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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

imputed SD on both comparison groups, iii) imputing a change-from-baseline SD using a correlation coefficient (Higgins and Green, 2011).

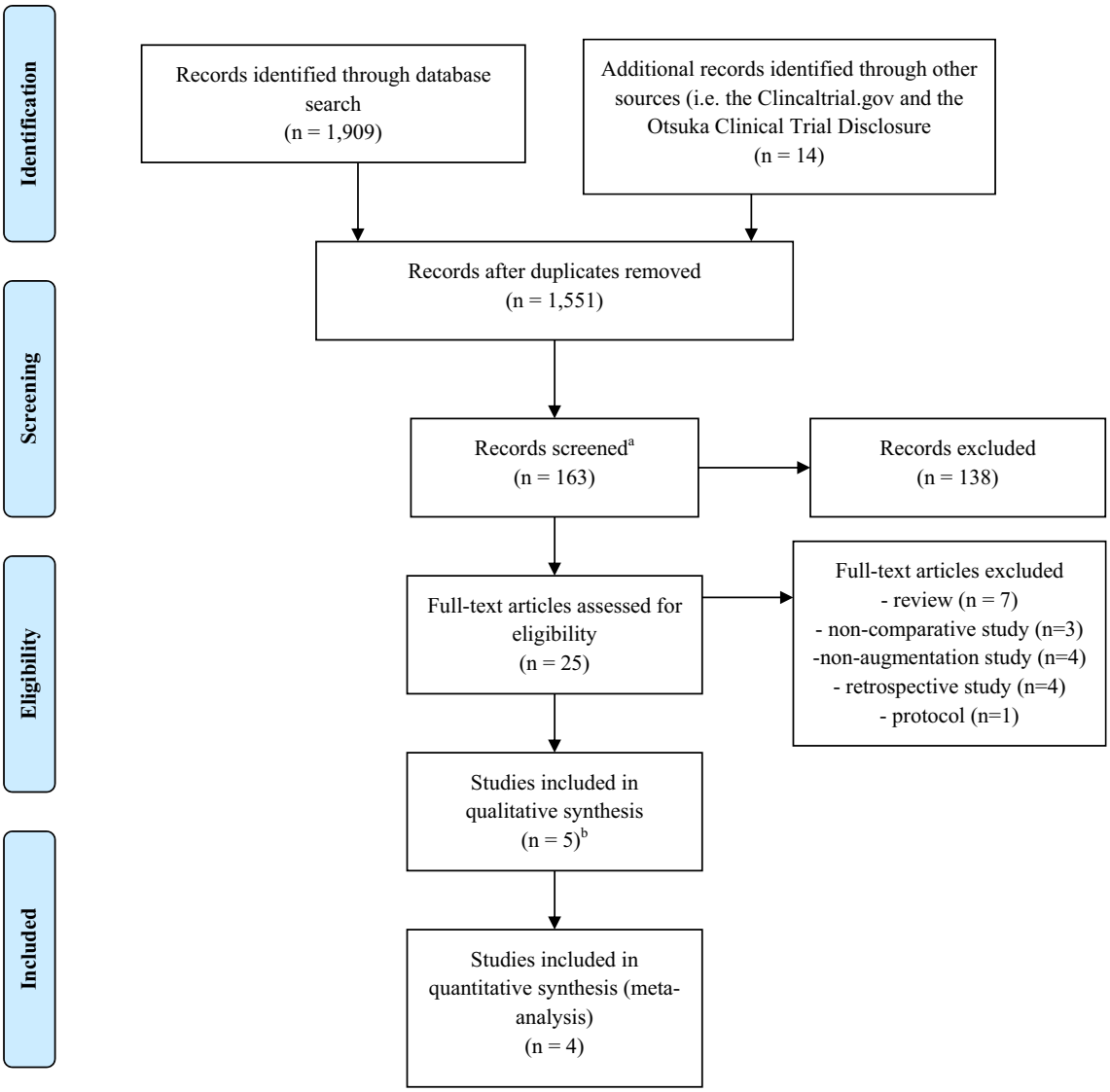
2.4. Risk of bias

MS and SS independently assessed risk of bias by using criteria described in the Cochrane Handbook for Systematic Reviews of Interventions v.5.1.0 (Higgins and Green, 2011). This set of criteria is based on the evidence of associations between effect overestimates and high risk of bias found in trial articles, including sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

For a meta-analysis of more than nine RCTs, we would use a funnel plot to inspect each study against some measures of each trial's size or accuracy. This decision was made because tests for funnel plot asymmetry should be used only when there are at least ten studies included in the meta-analysis (Higgins and Green, 2011).

2.5. Data analysis

The data were synthesized on an intention-to-treat basis. A relative risk (RR) with 95% confidence interval (CI) was computed using the Mantel-Haenszel method. Because various measures are likely to be used for assessing overall psychotic, positive, and negative symptoms, standardized mean differences (SMDs) with 95% CIs were used to synthesize the symptom outcomes. Because the measure of a cardiometabolic index is likely to be similar, a mean difference (MD) with 95% CI was used to combine each index. In synthesizing a continuous outcome, we used the inverse-variance method to weight each study. For each pooled outcome,



[a] Only the articles with the following terms in any fields were included for screening: augment*, adjunct*, combin*, conjunct*, add*, plus, or supplement.

