Armodafinil as Adjunctive Therapy in Adults With Cognitive Deficits Associated With Schizophrenia: A 4-Week, Double-Blind, Placebo-Controlled Study

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Objective: To evaluate the efficacy and tolerability of armodafinil, the longer-lasting isomer of modafinil, as adjunctive therapy in patients with schizophrenia.

Method: This 4-week, randomized, double-blind, placebo-controlled, proof-of-concept study was conducted between July and December 2007. Patients had a history of stable schizophrenia (*DSM-IV-TR* criteria) for ≥ 8 weeks and were treated with oral risperidone, olanzapine, or paliperidone for ≥ 6 weeks at stable doses for ≥ 4 weeks. Patients were randomly assigned to once-daily placebo or armodafinil 50, 100, or 200 mg. The primary efficacy measure was the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessment of Negative Symptoms (SANS).

Results: Sixty patients were randomly assigned (15 in each group). No apparent differences between groups in the MATRICS composite score were observed (mean ± SD change from baseline to final visit: armodafinil 50 mg, 1.9 ± 6.22; 100 mg, 2.8 ± 7.98; 200 mg, 2.9 ± 4.72; placebo, 2.2 ± 5.06). The mean ± SD changes in PANSS total scores were −6.3 ± 7.25 for armodafinil 200 mg and −1.7 ± 4.89 for placebo at final visit (effect size = 0.73; 95% CI, −0.08 to 1.54) and PANSS negative symptoms scores were −3.4 ± 2.07 and 0.1 ± 1.93 (effect size = 1.69; 95% CI, 0.78 to 2.60), respectively. Although reductions in SANS total score were observed with both armodafinil and placebo at final visit, no between-group difference was shown. Armodafinil was generally well tolerated, with diarrhea and headache the most commonly reported adverse events. There was no evidence of worsening of psychosis with adjunctive armodafinil.

Conclusions: In this 4-week study, adjunctive armodafinil was not associated with an improvement in cognitive measures, but armodafinil 200 mg/d appeared to mitigate the negative symptoms of schizophrenia. Treatment was generally well tolerated.

Trial Registration: clinicaltrials.gov Identifier: NCT00487942.

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Schizophrenia is a chronic, severely debilitating psychiatric disorder that affects up to 1% of the population worldwide.[1] Characteristics of schizophrenia include overt psychotic, ie, positive, symptoms, such as hallucinations and delusions, as well as negative symptoms, such as social withdrawal and loss of drive.[2] Although currently available antipsychotic medications generally mitigate the positive symptoms of schizophrenia, they are not effective for the negative symptoms of some patients, leading to continuing disability.[3–6]

Modafinil, a racemic compound containing *R*-modafinil and *S*-modafinil, has been investigated as a treatment for sedation associated with antipsychotic medications[7] because it has less potential for abuse and is associated with fewer peripheral and central adverse events compared with amphetamines.[8,9] Modafinil has also been evaluated for its effects on negative symptoms and cognitive deficits in schizophrenia, with mixed results. In randomized, placebo-controlled, repeated-dose studies in patients with schizophrenia, modafinil treatment significantly improved short-term verbal memory span and attentional set shifting,[10] and it increased functional magnetic resonance imaging activation in the anterior cingulate cortex during the working memory task, which was associated with improved cognition in some patients.[11] A randomized, placebo-controlled crossover study found that a single dose of modafinil decreased motor avolitional behavior as measured by actigraphy,[12] and an open-label, 4-week study also showed that modafinil significantly improved global functioning, overall clinical condition, and fatigue, while tending to improve cognitive functioning scores, in patients with schizophrenia.[13] However, in two 8-week, randomized, placebo-controlled studies in patients with schizophrenia, treatment with adjunctive modafinil did not demonstrate an effect on negative symptoms, and did not improve a range of cognitive measures, including Continuous Performance Test, Letter-Number Span, Oculomotor Delayed Response, Delayed Match to Sample Task, Controlled Oral Word Association Test, and Rey Auditory Verbal Learning Test.[14,15] Overall, the efficacy of modafinil for treatment of cognitive symptoms in patients with schizophrenia remains unclear.

