Treatment options for Tourette syndrome

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ABSTRACT

Tics are commonly observed in children, and Tourette Syndrome (TS) represents one end of the spectrum of tic disorders. This article reviews the treatment options for TS.

KEYWORDS

Tourette Syndrome (TS), tic, treatment

INTRODUCTION

First described by George Gilles de la Tourette in 1885, Tourette Syndrome (TS) represents one end of the spectrum of tic disorders. Studies have shown that tics are common in children with an incidence of up to 20% in a classroom setting, while the prevalence of TS causing impairment is 1-10 per 1000.[1,2] The occurrence of TS between boys and girls shows a male predominance of 5:1, with a range of 1:6 to 10:1.[2] Individuals with TS commonly present with comorbidities, namely, obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), learning disorders, anxiety, depression, rage, and aggression.

A tic is described as a sudden, rapid, recurrent, involuntary or semi-voluntary motor movement or vocalization. Examples of motor tics are eye blinking, lip licking, facial twitching, shoulder shrugging, squatting, and twirling, while vocal tics can present as clicks, grunts, barking, yelping, throat clearing, echolalia, coprolalia, and palilalia.[3]

The DSM-IV Criteria for the diagnosis of TS are: 1) multiple motor tics and one or more vocal tics must have been present at some time over the course of the illness, but not necessarily concurrently; 2) the tics must occur many times a day nearly every day or intermittently over a period of more than 1 year, during which time there must not have been a tic-free period of more than three consecutive months; 3) the age of onset is younger than 18 years; and 4) the disturbance must not be due to the direct physiologic effects of a substance or a general medical condition.[4]

CO-MORBIDITIES ASSOCIATED WITH TS

Obsessive-compulsive behaviors in individuals with TS is reported to have a 20% to 89% occurrence rate.[5] This may make it difficult to separate major tics from compulsions. While compulsions may commence several years after the initial diagnosis of tics, they may persist past the resolution of the tics.

ADHD is another comorbidity that is common in patients with TS, occurring in an average of 50% of patients (range 21-90%).[5] ADHD usually presents at age 4-5 years and often precedes the onset of tics. Patients with tics and ADHD symptoms can also be associated with increased disruptive behavior, peer rejection and emotional problems.

The learning difficulties that are seen in patients with TS and other comorbidities stem mainly from the lack of planning and decision-making abilities rather than any deficit in intellectual capacity.[5, 6] The inability of the child to cope with their tics may lead to a decline in grades as well as other disciplinary problems.

TREATMENT OPTIONS BY CLASS

Choosing the proper treatment of TS can be controversial, since the practitioner needs to weigh the higher effectiveness of dopamine-2 receptor antagonists with the less effective yet safer α-2 adrenergic agonists. As with all medication therapies, patient needs have to be considered in choosing the proper medication. See Table 1.

Generally, the first line of treatment for TS is the α -2 adrenergic agonist drug class, clonidine and guanfacine, while second line is the dopamine 2 receptor antagonist class of medications. The options for these two classes are explained below.

A -2 AGONISTS

Clonidine

Clonidine is often prescribed as an initial drug in patients with mild tics, due to its relatively benign side effect profile. It is also a good choice for patients with behavior problems, such as hyperactivity, impulsiveness, and inattentiveness.[7] Clonidine is an imidazole derivative and α -2 agonist that acts selectively at the presynaptic level in lower doses, primarily activating presynaptic autoreceptors in the locus ceruleus, thereby reducing norepinephrine release and turnover.

Table 1. Treatment options for Tourette Syndrome[7,16]

Class	Drug	Starting Dose	Adjusting Dose	Max Dose	Adverse Effects
α-2 Agonist	Clonidine (CATAPRES, KAPVAY)	0.05 mg at bedtime	Increase 0.05 mg/day Q 7 days	0.3 mg per day	Sedation, Hypotension
	Guanfacine (INTUNIV, TENEX)	0.5 mg at bedtime	Increase by 0.5 mg Q 7 days	4 mg in 2-3 divided doses	Dizziness, Drowsiness
Antiepileptic	Topiramate (TOPAMAX)	25 mg/day	Mean effective dose 118 mg	300 mg per day	Memory impairment, Confusion, Paresthesias
GABAb Receptor Agonist	Baclofen (LIORESAL, GABLFEN)	5-10 mg, 3 times a day	Titrate slowly	60 mg per day	Somnolence, Dizziness, Confusion, Headache
Conventional Antipsychotics	Haloperidol (HALDOL)	0.25-0.5 mg at bedtime	Increase weekly by 0.25-0.5 mg	5 mg per day	Drowsiness, Anxiety, Extrapyramidal reactions
	Pimozide (ORAP)	0.5-1 mg at bedtime	Increase every 5-7 days	Do not exceed 10 mg per day	Sedation, Dysphoria, Extrapyramidal reactions
	Fluphenazine (PROLIXIN, PERMITIL)	0.5-1 mg at bedtime	Increase gradually every week	5 mg per day	Drowsiness, Anxiety, Extrapyramidal reactions
Second Generation Antipsychotic	Risperidone (RISPERDAL)	0.25-0.5 mg at bedtime	Gradually titrate up to 2-4 mg/day		Hypotension, Somnolence, Weight gain, Caution: QTc prolongation

