A Randomized, Double-Blind, Placebo-Controlled Trial of Modafinil for Negative Symptoms in Schizophrenia

Joseph M. Pierre, M.D.; John H. Peloian, M.A.; Donna A. Wirshing, M.D.; William C. Wirshing, M.D.; and Stephen R. Marder, M.D.

Objective: Negative symptoms are core features of schizophrenia that are functionally debilitating, associated with poor outcomes, and resistant to existing pharmacotherapies. We performed a randomized, double-blind, placebo-controlled study of modafinil, a medication approved for the treatment of excessive daytime sleepiness, to explore its efficacy as an adjunctive therapy for negative symptoms in schizophrenia.

Method: Twenty subjects with DSM-IV schizophrenia or schizoaffective disorder were randomly assigned to double-blind treatment with modafinil or placebo for 8 weeks. The study ran from March 2002 through March 2006. Outcome measures included the Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI) scale, Quality of Life Interview, neurocognitive assessments (California Verbal Learning Test, Degraded Performance-Continuous Performance Test, Trail-Making Test B), and somatic measures (sleep, weight, side effects).

Results: Modafinil treatment was associated with a greater rate (CGI-Improvement [CGI-I] score ≤ 3, 7/10 vs. 1/10) and degree (mean CGI-I score, 3.2 vs. 4.1) of global improvement at study endpoint compared with placebo. However, modafinil did not significantly improve global negative symptoms as measured by the total SANS or SANS individual global items. Modafinil did not significantly worsen psychopathology (according to the BPRS), compared with placebo, and was well tolerated.

Conclusions: Although no effect on negative symptoms was found, adjunctive therapy with modafinil may result in global improvements in patients with schizophrenia who have prominent negative symptoms.

(J Clin Psychiatry 2007;68:705–710)

Received May 4, 2006; accepted Aug. 17, 2006. From the Department of Psychiatry, Veterans Administration (VA) Greater Los Angeles Healthcare System, and the Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at the University of California Los Angeles (UCLA), Los Angeles.

This research was supported by grants from the Stanley Research Foundation and a West Coast College of Biological Psychiatry/Janssen Research Foundation Junior Faculty Research Award (Dr. Pierre). Cephalon, Inc. provided medication and support for an open-label extension phase designed to enhance recruitment.

Results were presented at the International Congress on Schizophrenia Research, April 2–6, 2005, Savannah, Ga.; the 60th Annual Convention and Scientific Program for the Society for Biological Psychiatry, May 19–21, 2005, Atlanta, Ga.; and the 44th annual meeting of the American College of Neuropsychopharmacology, Dec. 11–15, 2005, Waikoloa, Hawaii.

The authors would like to thank Sun Hwang, M.S., Principal Statistician, NPI Biostatistics Core, UCLA Neuropsychiatric Institute, for statistical support. Ms. Hwang has no potential conflicts of interest in relation to this article.

Financial disclosure appears at the end of the article.

Corresponding author and reprints: Joseph M. Pierre, M.D., 11301 Wilshire Blvd., Building 210 [B-151H], Los Angeles, CA 90073 (e-mail: drjoe@ucla.edu).

Negative symptoms of schizophrenia (affective flattening, alogia, avolition) were recognized as a core feature of the illness by both Emil Kraepelin and Eugen Bleuler nearly a century ago. Although historically neglected in clinical research, negative symptoms are now considered distinct and important targets of pharmacotherapy given that they are functionally debilitating, associated with poor overall outcome, and only modestly responsive to antipsychotic treatment.[1–6] While the second-generation antipsychotic medications were heralded as having a greater therapeutic impact on negative symptoms than their conventional antipsychotic counterparts, the size of this effect is modest and may be largely attributable to the remediation of secondary negative symptoms (e.g., those attributable to positive symptoms, depression, or medication side effects such as sedation or extrapyramidal toxicity).[7,8] In contrast, several studies have concluded that second-generation antipsychotics are no better than conventional agents at treating primary negative symptoms when samples of patients meeting criteria for the "deficit syndrome" were assessed.[9–12]

