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Comparative efficacy and tolerability of antipsychotics as augmentations in adults with treatment-resistant obsessive-compulsive disorder: A network meta-analysis

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ABSTRACT

We performed a network meta-analysis to build clear hierarchies of efficacy and tolerability of antipsychotics to augment serotonin reuptake inhibitors (SRIs) for treatment-resistant obsessive-compulsive disorder (OCD) in adults. PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched on September 8, 2018. Randomized controlled trials investigating antipsychotics as augmentation agents were included. Network meta-analyses were performed using frequentist methods. Efficacy was measured by the Yale-Brown Obsessive-Compulsive Scale. Tolerability was measured by side-effect discontinuations. Mean differences (MDs) and odds ratios (ORs) were reported with 95% confidence intervals (CIs). Twenty articles with 790 patients were included. Our analyses showed that there was no significant difference in efficacy between antipsychotic agents. The order of efficacy rankings was inconsistent between primary analysis and sensitivity analyses. We found that there was considerable heterogeneity between studies. Comorbid tics was identified as a significant moderator. All antipsychotics except paliperidone were significantly superior to placebo in the subgroup without comorbid tics, while no antipsychotics was significantly superior to placebo in the comorbid tics subgroup. With respect to tolerability, quetiapine (OR, 3.45; 95% CI, 1.04–11.11) and paliperidone (20.00; 1.01- > 100) were significantly less tolerable than placebo. Based on this network meta-analysis, antipsychotic agents as augmentations to SRIs might be more effective in treatment-resistant OCD patients without comorbid tics. Definitive determination of which drug is optimal cannot be drawn currently because of the limited numbers of studies and heterogeneity across studies.

1. Introduction

About 1.1–1.8% of population is diagnosed with obsessive-compulsive disorder (OCD) every year (American Psychiatric Association, 2013). Obsessions refer to recurrent and intrusive thoughts, urges, or images that generally cause notable distress and anxiety. Compulsions refer to repetitive behaviors that often occur after obsessions to relieve the secondary anxiety caused by the obsessions. This relief is transient and the anxiety and obsessions often return soon. The patients become stuck in this vicious circle, wasting much time. The patients know that they should not think or act repeatedly; nevertheless, symptoms are overwhelming and incontrollable. OCD patients experience extreme distress from these irresistible symptoms. Generally, family members have to accommodate themselves to the needs of OCD patients. Severe symptoms often render patients unable to work, to care for family, or even to take care of themselves. Patients often lose their source of income, and must spend considerable amounts of money on treatments. Therefore, OCD causes substantial family burdens (Vikas et al., 2011). First-line treatments for OCD have been established, primarily including exposure with response prevention (ERP), and serotonin reuptake inhibitors (SRIs) (Katzman et al., 2014). Nevertheless, about 40%–60% OCD patients do not obtain full response after SRI treatment (Pallanti and Quercioli, 2006). Alternatives include intravenous clomipramine, intravenous citalopram, or adding another drug as an augmentation agent, generally one with a different mechanism (Albert et al., 2017; Katzman et al., 2014). Currently, most strategies involve

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augmentation with antipsychotic agents (Albert et al., 2017).

Randomized controlled trials (RCTs) addressing antipsychotic augmentations have been performed; however, their results were controversial (Albert et al., 2017). Several conventional pair-wise meta-analyses have been performed; RCTs comparing antipsychotics and placebos were included (Bloch et al., 2006; Dold et al., 2013, 2015; Fineberg et al., 2006; Komossa et al., 2010; Skapinakis et al., 2007; Veale et al., 2014). The latest meta-analysis was published in 2015 (Dold et al., 2015), including 14 studies with 491 participants; that study concluded that antipsychotics are effective augmentation agents. Regarding individual agents, aripiprazole, risperidone, and haloperidol were found to be significantly superior to placebos. Head-to-head RCTs addressing this issue have also been conducted (Assarian et al., 2018; Atmaca et al., 2002; Maina et al., 2008; Selvi et al., 2011; Shoja Shafti and Kaviani, 2015). However, previous meta-analysis did not include these kinds of studies. Moreover, pair-wise meta-analyses could only provide evidences from direct comparisons; therefore, their results were incomprehensive with respect to antipsychotic augmentation of SRIs. Network meta-analysis is a powerful method, providing evidence from both direct and indirect comparisons, and can include both placebo-controlled and head-to-head RCTs. Moreover, clear hierarchies of various treatments can be made according to the surface under the cumulative ranking curve (SUCRA) (Salanti et al., 2011). In the present case, it is necessary to perform this network meta-analysis. We provided comprehensive evidence and built clear hierarchies of efficacy and tolerability of antipsychotics as augmentation agents to SRIs for treatment-resistant adult OCD patients.

