Rev Bras Psiquiatr 2000;22(4):189-93

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# Contemporary approaches to the treatment of tics in Tourette syndrome

## Abordagem contemporânea para o tratamento de tiques na síndrome de Tourette

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**Abstract** Tic disorders are relatively common disorders of childhood. The tics range from mild to severe and show a fluctuating course over time. Moreover, in most cases, the tics tend to decline in number and frequency by early adulthood. Given this range of severity and natural history, tics may not require treatment. When tics are frequent, forceful and cause interference in everyday life, medication is indicated. Several medications have been used in the treatment of tics, but only a few have been carefully studied. This paper reviews the range of medications that have been used in the treatment of tics and provides practical information about clinical management of children and adolescents with tic disorders.

**Keywords** Tourette syndrome. Pediatrics. Drug treatment.

**Resumo** Os transtornos coréicos são relativamente comuns durante a infância. Os automatismos apresentam graus variáveis, de leve a grave, e flutuam ao longo do tempo. Além disso, na maioria dos casos, os automatismos tendem a diminuir em número e freqüência no início da vida adulta. Dada a gravidade variável e sua história natural, muitas vezes não é necessário tratar os automatismos. O tratamento medicamentoso está indicado quando as manifestações são freqüentes, vigorosas e interferem com a vida diária. Vários medicamentos têm sido usados no tratamento dos automatismos, mas apenas alguns deles vêm sendo estudados a fundo. O artigo revisa a variedade de medicamentos que vêm sendo usados no tratamento dos automatismos e proporciona informações práticas para o tratamento clínico de crianças e adolescentes com transtornos coréicos.

**Descritores** Síndrome de Tourette. Pediatria. Tratamento medicamentoso.

## Introduction

Tourette syndrome (TS) is defined by the presence of both motor and phonic tics that have persisted for at least a year. A diagnosis of chronic tic disorder (CTD) is made when either motor or phonic tics (but not both) have been present for at least a year.[1] These tic disorders exhibit a wide range of severity from mild to marked across patients. Within patients, the tics of CTD and TS show a fluctuating course with general tendency to worsen after onset and then decline by early adulthood.[2] In addition to tics, CTD and TS may be complicated by obsessions and compulsions, impulsiveness, overactivity, inattention, defiance, anxiety, mood instability, low frustration tolerance, angry outbursts and aggression.[3-6] It is not clear whether any or all of these features are part of the tic disorder phenotype. In clinical populations, however, the presence of one or more of these comorbid features may be the reason for seeking treatment and can have an important impact on treatment planning. The purpose of this chapter is to review current approaches to the treatment of tics in children and adolescents with tic disorders.

For reviews on the treatment of obsessive-compulsive disorder and non-stimulant treatment for comorbid attention deficit hyperactivity disorder see Grados et al, 1999; Scahill et al, 2000.[7,8]

### Treatment of tics

Several medications have been used for the treatment of tics. Of these, only a few have been evaluated in placebo-controlled studies, several other medications have at least open-label data supporting their use for reducing tics.

Last version received on 11/8/2000. Approved on 21/8/2000.
This work has been supported by the following USPHS grants: MH-70009, MH-30929, MH-49351, HD-03008, MO1-RR-06022 and by a grant from the Tourette Syndrome Association.
Inexistent conflict of interests.

***Typical neuroleptics***

Haloperidol and pimozide are the best studied and the most effective medications for the treatment of tics. Head to head comparisons suggest that these two drugs are equally effective, though haloperidol is associated with greater side effect burden.[9-13] It is worth noting that the older studies used much higher dosages of these medications than are currently used in practice. For example, Shapiro et al[13] cited a range of 2 mg to 20 mg per day for haloperidol and a range of 2 mg to 48 mg per day for pimozide. In current clinical practice, however, the dose range is typically 1 mg to 5 mg per day for haloperidol and 2 mg to 10 mg per day for pimozide.[8,14] In a recent cross-over study of 22 youngster, Sallee et al used 3.4 mg/day of pimozide and 3.5 mg/day of haloperidol.[12] Pimozide produced a 40% improvement in tics from baseline compared to 27% for haloperidol. Haloperidol was associated with higher frequency of extrapyramidal symptoms, depression and anxiety. At these doses, haloperidol was associated with a three-fold higher frequency of dose-limiting side effects (9 of 22 compared to 3 of 22 for pimozide). The findings of this study suggest that dose range of haloperidol is narrower than pimozide. Given its potency as a postsynaptic D2 receptor blocker, haloperidol is often effective at low doses.

