A Randomized, Double-Blind, Placebo-Controlled Trial of Modafinil for the Treatment of Apathy in Individuals With Mild-to-Moderate Alzheimer's Disease

Laura L. Frakey, PhD; Stephen Salloway, MD; Melissa Buelow, PhD; and Paul Malloy, PhD

ABSTRACT

Objective: This study examined the effects of modafinil on apathetic symptomatology, performance of activities of daily living (ADLs), and caregiver burden in individuals with Alzheimer's disease (AD).

Method: 23 participants with a diagnosis of mild-to-moderate probable AD according to National Institute of Neurologic and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorders criteria were randomized into the experimental (modafinil 200 mg daily) or control (placebo) groups. All participants were also receiving stable doses of a cholinesterase inhibitor medication. Participants completed assessments at baseline and after 8 weeks of treatment. Outcome measures included family report measures of apathy, ADL performance, and caregiver burden, as well as direct assessment of ADL performance. The study was conducted at a private psychiatric hospital in Rhode Island from September 2005 until September 2007.

Results: Both the experimental and control groups showed reductions in apathy on the Frontal Systems Behavior Scale between baseline and final assessments ($F_{1,20} = 18.017$, $P < .001$, $\eta^2 = 0.474$), and there was no significant additional reduction in apathy with modafinil ($F_{1,20} = 0.008$, $P = .932$, $\eta^2 = 0.000$). Groups did not show significant changes in caregiver report of ADL performance over time ($F_{1,19} = 0.268$, $P = .611$). The correlation between change in apathy and change in caregiver burden was not significant ($r = 0.355$, $P = .053$), but there was a trend toward improved levels of apathy being related to decreased levels of caregiver burden.

Conclusions: The addition of modafinil to the standard of care treatment (cholinesterase inhibitor medication) did not result in significant additional reductions in apathy or improvements in ADL functioning. The reduction in reported apathy observed in both groups between baseline and final assessments was likely due to placebo effect. However, reductions in perceived apathetic symptomatology were correlated with reductions in reported caregiver distress and burden. Larger studies with more statistical power are needed to confirm the absence of significant effects.

Trial Registration: ClinicalTrials.gov identifier: NCT01172145

In addition to the hallmark cognitive impairments observed in Alzheimer's disease (AD), as many as 80% of patients with AD will experience neuropsychiatric symptoms such as apathy, depression, anxiety, irritability, disinhibition, delusions, and hallucinations.[1] Apathy is one of the most common neuropsychiatric symptoms in AD with some studies finding it in 70% of patients with mild- and moderate-stage AD.[1,2] Apathy is defined as a loss of motivation that may be manifested as poor effort and initiation, loss of interest, poor insight, reduced social engagement, and a blunted emotional presentation.[2]

While apathy is often mistaken for depression, apathy is a distinct syndrome that can be distinguished from depression.[3–5] The syndromes of depression and apathy share some symptoms and may co-occur in AD, making diagnosis somewhat challenging.[6] Further, many clinical measures of depression include questions assessing symptoms of both apathy and depression, which may lead to misdiagnosis. While some symptoms of apathy may overlap with those of depression (ie, poor initiation and withdrawal), apathy may be distinguished from depression by the absence of dysphoric mood symptoms such as sadness, guilt, hopelessness, and helplessness.[4,7,8] Although there is some support for the notion that older individuals (60 years and older) with late-life depression may endorse feelings of sadness less often than their younger counterparts with depression,[9] these individuals often endorse other clear symptoms of dysphoric mood, including hopelessness, worthlessness, thoughts of death, and wanting to die.[10] When considering a differential diagnosis, apathy can be thought of as a syndrome of primary motivational loss and diminished emotional reactivity while depression reflects a syndrome of mood disturbance.

