Systematic Review and Meta-Analysis

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Safety of aripiprazole for tics in children and adolescents

A systematic review and meta-analysis

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Abstract

Background: Aripiprazole is widely used in the management of tic disorders (TDs), we aimed to assess the safety of aripiprazole for TDs in children and adolescents.

Methods: A systematic literature review was performed in the databases of MEDLINE, Embase, the Cochrane Library and 4 Chinese databases, from inception to February 2019. All types of studies evaluating the safety of aripiprazole for TDs were included. The quality of studies was assessed using the Cochrane Risk of Bias tool, the Newcastle–Ottawa Scale tool, the National Institute of Clinical Excellence, the CARE (Case Report) guidelines according to types of studies. Risk ratio (RR) and incidence rate with a 95% confidence interval (CI) were used to summarize the results.

Results: A total 50 studies involving 2604 children met the inclusion criteria. The result of meta-analysis of randomized controlled trials showed that there was a significant difference between aripiprazole and haloperidol with respect to rate of somnolence (RR = 0.596, 95% CI: 0.394, 0.901), extrapyramidal symptoms (RR = 0.236, 95% CI: 0.111, 0.505), tremor (RR = 0.255, 95% CI: 0.114, 0.571), constipation (RR = 0.148, 95% CI: 0.040, 0.553), and dry mouth (RR = 0.141, 95% CI: 0.046, 0.425). There was a significant difference between aripiprazole and placebo in the incidence rate of adverse events (AEs) for somnolence (RR = 6.565, 95% CI: 1.270, 33.945). The meta-analysis of incidence of AEs related to aripiprazole for case series studies revealed that the incidence of sedation was 26.9% (95% CI: 16.3%, 44.4%), irritability 25% (95% CI: 9.4%, 66.6%), restlessness 31.3% (95% CI: 13%, 75.1%), nausea and vomiting 28.9% (95% CI: 21.1%, 39.5%), and weight gain 31.3% (95% CI: 10.7%, 91.3%).

Conclusion: Aripiprazole was generally well tolerated in children and adolescents. Common AEs were somnolence, headache, sedation, nausea, and vomiting. Further high-quality studies are needed to confirm the safety of aripiprazole for children and adolescents with TDs.

Abbreviations: ADHD = attention-deficit hyperactivity disorder, AEs = adverse events, CI = confidence interval, OCD = compulsive disorder, RCTs = randomized controlled trials, RR = risk ratio, TDs = tic disorders.

Keywords: aripiprazole, children, safety, systematic review, tic disorders

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CY and QY contributed equally to this work.

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CY designed the review, collected data, developed the search strategy, undertook searches, appraised the quality of papers, selected trials for inclusion, extracted data from papers. Data management: carried out analysis and interpretation of the data and wrote the review.

QY collected data, undertook searches, appraised the quality of papers; selected trials for inclusion, extracted data from papers. Data management: checked the data and wrote the review.

LZ designed the review, collected data, undertook searches, appraised the quality of papers; selected trials for inclusion, extracted data from papers. Data management: checked the data and commented on drafts for previous version.

HC designed the review, selected trials for inclusion, extracted data from papers. Data management: checked the data and commented on drafts for previous version.

JM collected data, undertook searches, appraised the quality of papers; selected trials for inclusion, extracted data from papers.

JW collected data, appraised the quality of papers; selected trials for inclusion, extracted data from papers.

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1. Introduction

Tic disorders (TDs) are very common neurodevelopmental condition in children and adolescents[1] and are characterized by the presence of abrupt and repeated motor movements or vocalization. There are 3 kinds of TD: transient tic, chronic tic, and Tourette syndrome with prevalence rates 2.99%, 1.61%, and 0.77%, respectively.[2] In general, the severity of TDs wanes in late adolescence, and the prevalence rates of TDs in adulthood become much lower. There are various comorbid psychiatric conditions with TDs, such as obsessive–compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), and sustained social problems. TDs and these comorbidities are associated with many serious impairments in social functioning as well as emotional and educational impairment, which can have serious negative impacts on quality of life.[3–5]

Currently, pharmacological treatment is the most common intervention for patients with TDs, including typical antipsychotics (e.g., haloperidol, pimozide), atypical antipsychotics (e.g., risperidone, quetiapine), analgesics (e.g., naltrexone, propoxyphene), anticonvulsants (e.g., topiramate), antidepressants (e.g., desipramine), among others. However, the use of these treatments is associated with several adverse events (AEs), including tardive dyskinesia, extrapyramidal syndrome, and electrocardiographic abnormality.[6,7]

Aripiprazole, a dopamine agonist and 5-HT1A receptor, could act as a dopamine D2 partial agonist based on local dopamine system surroundings.[8,9] It is extensively used in the management of TDs in the United States, China, and other countries. Yang et al[10] reviewed 12 trials including 935 participants aged between 4 and 18 years, involving aripiprazole for children with TDs. Those authors confirmed that aripiprazole appears to be a new treatment approach for children with TDs; the systematic review also pointed out that drowsiness, increased appetite, nausea, and headache were common AEs with use of aripiprazole for tics. However, that study only included randomized controlled trials (RCTs) and did not include a quantitative analysis of safety; therefore, the safety of aripiprazole was not well evaluated.

A considerable number of trials have researched the efficacy and safety of aripiprazole for patients with TDs; these studies have provided evidence of the comparative efficacy and safety of aripiprazole for TDs.[11–14] However, several new reports have been published demonstrating that the findings for the relative safety of aripiprazole in children and adolescents need to be updated.

Therefore, to provide additional information on the safety of aripiprazole, we included all types of studies and performed a meta-analysis to assess the safety of aripiprazole for TDs in children and adolescents.

2. Methods

This meta-analysis was conducted strictly according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines, and the ethical approval and informed consent were unnecessary since the meta-analysis was aimed to summarize the previous studies.

2.1. Search strategy and study selection

A systematic literature review was performed in the databases of MEDLINE, Embase, the Cochrane Library, the Chinese Biomedical Literature Database, China Knowledge Resource Integrated Database, VIP Database, and Wanfang Database, from inception to March 2018. Citations of relevant studies were searched for appropriate articles as well. The search terms included "aripiprazole," "Tourette syndrome," "tic disorders," and "tics." According to the specific requirements of the database, the terms were combined into different retrieval expressions. (See Supplemental Digital Content, which illustrates search strategy for Each Database, http://links.lww.com/MD/D11).

2.2. Inclusion and exclusion criteria

The inclusion criteria were developed using the PICOS (P: population; I: intervention; C: comparison; O: outcome; S: study design) framework, as follows:

1. Population: aged <18 years old, with a clinical diagnosis of TD
2. Intervention: aripiprazole
3. Comparison: placebo or other types of pharmacotherapies
4. Outcome: prevalence rate of all types of AE
5. Study design: all types of studies, including RCT, non-RCT, cohort study, case-control study, case series study, and case report, with data extraction and quality assessment

Meanwhile, we restricted the language of publications English or Chinese. Through reading the title, abstract, and full text, we judged whether studies met the inclusion criteria.

Data were extracted by 1 author and checked by another author using an Excel form, which included the following information: study information, age, sex, intervention, control, treatment period, time of follow-up, diagnostic criteria, and prevalence rate of AEs.

The quality of all RCTs and non-RCTs was assessed using the Cochrane Risk of Bias tool according to the Cochrane Handbook for Systematic Reviews of Interventions (www.cochranehandbook.org): Random sequence generation; Allocation concealment; Blinding of participants; Blinding of outcome assessment; Incomplete outcome data; Selective reporting; Other sources of bias.[15] The qualities of case-control studies and cohort studies were assessed using the Newcastle–Ottawa Scale tool.[16] Assessment of risk of bias in case series was based on the recommendations of the National Institute of Clinical Excellence (NICE): Case series in more than 1 center, that is, multicenter study; Is the hypothesis/aim/objective of the study clearly described? Are the inclusion and exclusion criteria (case definition) clearly reported? Is there a clear definition of the outcomes reported? Were data collected prospectively? Is there an explicit statement that patients were recruited consecutively? Are the main findings of the study clearly described? Are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics).[17] Quality appraisal of case reports was conducted according to the CARE (CAse REport) guidelines: Title; Keywords; Abstract; Introduction; Patient Information; Clinical Findings; Timeline; Diagnostic Assessment; Therapeutic Intervention; Follow-up and Outcomes; Discussion; Patient Perspective; Informed Consent.[18]

2.3. Statistical analysis

All statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX). Risk ratio (RR) and incidence rate with a 95% confidence interval (CI) were used to summarize the results. The significance of evidence was evaluated using the Z-test. We used the Q test and I2 statistic to assess the percentage

of heterogeneity.[19] When the outcome of the Q test was $P < .1$ and $I^2 > 50\%$, revealing the significance of heterogeneity, then a random-effects model was applied to evaluate the summary results; otherwise, a fixed-effects model was applied. Sensitivity analysis was performed on a network excluding trials with low quality. Funnel plots were used to evaluate publication bias, if the number of included studies for 1 outcome was 10 or more.

3. Results

3.1. Included studies

Our initial database search yielded 211 studies. After reading the title, abstract, and full text, 50 studies met the inclusion criteria (Fig. 1); Of these, 24 were English articles and 26 were Chinese articles, involving a total of 2604 children with TDs. The characteristics of included studies are depicted in Table 1.

A total 17 RCTs[20–39] were included in our review, involving 1232 participants aged 0 to 18 years. The period of treatment ranged from 4 to 12 weeks. Thirteen studies were conducted in China, 2 in Iran, 1 in South Korea, and 1 multicenter trial conducted in the United States, Canada, Hungary, and Italy.

