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# Current drug therapy for Tourette's syndrome

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■ Tourette's syndrome is a tic disorder that is being diagnosed with increasing frequency. Its onset is always in childhood, and severity can range from mild to marked. Behavior and learning problems are often associated with Tourette's syndrome. Various medications may be used for symptomatic treatment, but no agent is effective in every case or is without potential side effects. The most commonly used medications include the neuroleptic agents haloperidol and pimozide. Alternatives of proven value include clonidine and clonazepam. Psychostimulant agents may be used to modify the associated attention-deficit disorder but can exacerbate tic problems in some children.

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TICS occur at one time or another in up to 24% of children, it is estimated.[1] The disorder, first described by Gilles de la Tourette in 1885,[2] is now known as Tourette's syndrome. This was considered a medical curiosity until the 1960s when the number of diagnosed cases increased rapidly. At that time, haloperidol was found to be an effective symptomatic treatment for some patients with tics. The discovery of an effective treatment has subsequently done more than any other finding to stimulate research and clinical interest. Although the exact incidence remains unknown, recent estimates are that three in every 10,000 persons have Tourette's syndrome, involving all races in many countries.

Tics are purposeless movements or utterances that occur suddenly, briefly, involuntarily, and repetitively. No biological markers are known. The diagnosis of Tourette's syndrome is made on the basis of criteria listed in the Diagnostic and Statistical Manual of Mental Disorders:[3]

1. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently;
2. The tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than one year;
3. The anatomic location, number, frequency, complexity, and severity of the tics change over time; and
4. Onset is before age 21.

Most patients become symptomatic between the ages of five and 10 years. At the Cleveland Clinic, we first became interested in Tourette's syndrome in the 1970s, and an initial report included a series of 12 cases.[4] More recently, findings involving 200 pediatric and adolescent patients were published.[5] We continue to see persons with this disorder and now have evaluated and cared for more than 450 children with Tourette's syndrome.

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## PATHOPHYSIOLOGY

In the past, the involuntary tics of Tourette's syndrome were thought to be of psychiatric or emotional origin. This was due, in part, to the observation that many patients with Tourette's syndrome have behavioral or learning problems. The most common associated behavioral difficulties are of the types listed as attention-deficit disorders with or without hyperac-

tivity. Other behavioral characteristics frequently include high levels of anxiety, emotional lability, and obsessive-compulsive behaviors. It is now believed that these associated behavioral problems are not the cause of but rather are an integral part of the disorder. The cause of the behavioral and learning problems is unknown.

The concept that Tourette's syndrome has an organic basis has been supported by recent clinical, biochemical, and genetic investigations.[6,7] In spite of these findings, no consistent abnormal biological feature has been determined. Neuropathological studies are limited and generally inconclusive, but a recent report has found an abnormality in endogenous opioid pathways.[8]

One hypothesis for Tourette's syndrome has been suggested by the often dramatic symptomatic response to dopamine receptor-blocking drugs such as haloperidol and pimozide. Other agents that affect dopaminergic systems also alter the symptoms of Tourette's syndrome. Examples include levodopa and methylphenidate, which may increase the frequency of symptoms,[9,10] and tetrabenazine, which decreases tic activity.[11]

The dopaminergic-system abnormality could represent either an excessive amount of dopamine or a hypersensitive response to this neurotransmitter. Measurement of cerebrospinal fluid homovanillic acid (HVA), a metabolite of dopamine, has revealed both low baseline levels and decreased accumulation following the administration of probenecid. HVA levels returned to normal following the administration of haloperidol, implicating dopamine-receptor hypersensitivity.[12] Other hypotheses have suggested the possibility of dysfunction in different central monoaminergic systems involving serotonin and norepinephrine.[13]

## MEDICATIONS

Many groups of medications have been used in an attempt to modify the symptoms of Tourette's syndrome.[14] Those that have proved unsuccessful include most anticonvulsants, antidepressants, antihistamines, anticholinergics, anti-spasticity agents, monoamine oxidase inhibitors, and beta blockers.

Although there are medications that can provide symptomatic relief, none are curative. It is difficult to assess the success of medical treatment in Tourette's syndrome since the tics go through periods of exacerbation and remission spontaneously. In addition, the therapeutic and toxic dosages are so similar that treatment is considered satisfactory if symptoms are decreased by 75%.

### Neuroleptic drugs

*Haloperidol.* This butyrophenone is a dopamine-blocking agent that remains the best known and most widely used for the treatment of Tourette's syndrome. The first successful use of haloperidol was reported by Seignot in 1961.[15] It has been reported to reduce tics in 70% of treated patients, but only 25% of patients report significant improvement without any side effects.