Apathy has been shown to contribute uniquely to the loss of independence observed in AD.[11] Patients with AD and comorbid apathy are more likely to be impaired on basic activities of daily living (ADLs; dressing, bathing, toileting, transferring, walking, and eating) than nonapathetic patients with AD.[11–13] Additionally, an earlier study carried out in our laboratory found that apathy accounted for 27% of the variance in instrumental activities of living scores in patients with AD.[14] A patient's apathetic presentation may be misinterpreted by the caregiver as a deliberate lack of concern or effort.[15] Some studies have suggested that this misperception may lead to increases in the abuse and neglect of apathetic patients with AD.[16] Due to impairments in motivation, patients with AD and apathy require more support and management from their caregivers. This additional level of support often results in increased burden on the caregiver. The caregivers of patients with AD-related apathy report significantly elevated levels of distress and perceived burden compared to those who are caring for less apathetic patients with similar levels of cognitive impairments.[17]

Caregiver distress secondary to neuropsychiatric symptoms, including apathy, has been implicated in the eventual institutionalization of many patients with AD.[16,18]

In recent years, cholinesterase inhibitors (ChIs), an approved treatment for cognitive decline in AD, have been found to be modestly helpful in reducing neuropsychiatric symptoms in some patients. One study found that 41% of patients showed some behavioral improvements, 28% worsened, and 31% were unchanged after ChI therapy.[1] Of note, those patients who were shown to have a good response to ChI therapy had higher levels of neuropsychiatric symptoms than nonresponders prior to the intervention. Results of a recent meta-analysis examining the treatment of neuropsychiatric symptoms with ChIs indicated that these drugs had only a modest impact on these symptoms and functional outcomes in patients with AD.[19]

Apathy is the neuropsychiatric symptom most consistently shown to improve with ChI therapy.[8] One large double-blind, placebo-controlled study found significant reductions in apathy, depression, and anxiety after 24 weeks of treatment with donepezil in patients with moderate-to-severe AD.[20] It should be noted that all of the above findings were derived from studies that examined the effects of ChIs on neuropsychiatric symptoms retrospectively. To our knowledge, no studies have investigated this question prospectively.

While modest improvements in neuropsychiatric symptoms have been seen in some patients with AD following ChI therapy, additional pharmacologic agents may be useful in the treatment of AD-related apathy. Some evidence suggests that combining ChIs with psychostimulants may reduce symptoms of apathy.[21,22] There is some concern, however, that traditional psychostimulant medication may exacerbate behavioral problems such as irritability, agitation, and psychosis in patients with dementia. In addition, psychostimulants may cause increases in blood pressure and elevate heart rates, which would be of concern for elderly individuals with cardiovascular disease and other cardiac abnormalities.[23] One small, open-label study examining the effect of methylphenidate on apathy in patients with AD reported adverse reactions, including decreased appetite, increased blood pressure, decreased sleep, and irritability. However, none of these reactions was severe enough that subjects dropped out of the study.[24]

Modafinil is a US Food and Drug Administration–approved medication for narcolepsy and obstructive sleep apnea that acts as a norepinephrine agonist in the hypothalamus and has a pharmacodynamic profile that is quite different from traditional psychostimulants such as methylphenidate.[25] Modafinil has also been shown to increase dopamine release in the brains of narcoleptic dogs[26] and to block dopamine transporters and increase dopamine in the human brain.[27] A recent study[28] found that modafinil increased histamine release and locomotor activity in rats immediately after administration. In contrast, while administration of methylphenidate also increased locomotor activity in rats, no concomitant immediate increase in histamine release was observed. This finding suggests that the wakefulness action of modafinil, unlike methylphenidate, may be mediated through its prohistaminergic effects in the hypothalamus. Off-label studies have suggested that modafinil may produce significant improvements in major depression when used adjunctively with antidepressant medication. In 1 open-label study, modafinil was used adjunctively with selective serotonin reuptake inhibitors (SSRIs) in a sample of patients who exhibited no response or only a partial response to monotherapy or combination therapy with antidepressant medications who were also lethargic and/or apathetic.[29] Results indicated that 80% of the sample had some improvement in their Global Assessment of Functioning (GAF) scores after combined treatment with modafinil. Sixty-three percent of those patients who showed improvement had substantial increases in their GAF scores, and, by the end of the study, 41% had GAF scores indicative of only mild or no residual symptoms. A recent double-blind, placebo-controlled study[30] investigating the adjunctive use of modafinil with patients with bipolar disorder was also suggestive of reductions in depressive symptomatology in the group receiving modafinil.

Review of the literature revealed only 1 case report of modafinil used to treat apathy in an elderly patient with dementia. Padala et al[31] reported a significant reduction in apathy, as measured by the Apathy Evaluation Scale, in an elderly man with dementia and depression after treatment with modafinil. To date, there has been no double-blind, placebo-controlled study of modafinil as a treatment of apathy in AD.

