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Adjunctive intranasal oxytocin for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials

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ABSTRACT

Objective: Findings on the efficacy of intranasal oxytocin (IN-OT) in schizophrenia have been inconsistent. This meta-analysis of double-blind randomized controlled trials (RCTs) examined the efficacy and tolerability of adjunctive IN-OT in the treatment of schizophrenia.
Methods: Standardized mean differences or risk ratios (SMDs or RRs) with their 95% confidence intervals (CIs) were used to synthesize the results of studies included in the meta-analysis.
Results: Ten RCTs (n = 344) with 172 schizophrenia subjects on adjunctive IN-OT [range = 40–80 International Units (IU)/day] and 172 schizophrenia subjects on adjunctive placebo over 2–16 weeks were included. No significant differences regarding total psychopathology measured with the total Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS) [8 RCTs, n = 203; SMD: −0.08 (95%CI: −0.53, 0.37), P = 0.74, I^2 = 59%] and the positive, negative and general symptom scores [SMD: −0.20 to −0.04 (95%CI: −0.75, 0.36), P = 0.28 to 0.78; I^2 = 0% to 72%] were found between the IN-OT and placebo groups. Similarly, subgroup analyses for total psychopathology found no group differences. Dose-response effect analyses showed that only 80 IU/day IN-OT had superiority over placebo in improving total psychopathology (P = 0.02) and positive symptom score (P = 0.01). No group differences between adjunctive IN-OT and placebo regarding discontinuation due to any reason [RR: 1.12 (95%CI: 0.67, 1.88), P = 0.67, I^2 = 0%] and adverse drug reactions were found.
Conclusions: Although the meta-analysis did not show a positive effect in general, the higher dose of adjunctive IN-OT (80 IU/day) appears to be efficacious and safe in improving total psychopathology and positive symptoms in schizophrenia.
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1. Introduction

Schizophrenia is a severe, chronic, and devastating disorder that leads to significant suffering as well as psychological, social and cognitive functioning deficits (Heringa et al., 2015). Despite advances in antipsychotic (AP) treatment, the response and remission rates in schizophrenia remain unsatisfactory (Torrey and Davis, 2012), particularly for patients with persistent negative symptoms and cognitive impairment associated with poor functional outcomes (Fervaha et al., 2014; Lepage et al., 2014). Therefore, augmentation of APs (Wolff-Menzler et al., 2010), such as APs polypharmacy (Galling et al., 2017; Galling et al., 2016), antidepressants (Helfer et al., 2016), antiepileptics (Zheng et al., 2016; Zheng et al., 2017c), anti-inflammatory drugs (Xiang et al., 2017; Zheng et al., 2017a), electroconvulsive therapy (Zheng et al., 2017b) and hormones (Heringa et al., 2015), are widely used for treatment-resistant schizophrenia.

Hormonal treatment for schizophrenia has been gaining increasing attention over the past decades (Heringa et al., 2015). Oxytocin, a

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pituitary hormone, is produced by the hypothalamus and secreted by the posterior pituitary gland (Oya et al., 2016). Apart from its role in parturition and lactation, oxytocin also modulates several aspects of social behaviour (Burkner et al., 2017; Lee et al., 2009). Some studies have found oxytocinergic dysfunction in schizophrenia (Goldman et al., 2008). Administration of intranasal oxytocin (IN-OT) was found to improve facial recognition and increase feeling of trust (Ditzen et al., 2009; Heinrichs et al., 2003; Shahrestani et al., 2013). Oxytocin also has the potential to regulate central dopamine function and exhibit antipsychotic effects (Feifel et al., 2010). Thus, IN-OT has been proposed as a potential therapeutic agent for schizophrenia (Heringa et al., 2015).

The effectiveness of IN-OT has been examined in animal schizophrenia model (Feifel and Reza, 1999; Shilling and Feifel, 2016), observational studies (Ota et al., 2017), and non-randomized clinical trials (Feifel et al., 2013). Findings from randomized controlled trials (RCTs) (Buchanan et al., 2017; Cacciotti-Saija et al., 2015; Dagani et al., 2016; Davis et al., 2014; Feifel et al., 2010; Gibson et al., 2014; Jarskog et al., 2017; Lee et al., 2013; Modabbernia et al., 2013; Pedersen et al., 2011) and meta-analyses (Burkner et al., 2017; Gumley et al., 2014; Heringa et al., 2015; Oya et al., 2016; Williams and Burkner, 2017) have been inconsistent.

The largest meta-analysis (Williams and Burkner, 2017) that examined the efficacy of adjunctive IN-OT for schizophrenia included 8 RCTs (n = 238). However, the Williams and Burkner study did not analyze specific outcome measures (i.e. adverse drug reactions (ADRs) and discontinuation rate) and did not include the two double-blind RCTs that have been recently published (Buchanan et al., 2017; Jarskog et al., 2017). To update the existing literature on the place of IN-OT in schizophrenia and provide more comprehensive and robust evidence for clinical practice, the present meta-analysis of double-blind RCTs was conducted to examine the efficacy and tolerability of adjunctive IN-OT in the treatment of schizophrenia.

2. Methods

2.1. Inclusion criteria

According to the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009), the inclusion criteria of this meta-analysis followed the ***PICOS*** strategy: ***P***articipants: adult patients with schizophrenia based on any diagnostic criteria who were receiving APs. ***I***ntervention and ***C***omparison: adjunctive IN-OT versus placebo. Cognitive therapies, such as social cognitive therapy (SCT), were allowed in order to investigate their potential moderating effect as recommended by a recent meta-analysis (Williams and Burkner, 2017). ***O***utcomes: the primary outcome measure was efficacy [improvement in total psychopathology measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) total scores]. The key secondary outcome measures included efficacy [positive symptoms, negative symptoms, and general psychopathology scores measured with the subscales of the PANSS, the BPRS, and the total scores of the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and/or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), where appropriate] and safety [any cause discontinuation, and ADRs]. ***S***tudy design: double-blind RCTs with data available on efficacy and/or safety outcomes. Following the methodology of a previous meta-analysis (Williams and Burkner, 2017), several RCTs that only reported other outcomes (i.e. social cognition) were excluded.

