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[Intervention Review]

Pimozide for tics in Tourette's syndrome

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ABSTRACT

Background

Neuroleptic drugs with potent D-2 receptor blocking properties have been the traditional treatment for tics caused by Tourette Syndrome. Pimozide is the most studied of these. Use of these medications is declining because of concerns about side effects, and new atypical neuroleptics are now available. The true benefit and risks associated with pimozide compared to other drugs is not known.

Objectives

To evaluate the efficacy and harms of pimozide in comparison to placebo or other medications in the treatment of tics in Tourette Syndrome.

Search methods

We cross-referenced pimozide and its proprietary names with Tourette Syndrome and its derivations, as MeSH headings and as text words, and searched the Cochrane Movement Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4), MEDLINE (1950-April 2007), and EMBASE (1980-April 2007). Reference lists of relevant articles were reviewed for additional trials.

Selection criteria

All randomized, controlled, double blind studies comparing pimozide to placebo or other medications for the treatment of tics in Tourette Syndrome were considered for inclusion in this review. Both parallel group and crossover studies of children or adults, at any dose and for any duration, were included.

Data collection and analysis

Data was abstracted independently by two authors onto standardized forms and disagreements were resolved by discussion.

Main results

Six randomized controlled trials were included (total 162 participants, age range 7 to 53 years). Pimozide was compared with: placebo and haloperidol (two trials), placebo (one trial), haloperidol (one trial), and risperidone (two trials). Methodological quality was rated 'fair' for all studies. Studies used different outcome measurement scales for assessing tic severity and adverse effects. Significant clinical heterogeneity made meta-analysis inappropriate. Pimozide was superior to placebo in three studies, though it caused more side effects than placebo in one of these. Pimozide was inferior to haloperidol in one of three studies (the other two showed no significant difference between the drugs), which also showed significantly fewer side effects associated with pimozide. No significant differences between pimozide and risperidone were detected.

Authors' conclusions

Pimozide is an effective treatment for tics in Tourette Syndrome, though the number of trials comparing its effect to placebo and other drugs is limited. Trials of longer duration (minimum six months) are needed to investigate the longer-term effects of pimozide compared to atypical neuroleptics. Future trials should use the Yale Global Tic Severity Scale to assess the main outcome measure, and quantify adverse events with the Extrapyramidal Symptoms Rating Scale.

PLAIN LANGUAGE SUMMARY

Pimozide is an effective treatment for tics in Tourette Syndrome.

Pimozide is a well-studied drug used to treat the tics (uncontrolled movements and noises) caused by Tourette Syndrome. There are concerns about side effects associated with pimozide, so it would be helpful to know how it compares to other drugs, and newer drugs.

The review authors searched the medical literature for clinical trials that compared pimozide to other drugs, or a dummy drug (placebo), for treating tics in patients with Tourette Syndrome. The trials identified showed that pimozide was more effective at reducing tics than placebo. It was slightly less effective than the drug haloperidol, but showed fewer side effects. There were no important differences between pimozide and risperidone for either reduction of tics or side effects. In future, if trials could be run for longer, it would help the investigation of the nature of side effects caused by these drugs.

BACKGROUND

Tourette Syndrome is a common childhood onset neuropsychiatric disorder, affecting approximately 1% of children (Khalifa 2005). Tourette Syndrome is defined by multiple motor and one or more vocal tics (repeated, largely involuntary movements/noises) that endure for more than a year (APA 2000).

Historically, the main treatment for tics has been neuroleptic drugs with potent D-2 receptor-blocking properties, such as haloperidol and pimozide. Over time, the use of these medications in Tourette Syndrome and other psychiatric disorders has become less common due to concerns about the risk of extrapyramidal side effects, and the availability of new atypical neuroleptics (Robertson 2000). These atypical neuroleptics have variable D-2 receptor-blocking properties as well as 5-HT receptor-blocking properties, and appear to have a lower risk of extrapyramidal side effects (Correll 2004). Nonetheless, the atypical neuroleptics are associated with metabolic side effects, including weight gain and hyperlipidemia (an abnormally high concentration of fatty substances in the blood) (Fedorowicz 2005).

