Modafinil for Clozapine-Treated Schizophrenia Patients: A Double-Blind, Placebo-Controlled Pilot Trial

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Background: Patients with schizophrenia often suffer from cognitive deficits and negative symptoms that are poorly responsive to antipsychotics including clozapine. Clozapine-induced sedation can worsen cognition and impair social and occupational functioning.

Objectives: To evaluate the efficacy, tolerability, and safety of modafinil for negative symptoms, cognition, and wakefulness/fatigue in *DSM-IV*–diagnosed schizophrenia patients treated with clozapine.

Method: A double-blind, placebo-controlled, flexible-dosed 8-week pilot trial was conducted between September 2003 and September 2007, adding modafinil up to 300 mg/d to stabilized schizophrenia outpatients receiving clozapine. Psychopathology, cognition, and wakefulness/fatigue were assessed with standard rating scales.

Results: Thirty-five patients were randomly assigned to treatment with study drug and included in the analysis. Modafinil did not reduce negative symptoms or wakefulness/fatigue or improve cognition compared to placebo. Modafinil was well tolerated and did not worsen psychosis.

Conclusions: Results of this pilot trial do not support routine use of modafinil to treat negative symptoms, cognitive deficits, or wakefulness/fatigue in patients on clozapine. However, given our limited power to detect a treatment effect and the clear possibility of a type II error, larger trials are needed to resolve or refute a potential therapeutic effect of uncertain magnitude.

Trial Registration: clinicaltrials.gov Identifier: NCT00573417

J Clin Psychiatry 2009;70(12):1674–1680

Submitted: *September 6, 2008; accepted November 11, 2008.*
Online ahead of print: *August 11, 2009 (doi:10.4088/JCP.08m04683).*
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Clozapine represented a significant advance in the treatment of schizophrenia. However, clozapine is not broadly effective against all psychopathological domains of schizophrenia, and its use is limited by tolerability. Like all antipsychotics, clozapine mostly treats positive symptoms, with meager efficacy at best for primary negative symptoms[1] and cognitive deficits.[2] This is of considerable clinical importance since negative symptoms and cognitive deficits are major determinants of the poor social and occupational functioning[3] that is characteristic of many patients with schizophrenia.[4] In addition, clozapine can be difficult for patients to tolerate, with sedation being one of the most problematic side effects,[5] adding insult to injury.

Stimulants are sometimes used to increase wakefulness in schizophrenia,[6] but they can worsen psychosis[7,8] and have a high potential for abuse. A chemically different medication, modafinil is a wakefulness-promoting agent that is indicated for the treatment of several sleep disorders associated with excessive sleepiness, including narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[9] A typical dose of modafinil for these conditions is 200 mg/d. Modafinil's mechanism of action remains incompletely understood but is believed to differ from stimulants like amphetamine by more selective activation of hypothalamic regions that promote wakefulness, including the tuberomammillary nucleus and orexin (hypocretin) neurons.[10] Consequently, modafinil is thought to have a low potential for abuse and a low propensity to induce psychosis. It is also advantageous in not adversely affecting cardiovascular or sleep parameters.[11]

Three controlled trials in schizophrenia have investigated the efficacy and safety of modafinil add-on therapy, with inconsistent results. Turner and colleagues[12] reported improved attentional set shifting and short-term verbal memory span following a single dose of 200 mg/d modafinil in a crossover trial of 20 subjects, mostly treated with clozapine. This trial did not examine effects on negative symptoms or fatigue. Cognitive benefit was not detected in two 8-week placebo-controlled, parallel-group trials[13,14] of modafinil, up to 200 mg/d in samples of 24 and 20 antipsychotic-treated schizophrenia patients, respectively, nor were effects on negative symptoms found. Sevy and colleagues[13] also failed to demonstrate an effect of modafinil

on fatigue when assessed with the Fatigue Severity Scale (FSS)[15] and a visual analog fatigue scale.

We report the results of a double-blind, placebo-controlled, flexible-dose pilot trial of modafinil up to 300 mg/d added for 8 weeks to a stable dose of clozapine in patients with schizophrenia. The trial was designed to assess tolerability and safety of modafinil as well as efficacy for negative and cognitive symptoms and effect on wakefulness and fatigue.

