Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia

Galling B, Vernon JA, Pagsberg AK, Wadhwa A, Grudnikoff E, Seidman AJ, Tsoy-Podosenin M, Poyurovsky M, Kane JM, Correll CU.

Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia.

Objective: To evaluate the efficacy and safety of antidepressant augmentation of antipsychotics in schizophrenia.

Methods: Systematic literature search (PubMed/MEDLINE/PsycINFO/Cochrane Library) from database inception until 10/10/2017 for randomized, double-blind, efficacy-focused trials comparing adjunctive antidepressants vs. placebo in schizophrenia.

Results: In a random-effects meta-analysis (studies = 42, n = 1934, duration = 10.1 ± 8.1 weeks), antidepressant augmentation outperformed placebo regarding total symptom reduction [standardized mean difference (SMD) = -0.37, 95% confidence interval (CI) = -0.57 to -0.17, P < 0.001], driven by negative (SMD = -0.25, 95% CI = -0.44–0.06, P = 0.010), but not positive (P = 0.190) or general (P = 0.089) symptom reduction. Superiority regarding negative symptoms was confirmed in studies augmenting first-generation antipsychotics (FGAs) (SMD = -0.42, 95% CI = -0.77 – 0.07, P = 0.019), but not second-generation antipsychotics (P = 0.144). Uniquely, superiority in total symptom reduction by NaSSAs (SMD = -0.71, 95% CI = -1.21, -0.20, P = 0.006) was not driven by negative (P = 0.438), but by positive symptom reduction (SMD = -0.43, 95% CI = -0.77, -0.09, P = 0.012). Antidepressants did not improve depressive symptoms more than placebo (P = 0.185). Except for more dry mouth [risk ratio (RR) = 1.57, 95% CI = 1.04–2.36, P = 0.03], antidepressant augmentation was not associated with more adverse events or all-cause/specific-cause discontinuation.

Conclusions: For schizophrenia patients on stable antipsychotic treatment, adjunctive antidepressants are effective for total and particularly negative symptom reduction. However, effects are small-to-medium, differ across antidepressants, and negative symptom improvement seems restricted to the augmentation of FGAs.
Limitations

- Outcomes are based on a relatively small number of double-blind studies with heterogeneous study origin, designs, study targets, and inclusion criteria, and a limited number of reported outcomes precluding more detailed analyses.
- Also, results could have been influenced by the increasing placebo-response in trials of patients with schizophrenia over time, potentially weakening results for SGAs compared to FGAs.
- Moreover, results on negative symptoms could be confounded by secondary negative symptoms.

Introduction

Despite a considerable increase in our understanding of schizophrenia and its multifaceted symptoms that involve thinking, perception, and emotion, medications that effectively treat all these dimensions are lacking (1, 2). All currently approved medications for schizophrenia act via dopamine modulation (3) and treat positive symptoms, agitation, and aggression, while the functionally important domains of negative symptoms and cognitive dysfunction remain relatively undressed (4). This fact has stimulated the search for extra-dopaminergic neurotransmitter modulation to address not only positive symptoms, but also other domains of schizophrenia (2, 5).

In clinical care, antidepressants are increasingly employed in patients with schizophrenia, most often targeting negative, cognitive, and depressive symptoms (6). This prescription practice is supported by evidence implicating dysfunction in the serotonergic (5-HT) system in the pathophysiology of psychosis, suggesting an alternate treatment target, and a potential role for serotonergic agents, which includes most classes of antidepressants (7, 8). Additionally, a potential therapeutic role of antidepressants in schizophrenia is supported by data suggesting antidepressant-related reduced transition from clinical high risk for psychosis to manifested psychosis (9, 10), and by fewer psychotic relapses in patients with schizophrenia and postpsychotic depression (11). Furthermore, previous meta-analyses have indicated the potential of antidepressants to improve negative symptoms, comorbid major depressive disorder (MDD), and cognition, either for all antidepressants pooled together (12–15) or for specific antidepressant classes or agents (16–19). However, concerns regarding augmentation strategies include the potential for pharmacokinetic interactions, decreased adherence, higher cost, and the risk of tolerability, particularly, the worsening of positive symptoms that has been described in MDD for tricyclic antidepressants as opposed to serotonergic antidepressant (20). However, worsening of psychosis through treatment with non-tricyclic antidepressants has not been proven true in patients with psychosis (14).

Meta-analyses combine information from studies, whose sample sizes are often insufficient to produce reliable outcomes in order to obtain a better understanding of the overall utility of an intervention. Subgroup- and metaregression-analyses enable researchers to gather additional information by contrasting results from multiple studies and identifying reasons for common effects across them. To enable researchers to do these analyses, the total population studied should be sufficiently large (≥1000 subjects) (21). However, it is also important to pool only data from studies whose methodologies and populations are sufficiently comparable to generate informative and meaningful results. Moreover, to yield clinically relevant information, it is vital that included and pooled studies reflect clinical reality.

Patient and illness characteristics of the studies examining the use of antidepressant co-treatment in schizophrenia vary widely depending on the target symptom (e.g., positive symptoms in chronic patients versus adverse events (AEs) in stable first episode patients) and the treatment strategy applied (i.e., augmentation strategies [adding an antidepressant to ongoing antipsychotic treatment in non-/partial-responders] versus co-initiation strategies [concurrent initiation of antipsychotic–antidepressant combination]). Merging results of such heterogeneous populations (varying study foci) and methodologies (augmentation vs. co-initiation) risks yielding spurious findings. Moreover, as antipsychotic monotherapy but not antidepressant–antipsychotic co-initiation is recommended as the first-line treatment for schizophrenia by all treatment guidelines (22–28), combining trials of the very different and clinically incompatible antidepressant–antipsychotic augmentation and co-initiation strategies in schizophrenia, as has been performed so far in meta-analyses (12, 14, 16–19,
Aims of the study

As about a third of patients with schizophrenia receive antidepressants to target either depressive symptomatology or other symptom domains of schizophrenia that are not adequately addressed by ongoing antipsychotic therapy (6, 32, 33), we conducted the first systematic review and meta-analysis that exclusively included studies of antidepressant augmentation of ongoing antipsychotic treatment (excluding co-initiation studies) for symptom-related efficacy (excluding studies focusing on smoking cessation or treatment of adverse events), hypothesizing that antidepressant augmentation would be superior to placebo, yet result in greater rates of some antidepressant-specific adverse events.

Methods

Search strategy and data abstraction

At least two independent authors (JAV, EG, AJS) searched PubMed/Ovid/PsycINFO/Cochrane Library from database inception until October 10, 2017 without language restriction for randomized controlled trials (RCTs) comparing adjunctive antidepressants with placebo for the treatment of schizophrenia, using the search terms: schizophrenia, random*, antidepressant, antidepressants, anti-depressant, anti-depressants, plus a list of all antidepressants ever approved for use in any country.

Endpoint data from each study were independently extracted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard by two independent investigators (JAV, EG, AJS, CUC, BG); inconsistencies were resolved by consensus. Authors were contacted for additional information.

