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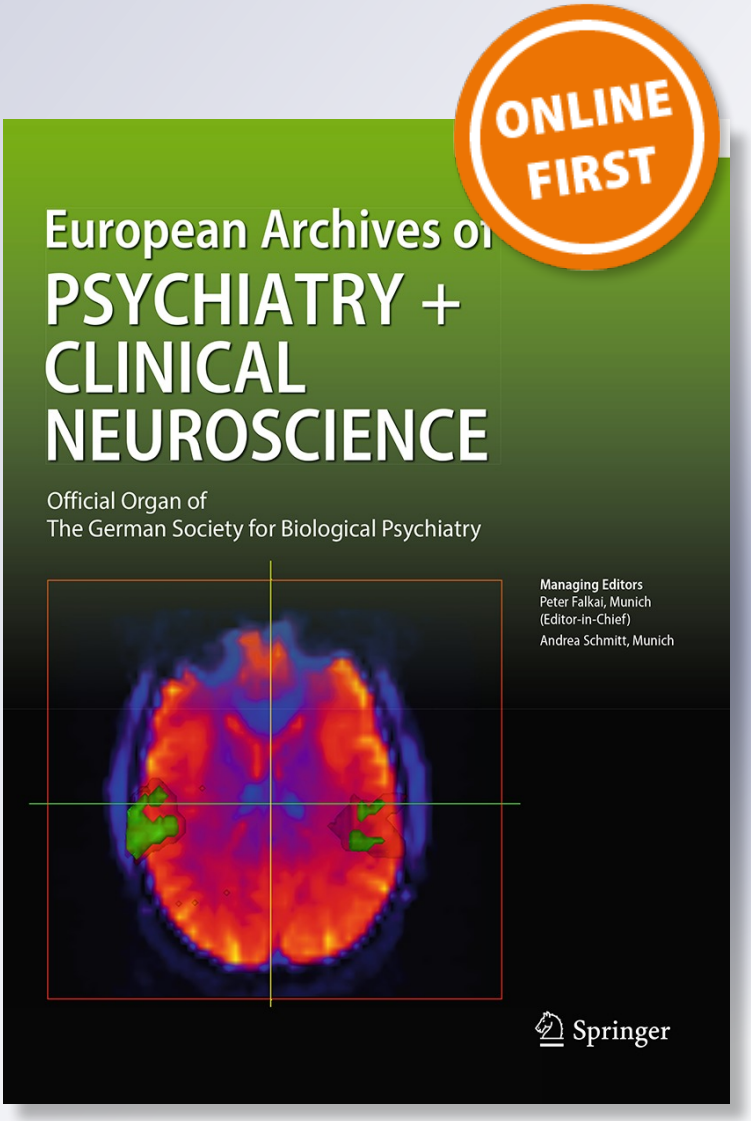

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ORIGINAL PAPER

Efficacy and safety of oxytocin augmentation therapy for schizophrenia: an updated systematic review and meta-analysis of randomized, placebo-controlled trials

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Abstract The aim of this study was to perform a systematic review and an updated and comprehensive meta-analysis of oxytocin augmentation therapy in patients with schizophrenia who received antipsychotic agents. Data published up to 07/11/2015 were obtained from PubMed, PsycINFO, and Cochrane Library databases. We conducted a systematic review and meta-analysis of patients' data from randomized controlled trials (RCTs) comparing oxytocin with placebo. Relative risk (RR), standardized mean difference (SMD), and 95 % confidence intervals (95 % CI) based on the random-effects model were calculated. We included seven RCTs; the total sample size was 206 patients. Oxytocin was superior to placebo for decreasing the Positive and Negative Syndrome Scale (PANSS) general subscale scores (SMD = −0.44, 95 % CI −0.82 to −0.06, $p = 0.02$, $I^2 = 0$ %, $N = 4$, $n = 112$); however, it was not different from placebo for total symptoms (SMD = −0.46, 95 % CI −1.20 to 0.28, $p = 0.22$, $I^2 = 80$ %, $N = 6$, $n = 162$), positive symptoms (SMD = −0.18, 95 % CI −0.87 to 0.51, $p = 0.60$, $I^2 = 81$ %, $N = 6$, $n = 192$), and negative symptoms (SMD = −0.34, 95 % CI −0.76 to 0.08, $p = 0.12$, $I^2 = 55$ %, $N = 7$, $n = 214$). However, a sensitivity analysis including only oxytocin administration on consecutive days studies was superior to placebo in negative symptoms (SMD = −0.44, 95 % CI −0.87 to −0.01, $p = 0.04$, $I^2 = 51$ %, $N = 6$ $n = 192$). There were no significant differences for all-cause discontinuation (RR = 1.02) and individual side effects such as headache and dizziness between oxytocin and placebo. Oxytocin may improve PANSS general subscale scores in schizophrenia and seems to be well tolerated. However, because the number of studies in the current analysis was small, further study will be required using larger sample sizes.

Keywords Oxytocin · Schizophrenia · Systematic review · Meta-analysis

Introduction

Schizophrenia has positive symptoms such as hallucinations and delusions, negative symptoms such as abulia and autism, and cognitive impairments [22]. Second-generation antipsychotics (SGAs) are widely used for treating schizophrenia, and there have been several reports about their effectiveness for positive symptoms; however, they do not improve negative symptoms and cognitive impairments sufficiently in comparison with first-generation antipsychotics (FGAs) [21, 26, 34]; this leads to poor functioning in the individuals with schizophrenia [32]. Cognitive impairments in patients with schizophrenia are strongly associated with quality of life and independent living [24]. Therefore, we need to find a treatment method that improves negative symptoms and cognitive impairments in schizophrenia. Oxytocin is a neuropeptide hormone that is produced by the hypothalamus and secreted by the posterior pituitary gland; this hormone modulates multiple social cognitive domains such as trust, attachment behavior, stress response, social memory, and the ability to recognize emotions and understand mental states [4, 15, 25]. Recent studies have found that intranasal oxytocin