METHOD

Study Setting and Sponsorship

The study was conducted between September 2003 and September 2007 at the Clozapine Program of the Freedom Trail Clinic, a community mental health center clinic in downtown Boston that serves as a referral clinic for schizophrenia patients who require clozapine treatment. The study was an investigator-initiated trial sponsored by the manufacturer of modafinil, Cephalon Inc.

Participant Selection

Patients were referred for this study by their clinicians. The research team assessed competency to participate in clinical research with a semistructured interview (available upon request). All patients or their guardians provided written informed consent to participate in this trial. The study was approved by the responsible institutional review boards.

Characteristics of Subjects

Patients had schizophrenia or schizoaffective disorder as their primary diagnosis, were clinically stable for at least 3 months, and had been taking clozapine for at least 6 months, with a stable dose for at least 1 month. Diagnoses were based on physician interview and chart review (O.F.), using the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (*DSM-IV*) criteria.[16]

Patients were excluded if they had an active substance use disorder (other than nicotine dependence), epilepsy or a serious medical illness, or suicidal ideation. Current treatment with a psychostimulant led to exclusion as well. Patients had to be able to complete the neuropsychological battery.

Study Design and Procedures

The study design was a parallel-group, placebo-controlled, double-blind escalating-dose trial in which patients were randomly assigned in a 1:1 ratio to placebo or up to 300 mg/d of modafinil added to ongoing clozapine treatment. In this 8-week study, patients were seen every 2 weeks for vital signs, hematology, and side effect monitoring. A clozapine level was drawn at the beginning of the study and at 4 and 8 weeks after initiating study treatment. Patients were assessed with scales (see below) for wakefulness, psychopathology, and side effects at screening and baseline and after weeks 2, 4, and 8. Cognition was assessed with a cognitive battery (see below) at baseline, and the assessment was repeated after 4 and 8 weeks. Time of testing was not controlled with regard to time of modafinil administration.

Drug Regimen

An independent research pharmacy prepared matching capsules that contained either 100 mg of modafinil or placebo and randomized subjects in blocks of 4. Patients initiated treatment with 1 capsule (100 mg) per day for 2 weeks, the dose could be increased to 2 capsules (200 mg) per day after 2 weeks, and a maximum of 3 capsules (300 mg/day) after 4 weeks. Dose was adjusted upward unless tolerability problems developed. After 8 weeks, study medication was discontinued. Adherence to study medication was assessed every 2 weeks by pill count. We chose 75% adherence by pill count as evidence of satisfactory adherence.

Ratings

Wakefulness. Modafinil's wakefulness-promoting properties were assessed with 2 self-rating scales: the Epworth Sleepiness Scale (ESS),[17] to quantify propensity to fall asleep due to excessive sleepiness, and the Fatigue Severity Scale (FSS),[15] which is a subjective measure of the feeling of fatigue.

Clinical psychopathology. Clinical psychopathology was assessed with well-established rating scales for schizophrenia: the Positive and Negative Syndrome Scale (PANSS)[18] for a global measure of psychopathology (PANSS total score) and psychosis (PANSS positive symptoms subscale score); the Scale for the Assessment of Negative Symptoms (SANS)[19,20] for negative symptoms; and the Global Assessment of Functioning (GAF)[16] and the Heinrichs-Carpenter Quality of Life Scale[21] for an overall measure of functioning and well-being, respectively. In the presence of missing item scores, total scores for these instruments were calculated as reweighted sums of the present responses if the rate of missing items was less than 25%. Side effects were collected with the Systematic Assessment for Treatment Emergent Events (SAFTEE),[22] a rating scale that contains both open-ended and closed inquiries.

Cognitive measures. The North American Adult Reading Test (NAART)[23] was used to estimate premorbid intelligence. The cognitive battery assessed several cognitive domains and included the following 8 tests, which were included to calculate a psychometric battery composite score: the Degraded Stimulus Continuous Performance Test (DS-CPT)[24] to assess sustained attention and vigilance; the Hopkins Verbal Learning Test (HVLT)[25] to assess secondary verbal memory; the Faces and Family Pictures subtests from the Wechsler Memory Scale-III (WMS-III)[26] to assess visual memory; the Wisconsin Card Sorting Test (WCST)[27] to assess executive function/problem solving; the Trail-Making Test to assess executive functioning/set shifting; the

