Comparative Efficacy and Safety of Antipsychotic Drugs for Tic Disorders: A Systematic Review and Bayesian Network Meta-Analysis

Authors
Chunsong Yang[1,2*], Zilong Hao[3*], Ling-Li Zhang[1,2], Cai-Rong Zhu[4], Ping Zhu[4], Qin Guo[5]

Affiliations
1 Department of Pharmacy, Evidence-Based Pharmacy Center, West China Second Hospital, Sichuan University
2 Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education
3 Department of Neurology, West China Hospital, Sichuan University, Chengdu, China
4 West China School of Public Health, Sichuan University
5 Department of Pediatrics, West China Second Hospital, Sichuan University

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Correspondence
Professor Ling-Li Zhang, MD, PhD
West China Second University Hospital
Sichuan University
No.20, Third Section, Renmin Nan Lu
Chengdu, 610041 Sichuan
P.R. China
zhlingli@sina.com

Professor Cai-Rong Zhu, PhD
West China School of Public Health
Sichuan University
cairong.zhu@hotmail.com

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ABSTRACT

Objective The purpose of this study was to evaluate the efficacy and safety of antipsychotic drugs for tic disorders (TDs) in a network meta-analysis.

Methods PubMed, Embase, Cochrane Library, and 4 Chinese databases were searched. Randomized controlled trials (RCTs) evaluating the efficacy of antipsychotic drugs for TDs were included.

Results Sixty RCTs were included. In terms of tic symptom score, compared with placebo, haloperidol, risperidone, aripiprazole, quetiapine, olanzapine, and ziprasidone can significantly improve tic symptom score (standardized mean differences [SMD] ranged from − 12.32 to − 3.20). Quetiapine was superior to haloperidol, pimozide, risperidone, tiapride, aripiprazole, and penfluridol for improving tic symptom score (SMD ranged from − 28.24 to − 7.59). Compared with tiapride, aripiprazole could significantly improve tic symptom score (SMD = − 4.27). Compared with all other drugs, penfluridol was not effective. Atypical antipsychotics were generally well tolerated.

Conclusions Atypical antipsychotics (risperidone and aripiprazole) appear to be the most robust evidence-based options for the treatment of TDs. Quetiapine may be a promising therapy. Ziprasidone and olanzapine are also effective, but the evidence is lacking. Further high-quality directly comparing different pharmacological treatment studies are justified.

* Chunsong Yang and Zilong Hao contributed equally to this study.

Introduction

Tic disorders (TDs) are common, childhood-onset, neuropsychiatric disorders with variable severity and prognosis, which are characterized by sudden, repetitive, nonrhythmic motor movement or vocalization [1]. TDs are classified into transient tic disorder (TTD), chronic tic disorder (CTD), and Tourette syndrome (TS) by duration and severity [2]. Symptoms of common comorbidities of TDs (i. e., attention-deficit hyperactivity disorder, obsessive-compulsive disorder, pervasive developmental disorder, and other mood disorders) often coexist [3]. Tics and co-occurring conditions have been associated with functional impairment and diminished quality of life, for instance by affecting subjective discomfort (i. e., pain or injury), sleep quality, and emotional status (i. e., anxiety or depression), and can cause sustained social problems (i. e., social isolation or bullying) especially in severe cases [4–7]. Knight's study presented that the prevalence of TS is 0.77 %. TTD is the most common TD, with a prevalence of 2.99 %, and CTD has a prevalence of 1.61 % [8].

Motor/vocal tics and comorbid symptoms are often managed by pharmacotherapy. Antipsychotic drugs are commonly used in the treatment of TDs, including typical antipsychotic drugs (i. e., haloperidol, pimozide) and atypical antipsychotic drugs (i. e., risperidone, aripiprazole, quetiapine) [6, 9, 10]. A number of randomized controlled trials (RCTs) and systematic reviews evaluating the efficacy of antipsychotic drugs for TDs have been published [11–14]. In our previous overview including 22 systematic reviews for treating TDs, we found some antipsychotics were efficacious in the reduction of tic severity; however, RCTs directly comparing different pharmacological treatment options for TDs are scarce [15].