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administered to normal human subjects increased perceived trustworthiness [10, 19, 33]. Neumann and Landgraf reported that oxytocin relieved anxiety and had antidepressant properties through the monoaminergic system [29]. The impairment of oxytocinergic dysfunction among the patients with schizophrenia has also been pointed out [17]. The amelioration of social deficits by administrating oxytocin has also been reported for the patients of schizophrenia [3, 9, 13]. Oxytocin is deconstructed through the gastrointestinal tract. However, several studies reported that intranasal oxytocin administration might cause central nervous system and demonstrate psychoactive properties [6, 23]. To date, only 1 meta-analysis of oxytocin for the treatment of schizophrenia has been reported [15]. The previous meta-analysis included four RCTs [8, 20, 27, 31] that evaluated the psychopathology and found that total symptoms, positive symptoms, and negative symptoms improved significantly in the oxytocin group; however, the Positive and Negative Syndrome Scale (PANSS) [18] general subscale scores did not improve in comparison with the placebo group (Table 1). However, seven RCTs with oxytocin have been conducted for the treatment of schizophrenia to date [5, 7, 8, 12, 20, 27, 31]. Therefore, the sample size of the current study ($n = 206$) is now larger than that of the previous study ($n = 105$). In addition, we analyzed discontinuation and individual side effects that the previous study had not evaluated. A meta-analysis can increase the statistical power for group comparisons and can overcome the limitations of sample size when larger trials are lacking. Using the random-effects model and SMD analysis, outcomes with different metrics can be combined [14] (Cochrane Collaboration. http://www.cochrane.org/). Considering this, we performed an updated meta-analysis of oxytocin augmentation therapy for the patients with schizophrenia using the data from the seven published RCTs [5, 7, 8, 12, 20, 27, 31]. It comprehensively evaluated the efficacy and safety of oxytocin in the management of schizophrenia (including the discontinuation rate and individual side effects).

Table 1 Comparison of our meta-analysis with previous meta-analysis

	Current meta-analysis	Gumley's meta-analysis
Included studies/total *n*	7/206	4/105[a]
Total symptom		
N/*n*	6/162	4/105
SMD (95 % CI)		
REM	−0.46 (−1.20 to 0.28)	−0.52 (−0.70 to −0.34)
FEM	−0.47 (−0.79 to −0.14)	−0.70 (−1.05 to −0.35)
I^2 (%)	80	99
Positive symptoms		
N/*n*	6/192	3/87
SMD (95 % CI)		
REM	−0.18 (−0.87 to 0.51)	−0.35 (−0.66 to −0.04)
FEM	−0.10 (−0.39 to 0.20)	−0.22 (−0.82 to 0.04)
I^2 (%)	81	81
Negative symptoms		
N/*n*	7/214	3/87
SMD (95 % CI)		
REM	−0.34 (−0.76 to 0.08)	−0.47 (−0.76 to −0.17)
FEM	−0.37 (−0.65 to −0.10)	−0.50 (−0.93 to −0.07)
I^2 (%)	55	86
PANSS general subscale scores		
N/*n*	4/112	3/87
SMD (95 % CI)		
REM	−0.44 (−0.82 to −0.06)	−0.25 (−0.57 to 0.07)
FEM	−0.44 (−0.82 to −0.06)	−0.27 (−0.70 to 0.16)
I^2 (%)	0	42

FEM fixed-effects model, *n* number of patients, *N* number of studies, *REM* random-effects model, *SMD* standardized mean difference, *95 % CI* 95 % confidence interval

[a] There were seven studies included in their systemic review, but Gumley et al. [15] included four studies in their meta-analysis regarding psychopathology. On the other hand, we included seven studies about psychopathology in our meta-analysis

Method

Inclusion criteria and search strategy

The current study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [28]. We performed a systematic literature review according to the PICO strategy: patients: schizophrenia diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) and who were stably medicated with no dose change for at least a month before the trial; intervention: intranasal oxytocin administration; comparator: placebo; and outcome: efficacy (total (primary outcome), positive, and negative symptoms and the PANSS general subscale scores) and safety (discontinuation due to all causes (primary outcome), adverse events, inefficacy, and individual side effects). We included only double-blind RCTs comparing oxytocin with placebo for patients with schizophrenia. Relevant

studies were identified through searches of PubMed, the Cochrane Library databases, and PsycINFO citations. There were no language restrictions, and we accepted data published up to July 11, 2015, using the key words "oxytocin," "schizophrenia," and "randomized" or "random" or "randomly." Additional eligible studies were also sought through scrutiny of the reference lists from the primary articles and relevant reviews. We excluded very short duration studies (<2 weeks) from the current systematic review and meta-analysis.

Data extraction

Two authors (K.O. and Y.M.) evaluated each of the identified reports against the study inclusion and exclusion criteria. There were no discrepancies between the two authors in the coding assignments made during the screening process. The same authors independently extracted, checked, and entered data into the Review Manager (Review Manager Version 5.3, Cochrane Collaboration, http://tech.cochrane.org/revman). When data required for the current study were missing from a publication, the first/corresponding author for that publication was contacted to request the additional information, including endpoint scores. We received the following data from Dr. Gibson: (1) number of patients who were randomized to each treatment arm, (2) discontinuations due to all causes, and (3) patient PANSS total scores. We also assessed the risk of bias in the trials using the Cochrane risk-of-bias criteria (domains: random sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias) [16].

