Using aripiprazole to reduce antipsychotic-induced hyperprolactinemia: meta-analysis of currently available randomized controlled trials

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Background: Hyperprolactinemia (HPL) is a common side effect of antipsychotic medications. Recent reports suggest that aripiprazole can ameliorate antipsychotic-induced HPL, but results are inconsistent and the single available systematic review only considered five studies.

Aim: Conduct an updated meta-analysis of all randomized controlled trials (RCTs) about the efficacy and safety of aripiprazole as an adjunctive treatment for antipsychotic-induced hyperprolactinemia.

Methods: English and Chinese databases were searched for RCTs about the use of aripiprazole in treating antipsychotic-induced HPL published by January 20, 2015. Studies were selected using pre-defined inclusion and exclusion criteria. The Cochrane Risk of Bias tool was used to evaluate risk of biases, the Cochrane GRADE measure was used to assess the quality of evidence, and Review Manager 5.3 software was used for data analysis.

Results: A total of 21 studies, 19 of which were conducted in mainland China, were included in the analysis. Meta-analysis of data from 8 of the studies with a pooled sample of 604 individuals found that compared to the control condition adjunctive aripiprazole significantly increased the proportion of participants who experienced HPL recovery (risk ratio [RR]=19.2, 95%CI=11.0-33.5). The proportion who experienced any adverse effect during follow-up did not differ between the two groups, but the aripiprazole group was more likely to report somnolence (RR=2.76, 95%CI=1.34-5.69) and headaches (RR=2.31, 95%CI=1.08-4.92). High-dose aripiprazole (>5mg/day) was more effective than low-dose (≤5mg/day) aripiprazole (RR=30.0, 95%CI=10.2-120.7 v. RR=15.1, 95%CI=8.1-28.1), but this difference was not statistically significant. The risk of bias in the studies was rated as 'high' in 6 of the studies and 'unclear' in 15 studies, and the quality of evidence was rated as 'high' for only 7 of the 57 outcome measures assessed.

Conclusions: This study systematically reviewed and evaluated all relevant RCTs and found that adjunctive aripiprazole is effective and safe to use in the treatment of antipsychotic-induced HPL. However, the low quality of some of the studies, the incomplete methodological information provided for most of the studies, and the relatively short follow-up time of the studies raises question about the validity of the results. Further work that resolves these methodological and reporting issues is needed.

Keywords: aripiprazole; hyperprolactinemia; randomized controlled trial; meta-analysis

1. Background

Hyperprolactinemia (HPL) is a common and severe side effect of using antipsychotic medications.[1] Both typical antipsychotic medications (e.g., chlorpromazine, perphenazine, sulpiride, and haloperidol) and atypical antipsychotic medications (e.g., risperidone, paliperidone, and amisulpride) can increase prolactin levels, especially among females. The reported occurrence of HPL among individuals taking antipsychotic medication ranges from 42 to 89%.[2-5] HPL is associated with both short-term and long-term physical and psychological problems, including sexual

dysfunction, amenorrhea, osteoporosis, the metabolic syndrome, depression, and anxiety.[2,6,7] There have also been reports that HPL can increase the risk of breast cancer and prostate cancer,[8,9] and exacerbate auto-immune diseases.[10] Problems related to HPL can decrease patient adherence to treatment with antipsychotic medications and, thus, lead to fluctuations of psychotic symptoms.[11]

Aripiprazole is a partial dopamine D2 receptor agonist which has been reported to improve antipsychotics-induced HPL.[12-17] Several clinical trials specifically focused on assessing the efficacy and safety of aripiprazole in treating antipsychotic-induced HPL[18-23] have had inconsistent findings. Some found that adjunctive treatment with aripiprazole was well tolerated and effective in reducing prolactin levels,[20,24] while others reported increased insomnia, headaches, and sedation after the use of adjunctive aripiprazole.[18] Two studies[25,26] reported that aripiprazole was effective at low doses, but another study did not support this finding.[27] The single available meta-analysis on this topic[28] reported the aripiprazole is effective and safe, but these results were based on pooling results from only five studies. This review aims to identify and pool results of all previous randomized controlled trials to summarize the current state of knowledge about the efficacy and safety of aripiprazole in the treatment of antipsychotic-induced HPL.

2. Methods

2.1 Search strategy

We searched the following databases for studies published by January 20, 2015: Pubmed, EMBASE, The Cochrane Library, EBSCO, Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP database for Chinese Technical Periodicals, WANFANG DATA, Chinese Biological Medical Literature Database, Taiwan Electronic Periodical Services, and ClinicalTrials.gov using keywords 'aripiprazole', 'hyperprolactinemia', 'prolactin abnormal', 'randomized controlled trial', 'controlled clinical trial', 'randomized, placebo', 'drug therapy', and 'randomly, trial'. Proprietary names for aripiprazole in Chinese were also included as the Chinese search terms. Various Boolean combinations of these keywords were used to search for articles; reference lists of included articles were hand-checked for further relevant studies; and experts in the field were asked about ongoing studies.

2.2 Inclusion and exclusion criteria

All reports of randomized controlled trails (RCTs) about treating antipsychotic-induced HPL among individuals with schizophrenia with aripiprazole were screened using the following inclusion criteria: (a) diagnosis of schizophrenia was based on criteria specified by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*,[29] the World Health Organization's *International Classification of Diseases*,[30] or the Chinese Society of Psychiatry's

Chinese Classification of Mental Disorders;[31] (b) HPL confirmed using blood tests; (c) comparison of aripiprazole to placebo or to no treatment; (d) reported data on sample size, number of HPL cases, and on serum prolactin levels before and after treatment. Studies published in either English or Chinese were considered. Observational studies, anthropologic studies, review articles, research protocols, case reports, and duplicated reports were excluded.

2.3 Screening of articles

All search results were imported into Endnote X5 software. Two authors (MM and LW) independently screened titles and abstracts after eliminating duplicates. The full text of the remaining articles were screened according to the above inclusion and exclusion criteria. When the two authors disagreed about the inclusion of an article and were unable to agree after discussing the article, a third author (LC) made the final determination.

2.4 Evaluation of risk of bias

Two authors (LW and MM) assessed the risk of bias for all included articles using the Cochrane Risk of Bias tool (ROB)[32] which considers seven specific items: sequence generation (randomization); allocation concealment; blinding of participants and treating clinicians about group assignment; blinding of evaluators of outcomes about group assignment; incomplete data (attrition and exclusions); selective outcome reporting; and other biases (including study-specific biases or concerns about fraudulent results). Each aspect was rated as 'low risk of bias', 'high risk of bias', or 'unclear' if insufficient information was provided in the article to make a determination. A third author's (LC) opinion was sought when the two raters disagreed. We also evaluated the quality and level of evidence of each of the 21 included studies using the Cochrane collaboration's GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) software which assesses the limitations of the design, consistency of results, indirect evidence, precision of results, publication bias, and effect size for each outcome.[32,33] The level of evidence was rated as high, medium, low, or very low.