2. Methods

Our study was registered with PROSPERO (CRD42018103031).

2.1. Literature search and inclusion criteria

PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched on September 8, 2018. We also screened the references of previous meta-analyses and all included studies to identify additional studies. A predefined search strategy was used to identify relevant articles. Search strategies of each electronic database are described in detail in the online supplementary materials. Two researchers independently retrieved the studies according to predefined inclusion and exclusion criteria. Any disagreement was resolved by discussion of all members. The inclusion criteria included the following items: a) RCTs with double-blind, single-blind, or open-label design, written in English and published in peer-review journals; b) participants diagnosed with OCD according to an acknowledged diagnostic criteria, and did not obtain full response after at least one trial of SRI at adequate dose and duration; c) intervention should be antipsychotic agent augmentation to SRIs; d) controlled condition included placebo or another antipsychotic augmentation agent; e) treatment efficacy was measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS). Any article that did not meet inclusion criteria was excluded.

2.2. Data extraction

Two researchers extracted data of included articles according to a predefined form independently. Any disagreement was resolved by discussion of all members. The following items were extracted: a) study characteristics (first author name, publication year, blind design, treatment resistant description, sample size of each arm); b) participant characteristics (female percentage, mean age, illness duration, previous SRI duration, previous SRIs and their doses, baseline severity, and comorbidities); c) intervention characteristics (name and dose of antipsychotic agents, treatment duration); d) outcome measures (dropouts due to adverse events, change from baseline or end-point of YBOCS scores). We used change from baseline of YBOCS scores as measurement of efficacy. If this was not available, we used endpoint YBOCS score instead. Intention-to-treat (ITT) data was used if available. Only phase one data was included for crossover trials. Missing standard deviation (SD) can be calculated if P value or F value are reported, or by introducing the correlation coefficient (Julian PT Higgins and Green, 2011). We used side-effect discontinuation as measurement of tolerability. Risk of bias was assessed according to Cochrane Handbook 5.1.0 (Julian PT Higgins and Green, 2011). We defined a study having an overall high risk of bias, if it met any of the following criteria: at least two domains at high risk of bias; at least three domains at unclear risk of bias; two domains at unclear risk of bias and one domain at high risk of bias.

2.3. Statistical process

Network meta-analyses were conducted using frequentist methods, by network package in STATA software (14.2) (Salanti et al., 2011). Global inconsistency was assessed using the Higgins' model (Higgins et al., 2012). Local inconsistency was assessed using node-splitting method (Dias et al., 2010). We ranked all antipsychotics according to the SUCRA of efficacy and tolerability. Adjusted funnel plots were generated to assess publication bias. Mean differences (MD) for continuous variables and odds ratios (OR) for binary variables were calculated as effect size, both with 95% confidence intervals (CI). League tables were presented to summarize the results of network meta-analyses. Meta-regression and subgroup analyses were conducted using a Bayesian framework. Markov chain Monte Carlo (MCMC) method was used to obtain posterior statistics of parameters of interest. The posterior median of SD (standard deviation) was used to evaluate the between-study heterogeneity. Model was adapted from Program 3(a) (for categorical variables) and Program 4(a) (for continuous variables) (Dias et al., 2011). Subgroup analyses and meta-regressions were conducted using OpenBUGS (version 3.2.3) with the following steps: a, check model (model was presented in the supplementary materials); b, load data (raw data for subgroup analysis was presented in the supplementary materials); c, input the number of Markov chains, we set three chains, then compile the model; d, model initialization; e, set nodes of interest such as MD, SUCRA, interaction term (B) and heterogeneity (SD); f, update the model. Posterior statistics of the nodes were based on 200,000 iterations after a burn-in of 50,000. Predefined meta-regression and subgroup analysis included the following moderators: baseline severity, illness durations, trial duration, and comorbidities. We classified studies including any proportion of patients with comorbid tics or depression into the comorbid tics or depression subgroup. Predefined sensitivity analysis was conducted after excluding studies with an overall high risk of bias.

3. Results

A total of 782 records were identified by electronic search. After review of abstracts, titles, and full text, 20 articles with 790 patients were finally included in the analysis (Assarian et al., 2018; Atmaca et al., 2002; Bystritsky et al., 2004; Carey et al., 2005; Denys et al., 2004a; Diniz et al., 2011; Erzegovesi et al., 2005; Fineberg et al., 2005; Hollander et al., 2003; Kordon et al., 2008; Maina et al., 2008; McDougle et al., 1994, 2000; Muscatello et al., 2011; Sayyah et al., 2012; Selvi et al., 2011; Shapira et al., 2004; Shoja Shafti and Kaviani, 2015; Simpson et al., 2013; Storch et al., 2013). A flow chart of study selection is presented in Fig. 1. Most trials (80%) were placebo-controlled studies, and only four studies (20%) were head-to-head RCTs. Antipsychotic augmentation agents included aripiprazole, risperidone, quetiapine, olanzapine, haloperidol, and paliperidone. Treatment duration varied from 4 to 16 weeks. Three studies were single-blind RCTs and 17 were double-blind RCTs. Characteristics of included studies are described in Supplemental Table S1. A network map is presented in Fig. 2. Ten studies (50%) were assessed as having a high risk

