



Antidepressants for cognitive impairment in schizophrenia – A systematic review and meta-analysis

Jeffrey A. Vernon^a, Eugene Grudnikoff^b, Andrew J. Seidman^b, Thomas W. Frazier^c, Mani Sandhya Vemulapalli^d, Priyanki Pareek^a, Terry E. Goldberg^{b,e,f}, John M. Kane^{b,e,f,g}, Christoph U. Correll^{b,e,f,g,*}

^a New York Medical College, Valhalla, NY, USA

^b The Zucker Hillside Hospital, Psychiatry, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA

^c Center for Autism, Pediatric Institute, Cleveland Clinic, Cleveland, OH, USA

^d Atlanta VA Medical Center, Decatur, GA, USA

^e Hofstra North Shore LIJ School of Medicine, Hempstead, NY, USA

^f The Feinstein Institute for Medical Research, Manhasset, NY, USA

^g Albert Einstein College of Medicine, Bronx, NY, USA

ARTICLE INFO

Article history:

Received 20 April 2014

Received in revised form 15 August 2014

Accepted 19 August 2014

Available online 18 September 2014

Keywords:

Schizophrenia

Cognition

Cognitive impairment

Antidepressants

Augmentation

Selective serotonin reuptake inhibitors

Alpha 2 antagonists

ABSTRACT

Background: Cognitive impairment in schizophrenia is disabling, but current treatment options remain limited. **Objective:** To meta-analyze the efficacy and safety of adjunctive antidepressants for cognitive impairment in schizophrenia.

Data sources and study selection: PubMed, MEDLINE, PsycINFO, and Cochrane Library databases were searched until 12/2013 for randomized controlled trials comparing antidepressant augmentation of antipsychotics with placebo regarding effects on cognitive functioning in schizophrenia.

Data extraction: Two authors independently extracted data. Standardized mean differences (SMDs) were calculated for continuous outcomes and risk ratios for categorical outcomes. SMDs of individual cognitive tests were pooled on a study level within domains (primary outcome) and across domains. When results were heterogeneous, random instead of fixed effects models were used.

Results: We meta-analyzed 11 studies (duration = 8.7 ± 3.7 weeks) including 568 patients (mean age = 39.5 ± 6.9 years, males = 67.2%, illness duration = 12.5 ± 8.0 years). Antidepressants included mirtazapine (4 studies; $n = 126$), citalopram (2 studies; $n = 231$), fluvoxamine (1 study; $n = 47$), duloxetine (1 study; $n = 40$), mianserin (1 study; $n = 30$), bupropion (1 study; $n = 61$), and reboxetine (1 study; $n = 33$). Statistically significant, but clinically negligible, advantages were found for pooled antidepressants compared to placebo in executive function (Hedges' $g = 0.17$, $p = 0.02$) and a composite cognition score (Hedges' $g = 0.095$, $p = 0.012$). Depression improved with serotonergic antidepressants ($p = 0.0009$) and selective serotonin reuptake inhibitors ($p = 0.009$), but not with pooled antidepressants ($p = 0.39$). Sedation was more common with pooled antidepressants ($p = 0.04$).

Conclusion: Adjunctive antidepressants do not demonstrate clinically significant effects on cognition in schizophrenia patients, however, larger studies, preferably in euthymic schizophrenia patients and using full neurocognitive batteries, are needed to confirm this finding.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Cognitive symptoms are amongst the earliest in schizophrenia. They often develop in the prodromal period (Lencz et al., 2006; Kane and Lencz, 2008) and can be significant by the time of the first episode (Mesholam-Gately et al., 2009). Specific deficits have been found in all cognitive domains, including executive function, memory, and

attention, and are between 0.5 and 1.5 standard deviations below matched control subjects (Mohamed et al., 1999; Bilder et al., 2000; Velligan et al., 2000; Buchanan et al., 2005; Green, 2006; Zanelli et al., 2010). Cognitive symptoms are highly disabling, having a strong correlation with functional outcome (Green et al., 2000; Green et al., 2004; Bowie et al., 2008; Bowie et al., 2010). While already present during the first episode, the relationship between cognitive symptoms and functional outcome may increase with time (Verdoux et al., 2002), although cognitive deficits themselves may not worsen over the course of illness (Albus et al., 2006; Mesholam-Gately et al., 2009).

Although negative symptoms may modulate the effect of cognition on clinical outcome (Lin et al., 2013), cognition seems to be an

* Corresponding author at: Division of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, NY 11004, USA. Tel.: +1 718 470 4812; fax: +1 718 343 1659.

E-mail address: ccorrell@lij.edu (C.U. Correll).

Table 1
Study, patient, and treatment characteristics.

| Study/sponsor | Design | Total N | Time (weeks) | Population | Mean age | Male sex (%) | Illness duration (years) | Treatments | Mean dose (mg/d) | Primary outcome(s) | Secondary outcomes |
|--|----------------------------------|---------|--------------|---|----------------|----------------|--------------------------|---|---|---|--|
| <i>Selective serotonin reuptake inhibitor</i> Dawes et al. (2012)/Zisook et al. (2009) ^a /Zisook et al. (2010)/Kasckow et al. (2010) NIMH Department of Veterans Affairs | DBRPCT | 212 | 8 | Schizophrenia (n = 117) or schizoaffective D/O (n = 81) All subjects had “subsyndromal depression” Outpatients Baseline total PANSS or CGI-S score NR | 52.5 (n = 198) | 78.3 (n = 198) | NR | AP + citalopram AP + PBO | AP doses not provided Citalopram = 28.9 | Cognitive tests; psychopathology; suicidality | EPS; quality of life; metabolic side effects |
| Friedman et al. (2005) ^a Forest Laboratories | DBRPCT Crossover ^b | 19 | 12 | Chronic schizophrenia (n = 17) or schizoaffective D/O (n = 2) Stable Inpatients (42.1%) and outpatients (57.9%) Baseline total PANSS score = 78.90 ± 14.46 Baseline CGI-S score = 4.00 ± 0.69 | 45.0 | 68.4 | 25.6 | AP + citalopram SGA + PBO | AP doses not provided Citalopram = 40 | Cognitive tests | Psychopathology; EPS |
| Niitsu et al. (2012) ^a No external funding | DBRPCT | 47 | 8 | Chronic schizophrenia Outpatients Baseline total PANSS score = 74.6 ± 10.7 | 37.4 | 61.7 | 11.5 | SGA + fluvoxamine SGA + PBO | SGA = 257.9 CPZ equivalents Fluvoxamine = 150 | Cognitive tests | Psychopathology; EPS; quality of life |
| <i>Serotonin–norepinephrine reuptake inhibitor</i> Micò et al. (2011) Funding source not specified | DBRPCT | 40 | 16 | Chronic schizophrenia Active positive and negative symptoms Outpatients Baseline total PANSS score = 65.7 ± 12.6 | 35.0 | 60.0 | 6.5 | Clozapine + duloxetine Clozapine + PBO | Clozapine = 518.3 (1036.6 CPZ equivalents) Duloxetine = 60 | Total psychopathology | Psychopathology; cognitive tests |
| <i>Norepinephrine Reuptake Inhibitor</i> Poyurovsky et al. (2009)/Poyurovsky et al. (2007) Stanley Medical Research Institute | DBRPCT | 33 | 6 | First-episode schizophrenia or schizophreniform D/O Remitted Inpatients Baseline CGI-S score = 4.18 ± 0.64 | 31.1 | 63.6 | 3.6 | Olanzapine + reboxetine Olanzapine + PBO | Olanzapine = 10 (200 CPZ equivalents) Reboxetine = 4 | Cognitive tests | Psychopathology; EPS |
| <i>Dopamine–norepinephrine reuptake inhibitor</i> Bloch et al. (2010) ^a National Alliance for Research on Schizophrenia and Depression Phillip Morris | DBRPCT | 61 | 14 | Schizophrenia (n = 41), schizoaffective D/O (n = 19) or diagnosis unclear (n = 1) Smokers Stable Outpatients Baseline total PANSS = 72.90 ± 21.63 (n = 60) | 41.67 (n = 60) | 75.4 | NR | AP + bupropion SR AP + PBO | AP doses not provided Bupropion = 300 | Smoking cessation; genetic testing | Psychopathology; cognitive tests |
| <i>Alpha 2 antagonist</i> Berk et al. (2009) ^a Organon Australia | DBRPCT | 38 | 6 | Schizophrenia NR Inpatients (39.5%) or outpatients (39.5%) with unreported data for 21.1% of patients | 36.8 | 84.2 | NR | SGA + mirtazapine SGA + PBO | SGA = 333.6 CPZ equivalents (n = 27) Mirtazapine = 30 | Total psychopathology | Psychopathology; cognitive tests |