Data synthesis and outcomes

We synthesized data when data were available from at least two studies for a particular outcome. The primary study outcome for efficacy was improvement in total symptoms, and that for safety was all-cause discontinuation rate. Total symptoms were measured using the PANSS total scores [8, 12, 27, 31] and the Brief Psychiatric Rating Scale (BPRS) [30] total scores [7, 20]. Secondary efficacy outcomes were positive and negative symptom scores and the PANSS general subscale scores. Positive symptoms were measured using the PANSS positive subscale scores [8, 12, 27, 31], the Scale for the Assessment of Positive Symptoms (SAPS) [2] total scores [5], and the BPRS positive subscale scores [20]. Negative symptoms were measured using the PANSS negative subscale scores [8, 12, 27, 31], the Scale for the assessment of negative symptoms (SANS) [1] total scores [5, 20], the clinical assessment interview for negative symptoms (CAINS) [11] total scores [7], and the PANSS general subscale scores [8, 12, 31]. Secondary safety outcomes were discontinuation due to adverse events or inefficacy. In addition, data were pooled to assess individual side effects.

Statistical analysis

We based analyses on intention-to-treat (ITT) or modified ITT data (i.e., at least one dose or at least one follow-up assessment); one observed case data [12] were included. To combine studies, the random-effects model by Der-Simonian and Laird, which is more conservative, was used in all cases because the underlying effects may differ across studies and populations that are usually heterogeneous. We also performed the meta-analysis using the fixed-effects model by Mantel–Haenszel because the previous meta-analysis used both random- and fixed-effects models. For continuous data, standardized mean difference (SMD) was used, combining the effect-size (Hedges' G) data. For dichotomous data, the risk ratio (RR) was estimated along with its 95 % confidential interval (CI). Study heterogeneity was measured using the Chi-square and I^2 statistics, with a Chi-square test of $p < 0.05$ and $I^2 \geq 50$ % indicating heterogeneity. In cases of $I^2 \geq 50$ % for the efficacy outcomes, sensitivity analyses were conducted to seek reasons for the heterogeneity. In addition, we performed a meta-regression analysis to evaluate the association between the results of meta-analyses regarding efficacy outcomes and some moderators {percent male, year of publication, PANSS total scores at baseline, the different scales utilized [PANSS, BPRS, SAPS (only positive symptoms), SANS (only negative symptoms) or CAINS (only negative symptoms)]}, oxytocin dose, duration of trial, and sample size (Supplementary appendix 4).

Results

Study characteristics

The search in the PubMed, Cochrane Library databases, and PsycINFO yielded 68 hits. We excluded 27 duplicate studies across the 3 databases as well as 24 studies on the basis of title or abstract review (Fig. 1). An additional ten full-text articles were excluded because they were short-duration studies (four articles), review articles (two articles), the same studies (two articles), a nonrandomized study (one article), or a single-arm study (one article; Supplementary appendix 2). No additional articles were identified by manually searching the review articles. Across seven RCTs (mean duration 4.9 weeks, range 2–8 weeks), 206 adult patients

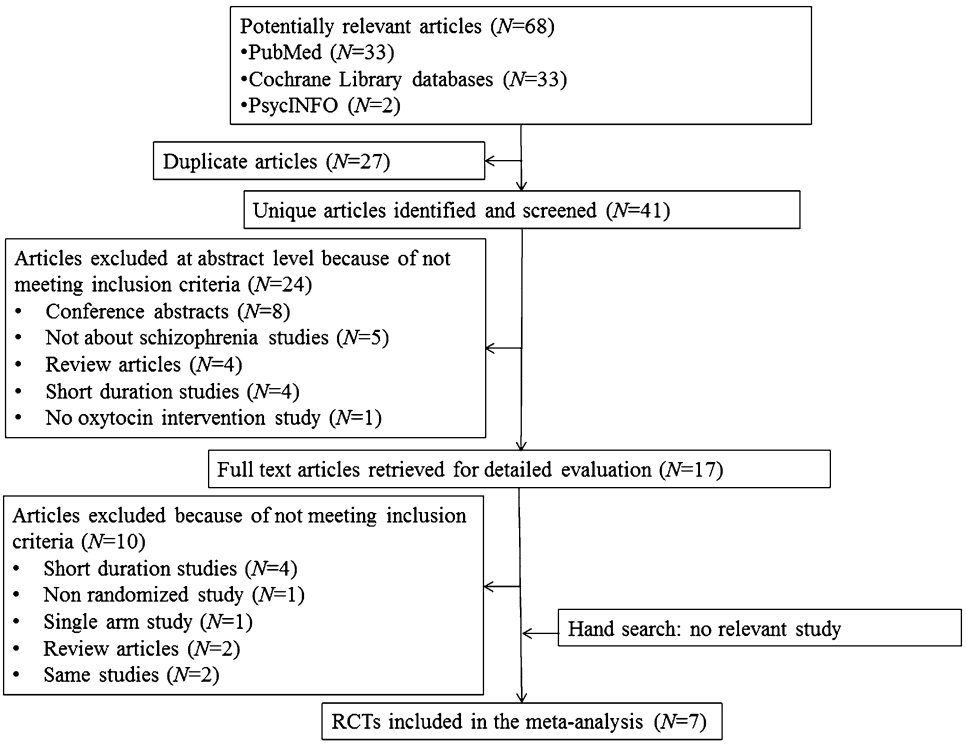

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA); flow diagram

with schizophrenia were randomized. Sample sizes ranged from 19 to 52 participants (Table 2). All studies were published in English and were not sponsored by the pharmaceutical industry. Two of seven studies were of high methodological quality based on Cochrane risk-of-bias criteria (i.e., they were double-blind RCTs that contained the required study design detail) [5, 27] (Supplementary appendix 3). The characteristics of the studies are shown in Table 2.

Results of the meta-analysis

Efficacy

Oxytocin was not different from placebo in total symptoms (SMD = −0.46, 95 % CI −1.20 to 0.28, $p = 0.22$, $I^2 = 80$, six studies, $n = 162$; Fig. 2). While oxytocin was superior to placebo in the reduction of the PANSS general subscale scores (SMD = −0.44, 95 % CI −0.82 to −0.06, $p = 0.02$, $I^2 = 0$, 4 studies, $n = 112$), it was not different from placebo for positive symptoms (SMD = −0.18, 95 % CI −0.87 to 0.51, $p = 0.60$, $I^2 = 81$, six studies, $n = 192$) and negative symptoms (SMD = −0.34, 95 % CI −0.76 to 0.08, $p = 0.12$, $I^2 = 55$, seven studies, $n = 214$) (Table 1).