Several trials have been conducted with clonidine compared with placebo,[8] with neuroleptics,[9] and with anti-seizure medications.[10] In a single-blind, placebo controlled trial, 46% of patients exhibited an improvement in motor and vocal tics.[8,11] In a double-blind, crossover study comparing clonidine and levetiracetam found that the total tic score improved significantly (p=0.013) with clonidine (25.2 to 21.8) than levetiracetam (22.7 to 23.6).[10,11]

Guanfacine

Guanfacine is a longer-acting α -2 agonist thought to be more selective for receptors in the prefrontal cortex. Two placebo-controlled trials of guanfacine have been done in children with tics and TS.[4] One trial showed a statistically significant improvement in tics compared with placebo with a 31% decrease in total tic score in the guanfacine group compared with 0% in the placebo group (p=0.05).[12] This same trial studied the effect of guanfacine on the ADHD Rating Scale and found a 37% drop in total score compared with an 8% drop in the placebo group, showing a statistically significant result of p<0.001.[12] These results demonstrate a positive treatment option of guanfacine for patients with co-morbid tics and ADHD, in addition to causing less sedation and less hypotensive effect than clonidine.

ANTIPSYCHOTICS

Haloperidol

Haloperidol is a conventional antipsychotic with D2 receptor antagonism, which is used in the treatment of tics. Haloperidol was the most commonly used antipsychotic in TS, prior to the development of second-generation antipsychotics. Although it is a widely used medication, it also has a higher observed frequency of side effects, such as sedation and extrapyramidal symptoms, than other agents in this category.

Fluphenazine

Fluphenazine has a similar mechanism of action to haloperidol. Studies have shown that fluphenazine is an effective agent for suppressing tics and may have fewer side effects than other neuroleptics.[4]

Pimozide

Pimozide, a diphenylbutylperidine conventional antipsychotic, is a potent centrally-acting D2 antagonist which also blocks calcium channels.[5,7] In one double-blind, placebo controlled, double crossover study, pimozide has been shown to be as effective as haloperidol in suppressing tics, with less side effects, with haloperidol exhibiting a 3-fold higher frequency of extrapyramidal effects.[13] However, pimozide must be used with caution due to possible cardiovascular side effects, which include orthostatic hypotension, syncope, and electrocardiogram (ECG) abnormalities. The most concerning of ECG

abnormalities is QTc prolongation.[7] In a study of pimozide's effect on QTc prolongation, it was found to increase it by 6.2% or a mean value of 24.3±15.9 ms. In one case, a patient who had a good response to pimozide had a QTc prolongation of 463 ms after 6 months of treatment.[7] Prior to beginning pimozide therapy, ECG monitoring should be conducted prior to and during treatment.

Risperidone

Risperidone, a second generation antipsychotic (SGA), is a highly potent serotonin and dopamine receptor antagonist, which binds to 5-HT_2-receptors at low doses while higher doses is a potent D2 antagonist. Studies have suggested that risperidone would be an effective therapy option for some patients with TS.[5,7] One of the most significant adverse effects of SGAs is weight gain. In a formal meta-analysis of SGAs in pediatric patients, risperidone was found to have a 1.76 kg increase in weight.[14] Weight gain is always a concern in patients due to the increased risk of developing metabolic syndrome, which could eventually lead to diabetes and cardiovascular disease.

Hyperprolactinemia was a significant dose dependent adverse effect found in 2 trials, and 4 studies found significant increases of prolactin with risperidone therapy.[15] However, these studies were not conducted in patients with Tourette Syndrome.

SUMMARY

Patients with TS need to be fully assessed prior to beginning a tic suppression therapy. This article has highlighted the medications that are most commonly prescribed for this condition. Due to the more favorable side effect profile of α-2 adrenergic agonists, it would be prudent to begin therapy with either clonidine or guanfacine as a first line treatment. Choosing between the two will depend on the patient's symptoms and need for a shorter (clonidine) or longer (guanfacine) acting agent, as well as their side effect profile. With respect to the side effect profile, guanfacine would be a good choice for a first time medication as it seems to have a lower incidence of sedation and orthostatic hypotension.

However, if tics are more severe, patients do not respond to the above drugs, and side effects are taken into consideration, conventional or second generation antipsychotics may be prescribed. Among the choices of antipsychotics, the one with the most favorable efficacy and safety balance would be risperidone, with special attention to monitoring for weight gain. The ultimate goal for treatment in TS should be to find a balance between tic suppression and minimizing any complications caused by co-morbidities and side effects.

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