Bayesian network meta-analysis is known as mixed treatment comparison, and it could combine direct and indirect evidence from multiple treatment comparisons to estimate the interrelations across all treatments, which allows the simultaneous comparison of multiple antipsychotic drugs within a single analysis while preserving randomization [16]. Multiple genes interacting with environmental factors could lead to the onset of symptoms, and multiple genes and chromosomal regions have been implicated in TS etiology, with SLITRK1 being the most prominent example [17]. If we screen out some antipsychotic treatments with better efficacy through indirect comparison, it could provide reference for the precise treatment for TDs from gene perspective.

Therefore, we aimed to provide a comprehensive and hierarchical evidence of the efficacy and safety of antipsychotic drugs in the treatment of TDs.

Methods

Inclusion and exclusion criteria

Types of studies

Only RCTs, including crossover and cluster randomized trials, evaluating the efficacy and safety of antipsychotic drugs for the treatment of TDs were included. We planned to use only data from the first period of any included crossover trials. Trials were excluded if (1) the same study was published in different languages and if (2) they compared different doses of drugs—that is, the treatment group used high (or low) doses and the control group used low (or high) doses.

Types of participants

We focused on the patients with clinical diagnoses of TDs who met the following diagnosis criteria: (1) the Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III), DSM-IV, or DSM-IV-Text Revision [18–20]; (2) the International Classification of Diseases-10 (ICD-10) [21]; and (3) the Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD) [22].

Types of interventions and controls

The interventions are all antipsychotic drugs, including typical antipsychotic drugs (i. e., haloperidol, tiapride, pimozide, penfluridol, fluphenazine) and atypical antipsychotic drugs (risperidone, olanzapine, aripiprazole, quetiapine, ziprasidone, paliperidone, sulpiride, tetrabenazine). The controls are also all antipsychotic drugs.

Types of outcome measurements

The primary outcome was the efficacy at post-treatment, as measured by mean change scores in tic severity symptoms from baseline to post-treatment. When an included study used more than 1 scale, the Yale Global Tic Severity Scale (YGTSS) was used as the primary measure, as it is the more commonly-used measure of tic severity symptoms [23], followed by the Clinical Global Impression (CGI) Scale [19], the Tourette Syndrome Global Scale (TSGS) [19], the Tourette Syndrome Severity Scale (TSSS), or other scales [24]. We used these scales in this order through published research and expert opinion in our hospital.

The secondary outcomes were the response and the reported adverse events (AEs). The response was defined as a reduction of 50 % or more in scores from baseline to post-treatment on the tic severity symptoms.

Search strategy

The following databases were searched from their respective inceptions up to January 2017 by 2 reviewers (Yang and Hao): PubMed, EMBASE, the Cochrane Library, Cochrane Controlled Trials databases (CENTRAL), the Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI,), the Chinese Science and Technique Journals Database (VIP), and the Wanfang Database (http://www.wanfangdata.com/). We also searched the additional studies in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews. The following search terms were used: "Tourette syndrome," "tic disorders," "Tourette disorders," "haloperidol," "tiapride," "pimozide," "penfluridol," "risperidone," "olanzapine," "aripiprazole," "quetiapine," "ziprasidone," "paliperidone," "sulpiride," "fluphenazine," "tetrabenazine," "antipsychotics," "typical antipsychotics," and "atypical antipsychotics."

Selection of studies and data extraction

Two reviewers (Yang and Hao) independently screened the titles and abstracts of every record. Full articles were obtained when either information provided in the title or abstracts conformed to the selection criteria outlined previously or could not be ascertained because of limited information. To include studies, data were independently extracted by each reviewer and entered into a standardized form. The data extraction form included the following contents: (1) general characteristics of studies, (2) the general char-

acteristics of patients, (3) the diagnostic criteria, (4) sample size, (5) interventions and comparisons, (6) outcome measurements, and (7) AEs. Discrepancies were resolved by consensus.

Quality assessment

Two reviewers (Yang and Hao) independently evaluated the methodological quality of identified studies using the "risk of bias tool" under the domains of 6 aspects, including (1) sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome, and (6) other biases. The methodological criteria referred to the Cochrane Handbook for Systematic Reviews of Interventions version 5.3 [25].

