Can Aripiprazole Worsen Psychosis in Schizophrenia?

A Meta-Analysis of Double-Blind, Randomized, Controlled Trials

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ABSTRACT

Background: Numerous case reports have reported psychotic worsening when switching to or adding aripiprazole in patients with schizophrenia. The risk of psychotic worsening related to aripiprazole was evaluated through a systematic review and meta-analysis.

Data Sources: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were systematically searched using the following keywords: *(schizophr** or *schizoaff*)* AND *aripiprazole*, with a limitation of randomized controlled trial and English language (last search: September 9, 2016) by the authors in an independent fashion.

Study Selection: Double-blind, randomized, controlled trials involving a switch to or addition of aripiprazole in schizophrenia spectrum disorders were selected by the authors in an independent fashion. A total of 22 studies (13 switching and 9 adding studies) involving 5,769 patients that met eligibility criteria were identified and included in the meta-analysis.

Data Extraction: Number of patients who experienced psychotic worsening, agitation, or anxiety as well as those who discontinued the study due to all causes, lack of efficacy, or adverse events were extracted.

Results: Psychotic worsening was reported as an adverse event in all studies. No significant difference in the risk of psychotic worsening was found between switching to aripiprazole and switching to another antipsychotic (RR = 1.17, 95% CI = 0.97–1.42, $P = .10$); however, switching to aripiprazole was related to a significantly greater risk of study discontinuation due to lack of efficacy (RR = 1.46, 95% CI = 1.10–1.93, $P = .009$). Lack of data resulted in no conclusive results as to clinical risks of adding aripiprazole.

Conclusions: Findings suggest that there is no direct evidence that a switch to aripiprazole is related to risk of psychotic worsening in participants in clinical trials, although a switch to aripiprazole may be associated with a higher risk of study discontinuation due to lack of efficacy.

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Numerous case reports have noted psychotic worsening induced by aripiprazole in patients with schizophrenia spectrum disorders. In total, we identified 22 cases through a systematic literature search in August 2012, and found that in 11 of these, psychotic exacerbation was highly associated with aripiprazole, while in 8 cases, psychotic symptoms worsened after simply adding aripiprazole to the current regimen.[1] Since, further case reports have been published,[2–4] suggesting that this issue still attracts attention in clinical practice. Psychotic worsening in conjunction with aripiprazole is assumed to pertain to its partial agonistic action at dopamine D_2 receptors, which stands in contrast to the action of other antipsychotic agents.[1] Taken together with aripiprazole's very high D_2 receptor affinity, patients already treated with antipsychotics may have a greater risk of psychotic worsening than drug-naïve patients because D_2 receptor up-regulation as a consequence of long-term antipsychotic exposure could result in increased dopaminergic activity (ie, supersensitivity psychosis). Indeed, most cases included in the systematic review were characterized as being chronic.[1]

This said, meta-analyses of randomized controlled trials (RCTs) have demonstrated non-inferiority in efficacy for aripiprazole versus other antipsychotics in schizophrenia.[5–7] To address this discrepancy in the literature and better estimate risk of psychotic worsening related to aripiprazole, which cannot be established from case reports, we conducted a systematic review and meta-analysis of double-blind RCTs switching to aripiprazole from another antipsychotic or adding aripiprazole to another antipsychotic. We hypothesized that risk of psychotic worsening increases with switching to or adding aripiprazole when compared to doing the same with other antipsychotics.

METHODS

Literature Search

We conducted a systematic literature search in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[8] MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched using the following keywords: *(schizophr** or *schizoaff*)* AND *aripiprazole*, with a limitation of randomized controlled

Clinical Points

- Psychotic worsening was reported as an adverse event in all 22 randomized controlled trials included in the current meta-analysis.
- For studies evaluating switching to aripiprazole, no significant difference was found in the risk of psychotic worsening between aripiprazole and other antipsychotics, while aripiprazole was related to a significantly greater risk of study discontinuation due to lack of efficacy.
- For studies evaluating adding aripiprazole, lack of data resulted in no conclusions as to clinical risks associated with aripiprazole.

trial and English language (last search: September 9, 2016). In addition, we performed hand-searches of 4 recently launched journals (ie, *BJPsych Open*, *npj Schizophrenia*, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, and *Schizophrenia Research: Cognition*) as these journals were not included in MEDLINE at the time when the literature search was conducted.

Study Selection

At least 2 of 3 authors (H.T., A.F., and S.T.) independently selected studies that met the following eligibility criteria: (1) double-blind RCTs with a parallel-group design (ie, not cross-over design); (2) inclusion of patients with schizophrenia spectrum disorders (ie, schizophrenia, schizoaffective disorder, or schizophreniform disorder); (3) evaluation of switching to aripiprazole versus a dopamine D_2 receptor antagonist antipsychotic (ie, not another partial agonist such as brexpiprazole and cariprazine) or adding aripiprazole versus placebo to another antipsychotic; and (4) study duration ≥ 1 week. We excluded studies where ≥ 70% of the sample was antipsychotic-naïve or -free or with a ≤ 2-week lifetime antipsychotic exposure, in line with our hypothesis as stated in the introduction. We considered studies using a placebo-washout period or antipsychotic-off period as a switching study since all except 2 studies had a short period, if applied (see Table 1). Although we included only switching to or adding aripiprazole studies, in fact we excluded only a single RCT simply because it was not considered as a switching study (ie, all excluded RCTs except 1 met at least 1 of the other eligibility criteria). Any disagreements about study selection were resolved by consensus with the lead author (H.T.). We assessed risk of bias for each included study according to the Cochrane Handbook for Systematic Reviews of Interventions (available at http://handbook.cochrane.org).

Data Extraction

Our primary interest was psychotic worsening. Notably, psychotic worsening can be included under lack of efficacy or adverse events, including serious adverse events. Accordingly, we started by reviewing how psychotic worsening was reported in the selected studies. Since all studies recorded it as an adverse event, we then extracted from the selected studies the number of patients who experienced, as primary outcomes, psychotic worsening as an adverse event, serious adverse event, adverse event leading to study discontinuation, or serious adverse event leading to study discontinuation in both aripiprazole and other antipsychotic groups. Additionally, we collected the number of patients who discontinued the study due to all causes, lack of efficacy, or adverse events and the number of patients who experienced agitation or anxiety as an adverse event as secondary outcomes. If a study consisted of double-blind and single-blind or open-label phases, we extracted the data during only the double-blind phase. At least 2 of 3 authors (H.T., A.F., and S.T.) independently extracted all the previously mentioned data. Any disagreements about data extraction were resolved by consensus with the lead author (H.T.).

If reports on the studies did not provide sufficient data, we contacted the corresponding authors and accessed the ClinicalTrials.gov website in an attempt to obtain additional information.