| | | | | | | | | | | | |
|--|--|-----|-----------|---|------------------|------------------|-----------------------|---|--|---|---|
| Caforio et al. (2013) ^a Stanley Medical Research Institute Organon Italy (Schering Plough) | DBRPCT | 28 | 8 | Baseline total PANSS score = 84.76 ± 19.85 Baseline CGI-S score = 4.13 ± 0.89 Schizophrenia Recent exacerbation of psychotic symptoms requiring hospitalization Inpatients Baseline total PANSS score = 67.05 ± 18.40 | 29.3 (n = 20) | 75.0 (n = 20) | 7.1 (n = 20) | Olanzapine + mirtazapine Olanzapine + PBO | Olanzapine = 17.3 (346.0 CPZ equivalents) (n = 20) Mirtazapine = 30 (n = 20) | Negative symptoms; cognitive tests | Psychopathology |
| Cho et al. (2011)/Lee et al. (2011) Funding source not specified | DBRPCT | 21 | 8 | Schizophrenia Stable Outpatients Baseline total PANSS score = 83.65 ± 13.55 | 35.7 (n = 20) | 50.0 (n = 20) | 6.5 (n = 20) | Risperidone + mirtazapine Risperidone + PBO | Risperidone = 3.5 (175 CPZ equivalents) (n = 20) Mirtazapine = 30 (n = 20) | Negative symptoms; cognitive tests; EPS; metabolic side effects | Cognitive tests; psychopathology; adherence |
| Poyurovsky et al. (2003) ^a Funding source not specified but author states in a personal communication "This trial was not funded by any external sources." | DBRPCT | 30 | 4 | Chronic schizophrenia Stable Inpatients Baseline CGI-S score = 3.5 ± 0.6 (n = 24) | 44.1 (n = 24) | 70.8 (n = 24) | 17.2 (n = 24) | FGA + mianserin FGA + PBO | FGA defined daily dosage = 4.0 (n = 24) Mianserin = 15 (n = 24) | Cognitive tests | Psychopathology; EPS |
| Stenberg et al. (2010) ^a /Joffe et al. (2009) ^a /Terevnikov et al. (2011) Stanley Medical Research Institute | DBRPCT | 39 | 6 | Chronic schizophrenia (n = 38) or schizoaffective D/O, depressive type (n = 1) Active positive and/or negative symptoms; at least moderate illness severity Inpatients (46.2%) and outpatients (53.8%) Baseline total PANSS score = 102.92 ± 13.77 Baseline CGI-S score = 4.33 ± 0.54 | 45.7 | 51.3 | 22.4 | FGA + mirtazapine FGA + PBO | FGA = 323.8 CPZ equivalents Mirtazapine = 30 | Psychopathology; cognitive tests | Psychopathology; patient-rated improvement |
| <i>Total (unweighted means)</i> | | | | | | | | | | | |
| 11 Trials; Industry: N = 4 Foundation: N = 4 Government: N = 1 Not reported/no external funding: N = 4 | DBRPCT: N = 11; Parallel: N = 10 Crossover: N = 1 | 568 | 8.7 ± 3.7 | SCZ: 91.3% SZA: 7.7% Chronic SCZ: 88.9%; first-episode SCZ or schizophreniform D/O: 5.8%; Outpatients: 60.1% Baseline total PANSS score = 78.5 ± 12.1 (N = 8) Baseline CGI-S score = 4.0 ± 0.34 (N = 5) | 39.5 ± 6.9 | 67.2 ± 10.9 | 12.5 ± 8.0 (N = 8) | Active: Mirtazapine = 4 Mianserin = 1 Citalopram = 2 Duloxetine = 1 Fluvoxamine = 1 Reboxetine = 1 Bupropion = 1 Comparator: SGA + PBO = 6; FGA + PBO = 2; CLO + PBO = 1; OLA + PBO = 2; RIS + PBO = 1 | Citalopram: 29.7 (weighted mean) Fluvoxamine: 150 Duloxetine: 60 Reboxetine: 4 Bupropion: 300 Mirtazapine: 30 Mianserin: 15 CPZ equivalents = 382.7 ± 285.1 (N = 7) | Cognitive tests: N = 8; Total psycho- pathology: N = 2; Psychopathology: N = 2 Negative symptoms: N = 2; Suicidality: N = 1 Smoking cessation: N = 1 Genetic testing: N = 1 EPS: N = 1 Metabolic side effects: N = 1 | Psychopathology: N = 10; EPS: N = 5; Cognitive tests: N = 4; Patient-rated improvement: N = 1; Metabolic side effects: N = 1; Adherence: N = 1 Quality of Life: N = 2 |

Abbreviations: AD = antidepressant; AP = antipsychotic; CGI-S = Clinical Global Impression–Severity Scale; CLO = clozapine; CPZ = chlorpromazine; DBRPCT = double-blind, randomized, placebo-controlled trial; EPS = extrapyramidal symptoms; FGA = first-generation antipsychotic; NR = not reported; OLA = olanzapine; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; RIS = risperidone; SGA = second-generation antipsychotic; SCZ = schizophrenia; SZA = schizoaffective disorder.

^a Additional, unpublished data were obtained from study author.

^b Pre-crossover data were obtained from study author.

independent, core symptom domain of schizophrenia that separately predicts long-term functional outcome and quality of life (Green et al., 2000; Keefe and Fenton, 2007; Kane and Lencz, 2008). Despite the clinical and functional importance of cognitive symptoms, there are no currently approved and clearly effective pharmacologic treatments for these deficits (Harvey and Keefe, 2001; Coyle et al., 2010; Choi et al., 2013; Menniti et al., 2013). The small-to-moderate improvements with antipsychotics may reflect improvements of interfering hallucinations and thought disorganization or even negative symptoms (Harvey and Keefe, 2001). In a meta-analysis of medications targeting cholinergic, glutamatergic, or serotonergic receptors for cognitive impairment in schizophrenia, small-to-moderate effect sizes were found for some cholinergic medications in some aspects of cognition (Choi et al., 2013). However, these agents also improved negative and general symptoms, confounding the results. Although cognitive remediation has attracted considerable attention, it provides, at best, moderate benefits (Wykes et al., 2011), and patients need to be motivated and adhere to the training schedule. Finally, much of the improvement seen in schizophrenia cognition studies reflect practice effects (Goldberg et al., 2007), and the translation of improvements in isolated cognitive domains to enhanced real-world functioning is unclear.

Antidepressants are safe and used frequently in schizophrenia patients to address depressive and negative symptoms (Rummel et al., 2006; Singh et al., 2010; Hecht & Landy, 2011). Theoretically, antidepressants could improve cognition via enhanced serotonergic, adrenergic, and dopaminergic transmission. These benefits may be anticipated to vary by antidepressant class, with, for example, those antidepressants showing marked anticholinergic activity (i.e., tricyclic antidepressants) expected to be less beneficial than other classes. While individual studies that used antidepressants to augment antipsychotics in schizophrenia have measured cognition, no meta-analysis has investigated the pooled efficacy of antidepressants for cognitive symptoms in schizophrenia. Therefore, we conducted a systematic review and meta-analysis to explore the effects of adjunctive antidepressants for cognition in patients with schizophrenia.

2. Methods

2.1. Search strategy and data extraction

PubMed, Ovid (MEDLINE), PsycINFO, and Cochrane Library databases were searched (without time or language restriction) for randomized controlled trials (RCTs) comparing adjunctive antidepressants with placebo in the treatment of schizophrenia. The final search update was performed on 12/27/2013. Keywords included *schizophrenia*, *random**, *antidepressant*, *antidepressants*, *anti-depressant*, *anti-depressants*, plus a list of all antidepressants ever approved for use in any country. This electronic search was supplemented by a hand search of references in review articles and articles pertinent to this meta-analysis. Article authors were contacted for additional data. Two of four authors (J.A.V., E.G., A.J.S., and M.S.V.) independently extracted study data. Two of three authors (J.A.V., E.G., and A.J.S.) independently entered and checked data entered into Review Manager Version 5.2.7 for Windows (Cochrane Collaboration, <http://ims.cochrane.org/revman>). Two authors (J.A.V. and C.U.C.) independently entered and checked data entered into Comprehensive Meta-Analysis V2 (Biostat, <http://www.meta-analysis.com>). Any discrepancies were resolved by consensus.