Statistical methods

First, we performed traditional meta-analysis for studies that directly compared different treatment arms. Results for dichotomous outcomes are expressed as risk ratios (RR) with 95 % confidence intervals (CIs). Results for continuous outcomes are expressed as the standardized mean difference (SMD). We evaluated heterogeneity among the included studies using the I^2 test. Regardless of the size of heterogeneity, the random effects model was used for statistical analysis. We conducted the meta-analysis using STATA 12.0 (Stata Corporation, College Station, Texas, USA). Publication bias was examined with the funnel plot method and the Egger's regression asymmetry test [26].

Then we performed Bayesian network meta-analyses to compare different antipsychotic drugs with a random-effects model within a Bayesian framework [27]. The pooled estimates of SMD with 95 % CIs were calculated for continuous outcomes, and odds ratios (ORs) with 95 % CIs for categorical outcomes. The pooled estimates were obtained using the Markov chain Monte Carlo method. Three Markov chains were run simultaneously with different arbitrarily chosen initial values [27]. To ensure convergence, trace plots were assessed [28]. A run-in period of 50,000 iterations was adequate to achieve convergence, and a further 100,000 samples were taken. Inconsistency refers to differences between direct and various indirect effect estimates for the same comparison. To assess inconsistency, we estimated the inconsistency factors in closed loop based on the method described by Chaimani et al. [29]. Probability values were summarized and reported as surface under the cumulative ranking curve (SUCRA) and rankograms. A higher SUCRA value suggests better results for respective treatment method. Moreover, network meta-regression analyses were used to investigate whether potential heterogeneity could be explained by differences in publication year and sample sizes. We will select better model for the network meta-analysis based on deviance information criterion. Results from intention-to-treat (ITT) analysis or modified ITT were preferred over results from completer analyses.

Network meta-analyses were performed using the WinBUGS software package (MRC Biostatistics Unit, Cambridge, UK) with random effects models for multi-arm trials. The other analyses were performed and presented by the Stata 12.0 software packages (Stata Corporation, College Station, Texas, USA).

The first sensitivity analysis was performed on a network excluding trials with small sample sizes (n < 20 patients), and the second sensitivity analysis was performed by omitting trials with long-term treatment period (treatment period > 24 weeks).

Results

Results of the literature search

The literature search process identified a total of 6312 potentially relevant articles. After removing duplicates, screening titles and abstracts, and reading full texts, 60 RCTs met the inclusion criteria (▶ **Fig. 1**).

The characteristics of the included studies (Table S1)

We included 60 studies involving 4077 participants. The sample size of included RCTs ranged from 4 to 180 (median 61). The location of the first author had the following distribution: China (47/60, 78.3 %), United States (7/60, 11.7 %), Canada (2/60, 3.3 %), South Korea (1/60, 1.7 %), Iran (1/60, 1.7 %), Italy (1/60, 1.7 %), and South Africa (1/60, 1.7 %). Only 4 trials were multicenter RCTs. Fifty-one studies were positive drug controls, and 9 studies used a placebo as a control. This study included 11 different types of antipsychotic agents: haloperidol (n = 44 RCTs), risperidone (n = 23 RCTs), aripiprazole (n = 15 RCTs), tiapride (n = 14 RCTs), pimozide (n = 8 RCTs), quetiapine (n = 4 RCTs), olanzapine (n = 3 RCTs), ziprasidone (n = 2 RCTs), paliperidone (n = 1 RCT), penfluridol (n = 1 RCT), and sulpiride (n = 1 RCT). The period of treatment ranged from 3 weeks to 20 months.

Characteristics of participants (Table S1)

The age of participants ranged from 2 to 65 years. Two categories of disorders were examined: TS (43/60, 71.7 %) and TDs (17/60, 28.3 %). The diagnostic criteria used were as follows: CCMD (22/60, 36.7 %), DSM-IV (17/60, 28.3 %), ICD-10 (5/60, 8.3 %), DSM-III (4/60, 6.7 %), DSM-III-R (3/60, 5 %), DSM-IV-TR (2/60, 3.3 %), both DSM-IV and CCMD-3 (1/60, 1.7 %), and both DSM-IV-TR and CCMD-3(1/60, 1.7 %). The diagnostic criteria were not mentioned in 5 studies (5/60, 8.3 %).