Armodafinil, a nonamphetamine, wakefulness-promoting medication, is the longer-lasting isomer of modafinil. Clinical studies have shown that it improves wakefulness throughout the day and aspects of memory and attention in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy.[16–19] The objective of this proof-of-concept study was to evaluate the efficacy and tolerability of armodafinil for cognitive deficits in adults with schizophrenia as an adjunctive agent to oral risperidone, olanzapine, or paliperidone therapy, and thereby generate hypotheses for future studies.

METHOD

Study Design and Patients

This was a randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept study conducted between July and December 2007 at 11 centers in the United States. The study design included a screening period of at least 1 week, a 4-week double-blind treatment period, and a 1-week follow-up period. Efficacy and tolerability assessments were performed at clinic visits at baseline and weeks 1, 2, and 4 of treatment.

The study protocol was approved by the Independent Ethics Committee or Institutional Review Board (according to national or local regulations). The study was conducted in full accordance with the Good Clinical Practice Consolidated Guideline approved by the International Conference on Harmonisation[20] and any applicable national and local laws and regulations. Written informed consent was obtained from each patient before he or she underwent any study procedures.

Eligible patients were aged 18–60 years; had a diagnosis of schizophrenia as determined by the Structured Clinical Interview for *DSM-IV-TR*[2]; were clinically stable in a nonacute phase of their illness for at least 8 weeks before the baseline visit; were being treated with oral risperidone, olanzapine, or paliperidone for at least 6 weeks before screening; and were receiving a stable dose of these antipsychotic medications for at least 4 weeks prior to screening. Patients meeting any of the following criteria were excluded from the study: Wide Range Achievement Test, Fourth Edition,[21] reading subtest raw score ≤ 36; Calgary Depression Scale for Schizophrenia (CDSS)[22] suicide item (item 8) score ≥ 2 (moderate or worse); moderate-to-severe depressive symptoms (CDSS score ≥ 11); any positive symptom subscale item score ≥ 4 (moderate or worse) on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS),[23] a clinician-rated instrument of the severity of psychopathology; modified Simpson-Angus Scale[24] score for extrapyramidal side effects ≥ 7 (moderate or worse); Barnes Akathisia Scale[25] global score ≥ 2; presence of tardive dyskinesia or other movement disorder; history or current active suicidal ideation or imminent risk of self-harm; diagnosis of any other axis I disorder, alcohol or substance abuse, or dependence within the previous 6 months.

Patients were randomly assigned (1:1:1:1) to receive armodafinil 50, 100, or 200 mg/d or placebo. Patients took 4 tablets once daily in the morning. The armodafinil or matching placebo dose was initiated at 50 mg/d and was titrated up by 50 mg/d on days 2, 4, and 6, as applicable, to the randomized dose.

Study Assessments

The primary efficacy measure was the mean change from baseline at final visit (last observation, ie, week 4 or early termination) in the composite score on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery. The MATRICS Consensus Cognitive Battery contains 10 tests to measure cognitive performance in 7 domains of cognition: speed of processing, attention/vigilance, working memory (nonverbal and verbal), verbal learning, visual learning, reasoning and problem solving, and social cognition.[26–28] Secondary efficacy measures included mean change from baseline to final visit in the following: the 7 individual MATRICS domain scores; ratings on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[29] a standardized, clinician-rated assessment of the severity of illness of the patient, at weeks 1, 2, and 4 or at final visit; the Scale for the Assessment of Negative Symptoms (SANS),[30] a clinician-rated instrument used to rate the severity of negative symptoms of schizophrenia; scores on the PANSS, which includes 7 items measuring positive symptoms (this subscale was assessed as a safety measure), 7 items measuring negative symptoms, and 16 items forming the general psychopathology subscale; and the Epworth Sleepiness Scale (ESS), a subjective measure of the patient's propensity for daytime sleepiness.[31]

Tolerability measures were determined by reports of adverse events and results of clinical laboratory tests, vital signs, modified Simpson-Angus Scale, Barnes Akathisia Scale, CDSS, PANSS, and actigraphy data related to sleep.

