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

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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.

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

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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
Selective serotonin reuptake inhibitor											
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
Serotonin–norepinephrine reuptake inhibitor											
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
Norepinephrine Reuptake Inhibitor											
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
Dopamine–norepinephrine reuptake inhibitor											
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
Alpha 2 antagonist											
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