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The effect of adjunctive armodafinil on cognitive performance and psychopathology in antipsychotic-treated patients with schizophrenia/schizoaffective disorder: A randomized, double-blind, placebo-controlled trial☆

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ABSTRACT

Background: The efficacy, safety and tolerability of adjunctive armodafinil for cognitive performance, and negative and affective symptoms, were examined in 60 patients with schizophrenia or schizoaffective disorder.

Method: This was a 6-week, double-blind, placebo-controlled, fixed dose trial of armodafinil (150 mg/d) augmentation in patients with clinically stable schizophrenia or schizoaffective disorder. Cognition, psychopathology, alertness/wakefulness and adverse effects were assessed with standardized rating instruments. The primary endpoint was performance on measures of attention/vigilance.

Results: Patients were randomly allocated to adjunctive armodafinil or placebo. There was a significant Drug × Time interaction effect for attention/vigilance, due to modest non-significant worsening in the armodafinil group and improvement in the armodafinil group [CPT-Pairs d′, $F(1,40) = 6.2$, $p = 0.017$]. However, it became non-significant after correction for multiple comparisons. There were no differences between armodafinil and placebo in other cognitive domains or psychopathology measures. However, armodafinil was associated with significant improvement in the Scale for the Assessment of Negative Symptoms (SANS) anhedonia–asociality [$F(1,41) = 4.1$, $p = 0.05$].

Conclusions: There were no significant differences in neurocognitive measures between adjunctive armodafinil and placebo in this 6-week study. Armodafinil improved anhedonia–asociality, but not other negative symptom domains.

1. Introduction

Patients with schizophrenia exhibit profound impairment in multiple cognitive domains, including attention, executive function, working and long-term memory, processing speed, and verbal fluency (Bowie and Harvey, 2005). It is well established that cognitive impairment is an important determinant of functional outcome in patients with schizophrenia. Even for the types of cognitive impairment where atypical antipsychotic drugs may be most effective—verbal fluency, long-term memory, and attention—the average improvement is modest, indicating the need for additional means of attaining further improvement (Harvey and Keefe, 2001; Woodward et al., 2005; Keefe et al., 2007a; Keefe et al., 2007b). One strategy is adjunctive pharmacologic treatment to supplement ongoing treatment with antipsychotic drugs.

Modafinil is a novel stimulant that modestly inhibits dopamine and norepinephrine transporters, leading to increased dopamine and norepinephrine efflux in cortical and other brain areas (Minzenberg and Carter, 2008). In humans, modafinil has been reported to attenuate cognitive disruptions caused by sleep disruption/deprivation (Walsh et al., 2004; Hart et al., 2006); to improve measures of attention and executive functioning in patients with attention-deficit/hyperactivity disorder (Turner et al., 2004a), major depression (DeBattista et al., 2004), and narcolepsy (Schwartz et al., 2004; Harsh et al., 2006); and to improve depression in patients with bipolar I disorder (Frye et al., 2007).

A variety of preclinical studies suggests that it might be an effective means of improving cognition in schizophrenia. For example, modafinil reversed phencyclidine (PCP)-induced impaired attention set shifting in rats (Pedersen et al., 2009), a preclinical model of cognitive impairment in schizophrenia. Modafinil also improves rodent spatial memory in the Morris Water Maze, a test of hippocampal memory (Shuman et al., 2009), and visual sustained attention in a dose-dependent manner (Waters et al., 2005).

In a 4-week open-label pilot study of 11 patients with stable schizophrenia or schizoaffective disorder, adjunctive modafinil produced significant improvement in working memory, attention, negative symptoms and fatigue (Rosenthal and Bryant, 2004). These

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results were confirmed in a placebo-controlled, double-blind cross-over study, which found that adjunctive modafinil (200 mg/d) significantly improved short-term verbal memory and attentional set shifting in 20 patients with schizophrenia(Turner et al., 2004b). However, five subsequent randomized, double-blind, placebo-controlled studies in patients with schizophrenia failed to demonstrate significant cognitive (Sevy et al., 2005; Spence et al., 2005; Hunter et al., 2006; Pierre et al., 2007; Freudenreich et al., 2009) or negative symptom benefit (Sevy et al., 2005; Pierre et al., 2007; Freudenreich et al., 2009) with adjunctive modafinil. The negative results in these studies may have been due, in part, to low modafinil doses (100–200 mg daily) and small sample sizes, the largest of which had 35 subjects. It has been suggested that modafinil's short elimination half-life may also have contributed to the negative results, particularly if neurocognitive testing did not occur at times of optimum plasma levels (Sevy et al., 2005). None of the studies systematically investigated the effects of modafinil on depressive symptoms.

