# Relative Efficacy of Haloperidol and Pimozide in Children and Adolescents With Tourette's Disorder

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*Objective:* *The authors evaluated the relative efficacy and safety of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome in children and adolescents.* *Method:* *A double-blind, 24-week, placebo-controlled double crossover study of equivalent dose formulations of haloperidol and pimozide was conducted with 22 subjects, aged 7–16 years, with Tourette's disorder who were randomly assigned to first one active drug treatment and then the other. Biweekly assessment and flexible dose titration mimicked clinical practice. The primary outcome variable was total score on the Tourette Syndrome Global Scale. Final outcome was determined after 6 weeks of each treatment (placebo, pimozide, haloperidol), with a 2-week placebo baseline period and intervening 2-week placebo washout periods between treatments.* *Results:* *Pimozide proved significantly different from placebo in affecting the primary outcome variable, whereas haloperidol failed to have a significant effect. Haloperidol exhibited a threefold higher frequency of serious side effects and significantly greater extrapyramidal symptoms relative to pimozide. Haloperidol-associated treatment-limiting adverse events were experienced by 41% of the patients. The therapeutic doses of pimozide and haloperidol were equivalent (mean=3.4 mg/day, SD=1.6, and mean=3.5 mg/day, SD=2.2, respectively).* *Conclusions:* *At equivalent doses, pimozide is superior to haloperidol for controlling symptoms of Tourette's disorder in children and adolescents.*

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Gilles de la Tourette's syndrome is a neurobehavioral disorder with childhood onset that is characterized by involuntary, stereotyped motor and phonic tics (1). The prevalence rate in the child and adolescent population is estimated at 2.8–4.3/10,000 (2). While Tourette's disorder is rare, it afflicts children in sizable proportion, with considerable morbidity. Neuroleptics (e.g., haloperidol, pimozide, fluphenazine) are standard therapy, and haloperidol is the neuroleptic of first choice (3). Approximately 84% of haloperidol-treated patients experience adverse events during the course of treatment, and only a minority (20%–30%) continue haloperidol for extended periods (3, 4). Among the commonly occurring adverse events, extrapyramidal symptoms (e.g., akathisia, bradykinesia, dystonia, and parkinsonism) are particularly troublesome for children and adolescents (5). Parkinsonism in this population interferes with age-specific neuromuscular activities (e.g., running, swimming), peer acceptance, and cognitive functioning (6). The prevalence of severe extrapyramidal symptoms in hospitalized children and adolescents treated with neuroleptics is estimated to be 34% and to be associated with length of treatment exposure (5). Samples of outpatient children with Tourette's disorder have relatively high cumulative exposures to neuroleptics, and discontinuation of these medications because of extrapyramidal symptoms is commonly observed (4).

When pimozide was first introduced as a treatment for Tourette's disorder, there was hope that side effects, particularly extrapyramidal symptoms, could be minimized (7, 8). In vitro pimozide is fivefold more potent than haloperidol with regard to dopamine $D_2$ receptor blockade, yet it has dopamine-releasing properties (9) that should limit the occurrence of withdrawal dyskinesia and extrapyramidal symptoms. Pimozide has the capacity to down-regulate $D_2$ receptors after chronic treatment, while haloperidol up-regulates $D_2$ receptor numbers (10). Pimozide also decreases serotonin turnover in the hippocampus (11), which may indirectly modulate dopamine transmission (12). Recent evidence suggests that the therapeutic and extrapyramidal-symp-

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**TABLE 1. Demographic and Clinical Characteristics of 22 Children and Adolescents With Tourette's Disorder**

| Variable | Value | | |
|---|---|---|---|
| | *Mean* | *SD* | *Range* |
| Age at onset of illness (years) | 8.0 | 2.1 | 3–12 |
| Duration of illness (years) | 2.4 | 1.5 | — |
| Socioeconomic status (Hollingshead index score) | 34.8 | 10.7 | — |
| Tourette Syndrome Global Scale score | 28.5 | 14.5 | 18–58 |
| Children's Global Assessment Scale score | 61.4 | 9.8 | 35–80 |
| | *N* | *%* | |
| Comorbid diagnosis | | | |
| Attention deficit hyperactivity disorder | 13 | 59 | |
| Obsessive-compulsive disorder | 5 | 23 | |
| Family history | | | |
| Tic disorder[a] | 5 | 23 | |
| Attention deficit hyperactivity disorder | 6 | 27 | |
| Obsessive-compulsive disorder | 5 | 23 | |
| Previous treatment | | | |
| Neuroleptic | 5 | 23 | |
| Stimulant | 3 | 14 | |
| Clonidine | 2 | 9 | |
| Other | 4 | 18 | |

[a]Tourette's disorder, chronic motor tic disorder.

tom-related effects of haloperidol and pimozide can be pharmacologically dissected in children with Tourette's disorder through a surrogate marker for dopamine transmission (13).