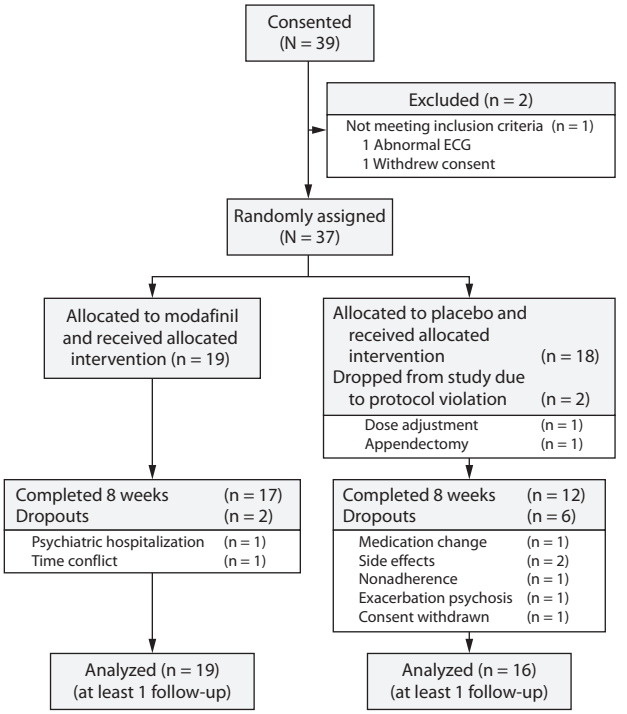
Letter-Number Sequencing subtest (WAIS-III)[26] to assess working memory; the Letter and Category Fluency (LCF)[28] to assess semantic fluency; and the Grooved Pegboard (model 32025, Lafayette Instrument Company) to assess psychomotor speed.

A composite score of neurocognitive battery (COGBAT) was calculated as the mean of the internally standardized scores (all study values adjusted to mean = 0 and standard deviation [SD] = 1 separately for each measure) from the following 8 assessments: sensitivity from the DS-CPT, total item recall from the HVLT, immediate face recall from the WMS-III, the mean of categories completed and 64 – perseverative errors from the WCST, Trails B scores (see below), the mean of recall with and without reordering from the WAIS-III, the mean total FAS letter word count (in which subjects name, in 1 minute for each, as many words as possible that begin with the letters 'F,' 'A,' and 'S') and animal word count (in which subjects name as many animals as possible in 1 minute) from the LCF, and the negative dominant-hand pegboard time. Trails B scores were derived by inverting Trails B times and normalizing to Trails A times as follows: using only baseline observations, a regression of Trails B time versus Trails A time was estimated. Using the coefficients from this regression, predicted Trails B times were estimated from observed Trails A times for all observations. Trails B scores were calculated as predicted Trails B times minus observed Trails B times. Larger Trails B scores indicate faster Trails B execution (lower Trails B times) relative to that expected from an individual's Trails A execution speed.

Data Analysis

Baseline comparisons were made by *t* test or Fisher exact test for continuous and categorical variables, respectively. Serum clozapine levels were log-transformed prior to analysis. Our primary aims were to examine the effects of modafinil on wakefulness/fatigue, negative symptoms, and cognition. Effect of modafinil versus placebo on change in clinical variables was analyzed in a mixed-model analysis of variance with fixed terms for treatment group, visit, and treatment × visit interaction and random participant-specific intercepts and slopes. The random slopes structure was chosen as optimal by Bayes information criterion over models with random intercepts only, random visits, and first-order auto-regressive errors. Treatment effect was summarized as the difference in mean slopes over time estimated from linear contrasts on the visit least square means. Effect sizes were calculated for the difference in slopes using a pooled standard deviation inferred from the standard error for the treatment contrast. All tests were 2-tailed, with level of significance set at .05. Both uncorrected *P* values and *P* values corrected for multiple comparisons by Hommel's closed testing procedure[29] are reported where applicable. All analyses were performed using SAS version 9.1.3 (SAS Institute, Inc, Cary, North Carolina).

Figure 1. Patient Flow Through a Double-Blind, Randomized Trial of Added Modafinil to Clozapine-Treated Patients With Schizophrenia



Abbreviation: ECG = electrocardiogram.

