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Adjunctive second-generation antipsychotics for specific symptom domains of schizophrenia resistant to clozapine: A meta-analysis

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ABSTRACT

A fair amount of subjects with schizophrenia do not respond to clozapine and are defined 'ultra-resistant'. In this systematic review and meta-analysis, we tested the efficacy of adjunctive second-generation antipsychotics (SGAs) for main symptom domains (positive, negative, and depressive symptoms) in individuals with clozapine-resistant schizophrenia. We searched main electronic databases till December 2017. We included twelve double-blind, randomized, placebo-controlled trials (RCTs), evaluating the efficacy of SGAs for clozapine non/partial responders. We did not find any difference between SGAs and placebo (standardized mean difference, SMD = −0.21; p = 0.170; I^2 = 68.0%) in improving positive symptoms. The effect size varied according to RCT duration (p = 0.025) and assessment methods (p = 0.016). Low-moderate effects of SGAs on both negative (SMD = −0.38; p = 0.005; I^2 = 62.7%) and depressive symptoms (SMD = −0.35; p = 0.003; I^2 = 4.9%), were estimated. In sum, our meta-analysis highlights the lack of efficacy of SGAs as add-on treatment for positive symptoms in clozapine-resistant schizophrenia. A small benefit of SGAs was estimated for both negative and depressive symptoms. Further RCTs are needed to establish efficacy and tolerability of SGAs or other augmentation strategies for different symptoms of clozapine-resistant schizophrenia.

1. Introduction

Treatment for schizophrenia is based on antipsychotic drugs combined with psychological therapies, social support, and rehabilitation (Owen et al., 2016). Despite the progresses due to second-generation antipsychotics (SGAs), a significant amount (30%–60%) of individuals with schizophrenia fail to respond to treatment (Gillespie et al., 2017), with remarkable societal and economic burden (Kennedy et al., 2014). Clozapine is the most efficacious antipsychotic agent (Leucht et al., 2013), recommended for treatment-resistant schizophrenia only (Siskind et al., 2016), due to its low tolerability profile (Bartoli et al., 2015; Wiciński and Węclewicz, 2018). A recent meta-analysis has shown that 10–20% of individuals with schizophrenia can be defined 'ultra-resistant', because they do not - or only partially - respond to clozapine (Siskind et al., 2017). Although different augmentation strategies have been investigated (Barber et al., 2017; Lally et al., 2016; Zheng et al., 2017), evidence for clozapine-resistant schizophrenia is poor (Muscatello et al., 2014b; Porcelli et al., 2012). Previous systematic reviews and meta-analyses (Barbui et al., 2009; Taylor et al., 2012) estimated a modest benefit of adjunctive antipsychotics in subjects treated with clozapine. SGAs may have different effects on the wide variety of schizophrenia features (Leucht et al., 2009; Veerman et al., 2014), including not only positive and negative (Carrà et al., 2018), but also depressive symptoms, which are often poorly considered in clinical practice (Schennach et al., 2015; Upthegrove et al., 2017; van Rooijen et al., 2018).

We conducted a systematic review and meta-analysis, investigating the efficacy of adjunctive SGAs for main symptom domains (positive, negative, and depressive symptoms) of clozapine-resistant schizophrenia. In addition, considering the methodological heterogeneity of trials published in this field (Taylor et al., 2012), we evaluated if different study characteristics, including duration, clozapine dose, assessment methods, antipsychotic agent and standardized dose, might be potential effect modifiers.

2. Material and methods

This systematic review and meta-analysis was conducted according

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to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The protocol was registered in PROSPERO - International Prospective Register of Systematic Reviews (21 December 2017; CRD42017084792).

2.1. Eligibility criteria

We included double-blind, randomized, placebo-controlled trials (RCTs) evaluating the efficacy of adjunctive SGAs in individuals with clozapine-resistant schizophrenia. SGAs, also called 'atypical antipsychotics', constitute a group of antipsychotics with lower risk of extrapyramidal side-effects as compared with high-potency first-generation antipsychotics, such as haloperidol (Jibson, 2017; Leucht et al., 2009). Since previous trials used heterogeneous definitions of treatment-resistant schizophrenia (Suzuki et al., 2011) and only recently an established definition has been provided (Howes et al., 2017), we considered 'non-responders', 'partial responders' or 'subjects with persistent symptoms', as defined by authors (Barbui et al., 2009). We included RCTs with data on treatment effects for at least one domain among positive, negative and depressive symptoms. We excluded case reports/case series, open and uncontrolled trials, as well as trials without a placebo arm. If results were published in multiple works (e.g., post-hoc analyses), we included in the meta-analysis the study with more comprehensive and complete information.

2.2. Outcomes

The primary outcome was efficacy of adjunctive SGAs as measured by change in (i) positive, (ii) negative, (iii) depressive symptoms. Standard instruments measuring different symptoms of schizophrenia were considered: the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS); the Scale for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS); the Calgary Depression Scale for Schizophrenia (CDSS); the Hamilton Depression Rating Scale (HDRS); and the Montgomery Asberg Depression Rating Scale (MADRS). The secondary outcome was the tolerability, measured by the difference in any-cause discontinuation rates between subjects on adjunctive SGAs and placebo.

2.3. Search strategy

We searched PubMed, Cochrane Library, and PsycINFO (via Ovid) electronic databases, from database inception till December 2017. No language restrictions were set. Our search phrases combined the term 'clozapine' with single SGAs, i.e., "*(amisulpride or aripiprazole or asenapine or brexpiprazole or cariprazine or iloperidone or lurasidone or olanzapine or paliperidone or quetiapine or risperidone or sertindole or sulpiride or ziprasidone) and clozapine*". In addition, we examined reference lists of systematic reviews and meta-analyses based on similar topics (Barber et al., 2017; Taylor et al., 2012).