The purpose of this study was to evaluate the efficacy of modafinil as a treatment for AD-related apathy and to examine the impact of a reduction in apathy on performance of ADLs in patients and on burden experienced by their caregivers. We hypothesized that those patients who received modafinil in addition to the standard of care ChIs would show significantly greater improvements in apathetic symptoms than the ChI-only group. We also hypothesized that the patients who received modafinil would show greater improvements in ADL functioning than the ChI-only group. Finally, we predicted that improvements in apathy symptomatology would be related to lowered ratings of caregiver distress and burden.

METHOD

A randomized, double-blind, placebo-controlled design was employed. Twenty-three participants with a diagnosis of mild-to-moderate stage probable AD were recruited from the Memory and Aging Program at Butler Hospital in Providence, Rhode Island. Participants met the full National Institute of Neurologic and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorders criteria for probable Alzheimer's dementia.[32] This diagnosis and the participant's disease staging (mild or moderate) were decided by consensus of the study neurologist (S.S.) and study neuropsychologists (L.L.F. and P.M.). All participants had been on a stable dose of a ChI for 30 days, and all showed clinically elevated symptoms of apathy (t score ≥ 65 on the Frontal Systems Behavior Scale [FrSBe][33]). Further, these elevations were at least 1 SD greater than retrospective, premorbid reports of apathetic symptomatology.

The study protocol was approved by the Butler Hospital Institutional Review Board, and written informed consent was obtained from each patient as well as the patient's study partner or caregiver. The study was conducted from September 2005 until September 2007. This clinical trial is registered with ClinicalTrials.gov (identifier: NCT01172145).

Participants were excluded if they had a diagnosis of major depression based on clinical interviews with patient and caregiver, focal brain lesion (eg, stroke or tumor) on neuroimaging, a history of significant substance abuse, or a history of significant head trauma (loss of consciousness > 10 minutes). Participants who were taking antidepressant medication were allowed to enroll as long as they did not meet diagnostic criteria for major depression at the time of enrollment. Patients with AD are often treated with psychoactive medications, such as antidepressant medications. Although it would have been ideal to exclude persons taking these medications from study participation, such an exclusion criterion would have posed potential recruitment difficulties and limited the generalizability of our findings. Participants who were taking memantine adjunctively with a ChI medication were also allowed to enroll. In our sample, 4 participants were prescribed an antidepressant medication, and 6 were prescribed memantine.

Participants were urn-randomized into either the experimental group (modafinil) or the control group (placebo) using apathy severity (mild, moderate, or severe), dementia severity (mild or moderate), presence of antidepressant medication, and presence of memantine as randomization factors. The experimental group (n = 11) received modafinil (100 mg in the morning for the first week and 200 mg in the morning for the remaining 7 weeks). The control group (n = 11) received a placebo added to their normal medication regimen. Both the physician (S.S.) and the clinician (L.L.F.) who performed the assessments were blind to the medication status of the participants. One experimental group participant was withdrawn from the study after 2 weeks due to an increase in motor tics. Please refer to Table

Table 1. Demographic and Clinical Characteristics for Experimental and Control Groups of Patients With Mild-to-Moderate Alzheimer's Disease

Characteristic	Experimental (n = 11)	Control (n = 11)
Age, mean (SD), y	75.27 (8.34)	79.36 (7.62)
Education, mean (SD), y	14.73 (2.9)	13.64 (2.16)
FrSBe apathy score at baseline, mean (SD)	95.64 (10.79)	88.91 (11.95)
Participants prescribed memantine, n	3	3
Participants prescribed antidepressant medication, n	3	2

Abbreviation: FrSBe = Frontal Systems Behavior Scale.

1 for demographic and clinical data for our experimental and control group participants.

All participants underwent a baseline assessment to determine disease staging, assess for the presence of significant apathy, and measure ADL performance and caregiver burden prior to urn randomization. Apathy was assessed using the FrSBe.[33] This measure has a mean t score of 50 and an SD of 10. Higher scores on this measure indicate more severe symptomatology.