Although side effects may be more frequent with haloperidol compared to pimozide, the side effect profiles are similar. Typical side effects include: sedation, dysphoria, cognitive dulling, and extrapyramidal symptoms (dystonia, dyskinesia, akathisia).[15] Haloperidol is usually started at 0.25 mg or 0.5 mg in the evening with the addition of 0.25 mg or 0.5 mg in the morning 4 to 7 days later. The total daily dose can be raised every 4 to 7 days alternating between the morning and evening dose as tolerated to a total daily dose of 0.75 mg to 2.0 mg. The therapeutic effects and adverse responses should be monitored closely in the dose adjustment phase. The use of low starting dose and a slow upward adjustment protects against acute dystonic reactions, though parents should be educated about this possibility. If dystonic reactions occur, anti-parkinsonian agents such as benztropine should be used. Other adverse effects can often be managed by reducing the dose. Beta blockers such as propranolol or pindolol may be useful to treat akathisia.[16]

Pimozide is only available in a 2 mg tablet. The typical starting dose is 0.5 mg in young children or 1mg per day in larger children. Because pimozide has a long half-life, a dose of 5mg can be accomplished by giving 1/2 tablet every other day or by cutting the tablet into quarters. The dosage may be increased every 4 to 7 days in 0.5 mg to 1mg increments over a 2 to 4 week period. The total dose in children typically ranges from 2 mg to 4 mg per day given in divided doses. Although rare at low doses, pimozide has a potential for QT prolongation.[17] Therefore, electrocardiograms at baseline, during dose adjustment and annually during maintenance therapy are recommended. Concomitant treatment with drugs that inhibit the cytochrome P450 3A4 isoenzyme (e.g. erythromycin, ketoconazole, cisapride) should be avoided because of the predictable and potentially dangerous rise in pimozide serum levels at the same oral dose.[18]

The traditional neuroleptic, fluphenazine, was evaluated in an open-label trial in 21 refractory patients (age 7 to 47 years). Approximately half of the 21 subjects (n=11) reported having a better response to fluphenazine compared to previous treatment with haloperidol, 6 patients showed a similar response to fluphenazine and 2 patients preferred haloperidol. The mean dose of fluphenazine was 7 mg per day (range 2 mg to 15 mg per day). Interestingly, of the 6 patients who reported akathisia on haloperidol, only one reported akathisia on fluphenazine.[19] Fluphenazine therapy may begin with 0.5 mg to 1mg per day, increasing to bid dosing in 5 to 7 days. In children the likely dose range is 2 mg to 5 mg per day in divided doses.

***Atypical neuroleptics***

Tiapride and sulpiride are substituted benzamides with selective D2 blocking properties. This family of neuroleptics also includes amisulpride, raclopride, remoxipride, and, the antiemetic, metoclompramide. Of these, only tiapride has been evaluated in controlled studies for TS. Eggers, Rothhenberger and Berghaus[19] conducted two placebo-controlled studies in a total of 27 children with tic disorders. In doses ranging from 5 mg/kg to 6 mg/kg of body weight per day, the investigators observed a 30% to 44% decrease in the video-taped tic count after six weeks of treatment.[20]

In a retrospective study of TS patients (age range 10 to 68 years), Robertson et al[21] observed a positive response to sulpiride in 60% of the sample (22 of 37). Treatment began with 100 mg twice daily and was gradually increased as needed to achieve adequate tic control. The modal daily dose among responders was 400 mg (range 200 mg to 1,000 mg per day). Common side effects included drowsiness, akathisia, depressed mood, amenorrhea, and weight gain. The results of this study are difficult to interpret because a third of the patients were concurrently receiving other medications such as haloperidol, pimozide, tiapride, clonidine, and tetrabenazine for their tics.