RESULTS

Study Population

Thirty-nine patients consented to the study and 37 were randomly assigned (1 patient withdrew consent and 1 patient had an abnormal electrocardiogram leading to exclusion prior to random assignment). Two patients in the placebo group were terminated immediately after random assignment (1 hospitalization for appendicitis, 1 protocol violation because the clozapine dose was adjusted) and were excluded from analysis. Of the final sample of 35 patients, 16 were randomly assigned to placebo and 19 to modafinil. Six patients in the placebo group and 2 patients in the modafinil group did not finish the trial (33% and 11%, respectively). All 35 patients took at least 1 dose of study medication and completed the first follow-up visit after 2 weeks. All analyses are based on the final sample of 35 patients. Further details regarding patient flow in the trial are provided in Figure 1.

The majority of patients were male (77%), with an average age of 45.2 ± 9.7 years (range 20–64 years). The mean (± SD) age of first hospitalization was 25.6 ± 8.0 years (range, 15–50 years), and patients had been ill for 19.5 ± 9.8 years (range, 2–35 years). The average PANSS total score at baseline was 66.7 ± 14.8 (range, 39–94), reflecting mild-to-moderate psychopathology. Average GAF score was 58.9 ± 10.6 (range, 40–90), and average Heinrichs-Carpenter Quality of Life

Table 1. Baseline Demographic and Clinical Characteristics of Participants With Clozapine-Treated Schizophrenia in a Modafinil Add-On Trial

Characteristic	Placebo (n = 16), N	Modafinil (n = 19), N
Sex		
Female	4	4
Male	12	15
Ethnicity		
White	13	17
Black	2	1
Hispanic	0	1
Other	1	0
Smoker	12	8
	Mean (SD)	Mean (SD)
Age, y	46.4 (6.4)	44.2 (12.0)
NAART verbal IQ	98.3 (11.9)	96.3 (12.8)
Age at first hospitalization, y	25.5 (7.8)	25.7 (8.5)
Duration of illness, y	20.2 (8.2)	18.9 (11.2)
ESS*	7.7 (4.9)	4.8 (3.5)
FSS**	39.7 (13.1)	27.8 (11.5)
PANSS total	70.3 (13.7)	63.8 (15.5)
SANS total	31.1 (10.6)	27.4 (9.4)
Clozapine dose, mg/d	361 (184)	379 (113)
Serum clozapine level, ng/mL[a]	278 (231)	340 (300)

[a]Median and width of interquartile range.
*$P = .06$.
**$P < .01$.
Abbreviations: ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, NAART = North American Adult Reading Test, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

scale score was 74.8 ± 15.1 (range, 42–109). By chance, both measures of fatigue (FSS and visual analog fatigue scale) were significantly higher at baseline among participants randomly assigned to the placebo group (see Table 1).

With few exceptions, pill count adherence was over 75% for both groups; 2 patients in the placebo group were discovered to have extended periods of nonadherence. Twenty-four (69%) patients reached a dose of 300 mg/d of study drug, including 17 (49%) who remained at 300 mg/d at the end of treatment (11 [58%] on modafinil and 6 [38%] on placebo, $P = .48$). Five patients taking modafinil (26%) versus 4 patients on placebo (25%) at least temporarily reduced their dose of study drug ($P = 1.0$). The average dose of modafinil at the end of treatment was 250 mg/d and 216 mg/d for placebo.

Outcome Measures

We observed no significant effect of modafinil on measures of wakefulness/fatigue, psychopathology, or cognition (see Figure 2 and Table 2). Among our primary outcomes, the possible benefit of modafinil was greatest for PANSS positive subscale scores (effect size = 0.35), but no treatment comparisons were significant and in favor of modafinil even without correction for multiple comparisons (data not shown). Among a total of 28 outcome measures, including individual scores on cognitive tests, trajectories differed significantly between treatment groups only for the Grooved Pegboard, which showed a greater improvement among subjects randomly assigned to placebo. There was no evidence for improved wakefulness with modafinil; ESS scores improved nonsignificantly more in the placebo group, with a 95% confidence interval that spans only modest benefit from modafinil. Although the estimated modafinil effect was modest at best for our outcomes of interest, the 95% confidence intervals do include potentially large beneficial effect of modafinil outcomes other than ESS (expressing the upper 95% confidence bound as an effect size in units of SD): FSS = 0.70, PANSS = 0.94, PANSS positive subscale = 1.03, SANS total = 0.88, COGBAT = 0.95.