2.5 Outcome measures

The primary outcome is the proportion of individuals whose prolactin levels returned to the normal range after adjunctive treatment with aripiprazole, that is, HPL recovery. Secondary outcomes are prolactin levels after the aripiprazole treatment, occurrence of adverse events based on use of the Treatment Emergent Symptom Scale (TESS),[34] and improvement of psychotic symptoms.

2.6 Data extraction

For each included study, two authors (LW and MM) independently extracted data using a pre-designed data

extraction form including names of authors, publication year, sample size, number of outcome events, age of participants, and antipsychotics used. Discrepancies were checked by a third author (ZS).

2.7 Analysis

Based on the results of a previous study about risk of bias,[35] the overall risk of bias for each of the 21 studies was classified as 'low' if the ratings were 'low' for all seven items on the ROB tool, 'unclear' if any item is rated as 'unclear' and all other items are rated as 'low', and 'high' if any of the items are rated as 'high'. The kappa statistic was used to measure the inter-rater agreement between the two independent raters for the ratings of each item and for the overall rating.[36] Review Manager (RevMan 5.3) and R 3.1.1 were used to estimate pooled standard mean difference (SMD) for continuous measures and risk ratios (RR) for categorical measures. Heterogeneity was measured using I^2.[37]
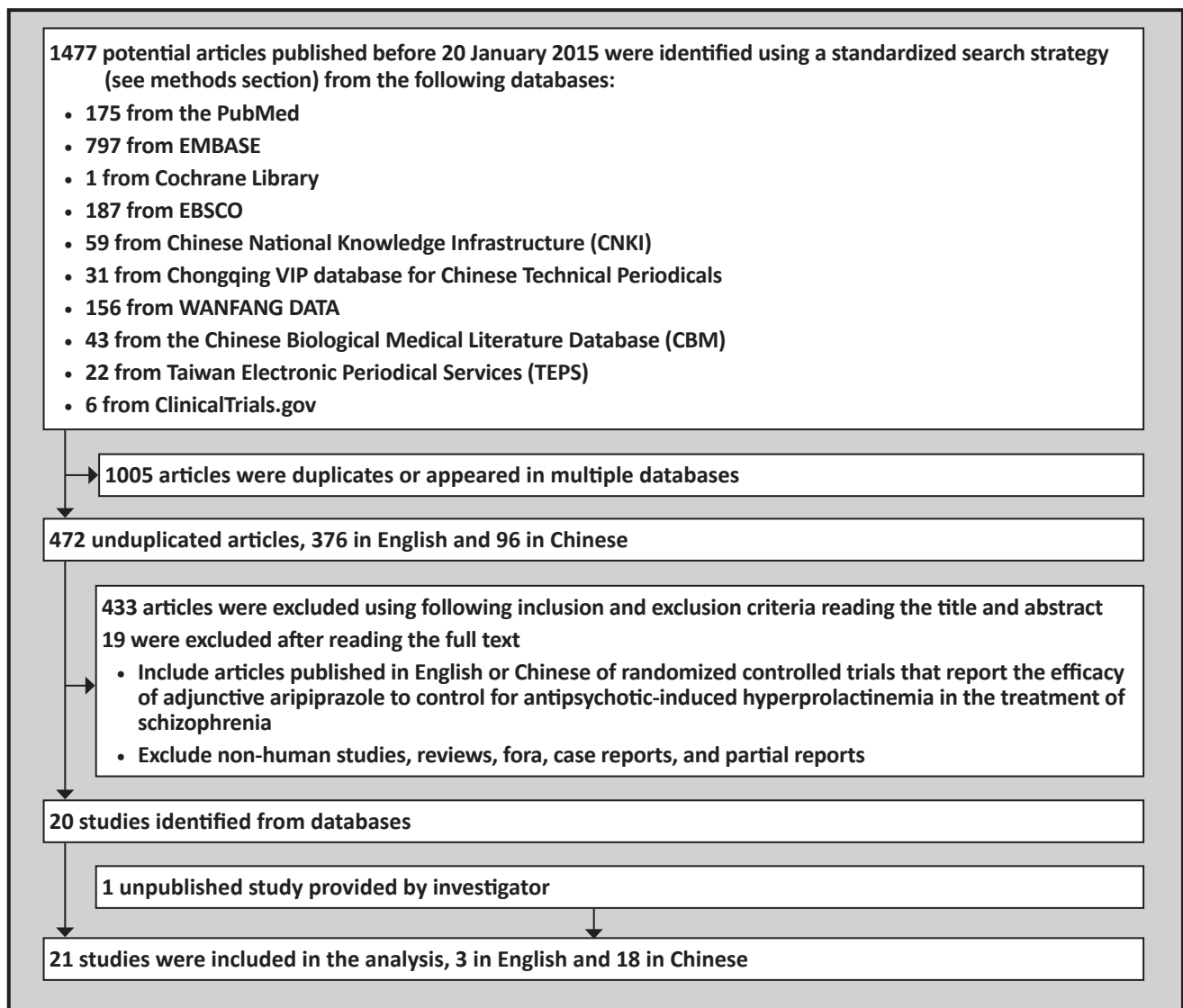
When I^2 is less than 50% and $p>0.10$, the results were considered homogeneous and the fixed-effect model was used; when I^2 is greater than 50% and less than 75%, results were considered heterogeneous and the random-effect model was used. If I^2 is 75% or greater, we conducted sensitivity analysis to identify potential contributors to heterogeneity; if I^2 remained 75% or greater after removing outliers we only provided descriptive results without pooling estimates. Subgroup analysis was conducted to explore the effect of the type of antipsychotic used and of the dosage of adjunctive aripiprazole on the outcome. A funnel plot was used to evaluate publication bias.[32]

3. Results

3.1 Characteristics of included studies

The identification of articles included in the analysis is shown in Figure 1. Using the search strategy, we found a

Figure 1. Identification of included studies

1477 potential articles published before 20 January 2015 were identified using a standardized search strategy (see methods section) from the following databases:

- **175 from the PubMed**
- **797 from EMBASE**
- **1 from Cochrane Library**
- **187 from EBSCO**
- **59 from Chinese National Knowledge Infrastructure (CNKI)**
- **31 from Chongqing VIP database for Chinese Technical Periodicals**
- **156 from WANFANG DATA**
- **43 from the Chinese Biological Medical Literature Database (CBM)**
- **22 from Taiwan Electronic Periodical Services (TEPS)**
- **6 from ClinicalTrials.gov**

1005 articles were duplicates or appeared in multiple databases

472 unduplicated articles, 376 in English and 96 in Chinese

433 articles were excluded using following inclusion and exclusion criteria reading the title and abstract

19 were excluded after reading the full text

- **Include articles published in English or Chinese of randomized controlled trials that report the efficacy of adjunctive aripiprazole to control for antipsychotic-induced hyperprolactinemia in the treatment of schizophrenia**
- **Exclude non-human studies, reviews, fora, case reports, and partial reports**

20 studies identified from databases

1 unpublished study provided by investigator

21 studies were included in the analysis, 3 in English and 18 in Chinese

total of 1477 references to articles in the 10 databases. Many of the references appeared in multiple databases; after removing these duplicates and studies that were reported in more than one article 472 unduplicated articles remained. Reading the title and abstract of these unduplicated articles identified 433 that did not meet our inclusion and exclusion criteria and reading the full text identified an additional 19 that did not meet our criteria. This left 20 articles;[18-21,24,27,38-51] data from one additional unpublished study[52] was provided by the investigator (available on request). These 21 articles, 3 in English and 18 in Chinese, were included in the subsequent analyses.