Inclusion criteria

Inclusion criteria were (i) populations containing ≥10 adults, (ii) focusing on patients with a primary diagnosis of schizophrenia (allowing for <50% schizoaffective, schizophreniform, or delusional disorder) by any diagnostic criteria, (iii) currently on any antipsychotic for ≥2 weeks, (iv) randomization to augmentation with either adjunctive antidepressant or placebo, (v) double-blind, (vi) focusing on treatment efficacy for psychopathology, and (vii) available meta-analyzable data. Whenever duration of previous antipsychotic treatment was not reported, but the study design indicated that patients were chronically ill and/or stabilized as much as possible with antipsychotics prior to randomization, we assumed that the previous antipsychotic treatment duration was ≥2 weeks prior to the randomization. Studies focusing on the amelioration of AEs or smoking cessation were excluded, as those studies could have included treatment responders.

Outcomes

The primary outcome was total psychopathology, measured with a validated scale, that is, Positive and Negative Syndrome Scale (PANSS) (34) or Brief Psychiatric Rating Scale (BPRS) (35). Key secondary outcomes were positive and negative symptoms [PANSS subscales, BPRS subscales, Scale for the Assessment of Positive Symptoms (SAPS) (36), Scale for the Assessment of Negative Symptoms (SANS) (37), and depressive symptoms [Hamilton Scale for Depression (HDRS) (38), Montgomery-Asberg Depression Rating Scale (MADRS) (39), Beck Depression Inventory (BDI) (40), Calgary Depression Scale for Schizophrenia (CDSS)] (41).

Other outcomes included (i) all-cause and specific-cause (inefficacy, intolerability) discontinuation, (ii) study-defined response (total symptoms, negative symptoms, depression), (iii) other efficacy outcomes including general symptoms (PANSS general subscale), clinical global impression (CGI-S), quality of life (QoL), and (iv) adverse events (AEs).

Endpoint data were abstracted except for one study reporting 12- and 48-week as co-primary outcomes where 12-week data were preferred for homogeneity reasons (42).

Data synthesis and statistical analysis

We conducted a random effects (43) meta-analysis of outcomes for which ≥3 studies contributed data, using Comprehensive Meta-Analysis V3 (http://www.meta-analysis.com). We explored study heterogeneity using the chi-square test of homogeneity, with \( P < 0.05 \) indicating significant heterogeneity. All analyses were two-tailed with \( \alpha = 0.05 \).

Group differences in continuous outcomes were analyzed as the pooled standardized mean difference (SMD) in either change from baseline to endpoint (preferred) or endpoint scores (preferred if change score results were not available or skewed,
i.e., SD > twice the mean), using intent-to-treat (ITT) data (preferred) and observed cases (OC). Categorical outcomes were analyzed by calculating the pooled risk ratio (RR), using ITT data only.

We conducted subgroup and exploratory maximum-likelihood random effects meta-regression analyses of the primary outcome (total symptoms) and three key secondary outcomes (positive, negative, and depressive symptoms).

Subgroup analyses included: (i) study-focus, (ii) analyzed data (ITT vs. OC), (iii) treatment setting, (iv) region, (v) antipsychotic class, agents, and initiation (continuation of previous antipsychotics vs lead-in phase with study-specific antipsychotic), (vi) antidepressant class and agents, (vii) inclusion criteria for negative symptoms (threshold/cutoff vs. irrelevant positive and negative symptoms) and depressive symptoms (threshold vs. irrelevant vs. cutoff vs. unclear), and (viii) sponsorship.

Meta-regression variables included: (i) age [mean in all but one study reporting median (44)], (ii) sample size, (iii) per cent males, (iv) study duration, (v) publication year, (vi) illness duration [mean in all but one study reporting median (45)], (vii) per cent with schizophrenia, (viii) PANSS baseline, (ix) BPRS baseline, (x) total PANSS/converted BPRS baseline (46), (xi) PANSS negative subscale baseline, (xii) SANS baseline, (xiii) HDRS baseline, (xiv) negative symptom improvement (SMD) in relationship to depressive symptom improvement and vice versa, (xv) antipsychotic chlorpromazine (CLZ) equivalents (47), (xvi) antidepressant fluoxetine (FLU) equivalents (48) and risk of bias (number of low-risk judgments).

Finally, we inspected funnel plots and used Egger’s regression test (49) and the Duval and Tweedie’s trim and fill method (50) to quantify whether publication bias could have influenced the results.

Results

Search results

The initial search yielded 5319 hits. A total of 5196 studies were excluded as duplicates and/or after evaluation on the title/abstract level. A total of 166 additional articles were identified via hand search. After exclusion of 11 duplicates between the initial search and hand search results, 278 full-text articles were reviewed. Of those, 204 were excluded because of not fitting inclusion criteria, yielding 42 studies that were included in the meta-analysis (Fig. 1).

Study, patient, and treatment characteristics. Altogether, 42 studies (n = 1934) were included (42, 44, 45, 51–89). About 40.5% of the studies focused on negative symptoms, 28.6% on total symptoms, 23.8% on depressive symptoms, and 7.1% on cognition. The mean study duration was 10.1 ± 8.1 weeks (range = 4–52) weeks.

The majority of patients were diagnosed with schizophrenia (94.6%), with a mean illness duration of 13.7 ± 6.6 (range = 4.0–33.8) years and a mean baseline total PANSS/converted BPRS of 74.8 ± 17.8 that differed regarding study focus (total symptoms = 80.7 ± 16.0; negative symptoms = 71.1 ± 20.0; depressive symptoms = 73.7 ± 19.7). The mean age was 40.0 ± 7.1 (range = 29–62.3) years.

In most studies, patients continued their previous antipsychotic (78%), whereas in seven studies (14%) patients started using a study-defined antipsychotic prior to randomization. Information was insufficient for categorization in two studies (77, 88). Additional details are displayed in Table 1.

Total symptom reduction. Antidepressant augmentation was superior to placebo for overall symptom reduction (studies = 30, n = 1311, SMD = −0.37, 95% CI = −0.57 to −0.17, P < 0.001). The Egger test (intercept = −2.41, 95% CI: −4.29 to −0.53, P = 0.013) indicated the potential presence of publication bias. After adjustment for missing studies, using the trim and fill method, the SMD decreased to −0.34 (95% CI = −0.45 to −0.23).

Superiority was replicated in studies focusing on total symptom severity and on negative symptoms, but not in studies focusing on depressive symptoms (for more details see Table S1).

In subgroup analyses of antidepressant classes, superiority was evident in studies augmenting antipsychotics with noradrenergic and specific serotonergic antidepressants (NaSSAs) and serotonin–norepinephrine reuptake inhibitor (SNRI; Table S1). In the analysis of single agents, superiority was seen for mirtazapine and fluoxetine (Table 2).

Meta-regression results showed that younger age (P = 0.042) and lower risk of bias (studies focusing on total symptom severity only, P < 0.001) moderated greater total symptom improvement (P = 0.042, Table S1).

Positive symptoms. Antidepressant augmentation was not superior to placebo for positive symptom reduction (studies = 30, n = 1193, SMD = −0.11, 95% CI = −0.26 to 0.05, P = 0.190; Fig. 2.
Table S1). The Egger test (intercept = 0.021, 95% CI: 1.62 to 1.57, \( P = 0.978 \)) did not indicate the presence of publication bias.