Armodafinil is the R-enantiomer of racemic modafinil (Wisor et al., 2006). Both drugs have identical mechanisms of action; however, armodafinil produces higher plasma concentrations than racemic modafinil (Dinges et al., 2006; Darwish et al., 2009) and has a comparatively longer elimination half-life (10–14 h) than the S-enantiomer (3–4 h) (Wong et al., 1999a; Wong et al., 1999b; Robertson, Jr. and Hellriegel, 2003). Like modafinil, armodafinil has been recently shown to improve cognitive functioning in patients with sleep disorders (Hirshkowitz et al., 2007; Roth et al., 2008), and to reduce depressive symptoms in patients with bipolar I disorder (Calabrese et al., 2010).

There is only one published report of armodafinil effects on cognition and negative symptoms in patients with schizophrenia (Kane et al., 2010). In that study, 60 patients were randomized to adjunctive placebo or armodafinil at one of three fixed doses. Although statistical hypothesis testing was not conducted, greater improvement in PANSS-negative subscale scores was observed with the highest armodafinil dose (200 mg/d), but not lower doses, compared with placebo. No apparent differences in cognitive measures were observed. Only 15 patients were randomized to each treatment arm; thus, there was insufficient power to detect differences between treatment groups. Armodafinil effects on depressive symptoms were not investigated. We conducted a 6-week randomized, double-blind, placebo-controlled study of adjunctive armodafinil for cognitive performance, and negative and depressive symptoms, in patients with stable schizophrenia or schizoaffective disorder. We hypothesized that adjunctive armodafinil would be associated with improvement in measures of attention and processing speed. We secondarily hypothesized that adjunctive armodafinil would be associated with greater improvement in negative symptoms and depressive psychopathology, compared with placebo.

2. Methods

2.1. Subject selection and recruitment

This study was conducted between October 2006 and December 2009. Subjects were recruited from four community-based clinical sites in Nashville, TN. All clinical visits were conducted at the same sites from which the subjects were recruited. Eligible subjects (ages 18–64 years) were men and women referred by their clinical providers, met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder, and were on stable doses of antipsychotic drug treatment ($\geq$2 months) with no concomitant psychotropic medications other than SSRIs. There were no specific restrictions as to type or dosage of pre-study antipsychotic drugs. Patients taking depot antipsychotics were eligible. All clinical diagnoses were verified by physician interview and chart review. All patients were required to be in a stable clinical condition and provided written consent.

Patients taking concomitant mood stabilizers, non-SSRI antidepressants, anticholinergic medications, or benzodiazepines were excluded. Additional exclusion criteria included being pregnant or nursing, exposure to investigational drugs within 4 weeks of screening, history of hypersensitivity/intolerance of modafinil or armodafinil, history of acute illness exacerbation requiring psychiatric hospitalization within 8 weeks of study entry, or presence of general medical comorbidity that, in the opinion of the primary investigator, precluded entry into a clinical study.

The study protocol was approved by the institutional review boards of Vanderbilt University School of Medicine and other individual sites. All subjects provided written informed consent for study participation. The protocol was registered on www.clinicaltrials.gov (NCT00373672).

2.2. Study design and procedures

This was a 6-week double-blind, placebo-controlled trial of adjunctive armodafinil for cognition, psychopathology and tolerability in antipsychotic-treated patients with schizophrenia or schizoaffective disorder. After diagnostic screening, patients were randomly assigned (1:1) to placebo or armodafinil. A random number list generated by the project biostatistician and maintained off-site by the project administrator was used for treatment allocation.

Screening assessments consisted of clinical history, physical exam, vital signs, height/body weight, and metabolic laboratory studies. Following screening and baseline assessments, study visits occurred at weeks 1 and 3 in order to assess medication tolerability and to provide additional study medication. No neurocognitive or psychopathology assessments were performed at these visits. The final study visit occurred at week 6, where all baseline assessments were repeated (as discussed below).

Study medication was prepared by an independent research pharmacy. Placebo and armodafinil tablets were physically indistinguishable. Subjects allocated to treatment with armodafinil received single 150 mg tablets, taken once daily in the morning, the dose of which did not change throughout the study. All subjects remained on their pre-study antipsychotic drugs. Antipsychotic dose adjustments were not permitted in either the placebo or armodafinil groups. For patients taking SSRIs, changes in dosage were also not allowed after screening. To assess compliance and monitor medication dosing, antipsychotic and SSRI dosage was recorded at each follow up visit (at weeks 1, 3, and 6) after interviewing the patients, and verifying patient self report by reviewing prescriptions, pill bottle labels, and/or clinical notes, and by interviewing caregivers and other collateral informants.