While ADL assessment in AD is most often performed via informant questionnaires of the patient's level of independence with various activities, there has been some question as to the accuracy of these proxy reports. Some studies have found that caregivers may overestimate the ability of patients with AD to perform certain ADLs.[34,35] Further, subjective caregiver burden may influence caregiver's judgments of functional capacity independent of the patient's performance on objective assessment of ADLs.[35] Given these methodological concerns, we assessed ADL performance in our participants with both caregiver reports and an objective measure of ADL performance. Caregivers completed the Lawton and Brody ADL Questionnaire (ADLQ),[36] a questionnaire that measures functional abilities in elderly patients. This measure has a score range of 0 (indicating complete dependence) to 28 (indicating full independence). Participants' ADL performance was also assessed with an objective measure using real-world tasks. The Direct Assessment of Functional Status scale (DAFS)[34] provides a behaviorally based assessment of functional activities in AD patients. This measure has a maximum score of 102 points, with higher scores indicating better or intact functional status.

Various studies have implicated apathy and poor ADL performance as predictors of increased caregiver burden.[13,17] Caregiver burden in our sample was measured with one of the most widely used and reliable measures of caregiver burden, the Zarit Burden Interview.[37] This measure has a score range from 0 (no burden) to 88 (severe caregiver burden and distress). Both groups underwent reassessment using the same measures after 8 weeks on their respective treatments.

RESULTS

To address the first hypothesis, a 2×2 analysis of variance (ANOVA) was conducted with pretreatment and

Table 2. Descriptive Statistics for Independent and Dependent Variables

Measure, mean (SD)	Experimental, Pretreatment	Control, Pretreatment	Experimental, Posttreatment	Control, Posttreatment
FrSBe Apathy	95.64 (10.79)	88.91 (11.95)	89.09 (9.61)	82.09 (13.52)
ADLQ	16.18 (4.81)	19.00 (5.25)	15.64 (5.43)	19.00 (5.54)
DAFS	84.55 (16.11)	89.09 (7.84)	85.27 (14.16)	88.36 (8.35)
Zarit	31.18 (8.73)	28.36 (21.09)	30.00 (4.17)	30.00 (20.56)

Abbreviations: ADL = activities of daily living; ADLQ = Lawton and Brody ADL Questionnaire, Total ADL Score; DAFS = Direct Assessment of Functional Status scale, Total ADL Score; FrSBe = Frontal Systems Behavior Scale; Zarit = Zarit Burden Interview.

posttreatment measures of apathy on the FrSBe as the within-subjects factor and treatment group as the between-subjects factor. No significant main effect of group was found ($F_{1,20} = 2.160$, $P = .157$, $\eta^2 = 0.097$). Both groups showed a significant decrease in level of apathy from pretreatment to posttreatment ($F_{1,20} = 18.017$, $P < .001$, $\eta^2 = 0.474$). However, no significant group × time interaction was found ($F_{1,20} = 0.008$, $P = .932$, $\eta^2 = 0.000$), indicating that there was no significant additional reduction in apathy following treatment with ChI plus modafinil.

To address the second hypothesis, two 2 × 2 ANOVAs were conducted with pretreatment and posttreatment measures of caregiver report of ADLs (ADLQ)[36] and objective assessment with the DAFS[34] as the within-subjects factors and treatment group as the between-subjects factor. No significant main effect of group was found on either the caregiver report of ADLs ($F_{1,19} = 1.769$, $P = .199$, $\eta^2 = 0.085$) or on the DAFS ($F_{1,20} = 0.555$, $P = .465$, $\eta^2 = 0.027$). No change was noted over time in terms of ADL function on either the caregiver report ($F_{1,19} = 0.268$, $P = .611$, $\eta^2 = 0.014$) or on the DAFS ($F_{1,20} = .000$, $P > .99$, $\eta^2 = 0.000$). The interaction terms were not significant (all P values > .350), indicating that there was not a positive effect of ChI plus modafinil, or of ChIs alone, on ADL functioning.

For the third hypothesis, that improved levels of apathy would relate to decreased caregiver burden, a 1-tailed correlational analysis was conducted. Pretreatment and posttreatment scores were calculated for both the FrSBe apathy and the Zarit Burden Interview. The correlation between change in apathy and change in caregiver burden was not significant ($r = 0.355$, $P = .053$), but there was a trend toward improved levels of apathy being related to decreased levels of caregiver burden.