2.2. Inclusion criteria

Eligible studies had to compare any antipsychotic plus any adjunctive antidepressant with any antipsychotic plus placebo and had to report on treatment effects on any cognitive domain. Agents with only theoretical antidepressant properties that have never been approved for the treatment of depression in any country were excluded from

this meta-analysis. We also excluded studies whose sole cognition outcome was a scale that did not measure a specific cognitive function or domain, such as the Mini-Mental State Examination or Positive and Negative Syndrome Scale (PANSS)—cognitive scale.

2.3. Outcomes

Primary outcomes were test scores of any cognitive measure pooled on a study level to derive the following nine cognitive domain scores: executive function, attention, processing speed, visuospatial processing, auditory verbal long-term memory, visuospatial long-term memory, auditory verbal working memory, visuospatial working memory, and verbal fluency. Key secondary outcomes included higher-level cognitive domain scores (auditory verbal memory, visuospatial memory, long-term memory, working memory, memory) as well as a composite cognition score comprised of all included tests per study (see details below). Additional, secondary outcomes included all-cause discontinuation; discontinuation due to intolerance, inefficacy, and other reasons; total psychopathology; positive symptoms; negative symptoms; depressive symptoms; Parkinsonism; akathisia; dyskinesia; and other adverse events. For specific information about outcomes measured by each study see Supplementary Table 1.

2.4. Data synthesis

For a detailed description of the data synthesis, see Supplementary Methods.

2.5. Statistical analysis

Analyses were performed using Review Manager Version 5.2.7, except for the pooling of effect sizes of individual cognitive tests within a specific domain in order to obtain and pool domain sum scores across studies, which was done using Comprehensive Meta-Analysis V2. Analyses were carried out on outcomes for which data from ≥ 3 studies were available. We calculated the standardized mean difference (SMD) \pm 95% confidence interval (CI) for continuous outcomes and the risk ratio (RR) \pm 95% CI for categorical outcomes. Cognitive outcomes were standardized so that a positive SMD favors the antidepressant group. For all other continuous outcomes, a negative SMD (i.e., reduction in symptoms) favors the antidepressant group. When both change scores and endpoint scores were available, change scores were used preferentially unless they were significantly skewed (i.e., standard deviation more than double the mean), in which case endpoint scores were utilized, unless they, too, were skewed. Analyses for continuous outcomes were based on intention-to-treat (ITT; i.e., all randomized subjects receiving ≥ 1 dose of study medication or placebo) or modified ITT (i.e., all randomized subjects receiving ≥ 1 dose of study medication or placebo and having ≥ 1 post-baseline assessments) data, using last-observation-carried-forward or mixed models repeated measures analyses. Analyses for categorical outcomes were based on ITT data. All data were initially analyzed using a fixed effects model. Heterogeneity was studied using the I^2 statistic, with $I^2 \geq 50\%$ indicating significant heterogeneity, as well as the chi square test for heterogeneity. All tests were two-sided, and alpha was set at 0.05.

In the case of significant heterogeneity, the outcome was reanalyzed using a DerSimonian and Laird (1986) random effects model. If the results remained significantly heterogeneous, preplanned subgroup analyses using the random effects model were conducted as follows when ≥ 3 studies were available for a given subanalysis: 1) not focusing on smoking cessation; 2) cognition as the primary outcome; 3) antipsychotic treatment – second-generation agents; 4) alpha-2 antagonist antidepressant (mirtazapine and mianserin) treatment; 5) mirtazapine treatment; 6) selective serotonin reuptake inhibitor (SSRI) treatment; 7) serotonergic antidepressant (SSRIs and duloxetine) treatment; and 8) noradrenergic antidepressant (duloxetine, reboxetine, and bupropion) treatment.

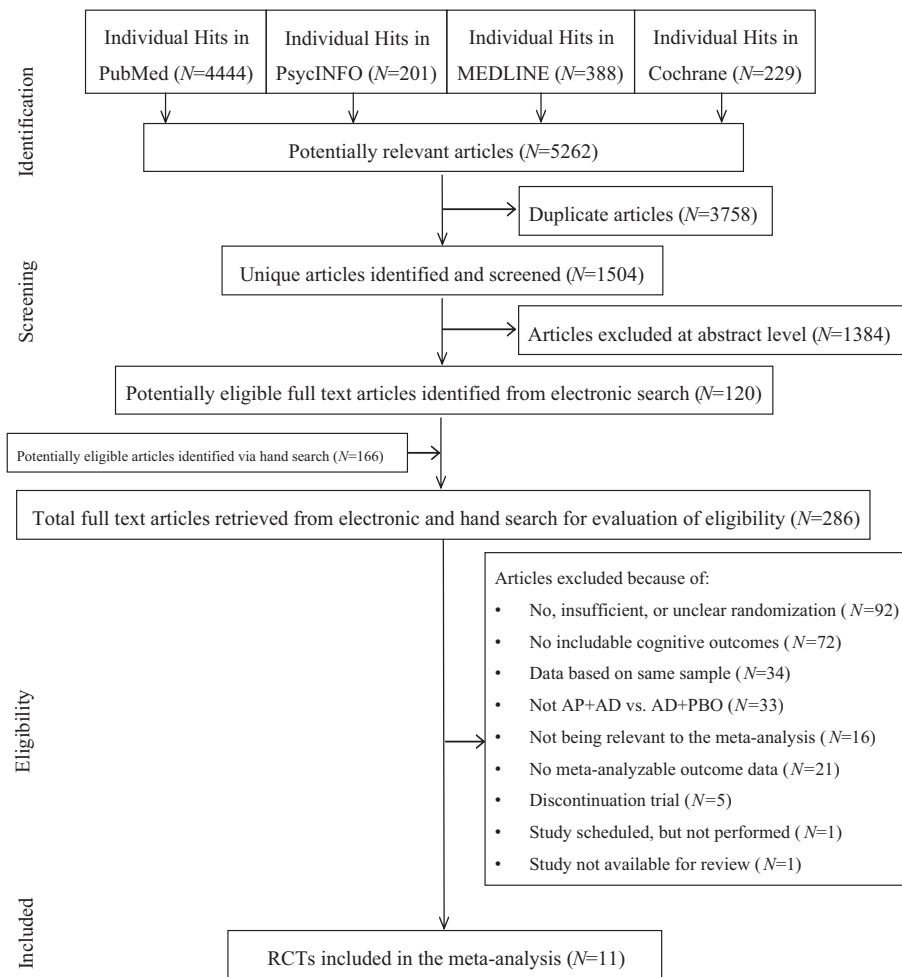


Fig. 1. Flow diagram of article search and review process.

Finally, for significant findings, pre-planned moderator analyses were conducted in studies: 1) not focusing on smoking cessation (as change in smoking status could affect outcomes) and 2) focusing on cognition as the primary outcome. Additionally, if the result for the cognitive composite was found to be significant, a third subanalysis was run utilizing only studies that measured ≥ 2 cognitive domains.

3. Results

3.1. Search

Our electronic search yielded 5262 hits (Fig. 1). After electronic filtering of duplicate records, 1504 unique articles remained, of which 1384 articles were excluded based on a review of titles/abstracts. The

Table 2
Cognitive test domain results.

| Pooled antidepressants vs. placebo | | | | | | |
|--|-----------|----------------|-----------|---------------|--------------|------------------|
| Cognitive domain | N studies | n participants | Hedges' g | 95% CI | p | I ² % |
| Executive function | 8 | 259 | 0.17 | 0.025, 0.31 | 0.02 | 47 |
| Attention | 5 | 321 | 0.022 | −0.19, 0.23 | 0.84 | 0 |
| Processing speed | 6 | 344 | 0.09 | −0.031, −0.21 | 0.15 | 16 |
| Visuospatial processing ^a | 3 | 94 | 0.14 | −0.73, 1.00 | 0.76 | 78 ^b |
| Auditory verbal long-term memory | 4 | 110 | 0.058 | −0.20, 0.31 | 0.66 | 41 |
| Visuospatial long-term memory ^a | 4 | 141 | 0.07 | −0.45, 0.59 | 0.79 | 66 ^b |
| Long-term memory ^a | 7 | 214 | 0.11 | −0.18, 0.40 | 0.45 | 45 |
| Auditory verbal working memory | 4 | 288 | 0.11 | −0.12, 0.34 | 0.34 | 0 |
| Visuospatial working memory | 4 | 123 | 0.063 | −0.18, 0.31 | 0.61 | 7 |
| Working memory | 8 | 412 | 0.074 | −0.087, 0.24 | 0.37 | 0 |
| Auditory verbal memory | 5 | 308 | 0.084 | −0.081, 0.25 | 0.32 | 20 |
| Visuospatial memory ^a | 5 | 160 | 0.065 | −0.16, 0.29 | 0.57 | 0 |
| Memory | 9 | 432 | 0.077 | −0.038, 0.19 | 0.19 | 46 |
| Verbal fluency | 5 | 327 | 0.019 | −0.14, 0.18 | 0.81 | 0 |
| Composite cognition score | 11 | 501 | 0.095 | 0.021, 0.17 | 0.012 | 45 |

Positive Hedges' g favors treatment group; fixed effects models, except where noted.

