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Designing a trial to evaluate potential treatments for apathy in dementia: the Apathy in Dementia Methylphenidate trial (ADMET)

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Abstract

Background—Research on efficacious treatments for apathy in Alzheimer's disease has been hindered by a lack of consensus diagnosis, difficulties in measurement, and studies with small sample sizes.

Methods—In designing the Apathy in Dementia Methylphenidate Trial (ADMET), a trial to evaluate the efficacy and safety of methylphenidate for the treatment of apathy in Alzheimer's disease, we encountered the following issues: defining and measuring apathy, distinguishing apathy and depression, determining an appropriate test treatment, selecting relevant secondary outcomes, recruiting participants, and deciding on a suitable method for treatment unmasking. ADMET is a 6-week randomized, double-masked, placebo-controlled multicenter clinical trial with two parallel treatment groups assigned in a 1:1 ratio with randomization stratified by clinical center. The recruitment goal is 60 randomized participants over 2 years. The primary outcomes are change in apathy severity as measured by the Apathy Evaluation Scale and the Alzheimer Disease Cooperative Study-Clinical Global Impression of Change.

Conclusion—The design decisions made for ADMET are important elements to be considered in trials assessing the safety and efficacy of medications for clinically significant apathy in Alzheimer's disease.

Keywords

Alzheimer dementia; methylphenidate; apathy; randomized trial

1. Introduction

The number of people living with Alzheimer's disease (AD) world-wide is expected to exceed 80 million by 2040 (1). Neuropsychiatric symptoms affect most people with AD at some point during the illness (2–5). Apathy is one of the most common neuropsychiatric symptoms with prevalence estimates ranging from 36% to 70% of people with AD (2,6) and is associated with increased care needs and caregiver burden and distress (7,8), increased

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risk of institutionalization (9), and higher costs of care (10). Given the prevalence and consequences of apathy in AD dementia, identifying methods of managing apathetic symptoms is an important public health priority.

The Apathy in Dementia Methylphenidate trial (ADMET) is an investigator-initiated clinical trial funded by an American Recovery and Reinvestment Act award from the National Institute on Aging (NIA) issued in September of 2009.

2. Issues in designing a trial to test treatments for apathy in people with dementia

2.1 Defining and measuring apathy

DSM-IV (TR) (11) supplies no formal definition or diagnostic criteria for apathy although it is cited as a symptom of several disorders. Apathy is particularly common in AD (12), fronto-temporal dementias (13), Parkinson's disease (14), and after stroke (15). Given these heterogenous contexts, it was important for ADMET to incorporate a definition of apathy that included both mood and cognitive symptoms. Existing definitions included those by Marin (16): "diminished motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress", a definition that seems to exclude dementia, and Stuss (17): "absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action", a perhaps easier definition to apply to demented AD patients. However, a consensus definition or diagnostic criteria for apathy in dementia did not exist.

We used the Neuropsychiatric Inventory (NPI) (18) apathy subscale to specify inclusion criterion in the study. We defined clinically significant apathy as apathy that 1) occurs daily (i.e., "very frequently" NPI rating), or 2) occurs at least once a week ("often" or "frequently" NPI rating) with evident severity ("moderate" or "marked" NPI rating). Our definition limited study participants to those with apathy based impairment of daily life at a clinically significant severity level for whom pharmacological treatment is appropriate.

After ADMET had begun recruitment, a task force proposed diagnostic criteria for apathy in neurodegenerative diseases (19) that show substantial overlap with our NPI inclusion criteria. A significantly increased apathy score on the NPI has been reported for individuals in a clinical practice setting who fulfilled the proposed diagnostic criteria for apathy (20).

We considered several scales for longitudinal assessment of apathy severity, including the NPI apathy subscale to be consistent with the entry criteria, or the Dementia Apathy Interview and Rating (DAIR) (21), scale which had been developed specifically for measuring apathy in dementia. We chose to use the Apathy Evaluation Scale (AES) because of its widespread use in measuring apathy (22) and previous use as a primary outcome measure in a trial of treatment of apathy in AD (23).