Three authors (CDB, TT, EV) independently performed the preliminary screening based on titles and abstracts, identifying potentially eligible articles. After the first screening, full texts were independently evaluated to check the final eligibility according to inclusion and exclusion criteria. Discrepancies between authors were resolved by consensus, involving the entire research team.

2.4. Data extraction

We collected from included studies information on: year of publication; trial protocol identifier; setting; inclusion criteria; sample size, participants' characteristics: SGA agent and standardized dose (as measured by the ratio between tested mean dose and daily dose as defined by WHO) (Nosè et al., 2008); trial duration; and main results. Three authors (CDB, TT, EV) independently conducted data extraction, and possible discordances were resolved by consensus with co-authors. Corresponding authors were contacted if clarification or additional information on methods or data were needed.

2.5. Risk of bias and quality of evidence

We used the standard Cochrane Collaboration's tool for assessing risk of selection, performance, detection, and attrition biases (Higgins et al., 2011). Selection bias was evaluated checking the appropriateness of random sequence generation and allocation concealment. Performance and detection bias were assessed evaluating whether blinding of participants/personnel and outcome assessors, respectively, was guaranteed. Attrition bias was ascertained assessing proportions of dropouts leading to incomplete outcome data, and strategies dealing with this issue (intention-to-treat analysis). Three authors (CDB, TT, EV) independently assessed the risk of bias. Possible differences were resolved by consensus with co-authors.

In addition, we followed the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for grading the quality of evidence for the primary outcome as 'high', 'moderate', 'low' or 'very low', based on risk of bias in individual studies, inconsistency and/or imprecision of findings, indirectness, and publication bias (Schünemann et al., 2008).

2.6. Data analysis

For the primary outcome (effect of SGAs on positive, negative, depressive symptoms), we estimated standardized mean differences (SMDs) with 95% confidence intervals (95% CI) from each study. SMDs were derived from mean change scores (with standard deviation, standard error, or 95%CI) or were estimated from reported statistics, according to standard conversion methods (Lipsey and Wilson, 2001). SMDs were pooled in meta-analyses according to random effects models. Standard cut-offs were used to classify the effect size as small (0.2), moderate (0.5) or large (0.8) (Cohen, 1988; Schünemann et al., 2008).

Sensitivity analyses were performed, including studies with low attrition (dropout rates less than 10% in both interventions and placebo arms) and/or those reporting ITT analyses.

In addition, we carried out Monte Carlo permutation test for meta-regression analyses to analyse possible variations of effect size due to RCTs' characteristics (trial duration, clozapine baseline mean dose, SGA agent and standardized dose, and psychometric scales used to assess symptoms).

Secondary analyses estimated random effects risk ratio (RR) of any cause discontinuation of SGAs vs. placebo, considering all randomized subjects who received at least one treatment dose (safety population).

Consistency was estimated according to the I^2 index, with values of 25%, 50% and 75% taken to indicate low, moderate and high levels of heterogeneity across studies, respectively.

Finally, testing for publication bias, we performed the Egger's test (Egger et al., 1997) for any meta-analysis including at least 10 studies (Sterne et al., 2008).

Statistical significance was set at $p < 0.05$ and results were summarised using conventional forest plots. Analyses were performed using Stata statistical software package.

3. Results

3.1. Study selection

Our search generated 3,784, 443 and 2171 records from PubMed, Cochrane Library and PsycINFO (via OVID), respectively. We screened 75 additional articles included in two relevant reviews (Barber et al., 2017; Taylor et al., 2012). The preliminary screening by titles and abstracts identified 43 potentially eligible studies. After full text evaluation, we excluded 31 studies: 16 without a placebo arm (uncontrolled