Statistical Analysis

The safety analysis set included all patients who received at least 1 dose of study drug, and the efficacy analysis set included all patients in the safety analysis set who had at least 1 postbaseline assessment on the MATRICS Consensus Cognitive Battery.

Patient demographic characteristics were summarized using descriptive statistics. For continuous variables, descriptive statistics were provided; for categorical variables, patient counts and percentages were provided. This study was not powered to detect significant differences between the armodafinil and placebo groups. For the primary efficacy variable, effect sizes and 95% confidence intervals (CIs) of the effect sizes for the primary efficacy measure were provided for each armodafinil treatment group (compared with the placebo group). Actual values and changes from baseline to final visit (4-week or last postbaseline measurement) were summarized using descriptive statistics. The final visit analyses were performed using the last postbaseline observation carried forward. All continuous secondary efficacy variables, at each visit and final visit, were summarized as specified for the primary efficacy variable. The categorical secondary
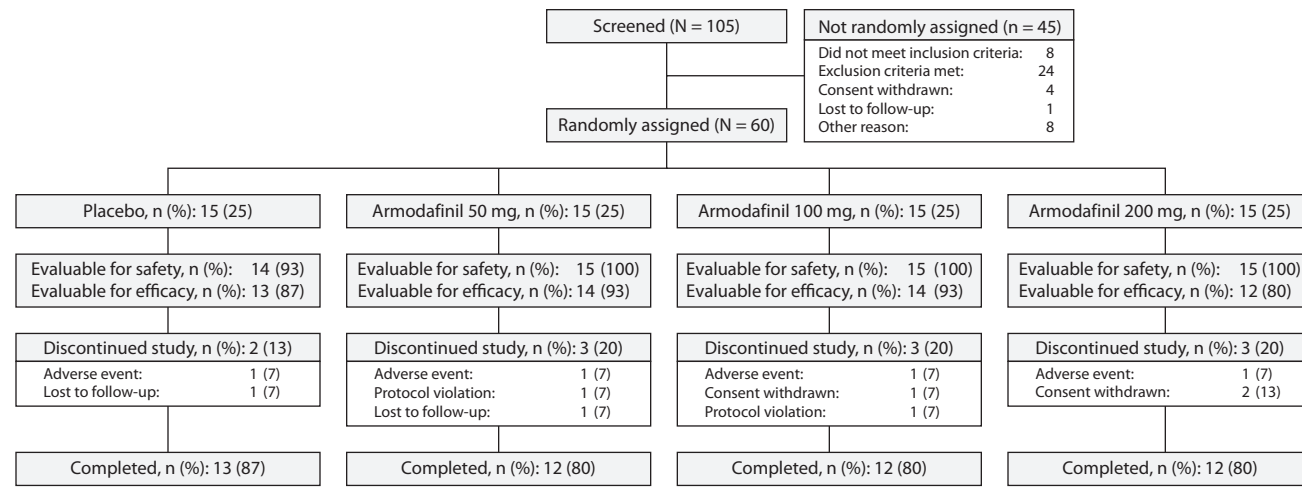
Figure 1. Patient Disposition


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                    ┌─────────────────────┐      ┌──────────────────────────────────────┐
                    │ Screened (N = 105)  │      │ Not randomly assigned (n = 45)       │
                    └─────────────────────┘      │ Did not meet inclusion criteria:   8 │
                              │                   │ Exclusion criteria met:           24 │
                              │                   │ Consent withdrawn:                 4 │
                    ┌─────────────────────┐      │ Lost to follow-up:                 1 │
                    │ Randomly assigned   │      │ Other reason:                      8 │
                    │ (N = 60)            │      └──────────────────────────────────────┘
                    └─────────────────────┘
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Placebo, n (%): 15 (25)	Armodafinil 50 mg, n (%): 15 (25)	Armodafinil 100 mg, n (%): 15 (25)	Armodafinil 200 mg, n (%): 15 (25)
Evaluable for safety, n (%): 14 (93) Evaluable for efficacy, n (%): 13 (87)	Evaluable for safety, n (%): 15 (100) Evaluable for efficacy, n (%): 14 (93)	Evaluable for safety, n (%): 15 (100) Evaluable for efficacy, n (%): 14 (93)	Evaluable for safety, n (%): 15 (100) Evaluable for efficacy, n (%): 12 (80)
Discontinued study, n (%): 2 (13) Adverse event: 1 (7) Lost to follow-up: 1 (7)	Discontinued study, n (%): 3 (20) Adverse event: 1 (7) Protocol violation: 1 (7) Lost to follow-up: 1 (7)	Discontinued study, n (%): 3 (20) Adverse event: 1 (7) Consent withdrawn: 1 (7) Protocol violation: 1 (7)	Discontinued study, n (%): 3 (20) Adverse event: 1 (7) Consent withdrawn: 2 (13)
Completed, n (%): 13 (87)	Completed, n (%): 12 (80)	Completed, n (%): 12 (80)	Completed, n (%): 12 (80)