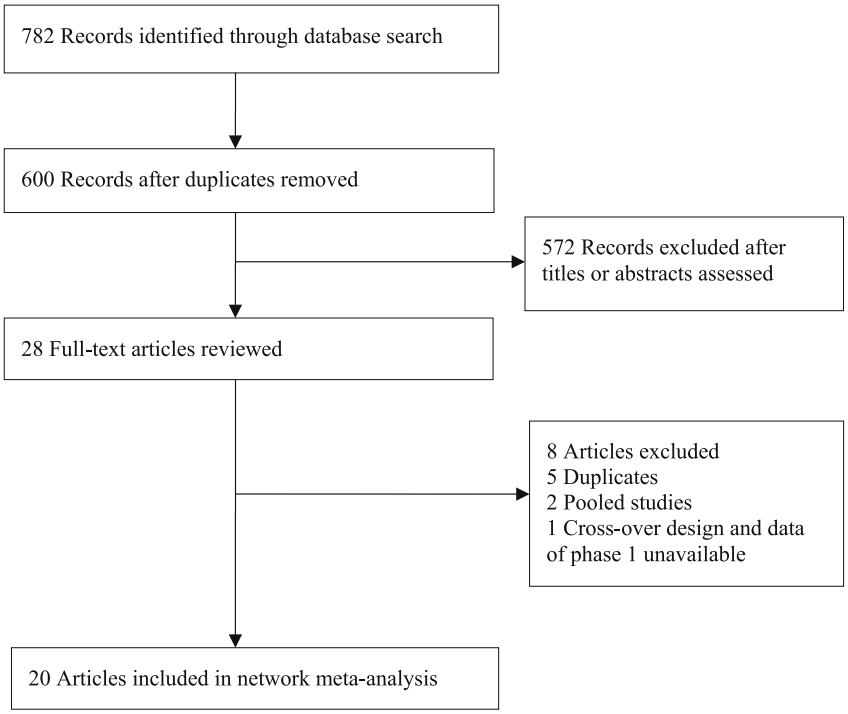

Fig. 1. Study selection.

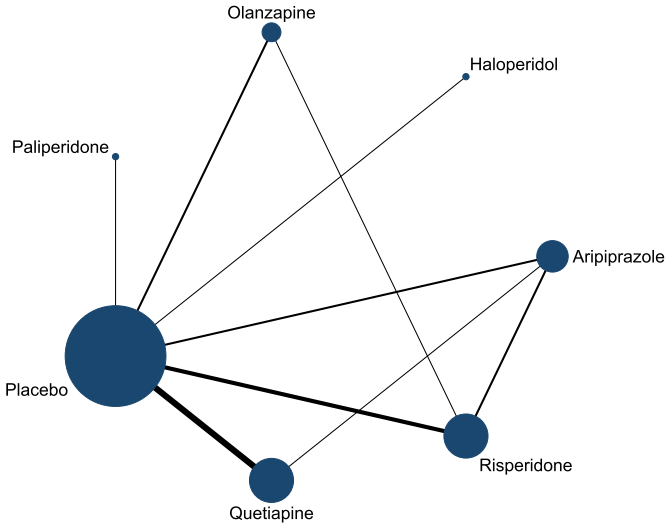

Fig. 2. Network map. The size of the node is proportional to the number of patients assigned to the drug. The lines indicate direct comparisons between drugs, and the size of the line is proportional to the number of trials comparing each pair of drugs.

of bias. Assessment of risk of bias for individual studies is presented in Supplemental Figs. S1 and S2.