2.3. Efficacy and safety assessments

Clinical efficacy was assessed at baseline and week 6. Cognitive performance was assessed using an electronic neurocognitive test battery (Cogtest plc, Kent, UK), supplemented with several paper-and-pencil neuropsychological tests, as listed in Table 1. The assessment time for cognitive measures, including the computerized and paper-and-pencil tests, was 60–120 min. The primary study endpoint was performance on neurocognitive tests of attention/vigilance (Continuous Performance Test (CPT) two-digit and four-digit d′, and the CPT flanker interference score, obtained by subtracting the congruent response time from incongruent response time for each subject).

Additional efficacy endpoints consisted of the remaining neuropsychological measures, Positive and Negative Syndrome Scale [PANSS] (Kay et al., 1987), Scale for the Assessment of Negative Symptoms [SANS] (Andreasen, 1989), Calgary Depression Scale [CDS] (Addington et al., 1993), Clinical Global Impression [CGI] scale (1976) the Epworth Sleepiness Scale [ESS] (Johns, 1991), and the Fatigue Severity Scale [FSS] (Krupp et al., 1989).

Table 1
Neurocognitive assessment battery: tests and domains.

Test name	Abbreviation	Domain measured
Continuous Performance Test, Identical Pairs version	CPT-IP	Attention/vigilance
Continuous Performance Test, Flanker version	CPT-Flanker	Attention/vigilance
Wisconsin Card Sorting Test	WCST	Executive functioning/reasoning
Controlled Oral Word Assn. Test	COWAT	Verbal fluency
Auditory Consonant Trigram	ACT	Working memory
Category Fluency Test	CFT	Verbal fluency
Face Memory Test	FMT	Secondary/declarative memory
Strategic Target Detection Test	STDT	Complex attention/executive function
Auditory Number Sequencing	ANS	Working memory/executive function
Digit Span (forward, backward)	DS-FWD, DS-BKWD	Attention/working memory
Penn's Emotional Acuity Test	PEAT	Emotion perception
Spatial Working Memory Test	SWMT	Working memory

Tolerability and safety were assessed at baseline, week 1 and week 6. General adverse effects were monitored with the Udvalg for Kliniski Undersogesler (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987). A clinician-rated scale was used to measure sexual functioning. The instrument included five questions that measured sexual desire, arousal, orgastic functioning, and menstrual regularity (females). Arousal and orgasm were rated on a 1 to 6 point scale, while sexual desire was rated on a 1 to 5 point scale; higher scores indicated greater dysfunction. Extrapyramidal effects were assessed with the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), Barnes Akathisia Scale (BARS) (Barnes, 1989), and Abnormal Involuntary Movement Scale (AIMS) (Lane et al., 1985). Body weight and laboratory studies were obtained at baseline and at 6 weeks. Body weight was measured in the fasting state, with light clothing. All laboratory specimens were processed and analyzed by the same fully accredited laboratory. Vital signs and 12-lead electrocardiograms were obtained at baseline, week 3, and week 6.

Clinical ratings were performed by raters who received rigorous training on each module of both the paper-and-pencil and automated cognitive assessments, psychopathology measures, and safety measures at the beginning of the trial, with periodic reassessment. Inter-rater reliability was approximately 95%, defined as percent agreement between raters, as well as comparison of each rater to gold standard ratings.

2.4. Statistical analysis

Treatment effects were analyzed using a repeated measures analysis of variance model with time (baseline, 6 weeks) as the within-subjects factor and treatment group (armodafinil, placebo) as the between-subjects factor. When Group × Time interaction effects were significant, post-hoc tests were conducted, including adjustment of α for multiple comparisons using the method of Bonferroni (significance was considered when the p value was ≤ 0.0167 based on three measures of attention/vigilance). Baseline GAF score was added as a covariate in order to examine sensitivity of cognitive effects to level of functioning. Demographic data of the two treatment groups were compared by two-tailed *t* test or chi-square test. Relationships between selected cognitive and psychopathology measures were assessed using Pearson correlation.

3. Results

3.1. Subject demography, clinical characteristics, and follow-up

Sixty patients were randomized, 58 of whom (29 in each group) completed the baseline assessment and received at least one dose of study drug (Fig. 1). There were no significant differences in demographic or clinical characteristics between patients who received armodafinil or placebo, as shown in Table 2. Antipsychotic drug treatment was similar for both allocation groups, including mean drug doses (Table 3). There were no significant differences in the proportion of subjects who received antidepressants in the armodafinil (total, n = 6 [20.7%] − citalopram, n = 3; esitalopram, n = 1; paroxetine, n = 2; sertraline, n = 1) and placebo groups (total, n = 7 [24.1%] − citalopram, n = 1; paroxetine, n = 1; sertraline, n = 4). Of the 58 randomized subjects who received study drug, 47 (81%) completed the study (armodafinil, n = 22 [75.9%] vs. placebo, n = 25 [86.2%]; p = NS).