The AES is an 18-item scale designed to measure apathy as a neuropsychiatric symptom, defined as "reduced motivation which is not due to emotional distress, intellectual impairment or loss of consciousness" (24). In ADMET, study personnel administer the AES informant version to participants' study partners. The informant version has good internal consistency (Cronbach's $\alpha = 0.94$) and test-retest (Pearson's $r = 0.94$) reliability (25).

ADMET will also use a clinician rating of target behavior change similar to the approach used in the Depression in Alzheimer's Disease Study-2 (DIADS-2) (26) and the Citalopram for Agitation in Alzheimer's Disease (CitAD) trial (27). We modified the ADCS-CGIC by adding apathy-specific interview questions and probes based on Marin's core features of apathy: lack of initiative, lack of interest and emotional blunting (16).

2.2 Distinguishing between apathy and depression

Although depressive symptoms overlap those of apathy (28–30) they are distinct (16,31,32) with respect to the patient's emotional and affective experience. Depression is characterized by dysphoria (i.e., sadness and distress) while apathy presents with emotional indifference. The locus of suffering and distress tends to be different. In depression, the *patient* is the primary sufferer; while in apathy, the *family* and *caregivers* are commonly distressed, but not the patient. Further, apathy is also associated with lack of insight (32). Marin, et al (33) found that people with AD frequently had elevated apathy scores unassociated with elevated depression; while individuals with major depressive disorder had elevation of both depression and apathy scores.

We believed that depression and apathy would respond differently to treatment and therefore chose to exclude individuals meeting DSM-IV criteria for Major Depressive Episode at enrollment. We do, however, include apathetic individuals currently taking antidepressant medication but not meeting DSM-IV depression criteria

2.3 Recruiting participants

We began recruitment for ADMET in May, 2010. Initially recruitment was slow; we enrolled only four participants between May 2010 and the end of July 2010. We quickly identified two recruitment barriers.

1. Focusing on the individual was not a fruitful approach. With most major neuropsychiatric symptoms in AD, the individual appears overtly to be in distress. In contrast, with apathy the individual does not complain and appears not to experience distress; rather the caregiver experiences increased distress. As a result, we focused recruitment efforts on caregivers.
2. Referring clinicians often did not appreciate apathy as neuropsychiatric symptom due to its 'silent' quality. We consequently found it necessary to enhance local educational efforts towards an increased appreciation of apathy symptoms. Identifying and overcoming these barriers resulted in markedly improved recruitment; since the beginning of August 2010, we have been recruiting a mean of four participants per month. ADMET is currently exceeding recruitment goals with completion of enrollment expected by October 2011.

2.4 Determining an appropriate test treatment

The evidence base for choosing a pharmacologic treatment of apathy is limited, and we considered several classes of known neuroactive medications. We chose not to test cholinesterase inhibitors even though they may be modestly effective in reducing apathy (34–36). Many potential participants would already be using a cholinesterase inhibitor. Discontinuation of medication was not in the patients' best interests and limiting the study population to individuals not currently taking a cholinesterase inhibitor would limit generalizability. To minimize the potentially confounding effect of changes in cholinesterase inhibitor treatment on our primary apathy outcomes, we required that these patients be on a stable dose of these medications for one month prior to randomization.

We rejected antipsychotics as treatment for apathy in AD given the lack of evidence from controlled trials suggesting treatment effect (37–40) and concerns about increased mortality risk resulting in an FDA "black box" warning (41–43).

There is no evidence to support the use of antidepressants for the treatment of apathy in AD (44) and, in fact, selective serotonin reuptake inhibitors (SSRIs) may increase apathy

(45,46). Thus we chose not to consider antidepressants as treatment for apathy in the ADMET study.