3.1. Predefined analyses

Global inconsistency (P = 0.54) and local inconsistency (Supplemental Table S2) were not significant. The heterogeneity across studies was considerable (SD = 3.97). Primary analysis showed that risperidone (MD, −4.45; 95% CI, −8.13 to −0.78) and aripiprazole (−4.42; −8.57 to −0.72) were significantly superior to placebo. Risperidone appeared to be the most effective agent according to the SUCRA. The league table is presented in Fig. 3. The funnel plot appeared symmetrical (Supplemental Fig. S3). Predefined subgroup and meta-regression analyses indicated that comorbid tics was identified as a significant moderator. All antipsychotics except paliperidone were significantly superior to placebo in the subgroup without comorbid tics, while no antipsychotics was significantly superior to placebo in the subgroup with comorbid tics (Fig. 4). The interaction terms of other moderators were not significant (Table 1). Aripiprazole, risperidone and quetiapine were significantly superior to placebo in the subgroup without comorbid depression, while no antipsychotics was significantly superior to placebo in subgroup with comorbid depression (Fig. 4). Detailed results were presented in the supplementary materials. After excluding studies with an overall high risk of bias, only aripiprazole (−7.32; −12.99 to −1.66) was significantly superior to placebo (Fig. 5). Regarding tolerability, quetiapine (OR, 3.45; 95% CI, 1.04–11.11) and paliperidone (20.00; 1.01- > 100) were significantly less tolerable than placebo (Fig. 6).

3.2. Post-hoc analyses

Sensitivity analysis was conducted after excluding Diniz et al. (2011), in which SRI dose was reduced in the quetiapine arm but was not reduced in the placebo arm. Global inconsistency (P = 0.55) and local inconsistency (Supplemental Table S3) were not significant. Heterogeneity across studies was reduced to 3.19. Sensitivity analysis showed that aripiprazole (−4.91; −8.24 to −1.59), quetiapine (−4.66; −7.60 to −1.72), and risperidone (−4.51; −7.50 to −1.52) were significantly superior to placebo. Aripiprazole obtained the largest SUCRA instead of risperidone (Fig. 7). The funnel plot appeared symmetrical (Supplemental Fig. S4). Post-hoc meta-regressions were performed by female percentage, age, publication year and previous SRI duration; the results were not significant (Table 1). Post-hoc subgroup analysis was performed by previous SRI duration at least 12 weeks, showing that no antipsychotics was significantly better than placebo in the subgroup with previous SRI duration less than 12 weeks; only aripiprazole, risperidone and quetiapine were significantly better than placebo in the subgroup with previous SRI duration at least 12 weeks. We conducted all meta-regressions and subgroup analyses again after excluding Diniz et al. (2011); the results were similar to those of the

Risperidone						
0.64 (-8.71,9.99)	Haloperidol					
-0.03 (-4.47,4.40)	-0.67 (-10.22,8.87)	Aripiprazole				
-0.94 (-6.54,4.67)	-1.58 (-11.60,8.45)	-0.90 (-7.25,5.44)	Olanzapine			
-1.57 (-6.38,3.23)	-2.21 (-11.44,7.01)	-1.54 (-6.34,3.26)	-0.64 (-6.75,5.48)	Quetiapine		
-2.35 (-13.24,8.53)	-2.99 (-16.36,10.38)	-2.32 (-13.37,8.74)	-1.41 (-12.89,10.06)	-0.78 (-11.56,10.00)	Paliperidone	
-4.45 (-8.13,-0.78)	-5.09 (-13.68,3.50)	-4.42 (-8.57,-0.27)	-3.51 (-8.67,1.64)	-2.88 (-6.24,0.48)	-2.10 (-12.35,8.15)	Placebo

Fig. 3. League table of efficacy. Drugs are presented in order of efficacy ranking estimated by SUCRAs. MD and 95% CI were presented. MD, mean difference; CI, confidence interval; SUCRA, surface under the cumulative ranking curve.

primary analyses (Fig. 4). Detailed results were presented in the supplementary materials. Sensitivity analysis after excluding studies that included patients with comorbid tics was performed. Quetiapine, aripiprazole, and risperidone were significantly superior to placebo; there was no significant difference between antipsychotic agents. League table was presented in Fig. S5.

4. Discussion

As far as we know, this is the first network meta-analysis of antipsychotic agent augmentation in treatment-resistant OCD. Twenty RCTs with 790 patients were included in the analysis. Aripiprazole and risperidone showed significantly better efficacy than did placebo, both in primary analysis and in sensitivity analysis after excluding Diniz et al. (2011). Only aripiprazole was significantly superior to placebo after excluding studies with overall high risk of bias. There was no significant difference between these antipsychotic agents. Although quetiapine showed significantly better efficacy than placebo in sensitivity analysis, its efficacy should be weighed against its lower tolerability. Several conventional pair-wise meta-analyses have been conducted previously (Bloch et al., 2006; Dold et al., 2013, 2015; Fineberg et al., 2006; Komossa et al., 2010; Skapinakis et al., 2007; Veale et al.,