In terms of case-control studies, a total 10 non-RCT[40–44] articles were eligible for inclusion. The included studies involved 826 children under the age of 18 years, with a treatment duration of 8 to 104 weeks. Seven were conducted in China, 1 in Italy, 1 in South Korea, and 1 in the United States.

In terms of case series, we identified a total of 15 studies[45–60] on the safety of aripiprazole in the treatment of Tourette syndrome, a total 538 children. Eight studies were conducted in China, 4 in the United States, and 3 in South Korea.

Eight case reports[61–68] were included in our review, with a total of 8 children. Three studies were carried out in China; the remaining 5 studies were conducted in South Korea, the United States, Greece, Turkey, and India, respectively.

3.2. Quality assessment

To assess the methodological quality of RCTs, only 9 studies (52.9%) used an adequate method of random sequence generation; the remaining studies did not mention any method or used an inappropriate allocation method. Three studies (17.6%) implemented allocation concealment. Similarly, blinding of participants and outcome assessment were not specified; 3 studies (17.6%) described blinding of participants and outcome assessment, and 2 studies (12.5%) were judged to be prone to a high risk of bias. The risk of bias regarding incomplete outcome data was judged to be high in 1 report (6.3%). Reporting bias was not detected in any of the included studies, and no other bias was found.

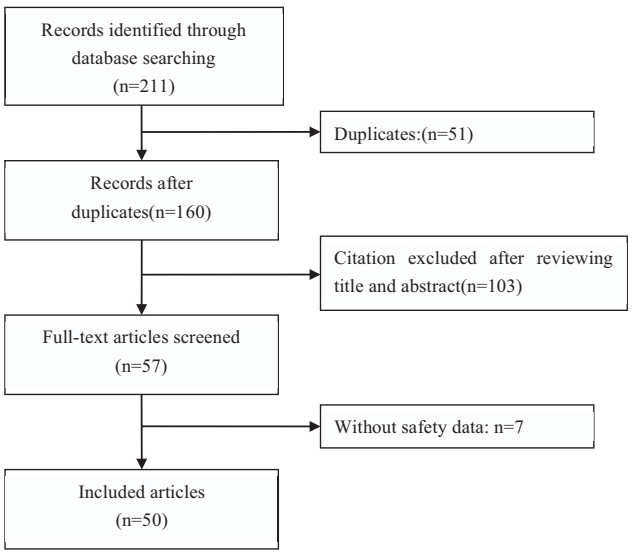

Figure 1. Flow chart of literature screening and the selection process.

In the assessment of methodology quality of non-RCTs, none of these studies described appropriate random sequence generation. Five studies (50%) described as open-label trials had adequate allocation concealment; the remaining 5 studies (50%) did not include sufficient information to evaluate this item, leading to the determination of unclear risk. For blinding, 3 studies (30%) were assessed as having high risk of bias in the blinding of participants and personnel. Similarly, 3 studies (30%) were judged to be prone to high risk of bias in the blinding of outcome assessment; the remaining studies (70%) could not be evaluated because of insufficient information. In terms of incomplete outcome data, 4 studies (40%) were described as unclear risk of bias, and the remainder (60%) showed low risk of bias. Reporting bias was not detected in any of the included studies; no other bias was found.

Case studies had a mean score of 5.67 points according to the NICE guidelines checklist. Only 2 studies were multicenter studies, and outcomes were not stratified in either study; the remaining indicators demonstrated fair good quality.

We assessed the methodological quality of case reports based on the 13 items of the CARE guidelines. All case reports described the items of title, patient information, clinical findings, time line, therapeutic interventions, follow-up and outcomes, and discussion. Six studies included the items of introduction and diagnostic assessment, and 5 studies comprised the items keywords and abstract. Only 2 reports had a low risk of informed consent. All reports had a high risk of patient perspective. The quality assessment of the included studies is summarized in Table 2.

3.3. RCT safety results

The most common AEs with aripiprazole in RCTs were somnolence (17.2%), increased appetite (13.5%), sedation (13.2%), dyspepsia (9.7%), and nasopharyngitis (9.1%).

3.3.1. Aripiprazole versus other pharmacotherapies

3.3.1.1. Neurological and psychiatric symptoms. We compared aripiprazole with haloperidol, risperidone, and sulfur with respect to various types of neurological and psychiatric AEs. The results of the meta-analysis showed that there was a significant difference between aripiprazole and haloperidol in the rates of somnolence (RR = 0.596; 95% CI: 0.394, 0.901; $P = .014$), extrapyramidal symptoms (RR = 0.236; 95% CI: 0. 0.111, 0.505; $P = .000$), and tremor (RR = 0.255; 95% CI: 0.114, 0.571; $P = .001$). The differences for the remaining AEs showed no statistical significance ($P > .05$).

3.3.2. Digestive system. The included studies reported that the occurrence of gastrointestinal AEs with aripiprazole was significantly lower than those with haloperidol for constipation (RR = 0.148; 95% CI: 0.040, 0.553; $P = .004$). Although the rate of AEs with use of aripiprazole with respect to the digestive

Table 1

General characteristics of included RCTs.

Study	Study type	Characteristics of participants			Interventions		Treatment period (wk)	Diagnostic criteria
		Age (y)	Sample (male%)	Disease types	Treatment group	Control group		
Ghanizadeh 2013	RCT	6–18	60 (49) T*:31 C*:29	Tic disorder	Aripiprazole (initial dose: 1.25 mg/d, gradually increase dose, final dose: 10–15 mg/d)	Risperidone (initial dose: 0.25 mg, gradually increase dose, final dose: 2–3 mg/d)	8	DSM-IV-TR YGTS
Yoo 2013	RCT	6–18	61 (53) T*:32 C*:29	Tourette disorder	Aripiprazole (initial dose: 2 mg/d, gradually increase dose, maximum dose: 20 mg/d)	Placebo (initial dose: 2 mg/d, gradually increase dose, maximum dose: 20 mg/d)	10	DSM-IV YGTSS
Chen 2012	RCT	T:8.1 ± 2.9 C:7.9 ± 3.2	62 (39) T*:31 C*:31	Tic disorder	Aripiprazole (initial dose: 2.5 mg, maximum dose: 10 mg/d)	Haloperidol (initial dose: 0.5 mg, maximum dose: 10 mg/d)	8	CCMD-3
Sun 2014	RCT	T:12.0 ± 3.4 C:12.5 ± 3.6	87 (56) T*:45 C*:42	Tic disorder	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 7.5 mg/d)	Haloperidol (initial dose:1–2 mg/d, maximum dose: 10 mg/d)	3	ICD-10 YGTSS
Zhang 2014	RCT	T:8.4 ± 4.2 C:8.8 ± 4.5	76 (56) T*:38 C*:38	Tic disorder Tourette syndrome	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 10 mg/d)	Sulfur (initial dose: 25 mg, Bid, maximum dose: 400 mg/d)	12	DSM- IV
Liu 2010	RCT	T:9.4 ± 1.9 C:8.5 ± 2.1	65 (57) T*:33 C*:32	Tic disorder Tourette syndrome	Aripiprazole (initial dose: 2.5 mg/d, increase dose every week: 2.5 mg, maximum dose: 10 mg/d)	Sulfur (initial dose: 25 mg, bid, increase dose every week: 25 mg, maximum dose: 400 mg/d)	12	DSM- IV -TR
Guo 2013	RCT	T:10.3 ± 2.1 C:10.8 ± 1.9	80 (55) T*:40 C*:40	Tic disorder	Aripiprazole (initial dose: 2.5 mg, maximum dose: 12.5 mg, average daily dose: 7.8 ± 1.1 mg)	Haloperidol (initial dose: 1 mg, maximum dose: 16 mg, average daily dose: 5.7 ± 0.8 mg)	8	ICD-10 YGTSS
Ren 2012	RCT	5–16	68 (58) T*:34 C*:34	Tic disorder Tourette syndrome	Aripiprazole (initial dose: 2.5 mg/d, gradually increase dose, final dose: 5–20 mg/d)	Haloperidol (initial dose: 1 mg/d, gradually increase dose, final dose: 2–8 mg/d)	8	DSM- IV -TR YGTSS
Zhou 2015	RCT	T:9.5 ± 4.5 C:11.5 ± 5.5	100 (68) T*:50 C*:50	Tic disorder Tourette syndrome	Aripiprazole (initial dose: 2 mg/d, maximum dose:15 mg/d)	Haloperidol (initial dose:1 mg/d, maximum dose:10 mg/d)	10	DSM- IV -TR
Qin 2014	RCT	T:10.32 ± 1.36 C:10.32 ± 1.36	87 (50) T*:45 C*:42	Tic disorder Tourette syndrome	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 7.5 mg/d)	Haloperidol (initial dose: 1–2 mg/d, maximum dose: 10 mg/d)	8	DSM
Bai 2014	RCT	T:11.80 ± 2.10 C:11.50 ± 1.83	60 (31) T*:30 C*:30	Tic disorder	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 12.5 mg/d) + cognitive treatment	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 12.5 mg/d)	8	ICD-10 YGTSS
Gao2013	RCT	T:11.2 ± 3.5 C:8.6 ± 2.9	48 (33) T*:31 C*:17	Tic disorder Tourette syndrome	Aripiprazole (initial dose: 2.5 mg/d, increase dose every week: 2.5–5.0 mg/d, maximum dose: 20 mg/d)	Haloperidol (initial dose: 1 mg/d, increase dose every week: 2 mg/d, maximum dose: 8 mg/d)	8	CCMD-3 YGTSS
Zhang 2015	RCT	T: 7.3 ± 2.5 C: 7.3 ± 2.5	80 (51) T*:40 C*:40	Tic disorder	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 10 mg/d)	Risperidone (initial dose: 0.5 mg/d, maximum dose: 3 mg/d)	12	CCMD-3 YGTSS
Sallee 2017	RCT	7–17 T1:11.1 ± 3.1 T2:11.8 ± 2.8 C: 11.6 ± 2.8	133 (104) T1:44 (36) T2:45 (35) C:44 (33)	Tourette disorder	Aripiprazole (T1: (<50 kg 5 mg/d, >50 kg 10 mg/d; T2: <50 kg 10 mg/d, >50 kg 20 mg/d)	Placebo	8	DSM-IV-TR
Ghanizadeh 2016	RCT	6–18 T:10.5 ± 3.1 C:10.8 ± 2.0	36 T:20 (16) C:16 (14)	Tic disorder	Aripiprazole (initial dose:1.25 mg/d, titrated up to 7.5 mg/d, bid, during 1 wk)	Aripiprazole (initial dose:1.25 mg/d, titrated up to 7.5 mg/d, during 1 week)	8	DSM-IV

(*continued*)

Table 1
(continued).