Antipsychotic augmentation directed at negative symptom improvement has been explored with mixed

success. Antidepressant therapy has yielded inconsistent results, while prodopaminergic strategies, such as amphetamine or L-dopa, have been shown to reduce negative symptoms but at the risk of positive symptom worsening.[13,14] More recently, promising results have been demonstrated with proglutamatergic agents such as glycine and D-cycloserine,[15,16] although a larger trial found no advantage with either agent compared with placebo.[17] The lack of medications with proven efficacy for negative symptoms therefore remains a gaping hole in the pharmacotherapy of schizophrenia, with investigation and development of newer therapies desperately needed.[2]

Modafinil is a wakefulness-promoting agent that is currently marketed for the treatment of excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. Its mechanism of action is unclear, with negligible affinity for dopaminergic, adrenergic, or serotonergic receptors, but the ability to increase glutamate in rats and activate hypothalamic orexins.[18,19] In several different clinical trials, modafinil has been shown to improve daytime sleepiness, fatigue, mood, short-term memory, reaction time, and quality of life in patients with narcolepsy.[20–22] Modafinil has likewise been reported to improve fatigue and sedation in a variety of off-label conditions including neurologic disorders,[23–25] antipsychotic-induced sedation,[25,26] and major depression.[27,28] Within schizophrenia, modafinil has been suggested to have a benefit in fatigue and possibly neurocognitive deficits.[29–31] Taken together, these findings highlight the potential for modafinil to impact negative symptoms in schizophrenia. This potential has been explored with positive findings in an anecdotal report[32] and in a small, 4-week, open-label study,[33] but to date no placebo-controlled trial has yet been published. Of concern, case reports have documented a possible role of modafinil in exacerbating psychosis or causing the emergence of clozapine-associated side effects in clozapine-treated patients.[34,35]

Given this clinical rationale, we performed a double-blind, placebo-controlled trial to test the efficacy of modafinil for the treatment of negative symptoms in schizophrenia. We hypothesized that modafinil would result in greater negative symptom improvements compared with placebo. We also examined for a potential effect of modafinil on sleep, weight, and neurocognition.

METHOD

Study Participants

Subjects were recruited from the outpatient clinics of the VA West Los Angeles Medical Center. Inclusion criteria were (1) age 18–65; (2) DSM-IV criteria for schizophrenia or schizoaffective disorder, based on the Structured Clinical Interview for DSM-IV (SCID)[36]; (3) subjects taking stable doses of antipsychotic medication (no change in dose in the preceding 4 weeks); (4) positive symptom severity ≤ 14 on the Brief Psychiatric Rating Scale (BPRS)[37] psychosis factor (sum of 4 items: suspiciousness, unusual thought content, hallucinatory behavior, conceptual disorganization); (5) negative symptom severity ≥ 20 on the Scale for the Assessment of Negative Symptoms (SANS)[38] total score and ≥ 2 on either the affective flattening or alogia global item; (6) no substance dependence in the 6 months prior to study; (7) no serious medical illness; (8) no concomitant use of monoamine oxidase inhibitors; and (9) no women of childbearing potential. The study, which was conducted from March 2002 through March 2006, received institutional review board approval, and all subjects signed informed consent and demonstrated their ability to provide consent by passing a quiz testing their knowledge of the consent process.[39]

Study Procedure and Assessment Measures

Subjects signing informed consent were screened for eligibility. If they met study criteria for participation, subjects were randomly assigned to either modafinil or placebo, initiated at 1 tablet daily of either modafinil 100 mg or placebo. After the first week, the dose was increased to a maximum dose of either 2 tablets daily of modafinil 100 mg or placebo. Thereafter, doses could be reduced back to 1 tablet daily of modafinil 100 mg or placebo in the event of tolerability issues. Subjects continued taking whatever antipsychotic medication they had been taking prior to the study.