Table 1. Baseline Patient Characteristics

		Armodafinil			
Characteristic	Placebo (n = 15)	50 mg (n = 15)	100 mg (n = 15)	200 mg (n = 15)	Total (N = 60)
Age, mean ± SD, y	46.0 ± 7.8	44.9 ± 10.9	40.4 ± 9.6	41.4 ± 9.8	43.2 ± 9.6
Sex, n (%)					
Men	12 (80)	11 (73)	10 (67)	11 (73)	44 (73)
Women	3 (20)	4 (27)	5 (33)	4 (27)	16 (27)
Race, n (%)					
White	6 (40)	7 (47)	4 (27)	5 (33)	22 (37)
Black	8 (53)	8 (53)	11 (73)	9 (60)	36 (60)
Asian	1 (7)	0	0	0	1 (2)
American Indian or Alaskan Native	0	0	0	1 (7)	1 (2)

Table 2. Mean ± SD Change in MATRICS Composite Score From Baseline to Final Visit

		Armodafinil		
Variable	Placebo (n = 13)	50 mg (n = 14)	100 mg (n = 14)	200 mg (n = 12)
Baseline				
n	13	13	13	11
Mean ± SD	22.3 ± 14.59	27.8 ± 8.59	20.8 ± 8.48	22.1 ± 16.44
Final visit				
n	13	14	14	12
Mean ± SD	24.5 ± 12.91	29.6 ± 11.55	23.6 ± 12.55	25.0 ± 16.51
Change				
n	13	13	13	11
Mean ± SD	2.2 ± 5.06	1.9 ± 6.22	2.8 ± 7.98	2.9 ± 4.72
Effect size		−0.04	0.09	0.15
95% CI		−0.81 to 0.73	−0.68 to 0.86	−0.66 to 0.95

Abbreviation: MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia.

efficacy variables of CGI-S ratings were summarized using descriptive statistics.

RESULTS

Patient Disposition and Characteristics

Of 105 patients screened, 60 were randomly assigned to receive armodafinil 50 mg/d (n = 15), 100 mg/d (n = 15), 200 mg/d (n = 15), or placebo (n = 15); a total of 49 patients (82%) completed the 4-week study (Figure 1). The most frequent reason for withdrawal from the study was adverse events (n = 4; n = 1 for each of the armodafinil groups and for the placebo group). The mean age of patients was 43 years; 60% (n = 36) were black, and 73% (n = 44) were men. Baseline characteristics were generally similar across the treatment groups (Table 1).

Effect of Armodafinil

Changes from baseline to final visit in cognitive deficits were similar following armodafinil or placebo on the MATRICS composite score (Table 2). No apparent differences between the armodafinil and placebo groups were observed in mean changes from baseline to final visit in any of the

7 individual MATRICS domain scores (Table 3). Mean ± SD changes from baseline to final visit in CGI-S scores were −0.07 ± 0.27 following armodafinil 50 mg, 0.07 ± 0.47 following armodafinil 100 mg, −0.17 ± 0.39 following armodafinil 200 mg, and no change with placebo. Reductions in the SANS total score were observed following armodafinil and placebo at final visit but were not considered clinically meaningful (Figure 2).