The characteristics of these 21 studies are shown in Table 1.

(a) Time of publication: all the articles were published between 2006 and 2015.

(b) Location of study: nineteen studies[20,39,41,45,47,21,24,27,38-52] are from mainland China, one[18] from the Republic of Korea, and one[19] from the United States.

(c) Gender of participants: nine studies[24,39,41,45,47,48,50-52] only included females, three studies[20,21,46] only included males, and the remaining nine studies[18,19,27,28,40,42-44,49] included both men and women.

(d) Age of participants: three studies[21,41,46] did not specify the age of participants; the remaining eightteen studies[18-20,24,27,38-40,42-45,47,48-52] were conducted in adults 18 years of age or older – one of these studies[49] was limited to elderly individuals.

(e) Type of control group: five studies[44,45,49,50,52] provided no treatment to individuals in the control group and sixteen studies[18-21,24,27,38-43,48,51] used placebo controls.

(f) Duration of follow-up: one study[43] followed patients for 4 weeks, eight studies[24,38-42,46,51] for 6 weeks, six studies[18,20,21,27,48,52] for 8 weeks, four studies[45,47,49,50] for 12 weeks, one study[19] for 16 weeks, and one study[44] for 26 weeks.

(g) Type of blinding: four studies[18,19,20,27] were double-blind, nine studies[21,24,38,39,41,42,46-48] were single-blind, and the reports for eight studies[40,43-45,49-52] did not provide information about blinding.

(h) Type of antipsychotic medication: seven studies[19,24,44,49-52] included patients with HPL induced by different types of antipsychotic medication; the remaining fourteen studies only included patients with HPL induced by a single type of antipsychotic medication (seven[20,27,39,43,46-48] only considered risperidone-induced HPL, two[18,41] haloperidol-induced HPL, two[21,42] sulpiride-induced HPL, one[40] chlorpromazine-induced HPL, one[38] perphenazine-induced HPL, and one[45] olanzapine-induced HPL). All participants in

the studies were using a single antipsychotic medication prior to the study.

(i) Dosage of aripiprazole: fourteen studies[20,21,24,38,39,40-42,44,46,48-52] used 5mg/day and seven studies[18,19,27,43,45,47,51] used 10mg/day or higher.

3.2 Risk of bias

The results of the assessment of risk of bias in the 21 studies is shown in Table 2. Only five studies[24,27,39,42,46] explicitly stated that the evaluators were blinded and only seven studies[20,24,38-40,42,51] described the method of randomization. The overall assessment of risk of bias in the 21 studies was based on the results of the 7 items in the ROB tool. Six studies[43-45,49,50,52] were classified as being at high-risk for bias; five[44,45,49,50,52] because of failure to blind participants or personnel (studies using no-treatment controls) and two[43,45] because of selective reporting. The risk of bias in the remaining 15 studies[18-21,24,27,38-42,46-48,51] was classified as 'unclear', primarily because none of the reports of the studies provided sufficient information to code the ROB 'concealment of allocation item' and several reports did not provide information about other ROB items. None of the studies was classified as being at low-risk of bias. The inter-rater reliability of the two independent coders' assessment of overall risk of bias in the studies was acceptable (kappa=0.62), but one of the seven items of the ROB tool, the item about blinding of participants and providers, had poor inter-rater reliability (kappa=0.30), suggesting that the included papers provided conflicting or confusing information about the blinding of treating clinicians.

3.3 Findings from meta-analyses

The results of the meta-analysis for the primary outcome are shown in the Forest plot in Figure 2 and those for the various secondary outcomes are shown in Table 3.

3.3.1 HPL recovery after treatment with aripiprazole

Eleven studies[18-20,24,27,39,41,47,48,51,52] with a pooled sample of 974 individuals provided information on the proportion of participants whose serum prolactin returned to the normal range by the end of follow-up. These studies were quite heterogeneous (I^2=83%), so a random-effect model was used to generate the pooled estimates. Compared to the control group, individuals in the aripiprazole group were more likely to have normal prolactin levels by the end of the follow-up (pooled RR=8.81, 95%CI=3.66-21.23). Sensitivity analyses found that after excluding three outlier studies (Kane,[19] Pan,[51] and Qiao[52]), there was little heterogeneity (I^2=0%) in the remaining eight studies. As shown in the Forest plot in Figure 2, using the fixed effect model on the results from the pooled sample of 604 individuals in these eight heterogeneous studies resulted in a pooled RR of 19.17 (95%CI=10.98-33.48).

Table 1. Characteristics of the included randomized controlled trials

study ID	blinding, type of control	gender of participants	age range	N	duration of trial (weeks)	primary antipsychotic medication(s) used	daily dosage of aripiprazole
Xu 2006[24]	single-blind, placebo-control	female	18-35	60	6	risperidone, sulpiride	5mg
Shim 2007[18]	double-blind, placebo-control	both genders	18-45	54	8	haloperidol	15mg-30mg
Zhang 2008[38]	single-blind, placebo-control	both genders	25-52	60	6	perphenazine	5mg
Ji 2008[39]	single-blind, placebo-control	female	18-35	117	6	risperidone	5mg
Jin 2008[40]	blinding not specified placebo-control	both genders	18-52	80	6	chlorpromazine	5mg
Chen 2009[20]	double-blind, placebo-control	male	18-50	72	8	risperidone	5mg
Kane 2009[19]	double-blind, placebo-control	both genders	>18	252	16	risperidone, quetiapine	10mg
Wang 2009[41]	single-blind, placebo-control	female	not specified	60	6	haloperidol	5mg
Song 2009[42]	single-blind, placebo-control	both genders	18-35	140	6	sulpiride	5mg
Chen 2010[21]	single-blind, placebo-control	male	not specified	60	8	sulpiride	5mg
Liu (L) 2011[43]	blinding not specified placebo-control	both genders	18-45	86	4	risperidone	5mg-10mg
Liu (Z) 2011[44]	blinding not specified no-treatment control	both genders	18-70	180	26	risperidone, clozapine, perphenazine, chlorpromazine	5mg
Sun 2011[45]	blinding not specified no-treatment control	female	18-45	56	12	olanzapine	10mg
Xue 2012[46]	single-blind, placebo-control	male	not specified	68	6	risperidone	5mg
Zhou 2012[47]	single-blind, placebo-control	female	18-45	60	12	risperidone	10mg
Zhu 2012[48]	single-blind, placebo-control	female	18-60	65	8	risperidone	5mg
Wu 2013[49]	blinding not specified no-treatment control	both genders	>60	63	12	risperidone, sulpiride, perphenazine, chlorpromazine	5mg
Guo 2013[50]	blinding not specified no-treatment control	female	18-45	86	12	risperidone, sulpiride, perphenazine, chlorpromazine	5mg
Chen 2014[27]	double-blind, placebo-control	both genders	18-45	116	8	risperidone	20mg
Pan 2014[51]	blinding not specified placebo-control	female	18-52	58	6	risperidone, sulpiride	10mg
Qiao 2015[52]	blinding not specified no-treatment control	female	18-45	60	8	risperidone, paliperidone	5mg