Sensitivity analysis and meta-regression analysis

Significant heterogeneity existed among the studies in the total symptom ($I^2 = 80$ %, $p = 0.0002$), positive symptom ($I^2 = 81$ %, $p = 0.0001$), and negative symptom ($I^2 = 55$ %, $p = 0.04$) subscale scores. Therefore, we performed 8 sensitivity analyses of the efficacy outcomes (antipsychotic class, study design, cognitive intervention, location of trial, sex, duration of trial, oxytocin dose, and administration interval; Table 3). However, all sensitivity analyses retained the significant heterogeneity for total symptoms and positive symptoms. For negative symptoms, when divided by antipsychotic class [only risperidone trial vs. other antipsychotics trials (various antipsychotic trials and trials that did not report the information about antipsychotics)], the heterogeneity in other antipsychotics trials disappeared. However, significant heterogeneities in other sensitivity analyses regarding negative symptoms have still remained.

The effect size in each trial regarding total symptoms was associated with age (slope = 0.0700, $p = 0.0276$), sample size (slope = −0.0918, $p = 0.0176$), duration of trial (slope = 0.00009, $p = -3.00$), oxytocin dose (slope = −0.0293, $p = 0.00112$), PANSS total scores at baseline (slope = −0.112, $p = 0.00818$), and scales (slope = 1.16, $p = 0.00117$) (Supplementary appendix 4). The effect size in each trial regarding positive symptoms was associated with oxytocin dose (slope = −0.0339, $p = 0.00014$), percent male (slope = −0.114, $p = 0.00001$), and scales (slope = 0.981, $p = 0.00000$) (Supplementary appendix 4). The effect size in each trial regarding negative symptoms was associated with oxytocin dose (slope = −0.0217, $p = 0.00917$) and PANSS total scores

Table 2 Study, patient, and treatment characteristics of included randomized controlled trials

Study	Total *n* study design	Patients	Diagnosis duration	Age (mean ± SD)	Male (%)	Race (%)	Drug	*n*	Intervention (IU)	Concomitant drugs (%)	Outcomes
Gibson et al. [12] (USA) nonindustry	20 DBRCT OC	Age: 18–55, stability of symptom severity, PANSS total ≥60, suspiciousness/paranoia item ≥4, suspiciousness/paranoia item 3 and socially relevant PANSS items ≥3, low-to-moderate depressive symptoms, same medication and dose ≥1 month	DSM-IV-TR 6 weeks	OXY: 37.0 ± 10.8	OXY: 75	Caucasian: 50	OXY	11	OXY: 48 [fixed]	Remained on their pre-study medication regimen	OXY had a significant decrease on PANSS positive, negative and general subscale scores. PLA had a significant decrease on PANSS positive and negative scores[a]
				PLA: 42.8 ± 9.1	PLA: 83	Caucasian: 50	PLA	9	PLA		
Lee et al. [20] (USA) nonindustry	28 DBRCT ITT	Age: 18–60, stable AP treatment ≥6 weeks, no change in dose ≥30 days	DSM-IV 3 weeks	OXY: 44.7 ± 11.7	OXY: 69	Caucasian: 77	OXY	13	OXY: 40 [fixed]	CLO (38), FGAs (31), SGAs (31), Anti-CHOs (15)	BPRS total: OXY > PLA, SANS: OXY = PLA, CGI: OXY = PLA
				PLA: 35.1 ± 8.2	PLA: 73	Caucasian: 53	PLA	15	PLA	CLO (40), FGA (7), SGAs (53), Anti-CHOs (27)	
Modabbernia et al. [27] (Iran) nonindustry	40 DBRCT ITT	Age: 18–50, stable dose of RIS ≥4 weeks and <20 % change on the PANSS in two subsequent visits 1 week apart, PANSS total ≥60, disease duration ≥2 years	DSM-IV-TR 8 weeks	OXY: 32.3 ± 7.4	OXY: 85	NR	OXY	20	OXY: 40 for 1 week, 80 after that [fixed]	BIP (55), RIS(100)	PANSS total: OXY > PLA, positive: OXY > PLA, negative: OXY > PLA, general: OXY = PLA
				PLA: 33.2 ± 6.9	PLA: 80		PLA	20	PLA	BIP (60), RIS (100)	
Pedersen et al. [31] (USA) nonindustry	20 DBRCT ITT	Age: 18–55, paranoid or undifferentiated schizophrenia ≥1 year, PANSS total ≥60, PANSS suspiciousness/persecutory items ≥4, PANSS score suspiciousness/paranoia items 3 and socially relevant PANSS items ≥3, AP medications ≥1 month, same medication doses and symptoms ≥1 month	DSM-IV 2 weeks	OXY: 39.0 ± 11.2	OXY: 82	OXY: African-American: 45 Caucasian: 55	OXY	11	OXY: 48 [fixed]	RIS (55), ARI (18) OLA (18), CLO (9) FLU (9), ZIP (9), ADs (27), ACs (45)	PANSS total: OXY > PLA, positive: OXY = PLA, negative: OXY = PLA, general: OXY = PLA
				PLA: 35.8 ± 9.5	PLA: 89	PLA: African-American: 56 Caucasian: 44	PLA	9	PLA	ARI (33), CLO (33), RIS (33), HAL (11), PAL (11), PER (11), THI (11), ADs (22)	

