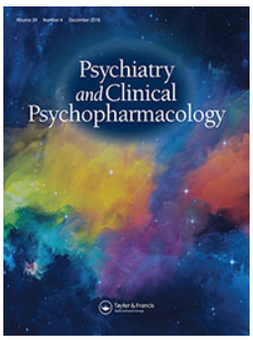

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Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Jianjie Huang, Min Chen, Ce Chen, Xiaodong Lin, Deguo Jiang, Yonghui Zhang, Lina Wang, Chuanjun Zhuo, Hongjun Tian & Chenyuan Du (2019) Efficacy and acceptability of three prolactin-sparing antipsychotics in patient with schizophrenia: a network meta-analysis, Psychiatry and Clinical Psychopharmacology, 29:4, 369-378, DOI: 10.1080/24750573.2019.1662629

To link to this article: https://doi.org/10.1080/24750573.2019.1662629

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2019, VOL. 29, NO. 4, 369–378
https://doi.org/10.1080/24750573.2019.1662629

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Efficacy and acceptability of three prolactin-sparing antipsychotics in patient with schizophrenia: a network meta-analysis

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ABSTRACT

Background: The present study aimed to systematically evaluate three prolactin-sparing antipsychotics for treating schizophrenia.

Methods: We performed a meta-analysis of three prolactin-sparing antipsychotics in patients with schizophrenia. Endpoints of interest were the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions-Severity (CGI-S) and acceptability (all cause discontinuation).

Results: A total of 12 trials (2,723 patients) and three drugs (aripiprazole, quetiapine, and ziprasidone) were included. On the PANSS scale, aripiprazole (mean difference [MD]: −6.98, 95% CrI: −12.35, −1.38) was statistically more effective than placebo. When assessed by BPRS, aripiprazole (MD: −9.01, 95% CrI: −15.81, −3.12), quetiapine (MD: −7.13, 95% CrI: −9.78, −4.29) and ziprasidone (MD: −4.97, 95% CrI: 9.96, −0.21) had greater efficacy, when compared to placebo. Regarding CGI-S, quetiapine (MD: −0.55, 95% CrI: −0.82, −0.25) was significantly superior to placebo. In terms of acceptability, aripiprazole (OR: 0.54, 95% CrI: 0.41, 0.73), quetiapine (OR: 0.49, 95% CrI: 0.36, 0.68) and ziprasidone (OR: 0.68, 95% CrI: 0.48, 0.96) were more acceptable than placebo. The benefit risk analysis revealed that quetiapine has the best efficacy and acceptability profile among the three prolactin-sparing antipsychotics.

Conclusions: Quetiapine may offer an optimal benefit-risk balance when a prolactin-sparing antipsychotic is indicated.

ARTICLE HISTORY
Received 22 July 2019
Accepted 29 August 2019

KEYWORDS
Schizophrenia; prolactin sparing antipsychotic; network meta-analysis; efficacy; acceptability; bebifit-risk balance

Introduction

Schizophrenia is a severe psychiatric disorder that originates from the dysfunction of dopaminergic neurotransmission and disturbances in synaptic function caused by genetic or environmental factors, or both [1]. Long-term maintenance treatment with antipsychotic drugs remains as the main treatment approach, and approximately 20 antipsychotic medications are presently available [2]. These drugs have the capability to acutely or chronically block dopaminergic D2 receptors, to a certain extent [3]. Since the inhibitory action of dopamine is responsible for physiological prolactin secretion, the chronic blockade of the dopamine D2 receptor could lead to the elevation of prolactin in blood serum through the disruption of the tonic dopamine inhibition of prolactin secretion, which is medically termed as hyperprolactinemia [4,5].

Antipsychotics differ in propensity to induce and sustain hyperprolactinemia due to the difference in receptor binding profiles and systemic actions [6]. Antipsychotic-induced hyperprolactinemia could occur in 70% of patients with schizophrenia, depending on the medication used [7]. Furthermore, prolactin has over 300 separate biological activities [8], and it is mainly responsive for the lactation in females, as well as the regulation of gonadotropic and reproductive hormones in both women and men.