Table 2. Evaluation of risk of bias in the included studies based on the seven items in the Cochrane Risk of Bias (ROB) tool[29]								
Study ID	random sequence generation	allocation concealment	blinding of participants and providers	blinding of outcome assessment	incomplete outcome data	selective reporting	other biases[a]	OVERALL RISK OF BIAS[b]
Xu 2006[24]	low	unclear	low	low	low	low	low	**Unclear**
Shim 2007[18]	unclear	unclear	unclear	unclear	low	low	low	**Unclear**
Zhang 2008[38]	low	unclear	low	unclear	low	low	low	**Unclear**
Ji 2008[39]	low	unclear	low	low	low	low	low	**Unclear**
Jin 2008[40]	low	unclear	unclear	unclear	low	low	low	**Unclear**
Chen 2009[20]	low	unclear	low	unclear	low	low	low	**Unclear**
Kane 2009[19]	unclear	unclear	unclear	unclear	low	low	low	**Unclear**
Wang 2009[41]	unclear	unclear	low	unclear	low	low	low	**Unclear**
Song 2009[42]	low	unclear	low	low	low	low	low	**Unclear**
Chen 2010[21]	unclear	unclear	low	unclear	low	low	low	**Unclear**
Liu (L) 2011[43]	unclear	unclear	unclear	unclear	unclear	high	low	**High**
Liu (Z) 2011[44]	unclear	unclear	high	unclear	low	low	low	**High**
Sun 2011[45]	unclear	unclear	high	unclear	low	high	low	**High**
Xue 2012[46]	unclear	unclear	low	low	low	low	low	**Unclear**
Zhou 2012[47]	unclear	unclear	low	unclear	low	low	low	**Unclear**
Zhu 2012[48]	unclear	unclear	low	unclear	low	low	low	**Unclear**
Wu 2013[49]	unclear	unclear	high	unclear	unclear	low	low	**High**
Guo 2013[50]	unclear	unclear	high	unclear	low	low	low	**High**
Chen 2014[27]	unclear	unclear	low	low	low	low	low	**Unclear**
Pan 2014[51]	low	unclear	unclear	unclear	unclear	low	low	**Unclear**
Qiao 2015[52]	unclear	unclear	high	unclear	low	low	low	**High**
kappa[c]	1.00	0.62	0.30	0.79	1.00	1.00	1.00	**0.62**

[a] Other biases considered include study-specific biases or concerns about fraudulent results

[b] If any of seven items are coded high-risk of bias the overall study is classified as high-risk, if all seven items are coded as low-risk the overall study is classified as low-risk; all other studies (i.e., those with some items coded a 'unclear' and no items coded as high-risk) are classified as 'unclear'

[c] Kappa values for inter-rater reliability of the two independent coders who assessed for each item for the 21 studies

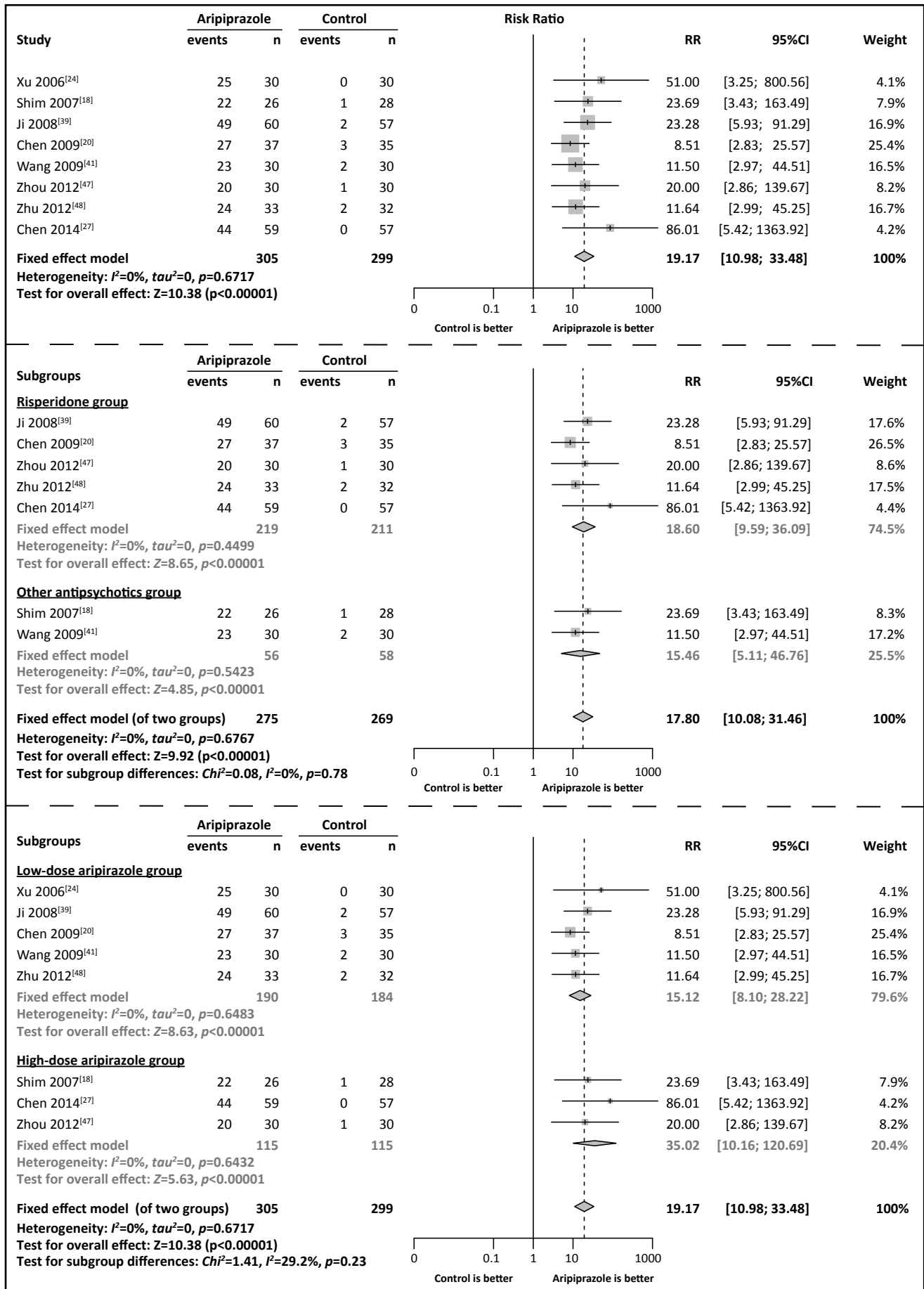*3.3.2 Comparison of serum prolactin levels at the end of the study*