Data Analysis

We performed meta-analyses using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2014). We combined and compared outcome data between aripiprazole and other antipsychotic groups. We separately analyzed studies switching to aripiprazole from another antipsychotic and adding aripiprazole to another antipsychotic; however, we also show results combining these studies. We calculated pooled estimates of risk ratios (RRs) with 2-sided 95% confidence intervals (CIs) using a random-effects model, as all outcomes represented dichotomous data.

We performed the following subgroup analyses: studies with a ≥ 8-week study duration (16 studies); studies using a < 2-week placebo-washout or antipsychotic-off period (20 studies); studies switching to aripiprazole or another second-generation antipsychotic (10 studies), a first-generation antipsychotic (3 studies), risperidone or paliperidone (4 studies), or olanzapine (4 studies); and studies adding aripiprazole or placebo to clozapine (4 studies).

All effect sizes with $P < .05$ were considered significant. Study heterogeneities were quantified using I^2 statistic, with I^2 values ≥ 50% indicating significant heterogeneity.

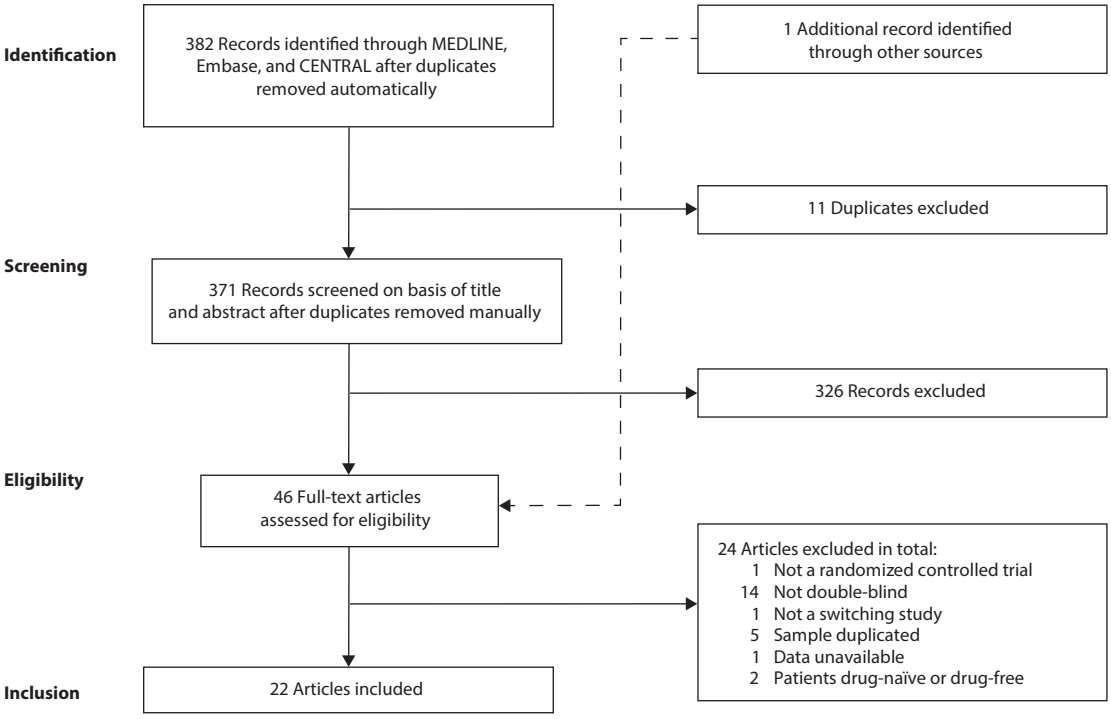
Finally, we assessed overall quality of the evidence regarding the risks of switching to and adding aripiprazole for psychotic worsening, study discontinuation, and agitation and anxiety according to the *GRADE Handbook* (Grading of Recommendations Assessment, Development, and Evaluation; available at http://gdt.guidelinedevelopment.org/app/handbook/handbook.html).

RESULTS

Included Studies

A total of 22 studies involving 5,769 patients (n = 3,258 and n = 2,511 for the aripiprazole and other antipsychotic group, respectively) that met eligibility criteria were

Figure 1. PRISMA Flow Diagram of the Literature Search



Abbreviation: CENTRAL = Cochrane Central Register of Controlled Trials.

identified and included in the meta-analysis (Figure 1). There were 13 studies[9–21] and 9 studies[22–30] switching to aripiprazole from another antipsychotic and adding aripiprazole to another antipsychotic, respectively. The characteristics of these studies are summarized in Table 1. All studies examined an oral formulation of aripiprazole, with the mean dose ≥ 10 mg/d. Among switching studies, all except 3 compared aripiprazole with a second-generation antipsychotic; among adding studies, all except 1 added aripiprazole to a second-generation antipsychotic. Results of risk of bias assessment are displayed in Supplementary eFigure 1. Although we included only double-blind RCTs, the study articles frequently failed to clearly describe random sequence generation, allocation concealment, or blinding procedures. All switching studies except 1 small study were sponsored by pharmaceutical companies.

Psychotic Worsening

How the studies reported and described psychotic worsening is detailed in Supplementary eTable 1. Psychotic worsening was reported as an adverse event in all included studies that reported it, and a variety of terms, including *worsening of psychosis*, *exacerbation of schizophrenia*, and *schizophrenic reaction,* were used to describe the phenomenology.

Switching to aripiprazole studies. No significant difference was found in the number of patients experiencing psychotic worsening reported as an adverse event (7 studies,[9,10,12–14,18,19] n = 3,458, RR = 1.17, 95% CI = 0.97–1.42, $P = .10$, $I^2 = 0\%$) (Figure 2), serious adverse event (7 studies,[9,12,13,15,17,19,21] n = 1,877, RR = 1.27, 95% CI = 0.81–1.97, $P = .29$, $I^2 = 0\%$), or adverse event leading to study discontinuation (5 studies,[9,14,17,18,20] n = 1,901, RR = 1.25, 95% CI = 0.97–1.63, $P = .09$, $I^2 = 0\%$) between the aripiprazole and other antipsychotic groups. Three studies[9,15,21] (n = 615) and 1 study[20] (n = 50) did not contribute the synthesized data for serious adverse event and adverse event leading to study discontinuation, respectively, as 0 events were reported in both groups. No syntheses were performed for serious adverse event leading to study discontinuation since 0 events occurred. The overall quality of the evidence was moderate.