The best treatment alternative for symptoms of apathy appears to be a dopamine enhancing agent. Activity in the dopaminergic mesolimbic brain reward system may correlate with motivated behavior in both healthy and neurologically impaired populations (47). Dysfunction in the brain reward system correlates with apathy symptoms in people with AD (48). We considered the psychostimulants dextroamphetamine, amantadine, and bupropion, but data on the use of these drugs for apathy is limited (49–51). Preliminary data on the on the efficacy and safety of methylphenidate for the treatment of apathy in AD in a double-blind, randomized, placebo-controlled crossover trial (13 participants) showed significantly greater improvement in apathy (as measured by the AES) in the methylphenidate phase compared with the placebo phase (see Figure 1), although a significantly greater proportion of participants also experienced at least one adverse event in the methylphenidate phase (23). Given this preliminary data and other data suggesting that methylphenidate causes fewer side-effects than other psychostimulants in the elderly (52), we chose methylphenidate (IR Ritalin®, target dose 10 mg BID) as the active comparator for ADMET.

2.5 Including other relevant secondary outcomes

Little is known about the effects of methylphenidate on cognitive functioning in AD. Galynker et al. (53) reported approximately 1.8 point increase in Mini Mental State Examination (MMSE) (54) scores associated with open-label treatment of AD patients with 10–20 mg daily of methylphenidate and preliminary data showed little difference in MMSE scores between treatment groups (see Figure 1) (23). We chose the MMSE as a brief measure of global cognitive function given its widespread use for assessment of efficacy and toxicity in neuropsychiatric trials (55).

Because the dopaminergic system also plays a key role in attention, inattention often coexists with apathy. Baseline attention may predict response to methylphenidate treatment of apathy which may in turn improve attention (23). We chose to measure attention with Wechsler Memory Scale – Revised (WMS-R) digit span tests (56) which has been reported to effectively measure attention, concentration, sequencing, number facility and auditory short-term memory (57–59) in dementia populations and to be a sensitive measure of drug response in methylphenidate trials (60).

Important secondary safety outcomes include incident delusions and hallucinations as measured by the NPI, weight loss, changes in blood pressure, incident abnormal electrocardiograms, other expected adverse events associated with methylphenidate, and all serious adverse events.

2.6 Determining when to unmask patients, study partners and study staff

Decisions regarding unmasking require striking a balance between facilitating clinical care and maintaining masking and allocation concealment. Unmasking each study participant at closeout might improve recruitment and facilitate clinical care, but could also sabotage masking and allocation concealment of other participants. We elected to inform patients and their study partners of the treatment assignment immediately after completing data collection at the close out visit but we do not simultaneously unmask clinical center personnel. Sealed envelopes with the treatment assignments and the study monitor’s contact information are given to participants and partners with instructions to discuss the study with their primary care physicians. Clinical center personnel remain masked until study end to prevent selection and information biases. Emergency unmasking before the week 6 visit is allowed in emergency situations only.

3. Design of Apathy in Dementia Methylphenidate trial

3.1 Study organization

ADMET has three recruiting clinical centers located in Baltimore, Charleston and Toronto, and two resource centers (chair's office and coordinating center). The ADMET Steering Committee (SC) is the primary decision-making body; and is comprised of one voting member from each center.

The ADMET Data Safety and Monitoring Committee (DSMC) includes three voting members who are appointed by the NIA and have expertise in biostatistics, psychiatry and neurology. They are independent of ADMET conduct and review accumulating, unmasked data on the safety and efficacy of methylphenidate compared with placebo. The DSMC makes recommendations to the SC and the NIA. NIA and study leadership participate in DSMC meetings to address trial conduct, including protocol implementation and data analysis.

3.2 Eligibility and consent

Study participants, who are recruited from outpatient facilities, nursing homes, and community outreach, have possible or probable Alzheimer's disease as defined by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (61) criteria with Mini-Mental State Examination (MMSE) (54) scores of 10 or higher. Participants also have "clinically significant apathy" and do not meet criteria for major depression. A study partner, who accompanies the participant to study visits, is a friend, family member or caregiver, spends several hours a week with the participant, and supervises the participant's care. Patients were excluded from participation if they had either a comorbid condition or were taking concomitant medications that made it unsafe to use methylphenidate. The detailed list of eligibility criteria for ADMET is given in Table 1.