In subgroup analyses, antidepressant augmentation was only superior for positive symptoms in studies augmenting with NaSSAs (\( P = 0.012 \), Table S1). No significant dose effect emerged within these studies.

Meta-regression results showed that a higher total PANSS/converted BPRS-score at baseline moderated greater positive symptom improvement (\( P = 0.049 \), Table S1).

**Negative symptoms.** Antidepressant augmentation was superior to placebo for negative symptom reduction (studies = 32, \( n = 1348 \), SMD = 0.25, 95% CI: 0.44 to 0.06, \( P = 0.010 \); Fig. 2, Table S1). The Egger test (intercept = -0.99 to 3.00, \( P = 0.312 \)) did not indicate the presence of publication bias.

Superiority was replicated in studies focusing on total and negative symptom severity, but not in studies focusing on depressive symptoms (for more details see Table S1).

Antidepressant augmentation was efficacious for negative symptoms in studies augmenting FGAs, but not SGAs. Superiority was evident in studies augmenting with SSRIs and SNRI, but not with other antidepressant classes or individual agents (Table 2, Table S1). Results were replicated in studies focusing on negative symptoms (Table S1). No significant dose effect emerged for SSRIs.

Meta-regression results showed that lower risk of bias (\( P = 0.044 \)) moderated greater total symptom improvement (Table S1).
Table 1. Study, patient, and treatment characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>ROB</th>
<th>n</th>
<th>Duration (weeks)</th>
<th>Setting</th>
<th>Study focus</th>
<th>Inclusion criteria</th>
<th>Depressive symptoms</th>
<th>Sample description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI) studies: Salokangas 1996 (5) (Finland)</td>
<td>DB/RCT</td>
<td>5</td>
<td>61</td>
<td>12</td>
<td>Inpatients</td>
<td>Negative symptoms (PANSS-N); Total psychopathology</td>
<td>Exclusion of MDD or BPRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 20.3 ± 0.06; CGI-S = 4.9 ± 0.08</td>
</tr>
<tr>
<td>Zucco 2009 (6) (Italy)</td>
<td>DB/RCT</td>
<td>4</td>
<td>198</td>
<td>12</td>
<td>Outpatients</td>
<td>Depression (HAMD, CGI)</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (HAMD) ≥ 20</td>
<td>Negative symptoms</td>
<td>PANSS = 4.00 ± 0.72</td>
</tr>
<tr>
<td>Imno 2010 (6) (Israel)</td>
<td>DB/RCT</td>
<td>5</td>
<td>40</td>
<td>10</td>
<td>In- and outpatients</td>
<td>Negative symptoms (PANSS-N); social functioning (BFS)</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 83.00 ± 18.90; CGI-S = 4.45 ± 0.75</td>
</tr>
<tr>
<td>Shin-Ja-Shti 2007 (6) (Iran)</td>
<td>DB/RCT</td>
<td>3</td>
<td>50</td>
<td>8</td>
<td>Inpatients</td>
<td>Negative symptoms (SANS)</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 7.2 ± 0.5</td>
</tr>
<tr>
<td>Arango 2000 (67) (USA)</td>
<td>DB/RCT</td>
<td>4</td>
<td>32</td>
<td>8</td>
<td>Outpatients</td>
<td>Primary outcomes not specified; Total symptoms (BPRS-S, HDRS); MIMS</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 20.3 ± 0.06; CGI-S = 4.9 ± 0.08</td>
</tr>
<tr>
<td>Buchanan 1996 (68) (USA)</td>
<td>DB/RCT</td>
<td>3</td>
<td>34</td>
<td>8</td>
<td>Outpatients</td>
<td>Positive symptoms (BPRS); negative symptoms (SANS)</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 34.05 ± 5.46</td>
</tr>
<tr>
<td>Geff 1995 (69) (USA)</td>
<td>DB/RCT</td>
<td>4</td>
<td>41</td>
<td>6</td>
<td>Outpatients</td>
<td>Primary outcomes not specified; Total symptoms (BPRS); parkinsonism</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 0.20 ± 0.06; CGI-S = 4.00 ± 0.7</td>
</tr>
<tr>
<td>Spina 1994 (60) (Italy)</td>
<td>DB/RCT</td>
<td>3</td>
<td>34</td>
<td>12</td>
<td>Inpatients</td>
<td>Negative symptoms (SANS)</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 7.2 ± 0.5</td>
</tr>
<tr>
<td>Nijs 2012 (61) (Italy)</td>
<td>DB/RCT</td>
<td>6</td>
<td>47</td>
<td>8</td>
<td>Outpatients</td>
<td>Cognition impairment; cognitive assessments</td>
<td>Exclusion of MDD or HDRS ≥ 20; Negative symptoms required: Total symptoms (BPRS) ≥ 40</td>
<td>Negative symptoms</td>
<td>PANSS = 20.3 ± 0.06; CGI-S = 4.9 ± 0.08</td>
</tr>
</tbody>
</table>

**Study description**

- **Design**: DB/RCT
- **ROB**: Randomized controlled trial
- **n**: Number of patients
- **Setting**: Inpatients or Outpatients
- **Study focus**: Inclusion criteria and depressive symptoms
- **Sample description**: Mean symptom severity, age, male gender, illness duration, antidepressant, antipsychotic dose, and Fisher's Z test

**Inclusion criteria**

- **Mean**: Mean dose of the antipsychotic
- **Severity**: Severity of depressive symptoms
- **Age**: Age of the patient
- **Male**: Percentage of male patients
- **Illness duration**: Duration of the illness
- **Antipsychotic**: Antipsychotic dose
- **Antidepressant**: Antidepressant dose

**Depressive symptoms**

- **Negative symptoms**: PANSS-N
- **Depressive symptoms**: HAMD, CGI
- **Negative symptoms**: SANS
- **Depressive symptoms**: BPRS
- **Negative symptoms**: MIMS
- **Depressive symptoms**: BPRS-S, HDRS

**Diagnoses**

- **PANSS**: Positive and Negative Syndrome Scale
- **CGI-S**: Clinical Global Impression-Severity
- **HAMD**: Hamilton Depression Rating Scale
- **SANS**: Scale for the Assessment of Negative Symptoms
- **BPRS**: Brief Psychiatric Rating Scale
- **MIMS**: Modified Illness Monitoring Scale