Adding aripiprazole studies. No difference was found in the number of patients experiencing psychotic worsening reported as an adverse event (3 studies,[26–28,] n = 383, RR = 0.61, 95% CI = 0.01–27.75, $P = .80$, $I^2 = 78\%$) (Figure 2), serious adverse event (4 studies,[22,24–26] n = 620, RR = 0.57, 95% CI = 0.01–23.22, $P = .77$, $I^2 = 76\%$), or adverse event leading to study discontinuation (only 1 study[22] contributed to the synthesized data) between the 2 groups. One study[27] (n = 31) and 2 studies[22,24] (n = 91) did not contribute to the synthesized data for adverse event and serious adverse event, respectively, as 0 events were reported in both groups. No syntheses were performed for serious adverse event leading to study discontinuation since 0 events occurred. The overall quality of the evidence was very low.

Study Discontinuation

Switching to aripiprazole studies. No significant difference was shown in study discontinuation due to all

Table 1. Double-Blind Randomized Controlled Trials Switching to or Adding Aripiprazole in Schizophrenia

			Aripiprazole Group			Other Antipsychotic Group		
Study	Study Duration, wk	Days of Placebo-Washout or Antipsychotic-Off	N	Previous or Concurrent Antipsychotic (mean dose, mg/d)	Intervention (mean dose, mg/d)	N	Previous or Concurrent Antipsychotics (mean dose, mg/d)	Intervention (mean dose, mg/d)
Switching Study								
Chan 2007[9]	4	3	49	NA	Aripiprazole (15)	34	NA	Risperidone (6)
Fleischhacker 2009[10]	52	≥2	355	NA	Aripiprazole (23.0)	348	NA	Olanzapine (15.4)
Kane 2002[11]	4	≥5	204	Risperidone (NA) Olanzapine (NA) Haloperidol (NA) Other	Aripiprazole (15 or 30)	104	Risperidone (NA) Olanzapine (NA) Haloperidol (NA) Other	Haloperidol (10)
Kane 2007[12]	6	2–10	154	Risperidone (NA) Olanzapine (NA)	Aripiprazole (28.8)	146	Risperidone (NA) Olanzapine (NA)	Perphenazine (39.1)
Kane 2009[13]	28	NA	285	NA	Aripiprazole (19.3)	281	NA	Olanzapine (16.7)
Kasper 2003[14]	52	≥5	861	NA	Aripiprazole (29.01)	433	NA	Haloperidol (8.90)
Li 2014[15]	6	0.5	139	NA	Aripiprazole (23)	140	NA	Risperidone (4.1)
McQuade 2004[16]	26	≥2	156	NA	Aripiprazole (25.1)	161	NA	Olanzapine (16.5)
Newcomer 2008[17]	16	NA	88	Olanzapine (NA)	Aripiprazole (16.0)	85	Olanzapine (NA)	Olanzapine (15.9)
Potkin 2003[18]	4	≥5	202	NA	Aripiprazole (20 or 30)	99	NA	Risperidone (6)
Savitz 2015[19]	26	≤21	115	Risperidone (NA) Olanzapine (NA) Quetiapine (NA) Other	Aripiprazole (11.56)	113	Risperidone (NA) Olanzapine (NA) Quetiapine (NA) Other	Paliperidone (6.75)
Shafti 2015[20]	12	≥10–14	25	NA	Aripiprazole (20.4)	25	NA	Quetiapine (463.04)
Zimbroff 2007[21]	4	1	129	NA	Aripiprazole (20.9)	127	NA	Ziprasidone (149.0)
Adding Study								
Chang 2008[22]	8	NA	30	Clozapine (304.3)	+ Aripiprazole (15.5)	32	Clozapine (290.6)	+ Placebo
Chen 2015[23]	8	NA	89	Risperidone (4.63, 4.79, or 5.07)	+ Aripiprazole (5, 10, or 20)	30	Risperidone (4.93)	+ Placebo
Fan 2013[24]	8	NA	20	Clozapine (397)	+ Aripiprazole (15)	18	Clozapine (400)	+ Placebo
Fleischhacker 2010[25]	16	NA	108	Clozapine (383.8)	+ Aripiprazole (11.1)	99	Clozapine (362.6)	+ Placebo
Kane 2009[26]	16	4–7	168	NA	Risperidone (4.6) or Quetiapine (513) + Aripiprazole (10.3)	155	NA	Risperidone (4.8) or Quetiapine (516) + Placebo
Muscatello 2011[27]	24	NA	20	Clozapine (310.7)	+ Aripiprazole (15)	20	Clozapine (341.2)	+ Placebo
Raghuthaman 2015[28]	8	NA	15	Risperidone (6.0[a])	+ Aripiprazole (10)	15	Risperidone (6.0[a])	+ Placebo
Shim 2007[29]	8	NA	28	Haloperidol (20.7)	+ Aripiprazole (30)	28	Haloperidol (24.8)	+ Placebo
Yasui-Furukori 2012[30]	12	NA	18	Risperidone (5.9) Olanzapine (12.1)	+ Aripiprazole (15.2)	18	Risperidone (5.0) Olanzapine (12.5)	+ Placebo

[a]Median dose.
Abbreviation: NA = not available or applicable.

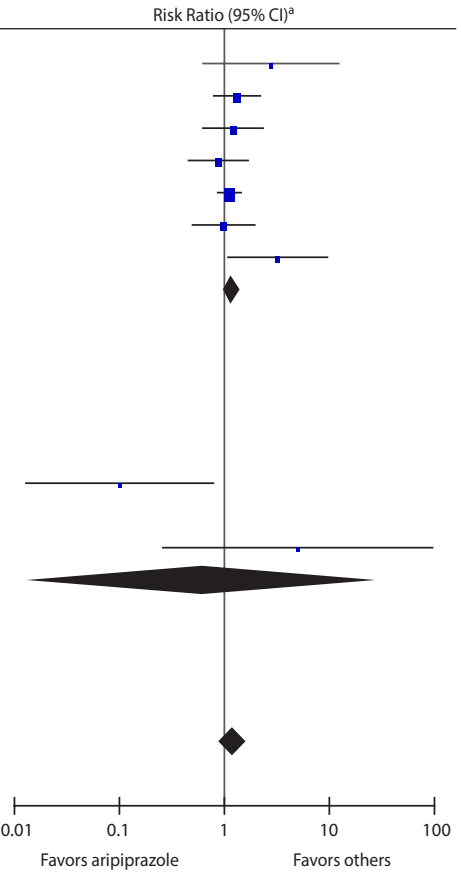
causes (13 studies,[9–21] n = 4,858, RR = 1.04, 95% CI = 0.92–1.19, $P = .52$, $I^2 = 70\%$) or adverse events (13 studies,[9–21] n = 4,858, RR = 1.01, 95% CI = 0.80–1.28, $P = .91$, $I^2 = 43\%$) (Figure 3) between the 2 groups, while switching to another antipsychotic demonstrated a significant superiority to switching to aripiprazole for the number of patients who discontinued the study due to lack of efficacy (13 studies,[9–21] n = 4,858, RR = 1.46, 95% CI = 1.10–1.93, $P = .009$, $I^2 = 37\%$) (Figure 4). One study[20] (n = 50) did not contribute to the synthesized data for study discontinuation due to both all causes and adverse events, as 0 events were reported in both groups. The overall quality of the evidence was moderate.