Bolded p-values: p < 0.05; ^arandom effects; ^b<3 studies available per subgroup so planned subanalyses were not run.

remaining 120 articles as well as 166 articles found via hand search underwent full-text inspection. Of these 286 articles, 16 were not relevant to the meta-analysis, 1 was not available for review, and—upon contacting the sponsoring agency—it was determined that 1 study had been scheduled but was not performed. Other reasons for exclusion were: no, insufficient, or unclear randomization (studies = 92); no cognitive outcomes (studies = 72); data based on a duplicate sample (studies = 34); study not conducted in antipsychotic + antidepressant vs. antipsychotic + placebo format (studies = 33); no meta-analyzable outcome data (studies = 21); and discontinuation trial (studies = 5). Ultimately, 11 studies were meta-analyzed (Table 1), including previously unpublished data from 8 studies (Acknowledgments).

3.2. Study, patient, and treatment characteristics

All 11 studies were published in English and were randomized, double-blinded, and placebo-controlled. 10 studies (91%) were parallel studies; one was a crossover study, and pre-crossover data were obtained. Mean study duration was 8.7 ± 3.7 weeks (range = 4–16 weeks). Altogether, 568 subjects were included (sample size: $n = 19$ –212, age = 39.5 ± 6.9 years, male = $67.2 \pm 10.9\%$). Only two studies reported ethnicity. All but one study (Poyurovsky et al., 2009), which included mostly first-episode schizophrenia patients, focused on patients with chronic schizophrenia (88.9% of patients). Mean illness duration was

12.5 ± 8.0 years (range = 3.6–25.6 years; studies = 8). Altogether, 60.1% were outpatients. The baseline total PANSS score was 78.5 ± 12.1 (studies = 8), while the baseline Clinical Global Impression-Severity (CGI-S) score was 4.0 ± 0.34 (studies = 5).

Six studies used second-generation antipsychotics (SGAs; 1 using clozapine), 2 used only first-generation antipsychotics (FGAs), and 3 used both SGAs and FGAs. The average antipsychotic dose was 382.7 ± 285.1 mg chlorpromazine (CPZ) equivalents (studies = 7).

Add-on antidepressants included: the alpha-2 antagonists (studies = 5) mirtazapine (studies = 4; $n = 126$; mean dose = 30 mg/d) and mianserin (study = 1; $n = 30$; mean dose = 15 mg/d); the SSRIs (studies = 3) citalopram (studies = 2; $n = 231$; mean dose = 29.7 mg/d) and fluvoxamine (study = 1; $n = 47$; mean dose = 150 mg/d); the serotonin-norepinephrine reuptake inhibitor (SNRI; study = 1) duloxetine ($n = 40$; mean dose = 60 mg/d); the norepinephrine reuptake inhibitor (NRI; study = 1) reboxetine ($n = 33$; mean dose = 4 mg/d); and the dopamine-norepinephrine reuptake inhibitor (DNRI; study = 1) bupropion ($n = 61$; mean dose = 300 mg/d).

3.3. Cognitive outcomes

For specific cognitive outcomes that were analyzed per study and domain, see Supplementary Tables 1–3. Statistically significant, but clinically negligible, advantages were found for pooled antidepressants

Table 3
Psychopathology and adverse effects outcomes.

| Pooled antidepressants vs. placebo | | | | | | |
|--|-----------|----------------|-----------|-------------|---------------|------------------|
| Continuous outcome | N studies | n participants | Hedges' g | 95% CI | p | I ² % |
| Total psychopathology ^a | 11 | 491 | −0.27 | −0.60, 0.07 | 0.12 | 65 |
| Positive symptoms ^a | 11 | 500 | −0.14 | −0.45, 0.17 | 0.38 | 60 |
| Negative symptoms ^a | 11 | 500 | −0.29 | −0.62, 0.05 | 0.09 | 64 |
| Depression (HAM-D-predominant) ^a | 9 | 455 | −0.14 | −0.47, 0.18 | 0.39 | 58 |
| Depression (CDSS-predominant) ^a | 9 | 455 | −0.22 | −0.53, 0.09 | 0.17 | 54 |
| EPS: Any | 8 | 407 | −0.13 | −0.33, 0.06 | 0.18 | 13 |
| Parkinsonism | 7 | 360 | −0.11 | −0.32, 0.10 | 0.30 | 21 |
| Akathisia ^a | 4 | 265 | −0.64 | −1.71, 0.43 | 0.24 | 85 ^b |
| Dyskinesia | 3 | 230 | −0.13 | −0.39, 0.13 | 0.32 | 39 |
| Categorical outcome | N | n | RR | 95% CI | p | I ² % |
| Discontinuation: All-cause | 11 | 568 | 1.16 | 0.85, 1.59 | 0.36 | 0 |
| Discontinuation: Inefficacy | 10 | 540 | 0.39 | 0.12, 1.33 | 0.13 | 0 |
| Discontinuation: Intolerability | 10 | 540 | 1.79 | 0.75, 4.27 | 0.19 | 0 |
| Discontinuation: Other reasons | 10 | 540 | 1.33 | 0.84, 2.11 | 0.22 | 0 |
| <50% decrease in PANSS total score | 7 | 442 | 1.00 | 0.98, 1.03 | 0.71 | 0 |
| <20% decrease in any negative symptom rating scale | 7 | 236 | 0.96 | 0.87, 1.06 | 0.47 | 0 |
| ≥20% increase in PANSS total score | 4 | 163 | 2.70 | 0.47, 15.32 | 0.26 | 0 |
| Study-defined inefficacy (with HAM-D) | 3 | 272 | 0.78 | 0.68, 0.91 | 0.0009 | 0 |
| Study-defined inefficacy (with CDSS) | 3 | 272 | 0.76 | 0.65, 0.90 | 0.0009 | 0 |
| Total neuropsychiatric adverse events | 4 | 312 | 1.11 | 0.96, 1.28 | 0.16 | 0 |
| Total neurological adverse events | 4 | 312 | 1.24 | 0.83, 1.85 | 0.30 | 12 |
| Headache | 4 | 312 | 1.06 | 0.56, 2.00 | 0.86 | 16 |
| Total psychiatric adverse events | 6 | 389 | 1.08 | 0.85, 1.39 | 0.53 | 0 |
| Suicidal ideation | 4 | 213 | 0.50 | 0.18, 1.39 | 0.19 | N/A |
| Worsening of psychosis | 5 | 168 | 3.08 | 0.65, 14.54 | 0.16 | 0 |
| Psychiatric hospitalization | 4 | 359 | 1.39 | 0.43, 4.49 | 0.58 | 0 |
| Insomnia | 4 | 312 | 1.45 | 0.82, 2.57 | 0.21 | 17 |
| Sedation | 4 | 118 | 2.91 | 1.03, 8.17 | 0.04 | 0 |
| Weakness/fatigue | 3 | 272 | 0.71 | 0.41, 1.23 | 0.22 | 0 |
| Agitation/irritability | 4 | 319 | 1.03 | 0.44, 2.41 | 0.94 | 0 |
| Total GI adverse events | 4 | 312 | 1.17 | 0.99, 1.39 | 0.06 | 0 |
| Total metabolic adverse events ^a | 3 | 272 | 2.67 | 0.52, 13.84 | 0.24 | 62 ^b |
| Increase in appetite | 3 | 272 | 1.34 | 0.59, 3.05 | 0.48 | 0 |
| Weight gain | 4 | 300 | 2.08 | 0.87, 4.97 | 0.10 | 1 |
| Total cardiorespiratory adverse events | 3 | 272 | 1.03 | 0.60, 1.77 | 0.92 | 0 |
| Total cardiac adverse events | 3 | 272 | 0.93 | 0.43, 2.00 | 0.85 | 0 |
| Total respiratory adverse events | 3 | 272 | 1.14 | 0.50, 2.61 | 0.75 | 0 |
| Total ophthalmological adverse events | 3 | 291 | 0.36 | 0.10, 1.33 | 0.13 | 15 |

For continuous outcomes, negative Hedges' g favors treatment group; for categorical outcomes, values <1 favor treatment group; fixed effects models, except where noted.