Given current concerns about the high prevalence of obesity in both children and adults, and the propensity of newer agents to cause weight gain, it is important to weigh the risks and benefits of traditional neuroleptic treatments with the other agents available for the treatment of tics in Tourette Syndrome. While no formal studies have documented the risk of extrapyramidal side effects in those patients with Tourette Syndrome who take neuroleptics, one would not expect the risk to be as high as in neurodegenerative disorders. For this review, we chose to look at pimozide, the most studied of the typical neuroleptics in Tourette Syndrome. A systematic review of all controlled studies of pimozide versus placebo or other drugs is needed in order to understand better the true benefit and risks associated with pimozide in comparison to other treatments.

OBJECTIVES

To evaluate the efficacy and harms of pimozide in comparison to placebo or other medications for the treatment of tics in patients with Tourette's syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized, controlled, double blind studies comparing pimozide to placebo or other medications for the treatment of tics in Tourette Syndrome were included. We included both parallel group and cross-over study designs. Data from both phases of cross-over trials were accepted.

Types of participants

All patients had a clinical diagnosis of TS. The majority of studies specified that patients met Diagnostic and Statistical Manual of Mental Disorders (DSM) III or IV criteria for the diagnosis of TS. Studies with both children and adults were included.

Types of interventions

Trials comparing pimozide to placebo or other medications were included in the review. Any dose of pimozide taken orally, at any stage of the disorder, was included. All trial durations were accepted.

Types of outcome measures

The primary outcome analysed for the review was tic severity, as measured using the following scales or methods:

1. Tourette Syndrome Severity Scale
2. Clinical Global Impression Scale
3. Videotape tic counts
4. Tourette Syndrome Global Scale
5. Tourette Syndrome Symptom List
6. Clinical Global Impression Tic Severity Scale
7. Yale Global Tic Severity Scale
8. Tic Symptom Self Report

The secondary outcome analysed for the review was adverse events, as measured using the following scales or methods:

1. Clinical Global Impressions Scale, Adverse Events
2. Abnormal Involuntary Movement Scale
3. Extrapyramidal Symptom Rating Scale
4. Weight gain (in kilograms)
5. Electrocardiogram (ECG) abnormalities or changes

Search methods for identification of studies

We used the search strategy recommended by the Cochrane Movement Disorders Group to find relevant articles for the review. The search cross-referenced pimozide, and its proprietary names, with Tourette Syndrome and its derivations, as MeSH headings and as text words. The following electronic databases were searched: the Cochrane Movement Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4); MEDLINE (1950- April 2007); and EMBASE (1980- April 2007).

MEDLINE search

- 1 tic disorders/ or tourette syndrome/
- 2 tourette:.mp.
- 3 (tic or tics).mp.
- 4 benzimidazoles/or pimozide;
- 5 (PIMOZIDE or diphenylbutylpiperidine or antalon or orap or (r-6238 or r6238)).mp.
- 6 4 or 5
- 7 or/1-3
- 8 6 and 7
- 9 limit 8 to (human and (clinical trial, all or controlled clinical trial or multicentre study or randomized controlled trial))
- 10 exp clinical trials/
- 11 double blind method/ or random allocation/ or single blind method/
- 12 (clin: adj25 trial).mp.
- 13 (SINGL: or DOUBL: or TREBL: or TRIPL:) adj25 (BLIND: or MASK:).mp.
- 14 or/10-13
- 15 8 and 14

169 or 15

The search was adapted as required for the other included electronic databases. There were no limitations set on language of publication. In addition, the reference lists of review articles on therapy for TS were reviewed for any additional relevant papers.