Study	Study type	Characteristics of participants			Interventions		Treatment period (wk)	Diagnostic criteria
		Age (y)	Sample (male%)	Disease types	Treatment group	Control group		
Wang 2015	RCT	5–18 T:8.7±2. 3 C:8.9±2.5	45 (38) T:28 (24) C:17 (14)	Tic disorder	Aripiprazole (initial dose 1.25 mg, bid, maximum dose: 10 mg, bid)	Tiaprde (initial dose 0. 5 mg/ (kg·d), bid, maximum dose: 2 mg/(kg d), bid)	9	DSM-IV -TR
Ying 2018	RCT	5-11 T: 8.1±1.0 C: 8.3±0.9	84 (54) T: 42 (28) C:42 (26)	Tourette syndrome	Aripiprazole (initial dose 2.5 mg/d, increase every week: 2.5 mg,until symptoms disappearance or maximizing to 10 mg/d)	Haloperidol (initial dose 1 mg/d, increase every week: 1 mg,until symptoms disappearance or maximizing to 6 mg/d)	12	NR
Yoo 2011	non-RCT	T:11.2±3.5 C:8.6±2.9	48 (33) T*:31 C*:17	Tic disorder	Aripiprazole (initial dose: 5 mg/d, increments every 2 weeks: 5–10 mg/d, maximum dose: 20 mg/d)	Haloperidol (initial dose 0.75 mg/d and increased in 1.5–3 mg/d increments every 2 weeks, maximum dose: 4.5 mg/d)	8	DSM-IV KSADS-PL and Total Tic scores
Rizzo 2012	non-RCT	T1:11.6±2.2 T2:11.2±3.1 C:10.2±2.8	75 (67) T*:25 C*:50	Tourette syndrome	T1: Aripiprazole (1.25–15 mg/d) T2: pimozide (1–4 mg/d)	free of medication	104	DSM-IV-TR
Liang 2010	non-RCT	T:10.40±2.46 C:10.35±2.41	82 (64) T*:41 C*:41	Tourette syndrome	Aripiprazol (5–30 mg/d)	Haloperidol (6–16 mg/d)	8	ICD-10 YGTSS
Liu 2011	Non-RCT	T:10.3±2.7 C:9.9±2.6	195 (156) T*:98 C*:97	Tourette syndrome	Aripiprazol (age < 8 y: initial dose: 2.5 mg, qd, increase dose every week: 2.5 mg, final dose 5–15 mg/d, qd. Age > 8 y: initial dose 5 mg, qd, increase dose every week: 5 mg, final dose: 10–25 mg/d, qd)	Sulfur (age < 8 y: initial dose: 25 mg, bid, increase dose every week: 50 mg, final dose 100–300 mg/d, bid or tid. Age > 8 y: initial dose 50 mg, bid, increase dose every week: 100 mg, final dose: 200–500 mg/d, bid or tid)	12	DSM- IV -TR YGTSS
Gulisano 2011	Non-RCT	T:13.1±2.3 C:9.1±2.9	50 (43) T*:25 C*:25	Tourette syndrome	Aripiprazole (mean dose: 5.3 mg/d)	Pimozide (mean dose: 4.4 mg/d)	104	DSM-IV-TR
Chen 2014	Non-RCT	T:9.4±2.3 C:9.2±2.0	59 (52) T*:26 C*:33	tic disorder Tourette syndrome	Aripiprazole (initial dose:1.25–2.5 mg, bid, maximum 10 mg,bid)	Aripiprazole (initial dose: 2.5 mg/d, maximum 10 mg/d)	12	DSM-IV-TR
Wang 2013	Non-RCT	T:7.5±3.8 C:7.8±3.4	60 (41) T*:30 C*:30	Tourette syndrome	Aripiprazole (initial dose: 2.5 mg/d, maximum dose: 10 mg/d)	Sulfur (initial dose: 50 mg/d, maximum dose: 300 mg/d)	8	ICD-10
Xu 2015	Non-RCT	T:9.0±5.0 C:9.0±5.0	88 (43) T*:44 C*:44	Tic disorder	Aripiprazole (mean dose: 5.3 mg/d)	Haloperidol (mean dose: 4.4 mg/d)	3	YGTSS
Zhao 2011	Non-RCT	T:8.1±3.5 C:7.9±3.3	108 (72) T*:54 C*:54	Tic disorder	Aripiprazole (initial dose: 5 mg, maintenance dose: 5–15 mg/d)	Haloperidol (initial dose: 2 mg, maintenance dose: 2–12 mg/d)	8	CCMD-3
Zheng 2015	Non-RCT	T:9.4±2.3 C:9.2±2.0	61 (42) T*:30 C*:31	Tic disorder	Aripiprazole (initial dose: 2.5 mg/d, increase dose every week: 2.5 mg, maximum 15 mg)	Haloperidol (increase dose, maximum 10 mg, bid)	8	YGTSS
Ho 2014	Case series	4–18	81 (60)	Tic disorder	Aripiprazole (initial dose 2.5 mg/d, maintenance dose: 2.5 mg/d)		14	YGTSS DSM-IV-TR
Lyon 2009	Case series	13.36±3.33	11 (10)	Tourette disorder	Aripiprazole (dose range:1.25–13.75 mg/d; mean daily dose: 4.5±3.0 mg)		>10	DSM-IV-TR
Cui 2010	Case series	6–18	72 (55)	Tic disorder	Aripiprazole (initial dosage: 1.25–2.5 mg/d in prepubertal children, 2.5–5 mg/d in adolescent; mean daily dosages: 4.88±0.63 mg,7.33±2.06 mg during weeks 2 and 4; final dose: 8.17±2.41 mg or 0.19 mg/kg)		8	DSM-IV

(*continued*)

Table 1

(continued).

