Schizophrenia Research 176 (2016) 220–230

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Safety and tolerability of long-acting injectable versus oral antipsychotics: A meta-analysis of randomized controlled studies comparing the same antipsychotics

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ARTICLE INFO

Article history:
Received 14 February 2016
Received in revised form 16 July 2016
Accepted 19 July 2016
Available online 4 August 2016

Keywords:
Long-acting injectable antipsychotics
Oral antipsychotics
Schizophrenia
Randomized controlled trial
Adverse events
Meta-analysis

ABSTRACT

Objective: We aimed to assess whether long-acting injectable antipsychotics (LAIs), which are initiated in a loading strategy or overlapping with oral antipsychotics (OAPs) and which cannot be stopped immediately, are associated with greater safety/tolerability issues than OAPs.
Method: Systematic review and meta-analysis of randomized controlled trials (RCTs) comparing LAIs and OAPs, including only LAI-OAP pairs of the same OAP (allowing oral risperidone and paliperidone as comparators for either risperidone or paliperidone LAI). Primary outcome was treatment discontinuation due to adverse events. Secondary outcomes included serious adverse events, death, ≥1 adverse event and individual adverse event rates.
Results: Across 16 RCTs ($n = 4902$, mean age = 36.4 years, males = 65.8%, schizophrenia = 99.1%) reporting on 119 adverse event outcomes, 55 (46.2%) adverse events were reported by ≥2 studies allowing a formal meta-analysis. Out of all 119 reported adverse events, LAIs and OAPs did not differ significantly regarding 115 (96.6%). LAIs were similar to OAPs regarding the frequency of treatment discontinuation due to adverse events, serious adverse events, all-cause death and death for reasons excluding accident or suicide. Compared to OAPs, LAIs were associated with significantly more akinesia, low-density lipoprotein cholesterol change and anxiety. Conversely, LAIs were associated with significantly lower prolactin change.
Conclusion: LAIs and OAPs did not differ on all serious and >90% of individual adverse events. However, more studies focusing on adverse event frequencies, severity and time course associated with LAI vs OAP formulations of the same antipsychotic are needed. Additionally, adverse events data for LAIs after stopping overlapping oral antipsychotic treatment are needed.

1. Introduction

Long-acting injectable antipsychotics (LAIs) were introduced in the 1960s in an attempt to improve the long-term treatment of schizophrenia (Kane and Correll, 2010). The use of LAIs is an important option because non-adherence rates that are as high as 50–75% can seriously compromise the efficacy of pharmacotherapy (Dolder et al., 2002; Kane et al., 2013; Velligan et al., 2007). However, LAIs remain an underutilized treatment option in most countries and settings (Kane and Garcia-Ribera, 2009). The reasons for the low prescribing rate of LAIs are manifold and complex (Correll, 2014a, 2014b; Haddad et al., 2015; Hamann et al., 2014; Heres et al., 2006; Heres, 2014), but one reason frequently cited is the fear that LAIs might be associated with significantly greater risk of common and, especially serious adverse events. Reasons for this fear include the fact that, different from oral antipsychotics (OAPs), LAIs are initiated in large single doses, either with a loading strategy or overlapping with OAPs, and that they cannot be discontinued rapidly (Nasrallah, 2007) should a serious adverse event emerge. However, it has also been postulated that LAIs that have lower peak to trough blood level variations (Sheehan et al., 2012) could be associated with less, rather than more adverse events than OAPs.

Due to the lack of clarity whether LAIs have a greater, similar or lower liability for adverse events than OAPs and due to the importance

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http://dx.doi.org/10.1016/j.schres.2016.07.018
0920-9964/

of the concerns about serious adverse events in the context of treatment that cannot be stopped immediately for or against a wider LAI use, we conducted a meta-analysis comparing adverse event outcomes in patients randomized to the same antipsychotic, either as an LAIs or OAPs.

2. Methods

2.1. Search

We conducted a systematic, electronic database search from database inception without language restrictions, using MEDLINE/PubMed, Cochrane library, Embase, PsycINFO and CINAHL (last search: 06/2015). To avoid publication bias, we also included unpublished studies, such as conference proceedings and clinical trial registries (http://clinicaltrials.gov/). Search terms included synonyms of (1) antipsychotic(s); (2) schizophrenia and related disorders, (3) randomized; and (4) depot, (long-acting) injection(s), microsphere, decanoate, palmitate, enanthate, pamoate and once-monthly. The electronic search was supplemented by hand search of reference lists of relevant publications. At least 2 independent investigators (FM, KH, TK) independently conducted the literature search.