While Tourette's disorder—and its aggressive management—usually begins during school age (4), no study has specifically investigated the efficacy of neuroleptics and their benefits versus their risks in children with Tourette's disorder. Clinical trials of pharmacotherapy for Tourette's disorder have included mixed populations of children and adults and were biased toward adult patients (14). In a pivotal study comparing the use of haloperidol with that of pimozide in adults with Tourette's disorder, pimozide was reported to be less efficacious, with no advantage in the side effect spectrum or benefit-to-risk ratio (14). That study, however, had two major limitations: 1) a systematic bias through the use of nonequivalent dose formulations and 2) a lack of subgroup analysis by age. These issues were addressed in the present study by focusing exclusively on children and adolescents with Tourette's disorder and through reformulation of pimozide into 1-mg tablets identical to haloperidol tablets.

The hypothesis of this study was that at equivalent doses, pimozide would be superior to haloperidol in relative efficacy for treating Tourette's disorder in children and adolescents. Any difference in efficacy would likely be based on differential side effect profiles and not necessarily on a difference in absolute efficacy.

## METHOD

The study included 22 children and adolescents (five female and 17 male) whose mean age was 10.2 years (SD=2.5, range=7–16) with a primary diagnosis of Tourette's disorder as defined by the DSM-III-R criteria. Subjects recruited in this study were outpatients of the Tic and Tourette Clinic of the Medical University of South Carolina, Charleston. After complete description of the study, all subjects gave assent, and guardians or parents gave written informed consent, before participation.

Suitability for participation was determined after a comprehensive medical, psychiatric, and neurologic evaluation. The comprehensive psychiatric examination was guided by a structured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present Episode Version (15). Severity criteria were used for inclusion, and severity warranting the clinical use of neuroleptic medication was required (appendix 1). Demographic and clinical characteristics of the subjects are listed in table 1. Notable clinical characteristics were the presence of comorbid attention deficit hyperactivity disorder and obsessive-compulsive disorder as well as the previous neuroleptic treatment of five patients (23%). Two of the five had had previous treatment with subtherapeutic doses of haloperidol; the remainder had had treatment of a past exacerbation with haloperidol (N=1, a responder), pimozide (N=1, a partial responder), or fluphenazine (N=1, a nonresponder). All patients had been medication free for a minimum of 2 weeks at study entry.

The study was designed as a double-blind, three-period, three-treatment crossover comparison. An initial 2-week placebo baseline period was followed by three 6-week treatment periods and two intervening 2-week placebo washout periods. Two-week washouts were chosen on the basis of previous open-label and controlled studies that demonstrated a return to control tic values after both active drugs during such a period. In total, each subject completed a 24-week trial. The placebo baseline was followed by random assignment to one of three orders of treatment, with the restriction that each treatment be represented at least once in each period. The random assignment to treatment order was performed by the research pharmacy, and only the research pharmacist (C.J.) was not blind to these assignments. A randomization schedule maintained a balanced distribution with respect to initial treatment and drug order. Endpoint ratings for each treatment period were made at week 6; the major dependent outcome variables encompassed tic control, behavior, and side effects (particularly extrapyramidal symptoms).

The study medications were haloperidol (1 mg), pimozide (1 mg), and lactose placebo in look-alike tablets. Subjects were given coded bottles at each biweekly visit. All medication was administered at bedtime. Subjects were asked to return all unused medication for pill counting. Patients who returned over 30% of their prescribed dose were judged noncompliant. Patients and their families were contacted by phone between appointments, primarily to monitor adverse events. Concomitant medications were excluded, with the exception of diphenhydramine hydrochloride for nasal congestion. Anticholinergic medication and adjunctive treatment were not used throughout the study period. Medication titration was initiated at 1 mg and increased on a flexible dosage schedule (2 mg/week) within a 4-week time frame, so the dose at endpoint (week 6) would be optimal. The goal of dose titration was to produce a 70% reduction in tic symptoms from placebo baseline on the basis of all available clinical data.