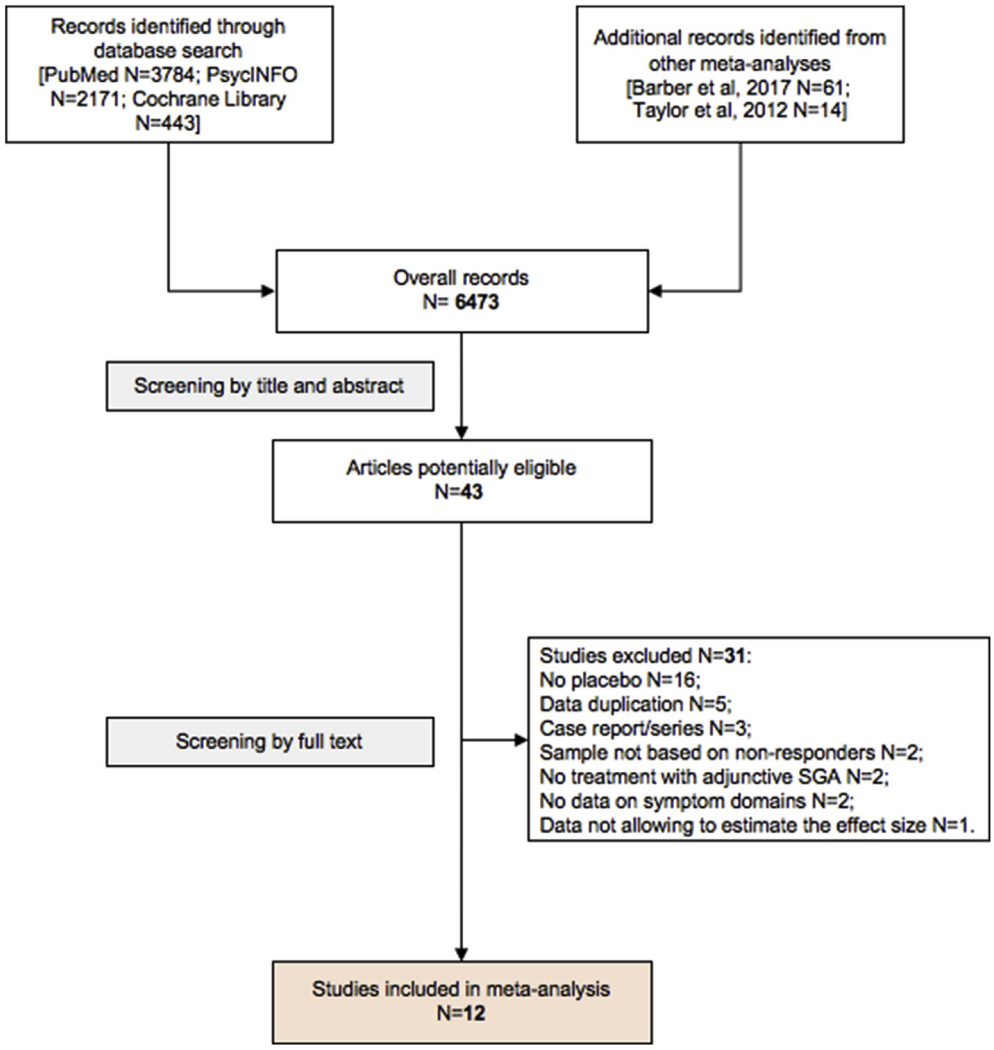

Fig. 1. Flow chart of study selection.
The flow chart illustrates the process of review of included/excluded studies.

studies or trials comparing active drugs); five duplicate publications or conference abstracts of RCTs already included; three case reports or series; two studies not including individuals with clozapine-resistant schizophrenia; two studies not based on adjunctive SGAs; two studies without data on symptom domains; and one study reporting data not allowing to estimate effect size.

Twelve RCTs (Anil Yağcioğlu et al., 2005; Barnes et al., 2017; Chang et al., 2008; Fleischhacker et al., 2010; Freudenreich et al., 2007; Honer et al., 2006; Josiassen et al., 2005; Muscatello et al., 2011, 2014a; Nielsen et al., 2012; Shiloh et al., 1997; Weiner et al., 2010) met inclusion criteria and were included in meta-analysis (Fig. 1).

Studies had been published from 1997 (Shiloh et al., 1997) to 2017 (Barnes et al., 2017), and all were in English language. Five studies tested risperidone (Anil Yağcioğlu et al., 2005; Freudenreich et al., 2007; Honer et al., 2006; Josiassen et al., 2005; Weiner et al., 2010) and three aripiprazole (Chang et al., 2008; Fleischhacker et al., 2010; Muscatello et al., 2011). Only one study was available for amisulpride (Barnes et al., 2017), sertindole (Nielsen et al., 2012), sulpiride (Shiloh et al., 1997) and ziprasidone (Muscatello et al., 2014a). Characteristics of included studies are summarised in Table 1.

3.2. Risk of bias of included studies

Seven studies had a low risk of selection bias, since appropriate methods for randomization and allocation concealment were used (Barnes et al., 2017; Chang et al., 2008; Fleischhacker et al., 2010; Honer et al., 2006; Muscatello et al., 2011, 2014a; Nielsen et al., 2012). On the other hand, five RCTs (Anil Yağcioğlu et al., 2005; Freudenreich et al., 2007; Josiassen et al., 2005; Shiloh et al., 1997; Weiner et al., 2010) did not provide sufficient information to evaluate the risk of selection bias. All studies were double-blind RCTs with low risk of performance and detection bias. Risk of attrition bias was low in 10 out of 12 studies, which had low discontinuation rates (< 10% in both treatment and placebo arms) and/or used ITT approaches. One study (Muscatello et al., 2011) considered only participants who completed the trial, despite the high drop-out rate in both SGA (30%) and placebo (15%) groups. In addition, another study (Barnes et al., 2017), provided data at the endpoint only for a portion of randomized subjects (32 out of 35 treated with SGA and 25 out of 33 with placebo). Summary assessment of risk of bias is available in Supplementary Table 1.

3.3. Synthesis of results

SMDs for different symptoms were derived from mean change scores in nine studies (Anil Yağcioğlu et al., 2005; Barnes et al., 2017; Chang et al., 2008; Fleischhacker et al., 2010; Freudenreich et al., 2007; Muscatello et al., 2011, 2014a; Nielsen et al., 2012; Shiloh et al., 1997). For three studies (Anil Yağcioğlu et al., 2005; Barnes et al., 2017;

Table 1
Clinical trials included in the meta-analysis.