Risperidone is an atypical neuroleptic with potent D2 and 5-HT2 blocking properties. The 5HT blocking property is presumed to be protective against extrapyramidal side effects and perhaps tardive dyskinesia. In view of the potential for long-term neuroleptic treatment in children and adults with TS, these protective features of the atypical neuroleptics make them attractive an appealing alternatives to the traditional neuroleptics. Still, there are important pharmacological differences across this class of medications and, to date, they have not been well-studied in TS. The differences across these atypical neuroleptics appears to be the relative potency of D2 and 5-HT2 antagonism. Because D2 blocking properties appear to be fundamental to the treatment of tics, the potency of D2 blockade is probably relevant to the treatment of TS. For example, clozapine, which is a weak D2 blocker and a far more potent at the 5HT2 receptor blocker, was not effective in the treatment of tics.[22]

Risperidone was released in the US in 1994 and has shown promise for the treatment of tics in several open-label studies.[23-25] In the study by Lombroso et al[23] risperidone was effective in reducing tics in five of seven youngsters followed for three months (dose range 1.0 mg to 3.0 mg per day in two divided doses). These preliminary studies suggest that risperidone

is effective. Extrapyramidal symptoms are indeed uncommon when the dose is increased slowly. The potential for weight gain is a potentially important side effect that warrants clinical monitoring and more study. Placebo-controlled trials with risperidone are underway at several centers in North America and Europe, but none have been published to date.

Ziprasidone also has potent 5-HT2 and D2 blocking properties. In addition to these familiar pharmacological properties, ziprasidone also has 5-HT1A agonist properties and modest norepinephrine and serotonin reuptake blocking effects.[25] These additional pharmacological properties may contribute to anxiolytic and antidepressant effects. Ziprasidone was evaluated in a double-blind study in 28 children (age range 7 to 17 years) with moderate to severe tics and proved to be superior to placebo.[26] After eight weeks of treatment at a mean dose of 30mg per day given in two divided doses, the 16 youngsters randomized to active drug showed an average 35% decrease in tics. This was significantly better than the 7% drop in tic symptoms observed in the 12 subjects randomized to placebo. Side effects of ziprasidone included transient sedation (n=12), insomnia (n=4), akathisia (n=1). There were no clinically significant changes in cardiac conduction as measured by electrocardiogram; prolactin levels remained within normal limits at endpoint. Weight gain on the active drug was the same as observed in the placebo group.

***Non-neuroleptics***

Clonidine is an alpha-2 agonist that has been used in the treatment of TS since the late 1970s.[27] Clonidine acts presynaptically in the locus coeruleus and ultimately turns down the noradrenergic system. One controlled study has shown that clonidine is superior to placebo achieving a 35% reduction in tics on average.[28] However, an earlier study failed to observe clear benefit from clonidine.[29] Despite these inconsistent results, clonidine is commonly used in TS. Simply stated, clonidine does not raise concerns about long-term side effects associated with neuroleptics. Guanfacine, which is a newer alpha-2 agonist, was recently reported to be superior to placebo for tics and ADHD symptoms in a sample of 34 children.[30]

In school-age children, clonidine is usually started with a single 0.05 mg dose (0.025 mg in smaller children) and increased by an additional half tablet every three to four days to a total of 0.15 mg to 0.2 mg per day. Based on its relatively brief duration of action, clonidine is typically given three to four times per day. Sedation is common when treatment is first initiated, but it may also be present in ongoing treatment. Other side effects include dry mouth, headache, mid-sleep awakening and increased irritability. Irritability may be especially prominent as the medication is wearing off, hence clinicians should look for patterns in the child's behavior. Although clonidine was developed as an antihypertensive, low blood pressure is rarely a problem. Abrupt discontinuation, however, has been associated with rebound increases in blood pressure and should be avoided.[31] Clonidine also comes in a transdermal patch, but this preparation has not been well-studied in children and adolescents.