Adding aripiprazole studies. No significant difference was shown in study discontinuation due to all causes (9 studies,[22–30] n = 911, RR = 1.06, 95% CI = 0.81–1.40, $P = .65$, $I^2 = 0\%$), adverse events (8 studies,[22–27,29,30] n = 881, RR = 0.73, 95% CI = 0.33–1.65, $P = .46$, $I^2 = 15\%$) (Figure 3), or lack of efficacy (8 studies,[22–27,29,30] n = 881, RR = 2.08, 95% CI = 0.51–8.45, $P = .30$, $I^2 = 0\%$) (Figure 4) between adding aripiprazole and adding placebo. One study[30] (n = 36), 3 studies[27,29,30] (n = 132), and 3 studies[23,27,30] (n = 195) did not contribute to the synthesized data for study discontinuation due to all causes, adverse events, and lack of efficacy, respectively, as 0 events were reported in both groups. The overall quality of the evidence was moderate.

Agitation and Anxiety

Switching to aripiprazole studies. No significant difference was observed in the number of patients experiencing agitation (6 studies,[9,10,12,14,18,21] n = 2,918, RR = 1.06, 95% CI = 0.84–1.33, $P = .64$, $I^2 = 0\%$) or anxiety (10 studies,[9–14,16,18,19,21] n = 4,334, RR = 1.05, 95% CI = 0.89–1.23, $P = .57$, $I^2 = 0\%$) between the aripiprazole and other antipsychotic groups. The overall quality of the evidence was moderate.

Figure 2. Psychotic Worsening as an Adverse Event



Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Other Antipsychotics Events	Other Antipsychotics Total	Weight	Risk Ratio (95% CI)[a]
Switching to aripiprazole						
Chan 2007[9]	8	49	2	34	3.7%	2.78 (0.63–12.27)
Fleischhacker 2009[10]	32	349	24	346	18.1%	1.32 (0.80–2.20)
Kane 2007[12]	18	153	14	144	13.3%	1.21 (0.63–2.34)
Kane 2009[13]	16	285	18	281	13.5%	0.88 (0.46–1.68)
Kasper 2003[14]	156	859	70	431	29.3%	1.12 (0.86–1.45)
Potkin 2003[18]	22	201	11	99	12.8%	0.99 (0.50–1.95)
Savitz 2015[19]	13	114	4	113	6.3%	3.22 (1.08–9.58)
Subtotal (95% CI)		**2,010**		**1,448**	**97.0%**	**1.17 (0.97–1.42)**
Total events	265		143			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 5.98$ ($P = .43$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.62$ ($P = .10$)						
Adding aripiprazole						
Kane 2009[26]	1	169	9	153	2.0%	0.10 (0.01–0.78)
Muscatello 2011[27]	0	14	0	17		Not estimable
Raghuthaman 2015[28]	2	15	0	15	1.0%	5.00 (0.26–96.13)
Subtotal (95% CI)		**198**		**185**	**3.0%**	**0.61 (0.01–27.75)**
Total events	3		9			
Heterogeneity: $\tau^2 = 5.94$; $\chi^2_1 = 4.52$ ($P = .03$); $I^2 = 78\%$						
Test for overall effect: $Z = 0.25$ ($P = .80$)						
Total (95% CI)		**2,208**		**1,633**	**100.0%**	**1.19 (0.88–1.60)**
Total events	268		152			
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_8 = 12.36$ ($P = .14$); $I^2 = 35\%$						
Test for overall effect: $Z = 1.11$ ($P = .27$)						
Test for subgroup differences: $\chi^2_1 = 0.11$ ($P = .74$), $I^2 = 0\%$						

[a]Risk ratio is Mantel-Haenszel and random.

Adding aripiprazole studies. Only 1 study contributed to the synthesized data for both agitation[27] and anxiety.[25] The overall quality of the evidence was very low.

Subgroup Analyses

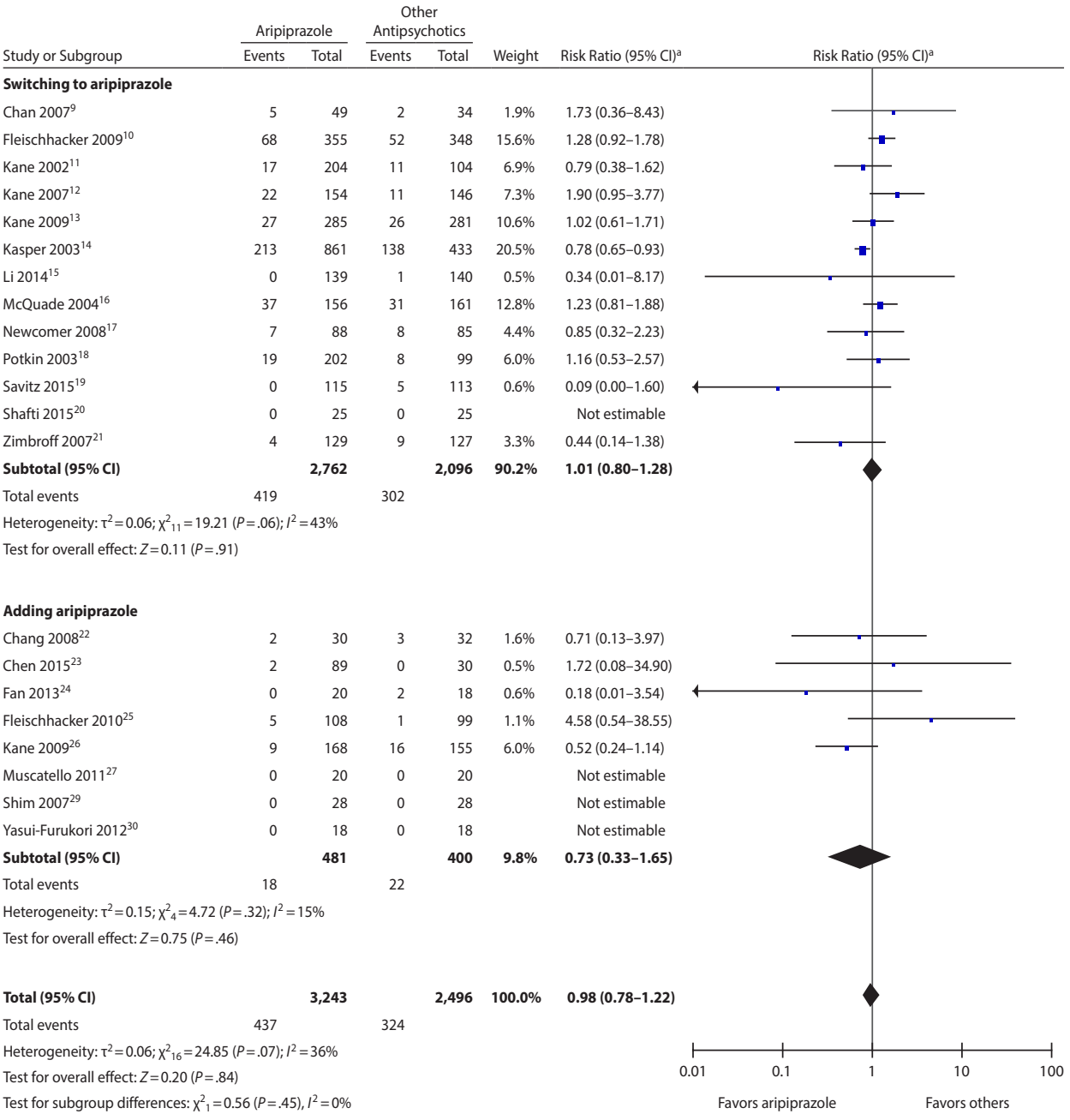
All findings remained unchanged after excluding studies with a < 8-week study duration (6 studies[9,11,12,15,18,21]) or using a ≥ 2-week placebo-washout or antipsychotic-off period (2 studies[19,20]). No significant differences were observed in any outcomes between aripiprazole and the counterparts in studies switching to aripiprazole or a first-generation antipsychotic (3 studies[11,12,14]) or risperidone or paliperidone (4 studies[9,15,18,19]) or in studies adding aripiprazole or placebo to clozapine (4 studies[22,24,25,27]) (all *P* values > .05) (data not shown). On the other hand, subgroup analyses revealed that switching to another second-generation antipsychotic (10 studies[9,10,13,15–21]) or olanzapine (4 studies[10,13,16,17]) was significantly superior to switching to aripiprazole for study discontinuation due to all causes and lack of efficacy (Supplementary eFigures 2 and 3); study heterogeneities for study discontinuation due to all causes were decreased in studies switching both to another second-generation antipsychotic and to olanzapine.