Study	Study participants	Psychometric scores for clozapine resistance	Clozapine mean dose	Sample size	Tested SGA and dose	Trial duration	Outcome measures
Anil Yağcioğlu et al. (2005)	Partial responders treated with clozapine (300–900 mg) for at least 6 months	PANSS ≥72, CGI score of ≥4, and all PANSS positive items ≥3	468.3 mg	Randomized: 30 Completers: 29 Analysed: 29	Risperidone 2–6 mg Mean dose: 5.1 mg Standardized dose: 1.02	6 weeks	PANSS CDSS
Barnes et al. (2017)	Non responders treated with clozapine for at least 12 weeks, at a stable daily dose of at least 400 mg	PANSS ≥80, CGI score of ≥4, and SOFAS score ≤40	394 mg	Randomized: 68 Completers: 57 Analysed: 53	Amisulpride up to 800 mg Mean dose: –Standardized dose: –	12 weeks	PANSS CDSS
Chang et al. (2008)	Non or partial responders treated with clozapine for more than 1 year, at a stable daily dose of at least 400 mg for at least 8 weeks	BPRS ≥35, at least two SANS items ≥3, and BPRS positive ≥8 or at least one item ≥4	297.1 mg	Randomized: 62 Completers: 56 Analysed: 61	Aripiprazole 5–30 mg Mean dose: 15.2 mg Standardized dose: 1.01	8 weeks	BPRS SANS MADRS
Fleischhacker et al. (2010)	Partial responders treated with a stable daily dose of clozapine (200–900 mg) for at least 3 months	Residual positive, negative or other symptoms (no specific scores were used)	373.7 mg	Randomized: 207 Completers: 190 Analysed: 205	Aripiprazole 5–15 mg Mean dose: 11.1 mg Standardized dose: 0.74	16 weeks	PANSS
Freudenreich et al. (2007)	Partial responders treated with clozapine for at least 6 months, at a stable daily dose for at least 8 weeks	PANSS ≥60	456 mg	Randomized: 24 Completers: 19 Analysed: 24	Risperidone 4 mg Mean dose: 4 mg Standardized dose: 0.80	6 weeks	PANSS
Honer et al. (2006)	Partial responders treated with clozapine for at least 12 weeks, at a stable daily dose of at least 400 mg	PANSS ≥80, CGI score of ≥4, and SOFAS score ≤40	490 mg	Randomized: 68 Completers: 65 Analysed: 68	Risperidone 3 mg Mean dose: 2.94 mg Standardized dose: 0.59	8 weeks	PANSS
Josiassen et al. (2005)	Non or partial responders treated with clozapine for at least 3 months, at a daily dose of at least 600 mg/day or a plasma level of at least 350 ng/ml	BPRS ≥45 or ≥4 in at least two BPRS positive symptom items	564.7 mg	Randomized: 40 Completers: 40 Analysed: 40	Risperidone up to 6 mg Mean dose: 4.43 mg Standardized dose: 0.89	12 weeks	BPRS SANS
Muscatello et al. (2011)	Non or partial responders treated with clozapine for at least 1 year, at the highest tolerable range (200–450 mg) for at least 1 month	BPRS ≥25	326.0 mg	Randomized: 40 Completers: 31 Analysed: 31	Aripiprazole 10–15 mg Mean dose: 12.5 mg Standardized dose: 0.83	24 weeks	SAPS SANS CDSS
Muscatello et al. (2014a)	Non or partial responders treated with clozapine (350–600 mg) for at least 1 year, at a stable daily dose for at least 1 month	BPRS ≥25	445.6 mg	Randomized: 40 Completers: 33 Analysed: 40	Ziprasidone 80 mg Mean dose: 80 mg Standardized dose: 1.00	16 weeks	PANSS CDSS
Nielsen et al. (2012)	Non or partial responders treated with clozapine (minimum 150 mg) for at least 6 months, at an optimized daily dose of at least 150 mg	PANSS ≥65	414.5 mg	Randomized: 50 Completers: 42 Analysed: 50	Sertindole 16 mg Mean dose: 16 mg Standardized dose: 1.00	12 weeks	PANSS
Shiloh et al. (1997)	Partial responders treated with clozapine for at least 12 weeks at an adequate dose	BPRS ≥25	421.4 mg	Randomized: 28 Completers: 28 Analysed: 28	Sulpiride 600 mg Mean dose: 600 mg Standardized dose: 0.75	10 weeks	SAPS SANS HRSD
Weiner et al. (2010)	Partial responders treated with clozapine for more than 6 months, at a dose producing a plasma level higher than 350 ng/ml	BPRS ≥45 or CGI ≥4, and BPRS positive ≥8, with at least one item ≥4	–	Randomized: 69 Completers: 53 Analysed: 64	Risperidone 3–4 mg Mean dose: 3.96 mg Standardized dose: 0.79	16 weeks	BPRS SANS

List of abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; CDSS = Calgary Depression Scale for Schizophrenia; HRSD = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SGA = Second-generation antipsychotic; SOFAS = Social and Occupational Functioning Assessment Scale.