Primary outcome measurements

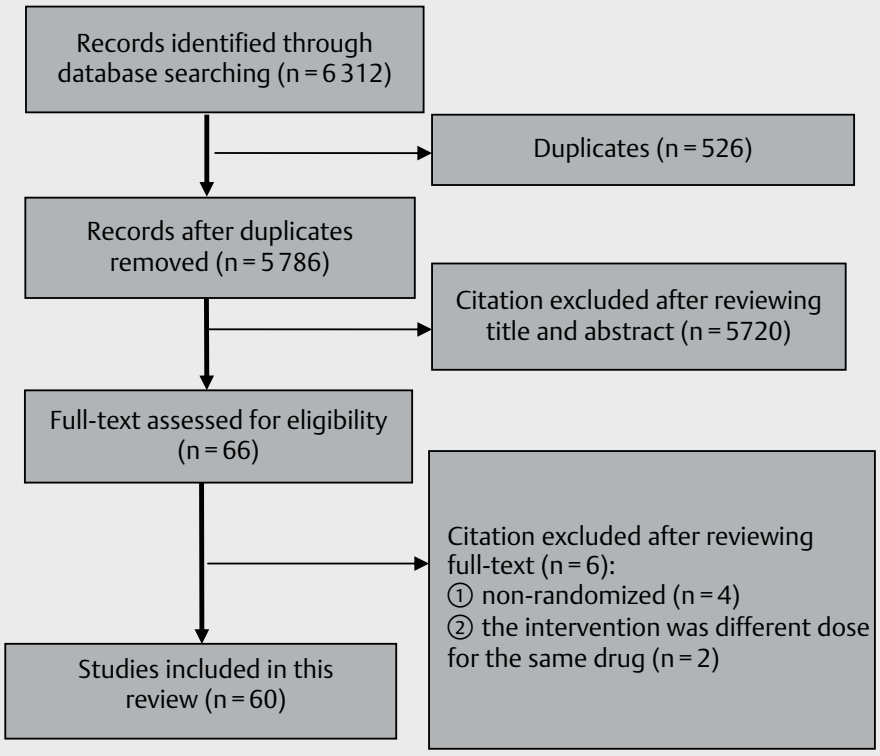
The majority of the included RCTs (37/60, 61.7 %) used the YGTSS as the primary outcome measurement, and other outcome measurements used in the included studies were the response rate (36/60, 60 %), the CGI Scale (4/60, 6.7 %), the TSGS (3/60, 5 %), the TSSS (2/60, 3.3 %), and tic counts (1/60, 1.7 %). Ninety-five percent (57/60) of included studies reported on AEs of treatment, of which 42 studies reported specific AEs.

Quality assessment

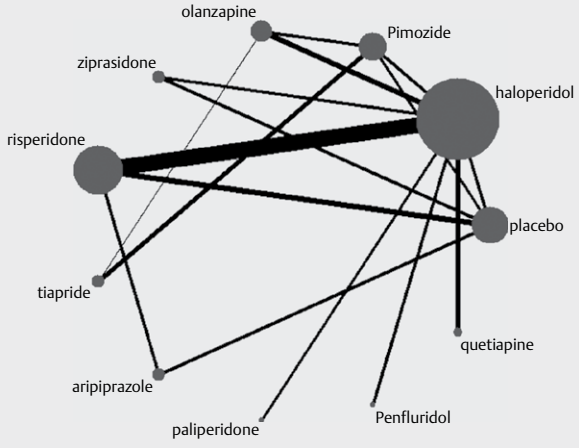
Twenty-five percent (15/60) of studies used an adequate method of random sequence generation. Ten percent (6/60) of studies implemented adequate allocation concealment, and 25 % (15/60) used the methods of blinding. Eight percent (5/60) of studies reported loss to follow-up, and none of the studies used an ITT analysis for incomplete outcome data. Only 5 % (3/60) of studies had registration for a protocol. Comparability of baseline in 4 of the studies was unclear. In other trials, there were no significant differences in the comparability of baseline between the treatment group and the control group.

Results of pairwise meta-analyses

Table S2 presents the results of the pairwise meta-analyses. Compared with haloperidol, risperidone, aripiprazole, quetiapine,



▶ **Fig. 1** Flow chart of literature screening and selection process.



▶ **Fig. 2** Network plot of eligible comparisons for primary outcome.