2.2. Search strategy

Relevant studies comparing IN-OT augmentation and placebo were systematically searched and identified by two independent investigators (WZ and D-BC) through searching both Chinese (Wanfang Data, Chinese Journal Net, China Biology Medicine) and English (PubMed, Cochrane Library databases, and PsycINFO) databases from their inception date to September 25, 2017. The search strategy followed these key words: (random* OR placebo) AND (oxytocin OR pitocin) AND (schizophrenic disorder OR disorder, schizophrenic OR schizophrenic disorders OR schizophrenia OR dementia praecox). Additional eligible RCTs were also searched by two independent investigators (WZ and D-BC) through scrutiny of the reference lists of the primary articles and relevant reviews and meta-analyses (Burkner et al., 2017; Heringa et al., 2015; Oya et al., 2016; Williams and Burkner, 2017).

2.3. Data extraction

Two investigators (D-BC and X-HY) independently evaluated the identified trials according to the inclusion criteria of this meta-analysis, and later extracted, checked, and entered their data into the RevMan software (Version 5.3) (http://www.cochrane.org) (Higgins and Higgins, 2008). Disagreements were discussed between the investigators and a consensus was reached. When data were not available in an article, the first/corresponding authors were contacted or the data were extracted from previous meta-analyses if available (Oya et al., 2016; Williams and Burkner, 2017). For randomized cross-over studies, the data on ADRs were extracted from the study endpoint, while the data on efficacy in the first phase, i.e. prior to the cross-over, of randomized studies were extracted and analyzed.

2.4. Data synthesis and statistical analyses

The RevMan software (Version 5.3) was used to pool intention-to-treat (ITT) or observed cases (OC) data using the random effect model (DerSimonian and Laird, 1986) according to the recommendation of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Higgins, 2008). ITT was preferred when both ITT and OC data were available. For continuous data, standardized mean difference (SMD) was calculated by combining the effect size (Hedges' g) data of each RCT. For dichotomous data, the risk ratio (RR) with its 95% confidential interval (CI) was estimated. Study heterogeneity was analyzed using the Chi-square and I^2 statistics, with Q test P value < 0.1 and I^2 > 50%, to indicate heterogeneity, respectively (Higgins and Thompson, 2002).

In cases of $I^2 \geq 50\%$ for total psychopathology, the following 6 subgroup analyses were conducted to examine the reasons for the heterogeneity: 1) Jadad score: ≥4 versus <4 (using a median split); 2) analyses: using ITT versus OC data; 3) trial duration: ≥6 versus <6 weeks (using a median split); 4) age: ≥38.4 versus <38.4 years (using a median split); 5) administration interval: every day versus sessional; and 6) cognitive intervention: SCT versus no SCT. Additionally, a meta-regression analysis was conducted using the Meta-Analyst program (Wallace et al., 2009) to evaluate the association between the meta-analytic result for total psychopathology and continuous moderators: 1) baseline PANSS total score or converted PANSS total score from BPRS total score using established conversion guidelines (Leucht et al., 2013); 2) baseline positive symptom score, and 3) baseline negative symptom score. In order to examine the dose-response effect of IN-OT on total, positive, negative and general symptom scores, RCTs with the same dose of IN-OT were pooled separately.

Publication bias of the meta-analytic results for primary outcome was examined using funnel plots and Egger's test (Egger et al., 1997). All primary and secondary outcomes were considered significant at the level of P < 0.05 (two-sided).

2.5. Assessment of study quality

The Jadad scale (Jadad et al., 1996) and the Cochrane risk of bias (Higgins and Higgins, 2008) were used to measure the quality of

included studies by two independent investigators (D-BC and X-HY). The quality was defined as "high" when Jadad score was ≥3. The two investigators also independently assessed the overall evidence level of primary and secondary outcomes using the grading of recommendations, assessment, development, and evaluation (GRADE) system (Atkins et al., 2004; Balshem et al., 2011).

3. Results

3.1. Literature search

The PRISMA flow diagram of study search is presented in Fig. 1. A total of 198 hits were identified, of which finally 10 RCTs (Buchanan et al., 2017; Cacciotti-Saija et al., 2015; Dagani et al., 2016; Davis et al., 2014; Feifel et al., 2010; Gibson et al., 2014; Jarskog et al., 2017; Lee et al., 2013; Modabbernia et al., 2013; Pedersen et al., 2011) fulfilled the study entry criteria and were included for analyses.

3.2. Study, patient and treatment characteristics

In the 10 double-blind RCTs of 2–16 weeks duration (mean = 6.8 weeks; median = 6 weeks), 344 schizophrenia patients were randomized to the IN-OT (n = 172) and placebo (n = 172) groups (Table 1). The mean age was 37.1 (median = 38.4; range = 21.9–48.0) years, and 81.0% (range = 69.2%–100%) of the patients were males. Seven of the 10 RCTs were conducted in the USA (n = 220), and one each in Iran (n = 40), Australia (n = 52) and Italy (n = 32). The mean dose of IN-OT was 51 International Unit (IU)/day (range = 40–80 IU/day). Baseline AP was risperidone in one RCT (n = 40) and a variety of AP combinations in the remaining RCTs (n = 304).

