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Antidepressants for Cognitive Impairment in Schizophrenia – A Systematic Review and Meta-analysis

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1. Introduction

Cognitive symptoms are amongst the earliest in schizophrenia. They often develop in the prodromal period (Lencz, Smith, & McLaughlin, 2006; Kane & 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 (Velligan et al., 2000; Mohamed et al., 1999; Buchanan et al., 2005; Green, 2006; Zanelli et al., 2010; Bilder et al., 2000). Cognitive symptoms are highly disabling, having a strong correlation with functional outcome (Green, Kern, & Heaton, 2004; Green, Kern, & Braff, 2000; 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 independent, core symptom domain of schizophrenia

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that separately predicts long-term functional outcome and quality of life (Kane & Lencz, 2008; Keefe & Fenton, 2007; Green, Kern, & Braff, 2000). Despite the clinical and functional importance of cognitive symptoms, there are no currently approved and clearly effective pharmacologic treatments for these deficits (Harvey & Keefe, 2001; Coyle et al., 2010; Menniti et al., 2013; Choi, Wykes, & Kurtz, 2013). The small-to-moderate improvements with antipsychotics may reflect improvements of interfering hallucinations and thought disorganization or even negative symptoms (Harvey & 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, Wykes, & Kurtz, 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. 2005; Singh et al. 2010; Hecht and 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 never approved in any country for depression 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 intolerability, 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)±95% confidence interval (CI) for continuous outcomes and the risk ratio (RR)±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 modified ITT (i.e., all randomized subjects receiving ≥1 dose of study medication 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 case of significant heterogeneity, the outcome was reanalyzed using a DerSirmonian 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. 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 to be run utilizing only studies that measured ≥2 cognitive domains.

3. Results

3.1. Search

Our electronic search yielded 5,262 hits (Figure 1). After electronic filtering of duplicate records, 1,504 unique articles remained, of which 1,384 articles were excluded based on a review of titles/abstracts. The 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 (Acknowledgements).

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±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 Positive and Negative Syndrome Scale (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).

6 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 Supplemental Tables 1-3. Statistically significant, but clinically negligible, advantages were found for pooled antidepressants 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≥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 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; Lisman et al., 2012; Nakazawa et al., 2012; Miyamoto et al., 2012; Jones et al., 2012; Foster et al., 2010; Vohora & 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-Kluge et al., 2006; Sepehry et al., 2007; Singh et al., 2010; Hecht & Landy, 2012). However, these meta-analyses either focused on predominant negative symptom patients (Rummel-Kluge 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 (Culhane et al., 2008; Evins et al., 2007; Evins et al., 2005a; Evins et al., 2005b; George et al., 2002; George et al., 2008; George et al., 2006; 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 (Herman & Sofuoglu, 2010; Barr et al., 2008), 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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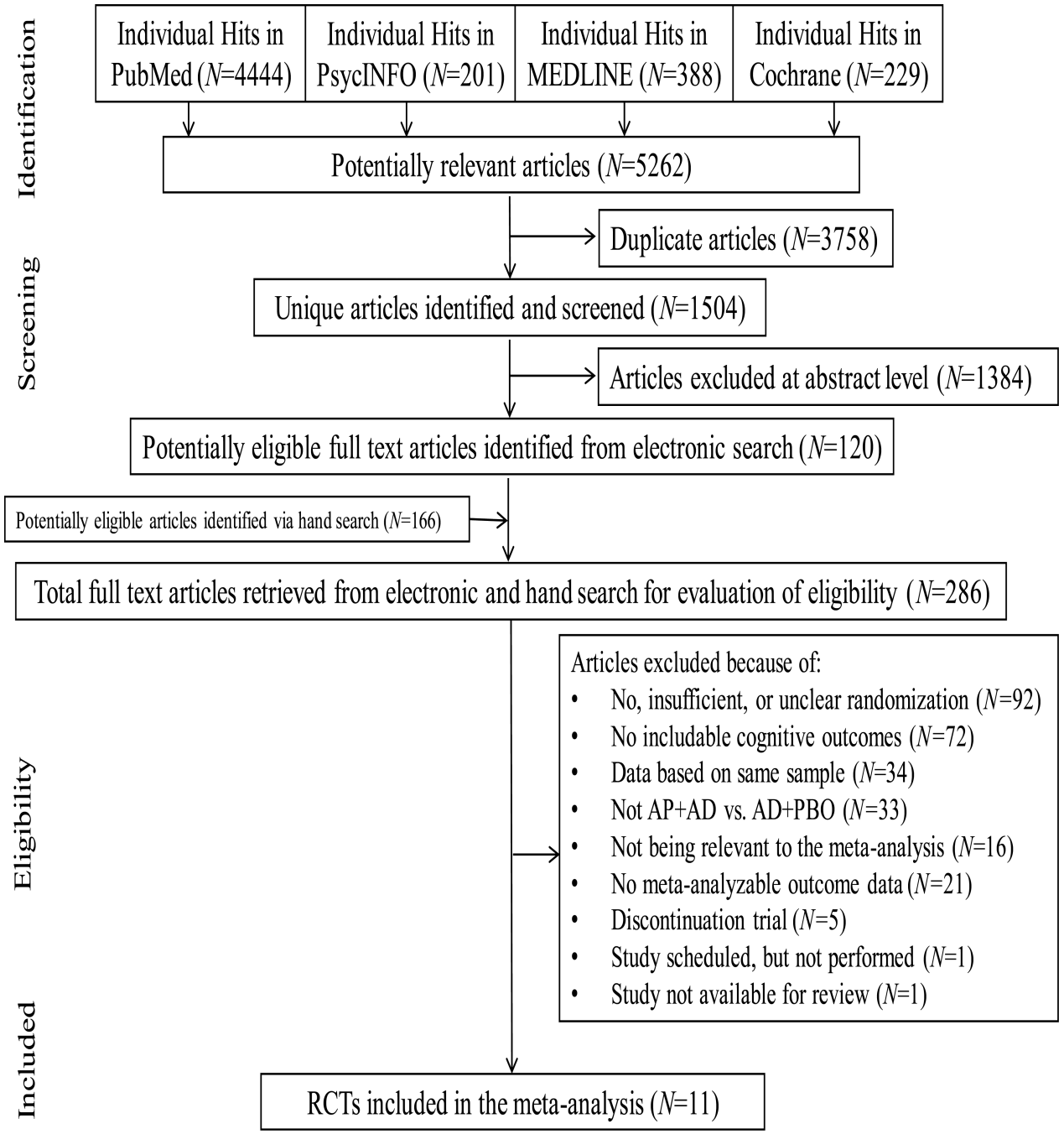