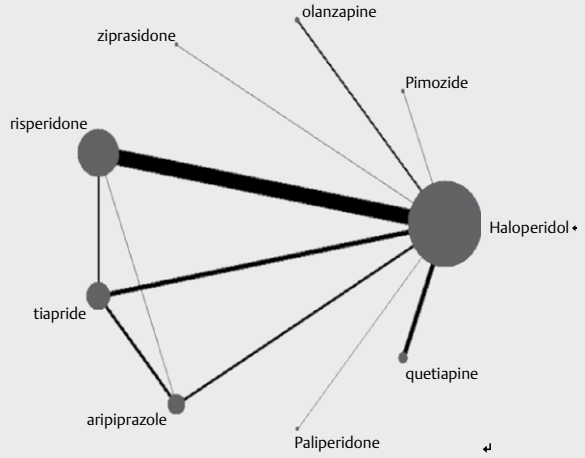
tiapride, pimozide, olanzapine, paliperidone, and ziprasidone could improve tic symptoms score, but there were no significantly difference between them. Haloperidol and risperidone could significantly improve tic symptoms scores compared with placebo, and pimozide also could improve tic symptoms scores, but there were no significantly difference between them. Aripiprazole was superior to tiapride in the improvement of tic symptoms, and there was significantly difference between them.

In terms of response rate, quetiapine was superior to haloperidol in the improvement of tic symptoms, and there were significantly difference between them. Compared with haloperidol, risperidone, tiapride, aripiprazole, olanzapine, ziprasidone, paliperidone, and pimozide could improve tic symptoms, but there were no significantly difference between them. Compared with tiapride, aripiprazole and risperidone could improve the tic symptoms, but there was no significantly difference between them. Compared with risperidone, aripiprazole could improve the tic symptoms, but there were no significantly difference between them (**Table S3**).

Results of network meta-analysis

In regard to the primary outcome, we included 39 RCTs involving 2417 participants for network meta-analysis. There were 11 comparisons of primary outcome in the network plot of different types of antipsychotic agents (▶ **Fig. 2**). In the network plot of eligible comparisons for outcomes, the connecting line represented that there was a direct comparison between 2 kinds of interventions. The thickness of the line represents the number of included studies, and the dot size represents the total sample size of interventions. The pooled effect estimates for primary efficacy from the network meta-analysis are provided (▶ **Fig. 4**). Compared with placebo, haloperidol (SMD = −3.20, 95 % CI [−6.52, −0.14]), olanzapine (SMD = −6.11, 95 % CI [−11.86, 0.55]), ziprasidone (SMD = −5.57, 95 % CI [−11.15, −0.048]), risperidone (SMD = −3.47, 95 % CI [−6.87, −0.37]), aripiprazole (SMD = −4.74, 95 % CI [−8.67, −1.06]), and quetiapine (SMD = −12.32, 95 % CI [−19.09, −5.63]) could significantly improve tic symptom score,

and there were significant differences between the treatment group and the placebo control group. Quetiapine was superior to haloperidol (SMD = −9.13, 95 % CI [−15.06, −3.21]), pimozide (SMD = −10.38, 95 % CI [−17.64, −3.11]), risperidone (SMD = −8.87, 95 % CI [−15.15, −2.56]), tiapride (SMD = −11.86, 95 % CI [−18.65, −5.02]), aripiprazole (SMD = −7.59, 95 % CI [−14.07, −1.00]), and penfluridol (SMD = −28.24, 95 % CI [−40.17, −28.26]) for improving tic symptom score, and the difference was statistically significant. Compared with tiapride, aripiprazole could significantly improve tic symptom score (SMD = −4.27, 95 % CI [−8.01, −0.58]). There were no significant differences between other drugs.



▶ **Fig. 3** Network plot of eligible comparisons for response rate.

In regard to the secondary efficacy outcomes for response rates, we included 33 RCTs involving 1791 participants for network meta-analysis. There were 9 comparisons of the secondary efficacy in the network plot of different types of antipsychotic agents (▶ **Fig. 3**). The pooled effect estimates for primary efficacy from the network meta-analysis are provided (▶ **Fig. 4**). The results were consistent with those of the primary outcome for efficacy, except that there were no significant difference comparing quetiapine with pimozide, ziprasidone, risperidone, tiapride, and aripiprazole.