A total of 19 studies[20,21,24,27,38-52] reported data on serum prolactin levels at the end of the trial. However, results from seven studies[24,27,40,48,49,51,52] were not included due to the non-normal distribution of the results. The pooled sample size from the remaining 12 studies[20,21,38,39,41-47,50] was 1016. The sample size for these 12 studies varied from 56[45] to 180[44] and all of them reported statistically significant lower serum prolactin levels in the aripiprazole group compared to the control group at the end of follow-up. But these studies were quite heterogeneous (I^2=94%) and sensitivity analysis did not identify a subset of results that were heterogeneous, so we did not pool the results in a meta-analysis.

3.3.3 Comparison of the occurrence of adverse events

Twelve studies[21,24,27,38-42,47,48,51] with a pooled sample of 962 individuals reported a total of 115 adverse events. No statistically significant differences were found in the proportion of participants who experienced an adverse event between the aripiprazole and control group (RR=1.16, 95%CI=0.82-1.64).

Reported adverse events included insomnia, somnolence, sedation, dry mouth, fatigue, anxious or depressive symptoms, extrapyramidal symptoms, and psychotic symptoms. Meta-analysis revealed no statistically significant differences in the occurrence of adverse events between the treatment and control group except for somnolence and headache:

Figure 2. Forest plots comparing the proportion of subjects who recovered from hyperprolactinemia (HPL) at the end of the trial between the aripiprazole group and the control group

Study	Aripiprazole events	n	Control events	n	Risk Ratio	RR	95%CI	Weight
Xu 2006[24]	25	30	0	30		51.00	[3.25; 800.56]	4.1%
Shim 2007[18]	22	26	1	28		23.69	[3.43; 163.49]	7.9%
Ji 2008[39]	49	60	2	57		23.28	[5.93; 91.29]	16.9%
Chen 2009[20]	27	37	3	35		8.51	[2.83; 25.57]	25.4%
Wang 2009[41]	23	30	2	30		11.50	[2.97; 44.51]	16.5%
Zhou 2012[47]	20	30	1	30		20.00	[2.86; 139.67]	8.2%
Zhu 2012[48]	24	33	2	32		11.64	[2.99; 45.25]	16.7%
Chen 2014[27]	44	59	0	57		86.01	[5.42; 1363.92]	4.2%
Fixed effect model		**305**		**299**		**19.17**	**[10.98; 33.48]**	**100%**

Heterogeneity: I^2=0%, tau^2=0, p=0.6717
Test for overall effect: Z=10.38 (p<0.00001)

0 0.1 1 10 1000
Control is better   Aripiprazole is better

Subgroups	Aripiprazole events	n	Control events	n		RR	95%CI	Weight
Risperidone group								
Ji 2008[39]	49	60	2	57		23.28	[5.93; 91.29]	17.6%
Chen 2009[20]	27	37	3	35		8.51	[2.83; 25.57]	26.5%
Zhou 2012[47]	20	30	1	30		20.00	[2.86; 139.67]	8.6%
Zhu 2012[48]	24	33	2	32		11.64	[2.99; 45.25]	17.5%
Chen 2014[27]	44	59	0	57		86.01	[5.42; 1363.92]	4.4%
Fixed effect model		219		211		18.60	[9.59; 36.09]	74.5%

Heterogeneity: I^2=0%, tau^2=0, p=0.4499
Test for overall effect: Z=8.65, p<0.00001

	Aripiprazole events	n	Control events	n		RR	95%CI	Weight
Other antipsychotics group								
Shim 2007[18]	22	26	1	28		23.69	[3.43; 163.49]	8.3%
Wang 2009[41]	23	30	2	30		11.50	[2.97; 44.51]	17.2%
Fixed effect model		56		58		15.46	[5.11; 46.76]	25.5%

Heterogeneity: I^2=0%, tau^2=0, p=0.5423
Test for overall effect: Z=4.85, p<0.00001

	Aripiprazole	n	Control	n		RR	95%CI	Weight
Fixed effect model (of two groups)		**275**		**269**		**17.80**	**[10.08; 31.46]**	**100%**

Heterogeneity: I^2=0%, tau^2=0, p=0.6767
Test for overall effect: Z=9.92 (p<0.00001)
Test for subgroup differences: Chi^2=0.08, I^2=0%, p=0.78

0 0.1 1 10 1000
Control is better   Aripiprazole is better

Subgroups	Aripiprazole events	n	Control events	n		RR	95%CI	Weight
Low-dose aripirazole group								
Xu 2006[24]	25	30	0	30		51.00	[3.25; 800.56]	4.1%
Ji 2008[39]	49	60	2	57		23.28	[5.93; 91.29]	16.9%
Chen 2009[20]	27	37	3	35		8.51	[2.83; 25.57]	25.4%
Wang 2009[41]	23	30	2	30		11.50	[2.97; 44.51]	16.5%
Zhu 2012[48]	24	33	2	32		11.64	[2.99; 45.25]	16.7%
Fixed effect model		190		184		15.12	[8.10; 28.22]	79.6%

Heterogeneity: I^2=0%, tau^2=0, p=0.6483
Test for overall effect: Z=8.63, p<0.00001

	Aripiprazole events	n	Control events	n		RR	95%CI	Weight
High-dose aripirazole group								
Shim 2007[18]	22	26	1	28		23.69	[3.43; 163.49]	7.9%
Chen 2014[27]	44	59	0	57		86.01	[5.42; 1363.92]	4.2%
Zhou 2012[47]	20	30	1	30		20.00	[2.86; 139.67]	8.2%
Fixed effect model		115		115		35.02	[10.16; 120.69]	20.4%

Heterogeneity: I^2=0%, tau^2=0, p=0.6432
Test for overall effect: Z=5.63, p<0.00001

	Aripiprazole	n	Control	n		RR	95%CI	Weight
Fixed effect model (of two groups)		**305**		**299**		**19.17**	**[10.98; 33.48]**	**100%**

Heterogeneity: I^2=0%, tau^2=0, p=0.6717
Test for overall effect: Z=10.38 (p<0.00001)
Test for subgroup differences: Chi^2=1.41, I^2=29.2%, p=0.23

0 0.1 1 10 1000
Control is better   Aripiprazole is better

Table 3. Summary of subgroup meta-analysis and GRADE[a] assessments of quality of data about different outcome measures comparing adjunctive treatment with aripiprazole with placebo (or blank control) in patients with schizophrenia treated with other antipsychotic medications