3.2. Neurocognitive performance and psychopathology

3.2.1. Cognition

There was a significant Group × Time interaction effect on the CPT-IP two-digit d′ [$F(1,40) = 6.2$, $p = 0.017$] (Table 4) due to modest but statistically significant improvement on this measure in the placebo group (+0.83, $p = 0.03$) compared to a slight decline in performance in the armodafinil group. However, this finding did not remain statistically significant following adjustment for multiple comparisons on measures of attention. Covarying for baseline GAF scores and age at baseline did not change these results, with the exception that the Group × Time interaction effect on the CPT-IP two-digit d′ became significant after adjusting for age ($p = 0.0164$). There was no significant relationship between change in CPT-IP two-digit d′ score and age at baseline, age of illness onset, duration of illness, or gender in the armodafinil group. No significant Time or Group × Time interaction effect was observed for CPT-IP four digit d′. A significant Time effect was observed for FMT delayed recall; however, no significant Group × Time interaction effect was observed for it or for any other measures of cognition, even after covarying for baseline GAF scores and age.

3.2.2. Psychopathology

There were significant Time effects for PANSS-Total scores, and PANSS-Cognitive, -Positive and -General psychopathology subscale scores, indicating that patients in both treatment groups improved as a whole over time (Table 5). No significant Group × Time interaction effect was observed for any of these measures, indicating that improvement did not differ significantly by treatment group. No significant Time or Group × Time interaction effects were noted for PANSS-Negative, SANS or CDS scores.

When the effects of drug treatment on individual scale items was analyzed, a significant Group × Time interaction effect was observed for the SANS anhedonia–asociality item [$F(1,41) = 4.1$, $p = 0.05$; $ES = 0.63$]. In the armodafinil group, LS-mean scores on the Anhedonia–Asociality item decreased (improved) modestly from baseline (2.7 ± 0.2) to study endpoint (2.4 ± 0.3). In the placebo group, LS-mean scores increased (worsened) slightly between baseline (2.1 ± 0.2) and study endpoint (2.3 ± 0.2). No significant Time or Group × Time interaction effects were observed for any other PANSS or SANS individual item scores. There was no significant correlation between change in CPT 2-digit d′ scores and change in either PANSS-Negative subscale or SANS global or individual item scores (including anhedonia–asociality) in either treatment group.

3.3. Safety and tolerability

Treatment with armodafinil was well tolerated. Discontinuation from the study due to adverse events was infrequent (Fig. 1), as were the most common adverse effects (Table 6). There were no statistically significant Time or Group × Time interaction effects for ESS, FSS, sexual functioning scale, AIMS, BARS, or SAS scores (data not shown). No clinically relevant changes from baseline in body weight,

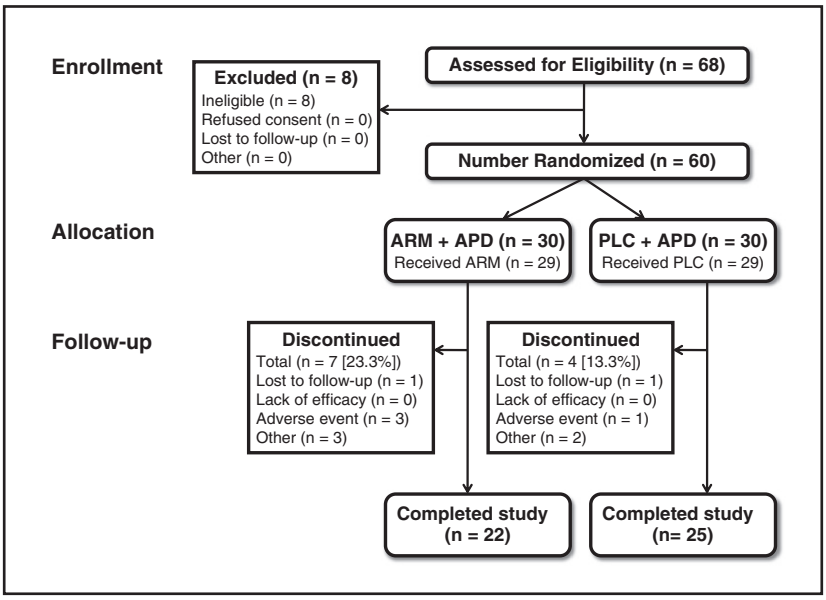

Fig. 1. Disposition and patient flow. Key: APD = antipsychotic drug; ARM = adjunctive armodafinil; PLC = adjunctive placebo.

laboratory evaluations, vital signs, or QTc interval occurred in either group (data not shown).