An evaluation of the effect of each treatment on tic symptoms, behavior, and side effects was performed four times during the protocol, the first taking place at the end of the placebo baseline period and the remainder at the end of each treatment period. Each evaluation was performed by the same clinician (F.R.S.) and took approximately 2 hours to complete. Physician-rated efficacy items were from standardized and validated instruments, the Tourette Syndrome Global Scale (16) and the Clinical Global Impression (CGI) tic severity scale (17). Subject self-ratings of tic symptoms on a daily basis were obtained with the Tourette's Syndrome Symptom List (18). Behavioral assessment was accomplished with clinician, self, and parent report instruments, including the behavioral subscales of the Tourette's Syndrome Symptom List and the Tourette Syndrome Global Scale. Broad general functioning was assessed by means of the physician-rated Children's Global Assessment Scale (19). Side effects were assessed with a semistructured review at each visit. Abnormal involuntary movements were assessed formally with the Abnormal Involuntary Movement Scale (AIMS) (20), and extrapyramidal symptoms by the Extrapyramidal Symp-

**TABLE 2. Efficacy of Pimozide and Haloperidol for Tic Symptoms in 22 Children and Adolescents With Tourette's Disorder**

| | At Baseline | | With Placebo | | With Pimozide | | With Haloperidol | |
|---|---|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Tourette Syndrome Global Scale | | | | | | | | |
| Total score[a] | 28.5 | 14.5 | 26.8 | 15.9 | 17.1 | 14.1[b] | 20.7 | 17.3 |
| Tic subscale score[c] | 15.3 | 6.9 | 13.5 | 10.1 | 7.0 | 5.1[b] | 8.8 | 8.8 |
| Tourette's Syndrome Symptom List, tic subscale score[d] | 54.8 | 40.5 | 54.1 | 40.9 | 28.8 | 56.1[b] | 35.5 | 47.1 |

[a]Range=0–100; significant difference among treatments (F=3.9, df=2, 38, p=0.02).
[b]Significantly different from the value for placebo (p<0.05, Newman-Keuls post hoc test).
[c]Range=0–50; significant difference among treatments (F=4.0, df=2, 38, p=0.02).
[d]Range=0–336; significant difference among treatments (F=5.9, df=2, 38, p=0.005).

toms Rating Scale (21). ECGs were performed at baseline and at the end of each treatment period.

In the preliminary statistical analysis, all data were checked for violation of normality assumption by plotting the points on a normal probability paper. Bartlett's test of homogeneity of group variances was then applied to the data as follows: 1) to the placebo scores of all three periods, 2) to the pimozide scores of all three periods, and 3) to the haloperidol scores of all three periods. There was no significant difference among the variances for all three treatments and any of the variables analyzed. Bartlett's test was applied to the scores for placebo, pimozide, and haloperidol irrespective of period and for each period separately.

In the primary analysis, for continuous-type data including the primary outcome variable (total score on the Tourette Syndrome Global Scale), a separate analysis of variance (ANOVA) was performed for each variable as follows. The scores of all three periods taken together were analyzed, with sources of variation being 1) subject, 2) period, 3) direct treatment, 4) carryover effects, and 5) error. The level of significance was set at p=0.025 to account for two planned intermediary analyses. The mean sums of squares for subject, period, direct treatment, and carryover were compared with the mean sum of squares for error in the standard ANOVA layout. Each factor included in the analyses (period, direct treatment, and carryover) was considered statistically significant if the p value corresponding to that factor in the ANOVA table was less than 0.025.

Carryover effects were analyzed within subjects, and if they were significant, only first-period data were used for analysis. The only detection of carryover occurred in the analysis of data from the Extrapyramidal Symptoms Rating Scale, and for this variable first-period scores alone were used. For variables having a p value less than 0.025 for direct treatment and a carryover effect that was not statistically significant, pairwise comparisons between the treatments were performed with the Newman-Keuls test for multiple comparisons, and the mean sum of squares for error was used as the estimate of the common variance (22). Two treatment groups were deemed different if the absolute difference between their means was greater than the critical value corresponding to the Newman-Keuls table.