3.3. Assessment of study quality

Using the Cochrane risk of bias, random sequence generation and allocation concealment were rated as low risk in 5 RCTs and 4 RCTs, respectively (Supplemental Fig. 1). Attrition bias (i.e. using ITT analysis) was rated as low risk in 9 RCTs while other bias was rated as unclear in all RCTs. The Jadad score ranged from 3 to 5 (mean = 4; median = 4) (Table 1), indicating that all RCTs were rated as high quality (Jadad score ≥ 3). The overall evidence level for primary (n = 1) and secondary (n = 27) outcomes were rated as "low" (7.1%) and "moderate" (92.9%), respectively using the GRADE approach (Supplemental Table 1).

3.4. Psychotic symptoms

Meta-analyses of total psychopathology [8 RCTs, n = 203; SMD: −0.08 (95%CI: −0.53, 0.37), P = 0.74, I^2 = 59%; Fig. 2] did not show superiority of IN-OT over placebo. Similar findings were obtained in all subgroup analyses (Table 2).

In meta-regression analyses higher baseline positive symptom score (coefficients = −0.080, P = 0.006, Supplemental Fig. 2) and lower baseline negative symptom score (coefficients = 0.074, P = 0.007, Supplemental Fig. 3) were significantly associated with superiority of

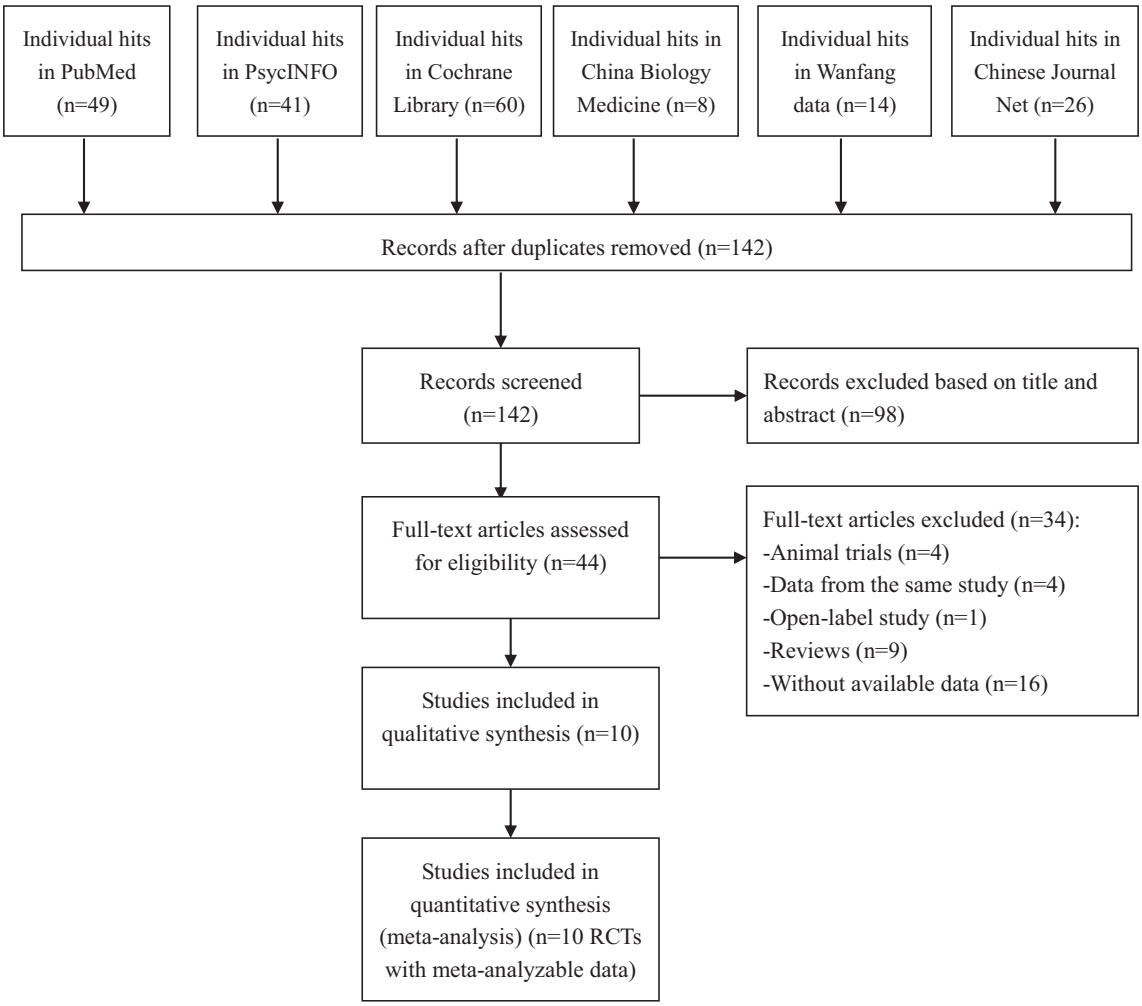

Fig. 1. PRISMA flow diagram.

Table 1
Study, patient and treatment characteristics of the studies included in the meta-analysis.