Study	Study type	Characteristics of participants			Interventions		Treatment period (wk)	Diagnostic criteria
		Age (y)	Sample (male%)	Disease types	Treatment group	Control group		
Murphy 2009	Case series	12.0±2.8	16 (15)	Tic disorder	Aripiprazole (average dose: 3.3±2.1 mg/d (range 1.25–7.5 mg))		6	DSM-IV
Seo 2008	Case series	7–19	15 (14)	Tic disorder Tourette disorder	Aripiprazole (initial dosage: 2.5–7.5 mg, and the mean dosage of week 1: 5.33±1.29 mg; mean daily dosages were 5.33±0.88 mg, 6.83±2.00 mg, 7.33±3.06 mg, 8.33 ±3.86 mg during weeks 2, 3, 5, 9, and the final dose was 8.17±4.06 mg or 0.20 mg/kg (range from 0.1 to 0.58 mg/kg))		12	DSM-IV-TR
Yoo 2007	Case series	7–18	24 (19)	Tic disorder	Aripiprazole (initial dose: 5 mg/d for 2 wk, mean dose: 9.8±4.8 mg/d; maximum allowable dose was 20 mg/d)		8	DSM-IV
Yoo 2006	Case series	11.93±3.41	14 (12)	Tourette disorder	Aripiprazole (mean dose:10.89 mg (from 2.5 to 15 mg) or 0.22 mg/kg (from 0.083 to 0.55 mg/kg))		8	DSM-IV
Budman 2008	Case series	13.4±2.8	37 (26)	Tourette disorder	Aripiprazole (initial dose:1.25–2.5 mg/d in prepubertal children and 2.5–5 mg/din adolescents, mean dose: for the entire sample 11.69±7.15 mg; for the 29 completers: 12.33±7.49 mg;		12	DSM-IV-TR
Murphy 2005	Case series	12.1±4.05	6 (3)	Tourette syndrome	Aripiprazole (average dose: 11.7 mg (range 5–20 mg) or 0.21 mg/kg (range 0.08–0.6 mg/kg))		12	NR
Sun 2011	Case series	7–18	47 (28)	Tourette disorder	Aripiprazole (initial dose: 2.5 mg/d, qd, maintenance dose: 5–30 mg/d)		8	ICD-10 YGTSS
Zhao 2012	Case series	6–16	39 (31)	Tourette disorder	Aripiprazole (increase dose in 1–2 wk, to 5–20 mg/d)		8	DSM- IV YGTSS
Liang 2010	Case series	12.01±3.57	86 (68)	Tic disorder	Aripiprazole (increase dose in 7–10 d to 5–25 mg/d)		8	ICD-10 YGTSS
Bi 2012	Case series	11±4	38 (17)	Tic disorder	Aripiprazole (initial dose: 2.5 mg/d, maximum dose:15 mg/d, qd)		8	DSM- IV YGTSS
Gao 2014	Case series	10.62±3.33	25 (15)	Tic disorder	Aripiprazole (initial dose: 25–50 kg 1.25 mg /d, 50–70 kg 2.5 mg/d. Increase dose in 5–7 d to 1.25–2.5 mg; dose range: 2.25–13.75 mg/d, mean dose: 4.5±3 mg/d)		10	CCMD-3
Zhao 2015	Case series	10.8±1.91	27 (21)	Tourette disorder	Aripiprazole (5–15 mg/d)		8	YGTSS ADHD-RS-IV
Shim 2014	Case report	15	1 (1)	Tourette syndrome	Aripiprazole+Tomoxetine+Valproate (initial dose: 20 mg aripiprazole and 20 mg atomoxetine, maximum dose: 25 mg aripiprazole and 40 mg atomoxetine, maintenance dose: 20 mg aripiprazole, 25 mg atomoxetine and 500 mg valproate)		NR	DSM-IV YGTSS
Bhatia 2014	Case report	16	1 (1)	Tourette syndrome	Aripiprazole (initial dose: 5 mg/d, maximum dose:10 mg/d)		1	NR
Lai 2009	Case report	16	1 (1)	Tic disorder	Risperidone+Paroxetine+Aripiprazole (Risperidone (2 mg)+paroxetine (40 mg), sustained 2 wk Risperidone (4 mg)+paroxetine (80 mg), sustained 6 mo, Aripiprazole (10 mg), sustained 1 mo, Aripiprazole (20 mg), sustained 6 mo		13	YGTSS DYBOCS
Fountoulakis 2006	Case report	18	1 (1)	Tourette disorder	Aripiprazole (initial dose: 10 mg/d)		NR	YGTSS
Yu 2010	Case report	6	1 (1)	Tourette syndrome	Atomoxetine+Aripiprazole (initial dose: atomoxetine 25 mg/d and aripiprazole 5 mg/d maintenance dose: atomoxetine 40 mg/d and aripiprazole 3.3 mg/d)		>12	NR
Wang 2009	Case report	10	1 (1)	Tourette syndrome	Aripiprazole+Lithium+Risperidone (Lithium (initial dose:700 mg/d, maintenance dose:1200 mg/d),Risperidone (initial dose: 2 mg/d, maintenance dose: 2 mg/d))		6	NR
Lewis 2010	Case report	17	1 (1)	Tourette syndrome	Aripiprazole +Escitalopram+Vitamin B-complex +g-aminobutyric acid (GABA)+ Omega 3, 6, 9 (aripiprazole 10 mg/d, escitalopram 5 mg/d, vitamin B-complex daily, g-aminobutyric acid (GABA) 1500 mg daily, and Omega 3, 6, and 9 twice daily)		NR	DSM-IV TR
Mazlum 2015	Case report	15	1 (1)	Tic disorder	Imipramine+Pimozide+Sertraline+Aripiprazole (imipramine 50 mg/d and pimozide 2–3 mg/d for 5 mo, sertraline 50 mg/d and pimozide 3 mg/d for 10 mo, Aripiprazole 2.5 mg/d for 10 d)		>15	NR

Table 2

Quality assessment of includes studies.

	RCT			Non-RCT						
Cochrane	High risk	Low risk	Unclear	High risk	Low risk	Unclear	NICE	Case series	CARE	Case report
Item 1	0 (0%)	9 (52.9%)	8 (47.1%)	9 (90%)	0 (0%)	1 (10%)	Item 1	2 (13.3%)	Item 1	8 (100%)
Item 2	1 (5.9%)	3 (17.6%)	13 (76.5%)	5 (50%)	0 (0%)	5 (50%)	Item 2	15 (100%)	Item 2	5 (62.5%)
Item 3	2 (11.8%)	3 (17.6%)	12 (70.6%)	3 (30%)	0 (0%)	7 (70%)	Item 3	14 (93.3%)	Item 3	5 (62.5%)
Item 4	1 (5.9%)	3 (17.6%)	13 (76.5%)	3 (30%)	0 (0%)	7 (70%)	Item 4	14 (93.3%)	Item 4	6 (75%)
Item 5	1 (5.9%)	9 (52.9%)	7 (41.2%)	0 (100%)	6 (60%)	4 (40%)	Item 5	15 (100%)	Item 5	8 (100%)
Item 6	0 (0%)	10 (58.8%)	7 (41.2%)	0 (0%)	6 (60%)	4 (40%)	Item 6	10 (66.7%)	Item 6	8 (100%)
Item 7	0 (0%)	4 (23.5%)	13 (76.5%)	0 (0%)	5 (50%)	5 (50%)	Item 7	15 (100%)	Item 7	8 (100%)
							Item 8	0 (0%)	Item 8	6 (75%)
							mean score	5.67	Item 9	8 (100%)
									Item 10	8 (100%)
									Item 11	8 (100%)
									Item 12	2 (25%)
									Item 13	0 (0%)
									mean score	10

Yes = 1, No = 0.

RCTs and non-RCTs: item 1 Random sequence generation; item 2 Allocation concealment; item 3 Blinding of participants; item 4 Blinding of outcome assessment; item 5 Incomplete outcome data; item 6 Selective reporting; item 7 Other sources of bias.

Case series: item 1 Case series in more than one center, that is, multicenter study; item 2 Is the hypothesis/aim/objective of the study clearly described? item 3 Are the inclusion and exclusion criteria (case definition) clearly reported? item 4 Is there a clear definition of the outcomes reported? item 5 Were data collected prospectively? item 6 Is there an explicit statement that patients were recruited consecutively? item 7 Are the main findings of the study clearly described? item 8 Are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics).

case reports: item 1 Title; item 2 Keywords; item 3 Abstract; item 4 Introduction; item 5 Patient Information; item 6 Clinical Findings; item 7 Timeline; item 8 Diagnostic Assessment; item 9 Therapeutic Intervention; item 10 Follow-up and Outcomes; item 11 Discussion; item 12 Patient Perspective; item 13 Informed Consent.

system was lower than those with use of risperidone and sulfur, there was no statistical difference ($P > .05$).

3.3.3. Cardiovascular system. Four types of AEs of the cardiovascular system (abnormal electrocardiogram, chest discomfort, tachycardia, bradycardia) were reported among the aripiprazole and haloperidol groups. Nevertheless, the differences were not statistically significant ($P > .05$).

3.3.4. Urinary system. Only 2 studies reported AEs affecting the urinary system. There were no urinary AEs with aripiprazole; the use of sulfur had 1 reported case of urinary AEs. Nocturia occurred with risperidone in 4 cases; however, there were no significant differences ($P > .05$).

3.3.5. Respiratory system. The included studies reported that the occurrence of nasopharyngitis with aripiprazole was significantly lower than that with placebo ($P < .05$). As for upper respiratory infection, we found no significant differences.

3.3.6. Other AEs. Meta-analysis of 1 study (n = 60) that compared the occurrence of blurred vision and itching between aripiprazole and risperidone showed that there were differences, but without statistical significance ($P > .05$). A significant difference was observed in the incidence rate of dry mouth between aripiprazole and haloperidol treatment groups (RR = 0.141; 95% CI: 0.046, 0.425; $P = .001$).

3.3.7. Aripiprazole versus placebo. We retrieved 2 RCTs (n = 194) that reported AEs in a positive control group and placebo group. The results of meta-analysis showed that there was no significant difference ($P > .05$) in the incidence rate of AEs between aripiprazole and placebo, except for somnolence (RR = 6.565; 95% CI: 1.270, 33.945; $P = .025$), as shown in Table 3.

3.4. Non-RCT safety results

We compared aripiprazole with other pharmacotherapies with respect to safety in individual human systems. The most common AEs with aripiprazole in non-RCTs were somnolence (15.7%), sedation (10.9%), nausea and vomiting (8.4%), extrapyramidal symptoms (6.9%), and gastrointestinal disturbance (6.4%).

The results of meta-analysis revealed that there was no significant difference in the rate of AEs between aripiprazole and haloperidol, risperidone, sulfur, and pimozide. Similar statistical differences were found for the incidence of AEs between 2 aripiprazole treatment groups with different administration frequency (aripiprazole q.i.d. vs aripiprazole q.d.), as shown in Table 3.

3.5. Case series safety results

There were 13 studies describing AEs in detail whereas the other 2 only briefly mentioned AEs. The most common incidence of AEs with use of aripiprazole was sedation (26.9%; 95% CI: 16.3%, 44.4%), irritability (25%; 95% CI: 9.4%, 66.6%), restlessness (31.3%; 95% CI: 13%, 75.1%), nausea and vomiting (28.9%; 95% CI: 21.1%, 39.5%), and weight gain (31.3%; 95% CI: 10.7%, 91.3%) ($P < .05$). There were no significant differences for tiredness; stomach discomfort; or muscle, bone, or joint pain/conditions ($P > .05$) (Table 4).

3.6. Case report safety results

Five of 8 cases (62.5%) mentioned or described AEs, which included convulsions, mania, fidgeting, trembling, inarticulate speech, slow motion, dizziness, muscle cramps, nystagmus, torticollis, and insomnia.

3.7. Sensitivity analysis

In regard to the primary outcome, after excluding trials with low-quality RCTs which did not report appropriate randomized method and allocation, no material change of the pooled

Table 3

Meta-analysis of RCT and non-RCT.