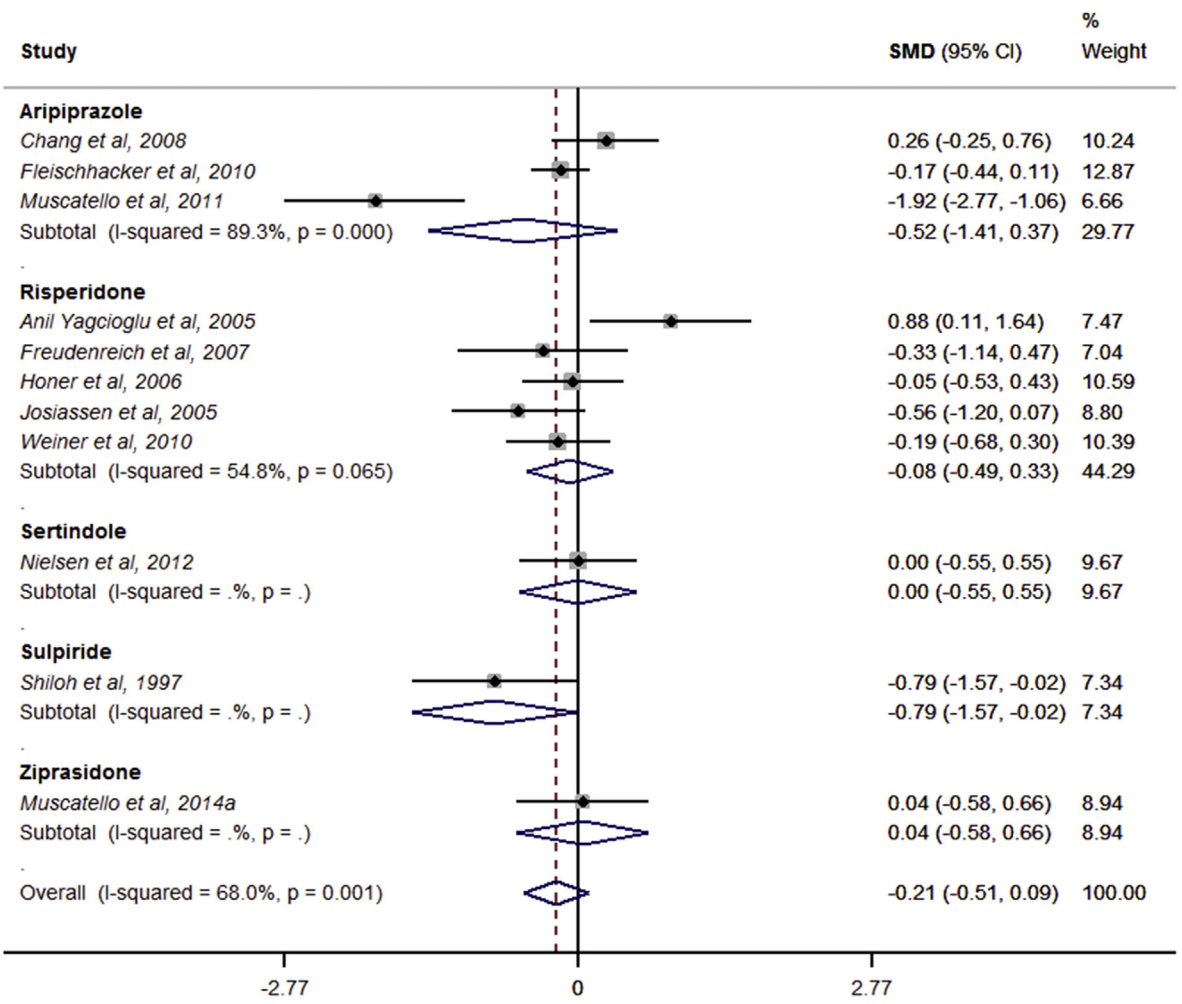

Fig. 2. Effect of SGA adjunctive treatment for positive symptoms in clozapine-resistant schizophrenia.
Forest plot of adjunctive second-generation antipsychotics effect (vs. placebo) for positive symptom change in clozapine-resistant schizophrenia. Error bars indicate 95% CI; SMD, standardized mean difference; SMD negative values favour second-generation antipsychotics, positive values favour placebo.

Muscatello et al., 2011), unpublished data were provided by the authors. Two studies (Honer et al., 2006; Weiner et al., 2010) reported Cohen's d. Finally, for one study (Josiassen et al., 2005), we computed SMDs from reported F-test values following standard methods (Lipsey and Wilson, 2001).

3.3.1. Positive symptoms

Eleven studies (Anil Yağcioğlu et al., 2005; Chang et al., 2008; Fleischhacker et al., 2010; Freudenreich et al., 2007; Honer et al., 2006; Josiassen et al., 2005; Muscatello et al., 2011, 2014a; Nielsen et al., 2012; Shiloh et al., 1997; Weiner et al., 2010), including 333 individuals randomized to SGAs and 325 to placebo, had data available on positive symptoms. The meta-analysis did not estimate any difference (SMD = −0.21; p = 0.170) between SGAs and placebo on improvement of positive symptoms, with moderate-high heterogeneity across studies (I^2 = 68.0%) (Fig. 2). The attrition-based sensitivity analysis excluding one study (Muscatello et al., 2011), confirmed the non-significant effect of SGAs on positive symptoms (p = 0.427). Although aripiprazole and sulpiride showed higher effect sizes, we could not uncover any significant difference among tested SGAs. In addition, meta-regression analyses (Table 2) showed a significant effect of both trial duration (p = 0.025) and assessment measures (p = 0.016). RCTs with longer follow-up and those using SAPS to measure changes in positive symptoms showed a significantly larger effect size. Finally, according to the Egger's test (p = 0.478), no risk of publication bias was found. The summary of quality of evidence for positive symptoms is reported in Supplementary Table 2.

3.3.2. Negative symptoms

Twelve studies (Anil Yağcioğlu et al., 2005; Barnes et al., 2017; Chang et al., 2008; Fleischhacker et al., 2010; Freudenreich et al., 2007; Honer et al., 2006; Josiassen et al., 2005; Muscatello et al., 2011, 2014a; Nielsen et al., 2012; Shiloh et al., 1997; Weiner et al., 2010), involving 368 subjects randomized to a SGA and 358 to placebo, had data available on negative symptoms. We estimated a significant effect of SGAs on improvement of negative symptoms (SMD = −0.38; p = 0.005), based on a moderate-high heterogeneity across studies (I^2 = 62.7%) (Fig. 3). The attrition-based sensitivity analysis excluding two studies (Barnes et al., 2017; Muscatello et al., 2011), confirmed the effect size magnitude (p = 0.009). Meta-regression analyses showed that none of characteristics considered could explain the degree of heterogeneity (Table 2). Although sulpiride and ziprasidone had higher effect sizes, no significant differences among tested SGAs were estimated. Finally, according to the Egger's test (p = 0.095), we could not detect any risk of publication bias. The summary of quality of evidence for negative symptoms is reported in Supplementary Table 2.

3.3.3. Depressive symptoms

The meta-analysis assessing changes of depressive symptoms was based on eight studies (Anil Yağcioğlu et al., 2005; Barnes et al., 2017; Chang et al., 2008; Freudenreich et al., 2007; Muscatello et al., 2011, 2014a; Shiloh et al., 1997; Weiner et al., 2010), including 181 subjects

Table 2
Influence of trial characteristics on effect size: Meta-regression analyses.

Study characteristics	Positive symptoms			Negative symptoms			Depressive symptoms		
	k	Coefficient	p-value	k	Coefficient	p-value	k	Coefficient	p-value
Trial duration	11	−0.073	0.025[e]	12	−0.011	0.713	8	−0.009	0.714
Clozapine mean dose	10	0.003	0.428	11	0.001	0.863	7	−0.001	0.714
SGA standardized dose	11	1.485	0.246	11	−1.185	0.309	7	0.290	0.801
Tested SGA	11		0.706	12		0.305	8		0.751
Amisulpride[a]					0.075			0.357	
Aripiprazole[a]		−0.334			−0.039			−0.096	
Sertindole[a]		0.074			0.203				
Sulpiride[a]		−0.719			−0.580			−0.084	
Ziprasidone[a]		0.114			−1.523			−0.363	
Psychometric scale	11		0.016 *	12		0.421	8		0.981
BPRS positive[b]		−0.063							
SAPS[b]		−1.254							
SANS[c]					−0.258				
BPRS anxiety/depression[d]								0.190	
HRSD[d]								−0.085	
MADRS[d]								0.028	
PANSS anxiety/depression[d]								−0.727	

List of abbreviations: BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; HRSD = Hamilton Rating Scale for Depression; MADRS = Montgomery Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SGA = Second-generation antipsychotic.