Study (country)	Number of patients[a]	Blinding	Analyses	Trial duration (wks)	-Diagnosis -Setting	Diagnostic criteria	-Illness severity[a] -Illness duration[a]	Age[a]: yrs (range)	Sex[a]: male (%)	IN-OT: Dose (IU): mean (range)	Jadad score
Buchanan et al., 2017 (USA)	T: 38 C: 21 I: 17	DB	ITT	6	-SCZ/SzA -Both	DSM-IV-TR	-33.3 (BPRS) -NR	44.5 (18–65)	86.1	Ø = 48 (FD)	5
Cacciotti-Saija et al., 2015 (Australia)[b]	T: 52 C: 25 I: 27	DB	ITT	6	-SCZ/SzA/SzD -Outpatients	DSM-IV-TR	-NR -NR	21.9 (16–35)	69.2	Ø = 48 (FD)	3
Dagani et al., 2016 (Italy)	T: 32 C: 16 I: 16	DB (crossover)[c]	ITT	16	-SCZ -NR	DSM-IV	-81.1 (PANSS) -3.7 yrs	30.4 (18–45)	81.3	Ø = 40 (FD)	5
Davis et al., 2014 (USA)[b]	T: 27 C: 14 I: 13	DB	OC	6	-SCZ -Outpatients	DSM-IV	-31.0 (BPRS) -NR	39.8 (NR)	100	Ø = 40 (FD)	3
Feifel et al., 2010 (USA)	T: 19 C: 10 I: 9	DB (crossover)[c]	OC	3	-SCZ -NR	DSM-IV	-81.8 (PANSS) -25.8 yrs	48 (≥18)	80.0	Ø = 80 (40–80)	5
Gibson et al., 2014 (USA)	T: 20[d] C: 9 I: 11	DB	OC	6	-SCZ -Outpatients	DSM-IV-TR	-75.5 (PANSS) -NR	37.5 (18–55)	78.6	Ø = 48 (FD)	3
Jarskog et al., 2017 (USA)	T: 68 C: 33 I: 35	DB	ITT	12	-SCZ/SzA -Outpatients	DSM-IV	-67.3 (PANSS) - ≥ 1 yrs	39.1 (18–65)	75.8	Ø = 48 (FD)	5
Lee et al., 2013 (USA)	T: 28 C: 15 I: 13	DB	ITT	3	-SCZ/SzA -Both	DSM-IV	-35.5 (BPRS) -NR	39.6 (18–60)	71.4	Ø = 40 (FD)	3
Modabbernia et al., 2013 (Iran)	T: 40 C: 20 I: 20	DB	ITT	8	-SCZ -Inpatients	DSM-IV-TR	-90.0 (PANSS) -6.4 yrs	32.8 (18–50)	82.5	Ø = 80 (40–80)	5
Pedersen et al., 2011 (USA)	T: 20 C: 9 I: 11	DB	ITT	2	-SCZ -Both	DSM-IV	-81.1 (PANSS) -14.6 yrs	37.6 (18–55)	85.0	Ø = 48 (FD)	3

Abbreviations: Both = inpatients and outpatients; BPRS = Brief Psychiatric Rating Scale; C = control; DB = double blind; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision; FD = fixed dosage; I = intervention; IU = International Units; ITT = intent to treat; IN-OT = intranasal oxytocin; NR = not report; OC = observed cases; PANSS = Positive and Negative Syndrome Scale; SCZ = schizophrenia; SzA = schizoaffective disorder; SzD = schizophreniform disorder; T = total; wks = weeks; yrs. = years; Ø = mean.

[a] Data were extracted based on mean baseline value of each included trials.

[b] Combined with social cognitive therapy.

[c] Apart from adverse drug reaction data extracted from the study endpoint; other data with only the first randomized study phase were extracted and analyzed.

[d] Data were extracted from the prior meta-analysis.

adjunctive IN-OT in improving total psychopathology, but the baseline PANSS total score (coefficients = −0.023, P = 0.126) did not show any significant association. Publication bias for total psychopathology could not be assessed using the funnel plots and Egger's test since the number of studies was <10 (Sterne et al., 2011).

Meta-analyses of positive, negative, and general psychopathology symptom scores did not show any group differences [SMD: −0.20 to −0.04 (95%CI: −0.75, 0.36), P = 0.28 to 0.78; I^2 = 0% to 72%; Fig. 2]. Dose-response effect analyses found superiority of IN-OT over placebo in improving total psychopathology (P = 0.02) and positive symptom scores (P = 0.01) in studies using 80 IU/day of IN-OT (Table 3).

3.5. ADRs and discontinuation rate

Meta-analysis of ADRs (such as akathisia and dizziness) [RR: 0.23 to 2.02 (95%CI: 0.03, 7.81), P = 0.17 to 1.00, I^2 = 0% to 3%; Supplemental Table 2] and discontinuation due to any reason [RR: 1.12 (95%CI: 0.67, 1.88), P = 0.67, I^2 = 0%; Supplemental Table 2] did not reveal group differences.

4. Discussion

In this meta-analysis of 10 RCTs comprising 344 schizophrenia patients, we found that adjunctive IN-OT (range = 40–80 IU/day) did not outperform placebo in treating schizophrenia. However, dose-response effect analyses revealed that adjunctive IN-OT (80 IU/day) was superior to placebo in the improvement of total psychopathology (I^2 = 0%) and positive symptom scores (I^2 = 28%). All-cause discontinuation and ADRs outcomes were similar, which is consistent with the findings of another meta-analysis (Oya et al., 2016).

The finding that 80 IU/day IN-OT improves total psychopathology and positive symptoms is partly consistent with another meta-analysis (Oya et al., 2016) that found that adjunctive IN-OT (80 IU/day) significantly improved positive and negative symptom scores. The improvement of positive symptoms may be partly attributed to the effects of IN-OT on decreasing paranoid ideation and fear, and enhancing social interaction, trust and calm and affiliative behaviour. (Ishak et al., 2011; Lee et al., 2009). Furthermore, IN-OT could significantly increase facial expressivity (Woolley et al., 2017) and improve cognitive function (Ota et al., 2017) in schizophrenia. The slight discrepancy between the present and the Oya et al. (2016) studies could be partly due to the fact that Oya et al. synthesized both change and endpoint data on psychopathology assessed with different rating scales directly, which is not recommended by the Cochrane Handbook (Higgins and Green, 2014).