Table 2 continued

Study	Total *n* study design	Patients	Diagnosis duration	Age (mean ± SD)	Male (%)	Race (%)	Drug	*n*	Intervention (IU)	Concomitant drugs (%)	Outcomes
Feifel et al. [8] (USA) nonindustry	19 DBCORCT ITT	Age: ≥18, AP medications: 1 or 2, same dose ≥4 weeks, PANSS total ≥55, CGI-S ≥4, PANSS score suspiciousness/paranoia items ≥4	DSM-IV 3 weeks	48.0 ± 8.9	80	Caucasian: 26.7 African-American: 53.3 others: 20	OXY	19	OXY: 40 for 1 week, 80 after that [fixed]	QUE (32), ARI (21), RIS (21), OLA (11), ZIP (5), CHL (5)	PANSS total: OXY > PLA, positive: OXY > PLA, negative: OXY > PLA, general: OXY = PLA, CGI-I: OXY > PLA
							PLA		PLA		
Davis et al. [7] (USA) nonindustry	27 DBRCT ITT	Clinically stable on AP, no dose change ≥10 % within 3 months	DSM-IV 6 weeks	OXY: 37.0 ± 10.8	100	NR	OXY	14	OXY: 40 on the session day [fixed] + SCT	Anti-CHOs (21)	BPRS total: OXY = PLA, CAINS: OXY = PLA
				PLA: 42.8 ± 9.1			PLA	13	PLA on the session day + SCT	Anti-CHOs (15)	
Cacciotti-Saija et al. [5] (Australia) nonindustry	52 DBRCT ITT	Age: 16–35, diagnosis: schizophrenia schizophreniform disorder, schizoaffective disorder, treatment for psychosis <3 years, medication was stabilized ≥8 weeks	DSM-IV-TR 6 weeks	OXY: 21.5 ± 4.2	OXY: 67	NR	OXY	27	OXY: 48 [fixed] + SCT[b]	APs (84), ADs (36), ACs (4), BENZs (4)	SAPS: OXY = PLA, SANS: OXY > PLA, CGI-S: OXY = PLA
				PLA: 22.3 ± 4.4	PLA: 72		PLA	25	PLA + SCT	APs (96), ADs (25), ACs (17), BENZs (4)	

ACs anticonvulsants, *ADs* antidepressants, *Anti-CHOs* anticholinergic drugs, *AP*(*s*) antipsychotic(s), *ARI* aripiprazole, *BENZs* benzodiazepines, *BIP* biperiden, *BPRS* the Brief Psychiatric Rating Scale, *CAINS* The Clinical Assessment Interview for Negative Symptoms, *CGI*-(*I, S*) The Clinical Global Impression-(Improvement, Severity), *CHL* chlorpromazine, *CLO* clozapine, *d*(*s*) day(s), *DB*(*CO*)*RCT* double-blind (crossover) randomized controlled trial, *DSM-IV*(*-TR*) diagnostic and statistical manual of mental disorders-IV (-text revision), *FGA*(*s*) first-generation antipsychotic(s), *FLU* fluphenazine, *HAL* haloperidol, *ITT* intention to treat, *IU* International Unit, *n* number of patients, *NR* not reported, *OC* observed cases, *OLA* olanzapine, *OXY* oxytocin, *PAL* paliperidone, *PANSS* Positive and Negative Syndrome Scale, *PER* perphenazine, *PLA* placebo, *QUE* quetiapine, *RIS* risperidone, *SANS* Scale for the Assessment of Negative Symptoms, *SAPS* Scale for the Assessment of Positive Symptoms, *SCT* social cognitive therapy, *SD* standard deviation, *SGA*(*s*) second-generation antipsychotic(s), *THI* thiothixene, *USA* the United States of America, *ZIP* ziprasidone

[a] The PLA group had significantly greater positive symptoms than OXY group at baseline

[b] Additional 24 IU of oxytocin was administered 15 min prior to each weekly session