**Fisher's Z test**

- **Z test**: Used to compare two proportions

Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Inclusion criteria</th>
<th>Exclusion of MDD</th>
<th>Depressive symptoms irrelevant</th>
<th>Negative symptoms required:</th>
<th>Depression Symptom severity</th>
<th>Duration</th>
<th>Setting</th>
<th>Study focus</th>
<th>Design</th>
<th>ROB n</th>
<th>Illness</th>
<th>Duration (weeks)</th>
<th>Setting</th>
<th>Antipsychotic</th>
<th>Antidepressant augmentation in schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jockers-Scherubl 2005 (64)</td>
<td>$^{[\text{343}]}$</td>
<td>Inpatients</td>
<td>Negative symptoms required:</td>
<td>$^{[\text{343}]}$</td>
<td>SANS moderate on 1 sub scale</td>
<td>Unclear/Unspecific</td>
<td>25</td>
<td>Outpatients</td>
<td>Negative Symptoms</td>
<td>DB/RCT</td>
<td>3</td>
<td>Scz (chronic)</td>
<td>12</td>
<td>NR</td>
<td>FGA: 200.55 mg/day, NR 30 mg/day</td>
<td>$^{[\text{343}]}$</td>
</tr>
<tr>
<td>Lee 1998 (66)</td>
<td>$^{[\text{344}]}$</td>
<td>Inpatients</td>
<td>Exclusion of MDD or HDRS $^{[\text{344}]}$</td>
<td>$^{[\text{344}]}$</td>
<td>Exclusion of MDD $^{[\text{344}]}$</td>
<td>Persistent negative symptoms</td>
<td>DB/RCT</td>
<td>6</td>
<td>NR</td>
<td>Primary outcomes not specified (PANSS-N, T, PANSS-N, T)</td>
<td>$^{[\text{344}]}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mulholland 2003 (67)</td>
<td>$^{[\text{345}]}$</td>
<td>Outpatients</td>
<td>Depressive symptoms required:</td>
<td>$^{[\text{345}]}$</td>
<td>Persistent negative symptoms</td>
<td>Unclear/Unspecific</td>
<td>DB/RCT</td>
<td>8</td>
<td>NR</td>
<td>Negative symptoms irrelevant</td>
<td>$^{[\text{345}]}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prusoff 1979 (72)</td>
<td>$^{[\text{346}]}$</td>
<td>Outpatients</td>
<td>Depressive symptoms required:</td>
<td>$^{[\text{346}]}$</td>
<td>Persistent negative symptoms</td>
<td>Tricyclic Antidepressants (TCA) (studies $^{[\text{346}]}$)</td>
<td>DB/RCT</td>
<td>24</td>
<td>Outpatients</td>
<td>Depressive symptoms</td>
<td>$^{[\text{346}]}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikbakht 2016</td>
<td>$^{[\text{347}]}$</td>
<td>NR</td>
<td>Negative symptoms required:</td>
<td>$^{[\text{347}]}$</td>
<td>Negative symptoms irrelevant</td>
<td>Tricyclic Antidepressants (TCA) (studies $^{[\text{347}]}$)</td>
<td>DB/RCT</td>
<td>8</td>
<td>NR</td>
<td>SR = 3.5, 8, NR</td>
<td>$^{[\text{347}]}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>ROB</td>
<td>n</td>
<td>Duration (weeks)</td>
<td>Setting</td>
<td>Study focus</td>
<td>Inclusion criteria</td>
<td>Sample focus</td>
<td>Sample description</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-----</td>
<td>---</td>
<td>------------------</td>
<td>---------</td>
<td>-------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volterra 1990 (73) (Italy)</td>
<td>DB/RCT</td>
<td>3</td>
<td>30</td>
<td>60 days</td>
<td>Inpatients</td>
<td>Depressive symptoms (HDS)</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic mean dose</td>
<td>Antidepressant</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hogarty 1990 (74) (USA)</td>
<td>DB/RCT</td>
<td>3</td>
<td>33</td>
<td>12</td>
<td>Inpatients</td>
<td>Depressive symptoms; ANX</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennett 1983 (75) (USA)</td>
<td>DB/RCT, x-over</td>
<td>3</td>
<td>20</td>
<td>20</td>
<td>Inpatients</td>
<td>Global improvement (MIP); PRP, CCE</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optima 2000 (76) (UK)</td>
<td>DB/RCT</td>
<td>3</td>
<td>72</td>
<td>6</td>
<td>In- and Outpatients</td>
<td>Depression Symptoms</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson 1981 (77) (UK)</td>
<td>DB/RCT</td>
<td>3</td>
<td>60</td>
<td>5</td>
<td>NR</td>
<td>Depression Symptoms (SAOS)</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shyta-Shafi 2001 (78) (Iran)</td>
<td>DB/RCT</td>
<td>3</td>
<td>60</td>
<td>6</td>
<td>Inpatients</td>
<td>Negative Symptoms (SANS)</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-synapse inhibitor (NSI) (studies = 148.3%), n = 199</td>
<td>DB/RCT</td>
<td>4</td>
<td>35</td>
<td>4</td>
<td>NR</td>
<td>Negative Symptoms and Clinical Improvement (PANSS-N, CCG)</td>
<td>Exclusion of MDD</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schuz and Berk 2001 (79) (E.Africa)</td>
<td>DB/RCT</td>
<td>3</td>
<td>30</td>
<td>6</td>
<td>Inpatients</td>
<td>Total symptoms (PANSS)</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usai 2014 (80) (Spain)</td>
<td>DB/RCT</td>
<td>4</td>
<td>67</td>
<td>26</td>
<td>Inpatients</td>
<td>Negative Symptoms (PANSS-N)</td>
<td>Exclusion of MDD</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holand 1981 (71) (USA)</td>
<td>DB/RCT</td>
<td>3</td>
<td>28</td>
<td>4</td>
<td>Inpatients</td>
<td>Depression Symptoms (HDS)</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroergic and specific serotonergic and antidepressant (NS/SA) (studies = 714.6%), n = 230</td>
<td>DB/RCT</td>
<td>2</td>
<td>26</td>
<td>5</td>
<td>Inpatients</td>
<td>Negative symptoms</td>
<td>Exclusion of MDD</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Payrovsky 2003 (81) (Israel)</td>
<td>DB/RCT</td>
<td>3</td>
<td>30</td>
<td>4</td>
<td>Inpatients</td>
<td>Cognition (ANAAM)</td>
<td>Exclusion of MDD</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aouid 2013 (82) (Italy)</td>
<td>DB/RCT</td>
<td>3</td>
<td>28</td>
<td>8</td>
<td>Inpatients</td>
<td>Total symptoms (PANSS T)</td>
<td>Negative symptoms</td>
<td>Mean</td>
<td>Illness duration</td>
<td>Antipsychotic</td>
<td>Ø dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study description:
- **Inclusion criteria**:
  - Negative symptoms Diagnoses
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant
  - Negative symptoms irrelevant

Sample description:
- **Symptom severity**
  - BL
  - Mean
  - Male (%)
  - Illness duration (years)
  - Antipsychotic mean dose (CPZ eq)
  - Antidepressant Ø dose

- **Diagnoses**
  - Depression (HDS ≥ 15)
  - Depression (HDS < 15)
  - Depression (HDS ≥ 15)
  - Depression (HDS < 15)
  - Depression (HDS ≥ 15)
  - Depression (HDS < 15)
  - Depression (HDS ≥ 15)
  - Depression (HDS < 15)

- **Antipsychotic**
  - AP
  - AP
  - AP
  - AP
  - AP
  - AP
  - AP
  - AP

- **Antidepressant Ø dose**
  - AP
  - AP
  - AP
  - AP
  - AP
  - AP
  - AP
  - AP