One patient assigned to placebo required psychiatric hospitalization for worsening psychosis and was discontinued from the study. One patient assigned to armodafinil was discontinued from the study due to worsening auditory hallucinations, which resolved after armodafinil discontinuation and a temporary increase in antipsychotic dosage. Finally, new-onset involuntary lingual dyskinesias were observed in one patient assigned to armodafinil at week 6. Dyskinetic movements were not evident during previous study visits, and resolved spontaneously over 4 weeks of post-study follow-up.

4. Discussion

In this placebo-controlled study, a beneficial effect of adjunctive armodafinil on cognitive performance or depressive psychopathology could not be demonstrated during 6 weeks of treatment. Armodafinil significantly improved one type of negative symptoms, anhedonia–asociality, compared to placebo augmentation.

These results are in accord with three 8-week randomized, placebo-controlled, parallel-group studies which failed to demonstrate significant improvement in attention or other cognitive performance measures with adjunctive modafinil. Our results are also consistent with the only other published study of armodafinil in antipsychotic-treated patients with schizophrenia (Kane et al., 2010). None of the three fixed doses of adjunctive armodafinil (50, 100, 200 mg/d) demonstrated a clear beneficial effect over placebo on the MATRICS consensus cognitive battery composite score, the primary study endpoint, or in any of the seven MATRICS battery domain scores. Thus, most studies of modafinil, and now armodafinil, in antipsychotic-treated subjects with schizophrenia, have not demonstrated cognitive improvement which contrasts with the beneficial effects of modafinil on some cognitive measures in higher-functioning

Table 2
Subject demographic and clinical characteristics at baseline.

Variable		Armodafinil (n = 29)	Placebo (n = 29)
Gender (No., %)	Male	15 (51.7)	20 (69.0)
	Female	14 (48.3)	9 (31.0)
Race (No., %)	Caucasian	13 (44.8)	11 (37.9)
	African American	16 (55.2)	17 (58.6)
	Other	0	1 (3.5)
Diagnosis (No., %)	Schizophrenia, paranoid	16 (55.2)	15 (51.7)
	Schizophrenia, undiff.	1 (3.4)	1 (3.4)
	Schizoaffective	12 (41.4)	13 (44.9)
Age in years (mean, SD)		44.0 (14.6)	38.8 (11.7)
Age of onset in years (mean, SD)		21.2 (10.1)	21.7 (7.0)
Duration of illness, years (mean, SD)		22.9 (15.5)	17.5 (11.1)
Number of previous hospitalizations (mean, SD)		3.5 (2.5)	5.5 (4.2)
Number of prior illness episodes (mean, SD)		6.6 (7.0)	6.4 (5.5)
Marital status, married (No., %)		4 (13.8)	4 (13.8)
Employment status, full- or part-time (No., %)		1 (3.4)	2 (6.8)
Education level, HS graduate or higher (No., %)		16 (55.2)	15 (51.7)

Table 3
Antipsychotic drugs and drug dosages.

Drug	Armodafinil	Placebo
Clozapine		
N	2	6
Dose, mean (SD) mg/d	400.0 (212.1)	462.5 (167.2)
Risperidone		
N	8	7
Dose, mean (SD) mg/d	4.9 (1.9)	4.9 (2.9)
Olanzapine		
N	4	5
Dose, mean (SD) mg/d	15.6 (7.2)	15.0 (10.0)
Quetiapine		
N	6	1
Dose, mean (SD) mg/d	635.0 (241.9)	600.0
Ziprasidone		
N	2	3
Dose, mean (SD) mg/d	140.0 (28.3)	146.7 (23.1)
Aripiprazole		
N	3	5
Dose, mean (SD) mg/d	18.3 (10.4)	25.0 (8.7)
Typical neuroleptics[a]		
N	4	2
Dose, mean (SD) mg/d	467.5 (259.9)	500.0 (141.4)

[a] Dosage of typical neuroleptics expressed in chlorpromazine equivalents (mg/d).

Table 4
Effects of adjunctive armodafinil and placebo on neurocognitive test performance.