Data collection and analysis

Assessment of Methodological Quality

Methodological quality was graded for each study according to the quality criteria developed by the US Preventative Services Task Force (Harris 2001). Studies were rated as "good", "fair" or "poor" according to fulfillment of the criteria, which includes:

1. Assembly and maintenance of comparable groups
2. Adequate randomization
3. Allocation concealment
4. Attention to confounders
5. Follow-up (no differential loss to follow-up or high loss to follow-up)
6. Equal, reliable and valid measurements
7. Clear definition of interventions
8. All important outcomes considered
9. Blinding of outcome analysis
10. Intention to treat analysis

According to this system, "good" study fulfills all criteria. A "fair" study fails to fulfill all criteria but does not have a fatal flaw that invalidates its results. A "poor" study contains a fatal flaw, including the assembly of noncomparable groups, the use of unacceptable or unequal measures, lack of blinding of outcome assessment, failure to address key confounders, and a lack of intention to treat analysis. Studies not providing adequate detail to assess a particular criterion (e.g. stating that the study was double blind but not describing the method of allocation concealment) were rated as not having met that criterion.

Selection of studies

All articles appearing to satisfy inclusion criteria were reviewed independently by two reviewers for the inclusion criteria. Disagreements between reviewers about inclusions were resolved by discussion.

Data extraction and management

For the studies included in the review, data was extracted independently by each reviewer (TP and CM) and entered into a summary sheet. Results were compared to ensure accuracy. Discrepancies were resolved by consensus.

Data synthesis

Due to significant clinical heterogeneity and unconventional methods used in the analysis of cross-over studies, we felt it was inappropriate to combine the results of the studies using meta-analysis. Results of each study will therefore be presented individually.

RESULTS

Description of studies

Full details of individual studies are provided in the 'Characteristics of included studies' table.

Our searches identified eight trials that compared pimozide to placebo, or other medications, for the treatment of tics in Tourette Syndrome. Two of the eight studies contained data which were published a second time in one of the six remaining studies; therefore, only six studies were included for the final analysis. One of the six studies was a parallel-group study, four were cross-over studies, and one had both a parallel-group phase and a cross-over phase.

The diagnosis of Tourette Syndrome was usually defined by DSM III or IV criteria. There were 162 patients in total participating in the included trials, with ages ranging from seven to 53 years.

Two of the six studies included in the review evaluated pimozide versus haloperidol versus placebo (Ross 1978; Sallee 1997); a further two evaluated pimozide versus risperidone (Bruggeman 2001; Gilbert 2004); one evaluated pimozide versus haloperidol (Shapiro 1989), and one evaluated pimozide versus placebo (Shapiro 1984). The dosage of pimozide used in patients ranged from 1 to 12 mg. The dosage of haloperidol ranged from 1 to 12 mg, and the dosage of risperidone ranged from 0.5 to 6 mg. The length of each treatment phase ranged from 12 days to eight weeks.

Outcome measures used for the assessment of tic severity varied considerably between studies. The scales used included the Yale Global Tic Severity Scale, the Clinical Global Impression Scale, the Tourette Syndrome Severity Scale, the Tourette Syndrome Global Scale, and the five-minute videotape tic count. In general, a higher score for each of these outcome measures indicates greater tic severity (greater number of tics, more obvious tics, or more disability from tics), except for the Clinical Global Impression Scale, in which a higher score indicates a more favourable response to treatment. The outcome measures used to assess harms of therapy included the Clinical Global Impressions Adverse Events Scale, the Abnormal Involuntary Movement Scale, the Extrapyramidal Symptoms Rating Scale, weight gain in kilograms, and ECG changes or abnormalities.

Three of the four cross-over studies included in the review used an unconventional approach in their analysis of study results. Rather than averaging the difference between treatments for each patient within each sequence and over sequences, results were pooled by treatment type and the means compared (Shapiro 1984; Shapiro 1989; Gilbert 2004). In addition, the method for assessing carry-over effects employed by the studies, the Grizzle Method (Grizzle 1965), has been discredited in recent times and is no longer recommended (Freeman 1989).

