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REVIEW

Treating dopamimetic psychosis in Parkinson's disease: Structured review and meta-analysis

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Meta-analysis

Abstract Psychosis due to dopamimetic treatment is a difficult problem in patients with Parkinson's disease (PD). The aim of this structured review with meta-analysis was to evaluate which neuroleptic drugs can efficiently be used to treat drug-induced psychosis (DIP) in Parkinson's disease. Electronic databases were screened for the key words Parkinson's disease and psychosis. Only 7 trials with a satisfactory allocation concealment and data reporting were included into the study. Two trials compared low-dose clozapine versus placebo with a significantly better outcome for clozapine regarding efficacy and motor functioning. In one trial clozapine was compared against quetiapine showing equivalent efficacy and tolerability. However, in two placebo controlled trials quetiapine failed to show efficacy. In two further placebo controlled trials olanzapine did not improve psychotic symptoms and significantly caused more extrapyramidal side effects. Based on randomized trial-derived evidence which is currently available, only clozapine can be fully recommended for the treatment of DIP in PD. Olanzapine should not be used in this indication.

1. Introduction

The treatment of Parkinson's disease (PD), one of the most common neurologic disorders, regularly includes the use of dopamimetic substances such as L-DOPA, bromocriptine and selegiline (Lim, 2005). Since the early days of L-DOPA treatment, drug-induced psychosis (DIP), mainly consisting of optical hallucinations and paranoid delusions, is one of the major challenges in the treatment of PD (Poewe and Seppi, 2001). DIP can be a dose-limiting side effect even in early dopamimetic therapy in drug naïve patients. Incidence of DIP was found to be between 6% and 22% in newly treated patients during randomized controlled trials (Wint et al., 2004). Occurrence of DIP poses a therapeutical dilemma as treating psychosis with antipsychotics as well as reducing dosage of dopamimetic drugs can lead to a worsening of motor symptoms and may not be tolerable.

Second or third generation antipsychotics are so-called "atypical" drugs because of their low ability to induce extrapyramidal side effects. Thus those drugs are thought to be a feasible treatment option in DIP (Friedman and Factor,

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2000). Especially clozapine has been widely used in this indication as it is virtually free of extrapyramidal side effects. However, it is associated with potentially fatal agranulocytosis (Fitzsimons et al., 2005). Almost all atypical antipsychotics have been used for the treatment of DIP associated with PD (Connemann and Schonfeldt-Lecuona, 2004; Fernandez et al., 2004; Marsh et al., 2001; Targum and Abbott, 2000; Wolters et al., 1990; Workman et al., 1997). However, only limited evidence exists on the efficacy and safety of the different drugs. Open-label studies of newer antipsychotics have yielded contradictory results for olanzapine, risperidone and ziprasidone (Aarsland et al., 1999; Connemann and Schonfeldt-Lecuona, 2004; Gomez-Esteban et al., 2005; Leopold, 2000; Marsh et al., 2001; Meco et al., 1997; Mohr et al., 2000; Molho and Factor, 1999; Rich et al., 1995; Wolters et al., 1996 Workman et al., 1997), while clozapine and quetiapine showed promising results (Arevalo and Gershanik, 1993; Brown, 1999; Fernandez et al., 1999; Frye et al., 1993; Juncos et al., 2004; Lew and Waters, 1993; Meltzer et al., 1995; Wagner et al., 1996; Wolters et al., 1990). However, only small evidence derived from randomized controlled trials exists on the optimal treatment for DIP in PD.

The aim of this structured review and meta-analysis was to examine the optimal treatment for DIP in Parkinson's disease. As no studies exist on tolerability and efficacy of dose reduction of dopamimetic treatment, this review concentrates on randomized controlled trials assessing the efficacy and safety of treatment with atypical antipsychotic drugs.

2. Experimental procedures

2.1. Search strategy

We performed an electronic search for randomized controlled trials assessing the safety and efficacy of atypical antipsychotic drugs. Study participants should be patients with Parkinson's disease suffering from drug-induced psychosis under dopamimetic treatment. Outcome parameters were defined to be: (1) amount of participants leaving the study early; (2) clinical response assessed by standardized psychometric scales; (3) worsening of motor function assessed by standardized rating scales; (4) adverse events.

On February 8, 2006 a search of the following electronic databases was conducted: MEDLINE (Pubmed, 1950–2005), EMBASE (1966–2005, using the DIMDI interface), COCHRANE CENTRAL (1966–2005), ISI-web of knowledge (1995–2005). Databases were screened for the key words Parkinson's disease and psychosis or hallucinations (Pubmed query: ((“parkinson disease”[TIAB] NOT Medline[SB]) OR “parkinson disease”[MeSH Terms] OR parkinson's disease[Text Word]) AND (((“psychotic disorders”[TIAB] NOT Medline[SB]) OR “psychotic disorders”[MeSH Terms] OR psychosis[Text Word]) OR “hallucinations”[MeSH Terms] OR “hallucinations”[Text Word])). Abstracts of all citations were obtained for study selection.

2.2. Study selection

Abstracts of all study citations identified by the searches were independently inspected by all authors, and full reports of the studies of agreed relevance were obtained. Criteria for study selection were:

- reports of randomized clinical trials using antipsychotic treatments including patients suffering from Parkinson's disease and subsequent psychosis due to treatment with dopaminergic drugs.
- Only trials that entertained validated rating scales to assess the psychotic symptoms and the motor symptoms.

Where agreement could not be reached, the full report was acquired for more detailed information. These articles were then independently inspected by all reviewers to assess their relevance for this review. In all cases, agreement could be found whether or not to include a study. Studies published as abstract only were also considered and authors were contacted to obtain additional data. For the screening, no limitations concerning the language were applied, if an English abstract was present. However, all reports considered were written in English.

2.3. Quality assessment

The methodological quality of the trials included in this review concerning allocation concealment, blinding, follow-up and data reporting was assessed. The potential of bias that is strongly related to the allocation concealment (Schulz, 1995) was defined below:

A Low risk of bias (adequate allocation concealment)
B Moderate risk of bias (some doubts about allocation concealment)
C High risk of bias (inadequate allocation concealment)

We included studies that met quality criteria A or B in the Cochrane Collaboration Handbook (Alderson et al., 2005).

2.4. Data collection and analysis

Two reviewers (H.F. and T.H.) independently extracted the data from included studies. In the case of disagreement, a third reviewer (S.B.) also checked the data and the decision was documented. Outcomes were assessed using continuous or dichotomous measures. For continuous data a weighted mean difference (WMD) or where eligible a standardized mean difference (SMD) between groups and a 95% confidence interval (CI) based on a fixed model was estimated. For dichotomous outcomes a relative risk (RR) with 95% CI was estimated also using a fixed model. Obtained results were tested for inconsistency employing the I-squared statistic. An I-squared estimate including 50% was interpreted as evidence of high levels of heterogeneity.

Data were analyzed using Review Manager (RevMan) Version 4.2 for Windows (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen).

Table 1 Characteristics of excluded studies

Study ID	Reason for exclusion
Ellis et al. (2000)	Sample size too small (n=10, 6 completers).
Goetz et al. (2000)	Data given are means (S.D.), while the analyses were based on the non-parametric data (median). As this indicates non-normal distribution of the data, the given figures were not includable into the WMD model.
Wolters et al. (1990)	Cross-over design without parallel groups, no control group, no randomization.