Group	Study type	Studies	n/N_1	n/N_2	Heterogeneity	RR (95% CI)	*P*
Neurological and psychiatric symptoms							
Somnolence							
Aripiprazole vs Haloperidol	RCT	3	18/107	18/93	$P=.405$, $I^2=0.0\%$	0.596 (0.394,0.901)	.014
	Non-RCT	2	20/61	18/48	$P=.683$, $I^2=0.0\%$	0.671 (0.449,1.004)	.053
Aripiprazole vs Risperidone	RCT	1	8/31	5/29	Not applicable	1.497 (0.553, 4.054)	.427
	Non-RCT	1	9/98	7/97	Not applicable	1.273 (0.494,3.281)	.618
Aripiprazole vs Sulfur	RCT	1	0/33	1/32	Not applicable	0.324 (0.014,7.661)	.485
Aripiprazole qd vs Aripiprazole biw	RCT	1	10/19	4/15	Not applicable	1.974 (0.770,5.060)	.157
Aripiprazole qid vs Aripiprazole qd	Non-RCT	1	0/26	1/26	Not applicable	0.420 (0.018,9.899)	.590
Aripiprazole vs Placebo	RCT	2	16/121	1/73	$P=.853$, $I^2=0.0\%$	6.565 (1.270,33.945)	.025
Lethargy							
Aripiprazole vs Placebo	RCT	1	5/89	0/44	Not applicable	5.500 (0.311,97.281)	.245
Headache							
Aripiprazole vs Haloperidol	RCT	7	13/276	17/256	$P=.167$, $I^2=34.2\%$	0.612 (0.336,1.114)	.108
	Non-RCT	1	5/31	10/17	Not applicable	0.274 (0.112,0.672)	.005
Aripiprazole vs Risperidone	Non-RCT	1	3/98	2/97	Not applicable	1.485 (0.254,8.691)	.661
Aripiprazole vs sulfur	RCT	1	1/33	0/32	Not applicable	2.912 (0.123,68.946)	.508
Aripiprazole qd vs Aripiprazole biw	RCT	1	2/19	2/15	Not applicable	0.789 (0.125,4.968)	.801
Aripiprazole qid vs Aripiprazole qd	Non-RCT	1	1/26	1/33	Not applicable	1.269 (0.083,19.340)	.864
Aripiprazole vs Placebo	RCT	2	12/121	2/73	$P=.853$, $I^2=0.0\%$	3.931 (0.908,17.024)	.067
Sedation							
Aripiprazole vs Sulfur	Non-RCT	1	0/30	2/30	Not applicable	0.200 (0.010,3.998)	.292
Aripiprazole vs Pimozide	Non-RCT	1	6/25	7/25	Not applicable	0.857 (0.335,2.192)	.748
Aripiprazole vs Placebo	RCT	2	16/121	4/73	$P=.181$, $I^2=44.2\%$	2.618 (0.850,8.061)	.094
Dizziness							
Aripiprazole vs Haloperidol	RCT	1	0/31	2/17	Not applicable	0.112 (0.006,2.217)	.151
	Non-RCT	2	2/70	2/58	$P=.231$, $I^2=30.4\%$	0.716 (0.144,3.550)	.683
Aripiprazole vs Risperidone	RCT	1	2/31	1/29	Not applicable	1.871 (0.179,19.549)	.601
	Non-RCT	1	4/98	3/97	Not applicable	1.320 (0.303,5.742)	.712
Aripiprazole vs Sulfur	Non-RCT	1	1/30	2/30	Not applicable	0.500 (0.048,5.224)	.563
Aripiprazole qd vs Aripiprazole biw	RCT	1	0/19	1/15	Not applicable	0.267 (0.012,6.114)	.408
Aripiprazole vs Placebo	RCT	1	1/32	4/29	Not applicable	0.227 (0.027,1.912)	.172
Extrapyramidal symptoms							
Aripiprazole vs Haloperidol	RCT	3	8/107	26/93	$P=.206$, $I^2=36.7\%$	0.236 (0.111,0.505)	.000
	Non-RCT	3	7/102	41/89	$P=.206$, $I^2=46.3\%$	0.127 (0.059,0.271)	.155
Aripiprazole vs Placebo	RCT	1	3/32	2/29	Not applicable	1.359 (0.244,7.570)	.726
Insomnia							
Aripiprazole vs Haloperidol	RCT	2	3/76	0/76	$P=.818$, $I^2=0\%$	4.000 (0.457,35.000)	.210
	Non-RCT	1	1/31	2/17	Not applicable	0.274 (0.027,2.808)	.276
Aripiprazole vs Risperidone	RCT	2	3/71	0/69	$P=.795$, $I^2=0\%$	3.889 (0.447,33.809)	.218
	Non-RCT	1	1/98	2/97	Not applicable	0.495 (0.046,5.369)	.563
Aripiprazole vs sulfur	RCT	1	1/33	0/32	Not applicable	2.912 (0.123,68.946)	.508
Aripiprazole vs Pimozide	Non-RCT	1	1/25	0/25	Not applicable	3.000 (0.128,70.296)	.495
Aripiprazole qid vs Aripiprazole qd	Non-RCT	1	1/26	1/33	Not applicable	1.269 (0.083,19.340)	.864
Aripiprazole vs Placebo	RCT	1	0/32	3/29	Not applicable	0.130 (0.007,2.412)	.171
Fatigue							
Aripiprazole vs Haloperidol	Non-RCT	1	1/41	3/41	Not applicable	0.333 (0.036,3.073)	.332
Aripiprazole vs Risperidone	RCT	2	3/71	5/69	$P=.075$, $I^2=68.4\%$	0.614 (0.162,2.327)	.474
	Non-RCT	1	2/98	3/97	Not applicable	0.660 (0.113,3.862)	.645
Aripiprazole qd vs Aripiprazole biw	RCT	1	2/19	2/15	Not applicable	0.789 (0.125,4.968)	.801
Aripiprazole vs Placebo	RCT	1	10/89	0/44	Not applicable	10.500 (0.629,175.169)	.102
Akathisia							
Aripiprazole vs Sulfur	Non-RCT	1	1/30	2/30	Not applicable	0.500 (0.048,5.224)	.563
Aripiprazole vs Placebo	RCT	2	5/121	4/73	$P=.223$, $I^2=32.6\%$	0.871 (0.239,3.173)	.834
Tiredness							
Aripiprazole vs Haloperidol	Non-RCT	1	2/41	6/41	Not applicable	0.333 (0.071,1.556)	.162
Anxiety							
Aripiprazole vs Haloperidol	RCT	5	8/203	2/197	$P=.804$, $I^2=0\%$	2.643 (0.793,8.810)	.114
Aripiprazole vs Risperidone	Non-RCT	1	2/98	0/97	Not applicable	4.949 (0.241,101.776)	.300
Aripiprazole vs sulfur	RCT	1	1/33	0/32	Not applicable	2.912 (0.123,68.946)	.508
	Non-RCT	1	0/30	4/30	Not applicable	0.111 (0.006,1.977)	.135
Tremor							

(*continued*)

Table 3

(continued).