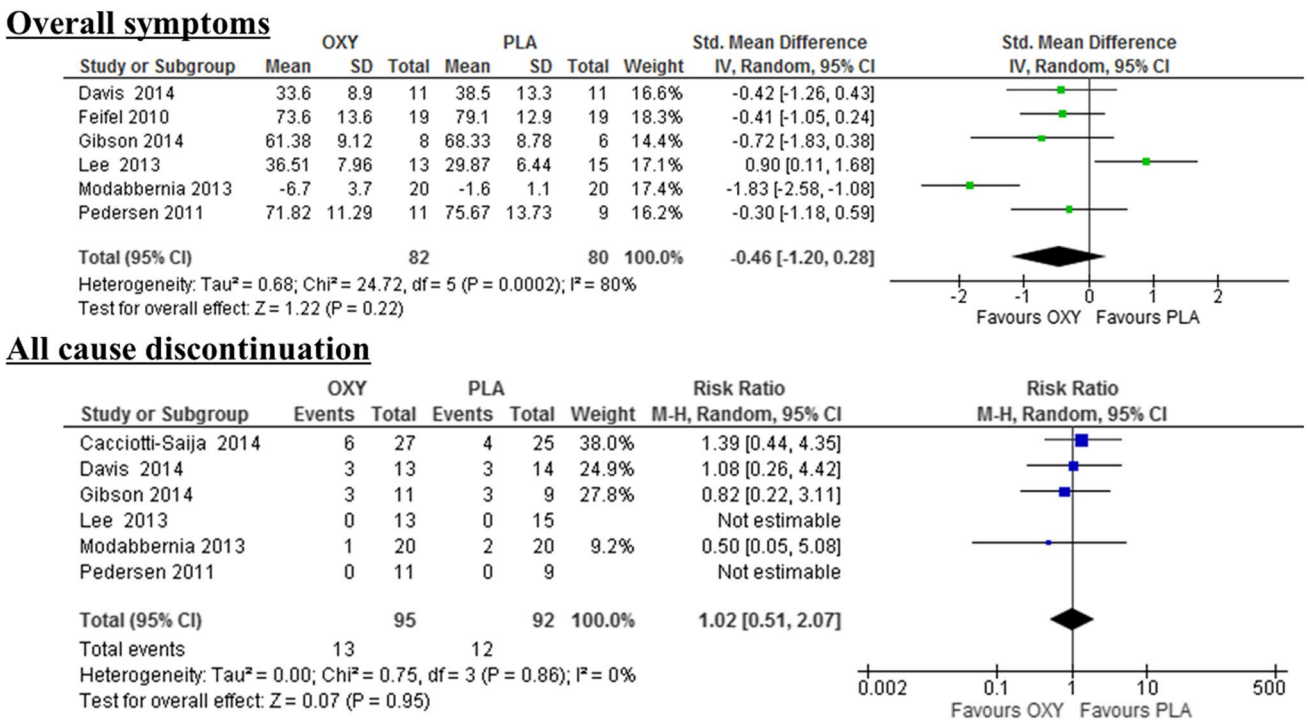

Fig. 2 Forest plot: improvement in total symptoms and discontinuation rate due to all causes

at baseline (slope = −0.111, $p = 0.00559$; Supplementary appendix 4). There were no modulators that were associated with the effect size of each trial regarding the PANSS general subscale scores (Supplementary appendix 4).

Safety

Oxytocin and placebo did not differ with regard to all-cause discontinuation (RR = 1.02, 95 % CI 0.51–2.07, $p = 0.95$, $I^2 = 0$ %, six studies, $n = 187$) (Table 4; Fig. 2). In addition, although six of seven studies reported discontinuations due to adverse events or inefficacy, all six studies reported that there were no patients who discontinued because of these reasons in each treatment group. Although we performed meta-analyses for individual side effects (e.g., daytime drowsiness, morning drowsiness, insomnia, sleep impairment, restlessness, sedation, tiredness, dizziness or light-headedness, dizziness, light-headedness, dry mouth, headache, stiffness, tremor, lethargy, malaise, burning nose, nasal irritation, salivation, sore throat, tinnitus, heart palpitations, shortness of breath, abdominal pain, constipation, decreased appetite, anorexia, diarrhea, dyspepsia or nausea, nausea, vomiting, increased appetite, increased frequency of nighttime urination, increased frequency of daytime urination, decreased frequency of daytime urination, decreased frequency of nighttime urination, skin rash, urticaria, and fever), there were no significant differences in individual side effects between oxytocin and placebo (Table 4).

Discussion

We performed an updated and comprehensive meta-analysis of oxytocin augmentation therapy for patients with schizophrenia. Although oxytocin was not superior to placebo with regard to total, positive, and negative symptoms, it was superior to placebo in the reduction of the PANSS general subscale scores. The previous meta-analysis [15] and RCTs [5, 7, 8, 12, 20, 27, 31] did not find that oxytocin was associated with the improvement of PANSS general subscale scores. Our meta-analysis enabled us to obtain greater statistical power than the previous meta-analysis because of the increase in sample size; therefore, we were able to establish that oxytocin was more effective than placebo at improving the PANSS general subscale scores. A recent review article [29] reported that oxytocin use was related to the pathophysiology of anxiety and depression, which are individual items in the PANSS general subscale. Gibson et al. [12] reported that oxytocin improved fear recognition and perspective compared with placebo. Thus, the improvement in the PANSS general subscale scores with oxytocin treatment might be caused by improvements in the items related to anxiety, depression, and cognitive functions. Further study will be required to determine which PANSS general subscale items are improved by oxytocin.

Significant heterogeneities were present in the meta-analyses pertaining to efficacy outcomes, with the exception of the

Table 3 Sensitivity analysis of efficacy of oxytocin augmentation therapy

Variable	Subgroup	*N*	*n*	I^2 (%)	SMD	95 % CI	*p*	Test for subgroup differences	
								p	I^2 (%)
(1) Total symptoms									
Study design[a]	Good quality	4	110	88	−0.42	−1.58 to 0.75	0.48	0.91	0
	Others	2	52	80	−0.49	−1.58 to 0.375	0.22		
AP class	RIS	1	40	N.A.	−1.83	−2.58 to −1.08	<0.00001	0.0005	91.9
	Various APs	5	122	55	−0.16	−0.72 to 0.40	0.58		
Cognitive intervention	SCT	1	22	N.A.	−0.42	−1.26 to 0.43	0.33	0.93	0
	Not SCT	5	140	84	−0.47	−1.37 to 0.43	0.31		
Country	USA	5	122	55	−0.16	−0.72 to 0.40	0.58	0.0005	91.9
	Iran	1	40	N.A.	−1.83	−2.58 to −1.08	<0.00001		
Sex	Only male	1	22	N.A.	−0.42	−1.26 to 0.43	0.33	0.93	0
	Male and female	5	140	84	−0.47	−1.37 to 0.43	0.31		
Study duration	>3 weeks	3	76	70	−1.02	−1.96 to −0.09	0.03	0.09	65.4
	≤3 weeks	3	86	71	0.06	−0.77 to 0.88	0.89		
OXY dose	40 IU	2	50	80	0.25	−1.04 to 1.54	0.70	0.37	0
	48 IU	2	34	0	−0.46	−1.16 to 0.23	0.19		
	80 IU[b]	2	78	87	−1.11	−2.50 to 0.29	0.12		
Administration interval	Every day	5	140	84	−0.47	−1.37 to 0.43	0.31	0.93	0
	Every session	1	22	N.A.	−0.42	−1.26 to 0.43	0.33		
(2) Positive symptoms									
Study design[a]	Good quality	4	140	87	0.01	−0.96 to 0.98	0.99	0.36	0
	Others	2	52	81	−0.51	−1.07 to 0.05	0.07		
AP class	RIS	1	40	N.A.	−1.12	−1.79 to −0.45	0.001	0.02	82.5
	Various APs	5	152	73	0.03	−0.63 to 0.69	0.93		
Cognitive intervention	SCT	1	52	N.A	0.63	0.08 to 1.19	0.03	0.03	78.4
	Not SCT	5	140	76	−0.37	−1.10 to 0.36	0.32		
Country	USA	4	100	71	−0.16	−0.94 to 0.62	0.69	0.94	0
	Others	2	92	94	−0.23	−1.95 to 1.49	0.79		
Study duration	>3 weeks	3	106	88	−0.42	−1.68 to 0.84	0.51	0.57	0
	≤3 weeks	3	86	76	0.03	−0.87 to 0.93	0.95		
Additional administration	OXY+	1	52	N.A.	0.63	0.08 to 1.19	0.03	0.03	78.4
	OXY−	5	140	76	−0.37	−1.10 to 0.36	0.32		
OXY dose	40 IU	1	28	N.A.	0.96	0.17 to 1.75	0.02	0.007	80.1
	48 IU	3	86	75	−0.15	−1.13 to 0.82	0.76		
	80 IU[b]	2	78	57	−0.75	−1.46 to −0.04	0.04		
(3) Negative symptoms									
Study design[a]	Good quality	5	162	68	−0.34	−0.92 to 0.24	0.25	0.98	0
	Others	2	52	0	−0.35	−0.90 to 0.20	0.42		
AP class	RIS	1	40	N.A.	−1.35	−2.04 to −0.65	0.0001	0.003	88.9
	Various APs	6	174	0	−0.19	−0.49 to 0.11	0.21		
Cognitive intervention	SCT	2	74	14	−0.04	−0.55 to 0.46	0.87	0.24	28.4
	Not SCT	5	140	57	−0.49	−1.02 to 0.05	0.07		
Country	USA	5	122	5	−0.17	−0.54 to 0.20	0.36	0.32	0.10
	Others	2	92	84	−0.76	−1.86 to 0.34	0.17		
Sex	Only male	1	22	N.A.	0.33	−0.51 to 1.17	0.44	0.11	60.7
	Male and female	6	192	51	−0.44	−0.87 to −0.01	0.04		