In regard to the primary outcome, the results in closed loop showed that the direct estimate of the summary effect was consistent with the indirect estimate in all loops except 1 (i. e., haloperidol-tiapridal-aripiprazole), since all their 95 % CIs included 0 (**Fig. S1**).

In regard to the secondary efficacy outcomes for response rates, their 95 % CIs included 1 in all closed loop, so the direct estimate of the summary effect was consistent with the indirect estimate (**Fig. S2**).

▶ **Table S1** presents the results of the overall SUCRA-based probabilities for all antipsychotic drugs in terms of efficacy and response rate. The few significant findings in the network meta-analysis restrict the interpretation of hierarchical evidence based on SUCRA (**Figs. S3** and **S4**).

Adverse events

Ninety-five percent (57/60) of the studies reported AEs. Of them, 42 studies reported specific AEs. The AEs of ziprasidone and penfluridol were not reported in included RCTs. For other antipsychotic drugs, the most common AEs of haloperidol were drowsiness, extrapyramidal reactions, and dry mouth. The most common AEs of tiapride were dizziness, nausea, and dry mouth. The most common AEs of aripiprazole were drowsiness and nausea/vomiting. The

placebo	–	–	–	–	–	–	–	–	–	–
−3.20* **(−6.52, −0.14)**	haloperidol	1.22 (0.15, 4.65)	1.51 (0.42, 3.98)	2.13 (0.27, 8.51)	0.82 (0.52, 1.24)	1.01 (0.54, 1.76)	0.54 (0.26, 1.02)	0.55 (0.07, 2.02)	–	**0.38*** **(0.15, 0.84)**
−1.94 (−6.53, 2.40)	1.26 (−2.96, 5.47)	pimozide	2.64 (0.20, 11.78)	3.84 (0.16, 19.9)	1.44 (0.17, 5.69)	1.79 (0.19, 7.14)	0.96 (0.10, 3.89)	0.97 (0.04, 4.99)	–	0.68 (0.06, 2.86)
−6.11* **(−11.86, −0.55)**	−2.92 (−7.85, 2.01)	−4.17 (−9.76, 1.43)	olanzapine	2 (0.16, 9.11)	0.76 (0.19, 2.08)	0.93 (0.21, 2.67)	0.93 (0.21, 2.67)	0.51 (0.04, 2.26)	–	0.36 (0.07, 1.14)
−5.57* **(−11.15, −0.048)**	−2.37 (−7.94, 3.34)	−3.64 (−10.3, 3.16)	0.51 (−6.81, 7.97)	ziprasidone	0.82 (0.09, 3.25)	1.02 (0.10, 4.04)	0.55 (0.05, 2.22)	0.54 (0.02, 2.71)	–	0.39 (0.03, 1.65)
−3.47* **(−6.87, −0.37)**	−0.28 (−2.38, 1.81)	−1.54 (−6.01, 2.94)	2.61 (−2.67, 7.90)	2.08 (−3.80, 7.82)	risperidone	1.28 (0.63, 2.31)	0.69 (0.3, 1.33)	0.7 (0.08, 2.58)	–	0.49 (0.16, 1.13)
−0.47 (−5.06, 3.89)	2.72 (−0.62, 6.10)	1.47 (−3.86, 6.81)	5.62 (−0.29, 11.57)	5.08 (−1.48, 11.49)	3.01 (−0.76, 6.82)	tiapride	0.56 (0.26, 1.08)	0.59 (0.07, 2.28)	–	0.41 (0.13, 1.04)
−4.74* **(−8.67, −1.06)**	−1.55 (−4.29, 1.18)	−2.8 (−7.71, 2.07)	1.35 (−4.24, 6.91)	0.82 (−5.40, 6.84)	−1.26 (−4.48, 1.91)	**−4.27*** **(−8.01, −0.58)**	aripiprazole	1.14 (0.12, 4.52)	–	0.79 (0.22, 2.09)
−4.89 (−14.44, 4.47)	−1.72 (−10.58, 7.17)	−2.97 (−12.82, 6.89)	1.17 (−9.01, 11.35)	0.65 (−9.91, 11.1)	−1.43 (−10.64, 7.74)	−4.43 (−13.95, 5.10)	−0.19 (−9.51, 9.13)	paliperidone	–	1.45 (0.13, 6.10)
16.48* **(5.43, 27.47)**	**19.67*** **(9.11, 30.18)**	**18.4*** **(7.10, 29.76)**	**22.55*** **(10.96, 34.17)**	**22.01*** **(10.06, 33.87)**	**19.93*** **(9.18, 30.7)**	**16.96*** **(5.88, 28.06)**	**21.21*** **(10.29, 32.08)**	**21.35*** **(7.55, 35.02)**	penfluridol	–
−12.32* **(−19.09, −5.63)**	**−9.13*** **(−15.06, −3.21)**	**−10.38*** **(−17.64, −3.11)**	−6.23 (−13.94, 1.51)	−6.78 (−14.96, 1.38)	**−8.87*** **(−15.15, −2.56)**	**−11.86*** **(−18.65, −5.02)**	**−7.59*** **(−14.07, −1.00)**	−7.43 (−18.04, 3.23)	**−28.24*** **(−40.17, −28.26)**	quetiapine