[b] Five RCTs of six articles included.

Fig. 1. Flow diagram: identified records, screened and assessed articles, and studies included in the systematic review.

$p < 0.05$ of the Z test was used to determine the significance of overall effect. Sensitivity analysis was applied for the studies including participants with special characteristics.

Because high heterogeneity might be unavoidable, a random effect model was used throughout the study (DerSimonian and Laird, 1986; Higgins et al., 2009). The inconsistency of data was examined by looking at the graphical display and using both the Cochrane Q's statistic and the inconsistency index (I^2) (Higgins et al., 2003). We defined I^2 of over 0.5 as high heterogeneity and looked for possible explanation if its corresponding p-value of the Q's test was also lower than 0.1 (Hatala et al., 2005). The statistical analysis was performed by using of Review Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

3. Results

3.1. Literature search

The number of records identified through database search and other sources were 1909 and 14, respectively. Records after the duplication removed and filtered were 1551 and 163, respectively. After the 25 full-text articles were assessed, six articles of five RCTs were included in this review (see Fig. 1).

3.2. Main characteristics of included RCTs

Four RCTs were short-term (8–24 weeks) comparison of aripiprazole and placebo in combination with clozapine (Chang et al., 2008; Fan et al., 2013; Fleischhacker et al., 2010; Muscatello et al., 2011) (see Table 1). The data of these four short-term RCTs (n = 347) were quantitatively synthesized. The other long-term RCT (1 year, n = 106, Clozapine Haloperidol Aripiprazole Trial or CHAT) was presented separately because it was clearly unique by comparing aripiprazole and haloperidol in clozapine-resistant schizophrenia (Barbui et al., 2011; Cipriani et al., 2013). All included studies were described as randomized.

Most participant were patients with schizophrenia not fully responding to clozapine. Of 347 short-term participants, ten patients in a study were those with schizoaffective disorder (Fan et al., 2013). The other 337 participants met the DSM-IV diagnostic criteria for schizophrenia. Schizophrenic patients with clozapine-resistant and −induced weight gain participated in a study (Fleischhacker et al., 2010). Because this later study included participants with special characteristics, sensitivity analyses were applied in determining the efficacy and cardiometabolic outcome differences. For the four placebo-controlled trials, the mean doses of aripiprazole and clozapine were 11.1–15.5 mg/day and 290.6–400.0 mg/day, respectively. In the CHAT, the mean doses of aripiprazole, haloperidol, and clozapine were 5.1 mg/day, 1.7 mg/day, and 142.0–161.0 mg/day, respectively. The Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), and Scale for the Assessment of Positive Symptoms (SAPS) and their subscales were used for assessing psychotic symptoms.

3.3. Risk of bias within studies

All included studies were described as randomized. While four trials were 'double-blind' (Chang et al., 2008; Fan et al., 2013; Fleischhacker et al., 2010; Muscatello et al., 2011), the CHAT study applied an open-label design. No study had the problem of incomplete outcome data and selective reporting. The methods of sequence generation and concealment were not described in one study (Fan et al., 2013). Two studies were fully/partly sponsored by Ostuka Pharmaceutical, the manufacturer of aripiprazole (Chang et al., 2008; Fleischhacker et al., 2010) (Fig. 2).

3.4. Imputing SDs

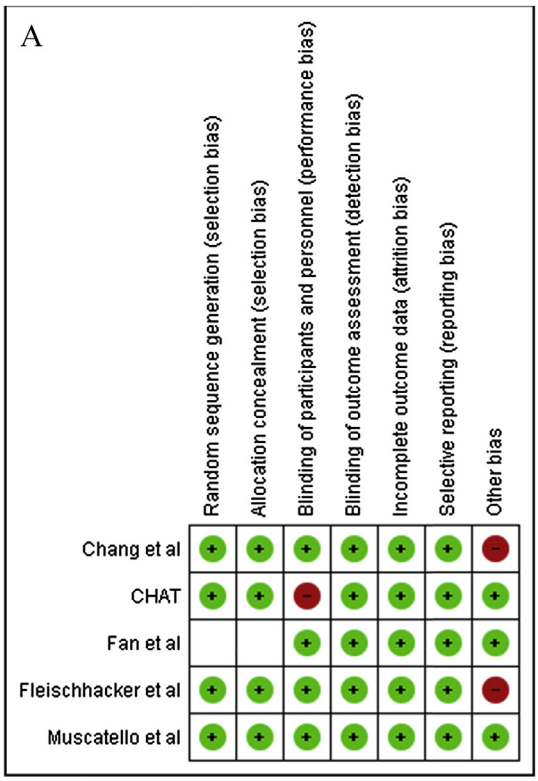
For the study conducted by Fleischhacker et al. (2010), we imputed the SDs of all outcomes from SEs. The SDs of weight changes were imputed from the 95% CI of the difference of weight change and applied on both comparison groups.

For the study of Muscatello et al. (2011), the SDs of the BPRS, SAPS, and SANS change scores were imputed by using the change-from-baseline SDs of another study (Chang et al., 2008) for computing the correlation coefficients.