This meta-analysis involving 10 studies (n = 344) improved upon (Williams and Burkner, 2017) Bayesian meta-analysis by adding two more RCTs (Buchanan et al., 2017; Jarskog et al., 2017). The larger

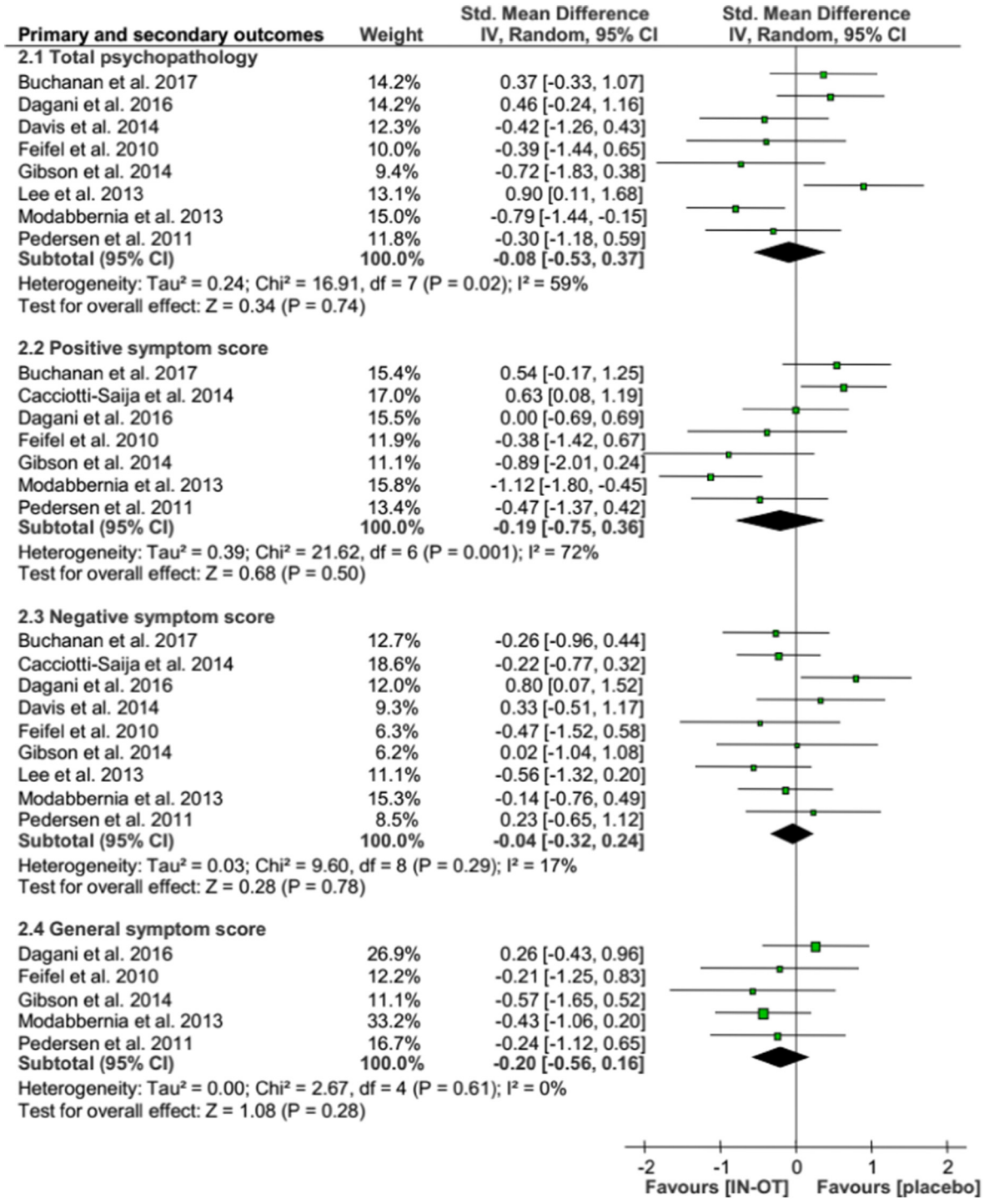

Fig. 2. Adjunctive intranasal oxytocin for schizophrenia: the forest plot of overall, positive, negative and general symptom scores.

sample size has enabled more sophisticated analyses, especially dose-response effect analyses, which yielded more comprehensive results and robust interpretations.

Augmentation with other sex hormones has also been a promising treatment option for schizophrenia. A recent review that examined estrogens (7 RCTs, n = 479), raloxifene (3 RCTs, n = 114), testosterone (1 RCTs, n = 30), dehydroepiandrosterone (4 RCTs, n = 160), and pregnenolone (4 RCTs, n = 222) found that estrogens and raloxifene appear to be effective and safe augmentation strategies in treating women with schizophrenia (Heringa et al., 2015). However, no head-to-head trials have compared the efficacy of IN-OT and estrogens/raloxifene in the treatment of schizophrenia.

There were several limitations to this study. First, the superiority of 80 IU/day IN-OT in improving the total psychopathology (SMD = −0.68) and positive symptom scores (SMD = −0.86) were only pooled from 2 RCTs, although the corresponding effect sizes were rated as "moderate" and "large", respectively (Cohen, 1988). Second, significant heterogeneity was found in the primary outcome in 8 of the 12 subgroups but not in the dose-response effect analyses in studies using 80 IU/day IN-OT for the total psychopathology and positive symptom scores. Third, important

Table 2
Subgroup analysis of the effect of mediating variables on the "total psychopathology" outcome.