Risk of bias in included studies

Study quality was graded according to the quality criteria developed by the US Preventive Services Task Force discussed in the "Methods of the Review" section (Harris 2001). According to these criteria, all 6 studies were rated as "fair". Four of the studies did not describe their methods of randomization (Ross 1978; Shapiro 1984; Shapiro 1989; Sallee 1997), 4 studies did not

describe allocation concealment (Ross 1978; Shapiro 1984; Shapiro 1989; Sallee 1997), 1 study had an unequal distribution of possible confounders (Bruggeman 2001), and one study had a drop-out rate over 20% (Gilbert 2004).

Effects of interventions

Shapiro and Shapiro compared pimozide to placebo in a cross-over study of 20 patients (Shapiro 1984). The mean dose of pimozide used was 6.9 mg per day, and there were two six-week treatment phases. Tic severity, measured using the Tourette Syndrome Severity Scale, was 1.52 at the end of the pimozide phase, versus 4.42 at the end of the placebo phase (P value 0.0001). Videotape motor and vocal tic counts were also significantly lower after the pimozide phase, at 49.36 versus 102.42 in the placebo group (P value 0.0001). Adverse events, measured using the Clinical Global Impressions Adverse Events Scale were significantly higher after the pimozide phase, at 0.65, versus the placebo phase, 0.1 (P value 0.0089). One child developed an asymptomatic abnormal ECG (nonspecific T wave changes) during the pimozide phase which resolved once the drug was stopped.

Sallee et al compared pimozide, haloperidol (Haldol) and placebo in a cross-over study of 22 patients (Sallee 1997). There were three six-week treatment phases, with a two-week washout period between each treatment phase. The mean pimozide dose was 3.4 mg, and the mean haloperidol dose was 3.5 mg. Tic severity, measured using the Tourette Syndrome Global Scale, was 17.1 after the pimozide phase, 20.7 after the haloperidol phase, and 26.8 after the placebo phase (P value 0.02 for pimozide versus placebo, nonsignificant for haloperidol versus placebo). Adverse events, measured using the Abnormal Involuntary Movements Scale, were not significantly different between treatment phases. The Extrapyramidal Symptoms Rating Scale showed that haloperidol had significantly more extrapyramidal side effects than pimozide (P value less than 0.05) and placebo (P value less than 0.01). Pimozide and haloperidol were indistinguishable from placebo in their effects on heart rate, rhythm, and waveform.

Shapiro compared pimozide, haloperidol and placebo in a study of 57 patients using both a parallel-group and cross-over study design (Shapiro 1989). All patients initially entered a six-week parallel study comparing pimozide, haloperidol and placebo. After this parallel phase was completed, patients entered a six-week cross-over study of pimozide versus haloperidol. The mean pimozide dosage used in the study was 10.6 mg, while the mean haloperidol dosage was 4.5 mg. On completion of the parallel phase of the study, pimozide was seen to be significantly superior to placebo in controlling tics as measured by the Clinical Global Impressions Scale, 3.2 versus 1.9 (P value 0.03), but not as measured by the Tourette Syndrome Severity Scale, 2.5 versus 2.9. Haloperidol was significantly superior to placebo on both measures. In the cross-over phase of the study, haloperidol was superior to pimozide using the Tourette Syndrome Severity Scale, 1.4 versus 2.0 (P value 0.011), but with the Clinical Global Impressions Scale, there was no significant difference between pimozide and haloperidol, 3.4 versus 3.5. Adverse events, measured according to the Clinical Global Impressions Adverse Events Scale, were significantly higher in the haloperidol group (but not the pimozide group) in the parallel group phase of the study compared to placebo. There was no difference in adverse events between pimozide and haloperidol during the cross-over phase. There were no clinically meaningful

ECG or cardiac adverse effects for patients treated with haloperidol or pimozide. The QTc interval was significantly prolonged by pimozide, but not by haloperidol or placebo. QTc changes were not associated with drug dosages or the age of patients.

Ross and Moldofsky compared pimozide to haloperidol in a cross-over study of nine patients (Ross 1978). This consisted of two 12-day treatment periods, with a six-day placebo washout between periods. Pimozide and haloperidol dosages ranged from 10 to 12 mg. Tic severity, measured using the mean five-minute videotape tic count, was not significantly different between treatment groups (pimozide 29.4, versus haloperidol 21.9). Adverse events were not formally assessed in this study.