treatment | tic symptom score (SMD with 95 % CrI) | response rate (OR with 95 % CrI)

▶ **Fig. 4** Relative effect size of efficacy at post-treatment according to network meta-analysis.

most common AEs of risperidone were drowsiness and increased appetite. The most common AEs of pimozide were acinesia and akathisia. The most common AEs of quetiapine was drowsiness. The most common AEs of olanzapine was dizziness, drowsiness, and dry mouth. The most common AEs of pailperidone were headache and nausea. The common AEs of different drugs are shown in **Table S4**.

Sensitivity analysis (Figs. S5 and S6) and meta-regression

In regard to the primary outcome, after excluding trials with mall sample sizes (n < 20 patients), no material change of the pooled estimated effects in sensitivity analysis was found. The minor changes of estimated effects between interventions were mainly as follows: haloperidol versus placebo, olanzapine versus placebo, risperidone versus placebo, and quetiapine versus aripiprazole.

After omitting trials with long-term treatment period (treatment period > 24 weeks), only 1 changed estimated effects was found. The minor changes were as follows: ziprasidone versus pimozide. In regard to the response rate, after excluding trials with mall sample sizes (n < 20 patients), no material change of the pooled estimated effects in sensitivity analysis was found. The minor changes were mainly as follows: aripiprazole versus haloperidol and aripiprazole versus pimozide. Because there was no study focused on more than 24 weeks in the evaluation of response rate, we could not conduct a sensitivity analysis after omitting trials with a long-term treatment period.

In the meta-regression analysis to assess potential biases in publication year, there was no statistical significance for this variable.

Publication bias

In regard to the primary outcome, according to the funnel plot asymmetry (**Fig. S7**) and Egger's test ($t = 1.66$, $p = 0.132$), we found there is no publication bias for risperidone and haloperidol in improving tic symptom scores outcomes. However in regard to the response rate, according to the funnel plot asymmetry (**Fig. S8**) and Egger's test ($t = -3.34$, $p = 0.007$), publication bias may exist.

Discussion

Statement of main findings

This systematic review and network meta-analysis identified 60 RCTs, providing a comprehensive picture of the efficacy and safety of 11 different types of antipsychotic agents for TDs. In terms of tic symptom score, the existing evidence indicated that haloperidol, risperidone, aripiprazole, quetiapine, olanzapine, and ziprasidone were significantly more effective than placebo in the improvement of tic symptom. Quetiapine was superior to haloperidol, pimozide, risperidone, tiapride, aripiprazole, and penfluridol for improving tic symptom score. Although current evidence showed quetiapine was effective, the number of included RCTs that evaluated the efficacy of quetiapine was very limited, and it has never been studied in a placebo controlled trial. Seventy percent of included RCTs reported specific AEs. Overall, tolerability of atypical antipsychotic drug was better than the typical antipsychotics. Because of the limitations of the number of included studies, the results of the overall SUCRA-based probabilities still need to be treated with caution.