To avoid acute dystonic reactions, treatment is begun with 0.25 mg each evening for the first week. The dosage can then be increased, if needed, by 0.25 mg per day, on a weekly basis. A twice-daily regimen of medication is generally prescribed. As increases in dosage are continued, the beneficial response is continually balanced against the occurrence of side effects. Most children receive 0.05 mg/kg per day, and most of our patients receive 1.5 to 2.5 mg daily. The effective dosage range is between 0.5 and 10 mg per day. Symptoms must be monitored closely so that the dosage can be decreased when tics are quiescent and increased when they become more noticeable.

Studies of haloperidol blood levels done at the Cleveland Clinic have confirmed that the dosages necessary to control tics are considerably less than those used to treat psychiatric disorders.[16] There is, however, no clear-cut relationship between the actual blood level and the degree of symptomatic relief. Haloperidol has a long half-life and accumulates until a steady blood state is reached in approximately four days.[17] Elimination of the drug also takes approximately four days. It is for these reasons that changes in medication are made every week to allow the full impact of the most recent change to be evaluated.

Unfortunately, side effects are quite frequent with haloperidol. Acute extrapyramidal reactions are generally avoidable if the medication is introduced in low dosages and if further adjustments are made slowly. If such reactions do occur, they can be rapidly reversed with antihistamine or anticholinergic agents. There is no evidence, however, that the prophylactic use of such medications is of any value. Chronic parkinson-like side effects are uncommon when treatment is maintained at low dosage. If they occur even with minimal amounts of medication, concomitant administration of anticholinergic agents, such as benztropine mesylate at 0.5 mg per day, should be considered.

In a survey of patients who had received haloperidol treatment, 84% indicated that they experienced side effects, which they considered significant.[18] The most common short-term side effects included lethargy, personality change, and increased appetite and weight. It is especially important to monitor children closely for the

more subtle side effects, such as cognitive blunting, depression, and fear of school. Other potential but uncommon side effects are anticholinergic reactions, galactorrhea, photosensitivity, impairment of liver function, and neuroleptic malignant syndrome. We have not found it necessary to routinely monitor liver function tests in persons receiving haloperidol.

Another concern is the possibility of tardive dyskinesia occurring with long-term use. Tardive dyskinesia has been reported in children with Tourette's syndrome, but has been uncommon and has disappeared in all cases with discontinuation of the medication.[19,20] Rapid discontinuation of neuroleptic agents can also lead to the withdrawal emergent syndrome.[20] This syndrome is characterized by choreoathetoid and myoclonic movements that disappear spontaneously within weeks to months. It can be avoided by lowering the dosage of medication slowly.

*Pimozide.* The high incidence of side effects seen with haloperidol has led to an ongoing search for other neuroleptic agents. Pimozide is a diphenylbutylpiperidine and is a potent dopamine-blocking agent thought to have less effect on the norepinephrinergic systems than haloperidol. Recently approved for use in this country, pimozide has shown clinical actions similar to haloperidol.[21] Studies performed here and elsewhere indicate that pimozide does have a lower incidence of side effects, but those encountered are the same as occur with haloperidol.[21,22]

As regards equivalent potency, 2.5 mg of pimozide is similar in action to 1 mg of haloperidol. Treatment is started with 1 mg of pimozide daily at bedtime. The dosage is increased by 1 mg daily on a weekly basis until symptoms are relieved or until intolerable side effects occur. The current recommendation is that children not receive more than 10 mg of pimozide daily. Adolescents and adults may receive a maximum of 20 mg per day.

There has been concern that pimozide, especially at a higher dosage, may cause Q-T interval prolongation or other adverse cardiac effects. At the Cleveland Clinic, serial ECGs performed on children receiving pimozide revealed no significant alterations.[22] Consequently, we do not believe that pimozide has a greater cardiac effect than other neuroleptic drugs, and we are no longer performing routine follow-up ECGs, although the manufacturer still recommends that this be done.

*Other neuroleptic agents.* In the past, several other neuroleptic agents were found ineffective in suppressing tics even though they shared the ability to block dopamine receptors. It is likely that the apparent lack of efficacy was based on insufficient dosages of these medications. Other neuroleptic agents that have been found effective include trifluoperazine and fluphenazine. Fluphenazine is the most studied of the alternative agents, and 4 mg is equal in potency to 3 mg of haloperidol.[23] Overall, fluphenazine appears to be similar to pimozide in both efficacy and potential for causing side effects.

*Clonidine.* This agent has been used for the treatment of Tourette's syndrome since 1979.[24] Clonidine is easier to use and has fewer side effects than neuroleptic agents. In addition to suppressing tic activity, it may be helpful in improving the associated behavioral difficulties common in children with Tourette's syndrome.[25] In general, the neuroleptic agents do not improve behavior.