Gilbert compared pimozide to risperidone in a cross-over study of 13 patients (Gilbert 2004). There were two four-week treatment phases, with a two-week placebo washout between treatments. The mean pimozide dosage used was 2.4 mg, while the mean risperidone dosage was 2.5 mg. Tic severity measured on the Yale Global Tic Severity Scale, was 34.2 at the end of the pimozide phase, versus 25.2 at the end of the risperidone phase (P value 0.05). The Extrapyramidal Symptoms Rating Scale showed that there was no difference between phases for adverse events, nor for mean weight gain. There were no significant differences between treatments in changes in ECG parameters. In particular, increases in QTc were minimal and did not approach 450 ms.

Bruggeman compared pimozide to risperidone in an eight week parallel group study of 41 patients (Bruggeman 2001). The mean pimozide dose used was 2.9 mg, compared to 3.8 mg of risperidone. The change in tic severity from baseline to end-point was not significantly different between treatment groups, with the pimozide group improving by 2.3 points, and the risperidone group improving by 2.4 points. There was no significant difference between treatment groups for adverse events, measured on the Extrapyramidal Symptoms Rating Scale, or mean weight gain. No clinically relevant differences in ECG parameters were detected between treatment groups.

DISCUSSION

Principal Findings

Pimozide is significantly superior to placebo for the treatment of tics in Tourette Syndrome. All three studies that compared pimozide to placebo found a significant difference between treatments on at least one outcome scale for tic severity. Side effects did not appear to limit the use of pimozide in the majority of patients during the trial period; only one of the three studies found that pimozide had significantly more side effects than placebo (Shapiro 1984). One study (Shapiro 1989) found that pimozide treatment caused a significantly greater QTc interval on ECG compared to haloperidol and baseline measurements.

Studies comparing pimozide to other agents obtained variable results, which prevent firm conclusions from being drawn. Haloperidol may have greater efficacy than pimozide in the treatment of tics, but this benefit appears to be offset by significantly more side effects, particularly extrapyramidal symptoms.

Currently, there is little evidence for any significant difference between pimozide and risperidone for the treatment of tics in Tourette Syndrome, in terms of either efficacy or side-effect profile.

Methodological heterogeneity, particularly in terms of the outcome measures used, may account for the variable findings. The most consistent shortcoming in the included studies was a failure to describe the randomization process or the method of allocation concealment. The analysis of carry-over effects for the cross-over studies however was generally flawed, as the Grizzle Method – popular at the time many of the studies were performed was discredited in 1989 (Freeman 1989). In addition, the pooling of results on the basis of treatment type is not a conventional method for reporting or analysing the results of cross-over studies. One must therefore take into consideration the flaws of these cross-over studies which may have led to overestimation or underestimation of the treatment effects. Although it is not possible to predict from the data given the direction of bias these analyses may have introduced, these limitations are an additional potential source of heterogeneity in the findings.

AUTHORS' CONCLUSIONS

Implications for practice

Pimozide is an effective treatment for tics in Tourette Syndrome. The balance of the evidence suggests that with short duration therapy (8 weeks or less), pimozide's treatment effect may be slightly inferior to haloperidol and may have fewer side effects, and that there is no significant difference between pimozide and risperidone with respect to efficacy or side effects. Pimozide can prolong the QTc interval, suggesting that ECG monitoring prior to and after initiating therapy is appropriate.

Implications for research

The short length of trials (less than eight weeks) makes it difficult to draw firm conclusions about the comparative risk of side effects such as tardive dyskinesia and weight gain that may not occur immediately. Parallel-group studies of longer duration are needed, therefore, to compare pimozide to other medications for six months or more, in order to evaluate more fully the comparative risk of adverse events of the drugs, and their benefit over longer periods. In addition, trials should sub-analyse results in children, as one might expect efficacy and side effects to differ between children and adults.