Categorical data (adverse effects) were analyzed as follows. Only the haloperidol and pimozide scores were considered, with the patient groups defined as those who received haloperidol before pimozide and those who received pimozide before haloperidol. The tests were performed according to the method developed by Zimmerman and Rahlfs (23), an analogue of Grizzle's method for continuous data (24). This test determined whether the proportions of patients experiencing adverse reactions differed between the two treatments. This method tests the hypothesis of equal residual effects by considering the order of drug administration (11 subjects received pimozide before haloperidol, and 11 subjects received haloperidol before pimozide). If a statistically significant difference exists between the residual effects, then only the first-period data are used.

## RESULTS

Twenty-four patients who met the study criteria were recruited. Twenty-two completed the protocol (table 1); two dropped out before random group assignment. All subjects remained in outpatient status throughout the 24-week protocol. Five patients had had previous treatment with neuroleptics, but only two required a 2-week tapering period before baseline assessment. On the basis of preselected criteria involving use of pill counts, all subjects were judged to be compliant throughout the study. During placebo treatment, three patients had an exacerbation of tics that prompted early evaluation and carrying forward of data to a week 6 endpoint. On active treatment with haloperidol, two patients had severe anxiety and depression that prompted early termination of the treatment and carrying forward of data to week 6.

The clinical goal of 70% tic reduction was chosen for dose titration on the basis of outcome data from previous controlled studies (14). According to total scores on the Tourette Syndrome Global Scale, 64% (N=14) of the 22 subjects achieved this goal during either of the active treatments, compared to 23% (N=5) with placebo treatment. The mean effective doses of pimozide and haloperidol were equivalent: 3.4 mg/day (SD=1.6, range=1–6) and 3.5 mg/day (SD=2.2, range=1–8), respectively. In 86% (N=6) of the seven patients who failed to meet the clinical tic reduction criteria, side effects precluded further dosage increases.

To evaluate treatment efficacy, an ANOVA on the primary tic outcome measure, the Tourette Syndrome Global Scale total score, was performed. This analysis revealed a treatment group effect (F=3.9, df=2, 38, p=0.02). A similar analysis of scores on the Tourette Syndrome Global Scale tic subscale also demonstrated a treatment group effect (F=4.0, df=2, 38, p=0.02). Carryover or period effects were not detected in the analysis. Scores on motor and vocal components of this subscale were as follows. With pimozide: mean=4.9 (SD=3.4) for motor tics, mean=2.1 (SD=2.4) for vocal tics; with haloperidol: mean=5.1 (SD=4.8) for motor, mean=3.7 (SD=5.5) for vocal; with placebo: mean=8.4 (SD=5.7) for motor, mean=5.1 (SD=6.0) for vocal. An ANOVA on the secondary tic outcome measures of severity (CGI) and patient self-rated tics (Tourette's Syndrome Symptom List) also demonstrated a treatment group effect (F=12.7, df=2, 38, p=0.00005, and F=5.9, df=2, 38, p=0.005, respectively).

Table 2 shows the post hoc analyses (Newman-Keuls test) of the primary (Tourette Syndrome Global Scale

total score) and secondary tic measures (Tourette Syndrome Global Scale and Tourette's Syndrome Symptom List tic subscales). The effect of pimozide was superior to that of placebo on the total Tourette Syndrome Global Scale scores and the tic subscale scores, whereas the effect of haloperidol failed to reach statistical significance. The effect of pimozide was superior to that of placebo on Tourette's Syndrome Symptom List tic measures in the post hoc analyses, while the effect of haloperidol was not significantly different from that of placebo. The CGI tic severity scale scores showed both pimozide (mean=3.1, SD=1.4) and haloperidol (mean=3.1, SD=1.4) to be superior to placebo (mean=4.6, SD=1.0) at the 1% level (Newman-Keuls test). Global assessment of functioning on the clinician-rated Children's Global Assessment Scale also revealed a treatment group effect ($F=5.1$, $df=2, 38$, $p=0.01$): scores with both pimozide (mean=75.9, SD=16.6) and haloperidol (mean=73.6, SD=16.5) were significantly different from those with placebo (mean=66.4, SD=12.8) ($p<0.05$, Newman-Keuls test, for both comparisons). Behavioral outcomes for each treatment were evaluated with the Tourette's Syndrome Global Scale behavioral subscale and the Tourette Syndrome Symptom List self-rated behavioral scale. Neither behavioral scale showed a treatment effect ($F=1.1$, $df=2, 38$, $p=0.30$, and $F=3.4$, $df=2, 38$, $p=0.04$, respectively).

