effect. Other adverse effects included constipation and mid-sleep awakening. As noted above, guanfacine was also evaluated in a second placebo-controlled study by Cummings and colleagues (2002). This study did not require that there be

subjects with ADHD, and baseline ratings varied widely from the normal to the pathological range. In addition, the Cummings et al. study (2002) included only 12 subjects per group. The heterogeneity in the sample and the small sample size make it difficult to interpret the findings of this study on ADHD symptoms.

PHARMACOTHERAPY OF ADHD IN CHILDREN AND ADOLESCENTS WITH TS – SUMMARY

Observational data accumulated over three decades suggest that the stimulants may worsen tics in some children and adolescents with ADHD. Well established animal models also support the view that stimulant exposure can induce stereotypic behavior (Solanto, Arnsten, & Castellanos, 2001). Nonetheless, several placebo-controlled trials have shown conclusively that stimulant-induced exacerbation of tics is not an inevitable outcome for children with TS and ADHD. Indeed, increased tics following stimulant exposure may occur only in a minority of cases with these combined conditions (TS Study Group, 2002). Given the added disability attributable to ADHD in children and adolescents with TS (Spencer et al., 2001; Sukhodolsky et al., 2003), aggressive treatment of ADHD in these cases is warranted. Following a review of the alternatives and the family's preference, treatment may start with an alpha 2 agonist (guanfacine or clonidine) or stimulant medication. Combined treatment with an alpha 2 agonist and stimulant may produce better outcomes than either treatment alone.

Atomoxetine is a selective norepinephrine reuptake inhibitor that has shown superiority to placebo in studies of children with ADHD not accompanied by tics. In contrast to desipramine, which is also a selective norepinephrine inhibitor, atomoxetine appears unlikely to induce cardiac arrhythmia. In a pair of double-blind, placebo-controlled studies involving 467 children with ADHD between the ages of 6 and 18 years, (Michelson et al., 2001, 2003) showed that atomoxetine at doses ranging from 1.3 to 1.8 mg per kg of body weight per day were superior to placebo on a measure of ADHD symptoms. The group receiving 0.5 mg/kg dose, however, fared no better than placebo (Michelson et al., 2001). The manufacturer suggests giving a single morning dose beginning with roughly 0.5 mg/kg per day followed by gradual increases to 1.0 to 1.5 mg/kg per day. However, to deal with adverse effects and maintain therapeutic benefit across the entire day, atomoxetine may be given in two divided doses. Common adverse effects with atomoxetine include nausea, vomiting, loss of appetite and insomnia. Other non-stimulants including bupropion, pindolol and deprenyl could be considered third line treatments.

Mood and Anxiety Disorders

The high prevalence of OCD and ADHD in TS populations is well documented. Less well documented, though commonly seen in clinical samples, are comorbid depression, bipolar disorder, generalized anxiety disorder and separation anxiety (Berthier, Kulisevsky et al., 1998; Comings & Comings, 1987a; Comings & Comings, 1987b; Comings & Comings, 1990; Coffey et al., 2000; Coffey & Park, 1997; Kerbeshian, Burd, & Klug, 1995). The high rates of these comorbid conditions may reflect spurious associations due to ascertainment bias, TS genetic pleiotropy (Comings, 1995), TS phenocopies (Palumbo, Maughan, & Kurlan, 1997) or secondary problems caused by the burden of having a chronic neuropsychiatric disorder (King & Scahill, 2001).

Despite the uncertainties about whether any or all of these comorbid conditions are etiologically related to TS, there is no evidence that TS patients with one or more of these comorbid conditions will respond differently than patients without TS. Thus, pharmacotherapy for comorbid Bipolar Disorder, Depression, Anxiety should proceed according to current practice.

Several consensus documents for both adults and children have been published and should be consulted for a detailed review of practice guidelines (Fava et al., 2003; Emslie & Mayes, 2001; Sachs, 2003; Expert Consensus, 1996; Gorman, 2003; http://www.fda.gov/cder/drug/antidpressants/SSRI labeling, 2004).