Unfortunately, not all studies have shown clonidine to be effective. While Leckman et al[25] indicated that up to 62% of treated patients respond favorably, Goetz et al[26] found clonidine to be no more effective than a placebo. In our experience at the Cleveland Clinic, clonidine was preferable to neuroleptic agents in 30% of patients, often because of the low incidence of adverse reactions. Sedation is the most common side effect, but higher dosages may also be associated with orthostatic hypotension and dizziness. Tardive dyskinesia has not been reported.

Treatment is started with 0.05 mg twice per day. If the initial dosage is tolerated, it is increased to 0.1 mg twice per day after one week. Clonidine does not lead to an immediate response; several weeks are necessary before improvement may be noted. The dosage is increased further after four weeks, at which time the schedule is changed to three times per day. Increases are continued until sedation or other side effects are reported. The usual dosage tolerated has been found to be approximately 5.5 μg/kg per day. If the medication is to be discontinued, it should be tapered gradually.

*Clonazepam.* There are few studies of the efficacy of this anti-epileptic agent for the treatment of Tourette's syndrome. One study indicated that approximately 50% of subjects show improvement.[27] Side effects are relatively uncommon, but include personality changes and sedation. Clonazepam has not been highly effective as a sole agent; we currently use this medication as an adjunct to either clonidine or a neuroleptic agent when monotherapy has not resulted in an adequate response. Treatment is started with 0.25 mg per day, and the dosage is increased weekly by a similar amount until there is a clinical response or the appearance of side effects.

*Stimulant drugs.* A number of case reports and small series have suggested that the use of psychostimulants in patients with attention-deficit disorder may precipitate Tourette's syndrome or may increase the number of tics in individual patients.[10,28,29] This property is shared by all

available psychostimulant agents, including methylphenidate, dextroamphetamine, and pemoline. The underlying mechanism is believed to be the ability of stimulants to augment catecholaminergic activity in the central nervous system.[30] Since more than 50% of patients with Tourette's syndrome have symptoms of attention-deficit disorder,[5] this remains an important issue. In general, most children with Tourette's syndrome will experience the onset of restless, inattentive behavior prior to the onset of tics.

At the Cleveland Clinic, we believe that psychostimulants have the potential for increasing or inducing tics in some, but not all, persons who are already destined to have Tourette's syndrome. If a child receiving such a drug begins to have tics, every attempt must be made to discontinue the medication. Unfortunately, discontinuing the stimulants often leads to a major deterioration in the child's school and home adjustment. If the tics remain at a low level, the stimulant drugs should be continued after the parents have been informed that the tics may worsen. If the level of tic activity is high or worsens, we discontinue the stimulant agent and offer a trial with clonidine or imipramine for the attention-deficit disorder. These agents either reduce tics or cause no further increase while having the potential for improving behavior. If these attempts fail, we may elect to treat with a combination of a stimulant drug and a neuroleptic agent.

## RECOMMENDATIONS

All available medications provide only symptomatic relief and are not curative. No medication will help in all cases without the possibility of significant side effects. There is also no evidence to indicate that early treatment alters the long-term prognosis. The tics are often more bothersome to the parents than to the involved children, and it is imperative that the entire family be educated about the nature of the disorder, the prognosis, and the availability of medication if it should be needed.

Because of the potential for side effects, medication is not recommended for milder cases, which have become more numerous with the rapid increase in the number of diagnosed cases overall. Among our patients at the Cleveland Clinic, 50% have mild symptoms and have never been treated with medication. However, psychological damage may occur if more pronounced and noticeable tics are not suppressed with medication. Since the ability to tolerate tics varies from family to family, it is important that families and patients become part of the decision-making process. When the family or the patient believes that medication is necessary, the physician usually finds that this is the correct decision and begins treatment.

Most patients in need of medication have tics of moderate severity. For these individuals, treatment is generally started with clonidine. Although the success rate is below that observed with the neuroleptic agents, the side effects are fewer. Neuroleptic agents are used for patients with severe tics or patients with moderate degrees of tics who have failed to improve with clonidine. When a neuroleptic drug is indicated, we prescribe pimozide because of a lower incidence of side effects as compared to haloperidol. In refractory cases, combinations of clonidine, pimozide, or clonazepam can be used. No studies are available, however, to prove that this "polypharmacy" approach leads to any additive benefits. Because of the natural tendency for tics to exacerbate and remit, alterations in dosage will be necessary periodically even after an initial medication program has been established.

Unfortunately, even physicians experienced in the treatment of Tourette's syndrome will find that in approximately one third of patients, tics will not be significantly relieved by currently available medications. This holds true also for patients whose major problems are due to their associated behavioral difficulties and not to their tics.

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