Figure 1.
Flow diagram of article search and review process

Table 1

Study, Patient, and Treatment Characteristics

Study/ Sponsor	Design	Total N	Time (wks)	Population	Mean Age	Male Sex (%)	Illness duration (years)	Treatments	Mean Dose (mg/d)	Primary Outcome(s)	Secondary Outcomes
Selective Serotonin Reuptake Inhibitor											
Dawes 2012/ Zisook 2009[a]/ Zisook 2010/ Kasckow 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; Psycho-pathology; Suicidality	EPS; Quality of Life; Metabolic side effects
Friedman 2005[a] Forest Laboratories	DBRPCT Cross over[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	Psycho-pathology; EPS
Niitsu 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	Psycho-pathology; EPS; Quality of Life
Serotonin-Norepinephrine Reuptake Inhibitor											
Mico 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 Psycho-pathology	Psycho-pathology; Cognitive Tests
Norepinephrine Reuptake Inhibitor											

Study/ Sponsor	Design	Total N	Time (wks)	Population	Mean Age	Male Sex (%)	Illness duration (years)	Treatments	Mean Dose (mg/d)	Primary Outcome(s)	Secondary Outcomes
Poyurovsky 2009/ Poyurovsky 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	Psycho-pathology; EPS
Dopamine-Norepinephrine Reuptake Inhibitor											
Bloch 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	Psycho-pathology; Cognitive Tests
Alpha 2 Antagonist											
Berk 2009[a] Organon Australia	DBRPCT	38	6	Schizophrenia NR Inpatients (39.5%) or outpatients (39.5%) with unreported data for 21.1% of patients Baseline total PANSS score = 84.76±19.85 Baseline CGI-S score = 4.13±0.89	36.8	84.2	NR	SGA+mirtazapine SGA+PBO	SGA = 333.6 CPZ equivalents (*n*=27) Mirtazapine = 30	Total Psycho-pathology	Psycho-pathology; Cognitive Tests
Caforio 2013[a] Stanley Medical Research Institute Organon Italy (Schering Plough)	DBRPCT	28	8	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	Psycho-pathology

Study/ Sponsor	Design	Total N	Time (wks)	Population	Mean Age	Male Sex (%)	Illness duration (years)	Treatments	Mean Dose (mg/d)	Primary Outcome(s)	Secondary Outcomes
Cho 2011/Lee 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; Psycho-pathology; Adherence
Poyurovsky 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	Psycho-pathology; EPS
Stenberg 2010[a]/Joffe 2009[a]/ Terevnikov 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	Psycho-pathology; Cognitive Tests	Psycho-pathology; Patient-rated Improvement
Total (unweighted means)											
11 Trials; Industry: N=4 Foundation: N=4 Government: N=1 Not reported/No external funding : N=4	**DBR PCT: N=11; Parallel: N=10 Cross-over: 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**	**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**	**Cognitive Tests: N=8; Total psycho-pathology: N=2; Psycho-pathology: 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**	**Psycho-pathology: 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 = 2**

Study/ Sponsor	Design	Total N	Time (wks)	Population	Mean Age	Male Sex (%)	Illness duration (years)	Treatments	Mean Dose (mg/d)	Primary Outcome(s)	Secondary Outcomes
				CGI-S score = 4.0±0.34 (N=5) **CGI-S score = 4.0±0.34 (N=5)**					**Mianserin: 15** **CPZ equivalents = 382.7±285.1 (N=7)**		

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

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: $p < 0.05$

[a] Random effects

[b] < 3 studies available per subgroup so planned subanalyses not run

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

Categorical Outcome	**N**	**n**	**RR**	**95% CI**	***p***	I^2**%**
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: $p < 0.05$

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

[a] Random effects

[b] < 3 studies available per subgroup so planned subanalyses not run

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

Positive Symptoms	**N**	**n**	**Hedges' *g***	**95% CI**	***P***	***I*²%**
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

Negative Symptoms	**N**	**n**	**Hedges' *g***	**95% CI**	***P***	***I*²%**
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

Depression (HAM-D-predominant)	**N**	**n**	**Hedges' *g***	**95% CI**	***P***	***I*²%**
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

Depression (CDSS-predominant)	**N**	**n**	**Hedges' *g***	**95% CI**	***P***	***I*²%**
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