Another problem with the existing pimozide trials was the use of different outcome measures, which made it difficult to compare them. At the time that most of these trials were performed, there was no accepted standard for measuring tic severity in patients with Tourette Syndrome. Over the past decade, the Yale Global Tic Severity Scale has been validated as a measure of tic severity in these patients (Leckman 1989; Storch 2007), and has gained widespread use both clinically and in research. Further trials should use the Yale Global Tic Severity Score as the means of assessing the primary outcome of tic severity.

Future trials should also consider the effect of treatment on co-morbidities common in patients with Tourette Syndrome. Neuroleptic medications, in particular, can reduce aggressive behaviour and obsessive compulsive behaviours in patients with Tourette Syndrome, and these should be included as outcomes in future trials.

ACKNOWLEDGEMENTS

The authors acknowledge Dr Prakeshkumar Shah and Dr Joseph Beyene for their comments and assistance with the review.

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References to studies included in this review

Bruggeman 2001 {published data only}

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Sallee F, Dougherty D, Sethuraman G, Vrindavanam N. Prolactin monitoring of haloperidol and pimozide treatment in children with Tourette's syndrome. *Biological psychiatry* 1996;**40**:1044-1050.

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APA 2000 [Computer program]

American Psychiatric Association. 307.23 Tourette Disorder, Diagnostic and Statistical Manual of Mental Disorders, Text Revision. American Psychiatric Publishing Inc, 2000.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Correll 2004

Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second generation antipsychotics: a systematic review of 1 year studies.. *American Journal of Psychiatry* 2004;**161**:414-425.

Fedorowicz 2005

Fedorowicz VJ, Fombonne E. Metabolic side effects of atypical antipsychotics in children: a literature review.. *Journal of Psychopharmacology* 2005;**19**(5):533-550..

Freeman 1989

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Grizzle JE. The two-period change over design and its use in clinical trials.. *Biometrics* 1965;**21**:467-480.

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Robertson 2000

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Storch 2007

Storch EA, Murphy TK, Fernandez M, Krishnan M, Geffken GR, et al. Factor analytic study of the Yale Global Tic Severity Scale. *Psychiatry Research* 2007;**149**(1-3):231-7.

* Indicates the major publication for the study

Bruggeman 2001

Methods	Randomized, double blind, parallel group study. Randomization done using computer generated randomization code. Location: 12 centres in Belgium, the Netherlands and South Africa. Duration: 8 weeks.
Participants	Patients meeting DSM criteria for TS included. 50 patients. 4 withdrawals from Pimozide group, 5 withdrawals from Risperidone group. Age range of participants 11-50. Patients comparable for age and tic severity as baseline. More patients in the Pimozide group had co-morbid Obsessive Compulsive Disorder.
Interventions	Pimozide and risperidone, up to 6 mg/day, blindly titrated by treating physician. Average pimozide dose 2.9 mg, average risperidone dose 3.8 mg.
Outcomes	Tourette Syndrome Severity Scale Clinical Global Impressions Scale Extrapyramidal Symptom Rating Scale Weight gain
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gilbert 2004

Methods	Randomized, double blind, cross-over trial. Randomization by a random number table. Subjects randomized by cluster (block size=8, by site) into sequence 1 (pimozide first, risperidone second) or 2 (risperidone first, pimozide second). Location: 2 centres in the USA. Duration: 12 weeks- 2 weeks placebo, 4 week treatment with drug A, 2 weeks placebo, 4 week treatment with drug B.
Participants	Patients meeting DSM criteria for TS included. 19 patients. 6 dropped out prior to study termination. Mean age 11 years.
Interventions	Pimozide and risperidone, up to 4 mg/day, blindly titrated by treating physician based on benefit and side-effects. Average pimozide dose 2.4 mg, average risperidone dose 2.5 mg. Each medication taken for 4 weeks.
Outcomes	Yale Global Tic Severity Scale Clinical Global Impression Scale- Improvement Tic Symptom Self Report Extrapyramidal Symptoms Ratings Scale Weight Gain
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Pimozide for tics in Tourette's syndrome (Review)