The Schedule for the Deficit Syndrome (SDS),[40] a scale that assesses for the presence of primary negative symptoms within the deficit syndrome, was administered at baseline by a trained independent rater, with all other ratings made by raters blinded to the SDS results. Double-blind assessments were performed at baseline and every 2 weeks thereafter using the following instruments: SANS (18-item version, without attentional items), BPRS, Clinical Global Impressions (CGI) scale,[41] Simpson-Angus Scale,[42] Barnes Akathisia Scale,[43] and the Abnormal Involuntary Movement Scale.[41] In addition, the Quality of Life Interview (QoLI)[44] and a brief neurocognitive battery with tests (Trail-Making Test B [TMT-B],[45] California Verbal Learning Test [CVLT],[46] Degraded Stimulus-Continuous Performance Test [DS-CPT][47]) selected based on deficits found to be associated with negative symptoms[48] were administered at baseline and at 8-week study endpoint. Vital signs, routine laboratory tests, and subjective reports of side effects, as well as the number of hours spent sleeping during the day and night, were monitored on a weekly basis. Subjects were compensated $10 per visit for weekly study participation. In order to enhance recruitment, all subjects were offered participation in an additional 8 weeks of open-label treatment with modafinil if they completed the 8-week, double-blind study.

Table 1. Baseline Characteristics, Endpoint Medication Dose, and Study Dropout Rate by Treatment Group

Variable	Placebo (N = 10)	Modafinil (N = 10)
Age, mean ± SD, y	49.8 ± 7.0	49.7 ± 6.8
Sex, N		
Male	9	10
Female	1	0
Ethnicity, N		
White	4	6
African American	4	3
Latino	2	0
Asian	0	1
Current depression, N	1	2
Antidepressant treatment, N	6	6
Deficit syndrome, N	5	5
Modafinil/placebo dose, mean ± SD, mg/d	180 ± 42	180 ± 42
Study dropout, N	2	1

Statistical Analyses

Baseline characteristics of the 2 treatment groups were compared using either t tests or χ^2 tests. The primary outcome measure was the change in total SANS score, while secondary outcome measures included SANS subscale, BPRS, CGI-Severity of Illness (CGI-S), CGI-Improvement (CGI-I), and QoLI scores; CVLT (no. of words); DS-CPT (A'); TMT-B (seconds); weight (lb); and sleep (reported no. of hours during day and night). Between-group comparisons were performed using last-observation-carried-forward (LOCF) repeated-measures analysis of variance, testing for the interaction of time and treatment group. For the CGI-I score (not measured at baseline), between-group comparison was analyzed using the t test. Subjects were also dichotomized into those with and without clinical improvement, based on the CGI-I score (CGI-I ≤ 3), with between-group comparisons performed using χ^2 analysis. Post hoc analyses using analysis of covariance were performed on SANS outcomes, with SDS results (deficit syndrome or not) and concomitant antidepressant status (yes or no) entered as covariates.

RESULTS

Twenty-six subjects signed informed consent to participate in the study. Three subjects failed to meet study criteria for participation, 1 withdrew consent, and 1 was lost to follow-up prior to baseline evaluation; these subjects were therefore not randomly assigned to study medication. Of the 21 remaining subjects who were randomly assigned to medication, 1 subject assigned to modafinil withdrew consent prior to taking any medication. Data from 20 randomly assigned subjects (N = 10 for modafinil, N = 10 for placebo) were therefore included in the study analysis.

Baseline demographic measures were similar, with no significant differences between treatment groups in terms of age, sex, ethnicity, percent taking concomitant antidepressant medication, or percent meeting SDS criteria for the deficit syndrome (Table 1). The majority (N = 15) of subjects were taking second-generation antipsychotic medications, 3 were taking clozapine, 2 were taking haloperidol, and 2 were taking concomitant divalproex sodium. Of the 20 subjects who started study medication, 17 (85%) completed double-blind treatment—all study dropouts occurred at the discretion of the investigator due to worsening of psychopathology (N = 2 for placebo, N = 1 for modafinil). There was no difference in medication dose between the 2 treatment groups at study endpoint (LOCF)—2 subjects in either group were being treated with 1 tablet daily (modafinil 100 mg or placebo), while all others tolerated the maximum 2 tablets daily (modafinil 200 mg or placebo).