Variables	Study (subjects)	SMDs (95%CI)	I^2 (%)	P-value for each subgroup	P-value across subgroups
1. Jadad score					
≥4[a]	4 (119)	−0.08 (−0.72, 0.57)	66	0.82	0.98
<4	4 (84)	−0.09 (−0.82, 0.64)	63	0.81	
2. Analyses					
Using ITT data	5 (152)	0.12 (−0.49, 0.73)	71	0.70	0.15
Using OC data	3 (51)	−0.49 (−1.06, 0.08)	0	0.09	
3. Trial duration (weeks)					
≥6[a]	5 (140)	−0.19 (−0.74, 0.37)	61	0.51	0.57
<6	3 (63)	0.11 (−0.75, 0.97)	63	0.80	
4. Age (years)					
≥38.4[a]	4 (97)	0.16 (−0.54, 0.78)	54	0.60	0.29
<38.4	4 (106)	−0.31 (−0.94, 0.32)	59	0.33	
5. Administration interval					
Every day	7 (181)	−0.03 (−0.54, 0.47)	63	0.90	0.45
Every session	1 (22)	−0.42 (−1.26, 0.43)	N/A	0.33	
6. Cognitive intervention					
SCT	1 (22)	−0.42 (−1.26, 0.43)	N/A	0.33	0.45
Not SCT	7 (181)	−0.03 (−0.54, 0.47)	63	0.90	

Abbreviations: CI = confidence interval; ITT = intent to treat; IN-OT = intranasal oxytocin; N/A = not applicable; OC = observed cases; SCT = social cognitive therapy; SMDs = standard mean differences.
[a] Analyzed using a median split.

outcome measures, such as neurocognitive functions, were not examined because the relevant data were not available.

5. Conclusion

Although the meta-analysis of adjunctive IN-OT in general did not show significant symptomatic improvement in schizophrenia, high dose adjunctive IN-OT (80 IU/day) appears to be efficacious and safe in improving total psychopathology and positive symptom scores. Further better quality RCTs of high dose adjunctive IN-OT for schizophrenia are warranted to clarify the place of IN-OT in the treatment of schizophrenia.

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Conflict of interest

The authors declare that they have no conflicts of interest concerning this paper.

CRediT authorship contribution statement

Wei Zheng: Conceptualization, Formal analysis, Methodology, Resources, Writing - original draft, Writing - review & editing. **Xiao-Min Zhu:** Formal analysis, Writing - review & editing. **Qing-E Zhang:** Formal analysis, Writing - review & editing. **Xin-Hu Yang:** Data curation. **Dong-Bin Cai:** Data curation. **Lu Li:** Writing - original draft. **Xian-Bin Li:** Writing - review & editing. **Chee H. Ng:** Writing - review & editing. **Gabor S. Ungvari:** Writing - review & editing. **Yu-Ping Ning:** Data curation, Funding acquisition, Resources, Supervision. **Yu-Tao Xiang:** Conceptualization, Methodology, Resources, Supervision.

Table 3
Dose-response effect analyses.

Variables	No of studies (no. of subjects)	SMDs (95%CI)	I^2 (%)	P-value for each subgroup	P-value across subgroups
Total psychopathology					
IN-OT dosage					
40 IU/day	3 (82)	0.33 (−0.38, 1.05)	61	0.36	0.08
48 IU/day	3 (66)	−0.11 (−0.74, 0.52)	35	0.73	
80 IU/day[a]	2 (55)	−0.68 (−1.23, −0.13)	0	**0.02**	
Positive symptom score					
IN-OT dosage					
40 IU/day	1 (32)	0.00 (−0.69, 0.69)	N/A	1.00	0.12
48 IU/day	4 (118)	0.07 (−0.61, 0.75)	66	0.85	
80 IU/day[a]	2 (55)	−0.86 (−1.56, −0.17)	28	**0.01**	
Negative symptom score					
IN-OT dosage					
40 IU/day	3 (82)	0.19 (−0.62, 1.00)	69	0.64	0.70
48 IU/day	4 (118)	−0.13 (−0.49, 0.24)	0	0.49	
80 IU/day[a]	2 (55)	−0.22 (−0.76, 0.31)	0	0.41	
General symptom score					
IN-OT dosage					
40 IU/day	1 (32)	0.26 (−0.43, 0.96)	N/A	0.46	0.31
48 IU/day	2 (34)	−0.37 (−1.05, 0.32)	0	0.29	
80 IU/day[a]	2 (55)	−0.37 (−0.91, 0.17)	0	0.18	

Bolded p-values: $P < 0.05$.
Abbreviations: CI = confidence interval; IU = International Units; IN-OT = intranasal oxytocin; N/A = not applicable; SMDs = standard mean differences.
[a] 40 IU/day for first week and 80 IU/day for thereafter.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.12.007.