Table 1
The characteristics of five randomized, controlled trials of aripiprazole augmentation of clozapine in schizophrenic patients with clozapine-resistant or clozapine-related cardiometabolic risk.

Study (authors, year)	Study duration	Participants		Aripiprazole (range, mean mg/d) or comparator	Characteristics		Clozapine dose for combination (mean, mg/d)	Measures of psychotic symptoms		
		Diagnosis	Key characteristics		Total subjects (% male)	Mean age (SD)		Global	Positive	Negative
Chang et al. (2008)	8-wk	DSM-IV schizophrenia	BPRS total score ≥35 or SANS ≥3	Aripiprazole (5–30, 15.5)	29 (75.9)	33.2 (8.2)	304.3[a]	BPRS-T	BPRS-P	BPRS-N[c] and SANS
				Placebo	32 (81.3)	31.7 (7.4)	290.6[a]			
Fleischhacker et al. (2010)	16-wk	DSM-IV-TR schizophrenia	Residual symptoms or safety/tolerability problems while on clozapine and ≥2.5 kg weight gain	Aripiprazole (5–15, 11.1)	108 (63.0)	37.6 (10.9)	384	PANSS-T	PANSS-P	PANSS-N
				Placebo	99 (66.7)	40.5 (9.9)	363			
Muscatello et al. (2011)	24-wk	DSM-IV schizophrenia	Persistent positive or negative symptoms	Aripiprazole (10–15, N/A)	14 (57.1)	31.9 (3.9)	310.7	BPRS-T	SAPS	SANS
				Placebo	17 (52.9)	30.7 (5.3)	341.2			
CHAT (2011) (Barbui et al., 2011; Cipriani et al., 2013)	1-yr	DSM-IV schizophrenia	Persistent presence of positive symptoms	Aripiprazole (N/A, 5.1)	53 (62.3)	40.3 (10.3)	142[b]	BPRS_T	No	No
				Haloperidol (N/A, 1.7)	53 (67.9)	41.5 (9.4)	161[b]			
Fan et al. (2013)	8-wk	Schizophrenia or schizoaffective disorder	Clozapine treatment ≥1 year and stable dose ≥1 month	Aripiprazole (10–15, N/A)	16 (81)	44.3 (8.2)	397	PANSS-T		
				Placebo	14 (64)	44.2 (8.9)	400			

[a] Dose prior to randomization.
[b] Dose at 3 months after randomization.
[c] Because this scale is dissimilar to those in other studies, its data were not included in the meta-analysis.



Green circles = low risk of bias; red circles = high risk of bias; blank space = unclear risk of bias.

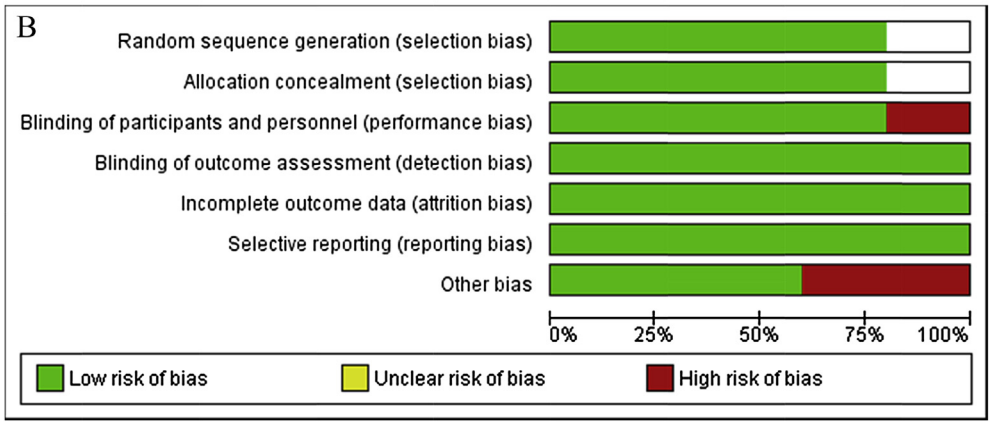


Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item: A. for each included study and B. presented as percentages across all included studies.

3.5. Treatment efficacy

Fig. 3 shows the forest plots of efficacy outcomes. The pooled risk ratio (RR, 95% CI) of the discontinuation rates was 1.41 (0.78 to 2.56) (n = 4; $Z = 1.14$, $p = 0.26$), indicating non-significant difference between groups. Heterogeneity among RCTs was low ($\chi^2 = 1.08$, $df = 3$, $p = 0.78$, $I^2 = 0\%$).

The pooled SMD (95% CI) of changed overall psychotic symptoms was −0.40 (−0.87 to 0.07). The overall effect Z test was 1.68 ($p = 0.09$), suggesting a trend on the benefit of aripiprazole augmentation. However, high heterogeneity among four RCTs was found ($\chi^2 = 9.26$, $df = 3$, $p = 0.03$, $I^2 = 68\%$).

