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Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies

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ABSTRACT

Recently, many authors highlighted the potential advantages of a broader prescription of long-acting injectable antipsychotics (LAIs) based on various assumptions, including favorable pharmacokinetic features. In this systematic review, data from randomized controlled trials comparing LAIs versus the oral formulation of the same antipsychotic were meta-analyzed in order to ascertain whether the route of administration may be associated with a different efficacy and tolerability profile. Of 21 included studies, 18 contributed to the meta-analysis, providing data for risperidone, olanzapine, aripiprazole, zuclopenthixol, fluphenazine and haloperidol. For all drugs, the number of dropouts for any reason (primary outcome) did not differ between the two formulations, except for a small effect in favor of LAI aripiprazole (2 comparisons; 986 patients; relative risk (RR) 0.78; 95% confidence interval (CI) 0.64 to 0.95). Similarly, no differences emerged in terms of dropouts for adverse events, extrapyramidal symptoms, prolactin increase (except for a small advantage for LAI risperidone), weight gain, non-response rate, relapse rate, and dropouts for inefficacy (except for a small advantage for oral olanzapine). Data on aripiprazole proved to be of high quality according to the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation), therefore we are confident that the effect estimate is close to the true effect. Data on risperidone were of moderate quality, while data on olanzapine, fluphenazine, zuclopenthixol and haloperidol were of low quality. In conclusion, there is no robust evidence to support doctors in choosing LAI instead of oral formulations in order to obtain better tolerability and efficacy.

1. Introduction

Schizophrenia is among the top 20 causes of disability worldwide (Vos et al., 2012). The burden of schizophrenia is evident in terms of decreased quality of life, mortality, and social and financial costs (McGrath et al., 2008). According to current evidence, a continued treatment from the early phases of disease may represent a key point for preserving neurocognitive abilities, for preventing structural brain changes, and for hindering the progression towards chronic functional deterioration (McEvoy, 2007; Murray et al., 2016; Pantelis et al., 2003; Perkins et al., 2005). However, treatment adherence is a major issue, considering that up to half patients suffering from schizophrenia may not take their medications as prescribed (Nosé et al., 2003), with serious repercussions on the course of disease in terms of relapse, hospitalization, chronic course and burden of family and caregivers (Haddad et al., 2014; Narasimhan et al., 2009; Wyatt, 1991). Long-acting injectable (LAI) antipsychotics were developed with the primary aim of addressing both hidden and overt non-adherence. Although the well-known disadvantages of LAIs, including pain on the injection site, lack of flexibility in dose adjustments and patients' perception of stigma and coercion (Brissos et al., 2014), several authors highlighted potential advantages of a broader and earlier prescription of these formulations on the basis of various assumptions. First, as LAIs allow a complete tracking of the drug consumption, they may prevent the devastating impact of the loss of even few doses of antipsychotic in early stages of the disease (Llorca et al., 2013; Patel, 2005; Stahl, 2014; Tiihonen et al., 2011). Second, LAIs allow avoiding daily administration, which may be perceived by patients as a practical advantage, and also minimize the risk of self-medication and harmful drug use (Maia-de-Oliveira et al., 2013; Patel, 2005; Taylor and Ng, 2013). Third, considering patients' experience of an overall good balance of efficacy and tolerability in the

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long term, some authors pointed out the need of de-stigmatizing LAIs and overcoming old misconceptions (Iyer et al., 2013; Patel, 2005; Patel et al., 2010; Pietrini et al., 2016; Stevens et al., 2015).

In recent years, it has been suggested that pharmacokinetic differences associated with the route of administration may also be at the basis of possible advantages for LAI over oral formulations. The higher bioavailability of LAI formulations may help identify the lower effective dose, reducing unnecessary toxic serum levels of the drug (Ereshefsky and Mascarenas, 2003). Further, a reduced fluctuation of serum drug levels, and therefore a more stable receptor occupancy (Mannaert et al., 2005), may reduce the troublesome impact of adverse events, including for instance motor symptoms, a challenging problem with oral formulations (Ereshefsky and Mascarenas, 2003; Fleischhacker et al., 1994). Such mechanisms may also lower the phenomenon of up-regulation of dopamine receptors, which underpins the so-called "super-sensitivity psychosis", a severe disease relapse triggered by sudden antipsychotic withdrawal (Moncrieff, 2006). These pharmacokinetic differences seem to primarily impact antipsychotics' tolerability, which may, in turn, affect adherence and overall effectiveness.