Although mean total SANS and SANS subscale scores improved modestly in both treatment groups, there were no significant differences in SANS change between the modafinil and placebo groups (Table 2). A similar pattern was observed for the total BPRS score, with slight improvement in mean total scores noted for both treatment groups but with no significant between-group differences. In order to address possible differences in depressive symptom change between treatment groups, the BPRS depression item as well as the BPRS depression cluster (depression, guilt, anxiety) were compared, with no significant differences found. While there was also no significant difference in the change in the mean CGI-S score between groups, there was a significant difference in the mean endpoint CGI-I score, with modafinil-treated subjects having greater improvement (mean CGI-I score, 3.2 vs. 4.1; $t = 3.35$, $df = 18$, $p = .004$). When a cut-off score of ≤ 3 on the CGI-I scale was used to dichotomize clinical improvement (on the CGI-I, a score of 4 or more indicates no improvement or worsening), there was a significantly greater proportion of responders in the modafinil group compared with placebo (7/10 vs. 1/10; $\chi^2 = 7.5$, $df = 1$, $p = .006$) (Figure 1). There was no significant effect of either antidepressant status or deficit syndrome status on SANS or CGI outcome measures when these factors were analyzed with analysis of covariance. Both factors were evenly distributed between treatment groups (Table 1).

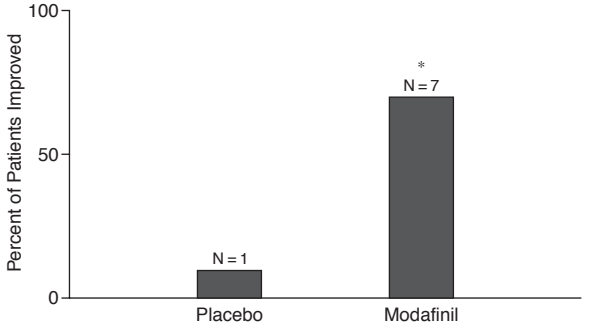
There were no significant differences in neurocognitive test score changes (CVLT, DS-CPT, TMT-B) between the 2 treatment groups. Modafinil-treated patients reported greater reductions in mean hours of daytime and nighttime sleep and experienced a greater degree of mean weight loss compared with placebo-treated patients, but these differences also failed to reach statistical significance (Table 3). There were no significant differences in baseline-to-endpoint changes in extrapyramidal symptoms, glucose, or lipids. For modafinil-treated subjects, reported side effects were infrequent but included edema (N = 1), tinnitus (N = 1), and a bitter taste (N = 1).

Table 2. Psychopathology Scores and Cognitive and Somatic Measures at Baseline and Endpoint by Treatment Group

Variable	Placebo		Modafinil		Effect Size
	Baseline, Mean ± SD	Endpoint, Mean ± SD	Baseline, Mean ± SD	Endpoint, Mean ± SD	
Psychopathology scores					
SANS total	38.5 ± 8.4	36.1 ± 7.7	38.2 ± 7.6	36.0 ± 7.7	0.02
SANS alogia	2.2 ± 1.3	2.0 ± 1.1	2.4 ± 1.1	2.4 ± 1.2	0.14
SANS affective flattening	3.0 ± 0.8	2.6 ± 0.5	2.8 ± 0.8	2.6 ± 1.0	0.27
SANS avolition-apathy	3.1 ± 0.7	2.6 ± 0.7	3.6 ± 0.7	2.9 ± 0.7	0.33
SANS anhedonia-asociality	3.4 ± 0.7	3.3 ± 0.9	3.3 ± 0.7	3.0 ± 0.8	0.25
BPRS	40.6 ± 4.5	37.8 ± 4.2	37.6 ± 8.2	34.4 ± 7.0	0.07
CGI-S	4.0 ± 0.7	4.1 ± 0.6	3.9 ± 0.7	3.6 ± 0.8	0.64
CGI-I[a]	NA	4.1 ± 0.6	NA	3.2 ± 0.6	1.50
QoLI	4.4 ± 1.2	4.2 ± 1.3	3.9 ± 1.4	4.0 ± 0.9	0.22
Cognitive measures					
CVLT, words	36.6 ± 14.6	39.7 ± 21.1	39.2 ± 9.9	43.2 ± 9.5	0.11
DS-CPT, A'	0.94 ± 0.05	0.93 ± 0.05	0.92 ± 0.08	0.92 ± 0.08	0.14
TMT-B, s	150.0 ± 82.5	122.4 ± 55.9	139.9 ± 46.6	134.1 ± 73.6	0.74
Somatic measures					
Weight, lb	204.4 ± 29.8	205.2 ± 31.9	218.4 ± 45.3	215.5 ± 40.2	0.49
Sleep, night, h	7.1 ± 1.3	7.1 ± 1.2	8.2 ± 2.1	7.9 ± 2.2	0.24
Sleep, day, h	1.0 ± 0.8	0.6 ± 0.7	1.1 ± 1.0	0.3 ± 0.4	0.52

[a]t test: t = 3.35, df = 18, p = .004.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CVLT = California Verbal Learning Test, DS-CPT = Degraded Stimulus-Continuous Performance Test, NA = not applicable, QoLI = Quality of Life Interview, SANS = Scale for the Assessment of Negative Symptoms, TMT-B = Trail-Making Test B.