Gilbert 2004 (Continued)

Allocation concealment?	Low risk	A - Adequate
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Ross 1978

Methods	Randomized, double blind, cross-over trial. Randomization method not stated. Location: 1 centre in Canada. Duration: 33 days- 4 days no medication, 12 days drug A, 6 days placebo, 12 days drug B.
Participants	Patients with TS (diagnostic classification system not specified). 9 patients. No withdrawals. Mean age 18.7.
Interventions	Placebo, pimozide and haloperidol, titrated blindly until symptoms disappeared or side effects unmanageable, to maximum dose of 12 mg. All patients received 10 to 12 mg of study drug.
Outcomes	Mean daily 5 minute tic count for last 4 days of each study condition
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B- unclear

Sallee 1997

Methods	Randomized, double blind cross-over trial. Method of randomization not stated. Location: 1 centre in the USA. Duration: 24 week trial. 2 week baseline, 6 week drug A, 2 week washout, 6 week drug B, 2 week washout, 6 week drug C.
Participants	Patients meeting DSM criteria for TS included. 24 patients. 2 withdrawals prior to completion of study. Mean age of participants 10.2 years.
Interventions	Placebo, pimozide and haloperidol, titrated blindly to achieve 70% tic reduction from baseline. Average effective dose 3.4 mg for pimozide, 3.5 mg for haloperidol. Each treatment taken for 6 weeks.
Outcomes	Tourette Syndrome Global Scale Clinical Global Impression Tic Severity Scale Tourette Syndrome Symptom List Abnormal Involuntary Movement Scale Extrapyramidal Symptoms Rating Scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pimozide for tics in Tourette's syndrome (Review)

Shapiro 1984

Methods	Randomized, double blind crossover study. Randomization method not described. Location: 1 centre in the USA. Duration: 14 weeks- 2 week drug free period, two 6 week treatment periods.
Participants	Patients meeting DSM criteria for TS included. 24 patients. 4 withdrawals prior to study completion. Mean age 24.65 years.
Interventions	Placebo and pimozide, titrated flexibly up to 20 mg/day for adults and 10 mg/day for children to achieve a 70% decrease in tic symptoms. Average pimozide dose 6.88 mg/day.
Outcomes	Tourette Syndrome Severity Scale Clinical Global Impressions Scale- Therapeutic effect and Adverse events Physician Global Evaluation Patient Global Evaluation Videotape Tic Counts Adverse Events Record
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Shapiro 1989

Methods	Randomized, double blind study with parallel group phase and cross-over phase. Haldol and pimozide compared to placebo in parallel phase, pimozide compared to haldol in cross-over phase. Randomization method not stated. Location: 1 centre in the USA. Duration: 15 to 21 weeks (depending if allocated to placebo in initial phase of study)
Participants	Patients meeting DSM criteria for TS included. 68 patients entered parallel phase. 11 withdrawals prior to completion of parallel phase. 57 patients entered cross-over phase. 2 withdrawals prior to completion of crossover phase of study. Average age of participants 21 years.
Interventions	Placebo, pimozide and haloperidol, titrated until optimum therapeutic response achieved. Mean pimozide dose 10.6 mg, mean haloperidol dose 4.5 mg.
Outcomes	Tourette Syndrome Severity Scale Clinical Global Impression Scale- Physician and Patient, effect of medication, and adverse events Videotape counts of tics per minute Adverse reaction record
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

WHAT'S NEW

Date	Event	Description
7 October 2008	Amended	Copy edits and reviewer comments incorporated
20 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 2, 2009

Date	Event	Description
4 February 2008	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Division of Neurology, University of Toronto, Canada.

External sources

- Canadian Institute of Health Research, Post-doctoral fellowship, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Dyskinesia Agents [adverse effects] [*therapeutic use]; Haloperidol [adverse effects] [therapeutic use]; Pimozide [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse effects] [therapeutic use]; Tics [*drug therapy]; Tourette Syndrome [*drug therapy]

MeSH check words

Humans