Laboratory Values

Serum clozapine levels increased from a geometric mean of 330 ng/mL at baseline to 377 ng/mL at week 8 in the modafinil group and decreased from 330 ng/mL to 260 ng/mL in the placebo group. The 8-week change in serum clozapine concentrations did not differ significantly between treatments (mean ratio of change with modafinil versus change with placebo = 154%, 95% CI, 77%–308%, $t_{14} = 1.34$; $P = .20$.

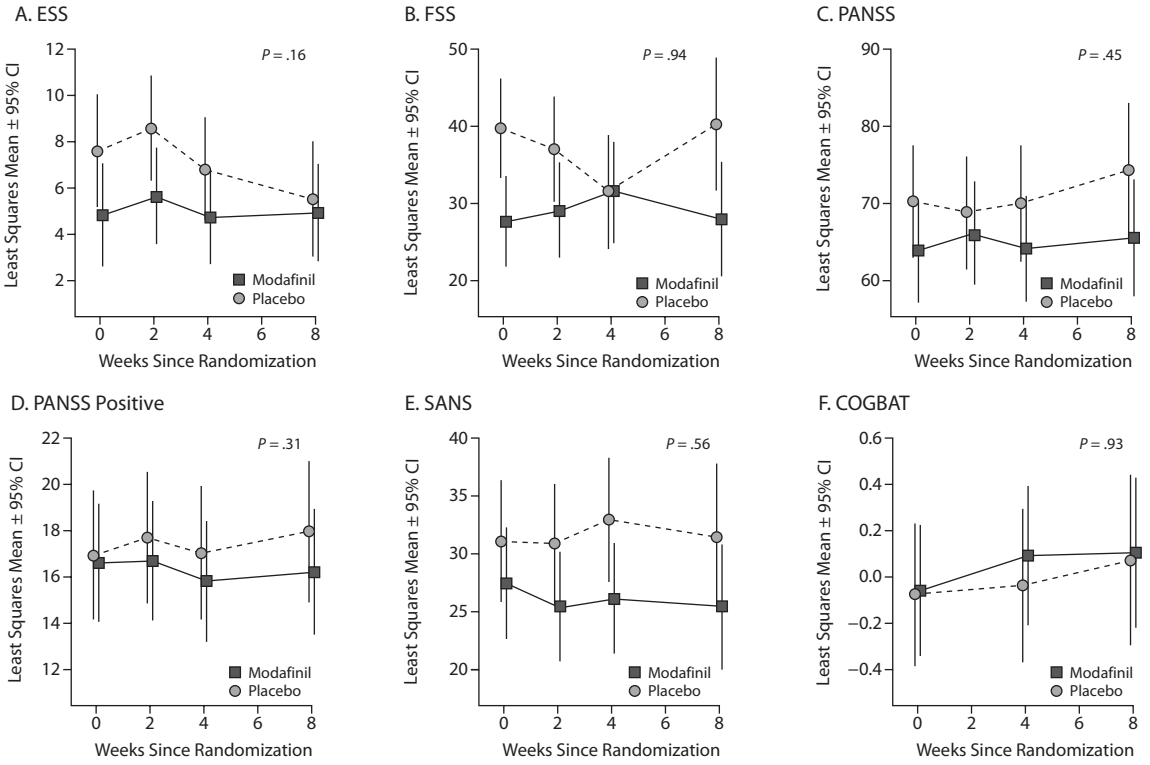
Safety and Tolerability

Modafinil was well tolerated. Dose reductions were less frequent among patients treated with modafinil than among those receiving placebo. There were 2 serious adverse events, 1 psychiatric hospitalization in a modafinil-treated subject and worsening of psychosis in a placebo-treated subject. Treatment-emergent or worsening side effects as collected with the SAFTEE were infrequent and not significantly different between the treatment group and placebo group (see Table 3).

DISCUSSION

We could not confirm benefit from modafinil for cognition, negative symptoms, or wakefulness/fatigue when added to ongoing treatment with clozapine in patients with schizophrenia. Unlike the only controlled trial that reported cognitive benefits from a single dose of 200 mg/d modafinil,[12] we did not see improvement with repeated administration of modafinil in attentional set shifting and short-term verbal memory. Single-dose administration was also reported to increase activation of the anterior cingulate[30] and the dorsolateral prefrontal cortex[31] in functional magnetic imaging studies of patients with poor baseline executive function. The disparity in results between our study and studies of single-dose administration raise the question of whether tachyphylaxis may occur with chronic dosing. In addition, timing of testing might be important. The positive Turner et al study[12] tested patients 2 hours after modafinil administration, while neither the Sevy et al study[13] nor our own controlled for time of testing in relation to drug administration.