Outcomes	number of studies (pooled sample)	test for heterogeneity		analytic model	test for overall effect		RR /SMD[b]	95%CI of RR/SMD[b]	GRADE[a]
		I^2	p		Z	p			
Prolactin level normalization	8 (604)	0%	0.67	fixed	10.38	<0.001	**19.17**	**10.98-33.48**	moderate
Risperidone group	5 (430)	0%	0.45	fixed	8.65	<0.001	**18.60**	**9.59-36.09**	high
Other antipsychotic group	2 (114)	0%	0.54	fixed	4.85	<0.001	**15.46**	**5.11-46.76**	low
Low-dose aripiprazole group	5 (374)	0%	0.65	fixed	8.53	<0.001	**15.12**	**8.10-28.22**	moderate
High-dose aripiprazole group	3 (230)	0%	0.64	fixed	5.63	<0.001	**35.02**	**10.16-120.69**	moderate
Any adverse events	12 (963)	0%	1.00	fixed	0.84	0.40	1.16	0.82-1.64	high
Risperidone group	5 (444)	0%	1.00	fixed	0.78	0.44	1.21	0.75-1.98	high
Other antipsychotic group	5 (400)	0%	1.00	fixed	0.33	0.74	1.10	0.62-1.95	moderate
Low-dose aripiprazole group	9 (698)	0%	1.00	fixed	0.50	0.62	1.11	0.74-1.67	moderate
High-dose aripiprazole group	4 (321)	0%	1.00	fixed	0.68	0.50	1.23	0.68-2.23	high
Insomnia	14 (948)	5%	0.39	fixed	1.32	0.19	0.77	0.52-1.14	low
Risperidone group	4 (336)	0%	0.91	fixed	1.44	0.15	0.51	0.20-1.28	moderate
Other antipsychotic group	5 (314)	51%	0.24	random	0.46	0.64	0.80	0.31-2.05	very low
Low-dose aripiprazole group	12 (835)	0%	0.74	fixed	2.19	0.03	**0.60**	**0.39-0.95**	very low
High-dose aripiprazole group	3 (169)	0%	0.39	fixed	1.32	0.19	1.69	0.77-3.67	moderate
Headache	9 (611)	0%	0.71	fixed	2.16	0.03	**2.31**	**1.08-4.92**	low
Risperidone group	3 (268)	0%	0.66	fixed	0.30	0.77	0.84	0.27-2.63	moderate
Other antipsychotic group	4 (254)	0%	0.90	fixed	2.55	0.01	**6.68**	**1.55-28.77**	low
Low-dose aripiprazole group	7 (498)	0%	0.71	fixed	1.04	0.30	1.58	0.67-3.73	low
High-dose aripiprazole group	3 (169)	25%	0.26	fixed	1.77	0.08	3.42	0.88-13.36	moderate
Sedation	2 (113)	0%	0.39	fixed	0.25	0.80	0.86	0.27-2.80	moderate
Risperidone group	1(59)	---	---	fixed	0.66	0.51	2.90	0.12-68.50	low
Other antipsychotic group	1(54)	---	---	fixed	0.64	0.52	0.65	0.17-2.44	low
High-dose aripiprazole group	2(113)	0%	0.39	fixed	0.25	0.80	0.86	0.27-2.80	low
Dry mouth	3 (185)	0%	0.80	fixed	0.78	0.43	1.35	0.63-2.90	high
Risperidone group	2(128)	0%	0.54	fixed	0.28	0.78	1.21	0.31-4.67	low
Other antipsychotic group	1 (44)	---	---	fixed	0.78	0.44	1.44	0.58-3.58	low
Low-dose aripiprazole group	2 (128)	0%	0.54	fixed	0.28	0.78	1.21	0.31-4.67	low
High-dose aripiprazole group	1 (44)	---	---	fixed	0.78	0.44	1.44	0.58-3.58	low
Fatigue	2 (140)	0%	0.32	fixed	0.72	0.47	1.61	0.44-5.86	moderate
Other antipsychotic group	2 (140)	0%	0.32	fixed	0.72	0.47	1.61	0.44-5.86	moderate
Low-dose aripiprazole group	1 (86)	---	---	fixed	0.00	1.00	1.00	0.21-4.68	low
High-dose aripiprazole group	1 (54)	---	---	fixed	1.10	0.27	5.37	0.27-106.88	moderate
Somnolence	9 (654)	0%	0.87	fixed	2.76	0.006	**2.76**	**1.34-5.69**	low
Risperidone group	3(250)	0%	0.73	fixed	2.08	0.04	**6.13**	**1.11-33.94**	moderate
Other antipsychotic group	3 (200)	0%	0.96	fixed	1.43	0.15	3.67	0.62-21.85	low
Low-dose aripiprazole group	8 (586)	0%	0.80	fixed	2.70	0.007	**2.85**	**1.33-6.10**	low
High-dose aripiprazole group	1 (58)	---	---	fixed	0.58	0.56	2.00	0.19-20.86	low

Table 3. Summary of subgroup meta-analysis and GRADE[a] assessments of quality of data about different outcome measures comparing adjunctive treatment with aripiprazole with placebo (or blank control) in patients with schizophrenia treated with other antipsychotic medications (cont'd)

Outcomes	number of studies (pooled sample)	test for heterogeneity		analytic model	test for overall effect		RR /SMD[b]	95%CI of RR/SMD[b]	GRADE[a]
		I^2	p		Z	p			
Anxiety and depressive symptoms	2 (126)	32%	0.23	fixed	0.26	0.79	1.15	0.40-3.35	moderate
Risperidone group	1 (72)	---	---	fixed	0.44	0.66	0.76	0.22-2.59	moderate
Other antipsychotic group	1 (54)	---	---	fixed	1.10	0.27	5.37	0.27-106.88	moderate
Low-dose aripiprazole group	1 (72)	---	---	fixed	0.44	0.66	0.76	0.22-2.59	moderate
High-dose aripiprazole group	1 (54)	---	---	fixed	1.10	0.27	5.37	0.27-106.88	moderate
Extrapyramidal symptoms	3 (218)	0%	0.92	fixed	0.40	0.69	1.18	0.53-2.60	low
Risperidone group	1 (72)	---	---	fixed	0.08	0.93	0.95	0.26-3.94	low
Low-dose aripiprazole group	3 (218)	0%	0.92	fixed	0.40	0.69	1.18	0.53-2.60	low
Lost to follow-up during study	7 (561)	0%	0.63	fixed	0.72	0.47	1.24	0.69-2.22	moderate
Risperidone group	3 (305)	0%	0.68	fixed	0.54	0.59	0.82	0.39-1.71	moderate
Other antipsychotic group	2 (110)	0%	0.76	fixed	1.48	0.14	3.77	0.65-21.96	low
Low-dose aripiprazole group	4 (335)	0%	0.52	fixed	0.10	0.92	0.97	0.48-1.95	low
High-dose aripiprazole group	3 (226)	0%	0.63	fixed	1.34	0.18	2.10	0.71-6.23	moderate
Improved psychotic symptoms	16 (1157)	1%	0.44	fixed	0.37	0.71	-0.02	-0.14-0.09	moderate
Risperidone group	5 (438)	11%	0.35	fixed	0.40	0.69	-0.04	-0.23-0.15	high
Other antipsychotic group	8 (510)	0%	0.47	fixed	0.53	0.60	-0.05	-0.22-0.13	low
Low-dose aripiprazole group	13 (931)	15%	0.29	fixed	0.49	0.63	-0.03	-0.16-0.10	moderate
High-dose aripiprazole group	3 (226)	0%	0.64	fixed	0.14	0.89	0.02	-0.24-0.28	high