Figure 1. Clinical Improvement (CGI-I ≤ 3) at Study Endpoint by Treatment Group



*χ^2 = 7.5, df = 1, p = .006.
Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

Table 3. Somatic Changes and Reported Adverse Events by Treatment Group

Variable	Placebo	Modafinil
Weight change,[a] lb	0.8	–2.9
Sleep change, h		
Night[b]	0.0	–0.3
Day[c]	–0.4	–0.8
No. of reported adverse events		
Psychosis worsening	2	1
Irritability	2	0
Insomnia	1	0
Infection	2	0
Edema	0	1
Tinnitus	0	1
Bitter taste	0	1

[a]F = 1.0, df = 14, p = .33.
[b]F = 0.25, df = 14, p = .63.
[c]F = 1.23, df = 18, p = .28.

DISCUSSION

In contrast to other open-label reports,[32,33] our preliminary, placebo-controlled trial did not reveal a greater impact on negative symptoms, as measured by the SANS, for modafinil compared with placebo. Such a negative finding is consistent with several other trials in which modafinil was, in the wake of positive open-label reports, not found to have a benefit on fatigue in a variety of conditions when compared with placebo under double-blind conditions.[31,49,50] Still, given the small sample size of our study, type II error remains a possibility. It is likewise possible that modafinil doses beyond 200 mg/day could be more effective—we limited the dose in order to minimize the risk of psychotic exacerbation.

We did find that modafinil was associated with a significantly greater degree of global improvement, as measured by the single-item CGI-I score, and a greater proportion of responders when CGI-I was used to dichotomize response. This was a robust finding that, in the absence of any detected difference on SANS measures, invites speculation. It is possible, for example, that modafinil treatment was associated with improvements in depressive symptoms not captured in the SANS ratings. However, this seems unlikely since only 3 subjects (2 in the modafinil group and 1 in the placebo group) had

active depression according to the SCID, and there were no significant differences in BPRS depression score changes between treatment groups. In addition, deficit syndrome status, as rated by the SDS, did not affect the improvement seen with modafinil treatment, suggesting that the benefit was not specific to those with secondary negative symptoms (e.g., due to comorbid depression). Anecdotally, several study subjects reported specific subjective improvements in anergia, anhedonia, and asociality. It is therefore also possible that a subjective negative symptom change may have been reflected in the CGI-I score but not in the SANS, in which rateable improvement often depends on an actual change in behavior or level of activity. Despite the established validity of the SANS, this and other existing negative symptom scales may be limited in their ability to detect subtle or very specific negative symptom changes.[51] Among our sample of board and care–residing, financially strapped patients with chronic schizophrenia, it is possible that there were improvements in some negative symptoms but that circumstances (lack of money, social skills, or opportunities to be more active) prevented subjects from acting upon them. Future research might therefore pair modafinil and placebo with a psychosocial intervention in a 2 × 2 design that would provide subjects who experience pharmacologic improvement in negative symptoms with an avenue to facilitate the enactment of behavioral change.

A recent consensus meeting indicated that while negative symptoms and neurocognitive deficits appear to be intertwined, their precise relationship remains to be elucidated.[2,52] We found no neurocognitive benefits with modafinil, looking at a fairly narrow range of deficits (episodic memory, attention, and frontal lobe function) reported to be associated with negative symptoms and the deficit syndrome.[48] This lack of cognitive improvement matches a recent report from another placebo-controlled trial.[31] However, others have reported neurocognitive improvement with modafinil in schizophrenia,[29,33] and it is possible that a more extensive cognitive battery or a sample of more severely impaired subjects might reveal specific domains responsive to treatment with modafinil.