DISCUSSION

In this meta-analysis of 22 double-blind RCTs, we focused on risk of psychotic worsening in switching to aripiprazole from another antipsychotic or adding aripiprazole to another antipsychotic. The strengths of the current meta-analysis are that we restricted the studies to clinical trials with a robust design (ie, double-blind RCTs) and included various outcomes potentially related to psychotic worsening (ie, study discontinuation due to all causes, lack of efficacy, and adverse events; agitation; and anxiety).

Our main findings are 5-fold: (1) psychotic worsening was reported as an adverse event in all included studies that reported it; (2) switching to aripiprazole did not significantly increase the risk of psychotic worsening compared to switching to another antipsychotic; (3) switching to aripiprazole was related to a greater risk of study discontinuation due to lack of efficacy than switching to another antipsychotic; (4) switching to aripiprazole was related to a greater risk of study discontinuation due to all causes and lack of efficacy than switching to another second-generation antipsychotic or olanzapine; and (5) because of the small sample size, no conclusion can be drawn as to

Figure 3. Study Discontinuation due to Adverse Events



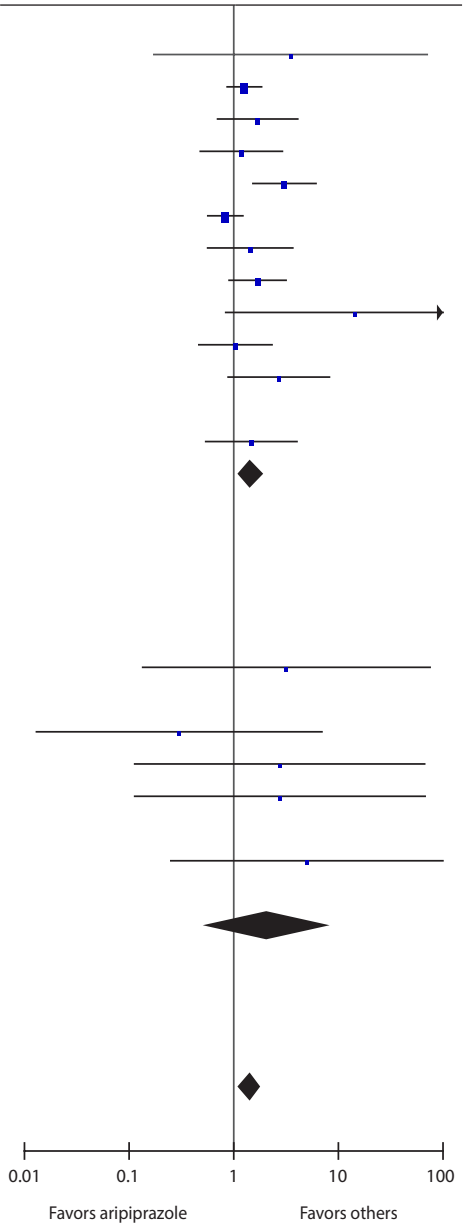
[a]Risk ratio is Mantel-Haenszel and random.

clinical risks associated with adding aripiprazole to another antipsychotic.

We hypothesized that switching to and adding aripiprazole have a potential risk of psychotic worsening in a certain population, that is, patients with chronic schizophrenia receiving long-term antipsychotic treatment, since aripiprazole's partial agonistic action at dopamine D_2 receptors and very high D_2 receptor affinity could theoretically evoke a relatively hyperdopaminergic state in conjunction with up-regulated dopamine D_2 receptors, namely supersensitivity psychosis.[1] However, these findings, established based on clinical trials, do not support evidence of aripiprazole-associated psychotic worsening that has been reported in numerous case reports. Case reports generally represent unusual or unique clinical presentations and, as such, may not accurately reflect true event rates. In addition, there are differences in those who participate in clinical trials versus patients in "real world" practice.[31–36] Both factors may have influenced the present results. On the other hand, the findings suggest that aripiprazole may be less effective than other second-generation antipsychotics, in particular olanzapine, in antipsychotic switching in patients with schizophrenia. This finding is consistent with a recent meta-analysis of RCTs demonstrating that olanzapine is