The sustained elevation of prolactin above the upper limits of normal could lead to galactorrhea, breast enlargement, hypogonadism and sexual dysfunction [9–11]. Chronic hyperprolactinemia can also contribute to osteopenia and osteoporosis [12]. cardiovascular disease, autoimmune activation [13], and breast cancer [14]. There are several strategies for the management of antipsychotic-induced hyperprolactinemia [15], such

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Supplemental data for this article can be accessed https://doi.org/10.1080/24750573.2019.1662629

as discontinuing the drug or switching to other antipsychotics, and adding a dopamine agonist to the treatment regime. However, most guidelines caution these treatment approach, because it might exacerbate psychosis in patients with schizophrenia [16]. Switching from prolactin-elevating to prolactin-sparing agents may provide an optimal solution for long-term antipsychotic therapy with relatively less risk of hyperprolactinemia and associated morbidity [15,17–19].

Prolactin-sparing agents are antipsychotics that might lead to a slight or transient increase in prolactin level within the upper limit of normal, and lower frequencies of hyperprolactinemia-associated side effects [20–22]. There is a general consensus that aripiprazole, quetiapine and ziprasidone are less likely to increase prolactin levels (prolactin-sparing) [15,20,22,23]. Although these prolactin-sparing antipsychotics have been evaluated in many clinical trials, there are still varying conclusions regarding the efficacy and acceptability. In order to provide useful evidence for clinical practice, it is of great importance to generate clear hierarchies for the efficacy and acceptability of these drugs. Therefore, a network meta-analysis was performed to comprehensively compare and rank the comparative performance of three prolactin-sparing antipsychotics for patients with schizophrenia.

Methods

Search strategy

The present systematic review and network meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline for Network Meta-Analyses [24]. A systematic review of articles published up to the 1st of March 2019 in Medline (*via* PubMed) and Web of Science was conducted. The following keywords were used: "schizophrenia", "aripiprazole", "quetiapine", "ziprasidone", and "randomized controlled trial". The search was limited to randomized controlled trials (RCTs) published in the English language. Full-text articles were chosen after screening the abstracts. The references obtained from retrieved publications were manually searched to identify potential studies.

Inclusion criteria and study selection

Studies that met the inclusion criteria were included: (i) Patients: Schizophrenia, schizoaffective disorder, or schizophreniform disorder as defined by any diagnostic criteria. (ii) Intervention: Acute treatment (4–12 weeks) with one of three prolactin-sparing antipsychotics (15–30 mg/day of aripiprazole, 400–1,000 mg/day of quetiapine, and 120–200 mg/day of ziprasidone) [25] as monotherapies, including both flexible and fixed-dose studies. (iii) Comparator: Placebo or another agent of the five mentioned above. (iv) Outcomes: Primary outcomes were the mean change in the total score of the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impressions-Severity (CGI-S) score from baseline to endpoint. The secondary outcome was acceptability (the proportion of patients who left the study early for any reason). (v) Study design: Randomized controlled trial (RCT).

The exclusion criteria were as follows: (a) studies without a designated intervention/comparator arm; (b) studies in which anti-Parkinson drugs were given prophylactically; (c) long-term studies without data for a 4–12-week period; (d) studies not reported in the English language. Two authors independently reviewed all retrieved studies according to the inclusion and exclusion criteria. Any inconsistencies were resolved by discussion or arbitrated by a third senior author.

Data extraction

Two researchers independently reviewed the full text to extract information using a structured data abstraction form. The information included the study design, patient characteristics, follow-up duration, treatment protocols, outcomes, etc. The original articles were double-checked when inconsistencies were found. Any disagreement regarding the data extraction and quality assessment was determined by a third senior investigator. Two individuals within the reviewing team independently reviewed the references and abstracts retrieved by the search, assessed the completeness of the data abstraction, and confirmed the quality rating. A structured data abstraction form was used to ensure the consistency of the appraisal for each study. The investigators were contacted and inquired to obtain data to supplement the incomplete reporting of original articles.

Risk of bias assessment

Two review authors assessed the risk of bias of the included studies using the methods recommended by the Cochrane Collaboration for the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting [26]. A summary of findings tables was created for every rated outcome following the Cochrane-compliant rules. Disagreements were initially resolved by discussion and consulted with a third senior author for arbitration.