In order to compare the consistency between direct and indirect comparisons for antipsychotic drugs in the treatment of TDs, we estimated the inconsistency factors in closed loop, and the results showed good consistence, except the direct estimate in 1 closed loop (i. e., haloperidol-tiapride-aripiprazole) was not consistent with the indirect estimate, the reasons may be as follows. (1) Tiapride was not approved and seldom used in the United States and the included RCTs of tiapride were all published in Chinese. (2) Fourteen RCTs evaluate the efficacy of tiapride; however, only 5 studies reported outcomes tic symptom score. The lack of RCTs may lead to the inconsistence. We also conducted sensitivity analysis to test the stability of the results, and no material change of the pooled estimated effects was found, but some minor changes were still existing. The potential reasons may be as follows: (1) small sample research may not be representative and low power; (2) results from long-term treatment may be different from that in short-term period treatment, so the sample size and treatment period may have influence on the results of this study.

Quality of the evidence

The main problems of included RCTs in our study are as follows. (1) Most studies were often labeled as "random" without providing details on random sequence generation. (2) The successful implementation of adequately concealed randomization sequences and blinding was not reported in majority of the included RCTs. (3) The majority of included RCTs were conducted in single center and the sample size was relatively small, with few multicenter studies. (4) RCTs focused on the evaluation of short-term efficacy and had no discussion of long-term efficacy. Therefore, the results of the study need to be treated with caution. Further studies should overcome these drawbacks.

Implications for clinical practice

Our study presented that typical antipsychotics (haloperidol, pimozide) were effective; however, these drugs have a poor tolerability profile (i. e., extrapyramidal and metabolic side effects), so they have been replaced stepwise by atypical antipsychotics [86]. The most thoroughly studied atypical antipsychotic to date are risperidone and aripiprazole, which appear to be the most robust evidence-based options for the treatment of TDs, while quetiapine is also a promising therapy. Ziprasidone and olanzapine also could improve tic symptoms, but the evidence is lacking. Among them, ziprasidone can be used for TS patients with baseline obesity or who have other risk factors for metabolic syndrome/diabetes [87]. Olanzapine may be used for the treatment of both tics and some symptoms of psychiatric comorbidities, but the current data supporting such efficacy are very scant. Moreover, the significant weight gain and excessive sedation that are commonly reported as AEs with olanzapine may limit widespread enthusiasm for treating tics with this medication [87]. The evidence of paliperidone and sulpiride was limited with rare clinical application.

Implications for future study

(1) The quality of the included RCTs is not high. It is recommended to carry out high-quality, multicenter, large-sample RCTs to

compare directly different pharmacological treatment. Several promising interventions should be given priority, including quetiapine, ziprasidone, and olanzapine.

(2)RCTs need to be registered in the international clinical trial registry platform to increase the transparency of clinical trials and avoid selective reporting.

(3)Future RCTs should be carried out with international cooperation to evaluate the efficacy and safety of different antipsychotic agents with more accurate dose for TDs in different ethnic groups and try to identify novel targets for improved therapies by the gradual availability of large-scale TS cohorts and novel methodologies for the study of both common and rare genetic variants.

(4)Future studies should pay more attention to long-term outcome measurements, especially outcomes reported by patients or their caregivers.

(5)In this network meta-analysis, there is a lack of evidence of direct comparison between some antipsychotic drugs. The efficacy of 3 interventions (i. e., paliperidone, penfluridol, and sulpiride) was evaluated in only 1 RCT. Future RCTs with direct comparison are needed in the future.

Limitations of the study

First, most of the included studies were conducted in a single center with a small sample. Therefore, the efficacy of antipsychotic agents needs to be tested in other ethnicities. Second, the outcome measurements varied across different studies, which made it difficult to compare the efficacy among different studies. Third, there was a lack of long-term evaluation of outcomes in the included studies. Fourth, monitoring the quality of implications and reporting of trials was difficult because of the lack of clinical trial registration, and publication bias may exist. 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.

Conclusion

Atypical antipsychotics (risperidone and aripiprazole) appear to be the most robust evidence-based options for the treatment of TDs. Quetiapine may be a promising therapy. Ziprasidone and olanzapine are also effective, but the evidence is lacking. Further high-quality directly comparing different pharmacological treatment studies are justified.

Contributions

Chunsong Yang and Zilong Hao contributed equally to this study.

Chunsong Yang: 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.

Zilong Hao: 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.

Ling-Li Zhang: 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.

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

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

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

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Conflict of Interest

No author declares any conflict of interest.

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