Figure 2. Treatment-Specific Trajectories of Six Measures of Fatigue, Positive and Negative Symptoms, and Cognitive Function[a]



[a]Each panel displays least squares means with 95% confidence intervals and the nominal *P*-value from a test of treatment-dependent differences in the mean rate of change of each measure from the mixed model analysis described in the text.
Abbreviations: COGBAT = composite score of neurocognitive battery, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

Table 2. Effects of Modafinil on Wakefulness, Psychopathology, and Cognition in an 8-Week, Placebo-Controlled, Double-Blind Trial of Clozapine-Treated Patients

	Placebo		Modafinil			95% CI			Raw *P*	Adjusted	Effect	
Assessment	Slope	SE	Slope	SE	Difference	Lower	Upper	*t*	Value[a]	*P* Value[b]	Size	n80[c]
Wakefulness												
ESS	−0.325	0.16	−0.022	0.14	0.303	−0.12	0.73	1.43	.159	.997	0.484	140
FSS	0.075	0.41	0.037	0.34	−0.038	−1.11	1.03	−0.07	.944	.997	0.024	>1000
Psychopathology												
PANSS	0.579	0.46	0.129	0.38	−0.450	−1.64	0.74	−0.76	.453	.997	0.257	494
PANSS positive subscale	0.096	0.12	−0.065	0.10	−0.161	−0.48	0.15	−1.02	.311	.997	0.347	272
SANS	0.076	0.35	−0.192	0.30	−0.269	−1.20	0.66	−0.58	.564	.997	0.197	840
Cognition												
COGBAT	0.028	0.01	0.018	0.01	−0.010	−0.04	0.02	−0.70	.491	.997	0.238	576

[a]Comparison-wise *P* value.
[b]Multiple-comparison–corrected *P* value for 28 comparisons using Hommel's closed testing procedure.
[c]Total sample size required for 80% power if the same trial were repeated under the assumption of a parallel-group design with equal allocation, equivalent measurement schedule, equivalent visit completion rates, and analysis by the same mixed-model analysis of variance with 2-tailed comparison of slopes estimated by linear contrasts at α = .05.
Abbreviations: COGBAT = composite score of neurocognitive battery, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

While modafinil was reported to improve antipsychotic-related sedation in 3 patients,[32] the only controlled trial that specifically measured fatigue did not find such benefit,[13] consistent with our results. It is also possible that effects of modafinil might be most pronounced in those patients with the greatest fatigue; we did not specify a threshold of severity for fatigue to enter the trial and did not find any interaction between baseline fatigue, treatment group, and rate of change in fatigue. Specifically targeting patients with impaired wakefulness or fatigue based on rating scale scores might be necessary to show drug effect (such as reported in cases selected for sedation[32]). However, in our representative sample of clozapine patients, few patients showed such serious impairment. Moreover, regression to the mean will

Table 3. Side Effects in a Double-Blind, Placebo-Controlled Pilot Trial of Modafinil Added to Clozapine in 35 Patients With Schizophrenia as Assessed by SAFTEE[a]

SAFTEE Term	Modafinil (n = 19)	Placebo (n = 16)
Dizziness	2	2
Stomach/abdominal pain	1	2
Depression	2	1
Headache	2	0
Tiredness/fatigue	3	0

[a]Events reported by 10% or greater of either treatment group.
Abbreviation: SAFTEE = Systematic Assessment for Treatment Emergent Events.

exaggerate drug efficacy in samples selected for symptom severity.

Because the mean daily modafinil dose by end of treatment was 250 mg/d, and compliance, as estimated by pill counts, was quite good, it is unlikely that underdosing explains our negative results. Modafinil 200 mg/d is a standard dose for narcolepsy and other disorders of wakefulness and was the dose used in the positive, single-dose trial in schizophrenia patients reported by Turner and colleagues.[12] Whereas tachyphylaxis as seen with other cognitive enhancing drugs (eg, d-cycloserine[33]) may account for the lack of cognitive benefit, an open-label, 12-week trial of modafinil as an adjunct to nasal continuous positive airway pressure in 125 patients with obstructive sleep apnea and residual fatigue found no evidence of tolerance to modafinil.[34] Since we relied on an "honor system" pill count, we cannot exclude that underdosing from poor adherence occurred.