References

Andreasen, N.C., 1983. Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City, IA.
Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City, IA.
Atkins, D., Best, D., Briss, P.A., Eccles, M., Falck-Ytter, Y., Flottorp, S., Guyatt, G.H., Harbour, R.T., Haugh, M.C., Henry, D., Hill, S., Jaeschke, R., Leng, G., Liberati, A., Magrini, N., Mason, J., Middleton, P., Mrukowicz, J., O'Connell, D., Oxman, A.D., Phillips, B., Schunemann, H.J., Edejer, T., Varonen, H., Vist, G.E., Williams Jr., J.W., Zaza, S., 2004. Grading quality of evidence and strength of recommendations. BMJ (Clin. Res. Ed.) 328 (7454), 1490.
Balshem, H., Helfand, M., Schunemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G.E., Falck-Ytter, Y., Meerpohl, J., Norris, S., Guyatt, G.H., 2011. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemiol. 64 (4), 401–406.
Buchanan, R.W., Kelly, D.L., Weiner, E., Gold, J.M., Strauss, G.P., Koola, M.M., McMahon, R.P., Carpenter, W.T., 2017. A randomized clinical trial of oxytocin or galantamine for the treatment of negative symptoms and cognitive impairments in people with schizophrenia. J. Clin. Psychopharmacol. 37 (4), 394–400.
Burkner, P.C., Williams, D.R., Simmons, T.C., Woolley, J.D., 2017. Intranasal oxytocin may improve high-level social cognition in schizophrenia, but not social cognition or neurocognition in general: a multilevel Bayesian meta-analysis. Schizophr. Bull. 43 (6), 1291–1303.
Cacciotti-Saija, C., Langdon, R., Ward, P.B., Hickie, I.B., Scott, E.M., Naismith, S.L., Moore, L., Alvares, G.A., Redoblado Hodge, M.A., Guastella, A.J., 2015. A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. Schizophr. Bull. 41 (2), 483–493.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Lawrence Erlbaum Associates, Hillsdale.
Dagani, J., Sisti, D., Abelli, M., Di Paolo, L., Pini, S., Raimondi, S., Rocchi, M.B., Saviotti, F.M., Scocco, P., Totaro, S., Balestrieri, M., de Girolamo, G., 2016. Do we need oxytocin to treat schizophrenia? A randomized clinical trial. Schizophr. Res. 172 (1–3), 158–164.
Davis, M.C., Green, M.F., Lee, J., Horan, W.P., Senturk, D., Clarke, A.D., Marder, S.R., 2014. Oxytocin-augmented social cognitive skills training in schizophrenia. Neuropsychopharmacology 39 (9), 2070–2077.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.
Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatry 65 (9), 728–731.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.
Feifel, D., Reza, T., 1999. Oxytocin modulates psychotomimetic-induced deficits in sensorimotor gating. Psychopharmacology 141 (1), 93–98.
Feifel, D., Macdonald, K., Nguyen, A., Cobb, P., Warlan, H., Galangue, B., Minassian, A., Becker, O., Cooper, J., Perry, W., Lefebvre, M., Gonzales, J., Hadley, A., 2010. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol. Psychiatry 68 (7), 678–680.
Feifel, D., MacDonald, K., Cobb, P., McKinney, R., Hadley, A., 2013. The long-term efficacy and safety of flexibly-dosed adjunctive intranasal oxytocin in patients with schizophrenia; an open-label study. Biol. Psychiatry 320s.
Fervaha, G., Foussias, G., Agid, O., Remington, G., 2014. Impact of primary negative symptoms on functional outcomes in schizophrenia. Eur. Psychiatry 29 (7), 449–455.
Galling, B., Roldan, A., Rietschel, L., Hagi, K., Walyzada, F., Zheng, W., Cao, X.L., Xiang, Y.T., Kane, J.M., Correll, C.U., 2016. Safety and tolerability of antipsychotic cotreatment in patients with schizophrenia: results from a systematic review and meta-analysis of randomized controlled trials. Expert Opin. Drug Saf. 15 (5), 591–612.
Galling, B., Roldan, A., Hagi, K., Rietschel, L., Walyzada, F., Zheng, W., Cao, X.L., Xiang, Y.T., Zink, M., Kane, J.M., Nielsen, J., Leucht, S., Correll, C.U., 2017. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World Psychiatry 16 (1), 77–89.
Gibson, C.M., Penn, D.L., Smedley, K.L., Leserman, J., Elliott, T., Pedersen, C.A., 2014. A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. Schizophr. Res. 156 (2–3), 261–265.
Goldman, M., Marlow-O'Connor, M., Torres, I., Carter, C.S., 2008. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr. Res. 98 (1–3), 247–255.
Gumley, A., Braehler, C., Macbeth, A., 2014. A meta-analysis and theoretical critique of oxytocin and psychosis: prospects for attachment and compassion in promoting recovery. Br. J. Clin. Psychol. 53 (1), 42–61.
Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54 (12), 1389–1398.
Helfer, B., Samara, M.T., Huhn, M., Klupp, E., Leucht, C., Zhu, Y., Engel, R.R., Leucht, S., 2016. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. Am. J. Psychiatry 173 (9), 876–886.
Heringa, S.M., Begemann, M.J., Goverde, A.J., Sommer, I.E., 2015. Sex hormones and oxytocin augmentation strategies in schizophrenia: a quantitative review. Schizophr. Res. 168 (3), 603–613.
Higgins, J., Green, S., 2014. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011).
Higgins, J., Higgins, J., 2008. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd., Chichester, UK.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Ishak, W.W., Kahloon, M., Fakhry, H., 2011. Oxytocin role in enhancing well-being: a literature review. J. Affect. Disord. 130 (1–2), 1–9.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17 (1), 1–12.