It is unclear, however, if these theoretical benefits are also supported by clinical studies comparing the two formulations (LAI versus oral) of the same antipsychotic. So far, in most systematic reviews comparing LAI with oral formulations, patients treated with a mix of different antipsychotics were pooled together and compared (Kirson et al., 2013; Kishimoto et al., 2013; Kishimoto et al., 2014; Leucht et al., 2011). Thus, these reviews are unable to answer whether the formulation alone may explain a different efficacy and tolerability of the same antipsychotic. A narrative review by Zhornitsky and Stip (2012) retrieved 14 randomized trials and 4 observational studies comparing LAI versus oral formulations of the same antipsychotic. A qualitative analysis of data for haloperidol, fluphenazine, zuclopenthixol, risperidone and olanzapine suggested that there may be relevant differences between formulations, however a meta-analysis was not performed. Four Cochrane Reviews (Hosalli and Davis, 2003; Quraishi and David, 2000; Sampson, 1996; Sampson et al., 1996) attempted to address this issue for different antipsychotics, but their searches are outdated and therefore very few studies were included, failing to show any difference between the two formulations. A recent meta-analysis by Misawa et al. (2016) retrieved 16 randomized controlled trials, however data from studies on different antipsychotics were pooled together in the meta-analysis, which prevents from detecting possible differences related to the specificity of each antipsychotic. Further, this review was strictly focused on safety outcomes, while possible differences in terms efficacy or cognition were not investigated. No differences between oral and LAIs emerged in terms of safety (treatment discontinuation due to adverse events: 3570 patients, RR 1.163, 95% CI 0.887 to 1.524).

Against this background, the present systematic review has the following objectives: (a) to ascertain whether the same antipsychotic may show a different tolerability and efficacy profile when given orally or as a LAI; (b) to critically appraise the quality of the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology (Guyatt et al., 2008), in order to produce a tabular synoptic overview of the main review findings and quality, easily understandable for patients, policy makers, research planners, guideline developers and other stakeholders.

2. Methods

The protocol for this review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews) (www.crd.york.ac.uk/PROSPERO/) (CRD42016029651). This review was reported in accordance with PRISMA guidelines (see Supplementary material).

2.1. Type of participants

This systematic review included patients aged 18 or older, of both sexes, with diagnosis of (a) schizophrenia and other related psychosis, or (b) bipolar disorder. Trials recruiting both in- and out-patients were included.

2.2. Type of studies

This systematic review included published and unpublished parallel-group randomized trials. Trials using quasi-random methods were excluded. No limitations were applied with regard to length of follow-up.

2.3. Types of interventions

Studies were included if they compared the LAI formulation with the oral formulation of the same antipsychotic drug. All available LAIs were eligible, including the following: haloperidol decanoate; bromperidol decanoate; zuclopenthixol decanoate; zuclopenthixol acetate; fluspirilene decanoate; fluphenazine decanoate; fluphenazine enanthate; flupenthixol decanoate; perphenazine decanoate; fluspirilene decanoate; pipotiazine undecylenate; pipotiazine palmitate; risperidone microsphere; paliperidone palmitate; olanzapine pamoate monohydrate; and aripiprazole monohydrate. If the control group included a mix of different oral antipsychotics (e.g. risperidone LAI vs. oral second generation antipsychotics), the study was included provided that the randomization was stratified according to the antipsychotic prescribed, as this allowed to include the comparison between the LAI formulation and the subgroup of patients receiving the oral formulation of the same drug, preserving random allocation. Only comparisons employing antipsychotics within therapeutic doses were included, according to Gardner et al. (2010).

2.4. Outcome measures

Dropouts for any reason was the primary outcome of this review. This measure was chosen because: (a) stopping or changing medications is in itself a frequent occurrence and major problem in the treatment of schizophrenia, (b) it is less subject to measurement error, and (c) it can be considered a pragmatic hard product of treatment effectiveness, safety and tolerability, as it integrates patients' and doctors' judgments of therapeutic benefits and harms into one discrete outcome (Barbui et al., 2008; Lieberman et al., 2005).

In addition, the following secondary outcomes were included:

- dropouts due to adverse events: proportion of patients dropping out due to adverse events;
- extrapyramidal symptoms: proportion of patients experiencing clinically relevant extrapyramidal symptoms;
- prolactin increase: proportion of patients experiencing clinically relevant increase of prolactin serum level;
- weight gain: proportion of patients experiencing clinically relevant weight gain;
- treatment responders: proportion of patients with clinically relevant symptom improvement according to change in PANSS score;
- relapse: proportion of patients experiencing at least one relapse, as defined by each study;
- dropouts due to inefficacy: proportion of patients dropping out due to lack of efficacy.

2.5. Search methods for study identification

Literature searches were performed using the following databases (last update: July 2016): PubMed, PsycINFO (database platform: HEBSCOHost), the Cochrane Central Register of Controlled Trials

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