Tetrabenazine is a non-neuroleptic that depletes presynaptic dopamine and has weak postsynaptic dopamine blocking properties as well. Because it is not available in many countries, there is only one open-label study. In that study, 11 of 17 TS patients showed an improvement in tics.[32] The safety and efficacy of tetrabenazine in TS warrant further study.

Pergolide is a mixed D2/D1 agonist developed for the treatment of Parkinson's disease. In conditions such as Parkinson's disease with decreased dopaminergic activity, pergolide acts as dopamine agonist. In TS with heightened dopaminergic tone, pergolide theoretically has dopamine antagonist effects. Lipinski et al evaluated the effects of pergolide in a six-week, open-label study of 32 TS patients between the ages of 7 and 19. At a mean daily dose of 177 $\pm$ 61 micrograms given in three divided doses, 24 (75%) patients reported a 50% improvement in tics. A personal or family history of restless legs syndrome was cited as a predictor of positive response.[33] In a series of 7 neuroleptic-refractory TS patients (age 11 to 48 years), only 1 of 7 patients responded to pergolide.*

Based on success in the treatment of dystonia, injections of dilute botulinum toxin have also been used in open trials with TS patients. Jankovic[34] reported that 10 of 10 patients had some reduction of tics in the area of the injection. These investigators tentatively concluded that slower, dystonic tics are more likely to respond to botulinum injections. In a single case involving an adult patient with severe and refractory phonic tics, botulinum toxin was reportedly successful in decreasing phonic tic severity by 40%.[35] The injections were given directly into the thyroarytenoid muscle every 3 months with sustained benefit for up to one year.

The added benefit of nicotine chewing gum in combination with haloperidol has been reported in two open-label studies.[36, 37] More recently, open trials have evaluated the use of transdermal nicotine patches with neuroleptics.[38,39] Twenty four hour exposure to the 7 mg patch reportedly provides added benefit for about 1-2 weeks. Confirmation of the clinical utility of nicotine in TS awaits the results of a placebo-controlled trial.

The androgen antagonist, flutamide, showed dramatic improvement in tics observed in a small case series.[40] However, a recently-completed double-blind, placebo-controlled, crossover study of flutamide failed to support the optimistic findings from prior case studies.[41] Although the antiandrogen mechanism is an appealing therapeutic approach, the potentially serious side effects of flutamide and the clinically insignificant findings in this controlled study indicate that it is unlikely to have a place in the treatment of tics.

## Conclusion

In summary, clinical practice has evolved over the past decade. The eradication of tics is no longer considered an appropriate goal of pharmacotherapy. Contemporary practice focuses on striking a balance between adequate tic control and minimizing side effects.[8,14] In practice, therefore, clinicians should advise children and families to accept a 40% to 50% decrease in

*Scahill L and Leckman JF, unpublished data.

tics because greater control make come with a cost in the form of increased side effects. Mild to moderate tics maybe managed by clonidine or guanfacine. The use of the traditional neuroleptics (such as haloperidol or pimozide) is reserved for patients with severe tic symptoms. The atypical neuroleptics (tiapride, risperidone and ziprasidone) appear to be better tolerated than haloperidol and pimozide – at least in the short-term. More study is needed to confirm the efficacy of these new neuroleptics. Furthermore, the risks and benefits of long-term treatment with any of the atypical neuroleptics in children with TS have not been established. For example, although the risk of neurological side effects and probably tardive dyskinesia appears to be lower with the atypical neuroleptics, clinical reports suggest that long-term use of risperidone may be associated with substantial weight gain.[42,*] Another unanswered question is the duration of treatment – especially with the neuroleptics. Placebo-controlled withdrawal studies may be the best way to answer this question.

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