

There has been very little progress in treating or preventing antipsychotic-induced tardive dyskinesia

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There has been very little progress in treating or preventing antipsychotic-induced tardive dyskinesia

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Commentary on: Bergman H, Walker DM, Nikolakopoulou A, *et al.* Systematic review of interventions for treating or preventing antipsychotic-induced tardive dyskinesia. *Health Technol Assess* 2017;21:1-218.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tardive dyskinesia (TD) is a relatively frequent side effect of long-term use of antipsychotics and there is conflicting evidence if the incidence of TD is lower with second-generation antipsychotics (excluding clozapine), compared with first-generation antipsychotics. Until now there is no evidence-based algorithm to prevent or to treat TD.

METHODS OF THE STUDY

This systematic review¹ evaluated any intervention for treating or preventing deterioration of symptoms of antipsychotic-induced TD in adult patients. Included were all relevant studies, regardless of language, about adults who had used antipsychotic drugs for ≥ 3 months and in whom the antipsychotic doses had been stable for at least 1 month. The authors included 112 randomised trials and eight prospective cohort studies. Seventy-nine separate interventions were the focus of the trials, whereas prospective cohort studies focused on comparing different strategies for antipsychotics. These were grouped into three broad categories: 1. Reducing antipsychotic dose. 2. Switching antipsychotic drug. (3) Adjunctive treatments in addition to antipsychotic drugs. If enough studies were substantively similar, a meta-analysis using fixed-effects analyses was carried out. The authors used the Grading of Recommendations, Assessment Development and Evaluation approach to assess the quality of the evidence for the various interventions. Furthermore, a small consultation of people ($n=6$) with TD/or at risk was planned to measure whether the outcomes of the studies matched service user priorities for managing TD.

WHAT THIS PAPER ADDS

- ▶ The low quality of many of the included trials prevents the construction of an algorithm for treating tardive dyskinesia
- ▶ The authors found low-quality evidence of (1) Clinically important improvement in TD symptoms after 12 weeks for switching antipsychotics to risperidone compared with withdrawing antipsychotics (with placebo) (one study, $n=42$; RR 0.45, 95% CI 0.23 to 0.89) (2) After 6 weeks for buspirone compared with placebo while continuing antipsychotics as usual (one study, $n=42$; RR 0.53, 95% CI 0.33 to 0.84). Also low quality evidence was found for the use of vitamin E to prevent deterioration of TD symptoms compared with placebo while continuing antipsychotics as usual after 1 year (five studies, $n=85$; RR 0.23, 95% CI 0.07 to 0.76).
- ▶ There is very low-quality evidence of clinically important improvement in TD symptoms (1) After 1 year of antipsychotic reduction compared with antipsychotic continuation (two studies $n=17$; RR 0.42, 95% CI 0.17 to 1.04). (2) After 2 weeks of clonazepam compared with phenobarbital as active placebo while continuing antipsychotics as usual (one study, $n=21$; RR 0.44, 95% CI 0.20 to 0.96). (3) Hypnosis or relaxation compared with placebo while continuing antipsychotics as usual for eight sessions (one study, $n=15$; RR 0.45, 95% CI 0.21 to 0.94).

- ▶ Service users ($n=6$) with TD or at risk of developing TD recognised TD as a serious condition that could increase stigma. They were disappointed that many trials have been done without resulting in concrete evidence-based advice. They support that outcomes should also include issues such as social stigma.

LIMITATIONS

- ▶ An issue that is not addressed is that dyskinesia can be 'spontaneous'. Dyskinesia is also present in antipsychotic-naive patients with psychotic disorders.² It has been suggested that 'spontaneous dyskinesia' in antipsychotic-naive patients should be considered as a symptom of psychotic disorders.³ Since there is no test, in patients using antipsychotics, to differentiate between drug-induced and 'spontaneous' dyskinesia, studies for TD will include both. It could be that each of these forms of dyskinesia requires different treatment. For example, if persisting dyskinesia is a psychotic symptom it could be that a switch to clozapine, which is often effective in treatment-resistant psychotic symptoms, is also effective in this form of dyskinesia and less in patients with drug-induced dyskinesia.
- ▶ Another issue that is not addressed is the substantial variability of TD over the years. Especially mild to moderate forms wax and wane, as is shown in the longest follow-up cohort study of inpatients with TD.⁴
- ▶ This systematic review does not differentiate between TD and tardive dystonia. Tardive dystonia is often more physically invalidating than tardive dyskinesia and the treatment also differs.⁵

WHAT NEXT IN RESEARCH

The author's suggest a need for large, long-term randomised-controlled trials or cohort studies and give more advice to increase the quality of the trials. Future research should use electronic instruments to assess the severity of tardive dyskinesia. Instrumental measurement is objective (lacks observer bias), highly reliable (IRR around 0.9), very sensitive (can detect subclinical TD), offers a continuous outcome, may be used in portable devices and requires minimal training.⁴

Although this systematic review does not include a switch to clozapine as one of the 10 interventions prioritised, a recent systematic review shows that patients often benefit with such a switch.⁶

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

No. Due to the disappointing results, this systematic review does not offer treatment options for patients with TD. However, in our specialised movement disorders clinic in Amersfoort (the Netherlands) we often see patients with severe forms of TD or tardive dystonia. We do treat them, and our clinical experience is that especially switching the antipsychotic used to clozapine or adding VMAT-2 inhibitors (tetrabenazine, valbenazine, deutetabenazine) is often helpful.⁷

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