Jarskog, L.F., Pedersen, C.A., Johnson, J.L., Hamer, R.M., Rau, S.W., Elliott, T., Penn, D.L., 2017. A 12-week randomized controlled trial of twice-daily intranasal oxytocin for social cognitive deficits in people with schizophrenia. Schizophr. Res. 185, 88–95.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Kring, A.M., Gur, R.E., Blanchard, J.J., Horan, W.P., Reise, S.P., 2013. The clinical assessment interview for negative symptoms (CAINS): final development and validation. Am. J. Psychiatr. 170 (2), 165–172.
Lee, H.J., Macbeth, A.H., Pagani, J.H., Young 3rd, W.S., 2009. Oxytocin: the great facilitator of life. Prog. Neurobiol. 88 (2), 127–151.
Lee, M.R., Wehring, H.J., McMahon, R.P., Linthicum, J., Cascella, N., Liu, F., Bellack, A., Buchanan, R.W., Strauss, G.P., Contoreggi, C., Kelly, D.L., 2013. Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: results from a randomized double blind placebo controlled pilot study. Schizophr. Res. 145 (1–3), 110–115.
Lepage, M., Bodnar, M., Bowie, C.R., 2014. Neurocognition: clinical and functional outcomes in schizophrenia. Can. J. Psychiatr. 59 (1), 5–12.
Leucht, S., Rothe, P., Davis, J.M., Engel, R.R., 2013. Equipercentile linking of the BPRS and the PANSS. Eur. Neuropsychopharmacol. 23 (8), 956–959.
Modabbernia, A., Rezaei, F., Salehi, B., Jafarinia, M., Ashrafi, M., Tabrizi, M., Hosseini, S.M., Tajdini, M., Ghaleiha, A., Akhondzadeh, S., 2013. Intranasal oxytocin as an adjunct to risperidone in patients with schizophrenia: an 8-week, randomized, double-blind, placebo-controlled study. CNS Drugs 27 (1), 57–65.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (4), 264–269 (W264).
Ota, M., Yoshida, S., Nakata, M., Yada, T., Kunugi, H., 2017. The effects of adjunctive intranasal oxytocin in patients with schizophrenia. Postgrad. Med. 130 (1), 1.
Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating-scale. Psychol. Rep. 10 (3), 799–812.
Oya, K., Matsuda, Y., Matsunaga, S., Kishi, T., Iwata, N., 2016. Efficacy and safety of oxytocin augmentation therapy for schizophrenia: an updated systematic review and meta-analysis of randomized, placebo-controlled trials. Eur. Arch. Psychiatry Clin. Neurosci. 266 (5), 439–450.
Pedersen, C.A., Gibson, C.M., Rau, S.W., Salimi, K., Smedley, K.L., Casey, R.L., Leserman, J., Jarskog, L.F., Penn, D.L., 2011. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr. Res. 132 (1), 50–53.
Shahrestani, S., Kemp, A.H., Guastella, A.J., 2013. The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38 (10), 1929–1936.
Shilling, P.D., Feifel, D., 2016. Potential of oxytocin in the treatment of schizophrenia. CNS Drugs 30 (3), 193–208.
Sterne, J.A., Sutton, A.J., Ioannidis, J.P., Terrin, N., Jones, D.R., Lau, J., Carpenter, J., Rucker, G., Harbord, R.M., Schmid, C.H., Tetzlaff, J., Deeks, J.J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D.G., Moher, D., Higgins, J.P., 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ (Clin. Res. eE.) 343, d4002.
Torrey, E.F., Davis, J.M., 2012. Adjunct treatments for schizophrenia and bipolar disorder: what to try when you are out of ideas. Clin. Schizophr. Relat. Psychoses 5 (4), 208–216.
Wallace, B.C., Schmid, C.H., Lau, J., Trikalinos, T.A., 2009. Meta-analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med. Res. Methodol. 9, 80.
Williams, D.R., Burkner, P.C., 2017. Effects of intranasal oxytocin on symptoms of schizophrenia: a multivariate Bayesian meta-analysis. Psychoneuroendocrinology 75, 141–151.
Wolff-Menzler, C., Hasan, A., Malchow, B., Falkai, P., Wobrock, T., 2010. Combination therapy in the treatment of schizophrenia. Pharmacopsychiatry 43 (4), 122–129.
Woolley, J.D., Chuang, B., Fussell, C., Scherer, S., Biagianti, B., Fulford, D., Mathalon, D.H., Vinogradov, S., 2017. Intranasal oxytocin increases facial expressivity, but not ratings of trustworthiness, in patients with schizophrenia and healthy controls. Psychol. Med. 47 (7), 1311–1322.
Xiang, Y.Q., Zheng, W., Wang, S.B., Yang, X.H., Cai, D.B., Ng, C.H., Ungvari, G.S., Kelly, D.L., Xu, W.Y., Xiang, Y.T., 2017. Adjunctive minocycline for schizophrenia: a meta-analysis of randomized controlled trials. Eur. Neuropsychopharmacol. 27 (1), 8–18.
Zheng, W., Xiang, Y.T., Xiang, Y.Q., Li, X.B., Ungvari, G.S., Chiu, H.F., Correll, C.U., 2016. Efficacy and safety of adjunctive topiramate for schizophrenia: a meta-analysis of randomized controlled trials. Acta Psychiatr. Scand. 134 (5), 385–398.

Zheng, W., Cai, D.B., Yang, X.H., Ungvari, G.S., Ng, C.H., Muller, N., Ning, Y.P., Xiang, Y.T., 2017a. Adjunctive celecoxib for schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials. J. Psychiatr. Res. 92, 139–146.

Zheng, W., Li, X.H., Yang, X.H., Cai, D.B., Ungvari, G.S., Ng, C.H., Wang, S.B., Wang, Y.Y., Ning, Y.P., Xiang, Y.T., 2017b. Adjunctive memantine for schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials. Psychol. Med. 1–10.

Zheng, W., Xiang, Y.T., Yang, X.H., Xiang, Y.Q., de Leon, J., 2017c. Clozapine augmentation with antiepileptic drugs for treatment-resistant schizophrenia: a meta-analysis of randomized controlled trials. J. Clin. Psychiatry 28.