Figure 4. Study Discontinuation due to Lack of Efficacy

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Other Antipsychotics Events	Other Antipsychotics Total	Weight	Risk Ratio (95% CI)[a]
Switching to aripiprazole						
Chan 2007[9]	2	49	0	34	0.7%	3.50 (0.17–70.69)
Fleischhacker 2009[10]	53	355	41	348	19.6%	1.27 (0.87–1.85)
Kane 2002[11]	20	204	6	104	6.6%	1.70 (0.70–4.10)
Kane 2007[12]	10	154	8	146	6.3%	1.19 (0.48–2.92)
Kane 2009[13]	31	285	10	281	9.5%	3.06 (1.53–6.12)
Kasper 2003[14]	63	861	38	433	19.3%	0.83 (0.57–1.23)
Li 2014[15]	10	139	7	140	5.9%	1.44 (0.56–3.67)
McQuade 2004[16]	23	156	14	161	11.0%	1.70 (0.91–3.17)
Newcomer 2008[17]	7	88	0	85	0.8%	14.49 (0.84–249.91)
Potkin 2003[18]	17	202	8	99	7.6%	1.04 (0.47–2.33)
Savitz 2015[19]	11	115	4	113	4.4%	2.70 (0.89–8.24)
Shafti 2015[20]	0	25	0	25		Not estimable
Zimbroff 2007[21]	9	129	6	127	5.3%	1.48 (0.54–4.03)
Subtotal (95% CI)		**2,762**		**2,096**	**96.9%**	**1.46 (1.10–1.93)**
Total events	256		142			
Heterogeneity: $\tau^2 = 0.08$; $\chi^2_{11} = 17.44$ ($P = .10$); $I^2 = 37\%$						
Test for overall effect: $Z = 2.60$ ($P = .009$)						
Adding aripiprazole						
Chang 2008[22]	1	30	0	32	0.6%	3.19 (0.14–75.49)
Chen 2015[23]	0	89	0	30		Not estimable
Fan 2013[24]	0	20	1	18	0.6%	0.30 (0.01–6.97)
Fleischhacker 2010[25]	1	108	0	99	0.6%	2.75 (0.11–66.79)
Kane 2009[26]	1	168	0	155	0.6%	2.77 (0.11–67.48)
Muscatello 2011[27]	0	20	0	20		Not estimable
Shim 2007[29]	2	28	0	28	0.7%	5.00 (0.25–99.67)
Yasui-Furukori 2012[30]	0	18	0	18		Not estimable
Subtotal (95% CI)		**481**		**400**	**3.1%**	**2.08 (0.51–8.45)**
Total events	5		1			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_4 = 1.91$ ($P = .75$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.03$ ($P = .30$)						
Total (95% CI)		**3,243**		**2,496**	**100.0%**	**1.44 (1.12–1.84)**
Total events	261		143			
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_{16} = 19.77$ ($P = .23$); $I^2 = 19\%$						
Test for overall effect: $Z = 2.84$ ($P = .005$)						
Test for subgroup differences: $\chi^2_1 = 0.24$ ($P = .62$), $I^2 = 0\%$						



[a]Risk ratio is Mantel-Haenszel and random.

superior to aripiprazole in terms of premature withdrawal for any reason including inefficacy.[5] To further scrutinize this result, we identified 3 RCTs[17,37,38] through the current systematic literature search that compared switching to aripiprazole versus maintaining the same antipsychotics (1 was included[17] in the meta-analysis and 2 were excluded[37,38] because the studies were not double-blind). Patients who had received olanzapine before the study were assigned either to switch to aripiprazole or stay on olanzapine (in 1 study,[37] patients received risperidone, olanzapine, or quetiapine at randomization, but data specific to the olanzapine subgroup were available). We conducted meta-analyses of the 3 studies for study discontinuation due to all causes, lack of efficacy, and adverse events; results indicated a robustly significant difference in study discontinuation due to lack of efficacy in favor of olanzapine (3 studies,[17,37,38] n = 309, RR = 20.12, 95% CI = 2.75–147.20, $P = .003$, $I^2 = 0\%$); 1 study[38] (n = 62) did not contribute the synthesized data, as 0 events were reported in both groups.

Psychotic worsening was reported as an adverse event with a variety of terms, which may align with terminology defined by Medical Dictionary for Regulatory Activities (MedDRA) at the time the studies were conducted (in fact, the majority of studies sought regulatory approval of the new

drug, ie, phase 3 studies). This said, the fact that all studies reported psychotic worsening as an adverse event raises the question: should it be reported as an adverse event or lack of efficacy of intervention? In a review on assessment of adverse effects in clinical studies of antipsychotics, Pope et al pointed out, "Tables of adverse effects could be difficult to interpret because they sometimes included symptoms of schizophrenia (eg, hallucinations) as well as physiological problems that could be related to drug-induced or psychiatric symptoms (eg, restlessness, which may be due to akathisia or anxiety)."[39(p70)] It is hard to say which is the better strategy, as insufficient clinical response to a new drug can also evoke exacerbation of underlying illness (ie, psychotic worsening in schizophrenia). This applies especially to switching studies; in the case of aripiprazole, for example, it can be difficult establishing whether symptom exacerbation with a switch to aripiprazole reflects diminished response compared to previous treatment or symptom exacerbation secondary to its partial dopamine agonist properties. In contrast to switching to aripiprazole, we could not draw any conclusion vis-à-vis the hypothesis that addition of aripiprazole worsens psychotic symptoms in this meta-analysis since only a small number of adding studies were included.

Other factors must be considered in interpreting the present results. The vast majority of studies only reported treatment-emergent adverse events that occurred at an incidence of 5% or more, meaning that psychotic worsening would not be reported if it occurred in less than 5% of participants. Furthermore, some studies did not describe the exact number of cases even though they mentioned psychotic worsening. Industry sponsorship may have an influence on reporting adverse events[40]; indeed, two-thirds of the included studies were supported by a pharmaceutical company. In general, the quality of safety reporting in clinical trials is poorer in mental health than other medical fields.[41] Taken together, further double-blind RCTs adding aripiprazole to another antipsychotic are required, and we would argue for precise reporting with respect to the number of patients experiencing psychotic worsening regardless of the number of cases. There are other limitations to the present study that warrant comment. We regarded studies using placebo-washout or antipsychotic-off period as switching studies, which may have biased findings, although most such studies used a short period and the findings remained essentially the same after excluding studies with a relatively longer period. In addition, study durations were relatively short, although psychotic worsening is reported to occur within weeks following aripiprazole introduction.[1]

In conclusion, the current meta-analysis of 22 double-blind RCTs demonstrated that, compared to other antipsychotics, switching to aripiprazole was not related to a significant increase in the risk of psychotic worsening, although it was associated with study discontinuation due to lack of efficacy in schizophrenia. While the findings in clinical trials do not directly support the notion reported in clinical practice that aripiprazole is linked to psychotic worsening, clinicians should closely monitor psychotic symptoms in patients with schizophrenia when conducting a switch to aripiprazole from another antipsychotic, in particular olanzapine, given reduced efficacy of aripiprazole relative to other antipsychotics.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Can Aripiprazole Worsen Psychosis in Schizophrenia? A Meta-Analysis of Double-Blind, Randomized, Controlled Trials