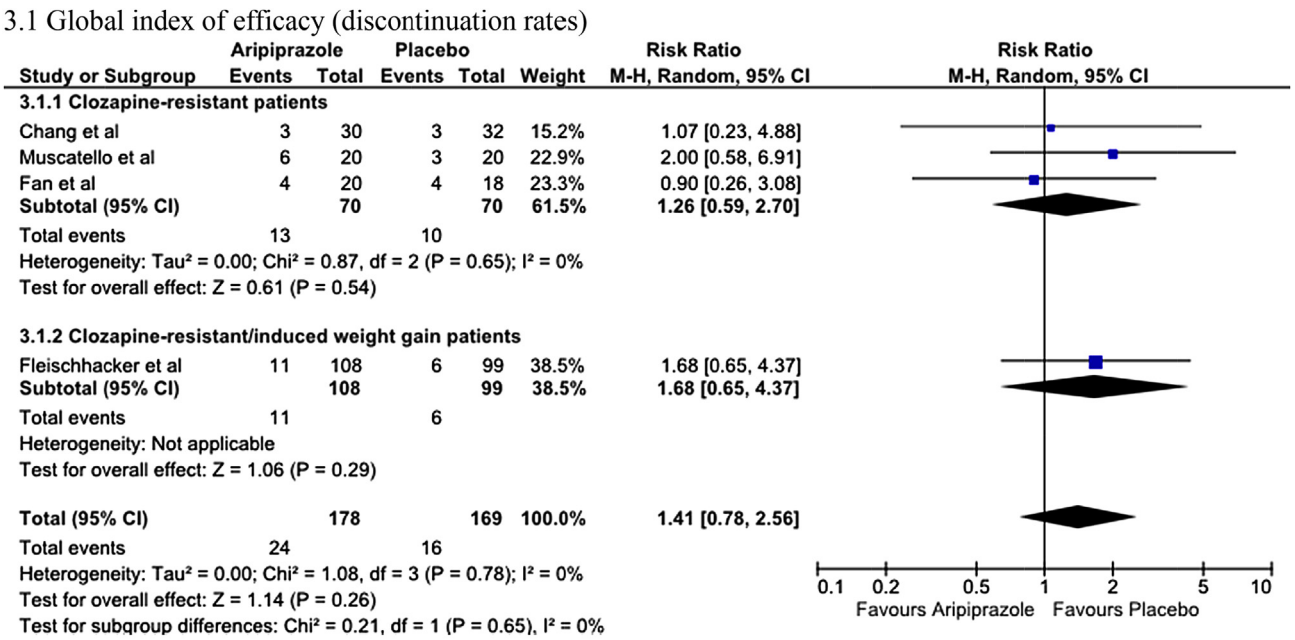
The pooled SMD (95% CI) of changed positive symptoms was 1.05 (−2.39 to 0.29) (n = 3; $Z = 1.54$, $p = 0.12$). The high heterogeneity among the three RCTs was found ($\chi^2 = 36.09$, $df = 2$, $p < 0.001$, $I^2 = 94\%$).

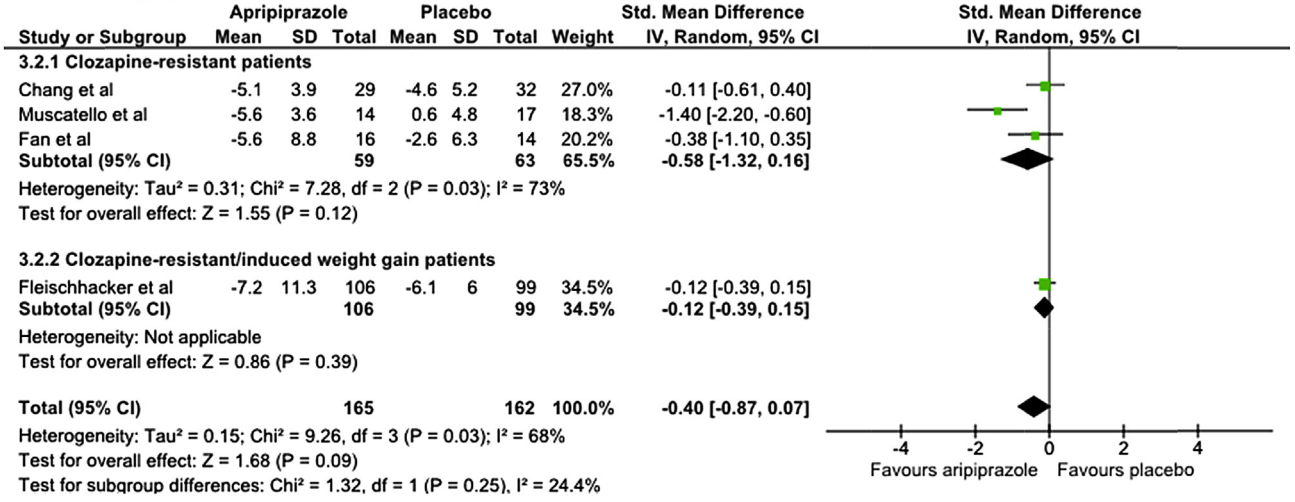
The pooled SMD (95% CI) of changed negative symptoms was −0.36 (−0.77 to 0.05). The overall effect Z test was 1.74 ($p = 0.08$), suggesting a trend on the benefit of aripiprazole augmentation. High but non-significant heterogeneity among the three RCTs was found ($\chi^2 = 4.35$, $df = 2$, $p = 0.11$, $I^2 = 54\%$).