Given concerns in the literature about possible modafinil-associated symptomatic worsening among patients treated with clozapine,[34,35] we note that subjects in our study did not as a group experience worsening of psychosis, as reflected by mild mean improvements in BPRS scores regardless of treatment condition. There were 3 study dropouts due to psychotic worsening, but 2 of these occurred in the placebo-treated group. Of the 2 subjects taking clozapine, 1 was randomly assigned to modafinil but requested a dose reduction to 100 mg/day after week 4 due to complaints of activation. This same patient developed unilateral lower extremity edema due to a Baker's cyst. Overall, however, modafinil was well tolerated, with few side effects reported in this trial.

In conclusion, this small, exploratory, double-blind study did not demonstrate a significant benefit for adjunctive modafinil in the treatment of core negative symptoms in schizophrenia. For these symptoms, there remains no treatment with proven efficacy. Modafinil may, however, result in global clinical improvement in patients with prominent negative symptoms, and larger studies incorporating nonpharmacologic interventions might yet reveal a therapeutic niche for modafinil in schizophrenia.

Drug names: clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), modafinil (Provigil).

Financial disclosure: Dr. Pierre has received grant/research support from Cephalon and is a member of the speakers or advisory boards for AstraZeneca, Bristol-Myers Squibb, Janssen, and Pfizer. Dr. D. Wirshing has been a consultant for Abbott, Bristol-Myers Squibb, Janssen, and Pfizer; has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Pfizer; and has served on the speakers or advisory boards for AstraZeneca and Bristol-Myers Squibb. Dr. W. Wirshing has been a consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, and Pfizer; has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Pfizer; and has served on the speakers or advisory boards for AstraZeneca and Bristol-Myers Squibb. Dr. Marder has been a consultant for Bristol-Myers Squibb, Otsuka, Pfizer, and Solvay; has received honoraria from Otsuka; and has served on the speakers or advisory boards for Bristol-Myers Squibb and Solvay. Mr. Peloian reports no additional financial or other relationships relevant to the subject of this article.

REFERENCES

1. Carpenter WT, Heinrichs DW, Alphs LD. Treatment of negative symptoms. Schizophr Bull 1985;11:440–452
2. Kirkpatrick B, Fenton WS, Carpenter WT, et al. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 2006;32: 214–219
3. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes, 2: positive and negative symptoms and long-term course. Arch Gen Psychiatry 1991;48:978–986
4. Arndt S, Andreasen NC, Flaum M, et al. A longitudinal study of symptom dimensions in schizophrenia: prediction and patterns of change. Arch Gen Psychiatry 1995;52:352–360
5. Tamminga CA, Buchanan RW, Gold JM. The role of negative symptoms and cognitive dysfunction in schizophrenia outcome. Int Clin Psychopharmacol 1998;13(suppl 3):S21–S26
6. Milev P, Ho BC, Arndt S, et al. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry 2005; 162:495–506
7. Carpenter WT. Serotonin-dopamine antagonists and treatment of negative symptoms. J Clin Psychopharmacol 1995;15(1 suppl 1):30S–35S
8. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr Res 1999;35:51–68
9. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994;151:20–26
10. Buchanan RW, Breier A, Kirkpatrick B, et al. Positive and negative symptom response to clozapine in schizophrenia patients with or without the deficit syndrome. Am J Psychiatry 1998;155:751–760
11. Rosenheck R, Dunn L, Peszke M, et al. Impact of clozapine on negative symptoms and on the deficit syndrome in refractory schizophrenia. Am J Psychiatry 1999;156:88–93
12. Kopelowicz A, Zarate R, Tripodis K, et al. Differential efficacy of olanzapine for deficit and nondeficit negative symptoms in schizophrenia.