[a] use of Cochrane collaboration's GRADE software (Grades of Recommendation, Assessment, Development, and Evaluation)[33] to assess quality of evidence for each outcome
[b] pooled standard mean difference (SMD) is used to compare continuous measures and risk ratio (RR) for categorical measures

somnolence was more commonly reported in the aripiprazole group (RR=2.76, 95%CI=1.34-5.69) and headaches were also more commonly reported in the aripiprazole group (RR=2.31, 95%CI=1.08-4.92).

3.3.4 Loss to follow-up

Seven studies[18,20,27,39,45,50,52] with a pooled sample of 561 individuals reported that 41 individuals (7.3%) were lost to follow-up during the trial. Meta-analysis did not find any differences between the treatment and control group in the proportion of enrolled participants that were lost to follow-up (RR=1.24, 95%CI=0.69-2.22).

3.3.5 Comparison of improvement of psychotic symptoms

Fifteen studies[18,20,21,27,38-42,45,46,48,49,50,52] with a pooled sample of 1157 individuals assessed changes in the severity of psychotic symptoms during the trial using the Positive and Negative Syndrome Scale (PANSS)[53] or

the Brief Psychiatric Rating Scale (BPRS).[54] The meta-analysis comparing the standardized mean difference in the final scale scores between the two groups found no significant difference in the improvement of psychotic symptoms between the aripiprazole groups and control groups (SMD=-0.02, 95%CI=-0.14~0.09).

3.4 Subgroup analysis

3.4.1 Analysis stratified by types of antipsychotics

Risperidone was the most commonly used medication in the studies, so we compared results of studies that only used risperidone with the results of studies that used other types of antipsychotic medications; studies that included participants that used different antipsychotic medications were not included in this analysis. As shown in Figure 2 and in Table 3, the results comparing five studies that reported the primary outcome (HPL recovery) in individuals using risperidone was not significantly different from that of the two studies reporting the primary outcome that used other

antipsychotic medications (in this case, haloperidol) (RR=18.60 v. RR=15.46; X^2=0.08, p=0.78).

The meta-analysis of results of the secondary outcomes of interest stratified by type of antipsychotic medication used are shown in Table 3. There were only two statistically significant differences in the prevalence of these secondary outcomes in individuals who did or did not use adjunctive aripiprazole: among individuals taking other antipsychotic medications (i.e., not risperidone), those using adjunctive aripiprazole were more likely to report headaches than those in the control group; and among individuals taking risperidone, those using adjunctive aripiprazole were more likely to report somnolence than those in the control group. Comparison of the risk ratios for these secondary outcomes of the risperidone group versus those of the other antipsychotic group only found one significant difference: this risk ratio of headaches in the risperidone group (RR=0.84) was significantly lower than that for the other antipsychotic group (RR=6.68) (X^2=4.80, p=0.03).

3.4.2 Analysis stratified by dosage of aripiprazole

We also stratified studies into a low-dose group (i.e., daily dosage of aripiprazole $\leq$5mg) and a high-dose group (i.e., daily dosage of aripiprazole >5mg). As shown in the Forest plot and in Table 3, the main outcome (HPL recovery) was significantly more common at both dosages of aripiprazole than in individuals in the corresponding control groups. The risk ratio for the high-dose group was more than double that of the low-dose group (35.0 v. 15.1), but this did not reach statistical significance (X^2=1.41, p=0.23) due to the wide confidence intervals around these estimates of the RR. Assessment of the secondary outcomes in each of these groups only identified two outcomes that were significantly different in individuals who did or did not take adjunctive aripiprazole: compared to controls, individuals taking low-dose aripiprazole were significantly less likely to report insomnia and significantly more likely to report somnolence. There were no significant differences in the risk ratios for any of these secondary outcomes between the low-dose group and the high-dose group.

3.5 Quality of the level of evidence in the meta-analyses

This analysis investigated a total of 12 outcomes (57 when including the 45 subgroup analyses stratified by type of antipsychotic medication and by dosage of aripiprazole) about the level of prolactin, the occurrence of adverse events, non-compliance, and improvement of psychotic symptoms. Table 3 shows the GRADE assessment of the level of evidence for these outcomes. As shown in Table 3, based on the GRADE measure, the quality of evidence was classified as 'high' for 7 (12.3%) of the 57 outcomes, 'medium' for 24 (42.1%) outcomes, 'low' for 24 (42.1%) outcomes, and 'very low' for 2 (3.5%) outcomes.

3.6 Risk of publication bias

Figure 3 shows the funnel plot used to assess the possibility of publication bias in the eleven studies[18-20,24,27,39,41,47,48,51,52] that reported the proportion of participants whose serum prolactin levels returned to the normal range by the end of the follow-up (HPL recovery). As shown in the figure, smaller studies tended to report larger risk ratios in favor of aripiprazole. Egger's test results indicate a statistically significant level of bias (Egger's bias parameter=3.17, 95%CI=2.20-4.15, p<0.001).

Figure 3. Funnel plot of potential publication bias in 11 studies that report the proportion of participants whose serum prolactin returned to the normal range by the end of follow-up. (Note: the sample size and results for two studies are almost identical, so only 10 points appear in the plot.)
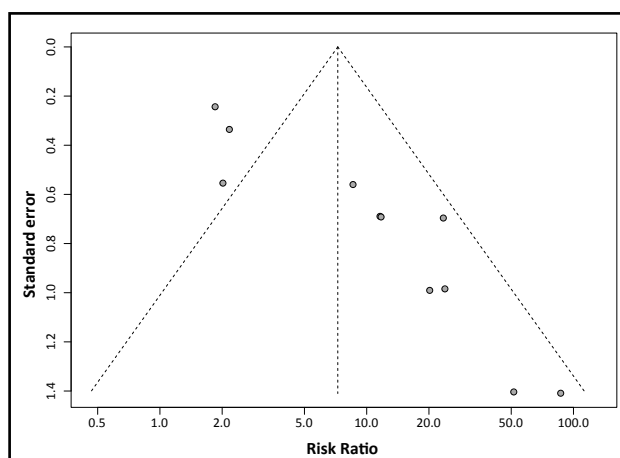
4. Discussion

4.1 Main findings

Extensive screening of English-language and Chinese-language databases identified 21 RCTs about the use of aripiprazole in the treatment of antipsychotic-induced hyperprolactinemia (HPL).

