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[Intervention Review]

Non-antipsychotic catecholaminergic drugs for antipsychotic-induced tardive dyskinesia

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ABSTRACT

Background

Tardive dyskinesia (TD) is a disabling movement disorder associated with the prolonged use of antipsychotic medication. Several strategies have been examined in the treatment of TD. Currently, however, there is no clear evidence of the effectiveness of these drugs in TD and they have been associated with many side effects. One particular strategy would be to use pharmaceutical agents which are known to influence the catecholaminergic system at various junctures.

Objectives

1. To determine the effects of any of the following drugs for antipsychotic-induced TD in people with schizophrenia or other chronic mental illnesses.
 - i. Drugs which influence the noradrenergic system.
 - ii. Dopamine receptor agonists.
 - iii. Dopamine receptor antagonists.
 - iv. Dopamine-depletor drugs.
 - v. Drugs that increase the production or release of dopamine.
2. To examine whether any improvement occurred with short periods of intervention (less than 6 weeks) and, if this did occur, whether this effect was maintained at longer periods of follow-up.
3. To examine if there was a differential effect for the various compounds.
4. To examine whether the use of non-antipsychotic catecholaminergic drugs are most effective in those with more recent onset TD (less than five years).

Search methods

We retrieved 712 references from searching the Cochrane Schizophrenia Group Trials Register (July 2015 and April 2017). We also inspected references of all identified studies for further trials and contacted authors of trials for additional information.

Selection criteria

We selected studies if they were randomised controlled trials focusing on people with schizophrenia or other chronic mental illnesses and antipsychotic-induced tardive dyskinesia. We compared the use of catecholaminergic interventions versus placebo, no intervention, or any other intervention for the treatment of antipsychotic-induced tardive dyskinesia.

Data collection and analysis

We independently extracted data from these trials and we estimated risk ratios (RRs) with 95% confidence intervals (CIs). We assumed that people who left the studies early had no improvement.

Main results

There are 10 included trials (N = 261) published between 1973 and 2010; eight are new from the 2015 and 2017 update searches. Forty-eight studies are excluded. Participants were mostly chronically mentally ill inpatients in their 50s, and studies were primarily of short (2 to 6 weeks) duration. The overall risk of bias in these studies was unclear, mainly due to poor reporting of allocation concealment and generation of the sequence. Studies were also not clearly blinded and we are unsure if data are incomplete or selectively reported, or if other biases were operating.

One small, three-arm trial found that both alpha-methyl dopa (N = 20; RR 0.33, 95% CI 0.14 to 0.80; *low-quality evidence*) and reserpine (N = 20; RR 0.52 95% CI 0.29 to 0.96; *low-quality evidence*) may lead to a clinically important improvement in tardive dyskinesia symptoms compared with placebo after 2 weeks' treatment, but found no evidence of a difference between alpha-methyl dopa and reserpine (N = 20; RR 0.60, 95% CI 0.19 to 1.86; *very low quality evidence*). Another small trial compared tetrabenazine and haloperidol after 18 weeks' treatment and found no evidence of a difference on clinically important improvement in tardive dyskinesia symptoms (N = 13; RR 0.93, 95% CI 0.45 to 1.95; *very low quality evidence*). No study reported on adverse events.

For remaining outcomes there was no evidence of a difference between any of the interventions: alpha-methyl dopa versus placebo for deterioration of tardive dyskinesia symptoms (1 RCT; N = 20; RR 0.33, 95% CI 0.02 to 7.32; *very low quality evidence*), celiaprolol versus placebo for leaving the study early (1 RCT; N = 35; RR 5.28, 95% CI 0.27 to 102.58; *very low quality evidence*) and quality of life (1 RCT; N = 35; RR 0.87, 95% CI 0.68 to 1.12; *very low quality evidence*), alpha-methyl dopa versus reserpine for deterioration of tardive dyskinesia symptoms (1 RCT; N = 20; not estimable, no reported events; *very low quality evidence*), reserpine or carbidopa/levodopa versus placebo for deterioration of tardive dyskinesia symptoms (2 RCTs; N = 37; RR 1.18, 95% CI 0.35 to 3.99; *very low quality evidence*), oxypertine versus placebo for deterioration of mental state (1 RCT; N = 42; RR 2.20, 95% CI 0.22 to 22.45; *very low quality evidence*), dopaminergic drugs (amantadine, bromocriptine, tiapride, oxypertine, carbidopa/levodopa) versus placebo for leaving the study early (6 RCTs; N = 163; RR 1.29, 95% CI 0.65 to 2.54; *very low quality evidence*), and tetrabenazine versus haloperidol for deterioration of tardive dyskinesia symptoms (1 RCT; N = 13; RR 1.17, 95% CI 0.09 to 14.92) and leaving the study early (1 RCT; N = 13; RR 0.23, 95% CI 0.01 to 4.00).

Authors' conclusions

Although there has been a large amount of research in this area, many studies were excluded due to inherent problems in the nature of their cross-over designs. Usually data are not reported before the cross-over and the nature of TD and its likely response to treatments make it imprudent to use this data. The review provides little usable information for service users or providers and more well-designed and well-reported studies are indicated.

PLAIN LANGUAGE SUMMARY

Non-antipsychotic catecholaminergic drugs for antipsychotic-induced tardive dyskinesia

Review question.

To determine if catecholaminergic drugs help in the treatment of tardive dyskinesia for people with schizophrenia or similar mental health problems.

Background.

People with schizophrenia often hear voices and see things (hallucinations) and have strange beliefs (delusions). The main treatment of schizophrenia is antipsychotic drugs. However, these drugs can have debilitating side-effects. Tardive dyskinesia is an involuntary movement that causes the face, mouth, tongue and jaw to convulse, spasm and grimace. It is caused by long-term or high-dose use of antipsychotic drugs, is difficult to treat and can be incurable. One suggested treatment is to use medication that affects the catecholaminergic system, which is a group of brain chemicals.

Study characteristics.

The review includes 10 small, short studies published mainly in the 1980s involving a total of 261 people.

Key results.

One small study found that after 2 weeks' treatment both alpha-methyl dopa and reserpine may lead to clinically important improvement in tardive dyskinesia symptoms compared with placebo, but the quality of evidence was low. We are uncertain about the effect of reserpine versus alpha-methyl dopa; quality of evidence was very low. Another small trial compared tetrabenazine and haloperidol after 18 weeks' treatment, but again we are uncertain about the effect as the quality of evidence was very low. The included studies did not report on any harmful effects of the drugs.

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Quality of the evidence.

Evidence is weak, limited, short term, and small scale. It is not possible to recommend these drugs as a treatment for tardive dyskinesia and their use is entirely experimental. There is a need for larger and more rigorous research in the area.

This plain language summary was adapted by the review authors from a summary originally written by Ben Gray, Senior Peer Researcher, McPin Foundation (mcpin.org/).