2.2. Inclusion criteria

We included randomized controlled trials (RCTs) that randomized patients to the same antipsychotic, either as an LAI and OAP formulation. In case that multiple antipsychotics were part of the OAP arm, we included only studies from which we could obtain data in the OAP group matching the specific antipsychotic used in the LAI group, contacting authors to provide subgroup data. Patients in the included studies had to be >18 years old and have a diagnoses of schizophrenia or schizoaffective disorder according to study diagnoses. We included studies with a duration of at least 8 weeks that provided information about safety/tolerability outcomes. We excluded penfluridol, a once-weekly OAP, considering it neither a LAI nor OAP.

2.3. Data extraction and outcomes

Data were extracted independently by ≥2 reviewers (FM, KH, TK). Authors and companies were contacted to provide missing information and unpublished data. Any disagreements were resolved by discussion.

The primary outcome was the rate of treatment discontinuation due to adverse events. Key secondary outcomes included study-defined serious adverse events, and death. Other secondary outcomes included the proportion of participants experiencing at least one adverse event, and individual adverse event frequencies. We extracted all reported adverse events except for those that were clearly irrelevant to antipsychotics (e.g., influenza, arthropod bite). Since many studies did not explicitly report the number of deaths, but detailed all reasons for study discontinuation, we judged that there was no death if these reasons did not include death.

2.4. Risk of bias assessment

Risk of bias with respect to randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases was assessed by at least 2 independent investigators (FM, KH, TK) using the risk of bias instrument described in the Cochrane Handbook (Higgins and Green, 2011).

2.5. Data analysis

We extracted adverse event data of only those patients who were randomized and who took ≥1 dose of study medication. The comparison of LAI versus OAP was performed across all pooled LAIs. In this analysis, we computed the pooled risk ratio (RR) and standardized mean difference (SMD) with its 95% confidence interval (CI) using the random-effects model (DerSimonian and Laird, 1986). RR values lower than 1 indicate superiority of LAI. SMD values lower than 0 indicate superiority of LAI. Number-needed-to-harm (NNH) was calculated where appropriate. With regard to the heterogeneity, Q, I^2 and p-values were reported. In addition to the primary and secondary outcome analyses, we also conducted subgroup analyses of the primary outcome, seeking to identify potential moderators, methodological biases and whether the findings extended to clinically relevant sub-populations and treatment groups. These analyses included subgroups based on (1) medication group (first-generation LAI (FGA-LAI)/second-generation LAI (SGA-LAI)), (2) individual antipsychotic (e.g., fluphenazine, risperidone), (3) country, (4) treatment concealment (double-blind/rater-masked/open label), (5) sponsorship (pharmaceutical company or not), (6) treatment setting (outpatients at baseline or shortly after initiation of antipsychotic treatment/inpatients/mixed patient status), (7) study duration (<52 weeks/≥52 weeks), (8) mean age (<40 years/≥40 years) (9) lead-in with OAPs before randomization (studies with lead-in phase with OAPs vs. without lead-in phase with OAPs), (10) required OAP overlap after the beginning of LAI treatment (risperidone and aripiprazole vs. other antipsychotics) and (11) study hypothesis (non-inferiority studies/superiority studies). Comprehensive Meta-Analysis, version 3 (http://www.meta-analysis.com) was used for all analyses that were two-tailed with alpha = 0.05, without adjustments for multiple comparisons. Publication bias was assessed with the funnel plot, Egger's regression test (Egger et al., 1997) and the 'trim and fill' method (Duval and Tweedie, 2000), an iterative procedure to assess whether small, extreme included studies and/or potentially unincluded studies biased the true RR estimate.

3. Results

3.1. Search results and study and patient characteristics

Out of 1170 non-duplicated hits, we ultimately identified 16 eligible RCTs with 4902 participants (for details, see Supplemental Fig. 1). Out of 16 RCTs, Two studies were unpublished. Participant numbers ranged between 46 and 1065 (median = 155), and mean study duration was 51.6 (range = 12–104) weeks. Eight studies had double-blind, double-dummy design, 3 were rater-masked, and 5 were open. There were 5 FGA-LAI studies (fluphenazine = 4, zuclopenthixol = 1) and 11 SGA-LAI studies (risperidone = 6, aripiprazole = 2, olanzapine = 2, paliperidone = 1) (Table 1). Patients were on average 36.4 years old, 65.8% were males, and 99.1% had a diagnosis of schizophrenia.

Altogether, 119 adverse event outcomes were reported, with 55 (46.2%) of them being reported by ≥2 studies, allowing for a formal meta-analysis, and with 44 (37.0%) adverse events being reported in >500 patients (Table 2).

3.2. Primary outcome: treatment discontinuation due to adverse events (Fig. 1)

Treatment discontinuation due to adverse events was not significantly different between LAIs and OAPs (RCTs = 14, n = 3570, RR = 1.163, 95%CI = 0.887–1.524, p = 0.275).

3.3. Key secondary outcome 1: serious adverse events (Fig. 2)

The incidence of serious adverse events was not significantly different between LAIs and OAPs (RCTs = 6, n = 1848, RR = 0.907, 95%CI = 0.662–1.242, p = 0.542).