Test name	Measure	Time point	LS-mean (SE)		Source, F-statistic, p-value	
			ARM (n = 29)	PLC (n = 29)	Time	Drug × Time
CPT-IP	2-digit d′	Baseline	2.8 (0.3)	2.5 (0.3)	F(1,40) = 0.9	F(1,40) = 6.2
		6 weeks	2.5 (0.4)	3.4 (0.4)	NS	p = 0.017
	4-digit d′	Baseline	1.3 (0.3)	1.3 (0.3)	F(1,24) = 1.2	F(1,24) = 0.1
		6 weeks	1.0 (0.2)	1.1 (0.2)	NS	NS
CPT-Flanker	Interference score[a]	Baseline	51.3 (13.2)	38.6 (11.4)	F(1,40) = 0.3	F(1,40) = −1.8
		6 weeks	59.7 (15.5)	19.7 (13.5)	NS	NS
WCST	Categories	Baseline	4.3 (0.6)	4.3 (0.4)	F(1,31) = 0.4	F(1,31) = 0.4
		6 weeks	4.3 (0.6)	4.0 (0.5)	NS	NS
	% Persev error[b]	Baseline	19.0 (2.9)	20.3 (2.5)	F(1,42) = 0.3	F(1,42) = 1.4
		6 weeks	20.2 (3.1)	17.2 (2.7)	NS	NS
COWAT		Baseline	27.9 (2.6)	28.8 (2.4)	F(1,45) = 2.5	F(1,45) = 0.7
		6 weeks	30.0 (2.7)	29.5 (2.5)	NS	NS
ACT		Baseline	37.6 (2.1)	39.2 (2.0)	F(1,45) = 3.1	F(1,45) = 0.4
		6 weeks	38.7 (1.9)	41.4 (1.7)	NS	NS
CFT		Baseline	16.7 (1.0)	16.9 (1.0)	F(1,44) = 0.03	F(1,44) = 0.2
		6 weeks	16.9 (1.1)	16.5 (1.0)	NS	NS
FMT (% correct)	Immediate recall	Baseline	0.7 (0.03)	0.7 (0.03)	F(1,44) = 1.2	F(1,44) = 0.5
		6 weeks	0.6 (0.03)	0.7 (0.03)	NS	NS
	Delayed recall	Baseline	0.7(0.02)	0.7 (0.02)	F(1,40) = 6.0	F(1,40) = 0.3
		6 weeks	0.6 (0.02)	0.6 (0.02)	p = 0.02	NS
STDT						
2 shape	Persev errors[c]	Baseline	11.8 (3.0)	4.8 (2.6)	F(1,29) = 0.02	F(1,29) = 0.06
		6 weeks	12.1 (2.0)	3.9 (2.6)	NS	NS
4 shape	Persev errors[c]	Baseline	13.0 (2.6)	12.3 (2.2)	F(1,24) = 2.5	F(1,24) = 0.2
		6 weeks	11.0 (1.6)	9.0 (1.4)	NS	NS
ANS (no.)	Correct sequences[d]	Baseline	7.6 (0.6)	7.3 (0.5)	F(1,39) = 2.9	F(1,39) = 0.1
		6 weeks	8.3 (0.6)	7.8 (0.5)	NS	NS
DS						
Forward	No. correct	Baseline	6.3 (0.3)	6.3 (0.2)	F(1,44) = 0.2	F(1,44) = 0.0
		6 weeks	6.4 (0.3)	6.4 (0.3)	NS	NS
Backward	No. correct	Baseline	4.7 (0.2)	4.5 (0.2)	F(1,43) = 0.02	F(1,43) = 0.02
		6 weeks	4.7 (0.2)	4.6 (0.2)	NS	NS
PEAT	Total correct	Baseline	10.2 (0.9)	11.5 (0.8)	F(1,43) = 2.5	F(1,43) = 0.0
		6 weeks	11.2 (0.8)	12.6 (0.8)	NS	NS
SWMT	Overall mean	Baseline	91.3 (11.1)	104.6(10.3)	F(1,43) = 1.1	F(1,43) = 0.5
		6 weeks	89.1 (10.5)	104.6(10.3)	NS	NS

All values are LS-mean (SD) unless otherwise specified.
Key: ACT = Auditory Consonant Trigram; ANS = Auditory Number Sequencing Test; CFT = Category Fluency Test; COWAT = Controlled Oral Word Association Test; CPT-Flanker = Continuous Performance Test, flanker version; CPT-IP = Continuous Performance Test, identical pairs version; DS = Digit Span test (forward digit span, backward digit span); FMT = Face Memory Test; NS = non-statistically significant p-value; PEAT = Penn's Emotion Acuity Test; RT = response time; STDT = Strategic Target Detection Test; SWMT = Spatial Working Memory Test; WCST = Wisconsin Card Sorting Test.
[a] Interference score on the CPT-Flanker task was obtained by subtracting the incongruent response time from the congruent response time for each subject.
[b] Refers to the LS-mean proportion of responses with perseverative error(s).
[c] Refers to the LS-mean number of perseverative errors.
[d] Refers to the LS-mean number of correct sequences.

patients (Minzenberg and Carter, 2008). This suggests that the deficits in cognition in schizophrenia are based upon structural or functional abnormalities which may be insensitive to the neurotransmitter changes elicited by either modafinil or armodafinil.