Group	Study type	Studies	n/N_1	n/N_2	Heterogeneity	RR (95% CI)	*P*
Aripiprazole vs Haloperidol	RCT	5	7/211	27/205	$P=.985$, $I^2=0\%$	0.255 (0.114,0.571)	.001
Irritability							
Aripiprazole vs Haloperidol	RCT	1	0/31	2/17	Not applicable	0.112 (0.006,2.217)	.151
Aripiprazole vs Risperidone	RCT	1	1/31	0/29	Not applicable	2.813 (0.119,66.399)	.521
Aripiprazole qd vs Aripiprazole biw	RCT	1	2/19	0/15	Not applicable	4.000 (0.206,77.528)	.359
Aripiprazole vs Placebo	RCT	1	0/32	2/29	Not applicable	0.182 (0.009,3.637)	.265
Slowness							
Aripiprazole vs Risperidone	RCT	1	2/31	0/29	Not applicable	4.688 (0.234,93.703)	.312
Aripiprazole qd vs Aripiprazole biw	RCT	1	1/19	0/15	Not applicable	2.400 (0.105,55.028)	.584
Restlessness							
Aripiprazole vs Placebo	RCT	1	3/89	1/44	Not applicable	1.483 (0.159,13.851)	.730
Somnambulism							
Aripiprazole vs Placebo	RCT	1	1/89	0/44	Not applicable	1.500 (0.062,36.090)	.803
Emotional hypersensitivity							
Aripiprazole vs Haloperidol	Non-RCT	1	1/31	2/17	Not applicable	0.274 (0.027,2.808)	.276
Nightmare							
Aripiprazole vs Haloperidol	Non-RCT	1	1/31	1/17	Not applicable	0.548 (0.037,8.225)	.664
Cognitive decline							
Aripiprazole vs Haloperidol	RCT	1	0/42	2/42	Not applicable	0.200 (0.010,4.045)	.294
Digestive symptoms							
Nausea vomiting							
Aripiprazole vs Haloperidol	RCT	5	15/202	20/182	$P=.533$, I2 = 0%	0.576 (0.298,1.111)	.100
		3	13/102	4/89	$P=.477$, $I^2=0\%$	1.853 (0.755,4.549)	.178
Aripiprazole vs Risperidone	RCT	2	3/71	4/69	$P=.795$, I2 = 61.6%	0.750 (0.188,3.000)	.684
		1	3/98	5/97	Not applicable	0.594 (0.146,2.417)	.467
Aripiprazole vs Sulfur	Non-RCT	1	2/30	4/30	Not applicable	0.500 (0.099,2.527)	.402
Aripiprazole vs Pimozide	Non-RCT	1	6/25	0/25	Not applicable	13.000 (0.771,219.107)	.075
Aripiprazole qd vs Aripiprazole bid	RCT	1	1/19	1/15	Not applicable	0.395 (0.039,3.949)	.429
Aripiprazole qid vs Aripiprazole qd	Non-RCT	1	0/32	1/33	Not applicable	0.420 (0.018,9.899)	.590
Aripiprazole vs Placebo	RCT	2	18/121	8/73	$P=.465$, I2 = 0%	1.473 (0.660,3.289)	.344
Increased appetite							
Aripiprazole vs Haloperidol	Non-RCT	1	1/31	1/17	Not applicable	0.548 (0.037,8.225)	.664
Aripiprazole vs Risperidone	RCT	1	8/31	8/29	Not applicable	0.935 (0.404,2.165)	.876
Aripiprazole qd vs Aripiprazole bid	RCT	1	6/19	2/15	Not applicable	2.368 (0.556,10.098)	.244
Aripiprazole vs Placebo	RCT	2	9/121	1/73	$P=.883$, I2 = 0%	3.766 (0.690,20.549)	.126
Dyspepsia							
Aripiprazole vs Haloperidol	RCT	1	6/40	3/40	Not applicable	2.000 (0.537,7.448)	.301
Aripiprazole vs Risperidone	Non-RCT	1	6/98	6/97	Not applicable	0.990 (0.331,2.962)	.985
Aripiprazole vs Placebo	RCT	1	1/32	2/29	Not applicable	0.453 (0.043,4.738)	.509
Decreased Appetite							
Aripiprazole vs Risperidone	RCT	1	4/31	0/29	Not applicable	8.438 (0.474,150.154)	.147
Aripiprazole vs sulphur	RCT	1	0/33	1/32	Not applicable	0.324 (0.014,7.661)	.485
Anorexia							
Aripiprazole vs Haloperidol	Non-RCT	1	1/31	2/17	Not applicable	0.274 (0.027,2.808)	.276
Aripiprazole vs Placebo	RCT	1	2/32	1/29	Not applicable	1.813 (0.173,18.953)	.619
Abdominal pain							
Aripiprazole vs Risperidone	RCT	1	3/31	2/29	Not applicable	1.403 (0.252,7.805)	.699
Aripiprazole qd vs Aripiprazole biw	RCT	1	1/19	1/15	Not applicable	0.789 (0.054,11.606)	.863
Constipation							
Aripiprazole vs Haloperidol	RCT	5	0/205	14/199	$P=.995$, I2 = 0%	0.148 (0.040,0.553)	.004
		1	0/30	4/31	Not applicable	0.115 (0.006,2.043)	.141
Gastrointestinal reaction							
Aripiprazole vs Haloperidol	RCT	1	0/31	2/17	Not applicable	0.112 (0.006,2.217)	.151
Drooling							
Aripiprazole qd vs Aripiprazole biw	RCT	1	1/19	0/15	Not applicable	2.400 (0.105,55.028)	.584
Gastrointestinal Disturbance							
Aripiprazole vs Haloperidol	Non-RCT	1	2/31	2/17	Not applicable	0.548 (0.085,3.553)	.529
Abnormal liver function							
Aripiprazole vs Risperidone	Non-RCT	1	1/98	0/97	Not applicable	2.970 (0.122,72.014)	.503
Cardiovascular system							
Abnormal electrocardiogram							
Aripiprazole vs Haloperidol	RCT	1	0/31	2/31	Not applicable	0.200 (0.010,4.003)	.292

(*continued*)

Table 3

(continued).

Group	Study type	Studies	n/N_1	n/N_2	Heterogeneity	RR (95% CI)	*P*
Aripiprazole vs Placebo	RCT	1	2/32	1/29	Not applicable	1.813 (0.173,18.953)	.619
Chest discomfort							
Aripiprazole vs Haloperidol	RCT	1	0/31	2/17	Not applicable	0.112 (0.006,2.217)	.151
	Non-RCT	1	1/31	2/17	Not applicable	0.274 (0.027,2.808)	.276
Tachycardia							
Aripiprazole vs Haloperidol	RCT	1	2/40	4/40	Not applicable	0.500 (0.097,2.577)	.407
Bradycardia							
Aripiprazole vs Haloperidol	RCT	1	1/40	0/40	Not applicable	3.000 (0.126,71.508)	.497
Urinary symptoms							
Nocturia							
Aripiprazole vs Haloperidol	Non-RCT	1	1/31	1/17	Not applicable	0.548 (0.037,8.225)	.664
Aripiprazole vs Risperidone	RCT	1	0/31	4/29	Not applicable	0.104 (0.006,1.854)	.124
Aripiprazole vs sulfur	RCT	1	0/33	1/32	Not applicable	0.324 (0.014,7.661)	.485
Aripiprazole vs Pimozide		1	1/25	0/25	Not applicable	3.000 (0.128,70.296)	.495
Respiratory system							
Nasopharyngitis							
Aripiprazole vs Placebo	RCT	2	11/121	0/73	$P=.966$, $I^2=0\%$	7.800 (1.026,59.325)	.047
Upper Respiratory Infection							
Aripiprazole vs Placebo	RCT	1	1/32	1/29	Not applicable	0.453 (0.043,4.738)	.509
Endocrine system							
Weight gain							
Aripiprazole vs Risperidone	Non-RCT	1	1/98	0/97	Not applicable	2.970 (0.122,72.014)	.503
Polydipsia							
Aripiprazole vs Risperidone	non-RCT	1	1/31	0/17	Not applicable	1.688 (0.072,39.304)	.745
Motor system							
dystonia							
Aripiprazole vs Placebo	RCT	1	0/32	2/29	Not applicable	0.182 (0.009,3.637)	.265
Joint pain							
Aripiprazole vs Haloperidol	Non-RCT	1	0/31	2/17	Not applicable	0.112 (0.006,2.217)	.151
Others							
Blurred vision							
Aripiprazole vs Haloperidol	Non-RCT	1	1/31	0/17	Not applicable	1.688 (0.072,39.304)	.745
Aripiprazole vs Risperidone	RCT	1	3/31	3/29	Not applicable	0.935 (0.205,4.269)	.931
Itches							
Aripiprazole vs Risperidone	RCT	1	1/31	3/29	Not applicable	0.312 (0.034,2.831)	.300
Dry mouth							
Aripiprazole vs Haloperidol	RCT	6	1/245	22/239	$P=.992$, $I2=0\%$	0.141 (0.046,0.425)	.001
Aripiprazole vs Risperidone	Non-RCT	1	1/98	0/97	Not applicable	2.970 (0.122,72.014)	.503
Aripiprazole vs Sulfur	Non-RCT	1	2/30	3/30	Not applicable	0.667 (0.120,3.709)	.643
Aripiprazole qid vs Aripiprazole qd	Non-RCT	1	0/26	1/33	Not applicable	0.420 (0.018,9.899)	.590
Febrile sense							
Aripiprazole vs Haloperidol	Non-RCT	1	0/31	1/17	Not applicable	0.188 (0.008,4.367)	.297
School refusal							
Aripiprazole vs Haloperidol	Non-RCT	1	0/31	1/17	Not applicable	0.188 (0.008,4.367)	.297

Notes: n means total events, N_1 means patients of treatment group; N_2 means patients of control group.

estimated effects in sensitivity analysis was found (Table 5). The minor change of estimated effects between interventions was as follows: Aripiprazole versus Placebo (Somnolence).

3.8. Publication bias

Finally, funnel plots were not used because the number of included studies in 1 comparison had insufficient statistical power, according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

4. Discussion

In this study, we evaluated the safety of aripiprazole for TDs in the wider context. To our knowledge, this is the first and most comprehensive meta-analysis of this topic. Our analyses were based on 50 studies (17 RCT, 10 case control, 8 case report, 15 case series) including 2604 children with TDs.

Results from the meta-analysis showed that the rate of AEs with aripiprazole was significantly lower than those with haloperidol in some fields. In terms of neurological and psychiatric symptoms, only the comparison of aripiprazole with haloperidol and aripiprazole with placebo showed a significant difference in RCTs; the other studies showed nonsignificant differences. In terms of AEs of the digestive system, only the comparison of aripiprazole and haloperidol showed a significant difference in RCTs. In terms of respiratory system AEs, a significant difference was found only between aripiprazole and placebo in RCTs; other studies showed a nonsignificant difference. In terms of AEs of the cardiovascular, urinary, and

Table 4

Meta-analysis of case series.