Of four efficacy outcomes, the sensitivity analysis showed that the SMD (95%CI) of the clozapine-resistant group tended to have more response to aripiprazole augmentation than the combined clozapine-resistant and -induced weight gain group on the improvement of negative symptoms (−0.62, −1.04 to −0.20 vs. −0.10, −0.37 to 0.16; I^2 for the subgroup difference = 75.8%).

3.6. Cardiometabolic parameters

The changes of five cardiometabolic indices were available from three RCTs. The pooled MDs (95% CIs) were significantly in favor of





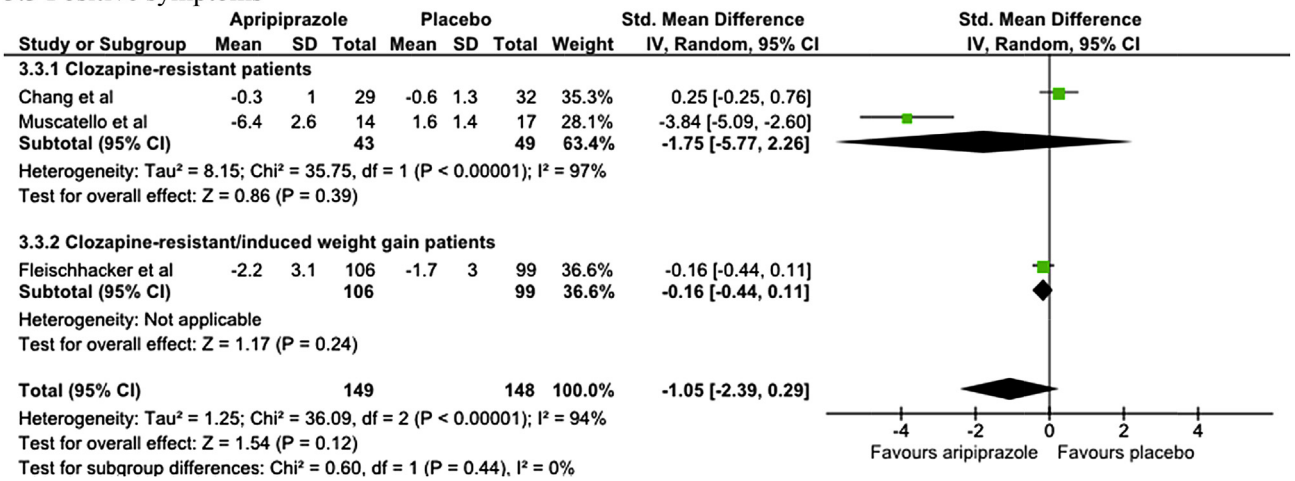


Fig. 3. The relative risks of discontinuation rate and standardized mean differences of psychotic symptoms, comparison between aripiprazole and placebo augmentation of clozapine.

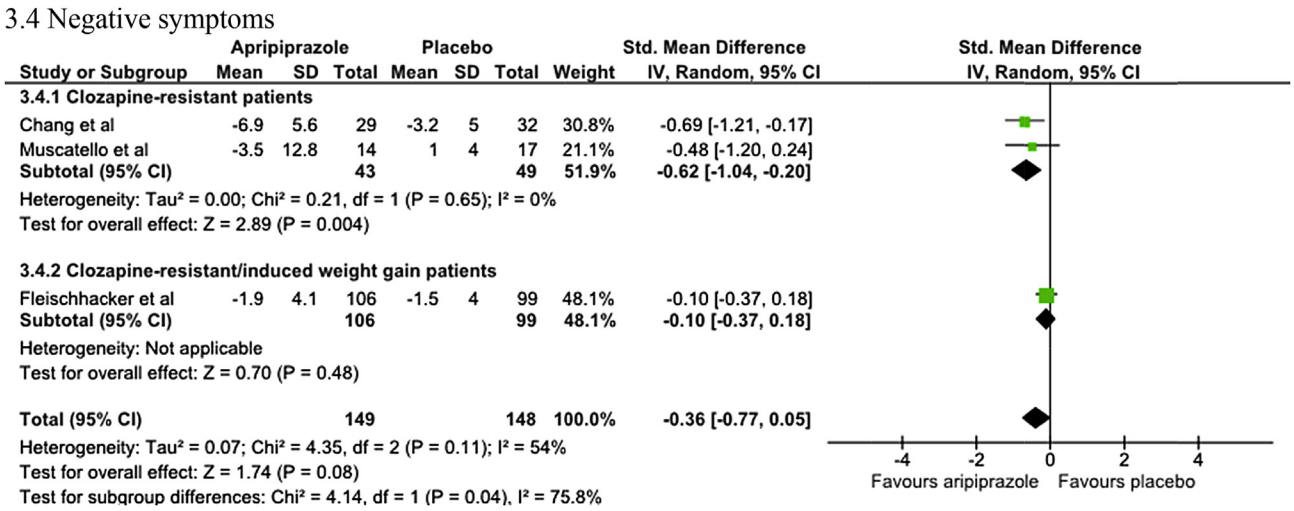


Fig. 3. (*continued*).