Am J Psychiatry 2000;157:987–993
13. Goff DC, Evins AE. Negative symptoms in schizophrenia: neurobiological models and treatment response. Harv Rev Psychiatry 1998;6:59–77
14. Silver H. Selective serotonin reuptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia. Int Clin Psychopharmacol 2003;18:305–313
15. Goff DC, Tsai G, Levitt J, et al. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch Gen Psychiatry 1999;56:21–27
16. Heresco-Levy U, Javitt DC, Ermilov M, et al. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch Gen Psychiatry 1999;56:29–36
17. Carpenter WT Jr, Buchanan RW, Javitt DC, et al. Is glutamatergic therapy efficacious in schizophrenia? Presented at the 43rd annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 2004; San Juan, Puerto Rico
18. Ferraro L, Antonelli T, O'Connor WT, et al. The antinarcoleptic drug modafinil increases glutamate release in thalamic areas and hippocampus. Neuroreport 1997;8:2883–2887
19. Scammell TE, Estabrooke IV, McCarthy MT, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J Neurosci 2000;20:8620–8628
20. Pigeau R, Naitoh P, Buguet A, et al. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work, 1: effects of mood, fatigue, cognitive performance and body temperature. J Sleep Res 1995; 4:212–228
21. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88–97
22. Beusterien KM, Rogers AE, Walsleben JA, et al. Health-related quality of life effects of modafinil for treatment of narcolepsy. Sleep 1999;22: 757–765
23. Rammohan KW, Rosenberg JH, Lynn DJ, et al. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry 2002;72: 179–183
24. Damian MS, Gerlach A, Schmidt F, et al. Modafinil for excessive daytime sleepiness in myotonic dystrophy. Neurology 2001;56:794–796
25. Teitelman E. Off-label uses of modafinil. Am J Psychiatry 2001;158:1341
26. Makela EH, Miller K, Cutlip WD. Three case reports of modafinil use in treating sedation induced by antipsychotic medications. J Clin Psychiatry 2003;64:485–486
27. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000;61: 378–381
28. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005;66:85–93
29. Turner DC, Clark L, Pomarol-Clotet E, et al. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. Neuropsychopharmacology 2004;29:1363–1373
30. Spence SA, Green RD, Wilkinson ID, et al. Modafinil modulates anterior cingulate function in chronic schizophrenia. Br J Psychiatry 2005; 187:55–61
31. Sevy S, Rosenthal MH, Alvir J, et al. Double-blind, placebo-controlled study of modafinil for fatigue and cognition in schizophrenia patients treated with psychotropic medications. J Clin Psychiatry 2005;66: 839–843
32. Yu BP, Maguire GA. Can a wakefulness-promoting agent augment schizophrenia treatment? Curr Psychiatry 2002;1:52–57
33. Rosenthal MH, Bryant SL. Benefits of adjunct modafinil in an open-label, pilot study in patients with schizophrenia. Clin Neuropharmacol 2004;27:38–43
34. Narendran R, Young CM, Valenti AM, et al. Is psychosis exacerbated by modafinil? Arch Gen Psychiatry 2002;59:292–293
35. DeQuardo JR. Modafinil-associated clozapine toxicity. Am J Psychiatry 2002;159:1243–1244
36. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (Version 2.0). New York, NY: Biometrics Research, New York State Psychiatric Institute; 1996
37. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
38. Andreasen NC. Negative symptoms in schizophrenia. Arch Gen Psychiatry 1982;39:784–788
39. Wirshing DA, Wirshing WC, Marder SR, et al. Informed consent: assessment of comprehension. Am J Psychiatry 1998;155:1508–1511
40. Kirkpatrick B, Buchanan RW, McKenney PD, et al. The Schedule for the Deficit Syndrome: an instrument for research in schizophrenia. Psychiatry Res 1989;30:119–124
41. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education and Welfare Publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
42. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:S11–S19
43. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
44. Lehman AF. A Quality of Life Interview for the chronically mentally ill (QOLI). Eval Program Plann 1988;11:51–62
45. Army Individual Test Battery. Manual of directions and scoring. Washington, DC: War Department, Adjutant General's Office; 1944
46. Delis DC, Kramer JH, Kaplan E, et al. The California Verbal Learning Test (manual). San Antonio, Tex: The Psychological Corporation; 1987
47. Nuechterlein KH, Edell WS, Norris M, et al. Attentional vulnerability indicators, thought disorder, and negative symptoms. Schizophr Bull 1986;12:408–426
48. Buchanan RW, Strauss ME, Kirkpatrick B, et al. Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. Arch Gen Psychiatry 1994;51:804–811
49. Ondo WG, Fayle R, Atassi F, et al. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry 2005;76:1636–1639
50. Stankoff B, Waubant E, Confavreux C, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005; 64:1139–1143
51. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull 2006;32:259–273
52. Harvey PD, Koren D, Reichenberg A, et al. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr Bull 2006;32:250–258