Bolded p-value: $p < 0.05$; ^arandom effects; ^b<3 studies available per subgroup so planned subanalyses were not run.

Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia; HAM-D = Hamilton Depression Rating Scale.

compared to placebo in executive function (Hedges' $g = 0.17$, 95% CI = 0.025–0.31, $p = 0.02$, $I^2 = 47\%$) and the cognitive composite (Hedges' $g = 0.095$, 95% CI = 0.021–0.17, $p = 0.012$, $I^2 = 45\%$) (Table 2). To explore possible moderating factors of significant results, pre-planned subanalyses were run for studies: 1) not focusing on smoking cessation (executive function = 7 studies; cognitive composite = 10 studies), and 2) using cognition as the primary outcome (executive function = 5 studies; cognitive composite = 8 studies). In these moderator analyses, results remained statistically significant, but all results became more heterogeneous. Moreover, results remained clinically negligible, except for executive function in studies where cognition was the primary outcome (Hedges' $g = 0.25$, 95% CI = 0.06–0.43, $p = 0.01$, $I^2 = 60\%$). Since this result was significantly heterogeneous, it was further explored using a random effects model, and the result remained heterogeneous but became statistically insignificant (Hedges' $g = 0.27$, 95% CI = –0.034 to 0.57, $p = 0.082$, $I^2 = 60\%$). As the initial fixed effects analyses for executive function and composite cognition were not significantly heterogeneous, preplanned subgroup analyses based on medication class were not conducted.

Antidepressants did not differ from placebo on any other cognitive domain scores for pooled antidepressants (Table 2). Significant heterogeneity ($I^2 \geq 50\%$) was found for visuospatial processing, visuospatial long-term memory, long-term memory, and visuospatial memory. Therefore, these domains were re-analyzed using a random effects model. Visuospatial processing and visuospatial long-term memory remained significantly heterogeneous, but too few studies had data to conduct preplanned subgroup analyses.

3.4. Psychopathology outcomes

Significant heterogeneity was found for total psychopathology, positive symptoms, negative symptoms, and depression. Therefore, these domains were explored using a random effects model. There were no significant differences between pooled antidepressants and placebo for total psychopathology (Hedges' $g = -0.27$, 95% CI = –0.60 to 0.07, $p = 0.12$, $I^2 = 65\%$), positive symptoms (Hedges' $g = -0.14$, 95% CI = –0.45 to 0.17, $p = 0.38$, $I^2 = 60\%$), or negative symptoms (Hedges' $g = -0.29$, 95% CI = –0.62 to 0.05, $p = 0.09$, $I^2 = 64\%$) (Table 3), but results were significantly heterogeneous. Therefore, subanalyses based on medication class were performed for SGAs (studies = 6); alpha-2 antagonists (mirtazapine and mianserin; studies = 5); mirtazapine (studies = 4); serotonergic antidepressants (SSRIs and duloxetine; studies = 4); SSRIs (studies = 3); and noradrenergic antidepressants (duloxetine, reboxetine, and bupropion; studies = 3). No significant differences were found (Table 4). Subanalyses excluding 1) 1 study focusing on smoking cessation and 2) 3 studies that did not use cognition as the primary outcome remained non-significant.

Antidepressants did not differ from placebo for depression in either the HAM-D-predominant analysis (Hedges' $g = -0.14$, 95% CI = –0.47 to 0.18, $p = 0.39$, $I^2 = 58\%$) or the CDSS-predominant analysis (Hedges' $g = -0.22$, 95% CI = –0.53 to 0.09, $p = 0.17$, $I^2 = 54\%$) (Table 3). Due to significant heterogeneity, subgroup analyses based on medication class were performed for SGAs (studies = 5); alpha-2 antagonists (studies = 4); mirtazapine (studies = 3); serotonergic antidepressants (studies = 4); and SSRIs (studies = 3). Depression

Table 4
Subanalyses of psychopathology: continuous outcomes.

| Subanalyses by medication class | | | | | | |
|---------------------------------------|-----------|----------------|-------------|--------------|-------------------|---------|
| Total psychopathology | N studies | n participants | Hedges' g | 95% CI | p | $I^2\%$ |
| SGAs | 6 | 196 | –0.42 | –0.92, 0.08 | 0.10 | 65 |
| Alpha 2 antagonists | 5 | 139 | –0.37 | –0.94, 0.20 | 0.20 | 62 |
| Mirtazapine | 4 | 115 | –0.50 | –1.17, 0.16 | 0.14 | 66 |
| Serotonergic ADs | 4 | 285 | –0.40 | –1.02, 0.23 | 0.21 | 79 |
| SSRIs | 3 | 245 | –0.08 | –0.47, 0.31 | 0.67 | 38 |
| Noradrenergic ADs | 3 | 107 | –0.26 | –1.23, 0.71 | 0.59 | 83 |
| | N | n | Hedges' g | 95% CI | p | $I^2\%$ |
| <i>Positive symptoms</i> | | | | | | |
| SGAs | 6 | 196 | –0.01 | –0.44, 0.43 | 0.98 | 56 |
| Alpha 2 antagonists | 5 | 139 | –0.50 | –1.12, 0.12 | 0.12 | 68 |
| Mirtazapine | 4 | 115 | –0.53 | –1.33, 0.27 | 0.19 | 76 |
| Serotonergic ADs | 4 | 285 | 0.07 | –0.30, 0.43 | 0.72 | 44 |
| SSRIs | 3 | 245 | 0.09 | –0.44, 0.61 | 0.75 | 62 |
| Noradrenergic ADs | 3 | 107 | 0.09 | –0.30, 0.48 | 0.65 | 0 |
| <i>Negative symptoms</i> | | | | | | |
| SGAs | 6 | 196 | –0.28 | –0.84, 0.27 | 0.32 | 72 |
| Alpha 2 antagonists | 5 | 139 | –0.42 | –0.96, 0.12 | 0.13 | 58 |
| Mirtazapine | 4 | 115 | –0.55 | –1.17, 0.07 | 0.08 | 61 |
| Serotonergic ADs | 4 | 285 | –0.32 | –0.96, 0.32 | 0.32 | 80 |
| SSRIs | 3 | 245 | –0.03 | –0.55, 0.48 | 0.90 | 61 |
| Noradrenergic ADs | 3 | 107 | –0.39 | –1.37, 0.58 | 0.43 | 83 |
| <i>Depression (HAM-D-predominant)</i> | | | | | | |
| SGAs | 5 | 178 | 0.00 | –0.60, 0.60 | 1.00 | 74 |
| Alpha 2 antagonists | 4 | 118 | 0.05 | –0.46, 0.55 | 0.85 | 46 |
| Mirtazapine | 3 | 94 | 0.01 | –0.68, 0.71 | 0.97 | 63 |
| Serotonergic ADs | 4 | 304 | –0.39 | –0.61, –0.16 | 0.0009 | 0 |
| SSRIs | 3 | 264 | –0.33 | –0.57, –0.08 | 0.009 | 0 |
| <i>Depression (CDSS-predominant)</i> | | | | | | |
| SGAs | 5 | 178 | –0.08 | –0.62, 0.47 | 0.78 | 68 |
| Alpha 2 antagonists | 4 | 118 | –0.06 | –0.44, 0.32 | 0.76 | 9 |
| Mirtazapine | 3 | 94 | –0.12 | –0.62, 0.38 | 0.64 | 31 |
| Serotonergic ADs | 4 | 304 | –0.51 | –0.74, –0.28 | <0.0001 | 0 |
| SSRIs | 3 | 264 | –0.47 | –0.71, –0.22 | 0.0002 | 0 |

Negative Hedges' g favors treatment group; random effects models.

Bolded p -values: $p < 0.05$.