Meta-analysis of the 11 studies that reported the proportion of participants whose serum prolactin returned to the normal range at the time of follow-up (i.e., HPL recovery) indicated that both low-dose ($\leq$5mg/day) and high-dose (>5mg/day) adjunctive treatment with aripiprazole can effectively treat antipsychotic-induced HPL. Two of the studies[18,24] also reported recovered menstrual cycle and disappearance of spontaneous lactation in the aripiprazole group but not the control group. These findings are consistent with results from the previous meta-analysis[28] on this topic, which pooled results from five studies. There is on-going controversy about the appropriate dose of aripiprazole to treat antipsychotic-induced HPL;[18,55]

our study found a much higher risk ratio among individuals treated with high-dose aripiprazole than those treated with low-dose aripiprazole (35 v. 15), but the difference was not statistically significant, so more studies with larger samples will be needed to resolve this issue. Previous studies[56-58] have reported that HPL is a relatively common condition among individuals taking risperidone; our study found that aripiprazole was equally effective in the treatment of risperidone-induced HPL and HPL induced by other antipsychotic medications.

Aripiprazole is a partial dopamine D2 receptor agonist,[59] but we found no evidence that it exacerbates existing psychotic symptoms. The occurrence of any adverse event during the follow-up period was similar in the aripiprazole and control groups, but – consistent with previously documented side-effects of aripiprazole[60,61]—analysis of each specific adverse event found that somnolence was significantly more common in the aripiprazole group than in the control group, particularly in individuals taking low-dose aripiprazole.[59] We also found that individuals taking adjunctive aripiprazole were more likely to report headaches than those in the control group, especially if they were using antipsychotic medications other than risperidone.

There were substantial concerns about the quality of the data provided by the identified RCTs. Only a minority of the reports provided sufficient information to assess the method of randomization, allocation concealment, and blinding of the outcome measure, so risk of bias (assessed using the Cochrane ROB tool) was classified as 'uncertain' in 15 of the 21 studies. The remaining 6 studies were classified as 'high-risk' of bias because of failure to blind the outcome assessment or because of selective reporting. Based on the Cochrane GRADE measure of the quality of evidence supporting the results for the 12 full-sample meta-analyses and the 45 subgroup meta-analyses, only 7 of the 57 outcomes had 'high-quality' evidence. And there was a suggestion of publication bias, with smaller studies reporting greater treatment effects of aripiprazole. Clearly, conducting RCTs about a topic of interest – usually considered the 'gold standard' for informing evidence-based clinical medicine[62,63] — is not enough to ensure high-quality data. Rigorous adherence to the reporting requirements specified in the CONSORT statement[64] and appropriate management of the issues discussed in the CONSORT statement when designing an RCT are essential to generating the high-quality data needed to inform clinical practice.

4.2 Limitations

In addition to concerns about the potential risk of bias and the quality of the evidence provided for the reported meta-analyses, there was substantial heterogeneity between the results of the studies. Partly due to this heterogeneity, only 8 of the 21 identified RCTs contributed data to the pooled sample used in the meta-analysis to assess the main outcome – recovery from hyperprolactinemia. This heterogeneity may be due to differences in the characteristics of participants, in the organization of the trials, or in the method of assessing the primary and secondary outcome measures between the different studies, but it may also mean that the results are inherently unstable.

Another issue is the duration of treatment. In clinical practice it is probable that aripiprazole will need to be taken continuously with antipsychotic medication to reduce the occurrence of HPL. The current studies only assess the effectiveness and safety of aripiprazole over relatively short follow-up periods, so long-term follow-up studies will be needed before aripiprazole can become a recommended treatment for antipsychotic-induced hyperprolactinemia.

4.3 Implications

The current study systematically reviewed and evaluated all available RCTs about the use of aripiprazole to treat antipsychotic-induced HPL. We found that adjunctive aripiprazole is effective and safe to use in the treatment of antipsychotic-induced HPL and that adjunctive aripiprazole is associated with increase reports of somnolence and headaches. However the potential for bias in the included studies was either 'high' or 'uncertain' and the level of evidence for most of the assessed outcomes was rated as 'moderate' or 'low'. Moreover, the appropriate dose of aripiprazole and the long-term effectiveness and safety of this treatment remain uncertain. Further work that resolves these methodological and reporting issues will be needed before a definitive conclusion about the usefulness and safety of adjunctive aripiprazole in the management of antipsychotic-induced hyperprolactinemia is justified.

用阿立哌唑治疗以减轻其他抗精神病药物所致的高泌乳素血症：现有随机对照研究的 meta 分析

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背景： 高泌乳素血症是抗精神病药物治疗中一种常见的不良反应。近年来有报道提示阿立哌唑能减轻其他抗精神病药所致的高泌乳素血症，但不同研究的结果不尽一致。虽然已有一篇相关系统综述，但是只纳入了 5 项研究。

目的： 对有关阿立哌唑辅助治疗其他抗精神病药物所致高泌乳素血症的有效性和安全性的所有随机对照研究进行 meta 分析。

方法： 检索国内外常用数据库中 2015 年 1 月 20 日前发表的所有关于阿立哌唑治疗其他抗精神病药物所致高泌乳血症的随机对照研究。按照预先规定的纳入标准及排除标准筛选相关研究。根据 Cochrane 偏移风险评估工具对纳入研究偏移风险进行评价，采用 Cochrane GRADE 评估证据质量，使用 Review Manager 5.3 和 R3.1.1 软件进行数据分析。

结果： 共纳入 21 项随机对照研究，其中在中国大陆开展的研究有 19 项。对 21 项研究中的 8 项研究共 604 例样本进行 meta 分析，发现与对照组相比，阿立哌唑辅助治疗后，泌乳素水平恢复的患者比例显著增加（RR=19.2，95%CI =11.0-33.5）。两组患者在随访中出现不良反应的总的比例没有差异，但阿立哌唑组报告嗜睡（RR=2.76，95%CI=1.34-5.69）和头痛（RR=2.31，95%CI=1.08-4.92）的比例相对高。高剂量阿立哌唑（>5mg /d）比低剂量（<5mg /d）更有效（RR=30.0，95%CI=10.2-120.7 比 RR=15.1，95%CI=8.1-28.1），但这种差异无统计学意义。这些研究中有 6 项被评为" 高 " 偏移风险，而其他 15 项的偏移风险" 不清楚 "。对 57 个研究结果的证据水平评估显示只有 7 个是" 高 " 质量的。

结论： 本研究系统地回顾和评估了所有相关的随机对照研究，发现阿立哌唑辅助治疗其他抗精神病药物所致的高泌乳素血症是安全有效的。然而，一些研究的质量较低，大多数研究的方法学信息不完善，研究中随访时间相对较短，这些都会影响研究结果的有效性。需要进一步工作以解决上述方法学和研究报告方面的问题。

关键词： 阿立哌唑；高泌乳素血症；随机对照研究；meta 分析

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