Table 3 continued

Variable	Subgroup	*N*	*n*	I^2 (%)	SMD	95 % CI	*p*	Test for subgroup differences	
								p	I^2 (%)
Study duration	>3 weeks	4	128	73	−0.34	−1.07 to 0.38	0.36	0.99	0
	≤3 weeks	3	86	6	−0.34	−0.78 to 0.11	0.14		
Additional administration	OXY+	1	52	N.A.	−0.22	−0.77 to 0.32	0.42	0.74	0
	OXY−	6	162	61	−0.35	−0.87 to 0.17	0.19		
OXY dose	40 IU	2	50	58	−0.13	−1.00 to 0.74	0.76	0.22	34.2
	48 IU	3	86	0	−0.08	−0.50 to 0.35	0.72		
	80 IU[b]	2	78	68	−0.91	−1.75 to −0.07	0.03		
Administration interval	Every day	6	192	51	−0.44	−0.87 to −0.01	0.04	0.43	0
	Every session	1	14	N.A.	0.02	−1.04 to 1.08	0.97		
(4) PANSS general subscale scores									
Study design[a]	Good quality	2	60	0	−0.55	−1.07 to −0.03	0.04	0.53	0
	Others	2	52	0	−0.31	−0.86 to 0.24	0.27		
AP class	RIS	1	40	N.A.	−0.72	−1.36 to −0.08	0.03	0.29	12
	Various APs	3	72	0	−0.29	−0.76 to 0.18	0.23		
Cognitive intervention	SCT	1	40	N.A.	−0.72	−1.36 to −0.08	0.03	0.29	12
	Not SCT	3	72	0	−0.29	−0.76 to 0.18	0.23		
Country	USA	3	72	0	−0.29	−0.76 to 0.18	0.23	0.29	12
	Iran	1	40	N.A.	−0.72	−1.36 to −0.08	0.03		
Study duration	>3 weeks	2	54	0	−0.68	−1.23 to −0.13	0.02	0.24	28
	≤3 weeks	2	58	0	−0.23	−0.74 to 0.29	0.39		
OXY dose	48 IU	2	34	0	−0.37	−1.05 to 0.32	0.29	0.81	0
	80 IU[b]	2	78	15	−0.47	−0.96 to 0.02	0.06		

AP(*s*) antipsychotic(s), *ITT* intention to treat, *IU* international unit, *n* number of patients, *N* number of studies, *N.A.* not applicable, *OXY* oxytocin, *RCT* randomized controlled trial, *RIS* risperidone, *SCT* social cognitive therapy, *SMD* standardized mean difference, *USA* the United States of America, *wks* weeks, *95 % CI* 95 % confidence interval

[a] Low-risk-of-bias studies (Cacciotti-Saija et al. [5] and Modabbernia et al. [27]) and other two studies include observed case (Gibson et al. [12]) and crossover study (Feifel et al. [8]) (see supplementary appendix 3)

[b] 40 IU for first weeks and 80 IU for thereafter

PANSS general subscale scores. The significant heterogeneity present only in the risperidone group (this was also an Iran-only study) [27] disappeared when the data were divided by antipsychotic class for negative symptoms. However, because the risperidone group had the largest effect size for all efficacy outcomes, it indicated that risperidone may be better suited for oxytocin augmentation therapy than other antipsychotics, in particular with regard to negative symptoms. In addition, there were two more important factors that may be associated with the observed heterogeneity. Gibson et al. [12] have shown that the placebo group had significantly greater positive symptoms than the oxytocin group at baseline. Cacciotti-Saija et al. [5] reported that although the administration of oxytocin combined with social cognitive therapy (SCT) did not improve social cognition, they did not provide a clear explanation for this result. Thus, we conducted subgroup analyses that separated these factors; however, significant heterogeneity was still detected (data not shown).