Statistical analysis

The network meta-analysis for PANSS, BPRS, CGI-S and acceptability, and multicriteria benefit-risk analysis [27] were performed. All data were comprehensively

analyzed using the ADDIS software [28,29] (version 1.16, https://drugis.org/software/addis1/addis1.16), based on the Bayesian framework. Random effect and consistency models were used with the ADDIS parameter (number of chains, 4; tuning iterations, 20,000; simulation iterations, 50,000; thinning interval, 10; inference samples, 10,000; variance scaling factor, 2.5). Convergence was assessed using the Brooks-Gelman-Rubin method, with the potential scale reduction factor (PSRF) as an indicator. A PSRF close to 1 indicates that an approximate convergence has been reached, while a PSRF of <1.2 was considered acceptable. Inconsistencies between the direct effect and indirect effect was assessed by node-splitting analysis.

Results

Characteristics of the included studies

The literature search identified a total of 1,436 studies. Based on the inclusion and exclusion criteria, 12 RCTs [30–41] were eligible for inclusion for the present study (Figure 1), which included a total of 2,723 patients with schizophrenia. Furthermore, the efficacy (PANSS, BPRS and CGI-S) and acceptability of the three prolactin-sparing antipsychotics (aripiprazole, quetiapine and ziprasidone) were analyzed. The earliest study was conducted in 1997, while the latest study was conducted in 2017. In general, the age of onset ranged within 13–30 years old, and the age of these patients ranged within 15–42 years old. Males accounted for more than 50% of the subjects in the included trials (Table 1). In terms of study quality, 10 (83.3%) trials were rated as low risk of bias, while two (16.7%) trials were rated as unclear risk of blinding of participants and personnel, and blinding of outcome assessment (sFigure 1 and sFigure 2). The network graphical structure displayed the available direct comparisons of the network of trials for efficacy and safety (sFigure 3).

Network meta-analysis of efficacy

A total of nine articles provided raw PNASS data (Figure S3-A), and the overall effects revealed that aripiprazole (MD: −6.98, 95% CrI: −12.35, −1.38) was significantly more effective than placebo (Table 2). Furthermore, the probabilities of rank 1 plot for PANSS were as follows: 47% for aripiprazole, 44% for quetiapine, 9% for ziprasidone, and 0 for placebo. Among these interventions, rank 1 was the best, while rank 4 was the worst (sTable 1).

A total of seven literatures reported the BPRS (Figure S3-B). The results demonstrated that aripiprazole (MD: −9.01, 95% CrI: −15.81, −3.12), quetiapine (MD: −7.13, 95% CrI: −9.78, −4.29) and ziprasidone (MD: −4.97, 95% CrI: 9.96, −0.21) have greater efficacy, when compared to placebo (Table 2). The probabilities of aripiprazole, quetiapine, ziprasidone and placebo, based on the

