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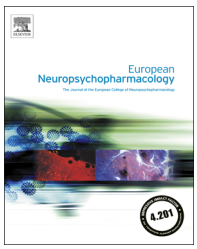

Chlorpromazine versus every other antipsychotic for schizophrenia: A systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs

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Abstract
It is one of the major psychiatric dogmas that the efficacy of all antipsychotic drugs is same. This statement originated from old, narrative reviews on first-generation antipsychotics, but this old literature has never been meta-analysed. We therefore conducted a meta-analysis of randomised controlled trials on the efficacy of chlorpromazine versus any other antipsychotic in the treatment of schizophrenia. If the benchmark drug chlorpromazine were significantly more or less effective than other antipsychotics, the notion of equal efficacy would have to be rejected. We searched the Cochrane Schizophrenia Group's specialized register, MEDLINE, EMBASE, PsychInfo and reference lists of relevant articles. The primary outcome was response to treatment. We also analyzed mean values of schizophrenia rating scales at endpoint and drop-out rates. 128, mostly small, RCTs with 10667 participants were included. Chlorpromazine was compared with 43 other antipsychotics and was more efficacious than four (butaperazine, mepazine, oxypertine and reserpine) and less efficacious than other four antipsychotics (clomacran, clozapine, olanzapine and zotepine) in the primary outcome. There were no statistically significant efficacy differences between chlorpromazine and the remaining 28 antipsychotics. The most important finding was that, due to low numbers of participants (median 50, range 8–692), most comparisons were underpowered. Thus we infer that the old

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antipsychotic drug literature was inconclusive and the claim for equal efficacy of antipsychotics was never evidence-based. Recent meta-analyses on second-generation antipsychotics were in a better position to address this question and small, but consistent differences between drugs were found.

1. Introduction

Despite more than four decades of research one of the major questions of psychopharmacology remains unanswered: do antipsychotic drugs differ in efficacy? The dogma of equal efficacy of antipsychotic drugs probably goes back to an influential narrative review by Klein and Davis who in 1969 found no efficacy differences between the predominantly phenothiazine-based antipsychotics available at that time (Klein and Davis, 1969). This dogma of equal efficacy has been since then codified in numerous textbooks (Buchanan and Carpenter, 2000; Davis et al., 1989; Stahl, 2000) and guidelines which make statements such as "comparable efficacy… among the different first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs)" (PORT Psychopharmacological Treatment Recommendations and Summary Statements) (Buchanan et al., 2010) or "with the possible exception of clozapine … antipsychotics have similar efficacy" (APA Practice Guidelines) (Lehman et al., 2004). However, apart from a methodologically insufficient 'vote count' approach in 1989 (Davis et al., 1989), the question on efficacy differences between first-generation ("typical") antipsychotics has never again been systematically addressed. The dogma has been challenged by meta-analyses which consistently found small, but robust efficacy superiorities of some SGAs compared to some FGAs and other SGAs (Davis et al., 2003; Kishimoto et al., 2013; Leucht et al., 2009, 2003; Zhang et al., 2012). These meta-analyses (Leucht et al., 2013, 2009) and the effectiveness studies CATIE (Lieberman et al., 2005b; McEvoy et al., 2006; Stroup et al., 2006) and CUtLASS (Jones et al., 2006; Lewis et al., 2006) have questioned the classification into 'typical' and 'atypical' antipsychotics and pointed out to the fact that older drugs should not just be abandoned. But the older literature on first-generation antipsychotics – on which the dogma of equal efficacy was originally based – has never been summarised by a systematic review and meta-analysis.

Chlorpromazine, together with haloperidol and fluphenazine depot, are the only antipsychotics listed as "essential drugs" by the World Health Organisation (WHO), (2011). Since chlorpromazine was the first antipsychotic drug developed, it has served as a benchmark for many other compounds. We, therefore, conducted a systematic review comparing the efficacy of chlorpromazine with every other antipsychotic drug, following the general approach of a pivotal Cochrane review comparing the benchmark antidepressant amitriptyline with all other antidepressants (Guaiana et al., 2007). If chlorpromazine were shown to be more or less effective than other antipsychotics, the long-standing dogma of equal eficacy would have to be rejected. As "equal efficacy of all antipsychotics" is one of the major dicta in psychopharmacology, we found it important to systematically address its origin, i.e. the old literature on first-generation antipsychotics, but we also decided to include comparisons with second-generation antipsychotics for completeness.

2. Experimental procedures

2.1. Inclusion criteria

We included all randomised controlled trials that compared oral formulations of chlorpromazine with any other oral antipsychotic for the treatment of schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder, irrespective of the diagnostic criterion used). We did not include trials of intramuscular chlorpromazine as it is mainly used for short-term sedation. Quasi-randomised studies (e.g. randomised by the day of the week) and studies in which allocation was clearly not concealed (e.g. alternate allocation) were excluded (Higgins and Green, 2011). We excluded Chinese studies to avoid a systematic bias as many of them do not use appropriate randomization procedures and do not report their methods (Bian et al., 2006; Wu et al., 2006). Moreover, we found in another meta-analysis that Chinese studies tended to overestimate differences between FGAs and SGAs (Leucht et al., 2009). The quality of all included studies was independently assessed by two out of three reviewers (MS, HC, and BH) using the Cochrane Collaboration's risk of bias tool (Higgins and Green, 2011). No restrictions in terms of age, gender, chronicity of illness, duration of trial and dose range were applied.

2.2. Search

The Cochrane Schizophrenia Group's Register was searched up to August 2009 using the term "chlorpromazin*" (later versions of the register were not available to us). The Schizophrenia Group's Register is compiled by regular systematic searches of more than 15 databases, clinical trial registers, hand searches and conference proceedings. We also searched MEDLINE, EMBASE, PsychInfo and Cochrane Central Register of Controlled Trials up to June 2013 using the term "chlorpromazin* AND schizophrenia". RCTs comparing chlorpromazine with second-generation antipsychotics were also identified through the comprehensive searches made for a recent network meta-analysis of our group (Leucht et al., 2013). Moreover, we inspected the reference lists of included studies and of other reviews on chlorpromazine (Adams et al., 2007; Ahmed et al., 2010; Leucht et al., 2008). No language restriction was applied apart from excluding Chinese trials (Egger et al., 1997b; Gregoire et al., 1995; Moher et al., 1996, 2000).

2.3. Data extraction and outcome variables

At least two of the following three reviewers (MS, HC, BH) independently extracted data from each trial on standard forms. We contacted pharmaceutical companies producing chlorpromazine

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