General side effects (e.g., headache, stomachache, irritability) did not differ among treatments ($F=0.06$, $df=2, 38$, $p=0.94$). Extrapyramidal symptoms, as measured by the Extrapyramidal Symptoms Rating Scale, demonstrated a decided treatment effect ($F=5.6$, $df=2, 38$, $p=0.007$). Because a carryover effect was also detected in this analysis ($F=5.0$, $df=2, 38$, $p=0.01$), only the first period was evaluated. A one-way ANOVA of first-period data from the Extrapyramidal Symptoms Rating Scale detected a group effect ($F=7.3$, $df=2, 19$, $p=0.004$). The number of extrapyramidal symptoms in the haloperidol group (mean=4.1, SD=6.9) was higher in comparison with both the placebo group (mean=1.4, SD=3.0) ($p<0.01$, Newman-Keuls test) and the pimozide group (2.0, SD=3.0) ($p<0.05$, Newman-Keuls test). The effect of pimozide was not significantly different from that of placebo according to the Extrapyramidal Symptoms Rating Scale. AIMS ratings did not differ among the treatments (placebo: mean=0.2, SD=0.7; pimozide: mean=0.4, SD=1.1; haloperidol: mean=0.3, SD=1.1).

The frequency of treatment-limiting side effects, defined as moderate to severe adverse events (e.g., depression, anxiety, severe dyskinesias) that compromise therapeutic benefit, differed according to treatment. These side effects occurred in 41% (N=9) of the 22 patients during haloperidol treatment—a rate threefold higher than that during pimozide treatment (14%, N=3). At least three haloperidol-treated patients developed treatment-emergent depression or anxiety, and two patients experienced academic failure attributed to effects of haloperidol. Most of haloperidol's adverse events were attributable to extrapyramidal symptoms and included akathisia (N=2) and akinesia (N=2). Two pimozide-treated patients experienced weight gain, and one had treatment-emergent anxiety. Electrocardiovascular effects of pimozide and haloperidol were not evident, and both treatments were indistinguishable from placebo in their effects on heart rate, rhythm, and waveform.

## DISCUSSION

Past clinical trials of pharmacotherapy for Tourette's disorder have not specifically studied children and adolescents but instead have studied mixed age groups, with no separate child analysis (7, 8, 14). Children, it may be argued, would be most vulnerable to neuroleptics' adverse effects, particularly extrapyramidal symptoms. This study established a difference in extrapyramidal symptoms between haloperidol and pimozide treatment of Tourette's disorder in children and adolescents. In the same dose range, pimozide was found to be superior to placebo according to the primary tic outcome measure (Tourette Syndrome Global Scale total score). Haloperidol was found not to be different from placebo according to the Tourette Syndrome Global Scale, yet it demonstrated higher Extrapyramidal Symptoms Rating Scale scores and a threefold higher rate of treatment-limiting side effects relative to pimozide.

The pimozide doses used in this study are one-third to one-fourth of those used in Tourette's disorder treatment studies of adults, while the haloperidol dose is comparable (14). The difference in pimozide dose between children and adults is not due to altered pharmacokinetic properties in children, since the biologic half-life of pimozide in children (mean=66 hours, SD=49) is one-half that in adults (mean=111 hours, SD=57), while the areas under the plasma concentration time curve are equivalent (25). A systematic dose bias is induced as the result of pimozide's commercial availability in a single formulation (2-mg tablets). This could explain daily dose ratios of pimozide to haloperidol of 2.5:1 to 1.9:1, even in controlled studies (14). The present study directly compared haloperidol to pimozide at equivalent dose formulations.

In a pivotal comparison in adults with Tourette's disorder (14), pimozide (mean dose=10.7 mg/day, SD=7.2), though demonstrating fewer extrapyramidal symptoms, failed to show a decided advantage in efficacy over haloperidol (mean dose=4.3 mg/day, SD=2.5) on the primary tic outcome measure, in contrast to our finding in the present study of children and adolescents with Tourette's disorder. Shapiro et al. (14) did report, however, a negative correlation of age with clinical improvement on the CGI tic severity scale with both haloperidol and pimozide, supporting greater responsiveness in younger patients. A recent report (13) demonstrating differences in prolactin output between children with Tourette's disorder treated with pimozide (mean=21.6 ng/ml, SD=19.5) and haloperidol (mean=12.9 ng/ml, SD=8.4) at equivalent doses argues for a

heightened pharmacodynamic effect of pimozide in this population (13).