Group	Studies	n/N_1	Heterogeneity	Incidence rate (95% CI)	*P*
Neurological and psychiatric symptoms					
Somnolence	6	22/151	$P=.001$, $I^2=76.1\%$	0.137 (0.052,0.364)	.000
Headache	6	22/195	$P=.000$, $I^2=86.6\%$	0.109 (0.029,0.408)	.001
Sedation	6	60/241	$P=.017$, $I^2=63.6\%$	0.269 (0.163,0.444)	.000
Dizziness	5	20/188	$P=.000$, $I^2=87.8\%$	0.110 (0.027,0.442)	.002
Extrapyramidal symptoms	1	2/24	Not applicable	0.083 (0.021,0.333)	.000
Insomnia	3	10/87	$P=.015$, $I^2=76.0\%$	0.086 (0.014,0.512)	.007
Fatigue	4	13/98	$P=.000$, $I^2=83.9\%$	0.118 (0.023,0.593)	.009
Akathisia	4	12/146	$P=.278$, $I^2=22.2\%$	0.091 (0.047,0.179)	.000
Tiredness	3	10/55	$P=.004$, $I^2=81.6\%$	0.172 (0.022,1.327)	.091
Anxiety	2	5/75	$P=.636$, $I^2=0.00\%$	0.068 (0.028,0.164)	.000
Tremor	3	4/67	$P=.068$, $I^2=62.7\%$	0.082 (0.016,0.431)	.003
Irritability	1	4/16	Not applicable	0.250 (0.094,0.666)	.006
Emotional hypersensitivity	2	5/118	$P=.193$, $I^2=41.1\%$	0.048 (0.015,0.153)	.000
Restlessness	1	5/16	Not applicable	0.313 (0.130,0.751)	.009
Somnambulism	1	3/81	Not applicable	0.037 (0.012,0.115)	.000
Became quiet	1	5/81	Not applicable	0.062 (0.026, 0.148)	.000
Inattention	1	3/16	Not applicable	0.188 (0.060,0.581)	.004
Decreased volition	1	2/24	Not applicable	0.083 (0.021,0.333)	.000
Increased agitation	2	10/62	$P=.072$, $I^2=69.0\%$	0.163 (0.049,0.543)	.003
Drug-induced Parkinsonism	1	1/37	Not applicable	0.027 (0.004,0.192)	.000
Digestive symptoms					
Nausea vomiting	5	39/141	$P=.511$, $I^2=0.0\%$	0.289 (0.211,0.395)	.000
Increased appetite	4	28/141	$P=.007$, $I^2=75.3\%$	0.194 (0.075,0.503)	.001
Dyspepsia	1	1/24	Not applicable	0.042 (0.006,0.296)	.001
Decreased appetite	3	14/117	$P=.001$, $I^2=85.3\%$	0.162 (0.040,0.654)	.011
Anorexia	1	1/24	Not applicable	0.042 (0.006,0.296)	.001
Constipation	2	3/74	$P=.308$, $I^2=3.6\%$	0.049 (0.015,0.154)	.000
Stomach discomfort	3	15/117	$P=.000$, $I^2=92.2\%$	0.154 (0.021,1.140)	.067
Cardiovascular system					
Electrocardiogram QT prolonged	1	13/72	Not applicable	0.181 (0.105,0.311)	.000
Tachycardia	1	1/47	Not applicable	0.021 (0.003,0.151)	.000
Bradycardia	1	2/47	Not applicable	0.043 (0.011,0.170)	.000
Urinary symptoms					
Frequent urination	1	2/16	Not applicable	0.125 (0.031,0.500)	.003
Endocrine system					
Weight gain	4	23/65	$P=.002$, $I^2=79.2\%$	0.313 (0.107,0.913)	.034
Weight loss	3	11/51	$P=.052$, $I^2=66.2\%$	0.225 (0.076,0.664)	.007
Polydipsia	1	1/24	Not applicable	0.042 (0.006,0.296)	.001
Others					
Blurred vision	1	1/24	Not applicable	0.042 (0.006,0.296)	.001
Dry mouth	5	11/113	$P=.090$, $I^2=50.3\%$	0.119 (0.049,0.289)	.000
Muscle, bone, or joint pain/condition	3	13/60	$P=.000$, $I^2=87.9\%$	0.165 (0.020,.345)	.092

motor systems, we found nonsignificant differences between aripiprazole and other pharmacotherapies. Overall, the results of our systematic review favored the clinical use of aripiprazole, which can be considered an excellent treatment option for TDs as aripiprazole shows good tolerability in children and adolescents. Our findings agreed with those of previous relevant studies. Considering that the quality of studies included here was poor, it is necessary to confirm our findings in future studies.

There are some strengths that should be noted in our meta-analysis. First, this study is based on the PRISMA reporting recommendations.[69] Second, to ensure the coverage of all relevant AEs, a comprehensive search of the literature was conducted in which we included any type of study, to reduce the possibility of publication bias. Third, 2 independent authors were involved in the phases of study retrieval, data extraction, and quality assessment. In addition, another author checked the consistency of the results and resolved disagreements. Fourth, the tools used in this review to assess the risk of bias are the most widely used and accepted.

Several important limitations of this review also emerged. First, although the report retrieval was comprehensive, it is still possible that unpublished reports were not found. In addition, we failed to search several websites of special agencies that report adverse drug events. Second, some of our results focused on short-term outcomes, which cannot be generalized to long-term safety. Third, the measures and definition of some AEs might differ among the included studies, which might cause clinical heterogeneity. Fourth, no protocol was established before the study was carried out. Fifth, we could not combine data from different dose arm. It is difficult to separate different dose arm, because every study gave the appropriate dose for patients according to the weight and age.

Table 5

Meta-analysis of high-quality RCT.

Group	Study type	Studies	n/N_1	n/N_2	Heterogeneity	RR (95% CI)	*P*
Neurological and psychiatric symptoms							
Somnolence							
Aripiprazole vs Placebo	RCT	1	12/89	1/44	Not applicable	5.933 (0.797,44.178)	.082
Lethargy							
Aripiprazole vs Placebo	RCT	1	5/89	0/44	Not applicable	5.500 (0.311,97.281)	.245
Headache							
Aripiprazole vs Placebo	RCT	1	7/89	1/44	Not applicable	3.461 (0.439, 27.259)	.238
Sedation							
Aripiprazole vs Placebo	RCT	1	12/89	1/44	Not applicable	5.933 (0.797,44.178)	.082
Fatigue							
Aripiprazole vs Placebo	RCT	1	10/89	0/44	Not applicable	10.500 (0.629,175.169)	.102
Akathisia							
Aripiprazole vs Placebo	RCT	1	3/89	0/44	Not applicable	3.500 (0.185,66.305)	.404
Restlessness							
Aripiprazole vs Placebo	RCT	1	3/89	1/44	Not applicable	1.483 (0.159,13.851)	.730
Somnambulism							
Aripiprazole vs Placebo	RCT	1	1/89	0/44	Not applicable	1.500 (0.062,36.090)	.803
Digestive symptoms							
Nausea vomiting							
Aripiprazole vs Placebo	RCT	1	12/89	3/44	Not applicable	1.978 (0.588,6.648)	.270
Increased appetite							
Aripiprazole vs Placebo	RCT	1	7/89	1/44	Not Applicable	3.461 (0.439,27.259)	.238
Respiratory system							
Nasopharyngitis							
Aripiprazole vs Placebo	RCT	1	7/89	044	Not applicable	7.500 (0.438,128.401)	.164

Notes: n means total events,N_1means patients of treatment group; N_2 means patients of control group.

5. Conclusion

In conclusion, we found that aripiprazole had clinically relevant tolerability in children and adolescents. Aripiprazole might be viewed as an important treatment option for patients with TDs in these age groups. The common AEs were somnolence, headache, sedation, and nausea and vomiting. There is a need for further studies to confirm the use of aripiprazole in children and adolescents with TDs.

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Author contributions

YCS, YQS, ZLL, CH, and MJP contributed to planning, supervision, writing, and analysis of the study; YCS, YQS, and ZLL independently selected titles, abstract and full text; YCS, YQS, CH, and MJP each contributed to data collection, writing the manuscript and review of the literature. All authors have read and approved the final manuscript.
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References

[1] Robertson MM, Eapen V, Cavanna AE. The international prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross-cultural perspective. J Psychosom Res 2009;67:475–83.
[2] Knight T, Steeves T, Day L, et al. Prevalence of Tic disorders: a systematic review and meta-analysis. Pediatr Neurol 2012;47:77–90.
[3] Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. Neurol Sci 2011;32:1213–7.
[4] Evans J, Seri S, Cavanna AE. The effects of Gilles De La Tourette syndrome and other chronic tic disorders on quality of life across the lifespan: a systematic review. Eur Child Adolesc Psychiatry 2016;25:939–48.
[5] Grados MA, Mathews CA. Latent class analysis of Gilles De La Tourette syndrome using comorbidities: clinical and genetic implications. Biol Psychiatry 2008;64:219–25.
[6] Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. Am J Psychiatry 2008;154:1057–62.
[7] Rampello L, Alvano A, Battaglia G, et al. Tic disorders: from pathophysiology to treatment. J Neurol 2006;253:1–5.
[8] Yoo HK. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. Eur Child Adolesc Psychiatry 2011;20:127–35.
[9] Bowles TM, Levin GM. Aripiprazole: a new atypical antipsychotic drug. Ann Pharmacother 2003;37:687–94.
[10] Yang CS, Huang H, Zhang L-L, et al. Aripiprazole for the treatment of tic disorders in children: a systematic review and meta-analysis. BMC Psychiatry 2015;15:179.
[11] Ghanizadeh A, Haghighi A. Twice-weekly aripiprazole for treating children and adolescents with tic disorder, a randomized controlled clinical trial. Ann Gen Psychiatry 2016;15:21.
[12] Waldon K, Hill J, Termine C, et al. Trials of pharmacological interventions for Tourette syndrome: a systematic review. Behav Neurol 2013;26:265–73.
[13] Rickards H, Cavanna AE, Worrall R. Treatment practices in Tourette syndrome: the European perspective. Eur J Paediatr Neurol 2012;16:361–4.