There was a greater reduction in PANSS negative symptoms subscale score in the armodafinil 200 mg group compared with the placebo group (effect size = 1.69 at final visit; 95% CI, 0.78 to 2.60), without worsening of positive symptoms (Figure 3). The reduction in the mean PANSS negative scale score was apparent by week 1 in the armodafinil 200 mg group (effect size = 0.89 at week 1; 95% CI, 0.05 to 1.74). The PANSS total score showed greater improvement in the armodafinil 200 mg group (−6.3) compared with the placebo group (−1.7) (effect size = 0.73 at final visit; 95% CI, −0.08 to 1.54). There were no clinically relevant changes in the general psychopathology subscale score: mean ± SD

Table 3. Mean ± SD Change in 7 MATRICS Domain Scores From Baseline to Final Visit

MATRICS Domain	Placebo (n = 13)	Armodafinil		
		50 mg (n = 14)	100 mg (n = 14)	200 mg (n = 12)
Speed of processing				
Score change, mean ± SD	0.9 ± 7.0	3.0 ± 8.8	0.0 ± 10.4	5.0 ± 9.1
Effect size		0.25	−0.10	0.49
95% CI		−0.51 to 1.01	−0.86 to 0.66	−0.31 to 1.28
Attention/vigilance				
Score change, mean ± SD	3.0 ± 6.6	0.4 ± 10.9	3.7 ± 5.0	1.8 ± 6.5
Effect size		−0.27	0.11	−0.18
95% CI		−1.03 to 0.48	−0.65 to 0.88	−0.97 to 0.60
Working memory				
Score change, mean ± SD	4.4 ± 6.3	2.3 ± 6.5	4.3 ± 6.0	3.5 ± 10.4
Effect size		−0.32	−0.02	−0.10
95% CI		−1.08 to 0.44	−0.77 to 0.74	−0.89 to 0.68
Verbal learning				
Score change, mean ± SD	−2.2 ± 5.9	−1.2 ± 6.3	−0.8 ± 4.5	0.8 ± 6.3
Effect size		0.15	0.25	0.46
95% CI		−0.61 to 0.90	−0.50 to 1.01	−0.34 to 1.25
Visual learning				
Score change, mean ± SD	0.2 ± 8.2	4.3 ± 9.6	3.9 ± 12.8	1.3 ± 8.8
Effect size		0.45	0.34	0.13
95% CI		−0.33 to 1.23	−0.42 to 1.10	−0.68 to 0.93
Reasoning and problem solving				
Score change, mean ± SD	−0.2 ± 4.6	1.6 ± 4.3	−0.4 ± 5.6	−0.3 ± 8.4
Effect size		0.39	−0.05	−0.01
95% CI		−0.37 to 1.15	−0.81 to 0.70	−0.80 to 0.77
Social cognition				
Score change, mean ± SD	3.8 ± 6.6	−3.1 ± 6.9	−1.3 ± 8.2	3.6 ± 8.3
Effect size		−0.99	−0.66	−0.03
95% CI		−1.79 to −0.19	−1.44 to 0.11	−0.82 to 0.75

Abbreviation: MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia.

Figure 2. Mean Change From Baseline to Final Visit in SANS Total Score[a]

Effect size (95% CI):
50 mg −0.05 (−0.80 to 0.71) ■ Placebo (n = 13)
100 mg −0.31 (−1.06 to 0.45) ■ Armodafinil 50 mg (n = 14)
200 mg 0.11 (−0.68 to 0.89) □ Armodafinil 100 mg (n = 12)
□ Armodafinil 200 mg (n = 12)
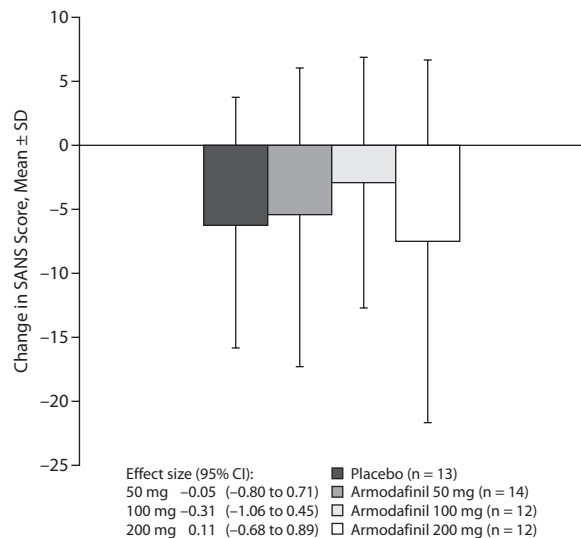
[a]Efficacy evaluable patients.
Abbreviation: SANS = Scale for Assessment of Negative Symptoms.