- **Other**
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
  - Depression (HDRS ≥ 30)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>ROB</th>
<th>n</th>
<th>Duration (weeks)</th>
<th>Setting</th>
<th>Study focus</th>
<th>Study description</th>
<th>Inclusion criteria:</th>
<th>Sample description</th>
<th>Antidepressant augmentation in schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho 2011 (83, S.Korea)</td>
<td>DB/RCT, x-over</td>
<td>3</td>
<td>20</td>
<td>8</td>
<td>Outpatients</td>
<td>60</td>
<td>Global improvement (IMP/S, PP, CGI)</td>
<td>Persistent negative symptoms (PANS-N)</td>
<td>Sce (chronic)</td>
<td></td>
</tr>
<tr>
<td>Joffe 2013 (84, Finland†)</td>
<td>DB/RCT</td>
<td>5</td>
<td>41</td>
<td>6</td>
<td>In- and Outpatients (n = 18/22)</td>
<td>Total symptoms; Cognition (PANSST)</td>
<td>Persistent negative symptoms required: ≥ moderate illness severity</td>
<td>Sce (chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuccoli 2004 (85, Italy)</td>
<td>DB/RCT</td>
<td>4</td>
<td>24</td>
<td>8</td>
<td>Outpatient</td>
<td>Negative symptoms (SANS)</td>
<td>Exclusion of MDD or HDRS</td>
<td>Sce (chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAO inhibitor (studies = 2 14.2%, n = 83)</td>
<td>DB/RCT</td>
<td>4</td>
<td>67</td>
<td>12</td>
<td>Outpatients</td>
<td>Negative symptoms (SANS)</td>
<td>Exclusion of MDD</td>
<td>Sce (chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jungerman 1989 (87, Israel)</td>
<td>DB/RCT, x-over</td>
<td>5</td>
<td>16</td>
<td>16</td>
<td>Outpatients</td>
<td>Negative symptoms (PANS-N)</td>
<td>Exclusion of MDD</td>
<td>Sce (chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAO inhibitor (study = 1 12.1%, n = 12)</td>
<td>DB/RCT, x-over</td>
<td>3</td>
<td>12</td>
<td>52</td>
<td>Inpatients</td>
<td>Global improvement (IMP/S, PP, CGI)</td>
<td>Persistent negative symptoms</td>
<td>Sce (chronic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Efficacy of SSRI and NaSSA (Total, positive, negative, and depressive symptom severity)

<table>
<thead>
<tr>
<th></th>
<th>N (n)</th>
<th>SMD</th>
<th>95% CI</th>
<th>Result: P-value</th>
<th>Heterogeneity</th>
<th>N (n)</th>
<th>SMD</th>
<th>95% CI</th>
<th>Result: P-value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total symptom severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>6 (428)</td>
<td>-0.100</td>
<td>-0.329</td>
<td>0.128</td>
<td>0.389</td>
<td>0.090</td>
<td>47.5</td>
<td>0.090</td>
<td>47.5</td>
<td>0.090</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>2 (71)</td>
<td>-0.823</td>
<td>-1.346</td>
<td>-0.301</td>
<td>0.002</td>
<td>0.172</td>
<td>46.4</td>
<td>-0.543</td>
<td>1.167</td>
<td>0.030</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3 (129)</td>
<td>-0.345</td>
<td>-0.726</td>
<td>0.036</td>
<td>0.076</td>
<td>0.855</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>3 (110)</td>
<td>-0.016</td>
<td>-0.421</td>
<td>0.390</td>
<td>0.940</td>
<td>0.785</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Positive symptom severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>5 (355)</td>
<td>-0.067</td>
<td>-0.277</td>
<td>0.143</td>
<td>0.534</td>
<td>0.519</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1 (39)</td>
<td>0.042</td>
<td>-0.500</td>
<td>0.676</td>
<td>0.980</td>
<td>1.000</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4 (136)</td>
<td>-0.108</td>
<td>-0.446</td>
<td>0.230</td>
<td>0.531</td>
<td>0.578</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>3 (129)</td>
<td>-0.297</td>
<td>-0.052</td>
<td>0.647</td>
<td>0.095</td>
<td>0.337</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1 (25)</td>
<td>0.297</td>
<td>-0.052</td>
<td>0.647</td>
<td>0.095</td>
<td>0.337</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>2 (84)</td>
<td>-0.250</td>
<td>-0.683</td>
<td>0.183</td>
<td>0.258</td>
<td>0.235</td>
<td>29.1</td>
<td>-0.556</td>
<td>-1.222</td>
<td>0.109</td>
</tr>
<tr>
<td><strong>Negative symptom severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>7 (462)</td>
<td>-0.298</td>
<td>-0.630</td>
<td>0.042</td>
<td>0.086</td>
<td>0.265</td>
<td>21.6</td>
<td>-0.517</td>
<td>-0.817</td>
<td>0.344</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1 (40)</td>
<td>-0.298</td>
<td>-1.181</td>
<td>0.123</td>
<td>0.112</td>
<td>0.002</td>
<td>89.1</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3 (106)</td>
<td>-0.257</td>
<td>-0.814</td>
<td>0.300</td>
<td>0.026</td>
<td>0.142</td>
<td>73.8</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>3 (62)</td>
<td>-0.232</td>
<td>-0.767</td>
<td>0.302</td>
<td>0.037</td>
<td>0.037</td>
<td>69.6</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1 (25)</td>
<td>-0.361</td>
<td>-1.412</td>
<td>0.691</td>
<td>0.501</td>
<td>1.000</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>3 (110)</td>
<td>0.031</td>
<td>-0.520</td>
<td>0.581</td>
<td>0.913</td>
<td>0.871</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>General symptom severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>6 (466)</td>
<td>-0.130</td>
<td>-0.424</td>
<td>0.165</td>
<td>0.388</td>
<td>0.109</td>
<td>44.4</td>
<td>0.150</td>
<td>1.131</td>
<td>0.020</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1 (40)</td>
<td>-0.044</td>
<td>-0.250</td>
<td>0.736</td>
<td>0.011</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1 (47)</td>
<td>-0.072</td>
<td>-0.173</td>
<td>1.317</td>
<td>0.133</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1 (36)</td>
<td>-0.009</td>
<td>-0.811</td>
<td>0.792</td>
<td>0.082</td>
<td>1.000</td>
<td>0.000</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Depressive symptom severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>4 (339)</td>
<td>0.013</td>
<td>-0.520</td>
<td>0.546</td>
<td>0.963</td>
<td>0.088</td>
<td>54.1</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1 (40)</td>
<td>0.250</td>
<td>-0.823</td>
<td>1.323</td>
<td>0.648</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3 (109)</td>
<td>0.216</td>
<td>-0.424</td>
<td>0.856</td>
<td>0.507</td>
<td>0.115</td>
<td>53.7</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>2 (77)</td>
<td>-0.244</td>
<td>-1.025</td>
<td>0.536</td>
<td>0.539</td>
<td>0.001</td>
<td>91.2</td>
<td>-0.009</td>
<td>-0.663</td>
<td>1.000</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1 (29)</td>
<td>0.499</td>
<td>-0.687</td>
<td>1.685</td>
<td>0.409</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>2 (74)</td>
<td>0.252</td>
<td>-0.527</td>
<td>1.030</td>
<td>0.525</td>
<td>0.884</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Galling et al.
Table 2. (Continued)