[14] Cavanna AE, Selvini C, Termine C, et al. Tolerability profile of aripiprazole in patients with Tourette syndrome. J Psychopharmacol 2012;26:891–5.
[15] Higgins JPT, Altman DG, Sterne JAC (Editors). Chapter8: Assessing Risk Of Bias In Included Studies. In: Higgins JPT, Green S (Editors). *Cochrane Handbook For Systematic Reviews Of Interventions*. Version 5.1.0 (Updated March 2011). The Cochrane Collaboration, 2011. Available From Www.Cochrane-Handbook.Org.
[16] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[17] NICE. Appendix 4 Quality of case series form. Available at: http://www.nice.org.uk/guidance/index. Accessed 2002.
[18] Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. BMJ Case Rep 2013;38–43.
[19] Higgins J, Thompson S, Deeks J, et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy 2002;7:51–61.
[20] Ghanizadeh A, Haghighi A. *Aripiprazole Versus Risperidone For Treating Children And Adolescents With Tic Disorder: A Randomized Double Blind Clinical Trial*. New York: Springer Science+Business Media; 2013.
[21] Yoo HK, Joung YS, Lee J-S, et al. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescent with Tourette's disorder. J Clin Psychiatry 2013;74:772–80.
[22] Cheng Z-M, Lei Q-H. Comparative study of aripiprazole and haloperidol in the treatment of the disorder. Med J Chin People's Health 2012;24:402–4.
[23] Chen L-B, Chen Y-H. Clinical study of low-dose aripiprazole in the treatment of tic disorder. Chin J Pract Pediatricsjul 2014;29:542–5.
[24] Sun Y, Wang H-P, Duan L-F. The clinical efficacy and safety of aripiprazole in the treatment of tic disorder. China Med Pharmacy 2014;4:64–6.
[25] Zhang Y, Su J, Hu Z-J, et al. Comparison of clinical efficacy and safety of aripiprazole and ciprofloxacin in the treatment of tic disorder in children. Shandong Med 2014;20:44–6.
[26] Liu Y-Y, Chen Y-H, Chen H, et al. A control study of aripiprazole and tiapride treatment for tic disorders in children. Chin J ContempPediatr 2010;12:421–4.
[27] Wang Y-H, Chen M-Z, Wang X-S. Comparison of the efficacy of aripiprazole and thiapride in the treatment of TOURETTE syndrome. Shandong Med 2013;39:58–9.
[28] Guo F, Qin X, Guo S-Q, et al. Aripiprazole and haloperidol in the treatment of tic disorder of childhood. China J Health Psychol 2013;21:1767.
[29] Zhao Z-L, Guo P, Guo H. A comparative study of aripiprazole and haloperidol in the treatment of tic disorder in children. World Health Dig Med Periodical 2011;8:111–3.
[30] Ren Z-B, Jin W-D, Wang H-Q. A comparative study of aripiprazole and haloperidol in the treatment of tic disorder in children. Chin J Ment Dis 2012;38:222–4.
[31] Zhou W, Zhang Y-M, Zhou C-X. A comparative study of ipiprazole and haloperidol in the treatment of tic disorder in children. Med Inform 2015;28:230–1.
[32] Qin J. Effects of aripiprazole on the efficacy and compliance of children in tic disorder. Yiayao Qianyan 2014;27:128–9.
[33] Guo F, Wang J-F, Guo S-Q, et al. Comparative study on efficacy of aripiprazole combined with psychotherapy in treatment of tic disorder for children and adolescents. Med J Chin People Health 2013;17:81–3.
[34] Bai Y-Y, Zhang T-T, Han J-Y, et al. Comparative study on efficacy of aripiprazole combined with cognitive therapy for tic disorder in children and adolescents. Medical Innovation China 2014;11:114–7.
[35] Gao R, Zhou Y-D, Huang Z-Y, et al. An open controlled study of aripiprazole and haloperidol in the treatment of tic disorder in children and adolescents. Sichuan Mental Health 2013;4:300–2.
[36] Zhang H, Huang H-Z, Lin G-D. A randomized controlled study of risperidone and aripiprazole in treatment of children with tic disorder. Clin Focus 2015;30:1393–6.
[37] Zheng Q-M, Li Y-D, Deng L-H, et al. A comparative study of aripiprazole orally disintegrating tablets and haloperidol in the treatment of tic disorder. Jilin Med 2015;36:2995–7.
[38] Xu X-X. Effects of aripiprazole on the efficacy and compliance of children in tic disorder. World Latest Med Inform 2015;15:77–8.
[39] Ying L-J. Comparison of the effects of aripiprazole and haloperidol in the treatment of children with Tourette syndrome. Chin J Rural Med Pharmacy 2018;01:20–34.
[40] Yoo HK, Lee JS, Paik KW, et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. Eur Child Adolesc Psychiatry 2011;20:127–35.
[41] Rizzo R, Eddy CM, Calí P, et al. Metabolic effects of aripiprazole and pimozide in children with Tourette syndrome. Pediatr Neurol 2012; 47:419–22.
[42] Masi G, Pfanner C, Brovedani P. Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: a naturalistic comparative study. J Psychiatr Res 2013;47:1007–12.
[43] Liang Y-Z, Zhou F-C, Zheng Y, et al. Aripiprazole treatment of Tourette syndrome. Chin J Nervous Mental Dis 2010;36:111–2.
[44] Liu Z-S, Chen Y-H, Zhong Y-Q, et al. A multicenter controlled study on aripiprazole treatment for children with Tourette syndrome. Chin J Pediatr 2011;49:572–6.
[45] Ho C-S, Chiu N-C, Tseng C-F, et al. Clinical effectiveness of aripiprazole in short-term treatment of tic disorder in children and adolescents: a naturalistic study. Pediatr Neonatol 2014;55:48–52.
[46] Lyon GJ, Samar S, Jummani R, et al. Aripiprazole in children and adolescents with Tourette's disorder: an open-label safety and tolerability study. J Child Adolesc Psychopharmacol 2009;19: 623–33.
[47] Cui Y-H, Zheng Y, Yang Y-P, et al. Effectiveness and tolerability of aripiprazole in children and adolescents with Tourette's disorder: a pilot study in China. J Child Adolescent Psychopharmacol 2010; 20:291–8.
[48] Murphy TK, Mutch PJ, Reid JM, et al. Open label aripiprazole in the treatment of youth with tic disorders. J Child Adolesc Psychopharmacol 2009;19:441–7.
[49] Seo WS, Sung H-M, Sea HS, et al. Aripiprazole treatment of children and adolescents with Tourette disorder or chronic tic disorder. J Child Adolescent Psychopharmacol 2008;18:197–205.
[50] Yoo HK, Choi S-H, Park S, et al. An open-label study of the efficacy and tolerability of aripiprazole for children and adolescents with tic disorders. J Clin Psychaitry 2007;68:1089–93.
[51] Yoo HK, Kim JY, Kim CY. A pilot study of aripiprazole in children and adolescents with Tourette's disorder. J Child Adolesc Psychopharmacol 2006;16:505–6.
[52] Budman C, Coffey BJ, Shechter R, et al. Aripiprazole in children and adolescents with Tourette disorder with and without explosive outbursts. J Child Adolescent Psychopharmacol 2008;18:509–15.
[53] Gulisano M, Calì PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. Neurol Sci 2011;32:1213–7.
[54] Murphy TK, Bengtson MA, Soto O, et al. Case series on the use of aripiprazole for Tourette syndrome. In J Neuropsychopharmacol 2005;8:489–90.
[55] Sun L, Zhou T-H, Lei T. Clinical study of aripiprazole oral tablet in the treatment of Tourette syndrome. Tianjin Pharmaceutical 2011;2: 39–41.
[56] Zhao H-A, Zhang Q-F, Sun M-Y. Clinical study of aripiprazole in the treatment of Tourette syndrome. China J Health Psychol 2011;20: 1782.
[57] Liang Y-Z, Zhou F-C, Zheng Y, et al. The effects of aripiprazole in the treatment of tic disorder. J Psychiatry 2010;23:34–5.
[58] Bi B, Liu L, Zhu Y-Z, et al. Clinical study of aripiprazole in children with tic disorder. Shanxi Med 2012;49:178–80.
[59] Gao R, Zhou Y-D, Zhou Z-Y, et al. Clinical study of aripiprazole in the treatment of tic disorder in children and adolescents. J Clin Psychaitry 2014;20:36–8.
[60] Zhao B, Hong X-Y, Zhang Z. Clinical study of aripiprazole in the treatment of Tourette syndrome in children with attention deficit hyperactivity disorder. J Clin Psychaitry 2015;15:334.
[61] Shim S-H, Kwon Y-J. Adolescent with Tourette syndrome and bipolar disorder: a case report. Clin Psychopharmacol Neurosci 2014;12:235–9.
[62] Bhatia M, Gautam P, Kaur J. Case report on Tourette syndrome treated successfully with aripiprazole. Shanghai Arch Psychiatry 2014;26:297–9.
[63] Lai C-H. Aripiprazole treatment in an adolescent patient with chronic motor tic disorder and treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol 2009;12:1291–3.

[64] Fountoulakis KN, Siamouli M, Kantartzis S, et al. Acute dystonia with low-dosage aripiprazole in Tourette's disorder. Ann Pharmacother 2006;40:775–81.
[65] Chen VC-H. Aripiprazole for the tic symptoms in a child receiving atomoxetine treatment for ADHD. Progr Neuro-Psychopharmacol Biol Psychiatry 2010;34:1355–6.
[66] Wang PW, Huang MF, Yen CF, et al. Diagnosis and treatment of comorbidities of Tourette's syndrome and bipolar disorder in a 10-year-old boy. Kaohsiung J Med Sci 2009;25:608–19.
[67] Lewis K, Rappa L, Sherwood-Jachimowicz DA, et al. Aripiprazole for the treatment of adolescent Tourette's syndrome: a case report. J Pharmacy Pract 2010;23:239–44.
[68] Mazlum B, Zaimoğlu S, Öztop DB. Exacerbation of tics after combining aripiprazole with pimozide a case with Tourette Syndrome. J Clin Psychopharmacol 2015;35:350–1.
[69] Moher , Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Ann Internal Med 2009;151:264–9.