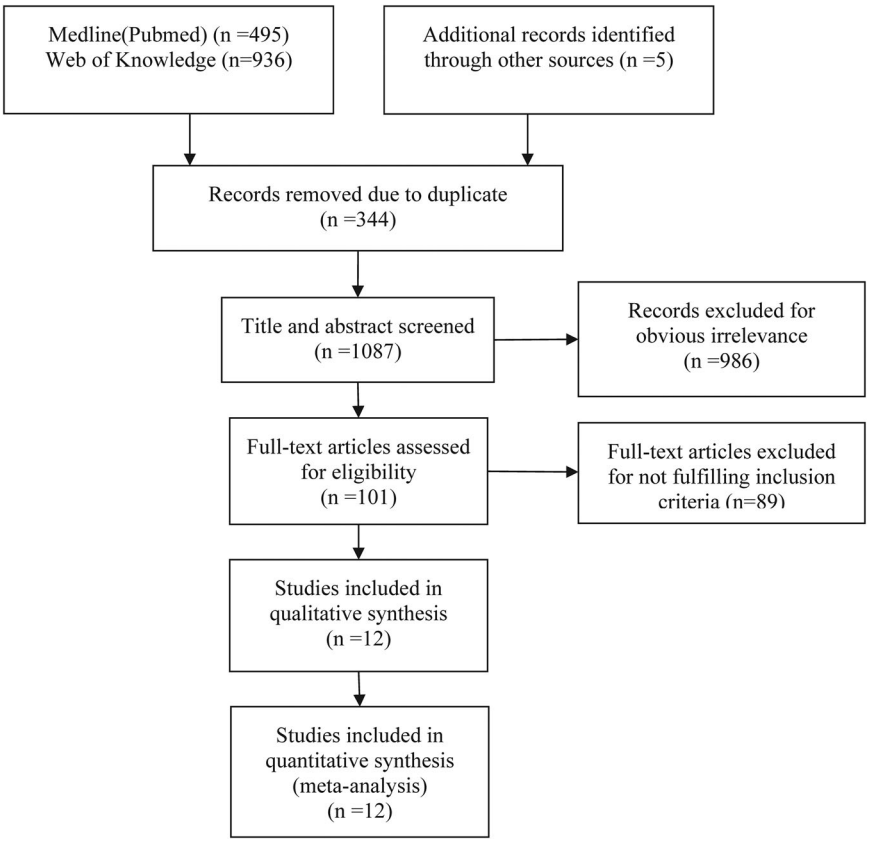

Figure 1. Flowchart of the literature search and study selection.

Table 1. Baseline characteristics of the included studies.

Study	Treatment group	N of patients	Duration (w)	Age	Male (%)
[40]	Quetiapine 750 mg/d	96	6	36 ± 9	69.0
	placebo	96		38 ± 10	67.0
[30]	Quetiapine 750 mg/d	54	6	35 ± 10	70.4
	Quetiapine 600 mg/d	51		39 ± 8	74.5
	Quetiapine 300 mg/d	52		38 ± 9	71.2
	Placebo	51		36 ± 8	80.4
[38]	Ziprasidone 120 mg/d	47	4	38.8 (19–59)	83.0
	Placebo	48		39.0 (21–76)	85.0
[41]	Aripiprazole 10–30 mg/d	128	4	39.8	63.0
	Ziprasidone 80–160 mg/d	125		40.8	71.0
[33]	Ziprasidone 160 mg/d	149	4	40.0 ± 9.9	75.8
	Placebo	149		40.7 ± 10.4	76.5
[37]	Aripiprazole 12–30 mg/d	21	8	42.1 ± 12.4	38.0
	Quetiapine 300–750 mg/d	20		39.8 ± 11.2	20.0
[36]	Quetiapine 800 mg/d	74	6	15.45 ± 1.34	59.5
	Quetiapine 400 mg/d	73		15.45 ± 1.25	58.9
	Placebo	73		15.34 ± 1.39	57.5
[32]	Aripiprazole 3–30 mg/d	81	6	32.6 ± 11.1	48.7
	Quetiapine 100–600 mg/d	73		31.0 ± 9.2	66.1
[35]	Ziprasidone 40–160 mg/d	193	6		56.5
	Placebo	90			68.9
[39]	Aripiprazole lauroxil 882 mg/m	208	12	39.7 ± 11.1	68.8
	Aripiprazole lauroxil 441 mg/m	207		39.9 ± 10.1	68.1
	Placebo	207		39.5 ± 11.9	66.8
[34]	Aripiprazole 10 mg/d	150	6	39.3 ± 10.8	61.8
	Placebo	149		38.2 ± 11.3	63.4
[31]	Aripiprazole 15 mg	20	4	35 ± 10	90.0
	placebo	38		36 ± 12	71.0

Note: w; weekly; d: daily; m: monthly.

BPRS to be the best intervention, were 73%, 24%, 3% and 0%, respectively (sTable 1).

A total of 10 studies reported the CGI-S (Figure S3-C). The present overall analysis indicated that quetiapine (MD: −0.55, 95% CrI: −0.82, −0.25) was significantly superior to placebo (Table 3). The probabilities of aripiprazole, quetiapine, ziprasidone and placebo, based on the CGI-S to be the best intervention, were 8%, 79%, 13% and 0%, respectively (sTable 1).

Network meta-analysis of acceptability

A total of 12 studies were analyzed for acceptability (Figure S3-D), and the pooled estimates revealed that aripiprazole (OR: 0.54, 95% CrI: 0.41, 0.73), quetiapine (OR: 0.49, 95% CrI: 0.36, 0.68) and ziprasidone (OR: 0.68, 95% CrI: 0.48, 0.96) have statistically lesser patients who discontinued treatment due to any reason, when compared to placebo (Table 3). The probabilities of the five prolactin-sparing second-generation antipsychotics, based on acceptability to be best intervention, were 31% for aripiprazole, 66% for quetiapine, 3% for ziprasidone, and 0% for placebo (sTable 1).

Overall rank according to the risk-benefit profile

The multicriteria benefit-risk analysis, with PANSS, BPRS and CGI-S as benefit and acceptability as risk, were generally consistent with the results of the network

Table 2. Network meta-analysis for PANSS and BPRS.