Abbreviations: AD = antidepressants; CDSS = Calgary Depression Scale for Schizophrenia; HAM-D = Hamilton Depression Rating Scale.

improved with serotonergic antidepressants compared to placebo for both the HAM-D-predominant analysis (Hedges' $g = -0.39$, 95% CI = -0.61 to -0.16 , $p = 0.0009$, $I^2 = 0\%$) and CDSS-predominant analysis (Hedges' $g = -0.51$, 95% CI = -0.74 to -0.28 , $p < 0.0001$, $I^2 = 0\%$) (Table 4). Depression also improved with SSRIs compared to placebo for both the HAM-D-predominant analysis (Hedges' $g = -0.33$, 95% CI = -0.57 to -0.08 , $p = 0.009$, $I^2 = 0\%$) and the CDSS-predominant analysis (Hedges' $g = -0.47$, 95% CI = -0.71 to -0.22 , $p = 0.0002$, $I^2 = 0\%$) (Table 4). Antidepressants outperformed placebo regarding study-defined inefficacy in both the HAM-D-included data condition (RR = 0.78, 95% CI = 0.68–0.91, $p = 0.0009$, $I^2 = 0\%$) and the CDSS-included data condition (RR = 0.76, 95% CI = 0.65–0.90, $p = 0.0009$, $I^2 = 0\%$) (Table 3). There were no statistically significant differences for any of the remaining psychopathology outcomes (Table 3).

3.5. Study discontinuation

Antidepressants did not differ from placebo in all-cause discontinuation (RR = 1.16, 95% CI = 0.85–1.59, $p = 0.36$, $I^2 = 0\%$) or in discontinuation due to inefficacy (RR = 0.39, 95% CI = 0.12–1.33, $p = 0.13$, $I^2 = 0\%$), intolerability (RR = 1.79, 95% CI = 0.75–4.27, $p = 0.19$, $I^2 = 0\%$), or other reasons (RR = 1.33, 95% CI = 0.84–2.11, $p = 0.22$, $I^2 = 0\%$) (Table 3).

3.6. Adverse events

Sedation was more common with pooled antidepressants compared with placebo (RR = 2.91, 95% CI = 1.03–8.17, $p = 0.04$, $I^2 = 0\%$) (Table 3), but this analysis was based entirely on alpha-2 antagonists. No other significant differences were found for any adverse event (Table 3).

4. Discussion

To our knowledge, this is the first meta-analysis of antidepressant augmentation of antipsychotics for the treatment of cognitive deficits in schizophrenia. Across 11 studies and 568 patients, no clinically meaningful improvement in any cognitive domain or the composite score was found for pooled antidepressants or any class of studied antidepressants compared with placebo. Though disappointing, the enhancement of serotonergic or noradrenergic neurotransmission on top of antipsychotic therapy does not appear to relevantly improve cognition in patients with chronic schizophrenia. The exact mechanism of cognitive dysfunction in schizophrenia is unclear, but glutamatergic, cholinergic, GABAergic, and histaminergic hypotheses have the most support (Abi-Dargham, 2004; Foster et al., 2012; Jones et al., 2012; Lisman et al., 2012; Miyamoto et al., 2012; Nakazawa et al., 2012; Vohora and Bhowmik, 2012). Since none of the studied antidepressants targets these neurotransmitter systems, it is not that surprising that they were ineffective for cognitive impairment in schizophrenia. While it is theoretically plausible that these neurotransmitter systems might be affected by the studied antidepressants via neurotransmitter cross-talk, the strength of such postulated indirect effects may be insufficient to significantly improve cognition.

Antidepressants have been found in some studies to significantly reduce depressive symptoms in schizophrenia patients with comorbid depression (Whitehead et al., 2003). However, in the schizophrenia patients included in this meta-analysis who were unselected for depression, antidepressants did not significantly improve depression. One exception was significant antidepressant efficacy in the 4 and 3 studies with serotonergic agents and SSRIs, respectively. Nevertheless, this non-significant effect on depression reduces the potential bias of a pseudo-specific finding of cognitive improvement secondary to improved depression.

Moreover, at least in chronic patients with schizophrenia unselected for any specific symptomatology or severity, antidepressant augmentation of antipsychotics was not associated with benefits in positive, negative, or general psychopathology symptoms. Likewise, except for a higher incidence of sedation confined to alpha-2 antagonists, antidepressants were not associated with higher drop-out rates or specific adverse effects. The lack of efficacy of antidepressants on schizophrenia psychopathology is in contrast to several meta-analyses that found antidepressant augmentation to significantly reduce negative symptoms (Rummel et al., 2006; Sepehry et al., 2007; Singh et al., 2010; Hecht and Landy, 2011). However, these meta-analyses either focused on predominant negative symptom patients (Rummel et al., 2006) or included many more studies measuring negative symptoms, whereas we only included studies with cognitive data.

There are several limitations of this study. The number of included studies and subjects was small. Data from five studies utilizing bupropion that tested cognition (George et al., 2002; Evins et al., 2005a,b; George et al., 2006; Evins et al., 2007; Culhane et al., 2008; George et al., 2008; Moss et al., 2009; Weiner et al., 2012) were not meta-analyzable as presented in the published papers and were not obtainable from the authors. Notably, however, all bupropion studies targeted smoking cessation, and cognition was only a secondary outcome. Moreover, since bupropion has been found to significantly reduce smoking in schizophrenia (Tsoi et al., 2013), and since nicotine has pro-cognitive effects (Barr et al., 2008; Herman and Sofuoglu, 2010), results of these studies might have been confounded by change in smoking status.

Statistically significant but likely clinically irrelevant effects on executive function and composite cognition were found for pooled antidepressants. It is possible that subgroups of patients may have a more robust, clinically meaningful response to treatment, and a search for relevant biomarkers to identify such subgroups may prove fruitful. Antidepressant doses were also low- to mid-range; thus, higher doses could possibly produce greater effects, which should be explored in future studies of non-depressed patients with schizophrenia. Additionally, studied antidepressants were heterogeneous, as were the cognitive tests and outcomes. No study contained a complete cognitive battery or a complete subscale of a cognitive battery. Future studies should comprehensively measure a broad range of cognitive domains using complete neurocognitive batteries. Further, baseline antipsychotics and degree of patient stability varied. Studies were also short-term, yet even with these short intervention periods statistically significant effects were found on some aspects of cognition. It is possible longer durations of treatment might lead to clinically relevant effects. Finally, the majority of analyzed studies used chronic patients with a long duration of illness. It may be that earlier intervention with add-on antidepressants has a greater chance of success in the treatment of cognitive symptoms, and future studies should investigate the use of antidepressants in people with first-episode or early-phase schizophrenia. However, the one study in first-episode patients did not find significant effects either, although it was small ($n = 33$).

Despite its limitations, this meta-analysis of adjunctive antidepressant treatment for cognition in schizophrenia provides important suggestive information about lack of efficacy. Additionally, results can guide the design of future studies of adjunctive antidepressants for cognitive impairment in schizophrenia.

Funding

This work was partially supported by the National Institute of Mental Health Advanced Center for Services and Intervention Research, the Zucker Hillside Hospital (P30MH090590); the National Institutes of Health (NIH) P50 Centers for Intervention Development and Applied Research (P50MH080173); and the Case Western Reserve University/Cleveland Clinic CTSA grant number UL1 RR024989 provided by the

National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH.

Role of funding source

The National Institute of Mental Health and National Institutes of Health had no role in the study design; collection, analysis, or interpretation of data; writing of the report; or decision to submit the paper for publication.

Contributors

Drs. Vernon and Correll had full access to all study data and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Correll and Vernon. Acquisition of data: Vernon, Grudnikoff, Seidman, Vemulapalli, and Pareek. Analysis and interpretation of data: Vernon, Frazier, Goldberg, and Correll. Drafting of the manuscript: Vernon and Correll. Critical revision of the manuscript draft: Vernon, Grudnikoff, Seidman, Vemulapalli, Pareek, Goldberg, Frazier, Kane, and Correll. Study supervision: Correll.

Conflict of interest

Drs. Vernon, Grudnikoff, Vemulapalli, Pareek, and Goldberg and Mr. Seidman have nothing to disclose.

Dr. Frazier has received federal funding or research support from, acted as a consultant to, received travel support from, and/or received a speaker's honorarium from the Simons Foundation, Ingalls Foundation, Forest Laboratories, Ecoeos, IntegraGen, Shire Development, Bristol-Myers Squibb, National Institutes of Health, and the Brain and Behavior Research Foundation.

Dr. Kane has been a consultant to Alkermes, Amgen, Astra-Zeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Pierre Fabre, Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis, Roche, Rules Based Medicine and Sunovion, and has received honoraria for lectures from Otsuka, Eli Lilly, Esai, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck and Janssen. He is a shareholder of MedAvante.

Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Actelion, Alexza; Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, MedAvante, Medscape, Merck, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Supernus, Takeda, Teva, and Vanda. He has received grant support from BMS, Janssen/J&J, Novo Nordisk A/S and Otsuka.