Aggression and Explosive Behavior

The frequency of aggression in patients with TS ranges from 26% to 75% depending on the clinic-ascertained samples (Budman et al., 2000; Moldofsky et al., 1974; Stefl 1984; Sukhodolsky et al., 2003). A variety of medications including anticonvulsants, lithium, propranolol, psychostimulants, clonidine, and antipsychotics have been used clinically in TS patients, but there are no controlled studies. A recent open-label trial of paroxetine (average dose 33.3 mg per day) in 45 patients with TS and explosive anger outbursts showed a significant decrease in both intensity and frequency of outbursts in 76% (N=34). Four subjects reported worsening of symptoms (Budman et al., 1998). Aggression and explosive behavior have been evaluated in placebo-controlled trials in other clinical populations including risperidone in children with autism (RUPP Autism Network, 2002); risperidone in children with sub-average intelligence and disruptive behavior (Aman et al., 2002); valproate in adolescents with average intelligence and disruptive behavior (Donovan et al., 2000). This is an area that warrants further study with both pharmacological and psychosocial interventions.

Combined Pharmacotherapy

There are few reports of combined pharmacotherapies in TS patients. Nonetheless, the use of multiple medications is probably quite common in clinical practice as evidenced by several open-label reports (Freeman et al., 2000; Gadow et al., 1999; Lombroso et al., 1995; Robertson et al., 1990) and a controlled study in which fluoxetine was added to existing medication treatment in children with TS and obsessive-compulsive symptoms (Kurlan et al., 1993). The primary reasons that clinicians resort to combined pharmacotherapy are to enhance effectiveness of the first medication (Tourette Syndrome Study Group, 2001), to treat a comorbid condition, or to manage side effects of the first medication. For example, although controversial, case reports suggest that the addition of clonidine can be used to offset the sleep problems associated with stimulant medication (Steingard et al., 1994) or the use of beta-blockers can alleviate antipsychotic-induced akathisia in TS (Chandler, 1990).

Two controlled studies in adults with refractory OCD illustrate the use of combined therapy to enhance an incomplete response to monotherapy. The first study compared the addition of either haloperidol or placebo to a stable dose of an SSRI in adults with refractory OCD (McDougle et al., 1994). In that study, haloperidol proved significantly better than placebo as an adjunct to an SSRI for OCD. Moreover, patients with a history of tics were more likely to benefit from the addition of this antipsychotic. A subsequent study by the same group evaluated the addition of risperidone compared to placebo in adults with refractory OCD. Risperidone was also effective as an adjunctive therapy, but a history of tics was not predictive of positive response (McDougle et al., 2000).

The use of combined drug therapy is tempered by the lack of data and the potential for drug-drug interaction. As noted previously, inhibition of hepatic enzyme systems by SSRIs may have a dramatic effect on blood level of the other medication in use. As evidenced by case reports of adding fluvoxamine to clomipramine in a child with severe OCD, clinicians may try to exploit this interaction for clinical benefit (Rosenberg, 1998), but this strategy has not been carefully studied. As noted previously, inhibition of hepatic metabolism has also been implicated in serious adverse events including death via cardiotoxic effects (Desta et al., 1999).

In conclusion, the decision to use medication for TS should follow careful assessment and identification of target symptoms that are interfering in the patient's quality of life. The selection of medication is based on available evidence and careful balance of the risks and benefits. For example, given the risks associated with antipsychotic medications, it would not be appropriate to use this class of medications in the treatment of mild tics. Selective serotonin reuptake inhibitors (SSRIs) are first line agents for obsessive-compulsive disorder, but the magnitude of response is typically modest. Given this modest response, anti-obsessional medication is indicated when symptom severity is moderate or greater. The disability associated with ADHD mandates medication treatment regardless of tic severity. Medications are unlikely to eliminate all symptoms in the targeted area. Thus, clinicians should remind patients and families that high levels of medication may tip the risk/benefit equation in a negative direction.

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