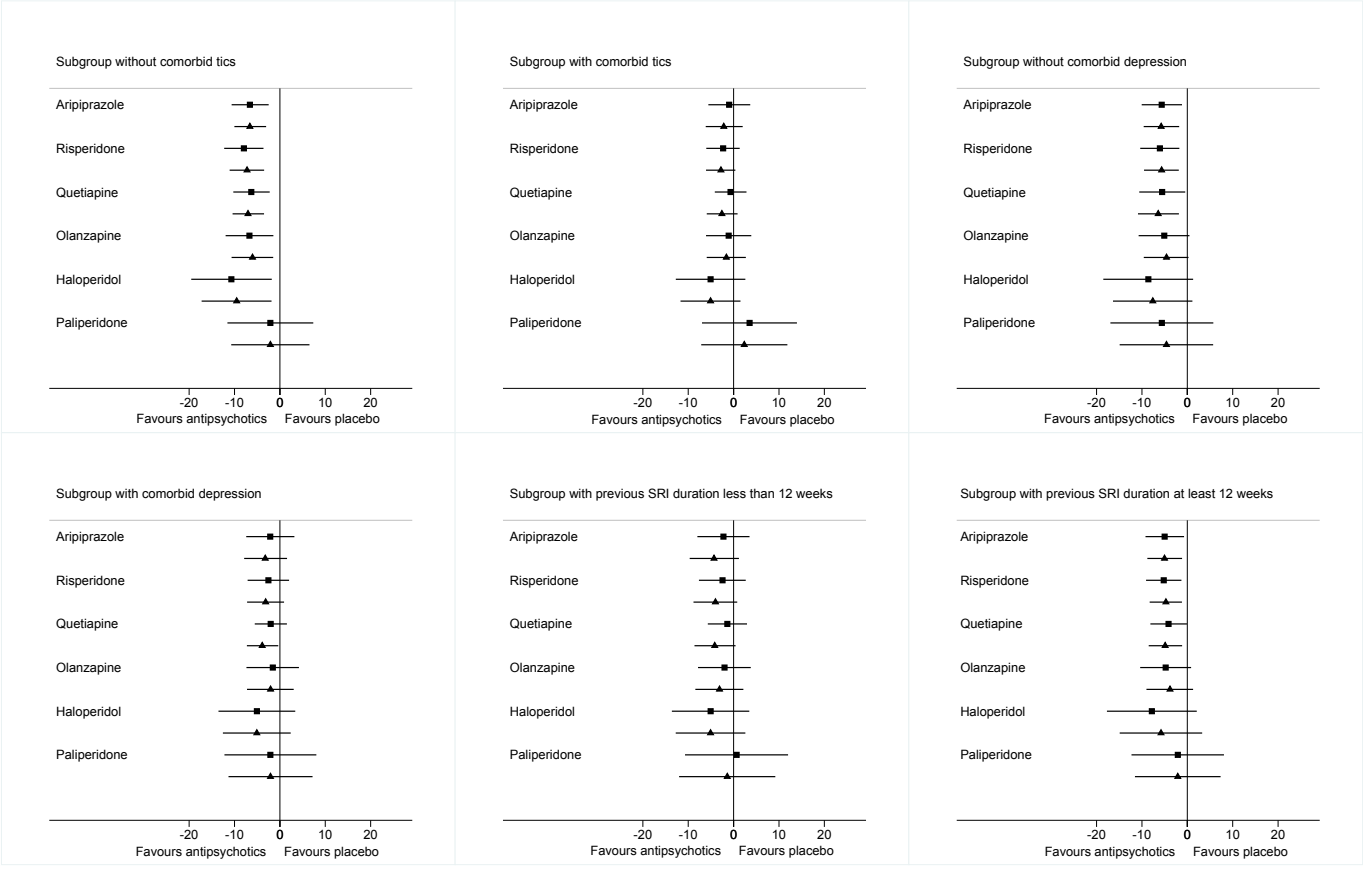

Fig. 4. Forest plots for efficacy of antipsychotics compared with placebo under various subgroup conditions. SRI, serotonin reuptake inhibitor.

Table 1
Meta-regression and subgroup analyses.

Moderators	Interaction term	95% lower limit	95% upper limit	Heterogeneity
Comorbid tics (1 = yes; 0 = no)	5.63 (4.44)[a]	1.18 (0.48)	10.12 (8.41)	3.33 (2.62)
Comorbid depression (1 = yes; 0 = no)	3.58 (2.52)	−1.56 (−2.04)	8.76 (7.15)	3.87 (3.17)
Previous SRI duration = 12w (1 = yes; 0 = no)	−2.77 (−0.71)	−7.72 (−5.60)	2.28 (4.12)	3.94 (3.33)
Age	0.00 (0.11)	−0.75 (−0.55)	0.75 (0.76)	4.06 (3.31)
Treatment duration	0.17 (0.02)	−0.64 (−0.72)	0.97 (0.75)	4.03 (3.33)
Illness duration[b]	0.47 (0.22)	−0.13 (−0.25)	1.07 (0.70)	4.02 (2.29)
Previous SRI duration	−0.65 (−0.30)	−1.78 (−1.35)	0.48 (0.76)	3.92 (3.29)
Female percentage	−0.07 (−0.07)	−0.38 (−0.38)	0.23 (0.23)	3.43 (3.43)
Baseline YBOCS	−0.35 (−0.27)	−1.57 (−1.36)	0.88 (0.83)	4.02 (3.29)
Publication year	0.44 (0.19)	−0.20 (−0.42)	1.08 (0.81)	3.84 (3.28)