<table>
<thead>
<tr>
<th>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</th>
<th>Total symptom severity</th>
<th>Positive symptom severity</th>
<th>Negative symptom severity</th>
<th>General symptom severity</th>
<th>Depressive symptom severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies focusing on total symptom severity</td>
<td>Studies focusing on total symptom severity</td>
<td>Studies focusing on negative symptom severity</td>
<td>Studies focusing on total symptom severity</td>
<td>Studies focusing on depressive symptom severity</td>
<td></td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSAs)</td>
<td>Total symptom severity</td>
<td>Positive symptom severity</td>
<td>Negative symptom severity</td>
<td>General symptom severity</td>
<td>Depressive symptom severity</td>
</tr>
<tr>
<td><strong>N (n)</strong></td>
<td>SMD</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Result: P-value</td>
<td>P-value</td>
</tr>
</tbody>
</table>

Note: **Bolded values relate to effect size results with \( P < 0.05 \); CI, confidence interval; \( N \), number of comparisons; \( n \), number of patients in the studies.

---

Antidepressant augmentation in schizophrenia
Superiority of antidepressant augmentation of antipsychotics for negative symptoms was seen in all available negative symptom subscales (affective flattening, anhedonia/asociality, avolition/apathy) except for inattention.

**Depressive symptoms.** Antidepressant augmentation was not superior to placebo for depressive symptom reduction (studies = 25, n = 1129, SMD = -0.13, 95% CI = -0.32 to 0.06, P = 0.19; Fig. 2, Table S1). The Egger test (intercept = 1.09, 95% CI: -0.94 to 3.12, P = 0.277) did not indicate the presence of publication bias.

Even in studies focusing on depressive symptoms that required a depressive symptom threshold for inclusion, no superiority for AD augmentation emerged (studies = 6, n = 434, SMD = -0.215, 95% CI = -0.593, 0.163, P = 0.265; Table S1).

Meta-regression results showed that a higher BPRS (P < 0.001) and a higher total PANSS/converted BPRS score at baseline (P = 0.013) moderated greater depressive symptom improvement (Table S1).

**Other efficacy outcomes.** Antidepressant and placebo augmentation did not differ regarding either total symptom response (studies = 7, n = 431, antidepressant augmentation = 59/217 (27.2%), placebo = 51/214 (23.8%), RR = 1.18, 95% CI = 0.88–1.58, P = 0.262, NNT = 29.4) nor depressive...
Antidepressant augmentation in schizophrenia

Table 3. Other efficacy and safety outcomes

<table>
<thead>
<tr>
<th>Response</th>
<th>N (n)</th>
<th>RR/SMD</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Result: PValue</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies (study defined)</td>
<td>7 (426)</td>
<td>1.181</td>
<td>0.883</td>
<td>1.581</td>
<td>0.262</td>
<td>0.354</td>
</tr>
<tr>
<td>Only studies with focus on total</td>
<td>4 (169)</td>
<td>1.148</td>
<td>0.869</td>
<td>1.516</td>
<td>0.331</td>
<td>0.577</td>
</tr>
<tr>
<td>symptoms (study defined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies (study defined)</td>
<td>7 (263)</td>
<td>1.616</td>
<td>1.137</td>
<td>2.296</td>
<td>0.008</td>
<td>0.313</td>
</tr>
<tr>
<td>Only studies with focus on negative symptoms (study defined)</td>
<td>3 (60)</td>
<td>1.779</td>
<td>0.989</td>
<td>3.203</td>
<td>0.055</td>
<td>0.177</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies (study defined)</td>
<td>4 (328)</td>
<td>1.339</td>
<td>0.984</td>
<td>1.822</td>
<td>0.063</td>
<td>0.288</td>
</tr>
<tr>
<td>Only studies with focus on depressive symptoms (study defined)</td>
<td>4 (329)</td>
<td>1.339</td>
<td>0.984</td>
<td>1.822</td>
<td>0.063</td>
<td>0.288</td>
</tr>
<tr>
<td>Other efficacy outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>30 (1193)</td>
<td>0.93</td>
<td>0.42</td>
<td>2.00</td>
<td>0.003</td>
<td>0.74</td>
</tr>
<tr>
<td>Thought disorder/Disorganization</td>
<td>4 (246)</td>
<td>0.067</td>
<td>0.10</td>
<td>0.73</td>
<td>0.604</td>
<td>0.11</td>
</tr>
<tr>
<td>Affective Flattening/Blunting</td>
<td>9 (331)</td>
<td>0.49</td>
<td>0.25</td>
<td>1.00</td>
<td>0.002</td>
<td>0.25</td>
</tr>
<tr>
<td>Alogia</td>
<td>9 (331)</td>
<td>0.58</td>
<td>0.30</td>
<td>1.00</td>
<td>0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>Anhedonia-Asociality</td>
<td>8 (284)</td>
<td>0.50</td>
<td>0.30</td>
<td>1.00</td>
<td>0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>Attention</td>
<td>8 (284)</td>
<td>0.12</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.25</td>
</tr>
<tr>
<td>Avolition-Apathy</td>
<td>8 (284)</td>
<td>0.53</td>
<td>0.30</td>
<td>1.00</td>
<td>0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>General symptoms (PANNS-G)</td>
<td>19 (981)</td>
<td>0.19</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.25</td>
</tr>
<tr>
<td>CGI-I</td>
<td>32 (1303)</td>
<td>0.25</td>
<td>0.10</td>
<td>1.00</td>
<td>0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>Quality of life (PGI/QLS/VAS)</td>
<td>5 (405)</td>
<td>0.25</td>
<td>0.10</td>
<td>1.00</td>
<td>0.001</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Italics are used for continuous outcomes; N = number of comparisons; n = number of patients in the studies.
Bold values relate to effect sizes results with P<0.05.

Symptom response (studies = 4, n = 328, antidepressant augmentation = 80/163 (49.1%), placebo = 58/165 (35.2%), RR = 1.34, 95% CI = 0.98–1.82, P = 0.063, NNT = 7.2). However, antidepressant augmentation outperformed placebo regarding negative symptom response (studies = 7, n = 263, antidepressant augmentation = 65/129 (50.3%), placebo = 39/134 (29.1%), RR = 1.62, 95% CI = 1.14–2.30, P = 0.008, NNT = 6.9) (Table 3, for response definitions see Appendix S1).

Superiority of antidepressant augmentation was also seen for clinical global impression (studies = 32 n = 1303, SMD = −0.25, 95% CI = 0.44 to −0.06, P = 0.010) and quality of life (studies = 5, n = 405, SMD = −0.25, 95% CI = −0.50 to −0.01, P = 0.039), but not for general symptoms (PANSS-G) (studies = 19, n = 881, SMD = −0.19, 95% CI = −0.42 to 0.03, P = 0.089). Furthermore, no differences emerged regarding all-cause and inefficacy-related treatment discontinuation (Table 3).