It is important to note that the oxytocin dose was associated with the effect size of each trial for total, positive, and negative symptoms. When the Davis study was excluded because of the administration interval, the study group with a daily administration of oxytocin showed significant efficacy with respect to negative symptoms compared with the placebo group (SMD = −0.44, 95 % CI −0.87 to −0.01, $p = 0.04$, $I^2 = 51$, six studies, $n = 192$). This result may indicate that oxytocin administration on consecutive days is better at ameliorating negative symptoms. The difference in the scale for each outcome was associated with the effect size of each trial for both total and positive symptoms. Although the number of studies and patients included in the meta-analysis was small and there was no overall effect, we cannot deny that these moderators reflect the results of the meta-analyses regarding the total, positive, and negative symptoms. On the other hand, no moderators were associated with the effect

Table 4 Discontinuation and individual side effects

	N	*n*	I^2 (%)	RR	95 % CI	*p*
All-cause discontinuation	6	187	0	1.02	0.51–2.07	1.02
Discontinuation due to adverse events	6	187	N.A.	N.E.		
Discontinuation due to inefficiency	6	187	N.A.	N.E.		
Daytime drowsiness	2	67	N.A.	1.20	0.44–3.30	0.72
Morning drowsiness	2	67	N.A.	1.00	0.34–2.93	1.00
Insomnia, sleep impairment	3	85	0	1.07	0.46–2.48	0.87
Restlessness	2	55	N.A.	1.15	0.36–3.72	0.81
Sedation	2	55	N.A.	3.46	0.41–29.36	0.25
Tiredness	2	79	N.A.	2.79	0.12–65.38	0.52
Dizzy or light-headed, dizziness, light-headed	5	177	0	1.16	0.57–2.34	0.68
Dry mouth	4	147	0	0.69	0.20–2.33	0.55
Headache	5	177	0	1.30	0.64–2.64	0.46
Stiffness	2	55	N.A.	2.31	0.24–22.62	0.47
Tremor	2	55	N.A.	1.15	0.19–7.08	0.88
Lethargy, malaise	4	125	0	0.65	0.20–2.15	0.48
Burning nose, nasal irritation	4	150	10	1.32	0.29–6.13	0.72
Salivation	2	55	N.A.	3.46	0.41–29.36	0.25
Sore throat	2	55	N.A.	0.23	0.01–4.37	0.33
Tinnitus	2	55	N.A.	0.23	0.01–4.37	0.33
Heart palpitations	2	79	N.A.	1.39	0.25–7.64	0.71
Shortness of breath	2	79	N.A.	1.54	0.41–5.80	0.52
Abdominal pain	2	55	N.A.	1.15	0.28–4.76	0.84
Constipation	4	147	0	1.00	0.30–3.26	1.00
Decreased appetite, anorexia	3	95	0	0.66	0.09–5.10	0.69
Diarrhea	3	107	0	1.01	0.26–3.97	0.98
Dyspepsia or nausea, nausea, vomiting	5	177	0	0.86	0.45–1.64	0.64
Increased appetite	2	67	N.A.	1.00	0.34–2.93	1.00
Increased frequency of daytime urination	2	79	N.A.	1.16	0.35–3.83	0.81
Increased frequency of nighttime urination	2	79	N.A.	1.23	0.31–4.98	0.77
Decreased frequency of daytime urination	2	79	N.A.	0.93	0.26–3.31	0.91
Decreased frequency of nighttime urination	2	79	N.A.	0.93	0.14–6.09	0.94
Skin rash, urticaria	3	107	0	0.55	0.12–2.47	0.44
Fever	2	55	N.A.	3.43	0.15–77.58	0.44

n number of patients, *N* number of studies, *N.A.* not applicable, *N.E.* not estimable, *RR* risk ratio, *95 % CI* 95 % confidence interval

size of each trial with regard to PANSS general subscale scores.

With regard to safety outcomes, there were no significant differences in the discontinuation rates and individual side effects between the oxytocin and placebo groups. Based on these findings, we determined that oxytocin add-on therapy seemed to be well tolerated.

The main limitation of the present study was the paucity of qualifying reports for inclusion in the analysis. We did not assess the presence of publication bias using the funnel plot because the number of studies included in the meta-analysis was small. In particular, future research should investigate the long-term efficacy and generate more safety data using larger samples. The second limitation was the shortness of the follow-up periods, which were all between 2 and 8 weeks. The third limitation was the difficulty in synthesizing the outcomes of cognitive functions that were assessed by various metrics in the included studies.

Conclusion

In conclusion, our results suggested that oxytocin is a well-tolerated treatment and oxytocin augmentation therapy may improve the PANSS general subscale scores of patients with schizophrenia. Future research should investigate the long-term efficacy and should generate more safety data for

patients with schizophrenia who receive oxytocin augmentation with antipsychotics.

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Author Contribution Drs. Oya and Matsuda had full access to all the data in the study and bear responsibility for the integrity of the data and accuracy of data analysis. Drs. Oya and Matsuda are responsible for the study concept and design. Drs. Oya and Matsuda conducted the analysis and interpretation of data and statistical analysis. Data were acquired by Drs. Oya and Matsuda. Drafting of the manuscript was performed by Drs. Oya, Matsuda, Matsunaga, and Kishi. The study was supervised by Drs. Kishi and Iwata.

Compliance with ethical standards

Conflict of interest Drs. Oya, Matsuda, Matsunaga, Kishi, and Iwata declare that they have no direct conflict of interest or grant support that is directly related to the content of the study. Dr. Oya has received speaker's honoraria from Eli Lilly and Otsuka; Dr. Matsuda has received it from Dainippon Sumitomo, Eli Lilly, and Otsuka; Dr. Matsunaga has received it from Eisai, Janssen, Novartis, Daiichi Sankyo, Ono, Eli Lilly, Takeda, and Otsuka; Dr. Kishi has received it from Abbott, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Eisai, Yoshitomi, Otsuka, Meiji, Shionogi, Tanabe-Mitsubishi, Tsumura, Novartis, and Pfizer; and Dr. Iwata has received it from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer.

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