Aripiprazole	−1.88 (−8.91, 3.97)	−4.06 (−10.22, 1.53)	**−9.01 (−15.81, −3.12)**
−0.31 (−9.13, 8.63)	Quetiapine	−2.14 (−7.30, 3.33)	**−7.13 (−9.78, −4.29)**
−3.42 (−11.22, 4.51)	−3.18 (−12.95, 6.91)	Ziprasidone	**−4.97 (−9.96, −0.21)**
−6.98 (−12.35, −1.38)	−6.66 (−13.57, 0.23)	−3.54 (−10.53, 3.46)	Placebo
Treatment	PANSS (MD, 95%CrI)		BPRS (MD, 95%CrI)

Comparisons between drugs should be read from left to right. The estimates are located at the crossing between the column-defining treatment and row-defining treatment. For PANSS and BPRS, an MD lower than 0.00 favours the column-defining treatment. The significant results are presented in bold. PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; MD, mean difference; CrI, credible interval.

Table 3. Network meta-analysis for acceptability and tolerability.

Aripiprazole	0.30 (−0.20, 0.72)	0.07 (−0.42, 0.52)	−0.25 (−0.68, 0.13)
1.11 (0.72, 1.74)	Quetiapine	−0.23 (−0.67, 0.28)	**−0.55 (−0.82, −0.25)**
0.80 (0.55, 1.18)	0.72 (0.45, 1.17)	Ziprasidone	−0.32 (−0.73, 0.06)
0.54 (0.41, 0.73)	**0.49 (0.36, 0.68)**	**0.68 (0.48, 0.96)**	Placebo
Treatment	Acceptability (OR, 95%CrI)		CGI-S (MD, 95%CrI)

Comparisons between drugs should be read from left to right. The estimates are located at the crossing between the column-defining treatment and row-defining treatment. For acceptability, an OR lower than 1.00 favuors the column-defining treatment. For CGI-S, an MD lower than 0.00 favours the column-defining treatment. The significant results are presented in bold. Acceptability, the proportion of patients who discontinued the study early due to any reason; CGI-S, Clinical Global Impressions of severity scale; OR, odds ratio; MD, mean difference; CrI, credible interval.

Table 4. Summary for the benefit risk analysis.

	Outcome	Type	Placebo	PSA	Difference (95% CI)
Aripiprazole vs Placebo					
Benefit	BPRS	Continuous	−3.50 (−8.90, 1.91)	−12.64 (−20.96, −4.32)	**−9.14 (−15.47, −2.82)**
Benefit	CGI severity	Continuous	−0.37 (−0.71, −0.03)	−0.63 (−1.15, −0.10)	−0.26 (−0.65, 0.14)
Benefit	PANSS	Continuous	−12.02 (−17.31, −6.74)	−18.95 (−26.45, −11.46)	**−6.93 (−12.24, −1.62)**
Risk	Acceptability	Rate	0.49 (0.41, 0.58)	0.35 (0.25, 0.45)	**0.54 (0.41, 0.72)**
Quetiapine vs Placebo					
Benefit	BPRS	Continuous	−3.50 (−8.90, 1.91)	−10.60 (−16.65, −4.56)	**−7.10 (−9.81, −4.40)**
Benefit	CGI severity	Continuous	−0.37 (−0.71, −0.03)	−0.92 (−1.36, −0.48)	**−0.55 (−0.83, −0.27)**
Benefit	PANSS	Continuous	−12.02 (−17.31, −6.74)	−18.69 (−27.21, −10.18)	−6.67 (−13.34, 0.00)
Risk	Acceptability	Rate	0.49 (0.41, 0.58)	0.32 (0.23, 0.44)	**0.49 (0.35, 0.69)**
Ziprasidone vs Placebo					
Benefit	BPRS	Continuous	−3.50 (−8.90, 1.91)	−8.53 (−15.75, −1.30)	**−5.03 (−9.82, −0.23)**
Benefit	CGI severity	Continuous	−0.37 (−0.71, −0.03)	−0.69 (−1.20, −0.18)	−0.32 (−0.70, 0.05)
Benefit	PANSS	Continuous	−12.02 (−17.31, −6.74)	−15.57 (−24.20, −6.95)	−3.55 (−10.36, 3.26)
Risk	Acceptability	Rate	0.49 (0.41, 0.58)	0.40 (0.29, 0.52)	**0.68 (0.48, 0.95)**