Acknowledgments

We thank the following authors for providing us with additional, unpublished data: Alessandro Bertolino, MD, PhD, Grazia Caforio, MD, PhD, Seetal Dodd, MD, PhD, Richard P. Ebstein, PhD, Joseph I. Friedman, MD, Shahrokh Golshan, MD, Kenji Hashimoto, PhD, Salomon Israel, PhD, Ilana Kremer, MD, Tomihisa Niitsu, MD, PhD, Michael Poyurovsky, MD, Viatcheslav Terevnikov, MD, and Sidney Zisook, MD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2014.08.015>.

References

- Abi-Dargham, A., 2004. Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int. J. Neuropsychopharmacol.* (Suppl. 1), S1–S5.
- Albus, M., Hubmann, W., Mohr, F., Hecht, S., Hinterberger-Weber, P., Seitz, N.N., Küchenhoff, H., 2006. Neurocognitive functioning in patients with first-episode schizophrenia: results of a prospective 5-year follow-up study. *Eur. Arch. Psychiatry Clin. Neurosci.* 256 (7), 442–451.
- Barr, R.S., Culhane, M.A., Jubelt, L.E., Mufti, R.S., Dyer, M.A., Weiss, A.P., Deckersbach, T., Kelly, J.F., Freudenreich, O., Goff, D.C., Evins, A.E., 2008. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology* 33 (3), 480–490.
- Berk, M., Gama, C.S., Sundram, S., Hustig, H., Koopowitz, L., D'Souza, R., Malloy, H., Rowland, C., Monkhouse, A., Monkhouse, A., Bole, F., Sathiyamoorthy, S., Piskulic, D., Dodd, S., 2009. Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: a double-blind, randomised, placebo-controlled clinical trial. *Hum. Psychopharmacol.* 24, 233–238.
- Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M., Woerner, M.G., Geisler, S., Kane, J.M., Lieberman, J.A., 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am. J. Psychiatry* 157 (4), 549–559.
- Bloch, B., Reshef, A., Cohen, T., Tafla, A., Gathas, S., Israel, S., Gritsenko, I., Kremer, I., Ebstein, R.P., 2010. Preliminary effects of bupropion and the promoter region (HTTLPR) serotonin transporter (SLC6A4) polymorphism on smoking behavior in schizophrenia. *Psychiatry Res.* 175 (1–2), 38–42.
- Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biol. Psychiatry* 63 (5), 505–511.
- Bowie, C.R., Depp, C., McGrath, J.A., Wolyniec, P., Mautsach, B.T., Thornquist, M.H., Luke, J., Patterson, T.L., Harvey, P.D., Pulver, A.E., 2010. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. *Am. J. Psychiatry* 167 (9), 1116–1124.
- Buchanan, R.W., Davis, M., Goff, D., Green, M.F., Keefe, R.S., Leon, A.C., Nuechterlein, K.H., Laughren, T., Levin, R., Stover, E., Fenton, W., Marder, S.R., 2005. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr. Bull.* 31 (1), 5–19.
- Caforio, G., DiGiorgio, A., Rampino, A., Rizzo, M., Romano, R., Taurisano, P., Fazio, L., DeSimeis, G., Ursini, G., Blasi, G., Nardini, M., Mancini, M., Bertolino, A., 2013. Mirtazapine add-on improves olanzapine effect on negative symptoms of schizophrenia. *J. Clin. Psychopharmacol.* 33 (6), 810–812.
- Cho, S.J., Yook, K., Kim, B., Choi, T.K., Lee, K.S., Kim, Y.W., Lee, J.E., Suh, S., Yook, K.H., Lee, S.H., 2011. Mirtazapine augmentation enhances cognitive and reduces negative symptoms in schizophrenia patients treated with risperidone: a randomized controlled trial. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35 (1), 208–211.
- Choi, K.H., Wykes, T., Kurtz, M.M., 2013. Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy. *Br. J. Psychiatry* 203, 172–178.
- Coyle, J.T., Balu, D., Benneyworth, M., Basu, A., Roseman, A., 2010. Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. *Dialogues Clin. Neurosci.* 12 (3), 359–382.
- Culhane, M.A., Schoenfeld, D.A., Barr, R.S., Cather, C., Deckersbach, T., Freudenreich, O., Goff, D.C., Rigotti, N.A., Evins, A.E., 2008. Predictors of early abstinence in smokers with schizophrenia. *J. Clin. Psychiatry* 69, 1743–1750.
- Dawes, S.E., Palmer, B.W., Meeks, T., Golshan, S., Kasckow, J., Mohamed, S., Zisook, S., 2012. Does antidepressant treatment improve cognition in older people with schizophrenia or schizoaffective disorder and comorbid subsyndromal depression? *Neuropsychobiology* 65, 168–172.
- DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. *Control. Clin. Trials* 7 (3), 177–188.
- Evins, A.E., Cather, C., Deckersbach, T., Freudenreich, O., Culhane, M.A., Olm-Shipman, C.S., Henderson, D.C., Schoenfeld, D.A., Goff, D.C., Rigotti, N.A., 2005a. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J. Clin. Psychopharmacol.* 25, 218–225.
- Evins, A.E., Deckersbach, T., Cather, C., Freudenreich, O., Culhane, M.A., Henderson, D.C., Green, M.F., Schoenfeld, D.A., Rigotti, N.A., Goff, D.C., 2005b. Independent effects of tobacco abstinence and bupropion on cognitive function in schizophrenia. *J. Clin. Psychiatry* 66, 1184–1190.
- Evins, A.E., Cather, C., Culhane, M.A., Birnbaum, A., Horowitz, J., Hsieh, E., Freudenreich, O., Henderson, D.C., Schoenfeld, D.A., Rigotti, N.A., Goff, D.C., 2007. A 12-week double-blind, placebo-controlled study of bupropion SR added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. *J. Clin. Psychopharmacol.* 27 (4), 380–386.
- Foster, D.J., Jones, C.K., Conn, P.J., 2012. Emerging approaches for treatment of schizophrenia: modulation of cholinergic signaling. *Discov. Med.* 14 (79), 413–420.
- Friedman, J.I., Ocampo, R., Elbaz, Z., Parrella, M., White, L., Bowler, S., Davis, K.L., Harvey, P.D., 2005. The effect of citalopram adjunctive treatment added to atypical antipsychotic medications for cognitive performance in patients with schizophrenia. *J. Clin. Psychopharmacol.* 25 (3), 237–242.
- George, T.P., Vessicchio, J.C., Termine, A., Sahady, D.M., Head, C.A., Pepper, W.T., Kosten, T.R., Wexler, B.E., 2002. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* 26 (1), 75–85.
- George, T.P., Vessicchio, J., Allen, T., Weinberger, A., Sacco, K.A., 2006. A randomized, double-blind, placebo-controlled trial of sustained-release bupropion combined with transdermal nicotine patch for smoking cessation in schizophrenia: neuropsychological predictors of treatment outcome. *ACNP Annual Meeting*, pp. S254–S255.
- George, T.P., Vessicchio, J.C., Sacco, K.A., Weinberger, A.H., Dudas, M.M., Allen, T.M., Creedon, C.L., Potenza, M.N., Feingold, A., Jatlow, P.I., 2008. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. *Biol. Psychiatry* 63, 1092–1096.
- Goldberg, T.E., Goldman, R.S., Burdick, K.E., Malhotra, A.K., Lencz, T., Patel, R.C., Woerner, M.G., Schooler, N.R., Kane, J.M., Robinson, D.G., 2007. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch. Gen. Psychiatry* 64 (10), 1115–1122.
- Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J. Clin. Psychiatry* 67 (Suppl. 9), 3–8.
- Green, M.F., Kern, R.S., Braff, D.L., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? *Schizophr. Bull.* 26, 119–136.
- Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr. Res.* 72, 41–51.
- Harvey, P.D., Keefe, R.S.E., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am. J. Psychiatry* 158, 176–184.
- Hecht, E.M., Landy, D.C., 2011. Alpha-2 receptor antagonist add-on therapy in the treatment of schizophrenia: a meta-analysis. *Schizophr. Res.* 134 (2–3), 202–206.
- Herman, A.I., Sofuoglu, M., 2010. Cognitive effects of nicotine: genetic moderators. *Addict. Biol.* 15 (3), 250–265.
- Joffe, G., Terevnikov, V., Joffe, M., Stenberg, J.H., Burkin, M., Tiihonen, J., 2009. Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: a double-blind, randomized, placebo-controlled trial. *Schizophr. Res.* 108, 245–251.
- Jones, C.K., Byun, N., Bubser, M., 2012. Muscarinic and nicotinic acetylcholine receptor agonists and allosteric modulators for the treatment of schizophrenia. *Neuropsychopharmacology* 37 (1), 16–42.
- Kane, J.M., Lencz, T., 2008. Cognitive deficits in schizophrenia: short-term and long-term. *World Psychiatry* 7 (1), 29–30.