[a] Compared with risperidone.
[b] Compared with PANSS positive.
[c] Compared with PANSS negative.
[d] Compared with CDSS.
[e] Influence on effect size at a significance level of 0.05.

randomized to SGAs and 180 to placebo. We estimated a significant (SMD = −0.35; p = 0.003) and consistent (I^2 = 4.9%) effect of SGAs on change of depressive symptoms as compared with placebo (Fig. 4). Findings were confirmed also excluding three studies (Barnes et al., 2017; Muscatello et al., 2011; Weiner et al., 2010) with high attrition (p = 0.002). We excluded an additional study (Weiner et al., 2010), since this provided data allowing SMD estimation only for completers. Meta-regression analyses did not show any influence of tested variables, including single SGAs, on effect size (Table 2). The summary of quality of evidence for depressive symptoms is reported in Supplementary Table 2.

3.3.4. Discontinuation

No differences (RR = 1.15; p = 0.526), with a high consistency (I^2 = 0%) across studies, were observed, on discontinuation rates between subjects treated with SGAs (41/363) and those treated with placebo (37/353).

4. Discussion

4.1. Synthesis and interpretation of findings

This meta-analysis, based on 12 RCTs, tested efficacy and tolerability of adjunctive SGAs for specific symptom domains of clozapine-resistant schizophrenia (positive, negative, depressive symptoms). In addition, we estimated the moderating effect of main study characteristics.

Four main set of findings can be highlighted. First, adjunctive SGAs do not improve positive symptoms. This is confirmed by the sensitivity analysis including only studies with low attrition. Meta-regression analyses showed that the overall findings might be influenced by single instruments used to assess symptoms and follow-up duration. In particular, studies using SAPS reported higher effect sizes. This is consistent with evidence showing that different scales for positive symptoms may not equally measure clinical variations (Lyne et al., 2012). Correlations between SAPS/SANS and PANSS may be lower for positive than for negative symptoms, because of SAPS disorganized symptom items and lower repeated reliability (van Erp et al., 2014). In addition, effect size estimates increased with trial duration, which may be surprising since a relatively recent meta-analysis has shown that the differences between antipsychotics and placebo in efficacy seem to decrease over time (Rutherford et al., 2014). However, it is likely that findings of this meta-regression could be driven by outlier data from a study (Muscatello et al., 2011), which excluded from analyses those participants who discontinued from the study before the primary efficacy endpoint.

Second, we estimated that adjunctive SGAs yielded improvement in negative symptoms. Similar results were highlighted considering only studies with low risk of attrition bias. Our findings, showing a small to moderate effect, seem consistent with previous systematic analyses reporting that effects of SGAs for negative symptoms, although statistically significant, may not be clinically meaningful (Fusar-Poli et al., 2015). In addition, following standard recommendations (Schünemann et al., 2008), we should consider that some factors might downgrade the quality of evidence. Despite the absence of publication bias, our findings are based on RCTs with some risk of bias and a certain degree of heterogeneity. For these reasons, the quality of evidence on SGAs efficacy for negative symptoms in clozapine-resistant schizophrenia should be considered 'low'. Although meta-regression analyses failed to identify characteristics that may explain the heterogeneity found across studies, most of inconsistency may be due to a single trial (Muscatello et al., 2014a), reporting an improvement of negative symptoms much greater than other RCTs.

Third, we could show that adjunctive SGAs were associated with a significant improvement also of depressive symptoms. Evidence was consistent and not influenced by study characteristics (i.e., trial duration, clozapine dose, SGA agent and standardized dose, specific psychometric scale). However, the relevant effect size was small to moderate, and based on a small amount of RCTs, suggesting the possibility of publication bias and potential power issues for meta-regression analyses. Moreover, we should consider that just four studies (Anil Yağcioğlu et al., 2005; Barnes et al., 2017; Muscatello et al., 2011, 2014a) used the CDSS, despite representing the gold standard for depression assessment in subjects with schizophrenia (Addington et al., 1996; Grover et al., 2017; Schennach et al., 2012). For these reasons,