Consent is obtained from the participant if he or she is capable of providing consent. If not, then consent is obtained from an authorized legal representative and the participant is asked to provide assent following the guidelines proposed by the Alzheimer's Association (62) and procedures approved by each clinical center's Institutional Review Board (IRB) or Research Ethics Board (REB) in accordance with local law. Consent is also obtained from the study partners who accompany the participants on study visits, if required by the local ethics board. The ADMET protocol was reviewed and approved by the IRB or REB at each clinical center, chair's office, and coordinating center.

3.3 Randomization and masking

The coordinating center created the treatment assignment schedule using a documented, auditable SAS program (SAS/STAT® software, Version 9.1 of the SAS System for Windows; Copyright © 2000–2004 SAS Institute Inc., Cary NC, USA). The randomization scheme was stratified by clinical center with permuted length blocks. Participants are randomized in a 1:1 ratio to receive methylphenidate or matching placebo. Clinical centers request and receive treatment assignments via the online ADMET data system following confirmation of eligibility. Participants, study partners, and clinical center personnel are all masked to treatment assignment.

3.4 Study treatment protocol

The dose, treatment administration, and treatment duration of methylphenidate were chosen based on strategies of previous trials in the elderly depressed (63,64), open label administration guidelines in demented populations (52), and primarily because of the

preliminary study of methylphenidate for apathy that provided data on the safety and efficacy of 10 mg BID methylphenidate (23).

Participants begin treatment by taking one study drug capsule twice a day (corresponding to 10 mg/day in the methylphenidate group) for three days. The study drug is administered by a caregiver or taken by the patient under the supervision of a caregiver. Study staff telephone the patient and/or study partner on day three to discuss tolerability and if acceptable, increase the dose to the target of two capsules twice a day (20 mg/day). Study physicians may recommend no dose increase if there are side-effects at the lower dose and may lower the dose if necessary for safety concerns.

All study partners and participants (when possible) receive the ADMET standardized psychosocial intervention, a 20 – 30 minute counseling session at study visits, educational materials, and 24-hour availability of study staff for crisis management assistance. During the psychosocial intervention a study clinician provides referrals for caregivers if they are in need of counseling or psychiatric assessment. This psychosocial intervention maintains compliance with the existing standard of care (65,66).

3.5 Data collection

Scheduled in-person study visits and telephone contacts occur regardless of adherence to assigned treatment to allow analyses to be performed according to the intention-to-treat philosophy. In-person visits are scheduled at baseline and weeks 2, 4 and 6 following baseline with telephone contacts scheduled at weeks 1, 3, and 5 (Table 2). Study personnel may conduct unscheduled visits or telephone contacts to provide medical monitoring, encourage compliance, or offer counseling.

Study personnel enter data into a web-based data entry system. Data are stored in redundant databases on a password protected web server and archived daily by the coordinating center. The data entry system performs error and consistency checks during data entry. The coordinating center also conducts audits of clinical center data during the trial.

3.6 Definition of comparisons, analyses and power calculations

The primary outcome measures are the AES (30) and the ADCS-CGIC scale (67). Secondary outcome measures include the NPI apathy scores (18), Digit span forward and backward tasks (68), MMSE (54) and adverse events.

Definition of primary comparisons—We will base the primary assessment of efficacy on the intention-to-treat comparison of the difference in the change in AES scores from baseline to week 6 and the comparison at week 6 of the ratings for the apathy domain of the ADCS-CGIC. We hypothesize that the methylphenidate group will have a larger reduction in AES scores (corresponding to more improvement in apathy symptoms) than the placebo group by week 6. We also hypothesize that the proportion of patients with scores indicating worsening of apathy at week 6 (compared with baseline) on the ADCS-CGIC will be lower on methylphenidate than placebo.