SRI, Serotonin reuptake inhibitor; YBOCS, Yale-Brown Obsessive Compulsive Scale; w, weeks.
[a] The values in parentheses are results of meta-regression and subgroup analyses after excluding Diniz et al. (2011).
[b] Only 12 studies were included in this analysis.

2014). Risk difference (RD), risk ratio (RR), standard mean difference (SMD), Hedge's g and weighted mean difference (WMD) were selected as effect sizes. We did not choose categorical variables for measurement of primary outcome in the protocol, because response criteria varied across studies. We used MD as effect size because all studies used YBOCS as measurement of symptoms and MD was easier to interpret. Most results of our analyses were consistent with previous meta-analyses. Fineberg et al. (2006) found that quetiapine was significantly effective, whereas Veale et al. (2014) and Dold et al. (2013) obtained the opposite conclusion. The inconsistent results of quetiapine primarily resulted from the inclusion or exclusion of the study by Diniz et al. (2011). Aripiprazole and risperidone were demonstrated to be effective agents consistently in two recent meta-analyses (Dold et al., 2015; Veale et al., 2014). Compared with previous conventional meta-analyses, this comprehensive network meta-analysis included the greatest number of studies and participants, as well as head-to-head RCTs, increasing the statistical power and providing both indirect and direct comparisons. Moreover, only separate subgroup analyses were conducted in previous meta-analyses; we used a Bayesian method to explore potential moderators. A shared heterogeneity parameter and interaction term was introduced to evaluate the effect. Additionally, this innovative method estimated the effects of all antipsychotics under various subgroup conditions.

Comorbid tics was identified as a significant moderator. The interaction term is 5.63 (1.18, 10.12), and the heterogeneity was reduced from 3.97 to 3.33 after considering this moderator. After excluding Diniz et al. (2011), the interaction term of comorbid tics (4.44; 0.48–8.41) remained significant and the heterogeneity became 2.62. The study by Diniz et al. (2011) and comorbid tics could explain 34% of the heterogeneity. Previous separate subgroup analysis (Skapinakis et al., 2007) also found that the subgroup without comorbid tics reported a better efficacy than the subgroup with comorbid tics. Our integrated subgroup analysis indicated that all antipsychotics except paliperidone were significantly better than placebo in the subgroup without comorbid tics, while all antipsychotics failed to demonstrate significant efficacies in the subgroup with comorbid tics. The results were consistent after excluding Diniz et al. (2011). Similarly, the interaction term of comorbid depression was 3.58 (−1.56, 8.76), indicating that treatment-resistant OCD patients with comorbid depression tend to obtain smaller effect sizes. Shetti et al. (2005) reported that SRIs were less effective in OCD patients with comorbid major depression. Integrated subgroup analysis showed that aripiprazole, risperidone and quetiapine were significantly better than placebo in the subgroup without comorbid depression; however, only quetiapine was significantly better than placebo in the subgroup with comorbid depression after excluding Diniz et al. (2011). Our results indicated that antipsychotics might be more effective for patients without such comorbidities.

We conducted both meta-regression and subgroup analysis for previous SRI duration, and the results were consistent. Both interaction terms are negative, showing the trend that studies with shorter previous SRI treatment (insufficient SRI duration) were more likely to report smaller effect sizes. This may be because patients in placebo arm could benefit from SRIs with adequate and longer duration, resulting in relatively less efficacy of the antipsychotic arm. Integrated subgroup analysis showed that no antipsychotics was significantly better than placebo if previous SRI duration was less than 12 weeks; only aripiprazole, risperidone and quetiapine were significantly better than placebo if previous SRI duration was adequate. The study by Diniz et al. (2011) is heterogeneous compared with other studies, because fluoxetine dose was reduced to 40 mg/d in the active arm, whereas it remained at 80 mg/d in the placebo arm. This might lead to the noneffective results of quetiapine in the primary analysis. Moreover, previous fluoxetine treatment duration in this study was only eight