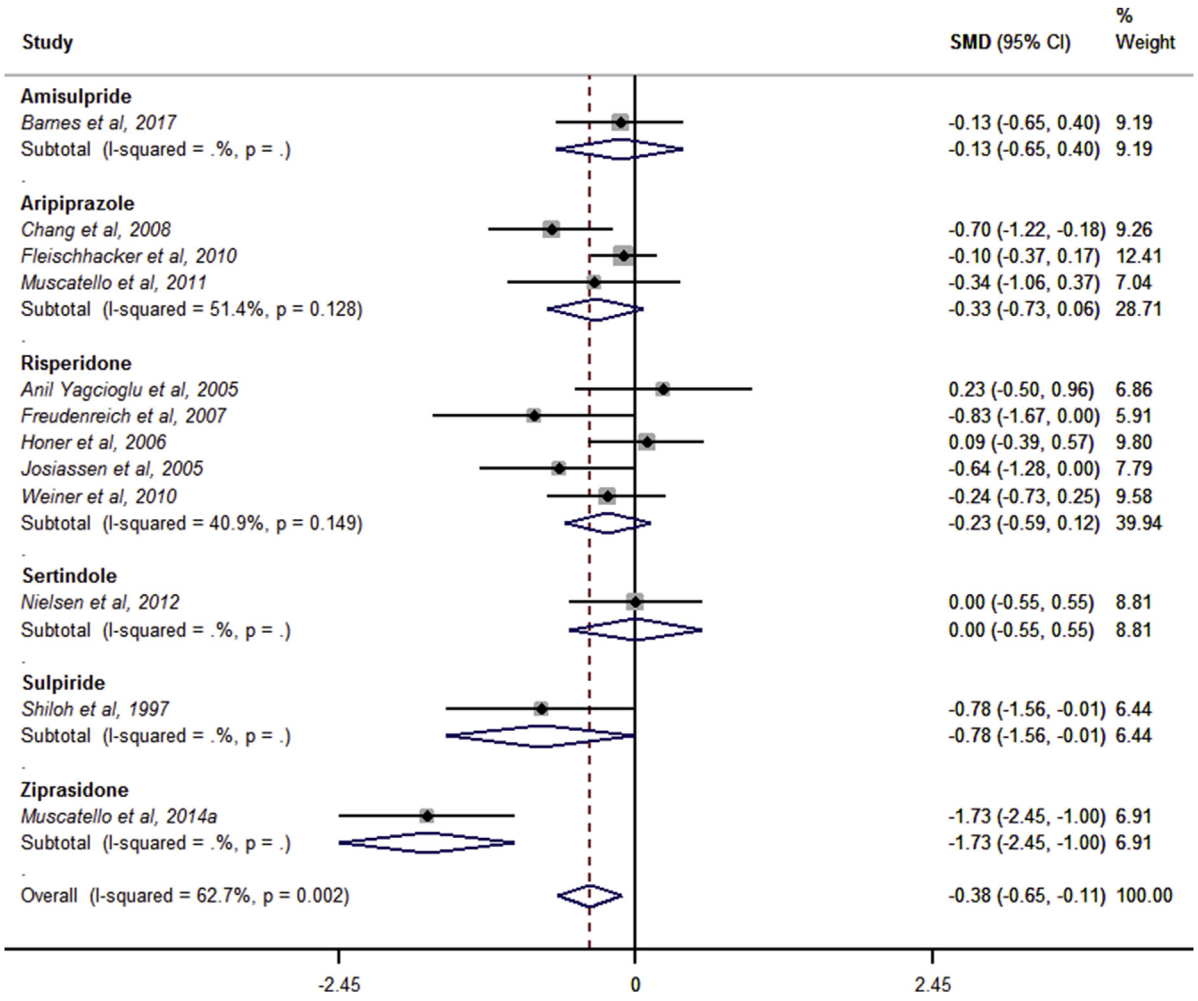

Fig. 3. Effect of SGA adjunctive treatment for negative symptoms in clozapine-resistant schizophrenia.
Forest plot of adjunctive second-generation antipsychotics effect (vs. placebo) for negative symptom change in clozapine-resistant schizophrenia. Error bars indicate 95% CI; SMD, standardized mean difference; SMD negative values favour second-generation antipsychotics, positive values favour placebo.

the overall level of evidence of adjunctive SGAs for depressive symptoms in clozapine-resistant schizophrenia, should be considered 'low'.

Finally, we did not find any difference between SGAs and placebo in terms of tolerability, using any-cause discontinuation as outcome measure. This is consistent with previous work (Taylor et al., 2012) testing both typical and atypical antipsychotics in clozapine non-responders with schizophrenia.

As a whole, the augmentation of clozapine with another SGA does not demonstrate any significant advantage on positive symptoms, while the effects on negative and depressive symptoms should be considered at best of moderate magnitude. Our results emphasize the need of reducing discrepancy between routine practice and evidence (Semisa et al., 2008), since clozapine is often augmented with other antipsychotic agents, despite the narrow evidence base (Pai et al., 2012). Nevertheless, from a clinical perspective, the improvement of negative and depressive symptoms can represent a meaningful achievement, considering their impact on the course and functional outcome of illness (Krynicki et al., 2018). Consistently, a recent redefinition of treatment resistant schizophrenia suggests to make clear which domain is resistant to treatment (Howes et al., 2017). Negative symptoms are indeed harsh to overcome, strictly connected with poor functioning and quality of life (Kirkpatrick et al., 2006), and relatively independent from positive symptoms (Kirkpatrick et al., 2001). On the other hand, depressive symptoms, which are often underestimated and can occur during any phase of schizophrenia, are also associated with unfavourable consequences, such as higher rates of relapse, re-hospitalizations, attempted and completed suicides, as well as poor treatment response and heavy burden of disease (Carrà et al., 2016; Conley et al., 2007). Therefore, even a small change in one of these symptom domains, could produce a meaningful clinical impact.

4.2. Limitations

Results of this meta-analysis may be influenced by several limitations and should be interpreted with caution.

First, we did not consider efficacy and tolerability of specific SGAs, aggregating them into a single class. Further RCTs with active drug comparisons (Barbui et al., 2011; Chang et al., 2011; Cipriani et al., 2013; Zink et al., 2009) are required to analyse potential differences among SGAs as add-on treatment to clozapine, since specific SGAs may have differential effects on various symptom domains of schizophrenia (Leucht et al., 2013). In addition, some SGAs, i.e., risperidone (data from five RCTs) and aripiprazole (data from three RCTs) were over-represented, whereas there were few or no RCTs testing other SGAs. Although meta-regression analyses did not show any influence of single tested SGAs on the overall effect size, more trials are required to evaluate efficacy of unexplored SGAs, such as paliperidone (Chang et al., 2011; Fernández-Miranda et al., 2017).