changes from baseline to final visit were −1.5 ± 4.8 following armodafinil 50 mg, −0.7 ± 4.1 following armodafinil 100 mg, −2.1 ± 3.7 following armodafinil 200 mg, and −0.9 ± 3.1 following placebo.

Mean changes in ESS score from baseline to final visit were −0.5 following placebo, −2.1 following armodafinil 50 mg (effect size = 0.25; 95% CI, −0.51 to 1.01), −0.6 following armodafinil 100 mg (effect size = 0.03; 95% CI, −0.73 to 0.78), and 1.0 following armodafinil 200 mg (effect size = −0.23; 95% CI, −1.01 to 0.56).

Tolerability

Armodafinil was generally well tolerated; diarrhea and headache were the most commonly reported adverse events (Table 4). One patient in each group discontinued treatment because of an adverse event, including psychotic disorder (placebo), folliculitis (armodafinil 50 mg), hostility (armodafinil 100 mg), and restlessness (armodafinil 200 mg). One adverse event was classified as serious: worsening psychosis in 1 patient in the placebo group. Psychiatric adverse events

included insomnia (2 in the placebo group, and 1 each in the armodafinil 50 and 200 mg groups), restlessness (3 in the armodafinil 200 mg group), and hostility (1 patient in the armodafinil 100 mg group). No deaths occurred during the study.

The nighttime actigraphy data indicated that, in patients receiving armodafinil 200 mg compared with placebo, mean ± SD values of sleep latency increased (by 9.8 ± 26.6 min following armodafinil 200 mg vs −1.4 ± 11.0 following placebo) and mean ± SD values of sleep efficiency and total sleep time decreased (by −5.5% ± 8.8 versus 2.3% ± 6.0 and −39.9 ± 57.3 min vs 22.7 ± 107.2 min, respectively); no other differences were seen between the armodafinil and placebo groups (Table 5).
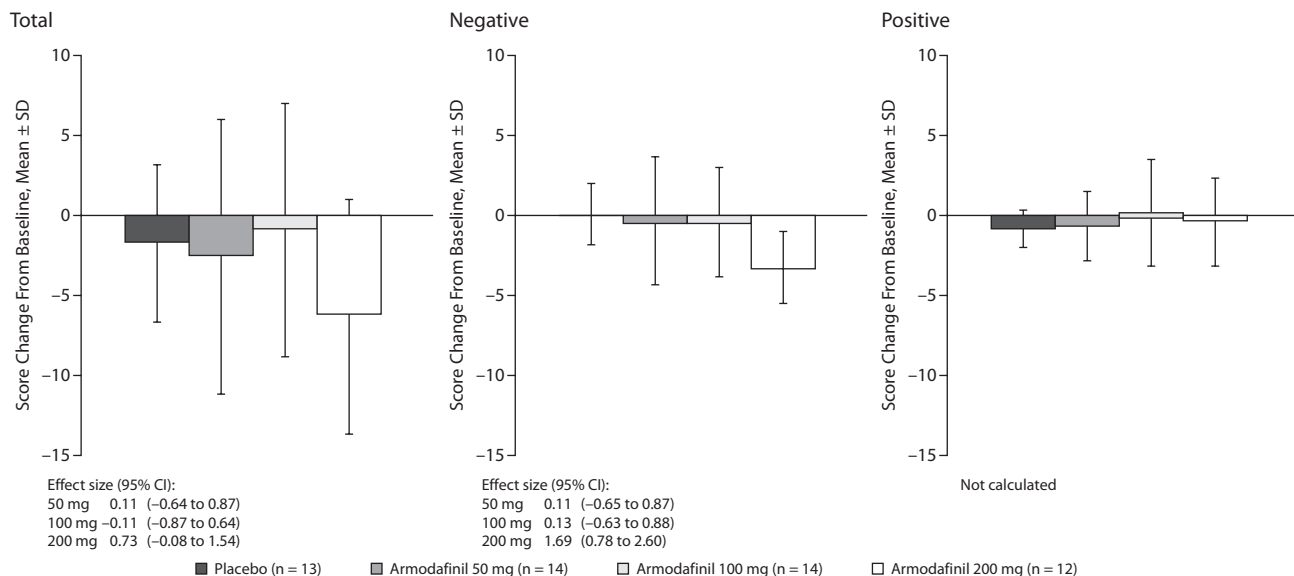
Mean changes from baseline to final visit in heart rate and diastolic blood pressure values were slightly greater among patients treated with armodafinil 200 mg (1.9 beats per min and 4.1 mm Hg, respectively) than with placebo (−3.2 beats per min and −0.6 mm Hg, respectively), but these were not considered to be clinically meaningful by investigators.