A major impact of this study is the demonstration of haloperidol's greater rate of extrapyramidal symptoms compared to pimozide. Extrapyramidal symptoms in children often go unrecognized by clinicians, but patients are cognizant of these symptoms and report them as "zombie-like" (6). Extrapyramidal symptoms in children with Tourette's disorder can be minimized by drug selection (e.g., pimozide) and treatment dose (≤2 mg/day) (13). It is well known that while Tourette's disorder is a chronic disorder, only 20%–30% of patients elect to continue using haloperidol over time (4). Side effects—extrapyramidal symptoms in particular—should play an important role in medication selection and maintenance.

It should be noted that during haloperidol treatment, two patients had substantial impairment in school performance that severely compromised continued therapy. Treatment-emergent psychiatric illness, such as major depression or anxiety disorder, has been reported in children with Tourette's disorder and attributed to neuroleptic medication (26, 27). In this study, during a 6-week treatment period, two haloperidol-treated patients developed frank depression, which resolved during 2-week placebo washout with no additional intervention. Separation anxiety disorder characterized by school phobia was also associated with haloperidol and resolved during placebo treatment. These patients had no previous history of similar symptoms or diagnoses; however, Stefl (28) reported a high incidence of spontaneous depression in Tourette's disorder. Assignment of causality to haloperidol was impossible because our patients were not rechallenged, but resolution of the depression upon placebo washout suggests this.

Pimozide is superior to haloperidol in relative efficacy in children and adolescents with Tourette's disorder, given equal consideration to its proven efficacy and low incidence of extrapyramidal symptoms in this population. For the individual patient with Tourette's disorder, however, there may be a clear preference for one neuroleptic over the other, suggesting that subtle differences may exist in the pharmacology of haloperidol and pimozide, which are accentuated by the variable expression of Tourette's disorder. Serious long-term neurologic sequelae (5, 29) can be prevented only if neuroleptic guidelines are established directly for potentially vulnerable Tourette's disorder populations and not just adapted from the available adult literature.

**APPENDIX 1. Inclusion and Exclusion Criteria for Subjects in a Study of Haloperidol and Pimozide for Children and Adolescents With Tourette's Disorder**

*Inclusion Criteria*

Principal DSM-III-R diagnosis of Tourette's disorder; may have multiple axis I and axis II diagnoses
Age between 7 years, 0 months, and 16 years, 11 months
Tourette Symptom Global Scale score greater than 20 (symptom severity is great enough to warrant medication)
May have had previous exposure to neuroleptics, but they must have been withdrawn a minimum of 2 weeks before baseline assessment

*Exclusion Criteria*

Diagnosis of chronic motor tic disorder or transient tic disorder
Serious medical illness (e.g., diabetes)
Abnormal ECG that would preclude the use of neuroleptics (e.g., QTc interval >0.47 seconds)
Inability to perform required measurements (e.g., WISC IQ <70)
Use of concurrent medication that may alter or interact with haloperidol or pimozide (e.g., theophylline for the treatment of asthma or stimulants for the treatment of attention deficit hyperactivity disorder)
History of drug or alcohol abuse
Diagnosis of autism or childhood schizophrenia

