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Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: A systematic review and meta-analysis of randomized-controlled trials

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ABSTRACT

Limited options are available for clozapine-resistant schizophrenia and intolerable side effects of clozapine. We conducted a systematic review of randomized-controlled trials (RCTs) to determine the efficacy and safety of aripiprazole augmentation of clozapine for schizophrenia. Electronic databases searched included PubMed, Scopus, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. This review synthesized the data of four short-term (8–24 weeks), placebo-controlled trials (N = 347). The overall relative risk (RR, 95% confidence interval) of discontinuation rates was not significantly different between groups (RR = 1.41, 95% CI = 0.78 to 2.56). The pooled standardized mean differences (SMDs, 95% CIs) (*Z*-test; number of study; I^2-index) suggested trends of aripiprazole augmentation benefits on overall psychotic [−0.40 (−0.87 to 0.07) (n = 3; $Z = 1.68$, $p = 0.09$; $I^2 = 68\%$)], positive [−1.05 (−2.39 to 0.29) (n = 3; $Z = 1.54$, p = 0.12; $I^2 = 94\%$)], and negative [−0.36 (−0.77 to 0.05) (n = 3; $Z = 1.74$, $p = 0.08$; $I^2 = 54\%$)] symptoms. Despite of no benefit on three cardiometabolic indices (i.e., fasting plasma glucose, triglyceride, and high-density lipoprotein), aripiprazole augmentation was superior for weight change with a mean difference (95% CI) of −1.36 kg (−2.35 to −0.36) (n = 3; $Z = 2.67$, $p = 0.008$; $I^2 = 39\%$) and LDL-cholesterol with a mean difference of −11.06 mg/dL (−18.25 to −3.87) (n = 3; $Z = 3.02$, $p = 0.003$; $I^2 = 31\%$). Aripiprazole augmentation was not correlated with headache and insomnia but significantly associated with agitation/akathesia (RR = 7.59, 95% CI = 1.43 to 40.18) (n = 3; Z = 2.38, p = 0.02; $I^2 = 0\%$) and anxiety (RR = 2.70, 95% CI = 1.02 to 7.15) (n = 1; Z = 2.00, p = 0.05). The limited short-term data suggested that aripiprazole augmentation of clozapine can minimize the cardiometabolic risk, causes agitation/akathesia, and may be effective in attenuating psychotic symptoms.

1. Introduction

Although treatment-resistant schizophrenia causes a huge social and economic burden, only clozapine is widely accepted as the treatment of choice. However, its efficacy and safety are still unsatisfactory. Many patients with schizophrenia have poor or partial response to clozapine. For the responders, most of them have to suffer from cardiometabolic abnormalities related with clozapine, e.g., weight gain, dyslipidemia.

Clozapine is a highly effective antipsychotic medication with serotonin/dopamine antagonism. Its efficacy is superior to many antipsychotic agents (Davis et al., 2003), both the first- and the second-generation antipsychotics (Essali et al., 2009; McEvoy et al., 2006). In addition, it reduces the suicide risk and possibly extends the lifespan of patients with schizophrenia (Meltzer et al., 2003; Tiihonen et al., 2009). However, at least 50% of patients with refractory schizophrenia have poor response to clozapine (Conley and Kelly, 2001), which has been a challenge since those patients need huge assistance for living (Kennedy et al., 2014).

Given that the efficacy of clozapine is superior to other antipsychotic medications, clozapine augmentation by other agents appears to be a common strategy for clozapine-resistant or -intolerant schizophrenia (e.g., severe weight gain). Of 15 augmentation strategies reviewed by Sommer et al. (2012), a fair amount of

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evidence suggests the limited benefits of antipsychotic, lamotrigine, and citalopram augmentation (Miyamoto et al., 2014). Adjunct an antipsychotic medication to clozapine may result in a small benefit (Taylor et al., 2012). Although a meta-analysis found the modest efficacy of lamotrigine augmentation (Sommer et al., 2012), negative findings of a recent RCT caused this add-on strategy more doubtful (Vayisoglu et al., 2013). The benefit of citalopram augmentation was reported in a single RCT (n = 61) and has never been replicated (Lancon et al., 2006). The evidence supporting clozapine augmentation by any pharmacological agent was, therefore, very limited (Porcelli et al., 2012; Sommer et al., 2012).

Another concern of clozapine treatment is its adverse effects, in particular weight gain that is relevant to cardiometabolic risk. Among all antipsychotic medication, clozapine has the highest propensity to cause severe weight gain that can lead to an intolerability of this medication yet after a very short period of treatment (Davis et al., 2014; Mitchell et al., 2013). Limited options are available to mitigate these metabolic problems. Metformin and exercise, commonly used options, may have only modest benefits for clozapine-induced weight gain or metabolic abnormalities (Caemmerer et al., 2012; Maayan et al., 2010).

