Pimozide was superior to haloperidol for children and adolescents with Tourette's disorder and caused fewer side effects

Sallee FR, Nesbitt L, Jackson C, et al. *Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder*. *Am J Psychiatry* 1997 Aug;154:1057-62.

Objective

To determine the effectiveness of pimozide, compared with haloperidol, in children and adolescents with Tourette's disorder.

Design

24 week randomised, double blind, crossover trial.

Setting

Tic and Tourette clinic of a university medical centre in Charleston, South Carolina, USA.

Patients

22 children and adolescents (mean age 10 y, 77% boys) who had a primary diagnosis of Tourette's disorder according to *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised* criteria. Inclusion criteria were age between 7 and 17 years; Tourette Syndrome Global Scale (TSGS) score >20 ; and if patients had previous exposure to neuroleptics, their withdrawal must have been ≥ 2 weeks before baseline assessment. Exclusion criteria were chronic motor or transient tic disorder, serious medical illness, abnormal electrocardiogram that would preclude the use of neuroleptics, inability to complete required measurements, use of medication that would interfere with study drugs, history of drug or alcohol abuse, or diagnosis of autism or childhood schizophrenia.

Intervention

All patients completed a 2 week placebo baseline period followed up by three 6 week treatment periods consisting of haloperidol, 1 mg/day; pimozide, 1 mg/day; and placebo. 2 week washout periods occurred between the treatment periods. Medication was titrated on a flexible schedule of 2 mg/week within a 4 week period so that the dose at 6 weeks would be optimal. The target was a 70% reduction in tic symptoms from placebo baseline.

Main outcome measures

The primary tic outcome measure was assessed by the TSGS total score. Tic symptoms and behaviour were also assessed using the TSGS subscales, the Clinical Global Impression (CGI) tic severity scale, the Tourette's Syndrome Symptom List (TSSL), and the Children's Global Assessment Scale (CGAS). Side effects were assessed using the Abnormal Involuntary Movement Scale and the Extrapyramidal Symptoms Rating Scale.

Main results

Patients who received pimozide had better mean scores than patients who received placebo on the TSGS total score (17.1 v 26.8, $p < 0.05$), tic subscale score (7.0 v 13.5, $p < 0.05$), and the TSSL tic subscale score (28.8 v 54.1, $p < 0.05$). The mean scores for haloperidol did not differ from placebo. The mean scores for pimozide and haloperidol were superior to placebo on the CGI tic severity scale (3.1 and 3.1 v 4.6) and mean scores on the CGAS for pimozide and haloperidol were also superior to placebo (75.9 and 73.6 v 66.4, $p < 0.05$ for both comparisons). No treatment effect was seen for behavioural outcomes. The groups did not differ for general side effects. For extrapyramidal side effects, however, a greater number occurred when patients were given haloperidol (mean 4.1) compared with placebo (mean 1.4) ($p < 0.01$ for the comparison) or pimozide (mean 2.0) ($p < 0.05$ for the comparison).

Conclusions

Pimozide was effective in the treatment of Tourette's disorder in children and adolescents. Haloperidol was no more effective than placebo according to the Tourette Syndrome Global Scale and was associated with extrapyramidal side effects.

Sources of funding: National Institute of Mental Health; Gate Pharmaceuticals; McNeil Laboratories.

For article reprint: Dr F R Sallee, Institute of Psychiatry, 67 Presidents Street, Room 246, Charleston, SC 29425, USA. Fax +1 803 792 7352.

Commentary

For many reasons, outcome studies in Tourette's syndrome can be fraught with methodological difficulties. Tourette's syndrome is a disorder in which no 2 individuals have exactly the same involuntary movements or vocalisations; motor and vocal ties have a waxing and waning course exacerbated by external factors; and no single tic severity scale adequately measures all aspects of the disorder. The use of neuroleptic medications further complicates the potential study design. For tic suppression, there is no specific dose (eg, pimozide can vary from 1 to 10 mg/d for children) or known therapeutic level.

Clearly, one study can not resolve all of the afore mentioned issues, and although Sallee *et al* are to be complimented on their efforts, some concerns should be raised none the less. Their study design was based

on comparisons of final measurements which is potentially a problem because of the natural fluctuation of tics, that is, tic levels were not reset to a common baseline before each phase. The protocol used a flexible medication titration scale of 2 mg/week which is possibly too rapid for some individuals; the 2 week washout period between treatments may be too brief for neuroleptics and one that could easily produce an order effect; and the results were presented for outcomes at the end of each phase as a single summary mean value, but the large standard deviations presented suggest a wide range of tic severity at the end of each treatment phase.

The strongest evidence and possibly the most generalisable information supporting the use of pimozide over haloperidol in the treatment of tics is related

to side effects. Sallee *et al* show that for this sample of children extrapyramidal symptoms were substantially more common during haloperidol treatment than they were with pimozide and placebo. In our institution, we have had similar results, and pimozide is currently our initial neuroleptic choice after a trial with non-neuroleptic agents (usually clonidine). Lastly, although not mentioned in the study, an electrocardiogram is recommended before the initiation of pimozide because this medication may lead to prolongation of the QT interval and potentially life threatening cardiac arrhythmias.

Joseph Giuliano, RN, BSN
Harvey S Singer, MD

Johns Hopkins University School of Medicine
Baltimore, Maryland, USA