It has been suggested that certain sub-types of patients with schizophrenia may be more likely to experience cognitive benefit from adjunctive modafinil, including those who have relatively intact intelligence levels but still manifest impaired attention and executive dysfunction at baseline (Morein-Zamir et al., 2007), or those treated with typical neuroleptics (Spence et al., 2005). Indeed, because armodafinil's pro-cognitive effect may be mediated by increasing DA and NE neurotransmission (Minzenberg and Carter, 2008), armodafinil may have limited capacity to improve cognition when added to atypical antipsychotics compared with typical neuroleptics, since atypical antipsychotic drugs, but not typical neuroleptics, have been shown to increase cortical DA and NE release (Ichikawa et al., 2001; Westerink et al., 2001; Liegeois et al., 2002). However, armodafinil's cognitive benefits may be less evident in patients treated with typical neuroleptics which may be more potent dopamine D_2 receptor antagonists at clinically effective doses than are atypical antipsychotic drugs (Morein-Zamir et al., 2007). Our sample was of insufficient size to reliably assess effect modification by baseline cognitive measures or by antipsychotic drug class. Thus, the issue of whether or not modafinil or armodafinil improves cognition in patients when these baseline or treatment measures are taken into account is still open.

In our study, armodafinil resulted in significantly greater improvement in anhedonia–asociality than did adjunctive placebo. However, similar to previous reports with modafinil (Sevy et al., 2005; Pierre et al., 2007; Freudenreich et al., 2009) we found no significant improvement in global negative symptom measures over time. Kane et al. (2010) reported numerically greater reduction in PANSS negative subscale score in a comparison of adjunctive armodafinil (200 mg/d) and placebo; however, no hypothesis tests were conducted, and no such differences were observed between placebo and the lower dosage groups. In addition, no between-groups differences in SANS scores were evident. Nevertheless, the Kane et al. (2010) study raises the possibility that the armodafinil dose (150 mg/d) in this study may have been too low. Changes in individual SANS items according to treatment group were not reported by Kane et al. (2010); thus, the effect of armodafinil on anhedonia–asociality requires replication.

Table 5
Effects of adjunctive armodafinil and placebo on psychopathology measures.

Test name	Scale/ subscale	Time point	LS-mean (SE) Armodafinil (n = 29)	LS-mean (SE) Placebo (n = 29)	Source, F-statistic, p-value Time	Source, F-statistic, p-value Drug × Time
PANSS	Total	Baseline	62.6 (2.5)	60.8 (3.2)	F(1,44) = 21.4	F(1,44) = 0.5
		6 weeks	56.7 (3.1)	56.4 (2.9)	p = 0.0001	NS
	Positive	Baseline	16.1 (1.2)	15.0 (1.1)	F(1,44) = 12.0	F(1,44) = 0.4
		6 weeks	14.3 (1.1)	13.8 (1.0)	p = 0.001	NS
	Negative	Baseline	14.2 (0.9)	15.4 (0.8)	F(1,44) = 2.4	F(1,44) = 1.3
		6 weeks	14.1 (1.0)	14.5 (0.9)	NS	NS
	Cognitive	Baseline	7.7 (0.7)	8.4 (0.6)	F(1,44) = 12.9	F(1,44) = 1.8
		6 weeks	7.1 (0.6)	7.2 (0.6)	p = 0.0008	NS
	General	Baseline	32.3 (1.8)	30.4 (1.7)	F(1,44) = 23.1	F(1,44) = 1.8
		6 weeks	28.2 (1.6)	28.2 (1.4)	p = 0.0001	NS
SANS	Total	Baseline	6.6 (0.8)	6.2 (0.7)	F(1,42) = 0.1	F(1,42) = 0.1
		6 weeks	6.4 (0.9)	6.2 (0.8)	NS	NS
CDS	Total	Baseline	4.2 (1.0)	3.5 (0.9)	F(1,32) = 0.9	F(1,32) = 0.07
		6 weeks	3.4 (1.0)	3.1 (0.8)	NS	NS

All values are LS-mean (SD), unless otherwise specified.
Key: CDS = Calgary Depression Scale; NS = non-statistically significant p-value; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms.

Adjunctive armodafinil was generally well tolerated. One patient randomized to armodafinil experienced an exacerbation of auditory hallucinations that resolved within one week following drug discontinuation, without need for psychiatric hospitalization. It cannot be concluded that this was drug related, however. One other case of worsening psychosis occurred in a patient who received placebo. There have been sporadic reports of modafinil-associated exacerbation of psychotic symptoms in patients with schizophrenia (Narendran et al., 2002; Rosenthal and Bryant, 2004; Sevy et al., 2005; Pierre et al., 2007). Reversible lingual dyskinesia observed in one armodafinil-treated patient in our study was similar to other cases of treatment-emergent oral or facial dyskinesias associated with modafinil (Luborzewski et al., 2006; Vytopil et al., 2007; Maser et al., 2010). To our knowledge, this adverse effect has not been observed in large-scale studies of modafinil or armodafinil.