Together with other antipsychotic agents, aripiprazole is a first-line treatment for schizophrenia (Osser et al., 2013). It differs from others by stabilizing dopamine function through dopamine D2 receptor partial agonism, not D_2 antagonism (Croxtall, 2012). Other pharmacodynamic actions include partial serotonin 5-HT_{1A} agonism and serotonin 5-HT_{2A} antagonism. Although agitation, anxiety, headache, and insomnia are its common adverse effects (Marder et al., 2003; Swainston Harrison and Perry, 2004), aripiprazole is unlikely to cause weight gain or dyslipidemia (Stip and Tourjman, 2010). Little has been known about aripiprazole monotherapy and the combination of aripiprazole with psychotropic medications for clozapine-resistant schizophrenia (Mossaheb and Kaufmann, 2012). However, some open trials of aripiprazole augmentation of clozapine reported the benefits of this regimen in attenuating psychotic symptoms and/or minimizing weight gain (Henderson et al., 2006; Mitsonis et al., 2007; Ziegenbein et al., 2006).

As treatment options for clozapine-resistant schizophrenia are limited and adverse events are an issue of concern, we proposed to carry out a systematic review of randomized-controlled trials to determine the efficacy and safety of aripiprazole augmentation for patients with clozapine-resistant schizophrenia or clozapine-related cardiometabolic risk.

2. Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement (Moher et al., 2009).

2.1. Inclusion criteria

We included all parallel, randomized-controlled trials carried out in patients with schizophrenia who had an unsatisfactory response to clozapine, including not fully responsive and having cardiometabolic risk. Studies with a cross-over design were excluded because antipsychotics are likely to have long lasting effects on psychotic symptoms and cardiometabolic health. Schizophrenia could be diagnosed with any criteria. Aripiprazole was compared with placebo and/or other pharmacological agents as an agent adjunct to clozapine. Other concomitant pharmacological or psychosocial interventions were allowed. Outcomes of interest included treatment efficacy, cardiometabolic indices, and adverse effects.

2.2. Search

Published and unpublished studies were sought by MS. Literature search was done through July, 2014. Electronic databases searched included PubMed, Scopus, Cochrane Central Register of Controlled Trails, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. A set of search terms were 'aripiprazole AND clozapine AND schizophrenia AND (random* OR rct OR control* OR compar* OR placebo)'. The term set of 'aripiprazole AND clozapine AND schizophrenia' was used to search records at the ClinicalTrial.gov (www.clinicaltrials.gov). The Otsuka Clinical Trial Disclosure website (http://clinicaltrialdisclosure.otsukaoiaa.com/) was scanned, and the manufacturer of aripiprazole was contacted. No language or publication restriction was applied.

Articles from all sources were included, duplicates were excluded, and the rest were filtered by using the terms augment*, adjunct*, combin*, conjunct*, add*, plus, or supplement in titles, abstracts, or keywords. Full-text papers of candidate studies were examined.

2.3. Outcomes and data abstraction

Data extraction form was designed to collect study outcomes. Given that antipsychotic discontinuation reflects the judgment of both patients and clinicians on the medication's effectiveness, safety, and tolerability (Lieberman et al., 2005), the global index of treatment effectiveness was defined by the treatment discontinuation rates. Other outcomes of interest were the severity of psychotic symptoms, cardiometabolic risk, and adverse events. The four most frequent treatment-emergent adverse events associated with aripiprazole monotherapy were also examined.

Outcomes were categorized into short- (up to and including 24 weeks or 6 months) and long- (more than 24 weeks or 6 months) terms. For any outcome assessed more than once in a particular term, we extracted only the longest duration results. MS and SS independently extracted the data.

Outcomes related to the severity of psychotic symptoms rated by published rating scales were accepted. When more than one rating scale or subscale was applied, we selected the one that was similar to the rest of data in that particular domain.

Cardiometabolic risks of interest were body weight, low-density lipoprotein (LDL) cholesterol, fasting plasma glucose levels, triglycerides, and high-density lipoprotein (HDL) cholesterol. These five indices were chosen because: i) very good evidence supports the association between obesity/metabolic syndrome and schizophrenia (Leucht et al., 2007), ii) antipsychotic medications have highly differential metabolic effects with the highest risk observed in clozapine-treated patients (American Diabetes et al., 2004; Mitchell et al., 2013), and iii) these parameters are recommended to be regularly monitored in clinical practice (De Hert et al., 2011). Four most frequent treatment-emergent adverse events associated with aripiprazole monotherapy were also examined, including agitation/akathesia, anxiety, headache, and insomnia (Marder et al., 2003; Swainston Harrison and Perry, 2004).

The total number of participants randomized to a study group was considered as the total participants at risk. Means and standard deviations of the change outcomes were extracted. This review gave priority to the change scores because they can remove a component of between-person variability from the analysis. If the change scores were not available, we imputed them by subtracting the baseline means from the endpoint means. For a missing SD, we imputed it from the following data in order: i) standard error, ii) 95% confidence interval (CI) of the outcome of each group, iii) 95% CI or *p*-value of the difference of outcomes and applying the