PSA: Prolactin Sparing Antipsychotics; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale, CGI-S, Clinical Global Impressions of severity scale, Acceptability, the proportion of patients who discontinued the study early due to any reason. The significant results are presented in bold.

meta-analysis. Aripiprazole (MD: −6.93, 95%CI: −12.24, −1.62) and quetiapine (MD: −0.55, 95%CI: −0.83, −0.27) could significantly alleviate the clinical symptoms of schizophrenia in terms of PANSS and CGI-S, respectively. Furthermore, aripiprazole (MD: −9.14, 95%CI: −15.47, −2.82), quetiapine (MD: −7.10, 95%CI: −9.81, −4.40) and ziprasidone (MD: −5.03, 95%CI: −9.82, −0.23) could significantly improve the clinical symptoms of schizophrenia in terms of BPRS. Moreover, aripiprazole (OR: 0.54, 95% CrI: 0.41, 0.72), quetiapine (OR: 0.49, 95% CrI: 0.35, 0.69) and ziprasidone (OR: 0.68, 95% CrI: 0.48, 0.95) were acceptable, when compared to placebo (Table 4). Considering the risk–benefit profile, the overall rank of these three prolactin-sparing antipsychotics were quetiapine, aripiprazole and ziprasidone (Figure 2).

Consistency and convergence analysis

Regarding the node-splitting analysis of inconsistency, no inconsistency factors were identified (P-value >0.05 in all analyses), indicating the robustness of the present network. Furthermore, all PSRF values for PANSS, BPRS, CGI-S, and acceptability were <1.02, which demonstrate that the present analysis achieved good convergence.

Discussion

The present study provides not only evidence-based hierarchies, but also a benefit risk analysis for the efficacy and acceptability of these three prolactin-sparing antipsychotics for patients with schizophrenia. In addition, flexible and fixed dose monotherapy were included for these three prolactin-sparing antipsychotics, which are similar to a previous network meta-analysis of 15 antipsychotic drugs in schizophrenia [25], and the target doses were up to the maximum doses for fixed-dose studies, based on the international consensus [42]. Although these three antipsychotics are known as prolactin-sparing potency drugs, these could also induce hyperprolactinemia and side effects potentially related to hyperprolactinemia [43]. Thus, monitoring prolactin levels among patients receiving prolactin-sparing antipsychotics is recommended [22].

Although aripiprazole has high affinity for the D2 receptor, it has low rates of hyperprolactinemia similar to clozapine (<5%), which is presumably due to the partial agonist at the D2 receptor [44–46]. Both short- and long-term studies have revealed minimal increases or decreases in prolactin levels in patients with aripiprazole [45,47,48]. Three studies reported aripiprazole-related new-onset hyperprolactinemia [45,49,50]. Aripiprazole even revealed a lower

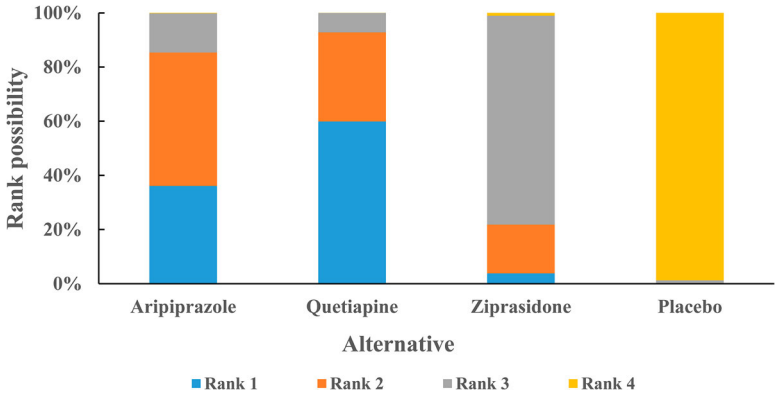

Figure 2. The overall benefit-risk rank to be the best treatment in terms of PANSS, CGI-S, BPRS, acceptability. Rank 1 is the best; rank n is the worst.

likelihood of prolactin elevation, when compared to other prolactin-sparing antipsychotics [47,51]. The prevalence rate of aripiprazole-induced hyperprolactinemia was 3.1–9.0% [45,46,50,52–55].