Table 6
Adverse effects[a] of adjunctive armodafinil or placebo.

Adverse effect	Armodafinil (n = 29)	Placebo (n = 29)
Reduced duration of sleep	4 (13.8)	7 (24.1)
Sense of tension/inner unrest	5 (17.2)	6 (20.7)
Extrapyramidal side-effects[b]	3 (10.3)	7 (24.1)
Sexual dysfunction[c]	4 (13.8)	5 (17.2)
Depressed mood	3 (10.3)	5 (17.2)
Diaphoresis	3 (10.3)	3 (10.3)
Constipation	3 (10.3)	2 (6.9)
Gastrointestinal upset	2 (6.9)	3 (10.3)
Palpitations/tachycardia	2 (6.9)	3 (10.3)
Orthostatic dizziness	2 (6.9)	2 (6.9)
Fatigue	2 (6.9)	2 (6.9)

All values are no. (%) unless otherwise indicated. There were no significant differences between groups for any adverse effects (Fisher's exact test).
[a] Adverse effects were assessed via the Udvalg for Kliniski Undersogesler (UKU) Side Effect Rating Scale and spontaneous subject report.
[b] Extrapyramidal side effects included subject self-report and positive responses on the following UKU Side Effect Rating Scale items: dystonia, rigidity, hypokinesia, tremor, and akathisia.
[c] Sexual dysfunction included subject self-report and positive responses on the following UKU Side Effect Rating Scale items: diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Interpretation of our findings should proceed with limitations in mind. Given the relatively small sample size in our study, we cannot exclude the possibility of type II error for attention/vigilance and other cognitive measures. The small sample size also limited our ability to conduct rigorous subgroup analyses to test hypotheses related to clinically important potential effect modifiers (discussed above) and clinical subgroups, including those with greater impairment of executive functioning, which could be due to greater deficits in prefrontal cortical dopaminergic activity (Floresco and Magyar, 2006; Morein-Zamir et al., 2007). Thus, larger studies with adequate power will be needed to identify patient sub-types that may particularly benefit from adjunctive armodafinil.

We also cannot rule out that a higher dose of armodafinil might have produced more positive findings. Our resources permitted the testing of only a single armodafinil dose. A 150 mg dose was considered to provide the best choice to achieve a therapeutic benefit with minimal adverse effects. This decision was based on cognitive improvement with—and good tolerability of—adjunctive modafinil at a dose of 200 mg daily in antipsychotic-treated patients with schizophrenia (Rosenthal and Bryant, 2004; Turner et al., 2004a) and the tendency for armodafinil to have greater plasma drug concentrations (Darwish et al., 2009) and longer elimination half-life (Wong et al., 1999a; Wong et al., 1999b) than modafinil at a given dose.

The utility of traditional cognition assessment methods to evaluate possible adjunctive treatments in patients with schizophrenia has been questioned (Barch et al., 2008). The recently-launched Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative has been proposed as an alternative or supplement (Carter et al., 2008). These methods were not available to us so we chose to utilize classical neuropsychological measures, which are still the standard methodology in most studies of this type. Finally, given the common use of adjunctive psychotropic medications for treating schizophrenia in community settings (Citrome et al., 2000; Tapp et al., 2003; Ganguly et al., 2004), our results may not be broadly applicable to all antipsychotic-treated patients with schizophrenia. Exclusion of individuals treated with antipsychotic combinations and extensive cotherapy with other agents was necessary, however, in order to limit potential confounding introduced by these other drugs.

In conclusion, there were no significant differences in neurocognitive measures between patients treated with adjunctive armodafinil and placebo in this 6-week study. A number of factors, including small sample size, may have limited our ability to detect a treatment effect. Armodafinil was associated with significant improvement in SANS ratings for anhedonia–asociality, but no other measure of negative symptoms.

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Contributors
Authors William V. Bobo, MD, MPH and Herbert Y. Meltzer, MD designed the study and wrote the protocol. Authors William V. Bobo, MD, MPH and Neil D. Woodward, PhD managed the literature searches and analyses. Author Karuna Jayathilake undertook the statistical analysis. Authors William V. Bobo, MD, MPH and Herbert Y. Meltzer, MD collaborated on writing all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
William V. Bobo has been a grantee of Cephalon, Inc. and, in the past, has been a lecturer for Janssen and Pfizer. Herbert Y. Meltzer is, or has been, a consultant or

grantee to Abbott Laboratories, ACADIA, Astra Zeneca, Bristol Myers Squibb, Cephalon, Eli Lilly, Glaxo Smith Kline, Litmus Molecular Design, Memory, Novartis, Organon, and Pfizer; and has been a lecturer for Janssen and Pfizer. All other authors declare that they have no conflicts of interest.

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