The mean scores and SDs for our 2 groups for each of the outcome measures are presented in Table 2.

DISCUSSION

No randomized clinical trials prior to ours have investigated the efficacy of modafinil in treating apathetic symptomatology in AD. Contrary to our predictions, the addition of modafinil to the standard of care treatment of a ChI medication did not result in an increased reduction in apathetic symptomatology in patients with clinically significant apathy and mild-to-moderate stage dementia of the Alzheimer's type. Results suggest that, while a reduction in apathy was reported for both our experimental and control groups between baseline and final assessments, there was no additional reduction associated with the addition of modafinil to the standard of care treatment of a ChI medication. Further, the addition of modafinil did not result in improvement of ADL performance as measured by either caregiver report or direct assessment.

Other research has found that apathy in dementia is associated with high levels of caregiver distress and burden. In the current study, we were able to show some support for our hypothesis that a reduction in apathy would be associated with a reduction in caregiver burden. While the presence of significant apathy has been shown to be associated with higher levels of caregiver burden,[17] ours is the first study to show that reductions in apathetic symptomatology were associated with reductions in reported levels of caregiver burden.

As discussed earlier, apathy and depression represent 2 clinical syndromes but often have some overlapping features and symptoms. While there is an abundance of research on interventions for depression, there is very little on interventions for apathy. Some research has examined the use of modafinil adjunctively for the treatment of depressive symptoms. Most of the studies reporting positive effects have been open-label studies[38,39] or case reports.[31,40] Results of 2 recent randomized, double-blind, placebo-controlled studies examining the effects of modafinil used adjunctively with patients with major depression failed to find significant effects.[41,42] In fact, these studies reported reductions in depressive symptomatology that were observed for both the experimental and control groups. This finding is not dissimilar to our observations of reduced symptoms of apathy being reported for both our control and modafinil groups. Taken together, these findings suggest that a placebo effect might have been responsible for the changes observed in these studies.

There were several limitations to our study. Although we used a double-blind, placebo-controlled study design to maximize experimental control, our sample size was small. As the effect of modafinil on apathy had not been examined before, we based our sample size on a study examining the adjunctive effects of modafinil combined with an SSRI to treat depression in nondemented adults.[29] While apathy is a distinct syndrome from depression, the study we used specifically selected for patients who had current major depression or prominent depressive symptomatology *accompanied by lethargy and/or apathy*. This study found a large effect size (Cohen $d = 1.19$) with only 27 subjects. Nonetheless, it is possible that any effects of modafinil on apathy in AD may be quite small and require a substantially larger sample size than our own to adequately discern an effect. A priori power analyses revealed that a sample size of 54 would be required to discern a moderate effect size (effect size $f = 0.25$) for modafinil on our outcome measures and to detect a small effect size (effect size $f = 0.10$), we would have needed a sample of 328 participants. While we cannot say

with certainty whether some small or modest effect might have been observed with a much larger sample, clinicians considering whether or not to use modafinil to treat apathy in patients with dementia may use the results of the current study to temper their expectations for treatment effects.

Additionally, our trial was of 8 weeks' duration. This duration was selected based on the immediate therapeutic effects of modafinil, which do not require repeated administration over time for therapeutic efficacy. Though modafinil is fast-acting, it may be that the 8-week trial was not long enough for caregivers to notice a change in subject behavior, which may have in turn resulted in improved ratings on ADL performance. However, this explanation seems less likely, as small reductions in apathy were reported for both the experimental and control groups without commensurate changes in caregiver reports of ADL functioning or changes in ADL performance observed directly using the DAFS.

In conclusion, while modafinil was generally well-tolerated by our sample, it did not appear to confer any additional benefit toward reducing symptoms of apathy in patients with mild-to-moderate stage Alzheimer's dementia already taking a ChI. However, larger studies with more statistical power are needed to confirm the absence of significant effects. The effects of modafinil on apathy among patients with AD not taking a ChI (perhaps because of intolerability or the increasing recognition of the modest effects of these drugs) cannot be addressed by this study.

Apathy is a clinical syndrome that is common in patients with dementia, and apathy has been associated with greater functional impairment and caregiver distress and burden. As the number of individuals developing dementia increases with our aging population, research on the causes of and treatments for apathy will become increasingly important in the future.

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