Aripiprazole					
-2.58 (-13.80,8.63)	Olanzapine				
-3.78 (-10.22,2.67)	-1.19 (-12.45,10.06)	Risperidone			
-5.22 (-17.47,7.02)	-2.64 (-17.19,11.91)	-1.45 (-13.72,10.83)	Paliperidone		
-7.07 (-14.97,0.82)	-4.49 (-15.63,6.65)	-3.30 (-11.24,4.65)	-1.85 (-14.02,10.32)	Quetiapine	
-7.32 (-12.99,-1.66)	-4.74 (-14.42,4.94)	-3.55 (-9.28,2.19)	-2.10 (-12.96,8.76)	-0.25 (-5.75,5.25)	Placebo

Fig. 5. League table of sensitivity analysis after excluding studies with an overall high risk of bias. Drugs are presented in order of efficacy ranking estimated by SUCRAs. MD and 95% CI were presented. MD, mean difference; CI, confidence interval; SUCRA, surface under the cumulative ranking curve.

Placebo						
1.00 (0.02,53.28)	Haloperidol					
0.78 (0.26,2.34)	0.78 (0.01,48.07)	Risperidone				
0.76 (0.20,2.98)	0.76 (0.01,50.96)	0.98 (0.34,2.82)	Aripiprazole			
0.66 (0.16,2.66)	0.66 (0.01,44.53)	0.85 (0.20,3.68)	0.86 (0.15,4.86)	Olanzapine		
0.29 (0.09,0.96)	0.29 (0.00,18.29)	0.37 (0.08,1.80)	0.38 (0.07,2.11)	0.43 (0.07,2.70)	Quetiapine	
0.05 (0.00,0.99)	0.05 (0.00,7.23)	0.07 (0.00,1.55)	0.07 (0.00,1.74)	0.08 (0.00,2.04)	0.18 (0.01,4.37)	Paliperidone

Fig. 6. League table of tolerability. Drugs are presented in order of efficacy ranking estimated by SUCRAs. OR and 95% CI were presented. OR, odds ratio; CI, confidence interval; SUCRA, surface under the cumulative ranking curve.

weeks; patients could continue to benefit from additional treatment weeks of primary SRI.

Considerable heterogeneity was identified in our analysis. Coincidentally, a previous network meta-analysis (Skapinakis et al., 2016), investigating treatments for non-refractory OCD patients, found notable heterogeneity (SD = 3.1), similar to our results (SD = 3.97). No significant moderators were identified by subgroup analyses and meta-regression in the previous network meta-analysis. Veale et al. (2014) stated that the heterogeneity might be due to RCTs recruiting different patients and the heterogeneous nature of OCD. Although OCD is a distinctive disorder, there are varieties of forms of symptoms, including compulsive washing, ordering, checking, and counting. Previous studies indicated that compulsive washing and mixed compulsions were associated with poor response to SRI (Shetti et al., 2005). Furthermore, hoarding had been considered a symptom of OCD in the past; however, hoarding disorder was reclassified as a separate disorder in DSM-5 (American Psychiatric Association, 2013), and few studies stated that whether their OCD patients exhibited hoarding or not, possibly contributing to heterogeneity. An early meta-analysis by Skapinakis et al. (2007) stated that the definition of treatment resistance, comorbidities and individual agents may contribute to the significant heterogeneity. Additionally, the heterogeneity may also result from combinations of various types and dosages of SRIs. In an individual participant data analysis (Denys et al., 2007), three double-blind RCTs investigating quetiapine as augmentation agents for treatment-resistant OCD were included. The study found that better improvement was associated with lower doses of SRIs, and individual SRIs (e.g., fluvoxamine, fluoxetine, and clomipramine).

Although the serotoninergic neurotransmitter system is the primary underlying pathophysiological mechanism of OCD (Aouizerate et al., 2005), the dopaminergic neurotransmitter system has also been proposed as an underlying mechanism (Denys et al., 2004b; Kim et al., 2007). Effectiveness of antipsychotics as augmentation agents should be attributed to their effects on the dopaminergic neurotransmitter system, primarily involving dopamine D2 receptor blockade (Ramasubbu et al., 2000). In a meta-regression analysis, Ducasse et al. (2014) showed that antipsychotics with higher D2 and D3 receptor affinities predict better efficacy for treating OCD. However, they included Diniz et al. (2011) in the analysis, resulting in quetiapine obtaining the lowest SMD. After excluding Diniz et al. (2011), in which SRI dose was different between quetiapine arm and placebo arm, quetiapine showed better efficacy. Olanzapine have higher D2 and D3 affinities than quetiapine; however, our primary analysis and sensitivity analysis showed that olanzapine was not significantly superior to placebo. We observed that the study by Shapira et al. (2004) recruited patients with lower baseline YBOCS scores compared with other studies. Higher baseline YBOCS score was associated with better response with SRIs augmented by quetiapine (Carey et al., 2012). Moreover, Shapira et al. (2004) recruited patients with shorter previous SRI duration and comorbid tics, both of which were associated with lower treatment effects. Paliperidone is the primary metabolite of risperidone, with similar D2 and D3 affinities as those of risperidone (Richtand et al., 2008). Nevertheless, paliperidone was not significantly superior to placebo in our analysis. A total of 38.2% of patients had comorbid depression, and the patients had the