There was no worsening of symptoms as assessed by Simpson-Angus Scale, Barnes Akathisia Scale, CDSS, or PANSS positive scale score (Figure 3C); no notable differences were observed regarding laboratory values or electrocardiograms (data not shown).

DISCUSSION

In this 4-week study, adjunctive armodafinil had no apparent beneficial effect on cognitive measures in patients with schizophrenia. Changes from baseline to final visit in the MATRICS composite score were similar in the armodafinil and placebo groups. Armodafinil 200 mg/d, however,

Figure 3. Mean Change From Baseline to Final Visit in PANSS Total,[a] Negative,[a] and Positive Scores[b]

Effect size (95% CI):
50 mg   0.11   (−0.64 to 0.87)
100 mg −0.11 (−0.87 to 0.64)
200 mg 0.73   (−0.08 to 1.54)

Effect size (95% CI):
50 mg   0.11   (−0.65 to 0.87)
100 mg 0.13   (−0.63 to 0.88)
200 mg 1.69   (0.78 to 2.60)

Not calculated

■ Placebo (n = 13)   ▨ Armodafinil 50 mg (n = 14)   ▢ Armodafinil 100 mg (n = 14)   ▢ Armodafinil 200 mg (n = 12)

[a]Efficacy evaluable patients.
[b]Positive scores for only safety evaluable patients; thus, effect sizes were not calculated.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 4. Adverse Events Reported by > 3% of All Patients

| | | Armodafinil | | | |
Adverse Event, n (%)	Placebo (n = 14)	50 mg (n = 15)	100 mg (n = 15)	200 mg (n = 15)	All (N = 45)
Diarrhea	1 (7)	2 (13)	2 (13)	1 (7)	5 (11)
Headache	1 (7)	2 (13)	0	2 (13)	4 (9)
Muscle spasms	0	0	2 (13)	0	2 (4)
Restlessness	0	0	0	3 (20)	3 (7)
Dizziness	0	1 (7)	1 (7)	0	2 (4)
Dry mouth	1 (7)	0	1 (7)	1 (7)	2 (4)
Insomnia	2 (14)	1 (7)	0	1 (7)	2 (4)

Table 5. Change in Actigraphy of Nighttime Sleep From Baseline to Final Visit

| | | Armodafinil | | |
Measure, mean ± SD	Placebo (n = 14)	50 mg (n = 15)	100 mg (n = 15)	200 mg (n = 15)
Sleep efficiency, %	2.3 ± 6.0	3.1 ± 7.8	−4.8 ± 7.6	−5.5 ± 8.8
Sleep latency, min	−1.4 ± 11.0	−6.4 ± 20.3	3.5 ± 11.6	9.8 ± 26.6
Total sleep time, min	22.7 ± 107.2	16.3 ± 97.3	19.9 ± 96.1	−39.9 ± 57.3

did appear to improve the negative symptoms of schizophrenia, as indicated by a reduction from baseline to final visit compared with placebo in the mean PANSS negative symptoms scale score (−3.4 versus 0.1; 95% CI, 0.78 to 2.60). The difference in the negative subscale score, combined with the similarity of changes on the positive and general psychopathology subscale scores between the 200 mg/d and placebo treatment groups, drove a reduction from baseline to final visit compared with placebo in mean PANSS total score (−6.3 vs −1.7; 95% CI, −0.08 to 1.54). Armodafinil was generally well tolerated.