REFERENCES

1. Singer HS, Walkup JT: Tourette syndrome and other tic disorders: diagnosis, pathophysiology, and treatment. Medicine 1991; 70:15–32
2. Apter A, Pauls DL, Bleich A, Zohar AH, Kron S, Ratzoni G, Dycian A, Kotler M, Weizman A, Gadot N, Cohen DJ: An epidemiologic study of Gilles de la Tourette's syndrome in Israel. Arch Gen Psychiatry 1993; 50:734–738
3. Erenberg G, Cruse RP, Rothner AD: The natural history of Tourette's syndrome: a follow-up study. Ann Neurol 1987; 22:383–385
4. Chappell PB, Leckman JF, Riddle MA: The pharmacologic treatment of tic disorders. Child and Adololescent Psychiatr Clin North Am 1995; 4:197–216
5. Richardson MA, Haugland G, Craig TJ: Neuroleptic use, parkinsonian symptoms, tardive dyskinesia, and associated factors in child and adolescent psychiatric patients. Am J Psychiatry 1991; 148:1322–1328
6. Bruun RD: Subtle and underecognized side effects of neuroleptic treatment in children with Tourette's disorder. Am J Psychiatry 1988; 145:621–624
7. Ross MS, Moldofsky H: A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome. Am J Psychiatry 1978; 135:585–587
8. Shapiro AK, Shapiro E, Eisenkraft GJ: Treatment of Gilles de la Tourette syndrome with pimozide. Am J Psychiatry 1983; 140: 1183–1186
9. Walters JR, Roth RH: Dopaminergic neurons: alteration in the sensitivity of tyrosine hydroxylase to inhibition by endovenous dopamine after cessation of impulse flow. Biochem Pharmacol 1976; 25:649–654
10. Tecott LH, Kwong LL, Uhr S, Peroutka SJ: Differential modulation of dopamine D2 receptors by chronic haloperidol, nitrendipine, and pimozide. Biol Psychiatry 1986; 21:1114–1122
11. Messiha FS: Genetics, haloperidol and pimozide: a comparative study in two mouse strains. Neurotoxicology 1991; 12:47–54
12. Blandina P, Goldfarb J, Craddock-Royal B, Green JP: Release of endogenous dopamine by stimulation of 5-hydroxytryptamine receptors in rat striatum. J Pharmacol Exp Ther 1989; 251:803–809
13. Sallee FR, Dougherty D, Sethuraman G, Vrindavanam N: Prolactin monitoring of haloperidol and pimozide treatment in children with Tourette's syndrome. Biol Psychiatry 1996; 40:1044–1050
14. Shapiro E, Shapiro AK, Fulop G, Hubbard M, Mandeli J, Nordlie J, Phillips RA: Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1989; 46:722–730

15. Chambers WJ, Puig-Antich J, Hirsch M: The assessment of affective disorders in children and adolescents by semistructured interview. Arch Gen Psychiatry 1985; 42:696–702
16. Harcherik DF, Leckman JF, Detlor J, Cohen DJ: A new instrument for clinical studies of Tourette's syndrome. J Am Acad Child Psychiatry 1984; 23:153–160
17. Walkup JT, Rosenberg LA, Brown J, Singer HS: The validity of instruments measuring tic severity in Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1992; 31:472–477
18. Leckman JF, Towbin KE, Ort SI, Cohen DJ: Clinical assessment of tic disorder severity, in Tourette's Syndrome and Tic Disorders. Edited by Cohen DJ. New York, John Wiley & Sons, 1988, pp 55–78
19. Shaffer D, Gould MS, Brasic JA: Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 1983; 40:1228–1231
20. Guy W: ECDEU Assessment Manual for Psychopharmacology. Washington, DC, US Department of Health, Education, and Welfare, 1976
21. Chouinard G, Annable L, Ross-Chouinard A, Kropsky ML: Ethopropazine and benztropine in neuroleptic-induced parkinsonism. J Clin Psychiatry 1979; 40:147–152
22. Keuls M: The use of the Studentized range in connection with an analysis of variance. Euphytica 1952; 1:112–122
23. Zimmerman H, Rahlfs V: Testing hypotheses in the two-period change-over design with binary data. Biometrical Journal 1978; 20:133–141
24. Grizzle JE: The two-period change-over design and its use in clinical trials. Biometrics 1965; 21:467–480
25. Sallee FR, Pollock BG, Stiller RL, Stull S, Everett G, Perel JM: Pharmacokinetics of pimozide in adults and children with Tourette's syndrome. J Clin Pharmacol 1987; 27:776–781
26. Caine ED, Polinsky RJ: Haloperidol-induced dysphoria in patients with Tourette syndrome. Am J Psychiatry 1979; 136: 1216–1217
27. Mikkelsen EJ, Detlor J, Cohen DJ: School avoidance and social phobia triggered by haloperidol in patients with Tourette's disorder. Am J Psychiatry 1981; 138:1572–1576
28. Stefl ME: Mental health needs associated with Tourette syndrome. Am J Public Health 1984; 74:1310–1313
29. Silva R, Magee H, Friedhoff A: Persistent tardive dyskinesia and other neuroleptic-related dyskinesias in Tourette's disorder. J Child and Adolescent Psychopharmacology 1993; 3:137–144