- Kasckow, J., Lanouette, N., Patterson, T., Fellows, I., Golshan, S., Solorzano, E., Zisook, S., 2010. Treatment of subsyndromal depressive symptoms in middle-aged and older adults with schizophrenia: effect on functioning. *Int. J. Geriatr. Psychiatry* 25, 183–190.
- Keefe, R.S.E., Fenton, W.S., 2007. How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophr. Bull.* 33 (4), 912–920.
- Lee, J.E., Cho, S.J., Lee, K.S., Yook, K.H., Choe, A.Y., Lee, S., Kim, B., Kim, K.H., Choi, T.K., Lee, S.H., 2011. The tolerability of mirtazapine augmentation in schizophrenic patients treated with risperidone: a preliminary randomized placebo-controlled trial. *Clin. Psychopharmacol. Neurosci.* 9 (2), 73–77.
- Lencz, T., Smith, C.W., McLaughlin, D., 2006. Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biol. Psychiatry* 59, 863–871.
- Lin, C.H., Huang, C.L., Chang, Y.C., Chen, P.W., Lin, C.Y., Tsai, G.E., Lane, H.Y., 2013. Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. *Schizophr. Res.* 146 (1–3), 231–237.
- Lisman, J., Yasuda, R., Raghavachari, S., 2012. Mechanisms of CaMKII action in long-term potentiation. *Nat. Rev. Neurosci.* 13 (3), 169–182.
- Menniti, F.S., Lindsley, C.W., Conn, P.J., Pandit, J., Zagouras, P., Volkman, R.A., 2013. Allosteric modulators for the treatment of schizophrenia: targeting glutamatergic networks. *Curr. Top. Med. Chem.* 13 (1), 26–54.
- Mesholam-Gately, R.L., Giuliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology* 23 (3), 315–336.
- Micò, U., Bruno, A., Pandolfo, G., Maria Romeo, V., Mallamace, D., D'Arrigo, C., Spina, E., Zoccali, R.A., Muscatello, M.R.A., 2011. Duloxetine as adjunctive treatment to clozapine in patients with schizophrenia: a randomized, placebo-controlled trial. *Int. Clin. Psychopharmacol.* 26 (6), 303–310.
- Miyamoto, S., Miyake, N., Jarskog, L.F., Fleischhacker, W.W., Lieberman, J.A., 2012. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Mol. Psychiatry* 17 (12), 1206–1227.
- Mohamed, S., Paulsen, J.S., O'Leary, D., Arndt, S., Andreasen, N., 1999. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch. Gen. Psychiatry* 56 (8), 749–754.
- Moss, T.G., Sacco, K.A., Allen, T.M., Weinberger, A.H., Vessicchio, J.C., George, T.P., 2009. Prefrontal cognitive dysfunction is associated with tobacco dependence treatment failure in smokers with schizophrenia. *Drug Alcohol Depend.* 104, 94–99.
- Nakazawa, K., Zsiros, V., Jiang, Z., Nakao, K., Kolata, S., Zhang, S., Belforte, J.E., 2012. GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology* 62 (3), 1574–1583.
- Niitsu, T., Fujisaki, M., Shiina, A., Yoshida, T., Hasegawa, T., Kanahara, N., Hashimoto, T., Shiraishi, T., Fukami, G., Nakazato, M., Shirayama, Y., Hashimoto, K., Iyo, M., 2012. A randomized, double-blind, placebo-controlled trial of fluvoxamine in patients with schizophrenia: a preliminary study. *J. Clin. Psychopharmacol.* 32 (5), 593–601.
- Poyurovsky, M., Koren, D., Gonopolsky, I., Schneidman, M., Fuchs, C., Weizman, A., Weizman, R., 2003. Effect of the 5-HT₂ antagonist mianserin on cognitive dysfunction in chronic schizophrenia patients: an add-on, double-blind placebo-controlled study. *Eur. Neuropsychopharmacol.* 13, 123–128.
- Poyurovsky, M., Fuchs, C., Pashinian, A., Levi, A., Faragian, S., Maayan, R., Gil-Ad, I., 2007. Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* 192, 441–448.
- Poyurovsky, M., Faragian, S., Fuchs, C., Pashinian, A., 2009. Effect of the selective norepinephrine reuptake inhibitor reboxetine on cognitive dysfunction in schizophrenia patients: an add-on, double-blind placebo-controlled study. *Isr. J. Psychiatry Relat. Sci.* 46 (3), 213–220.
- Rummel, C., Kissling, W., Leucht, S., 2006. Antidepressants for the negative symptoms of schizophrenia. *Cochrane Database Syst. Rev.* 3, CD005581.
- Sepehry, A.A., Potvin, S., Elie, R., Stip, E., 2007. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. *J. Clin. Psychiatry* 68, 604–610.
- Singh, S.P., Singh, V., Kar, N., Chan, K., 2010. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br. J. Psychiatry* 197, 174–179.
- Stenberg, J.H., Terevnikov, V., Joffe, M., Tiihonen, J., Tchoukhine, E., Burkin, M., Joffe, G., 2010. Effects of add-on mirtazapine on neurocognition in schizophrenia: a double-blind, randomized, placebo-controlled study. *Int. J. Neuropsychopharmacol.* 13, 433–441.
- Terevnikov, V., Stenberg, J.H., Tiihonen, J., Joffe, M., Burkin, M., Tchoukhine, E., Joffe, G., 2011. Add-on mirtazapine improves depressive symptoms in schizophrenia: a double-blind randomized placebo-controlled study with an open-label extension phase. *Hum. Psychopharmacol.* 26, 188–193.
- Tsoi, D.T., Porwal, M., Webster, A.C., 2013. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst. Rev.* 2, CD007253.
- Velligan, D.I., Bow-Thomas, C.C., Mahurin, R.K., Miller, A.L., Halgunseth, L.C., 2000. Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? *J. Nerv. Ment. Dis.* 188 (8), 518–524.
- Verdoux, H., Liraud, F., Assens, F., Abalan, F., van Os, J., 2002. Social and clinical consequences of cognitive deficits in early psychosis: a two-year follow-up study of first-admitted patients. *Schizophr. Res.* 56, 149–159.
- Vohora, D., Bhowmik, M., 2012. Histamine H3 receptor antagonists/inverse agonists on cognitive and motor processes: relevance to Alzheimer's disease, ADHD, schizophrenia, and drug abuse. *Front. Syst. Neurosci.* 6 (72), 1–10.
- Weiner, E., Ball, M.P., Buchholz, A.S., Gold, J.M., Evins, A.E., McMahon, R.P., Buchanan, R.W., 2012. Bupropion sustained release added to group support for smoking cessation in schizophrenia: a new randomized trial and a meta-analysis. *J. Clin. Psychiatry* 73 (1), 95–102.
- Whitehead, C., Moss, S., Cardno, A., Lewis, G., 2003. Antidepressants for the treatment of depression in people with schizophrenia: a systematic review. *Psychol. Med.* 33, 589–599.
- Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am. J. Psychiatry* 168 (5), 472–485.
- Zanelli, J., Reichenberg, A., Morgan, K., Fearon, P., Kravariti, E., Dazzan, P., Morgan, C., Zanelli, C., Demjaha, A., Jones, P.B., Doody, G.A., Kapur, S., Murray, R.M., 2010. Specific and generalized neuropsychological deficits: a comparison of patients with various first-episode psychosis presentations. *Am. J. Psychiatry* 167 (1), 78–85.
- Zisook, S., Kasckow, J.W., Golshan, S., Fellows, I., Solorzano, E., Lehman, D., Mohamed, S., Jeste, D.V., 2009. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. *J. Clin. Psychiatry* 70 (4), 562–571.
- Zisook, S., Kasckow, J.W., Lanouette, N.M., Golshan, S., Fellows, I., Vahia, I., Mohamed, S., Rao, S., 2010. Augmentation with citalopram for suicidal ideation in middle-aged and older outpatients with schizophrenia and schizoaffective disorder who have sub-threshold depressive symptoms: a randomized controlled trial. *J. Clin. Psychiatry* 71 (7), 915–922.