Intolerability-related study-withdrawal and adverse events. No differences emerged regarding intolerability-related discontinuation (studies = 37, n = 664, RR = 1.44, 95% CI = 0.77–2.66, P = 0.251). The only side-effect that significantly differed between antidepressant and placebo augmentation was dry mouth (studies = 3, n = 140, RR = 1.57, 95% CI = 1.04–2.36, P = 0.031), being more likely in the augmentation group (Table S2).

Discussion
This meta-analysis of 42 randomized controlled trials and 1934 patients is the first one to exclusively investigate antidepressant versus placebo augmentation of ongoing antipsychotic treatment in patients with schizophrenia and insufficient treatment response. All prior meta-analyses have mixed augmentation and co-initiation and/or included studies focusing on smoking cessation and/or AE amelioration in stable patients.
The results of this meta-analysis indicate that antidepressant augmentation is superior to placebo for improvement in total symptoms, which was driven by negative, but not positive or general symptom reduction. In predefined subgroup analyses, superiority for negative symptoms was confirmed in studies augmenting FGAs, but not SGAs. Singly, superiority in total symptom reduction by NaSSAs was not driven by negative, but by positive symptom reduction. Somewhat surprisingly, antidepressants did not improve depressive symptoms more than placebo. Antidepressant augmentation did not lead to greater all-cause discontinuation and was generally well tolerated, although significantly greater dry mouth was seen with antidepressant augmentation.

The total symptom improvement found in our meta-analysis is generally consistent with the most recent meta-analysis of antipsychotic cotreatment in schizophrenia by Helfer et al. (14), but ESs were smaller than in our more targeted meta-analysis (ES −0.24 vs. −0.37).

In our analysis, ESs for total symptom reduction were similar in patients with predominantly negative symptoms and those with chronic symptoms (who had a 7- to 10-point higher baseline PANSS/converted BPRS score compared to those studied for negative or depressive symptoms). In patients with chronic symptoms, the total symptom amelioration was not only driven by negative symptom reduction but additionally by the decrease in positive and general symptoms.

The larger efficacy signal for overall symptom reduction in studies conducted in Europe was likely driven by the fact that two of the four studies used OC data, which both reported large ESs, and that three studies used augmentation with mirtazapine, which had relatively large ESs for total symptom reduction.

ESs for negative symptom improvement were small and comparable with results from Helfer et al. (14), while we observed medium ESs for the core negative symptoms of avolition/apathy and anhedonia/asociality, which had not been investigated in detail by Helfer et al. (14).

Augmentation of both FGAs and SGAs was effective for total symptom reduction. However, for negative symptoms, adjunctive antidepressants were only beneficial in patients treated with FGAs. First, this finding could be because of changes in populations and study conduct over time that have been associated with an increased placebo response (90, 91), making it potentially more difficult for newer studies (in which SGAs are augmented with antidepressants) to show robust effects. Second, the reduced efficacy of antidepressants when added to SGAs is in line with the hypothesis that serotonergic mechanisms seem to moderate negative symptoms, and SGAs but not FGAs already have dopaminergic and serotonergic effects. However, the precise mechanisms are unclear, as SGAs block certain serotonin receptors, whereas antidepressants indirectly stimulate serotonin receptors.

Nevertheless, it seems that antipsychotic blockade of 5-HT2a, 5-HT6, and/or 5-HT7 receptors ultimately leads to an increase in serotonin transmission (92). Additionally, certain SGAs (or their metabolites) also have partial 5-HT1a-agonism, alpha-2 antagonism, or SSRI or SNRI activity, emulating antidepressant activity (92). Moreover, although not all studies restricted the degree of depressive symptoms (which may even present as secondary negative symptoms) (4), meta-regression analyses indicated no relationship between negative symptom improvement and change in depressive symptoms. Together with the finding that, overall, antidepressants were not superior to placebo for depressive symptoms, these results suggest that the improvement in negative symptoms in schizophrenia are not merely because of a halo effect of improving subsyndromal or syndromal depression. However, based on the information provided by the original studies, misclassification of extrapyramidal symptoms as negative symptoms cannot be excluded. Moreover, any distinction between primary and secondary negative symptoms (e.g., because of anxiety, depression, paranoia or sedation), and between enduring negative symptoms (‘deficit symptoms’) and transient negative symptoms was precluded because of restricted information (4, 93).

The finding that antidepressant augmentation of SGAs resulted in a robust total symptom improvement was most likely driven by an improvement in general symptoms or by cumulative small effects across the different symptom domains.

Helfer et al. (14) identified a positive symptom effect across all studies, while we were only able to identify this signal in studies that tested the addition of NaSSAs. This interesting finding, which should be followed up in future studies, was mainly driven by mirtazapine, which also significantly reduced overall symptom severity. These results are contrary to a previous meta-analysis (19) that had found benefits of NaSSAs for negative symptoms only. That finding was replicated by Helfer et al. (14), while their subgroup analyses did not include positive symptom outcomes. However, the divergent results between the two prior meta-analyses and our own analyses can be explained by different methodological approaches in the other meta-
analyses, including (i) handling of missing change score SDs by mathematically estimating a change score SD using ‘the covariance method’ and a correlation of 0.5” (19) [whereas we used actually reported endpoint and SD values (80, 83, 85) or author-supplied, original data (81)], and/or (ii) using different study selection criteria, that is, inclusion of three co-initiation studies (two of which had very large ESs of 1.6 and 2.2 for negative symptoms) (94–96), in the meta-analyses by Hecht (19) and Helfer (14) (while we excluded these trials by design and were able to add 2 other studies (69, 82) that were not included by Hecht).

Interestingly, in patients with comorbid depression (study focus/inclusion criterion: depressive symptoms), antidepressant augmentation did not lead to a significant decrease in either total, negative, or positive symptom severity. However, these findings might be influenced by the limited number of studies in patients with depressive symptoms and by the lower total symptom severity at baseline of patients with predominantly depressive symptoms (floor-effect) (studies = 4; total PANSS/converted BPRS = 73.6 ± 16.7).

Notably, different from our findings, where depressive symptoms were not significantly reduced by antidepressant augmentation either in the overall analysis or in the subgroup of studies focusing on patients with depressive symptoms, Helfer et al. (14) reported a significant effect of antidepressant augmentation for depressive symptoms. However, our findings are consistent with results from another meta-analysis focusing on patients with comorbid depression (30) that also could not provide convincing evidence for antidepressant augmentation for depressive symptoms in patients with schizophrenia (results were only significant when using a fixed effects model and when including ≥50% of studies with skewed data (30), allowing for one single study using observed case analyses (70) to drive the results). Importantly, our finding of non-superiority was not moderated by baseline depression severity.

Although not statistically significant, subgroup analyses suggested that these results were mainly driven by studies using SGAs as base agents, as there was nearly no change in depression severity in these studies, whereas depressive symptom changes were somewhat larger in patients previously treated with FGAs, and especially in studies focusing on depression.