Treating negative symptoms of schizophrenia is important because these symptoms are debilitating for patients and because antipsychotic therapies are often not adequate to treat them.[32–34] In 2 double-blind, placebo-controlled studies, there were no significant differences in the SANS scores of patients administered modafinil and those given placebo.[14,15] In the current study, armodafinil also did not appear to improve SANS scores, compared with placebo. However, armodafinil 200 mg/d improved negative symptoms from week 1 as assessed by the PANSS negative symptoms scale score.

The precise mechanisms of action of armodafinil and its effect on the neuronal pathways involved in schizophrenia are still unclear. Dopamine plays a role in the mechanism of action of the racemic mixture modafinil and, presumably, of armodafinil. Modafinil binds to the dopamine transporter (DAT),[35–37] with less affinity than do methylphenidate, benztropine, and bupropion,[38] and its activity at the DAT is necessary for its wakefulness-promoting effect.[39] Modafinil increases extracellular levels of dopamine in the prefrontal cortex,[40] and there is some evidence that it enhances activity in the prefrontal cortex in patients with schizophrenia.[41] Weinberger[42] proposed that underactivity of the dopaminergic connections to the prefrontal cortex, the mesocortical pathway, is the primary lesion in schizophrenia and is associated with negative symptoms. Decreased dopaminergic activity in the prefrontal cortex results in disinhibition of the mesolimbic function, which produces positive symptoms.[42] A weak DAT inhibitor such as armodafinil, which may preferentially influence the dopaminergic activity in the prefrontal cortex but not in the limbic system, could, hypothetically, reduce negative symptoms without worsening positive symptoms—the effect suggested in this study.

A limitation of the current study is that it was not powered to detect differences in effect between the armodafinil

and placebo groups, and so inferential statistics were not performed to compare differences in effect between study groups. The relatively small sample size (N = 60) also limits the application of these results to the general population of patients with schizophrenia in clinical practice. Although an improvement in negative symptoms following armodafinil 200 mg/d was indicated by the PANSS negative symptom score, there was no apparent improvement in SANS score. According to an analysis comparing the PANSS negative symptoms subscale and SANS scores in a sample of patients with schizophrenia, the total scores were highly correlated with each other, but the 2 scales predicted the various cognitive, motivational, and social dimensions of the negative syndrome to different degrees.[43] Together, these limitations point to the need for further characterization of armodafinil's effects in larger, adequately powered studies, involving populations of patients with schizophrenia defined in terms of baseline cognitive functioning and degree and type of negative symptoms. Future studies may also investigate whether changes in measures of cognitive functioning are accompanied by improvements in patients' quality of life or daily functioning.

The lack of a consensus cognitive battery has been a major barrier to the evaluation of the cognitive effects of new treatments in schizophrenia. The National Institute of Mental Health developed the MATRICS initiative, a consensus cognitive battery for use as a research tool in clinical studies in schizophrenia.[28,44] This study adds to the small but growing number of published studies to use the MATRICS Consensus Cognitive Battery to assess cognition in patients with schizophrenia.

CONCLUSION

In this proof-of-concept study, daily armodafinil 50 mg, 100 mg, or 200 mg, administered over 4 weeks as adjunctive treatment to oral risperidone, olanzapine, or paliperidone, was not associated with any apparent improvement in cognitive deficits in patients with schizophrenia as assessed by the MATRICS Consensus Cognitive Battery. Adjunctive armodafinil was generally well tolerated, with no evidence of worsening of psychosis. The effects of armodafinil 200 mg on negative symptoms warrant further study of the potential efficacy of this drug in their treatment.

Drug names: armodafinil (Nuvigil), benztropine (Cogentin and others), bupropion (Aplenzin, Wellbutrin, and others), modafinil (Provigil), olanzapine (Zyprexa), paliperidone (Invega), risperidone (Risperdal and others).

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