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4. **eFigure 3** Study Discontinuation Due to All Causes and Lack of Efficacy in Studies Switching to Aripiprazole or Olanzapine (n = 4)

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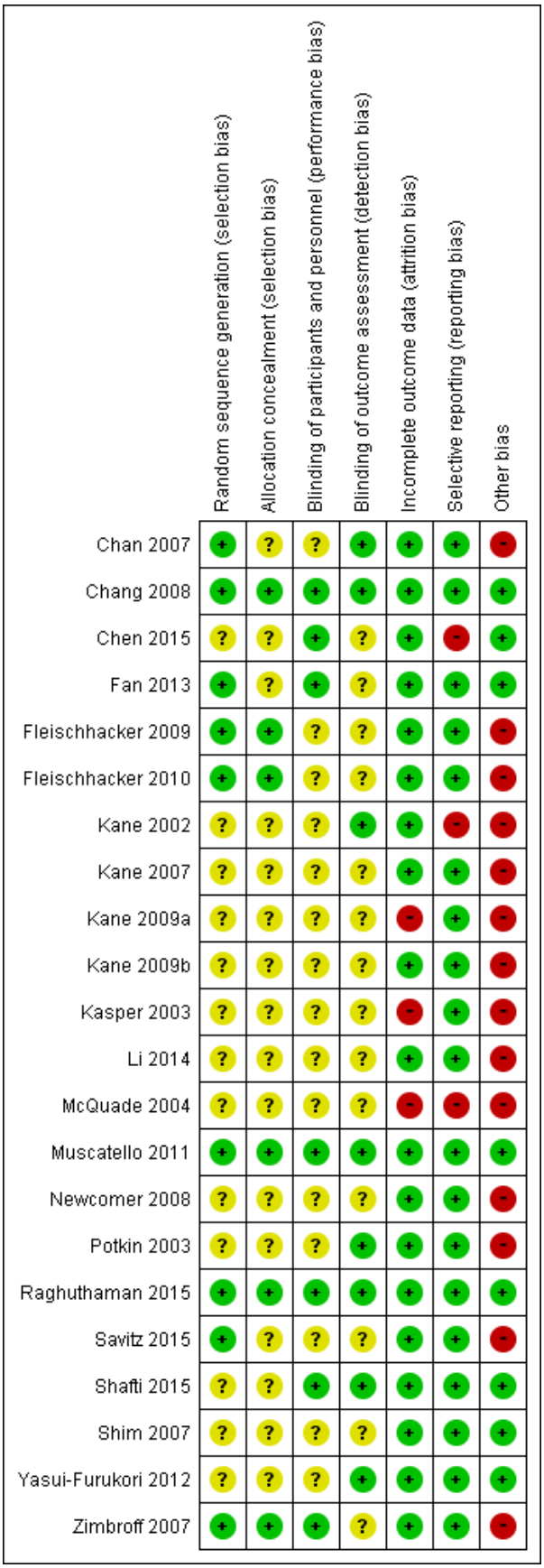
Supplementary eTable 1. How to report and describe psychotic worsening

Study	As adverse event	As serious adverse event	As adverse event leading to study discontinuation	As serious adverse event leading to study discontinuation
[Switching study]				
Chan 2007[9]	Psychotic disorder	NA	Worsening of psychosis	NA
Fleischhacker 2009[10]	Schizophrenic reaction	NR	Schizophrenic reaction	NR
Kane 2002[11]	NR	Psychosis	Worsening of psychosis	NR
Kane 2007[12]	Psychosis	Psychosis	NR	NR
Kane 2009a[13]	Exacerbation of schizophrenia	Exacerbation of schizophrenia/Psychotic disorder/Paranoia/Exacerbation of schizophrenia paranoid type/Delusion/Hallucination	NR	Exacerbation of schizophrenia/Psychotic disorder/Paranoia/Exacerbation of schizophrenia paranoid type/Delusion/Hallucination
Kasper 2003[14]	Psychosis	Schizophrenia	Worsening of schizophrenia	NR
Li 2014[15]	NR	NA	NR	NA
McQuade 2004[16]	NR	Psychosis/Schizophrenic reaction	NR	NR
Newcomer 2008[17]	NR	Psychotic disorder/Paranoia/Schizophrenia/ Disease progression/Schizoaffective	Psychotic disorder/Paranoia/Schizophrenia/ Disease progression/Schizoaffective	NR
Potkin 2003[18]	Psychosis	Psychosis	Psychosis	Psychosis
Savitz 2015[19]	Schizophrenia	Worsening of schizophrenia	NR	NA
Shafti 2015[20]	NR	NR	NA	NA
Zimbroff 2007[21]	NR	NA	NR	NA
[Adding study]				
Chang 2008[22]	NR	NA	Exacerbation of auditory hallucinations	NA
Chen 2015[23]	NR	NR	NR	NR
Fan 2013[24]	NR	NA	NR	NA
Fleischhacker 2010[25]	NR	Psychotic disorder/Auditory hallucinations	NR	NR
Kane 2009b[26]	Psychotic disorder	Psychotic disorder/Hallucinations/Paranoia	NR	NR
Muscatello 2011[27]	NA	NR	NA	NA
Raghuthaman 2015[28]	Worsening of psychotic	NR	NA	NA
Shim 2007[29]	NR	NR	NA	NR
Yasui-Furukori 2012[30]	NR	NR	NA	NA

Abbreviations: NA, not applicable; NR, not reported

Supplementary eFigure 1. Risk of bias summary



Note: +, low risk of bias; -, high risk of bias; ?, questionable risk of bias

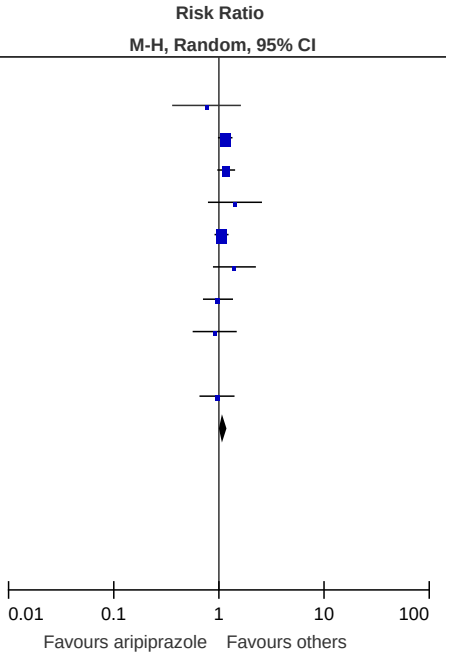
Supplementary eFigure 2. Study discontinuation due to all causes and lack of efficacy in studies switching to aripiprazole or another second-generation antipsychotic (N=10)