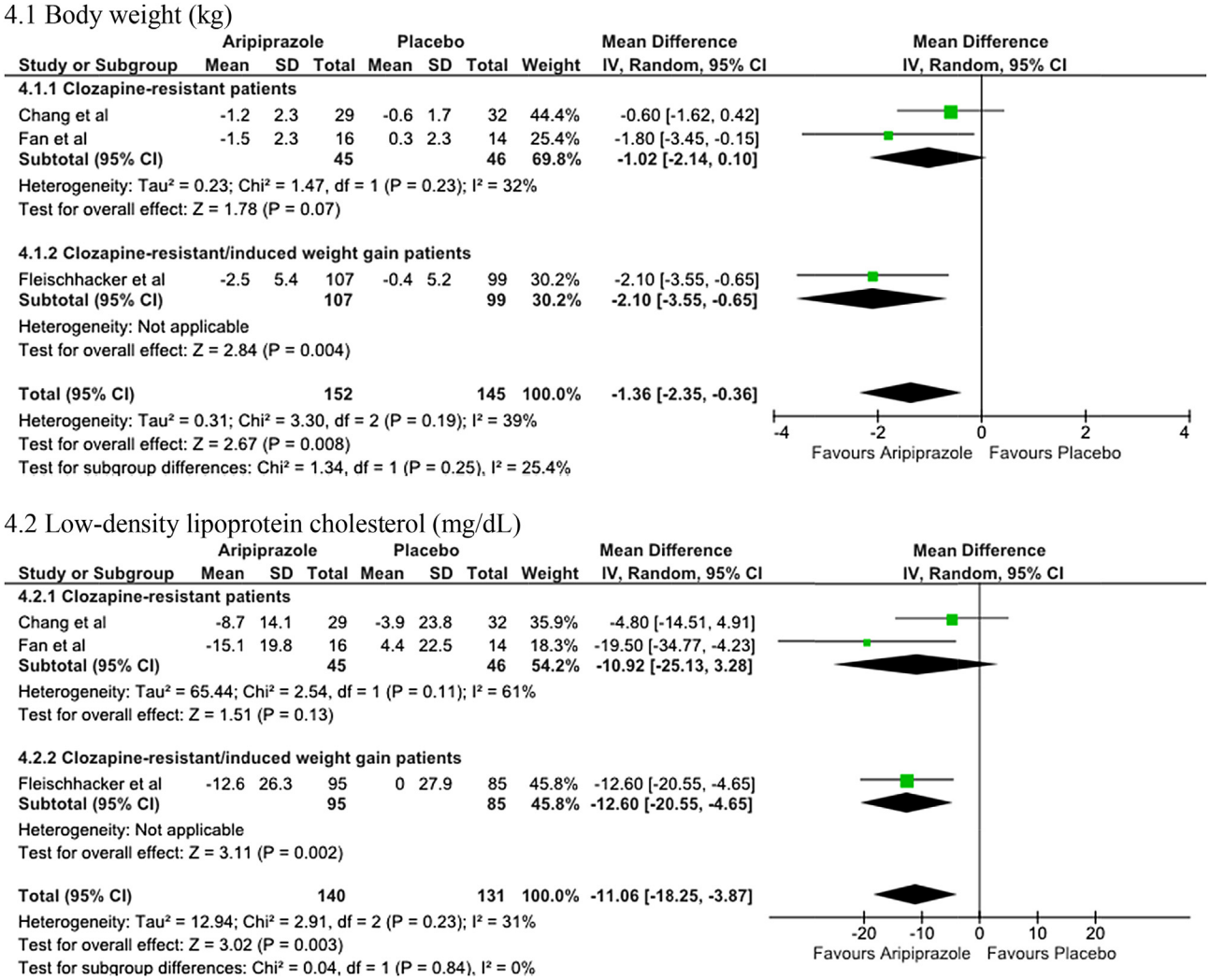


Fig. 4. Two cardiometabolic parameters (4.1 Body weight and 4.2 Low-density lipoprotein cholesterol) found statistically significant differences of the changed means, comparison between aripiprazole and placebo augmentation of clozapine (see Supplement 1 for the other three cardiometabolic parameters found nonsignificant differences of the changed means, including 4.3 Fasting plasma glucose, 4.4 Triglyceride, and 4.5 High-density lipoprotein cholesterol).