In addition, although RCTs were sufficiently comparable in terms of study design and clinical outcomes, we acknowledge a certain degree of methodological variability that we could only partially control for, using appropriate meta-regression analyses. This was true in terms of

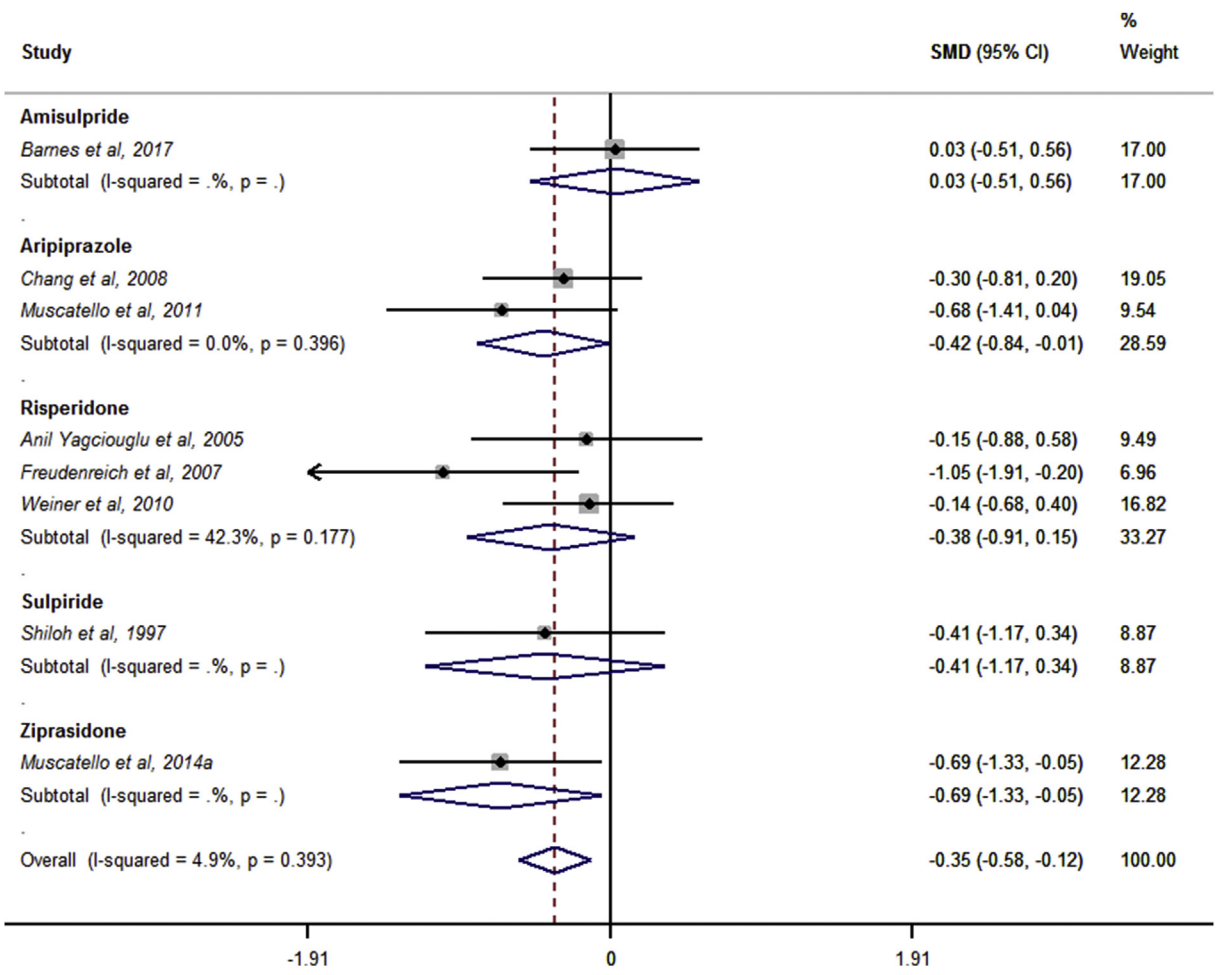

Fig. 4. Effect of SGA adjunctive treatment for depressive symptoms in clozapine-resistant schizophrenia.
Forest plot of adjunctive second-generation antipsychotics effect (vs. placebo) for depressive symptom change in clozapine-resistant schizophrenia. Error bars indicate 95% CI; SMD, standardized mean difference; SMD negative values favour second-generation antipsychotics, positive values favour placebo.

inclusion criteria, relevant diagnostic assessments, required length of clozapine treatment, as well as methods to define clozapine non/partial responders. For similar reasons, we could not consider further important symptom domains of schizophrenia such as cognitive impairment, which is crucial in the course and treatment of schizophrenia (Bowie and Harvey, 2006; Green, 2016). Indeed, the high variability in methods used to assess cognitive symptoms (e.g., Fleischhacker et al., 2010; Weiner et al., 2010) did not allow to carry out appropriate meta-analyses.

Finally, it should be acknowledged that the psychometric validity of some scales considered may be limited in terms of negative symptoms, for which a distinction between primary and secondary symptoms is essential (Kirkpatrick, 2014). For example, PANSS, though it is supposed to exclude secondary negative symptoms (Kay, 1990), whether 2-, 3-, or 5-factor models are identified, shows at least two separate factors, diminished expression and anhedonia-asociality, which are barely distinguishable from secondary negative symptoms (Blanchard and Cohen, 2006).

5. Conclusions

Despite some limitations, this meta-analysis showed that adjunctive SGAs for clozapine non/partial responders, have only partial benefit on main symptom domains of schizophrenia. We could not estimate any efficacy of SGAs for positive symptoms and only a small improvement for negative and depressive symptoms, based on a low quality of evidence. Additional RCTs are needed to explore if any SGA may be differently effective to treat specific symptoms of clozapine-resistant schizophrenia. Moreover, further research is required to establish efficacy and tolerability of different augmentation strategies, possibly including both pharmacological and non-pharmacological treatments.

Contributors

Bartoli and Carrà have full access to all study data and take responsibility for their integrity and accuracy of statistical analysis. Study concept and design: Bartoli, Carrà. Acquisition, analysis, or interpretation of data: All authors. Manuscript first draft: Bartoli, Di Brita, Tabacchi. Critical revision of the manuscript for important intellectual content: Carrà, Clerici, Crocamo, Esposito, Verrengia. Statistical analysis: Bartoli, Carrà, Crocamo. Technical and material support: Di Brita, Tabacchi, Verrengia. Supervision: Esposito, Clerici. All the authors have approved the final article.

Conflicts of interest

The authors declare no conflict of interest.

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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.2018.11.005.

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