A. Study discontinuation due to all causes

	Aripiprazole		Other antipsychotics			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
1.1.1 Switching to aripiprazole						
Chan 2007 (9)	11	49	10	34	1.1%	0.76 [0.37, 1.59]
Fleischhacker 2009 (10)	198	355	169	348	29.6%	1.15 [1.00, 1.32]
Kane 2009a (13)	143	285	120	281	18.9%	1.17 [0.98, 1.40]
Li 2014 (15)	24	139	17	140	1.8%	1.42 [0.80, 2.53]
McQuade 2004 (16)	116	156	113	161	32.2%	1.06 [0.92, 1.21]
Newcomer 2008 (17)	32	88	22	85	2.9%	1.40 [0.89, 2.21]
Potkin 2003 (18)	74	202	37	99	6.1%	0.98 [0.72, 1.34]
Savitz 2015 (19)	26	115	28	113	2.8%	0.91 [0.57, 1.45]
Shafti 2015 (20)	0	25	0	25		Not estimable
Zimbroff 2007 (21)	39	129	40	127	4.5%	0.96 [0.67, 1.39]
Subtotal (95% CI)		**1543**		**1413**	**100.0%**	**1.10 [1.02, 1.19]**
Total events	663		556			

Heterogeneity: Tau² = 0.00; Chi² = 5.67, df = 8 (P = 0.68); I² = 0%

Test for overall effect: Z = 2.48 (P = 0.01)

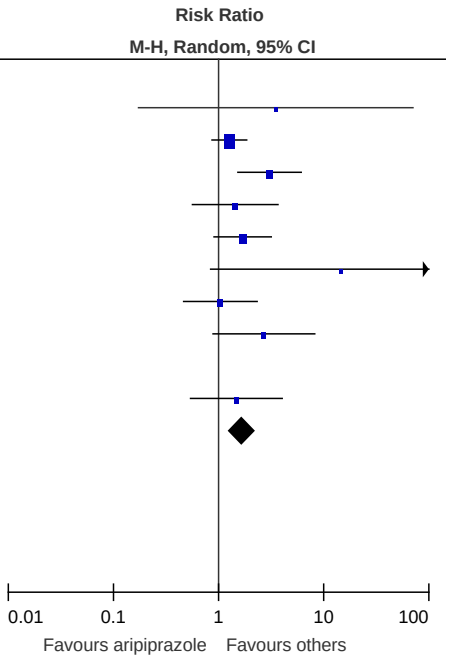


B. Study discontinuation due to lack of efficacy

	Aripiprazole		Other antipsychotics			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
1.2.1 Switching to aripiprazole						
Chan 2007 (9)	2	49	0	34	1.0%	3.50 [0.17, 70.69]
Fleischhacker 2009 (10)	53	355	41	348	32.3%	1.27 [0.87, 1.85]
Kane 2009a (13)	31	285	10	281	14.5%	3.06 [1.53, 6.12]
Li 2014 (15)	10	139	7	140	8.8%	1.44 [0.56, 3.67]
McQuade 2004 (16)	23	156	14	161	16.9%	1.70 [0.91, 3.17]
Newcomer 2008 (17)	7	88	0	85	1.1%	14.49 [0.84, 249.91]
Potkin 2003 (18)	17	202	8	99	11.3%	1.04 [0.47, 2.33]
Savitz 2015 (19)	11	115	4	113	6.4%	2.70 [0.89, 8.24]
Shafti 2015 (20)	0	25	0	25		Not estimable
Zimbroff 2007 (21)	9	129	6	127	7.8%	1.48 [0.54, 4.03]
Subtotal (95% CI)		**1543**		**1413**	**100.0%**	**1.65 [1.22, 2.22]**
Total events	163		90			

Heterogeneity: Tau² = 0.03; Chi² = 9.58, df = 8 (P = 0.30); I² = 16%

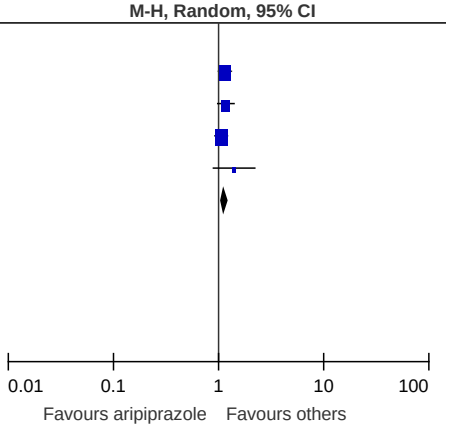
Test for overall effect: Z = 3.29 (P = 0.0010)



Supplementary eFigure 3. Study discontinuation due to all causes and lack of efficacy in studies switching to aripiprazole or olanzapine (N=4)

A. Study discontinuation due to all causes

	Aripiprazole		Other antipsychotics			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
1.1.1 Switching to aripiprazole							
Fleischhacker 2009 (10)	198	355	169	348	35.4%	1.15 [1.00, 1.32]	
Kane 2009a (13)	143	285	120	281	22.6%	1.17 [0.98, 1.40]	
McQuade 2004 (16)	116	156	113	161	38.5%	1.06 [0.92, 1.21]	
Newcomer 2008 (17)	32	88	22	85	3.5%	1.40 [0.89, 2.21]	
Subtotal (95% CI)		**884**		**875**	**100.0%**	**1.13 [1.04, 1.23]**	
Total events	489		424				
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 3 (P = 0.55); I² = 0%							
Test for overall effect: Z = 2.77 (P = 0.006)							



B. Study discontinuation due to lack of efficacy

	Aripiprazole		Other antipsychotics			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
1.2.1 Switching to aripiprazole							
Fleischhacker 2009 (10)	53	355	41	348	39.1%	1.27 [0.87, 1.85]	
Kane 2009a (13)	31	285	10	281	27.5%	3.06 [1.53, 6.12]	
McQuade 2004 (16)	23	156	14	161	29.8%	1.70 [0.91, 3.17]	
Newcomer 2008 (17)	7	88	0	85	3.6%	14.49 [0.84, 249.91]	
Subtotal (95% CI)		**884**		**875**	**100.0%**	**1.92 [1.10, 3.35]**	
Total events	114		65				
Heterogeneity: Tau² = 0.17; Chi² = 7.32, df = 3 (P = 0.06); I² = 59%							
Test for overall effect: Z = 2.29 (P = 0.02)