Our power to detect differences between modafinil and placebo was limited by sample size. While the estimated modafinil effect was at best modest for our outcomes of interest (effect size ≤ 0.35 in favor of modafinil), the 95% confidence intervals were wide and included potentially large beneficial effects of modafinil for outcomes other than ESS. Larger trials will be needed to better resolve the true therapeutic effect, if any, of modafinil in this population. For each variable, Table 2 shows total sample size required for 80% power if the same trial were repeated.

Modafinil was well tolerated, with no clear tolerability problem in this small sample. We did not detect worsening of psychosis, one of the safety concerns that has been raised with modafinil. According to the package insert[35] and a case report,[36] modafinil can in rare instances induce psychosis in individuals without a history of mental illness. Previous modafinil add-on trials also have not reported worsening of psychosis in stabilized patients with schizophrenia.[13,14] However, a case report suggests that it remains a possibility.[37] An additional, recent safety concern has been the reporting of serious rashes in the worldwide, postmarketing phase since modafinil's release. The package insert contains a warning about rare, life-threatening rashes including Stevens-Johnson syndrome. None were observed in our study.

We also examined drug-drug interactions between modafinil and clozapine. In vitro studies have shown that modafinil in addition to inhibiting cytochrome P450 (CYP)2C19 can lead to a small, concentration-dependent induction of (CYP)1A2, (CYP)2B6, and (CYP)3A4.[38,39] Clinical studies in healthy volunteers have confirmed the potential of modafinil to lower plasma concentrations of alprazolam and ethinyl estradiol, both medications with 3A4-dependent metabolism.[40] While clozapine is a substrate of (CYP)1A2, with minor contributions from other enzymes including (CYP)2C19 and (CYP)3A4,[41] we did not observe clinically meaningful changes in plasma clozapine levels from the addition of modafinil in our patients. However, increased plasma clozapine levels as a result of (CYP)2C19 inhibition by modafinil was thought to have been the cause of clozapine toxicity in a case report.[42] Because individual differences in clozapine metabolism might make it difficult to predict drug interactions with clozapine,[43] plasma clozapine level monitoring should be considered.

Future analyses should focus on the effects of clozapine on weight and metabolic parameters. Perhaps an important effect of modafinil is missed by only examining rating scales of negative symptoms. Using a double-blind, crossover design, Farrow and colleagues[44] detected increased motor activity (using a wrist-worn device to record motor activity) in patients following a single dose of 100 mg/d modafinil. If sustained, such an effect on motor activity could lead to accrued health benefits over time by reducing the time spent sedated. Henderson and colleagues[45] reported a case of significant weight loss in a clozapine-treated patient after addition of modafinil; this was attributed to less fatigue and increased activity during the day. Their case suggests that at least in individual patients, modafinil might have clear benefits that are not generalizable to all patients with schizophrenia.

While modafinil was well tolerated, our pilot trial could not confirm efficacy for modafinil when added to clozapine for the chronic treatment of wakefulness/fatigue, negative symptoms, or cognitive symptoms. However, we had limited power to detect a treatment effect, and a type II error is clearly possible in our small sample. If clinicians nevertheless consider prescribing modafinil on a case-by-case basis for an off-label indication like clozapine-induced sedation or negative symptoms, a recent warning regarding Stevens-Johnson syndrome must be taken into account.

Drug names: alprazolam (Xanax, Niravam, and others), amphetamine (Adderall, Desoxyn, and others), clozapine (FazaClo, Clozaril, and others), ethinyl estradiol (Ocella, Yasmin, and others), modafinil (Provigil).
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Financial disclosure: **Dr Freudenreich** receives grant/research support from Cephalon. **Dr Henderson** is a consultant for Covance, receives research support from Solvay and Takeda, and has received honoraria from Janssen, Bristol-Meyers Squibb, and Pfizer. **Dr Goff** receives

grant/research support from Cephalon. **Drs Macklin**, **Evins**, **Fan**, **Cather**, and **Mr Walsh** report no financial or other relationships relevant to the subject of this article.
Funding/support: Funding for this trial was provided by an investigator-initiated grant from Cephalon awarded to Dr Goff.

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