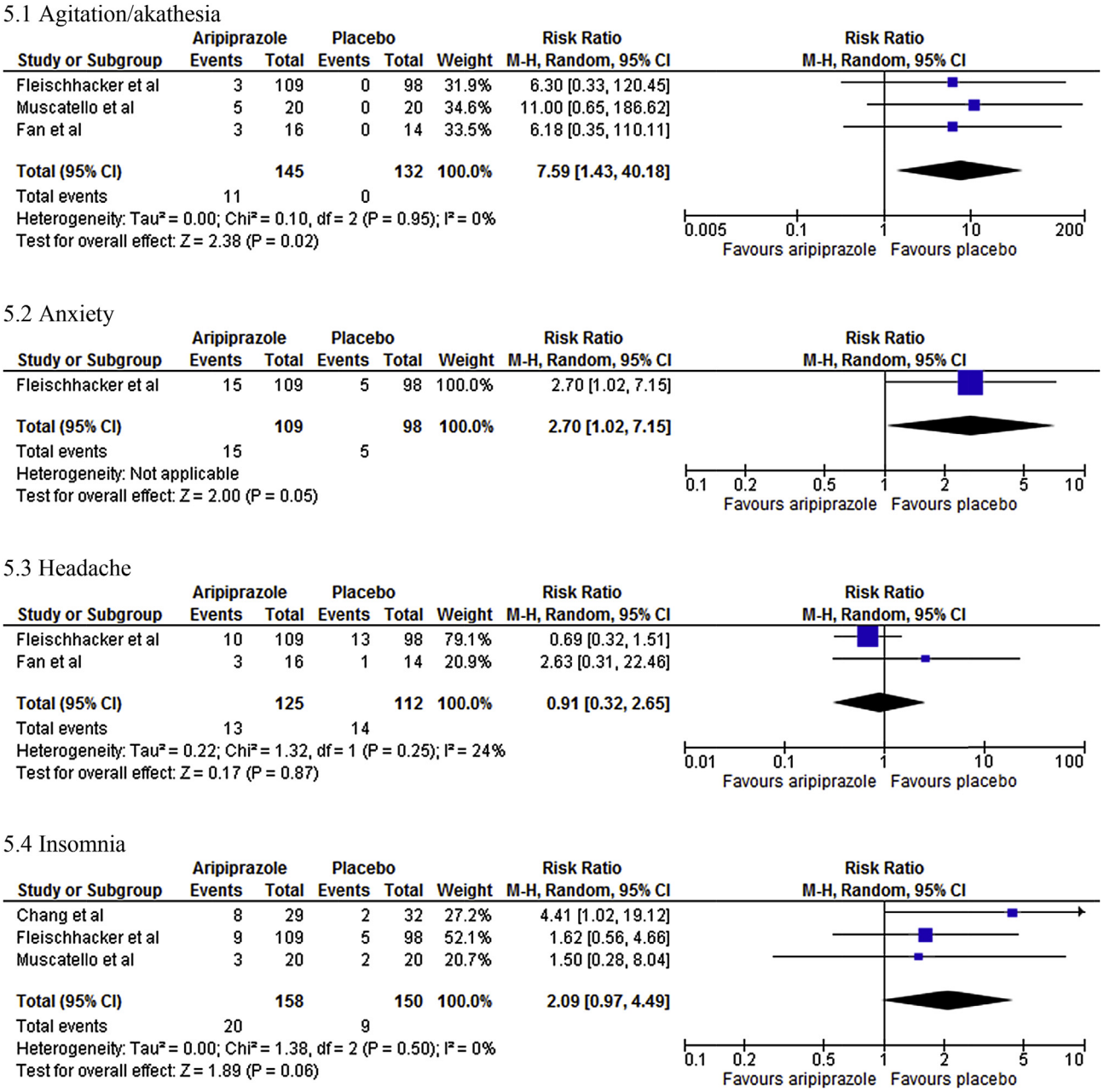


Fig. 5. The relative risks of common adverse effects related to aripiprazole treatment, comparison between aripiprazole and placebo augmentation of clozapine (5.1 Agitation/akatheia, 5.2 Anxiety, 5.3 Headache, and 5.4 Insomnia).

aripiprazole augmentation for weight change, −1.36 kg. (−2.35 to −0.36) (n = 3; $Z = 2.67$, $p = 0.008$) and LDL-cholesterol, −11.06 mg/dL (−18.25 to −3.87) (n = 3; $Z = 3.02$, $p = 0.003$) (see Fig. 4). The pooled MDs (95% CI) showed nonsignificant differences between groups for fasting plasma glucose −1.93 mg/dL (−7.00 to 3.14) (n = 3; $Z = 0.75$, $p = 0.46$), triglycerides −21.48 mg/dL (−51.29 to 8.38) (n = 3; $Z = 1.41$, $p = 0.16$), and high-density lipoprotein cholesterol 0.74 mg/dL (−1.51 to 2.98) (n = 3; $Z = 0.65$, $p = 0.52$) (see Supplement file 1), None of these pooled MDs had high heterogeneity (I^2 between 0% and 45%).

3.7. Common adverse effects

Fig. 5 shows the comparison of common adverse effects between groups. Aripiprazole augmentation was significantly associated with agitation/akathesia (RR = 7.59, 95% CI = 1.43 to 40.18) (n = 3; $Z = 2.38$, $p = 0.02$). We found two trends for the side effects of anxiety (RR = 2.70, 95% CI = 1.02 to 7.15) (n = 1; $Z = 2.00$, p = 0.05) and insomnia (RR = 2.09, 95% CI = 0.97 to 4.49) (n = 3; $Z = 1.89$, $p = 0.06$). The risks of headache were not significantly different (RR = 0.91, 95% CI = 0.32 to 2.65) (n = 2; $Z = 0.17$, $p = 0.87$). None of the pooled RRs had high heterogeneity (I^2 between 0% and 24%).

3.8. Descriptive comparison of aripiprazole and haloperidol augmentation

After 3 months, the discontinuation rates of aripiprazole and haloperidol groups were not significantly different (13.2% vs. 15.1%, $p = 0.78$). The mean changes of BPRS scores were also not

significantly different (−5.9 vs. −4.4, $p = 0.52$). The overall adverse effects, as measured by the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), was significantly decreased in the aripiprazole group (−7.4 vs. −2.0, $p = 0.006$).

