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Oral versus depot antipsychotic drugs for schizophrenia—A critical systematic review and meta-analysis of randomised long-term trials

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ABSTRACT

Objective: Non-adherence is a major problem in the treatment of schizophrenia. Depot antipsychotic drugs are thought to reduce relapse rates by improving adherence, but a systematic review of long-term studies in outpatients is not available.
Method: We searched the Cochrane Schizophrenia Group's register, ClinicalTrials.gov, Cochrane reviews on depot medication, and the reference sections of included studies for randomised controlled trials lasting at least 12 months in outpatients that compared depot with oral antipsychotics in schizophrenia. Data on relapse (primary outcome), rehospitalisation, non-adherence, and dropout due to any reason, inefficacy of treatment and adverse events were summarised in a meta-analysis using a random-effects model. Study quality was assessed with the Cochrane collaboration's risk of bias tool, and publication bias with funnel plots.
Results: Ten studies with 1700 participants met the inclusion criteria. Depot formulations significantly reduced relapses with relative and absolute risk reductions of 30% and 10%, respectively (RR 0.70, CI 0.57–0.87, NNT 10, CI 6–25, P = 0.0009), and dropout due to inefficacy (RR 0.71, CI 0.57–0.89). Limited data on non-adherence, rehospitalisation and dropout due to any reason and adverse events revealed no significant differences. There were several potential sources of bias such as limited information on randomisation methods, problems of blinding and different medications in the depot and oral groups. Other studies reduced a potential superiority of depot by excluding non-adherent patients.
Discussion: Depot antipsychotic drugs significantly reduced relapse. Due to a number of methodological problems in the single trials the evidence is, nonetheless, subject to possible bias.

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1. Introduction

Maintenance treatment with antipsychotic drugs is highly effective in reducing the relapse rates of people with schizophrenia (Davis et al., 1980; Gilbert et al., 1995). However, this effect is jeopardized by high rates of non-adherence to oral medication which has been estimated to occur in as many as 42% of the patients (Cramer and Rosenheck, 1998).

The introduction of second-generation antipsychotic drugs generated enormous hope that medication-adherence would be improved due to fewer side effects, in particular extrapyramidal side effects (Borison, 1997; Buckley, 1997). However, a number of epidemiological analyses have shown that non-adherence to second-generation antipsychotics is not much different than conventional compounds (Dolder et al., 2002; Gilmer et al., 2004; Valenstein et al., 2004).

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Depot antipsychotic drugs could have clear advantages in relapse prevention, because medication intake is assured and because the doctor immediately knows when a patient stops treatment. Nevertheless due to various reasons such as refusal of patients or reservations by psychiatrists (Hamann et al., 2010; Heres et al., 2007, 2008), in some countries such as the US (Ahn et al. 2008) depot formulations are rarely prescribed, while in others such as the UK (Barnes et al., 2009) they are used quite frequently. According to a survey among German psychiatrists less than 36% of patients have ever been offered an antipsychotic depot treatment (Heres et al., 2006).

Moreover, the evidence whether depot formulations really reduce relapse is unclear. While an early meta-analysis by Davis et al. (1994) suggested a significant superiority compared to oral medication, the Cochrane reviews of the various depots did not find any convincing difference (Abhijnhan et al., 2007; da Silva Freire Coutinho et al., 1999; David et al., 1999, 2004, 2005; Dinesh et al., 2004; Hosalli and Davis, 2003; Quraishi et al., 1999; Wong et al., 2004; summarised by Adams et al., 2000). However, these reviews also included studies in inpatients and short-term trials of just a few weeks duration. The inclusion of inpatient studies might have reduced the "depot-effect", because in hospitals medication is usually administered by nurses thereby improving adherence. Therefore outpatient settings are more appropriate to investigate the value of depot antipsychotics. Furthermore, short-term studies are not adequate to examine depot medication, because relapses usually do not occur right after stopping the medication, but often occur after a delay of several months (Gilbert et al., 1995).

2. Materials and methods

2.1. Inclusion criteria

We searched for randomised controlled trials (RCT) that compared intramuscular depot with oral formulations of antipsychotic drugs in people with schizophrenia or related disorders (schizophreniform, schizoaffective or delusional disorder, any diagnostic system, any age and gender, no language restrictions). As people with schizophrenia often do not relapse immediately after stopping medication, we included only long-term studies defined as 1 year or longer. In addition, we included only outpatient studies. In inpatients adherence with oral medication is improved, because nurses hand out the medication directly to the patients making it more difficult to forget or to intentionally not take the medication.

Studies with less than 25% inpatients or with an initial inpatient phase were eligible. We excluded trials with inappropriate randomisation processes (e.g. alternate randomisation, Higgins and Green, 2008).

2.2. Outcome parameters

The primary outcome was the number of participants relapsed as defined in the original studies. Further outcomes were rehospitalisation due to worsening of psychopathology, non-adherence (as defined in the individual studies), and dropout due to inefficacy of treatment, adverse events, and any reason.

2.3. Search

We initially searched the included, excluded and awaiting assessment study sections of the Cochrane Reviews on single depot antipsychotics for which exhaustive searches had already been undertaken (Abhijnhan et al., 2007; da Silva Freire Coutinho et al., 1999; David et al., 1999, 2004, 2005; Dinesh et al., 2004; Hosalli and Davis, 2003; Quraishi et al., 1999; Wong et al., 2004).

We then conducted update searches in the register of the Cochrane Schizophrenia Group (CSG, last search June 2009) which is generated by regular methodical searches in common electronic databases (BIOSIS, CINAHL, Dissertation Abstracts, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, RUSSMED, Sociofile), which was supplemented by hand searching of relevant journals and conference proceedings (for details of the CSG register see the description of the Cochrane Schizophrenia Group (http://szg.cochrane.org/). We made new searches for olanzapine pamoate and paliperidone palmitate. The search terms comprised the names of the respective drug and various terms to identify depot administration (a list of all search terms is presented online as Supplemental material).

We also searched ClinicalTrials.gov (http://clinicaltrials.gov/), the reference sections of all included articles, and we contacted the manufacturers of second-generation antipsychotic depots for further trials. CL selected the articles and SH verified the selection in a random sample of 20%.

2.4. Data extraction and management

Two authors (CL and SL) independently extracted data from the included trials onto standard forms. Disagreements were resolved by discussion or by involving a third reviewer (JD). First authors and pharmaceutical companies were sent our data extraction sheets with requests for missing information and to allow for corrections.

2.5. Risk of bias assessment

Risk of bias with respect to randomisation, allocation, blinding, data completeness, selective reporting and other biases was assessed independently by CL and SL using the instrument described in the Cochrane Handbook (Higgins and Green, 2008).

2.6. Meta-analytic calculations

The primary effect size was the relative risk (presented with 95% confidence intervals (CI)), but we also presented absolute risk differences and in case of significant results, numbers-needed-to-treat/harm (NNT/NNH), calculated as the inverse of the risk difference using the risk in the control groups as a baseline risk. We based the analyses on intention-to-treat data whenever available.

The studies were primarily combined using the Mantel-Haenszel random-effects model by Der-Simonian and Laird (1986), but a fixed-effects model was also used in a sensitivity analysis.

We explored study heterogeneity with a chi-square test of homogeneity ($p<0.1$) together with the I^2-statistic considering

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