The findings of the two RCTs supports that quetiapine is a relatively prolactin-sparing antipsychotic [30,56]. A great number of studies have shown that quetiapine induces virtually no elevation of prolactin in the blood [30,57–63]. In addition, the prolactin level during treatment with quetiapine, and after switching, decreased [64–67], even returned to normal values [68–72]. Meanwhile, few data suggests that quetiapine can bring about a transient increase in prolactin levels [57,58,73]. Quetiapine correlated low prevalence rates of hyperprolactinemia has been reported to range within 0–29% [74–77].

Ziprasidone was associated with transient elevations in prolactin, which could return to normal levels within the dosage interval [78]. Similar effects on prolactin have been observed in studies of ziprasidone in healthy volunteers [79]. Most reports have indicated that ziprasidone use is associated with a low incidence of prolactin elevation and low to moderate levels of hyperprolactinemia [57,58,61,80,81]. Some studies revealed that treatment with ziprasidone leads to decreased prolactin levels for six weeks [82], 4–8 weeks [83], 18 weeks [84], 44 weeks [85] and one year [86], respectively. However, few trials also reported that ziprasidone induced hyperprolactinemia [87–92].

The most important clinical implication of these findings was that quetiapine should be the best choice when starting a prolactin-sparing antipsychotic for schizophrenia patients due to the best balance between efficacy and acceptability. The results of the present analysis apply only for the acute treatment (4–12 weeks) of schizophrenia. Medical practitioners need to determine whether (and to what extent) these prolactin-sparing antipsychotics work within a clinically reasonable duration. In clinic, the evaluation of efficacy and acceptability after 12 weeks might lead to marked differences in treatment outcome. Globally, the age-standardized prevalence of schizophrenia in 2016 was estimated to be 0.28%, and prevalent cases increased from 13.1 million in 1990–20.9 million cases in 2016, which contributes 13.4 million years of life lived with disability to the burden of the disease globally [93]. Overall, for patients with schizophrenia, approximately half of women of reproductive age and men have elevated prolactin [75,94]. Optimally, patients with hyperprolactinemia secondary to antipsychotic drug treatment should be switched to a prolactin-sparing antipsychotic [95].

The present network meta-analysis was designed according to the standards of the PRISMA-NMA [24] principle. To our knowledge, the present network meta-analysis is the first to address the comparative effects of different prolactin-sparing antipsychotics with the explicit rankings of each outcome and the overall benefit-risk profile. Thus, these present findings may be useful to clinicians in deciding which drug to use. Industry sponsorship might influence the results of the biomedical research, because most studies that validate the newest antipsychotics are supported by pharmaceutical companies that market these drugs [96]. However, network meta-analysis incorporating indirect and direct comparisons could decrease the risk for possible sponsorship bias.

Care should be given in interpreting these conclusions due to the limitations of the present study. First, the present study included a limited number of trials, and some of the estimated results of the analysis relied on indirect comparisons. Second, the potential confounders of the primary studies, especially dose issues, might have influenced the validity of these findings. Third, most of the included studies were placebo-controlled trials, which are mainly designed to meet both ethical and safety requirements for regulatory approval. However, patients from these trials were more likely to be mild [97]. Therefore, a well-designed randomized controlled trial that compares different prolactin-sparing antipsychotics in schizophrenia patients with or without antipsychotic-induced hyperprolactinemia is required to formally determine the comparative benefit-risk profile of each drug.

Conclusion

Considering the low rate of hyperprolactinemia and the highest overall rank possibility, quetiapine may offer an optimal benefit-risk balance when a prolactin-sparing antipsychotic is indicated.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81871052 to C.Z., 81801679 and 81571319 to Y.X.), the Key Projects of the Natural Science Foundation of Tianjin (17JCZDJC35700 to C.Z.), the Tianjin Municipal Health Bureau (2014KR02 to C.Z.), the National Key Research and Development Program of China (2016YFC1307004 to Y.X.), the Shanxi Science and Technology Innovation Training Team's Multidisciplinary Team for Cognitive Impairment (201705D131027 to Y.X.), Zhejiang Public Welfare Fund Project (LGF18H090002 to D.J), Tianjin Anding Hospital Outstanding Award rewarding 300000 yuan to C.Z., and the key project of Wenzhou Science and Technology Bureau (ZS2017011 to X.L).

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