After 12 months, the discontinuation rates of aripiprazole and haloperidol group were still not significantly different (35.8% vs. 28.3%, $p = 0.41$).

4. Discussion

The short-term meta-analytic results suggested that aripiprazole augmentation of clozapine had trends of benefits on psychotic symptoms. The effect sizes for overall, positive, and negative psychotic symptoms were medium to large (SMDs between 0.36 and 1.05), but their trends (p's for the Z tests between 0.08 and 0.12) suggested the uncertainty of these benefits. It could minimize some cardiometabolic risks by reducing body weight for a mean of 1.36 kg and LDL for a mean of 11.06 mg/dL. However, it could also cause treatment-emergent agitation/akathesia and anxiety. The undifferentiated global index of efficacy, as determined by the discontinuation rates, was in line with the aforementioned findings of benefits and harms. Due to the dearth of long-term data, the results obtained from the haloperidol-controlled, randomized trial may not support or against the use of this approach.

By adding more evidence, the present review found a more optimistic view of aripiprazole augmentation in attenuating psychotic symptoms than the previous meta-analysis (Sommer et al., 2012). Mainly, such improved view was caused by the more favorable outcomes observed in the latest study carried out by Muscatello and colleagues (Muscatello et al., 2011). While the data of this study might be the cause of data heterogeneity, it is of interest to note that this is the placebo-controlled, randomized trial with the longest study duration (24 weeks). These later findings might suggest that the efficacy of aripiprazole for clozapine-resistant schizophrenia is delayed and can be observed only after several months of augmentation. Further placebo-controlled trial with study duration of 24 weeks or more may be helpful in determining the benefits of aripiprazole augmentation on psychotic symptoms.

The sensitivity analytic results may suggest that patients with clozapine-resistant schizophrenia would have more improvement on negative symptoms than those with clozapine-induced weight gain. In the study of Fleischhacker et al. (2010), participants with clozapine-induced weight gain might respond well to clozapine pre-trial treatment and had only mild psychotic symptoms before participating in the augmentation study. So, only the modest improvement on negative symptoms could be observed (floor effect).

By adding the results of a study (Chang et al., 2008), the present meta-analytic findings of 3 RCTs confirm the benefits of aripiprazole augmentation on weight reduction reported in a recent meta-analysis including 2 RCTs (Mizuno et al., 2014). New findings of this review are the benefits of this augmentation in decreasing LDL-cholesterol levels and its treatment-emergent adverse effects of agitation/akathesia, anxiety, and insomnia.

There were some limitations of this systematic review. First, the meta-analysis included only the data obtained from four short-term studies carried out in 347 patients who were mainly diagnosed as clozapine-resistant schizophrenia. In small studies or small meta-analyses, it is common for the range of effects contained in the confidence interval to include both no intervention effect and a substantial effect (Higgins and Green, 2011). Together with the heterogeneity of data, this small sample size problem may be a key for the uncertainty of therapeutic effects anticipated from aripiprazole augmentation. Second, only one placebo-controlled trial had a 6-month study duration, while the rest lasted between 8 and 16 weeks. Last, we did not test the publication bias of the present meta-analysis because only a small number of RCTs were found.

Despite of the aforementioned limitations, the present findings still suggest that aripiprazole augmentation may be a promising approach for patients with clozapine-resistant schizophrenia or clozapine-related cardiometabolic risk. The benefit on psychotic symptoms and cardiometabolic health should be weighed against its common side effects. Given that no treatment strategy for clozapine-resistant schizophrenia is widely accepted, a trial of this approach may be worth for some patients. Agitation/akathesia, anxiety, and insomnia should be closely monitored and properly handled. Further studies on aripiprazole and other augmentation treatments that might increase the efficacy or minimize the cardiometabolic side effects of clozapine are still needed. Priority should be given to clinical trials that last six months or more. Trends on the benefits of psychotic improvement suggest that some patients may be likely to improve with aripiprazole augmentation. Pharmacogenetic or other predictive studies may be useful in identifying patients who are likely to respond to this augmentation.

In conclusion, the limited data suggest that short-term aripiprazole augmentation of clozapine can minimize some cardiometabolic risk but also causes agitation/akathesia. We need more data to support its benefits in attenuating psychotic symptoms and its side effects of anxiety, and insomnia. Further studies on aripiprazole and other augmentation treatments that might increase the efficacy or minimize the cardiometabolic side effects of clozapine are still needed.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2015.01.004.

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Contributors

M. Srisurapanont conceived the idea, designed the meta-analyses, searched and collected data, extracted and analyzed data, and wrote first draft of the manuscript. S. Suttajit assisted with design of the meta-analyses, extracted and analyzed data, and manuscript preparation. N. Maneeton assisted with design of the meta-analyses, analyzed data, and manuscript preparation. B. Maneeton assisted with design of the meta-analyses, analyzed data, and manuscript preparation. All authors read and approved the final manuscript. No writing assistance was utilized in the production of this manuscript.

Conflict of interest

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