Results from a previous meta-analysis (17) reporting the marginally significant effects of NRIs on depressive symptoms could not be replicated. However, that meta-analysis had included five trials using stimulants (atomoxetine/mazindol) and three studies with an AE-amelioration focus (reboxetine).

Taken together, these results suggest three potential explanations for the absence of significant antidepressant efficacy for depressive symptoms in people with schizophrenia: (i) depression or depressive symptoms in people with schizophrenia are pathophysiologically different than in people with a primary depression who do not have schizophrenia; (ii) a potential drug-drug interaction that might interfere with antidepressant activity; or (iii) serotonergic effects that have already been exhausted by SGAs. However, there are currently no data supporting any each of these hypotheses, and there was also no difference in antidepressant efficacy, whether the baseline antipsychotics were FGAs or SGAs. Therefore, other pharmacologic and non-pharmacologic treatments and mechanisms of action should be considered and explored in people with schizophrenia and comorbid depression.

Unlike the results for total symptom severity, and different from Helfer et al.’s meta-analysis (14), response rates based on total symptoms were not significant in our meta-analysis. Conversely, response rates further supported the superiority of antidepressant augmentation for negative symptoms. Because very heterogeneous thresholds were used throughout the studies, these results should be interpreted with caution, as they are suspicious of having resulted from selective outcome reporting, as only <25% of studies that measured continuous negative symptom outcomes reported on response rates. This finding underscores that complete reporting of all possible outcomes in all studies is crucial to enable a valid evaluation of the evidence base.

When interpreting the differences between our meta-analysis and the one by Helfer et al. (14), several distinctions must be considered. Although Helfer et al. (14) included as many as 82 studies and 3,608 patients in their meta-analysis, the authors mixed together studies that added on antidepressants after antipsychotic monotherapy failed (‘augmentation’) with those that newly started both an antidepressant and an antipsychotic concurrently (‘co-initiation’) without knowing if the antipsychotic monotherapy would have failed or been sufficiently effective. Moreover, studies targeting symptom severity and those focusing on AE amelioration, two very different clinical targets, were pooled together. Thus, although we included fewer trials than Helfer et al., we did so deliberately to enhance the precision and clinical utility of

Antidepressant augmentation in schizophrenia
the analyses. By focusing on a more homogenous set of trials and populations, we aimed at mapping the studies and results to the commonly encountered clinical conundrum of what to do when antipsychotic monotherapy was ineffective for a given efficacy outcome.

We would argue that future meta-analyses in psychiatry should similarly aim for this greater degree of precision and homogeneity of the clinical approach when choosing included studies to yield more meaningful outcomes that can truly inform clinical decision-making. Studies testing clinical strategies that are incompatible should not be combined, but analyzed strictly separately, as has been performed recently for antipsychotic augmentation strategies (97).

Several limitations of this meta-analysis require consideration. These include (i) the relatively small number of double-blind studies comparing antidepressant to placebo augmentation of antipsychotic baseline treatment, which precludes more detailed analyses of individual antipsychotic–antidepressant combinations, (ii) heterogeneous study origins, designs, targets, and inclusion criteria, (iii) a limited number of reported outcomes, measured by heterogeneous scales, especially regarding AEs, (iv) that results could have been influenced by the increasing placebo response over time in trials of patients with schizophrenia (90, 91), potentially weakening results for SGAs compared to FGAs, the latter of which were mainly used in older studies, (v) that the negative symptom results could be confounded by secondary negative symptoms related to depression, paranoia, anxiety, extrapyramidal symptoms, or sedation (4, 93), although at least no association could be found between negative and depressive symptom improvement in meta-regression analyses, (vi) that schizophrenia-specific depression measurements were not used exclusively for the assessment of depressive symptoms that potentially present differently in this specific patient group and might therefore not have been captured adequately (98), and (vii) subgroup and meta-regression analyses were only exploratory, as they were based on different subsets of studies that differed in patient, illness or treatment characteristics from the overall sample in relevant ways.

An additional consideration is that we excluded co-initiation studies, thereby restricting the full picture of available studies on co-treatment options. However, as mentioned above, we consider co-initiation of an antipsychotic with an antidepressant a very distinct question and strategy and deliberately chose to focus on patients with inadequate therapeutic response to prior antipsychotic treatment in whom antidepressants would be added to target specific residual symptomatology.

Despite these limitations, this is the first, comprehensive meta-analysis that exclusively assessed antidepressant augmentation strategies of antipsychotic treatment in patients with insufficient response to antipsychotic monotherapy without intermingling the results of antipsychotic co-initiation trials or studies focusing on AE amelioration in stable patients. The results suggest that antidepressant augmentation of either FGAs or SGAs improves total psychopathology in patients with schizophrenia, while antidepressant augmentation of FGAs can help improve chronic negative symptoms. In contrast, antidepressant augmentation is most likely ineffective for positive symptoms (with the possible exception of NaSSAs) or depressive symptoms.

Acknowledgements

This work was supported in part through salary support by The Zucker Hillside Hospital National Institute of Mental Health (NIMH) Advanced Center for Intervention and Services Research for the Study of Schizophrenia P30MH090590. The funding sources had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Conflict of interest

Drs. Galling, Vernon, Wadhwa, Grudnikoff, Pagsberg, Seidman, Tsyp-Podosenin, and Poyurovsky have nothing to disclose.

Dr. Kane has received honoraria for lectures and/or consulting from Alkermes, Bristol Myers Squibb, Eli Lilly, Forrest Labs, Forum, Genentech, Intracellular Therapies, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Reviva, Roche, and Sunovion. He has received grant support from Genentech, Johnson and Johnson and Otsuka. He is a shareholder of MedAvante, LB Pharmaceuticals and Vanguard Research Group. He has received grant support from Otsuka and The National Institute of Mental Health.

Dr. Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Actavis, Actelion, Alexza; Alkermes, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, Intracellular Therapies, Janssen,J&J, Lundbeck, Medavante, Medscape, Merek, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, Takeda, Teva, and Vanda. He has received grant support from the American Academy of Child and Adolescent Psychiatry, the Bendheim Foundation, Bristol-Myers Squibb, the National Institute of Mental Health, Novo Nordisk A/S, Otsuka, Takeda, and the Thrasher Foundation.

References

Antidepressant augmentation in schizophrenia

4. CARBON M, CORRELL CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr 2014;19(Suppl. 1):38–52.
7. MELTZER HY. Serotonergic mechanisms as targets for existing and novel antipsychotics. Handb Exp Pharmacol 2012;87–124. https://doi.org/10.1007/978-3-642-25761-2_4
34. KAY SR, FISZBEIN A, OPLER LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276.
36. ANDREASEN NC. The scale for the assessment of positive symptoms (SAPS). Iowa City, IA: University of Iowa, 1984.
37. ANDREASEN NC. The scale for the assessment of negative symptoms (SANS). Iowa City, IA: University of Iowa, 1984.
Galling et al.


Antidepressant augmentation in schizophrenia


Supporting Information

Additional Supporting Information may be found in the online version of this article:
Table S1. Total, negative and depressive symptom severity: Subgroup Analyses and Meta-Regression.
Table S2. Safety outcomes.
Appendix S1. Definition response.