Aripiprazole						
0.18 (-7.47,7.82)	Haloperidol					
-0.26 (-4.16,3.65)	-0.43 (-7.92,7.05)	Quetiapine				
-0.40 (-3.96,3.16)	-0.58 (-8.08,6.93)	-0.14 (-4.17,3.89)	Risperidone			
-1.45 (-6.55,3.66)	-1.62 (-9.66,6.41)	-1.19 (-6.24,3.86)	-1.05 (-5.58,3.48)	Olanzapine		
-2.81 (-12.28,6.65)	-2.99 (-14.21,8.23)	-2.56 (-11.89,6.78)	-2.41 (-11.77,6.94)	-1.37 (-11.15,8.42)	Paliperidone	
-4.91 (-8.24,-1.59)	-5.09 (-11.97,1.79)	-4.66 (-7.60,-1.72)	-4.51 (-7.50,-1.52)	-3.47 (-7.62,0.68)	-2.10 (-10.96,6.76)	Placebo

Fig. 7. League table of sensitivity analysis after excluding Diniz et al. (2011). Drugs are presented in order of efficacy ranking estimated by SUCRAs. MD and 95% CI were presented. MD, mean difference; CI, confidence interval; SUCRA, surface under the cumulative ranking curve.

largest mean age in paliperidone study. Compared with risperidone studies, mostly defining treatment-resistant as inadequate response after at least one trial of SRI, paliperidone study recruited patients with inadequate response after at least two trials of SRIs. The relative differences observed between antipsychotics should not simply be interpreted as their different dopamine receptor affinities, but the heterogeneous characteristics across studies.

There are several limitations to our study. First, the numbers of included studies and recruited patients for each single agent were fairly limited. We should treat these results with caution because RCTs for each single agent may recruit biased samples, and the results may not apply well to general clinical practice. It is not enough to establish recommendations due to these limitations. Second, other antipsychotics (e.g., amisulpride) were also reported to be effective as augmentation agents in open-label trials (Metin et al., 2003); nevertheless, they have not been investigated in RCTs. Therefore, this study cannot evaluate their efficacy and tolerability. Third, there is considerable heterogeneity. Our inclusion criteria did not explicitly specify the dose and duration of previous SRI treatment that varied across included studies and could be contribute to the heterogeneity. Moreover, various combinations with SRIs and diversity symptoms of OCD are likely to contribute to heterogeneity. We could not explore these moderators in this analysis. Future RCTs are encouraged to report individual participant data, and IPD meta-analyses are needed to help better understand this heterogeneous clinical issue. Fourth, only short-term effect of antipsychotic agents was investigated in current RCTs; long-term RCTs are needed in future. Fifth, most of the studies excluded patients with comorbidities; nevertheless, OCD patients with comorbidities are common in daily clinical practice. Approximately 63% of OCD patients have lifetime depression, and 30% of patients have lifetime tic disorders (American Psychiatric Association, 2013). Our subgroup analysis was rough, because we classified studies including any proportion of patients with comorbid tics into the comorbid tics subgroup. Even so, the interaction term was significant and we can infer that treatments might be much less effective in subgroup with all comorbid tics patients. Other comorbidities (e.g., generalized anxiety disorder, personality disorder, and others) are also common (American Psychiatric Association, 2013). Therefore, it is more complicated in clinical practice, and clinicians should treat our results carefully. Finally, our analyses covered only patients with primary diagnosis of OCD; therefore, the results may not apply well to patients with OCD symptoms secondary to other psychotic disorders.

Based on this network meta-analysis, antipsychotics as augmentation agents should be administered after at least twelve weeks of SRI treatment. Current evidence indicated antipsychotics as augmentation agents to SRI might be more effective in patients without comorbid tics and depression. Due to the limitations mentioned above, a robust recommendation of which drug is optimal cannot be drawn currently.

Conflicts of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare no conflict of interest related to designing and conducting this study.

Contributors

DZ, XZ, XC, ZL, DL, CL, and LK were involved in the design of the network meta-analysis. DZ, XZ, LK, GW, DL, and WW selected the articles and extracted the data. DZ, XZ, ZL, CL, and WW analysed the data. DZ, XZ, and DL wrote the first draft of the manuscript. XC, ZL, DL, GW, WW, CL, and DZ contributed to the interpretation of the data and wrote the final version. All authors critically reviewed and approved the final article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.014.

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