Analysis of AES—The primary comparison will be the difference in the change in AES from baseline to week 6 using a t-test. We will also conduct longitudinal analyses of AES scores to compare treatment groups over time using a linear mixed effects model with random intercept and slope for each participant using all available data for that participant. Additionally, we will perform sensitivity analyses to assess the potential impact of missing data by imputing the missing outcomes using the method of multiple imputation (69,70).

Analysis of ADCS-CGIC—Proportional odds logistic regression will be used to compare the ADCS-CGIC ratings (ranging from 1 to 7) at week 6 between the groups to capitalize on the ordinal structure of the outcome.

Analysis of secondary outcomes—We will conduct analyses on change in the NPI domain ratings from baseline to week 6 using t-tests with transformations of the outcome variable if necessary. Other secondary outcomes to be examined longitudinally by treatment group include global cognition (MMSE), digit span and rates of adverse events. Time-to serious adverse events will also be compared using survival methods.

Power calculations—We conducted power calculations for the two primary hypotheses using information from our preliminary study (48). With 60 participants (1:1 allocation ratio), the power to detect a difference of 3.3 in the change from baseline to week 6 on the AES is at least 80% assuming a two-sided type I error of 5%. Significant attrition is not expected since the trial is only 6 weeks long so we did not adjust the sample size for potential losses to follow-up.

We calculated power for the ADCS-CGIC outcome by using standard two sample power estimations for comparing two proportions and assumed that 20% to 30% of participants assigned to placebo would show moderate or marked improvement. With 60 participants, the study will have greater than 80% power to detect a difference of 35% between the proportion of participants who improve (or worsen) in the methylphenidate group compared with the placebo group. The binary power calculation can be taken as a lower bound of the power for the proportional odds analysis described above.

3.7 Adverse event monitoring

Adverse events are collected by systematic, close-ended questions on known or expected side effects of methylphenidate, open-ended questions about unexpected side effects, and review of results of electrolyte panels and electrocardiograms (ECG). We also measure weight at each visit and have defined weight loss of 7% or more as an adverse event. Serious adverse events are collected at the time of event regardless of presumed association with methylphenidate and reported to IRBs and regulatory agencies as appropriate.

3.8 Quality assurance

Study personnel met for in-person training on all study assessments and passed a test for knowledge of study protocol and procedures prior to data collection. The study handbook and policy and procedures memoranda contain detailed information about standardized methods for performing study procedures. The coordinating center continually monitors performance of the clinical centers and presents performance information to the SC and DSMC; performance data include (but are not limited to) enrollment, completed and missed visits, losses to follow-up, protocol deviations, and data edit queries. The coordinating center performs site visits to all clinical centers to review facilities, staffing, study documentation, consent forms, IRB submissions and approvals, forms and data management and study drug accounting.

4. Discussion

There has been only limited study of treatment of apathy in dementia. Our preliminary data suggested that methylphenidate may be efficacious for treating apathy, and we will test this possibility in ADMET, the first parallel group, multicenter, randomized controlled trial of a medication intervention for apathy in AD. Given the current state of knowledge, we designed ADMET as a phase II trial, with the objective to show “proof-of-concept” rather

than definitively testing our hypothesis. Definitive testing requires a subsequent trial if ADMET demonstrates acceptable risk-benefit profile of methylphenidate treatment on apathy in AD.

ADMET's design involved decisions on several design issues, including developing an operational definition of apathy, selection of a promising intervention, and review and choice of an instrument to accurately measure change in apathy. We will carry the lessons learned to a possible phase III study. We discovered that excluding patients on antidepressants hindered recruitment as well as limiting generalizability of results, and the SC revised the protocol to allow stable treatment of both SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs). Early in the trial, we expected apathy to have higher prevalence in those with more cognitive impairment but have found apathy to also be prevalent in patients with higher levels of functioning and have adjusted our enrollment criteria accordingly. In a larger trial, we would like to collect more complete data on cognition and its relationship to both apathy and treatment with methylphenidate.

Trials for potential treatment of apathy symptoms in patients with AD are challenging to design and conduct. Research has been complicated by a lack of consensus diagnosis and difficulties in measurement. Our tribulations may be able to serve as a guide for future trials.

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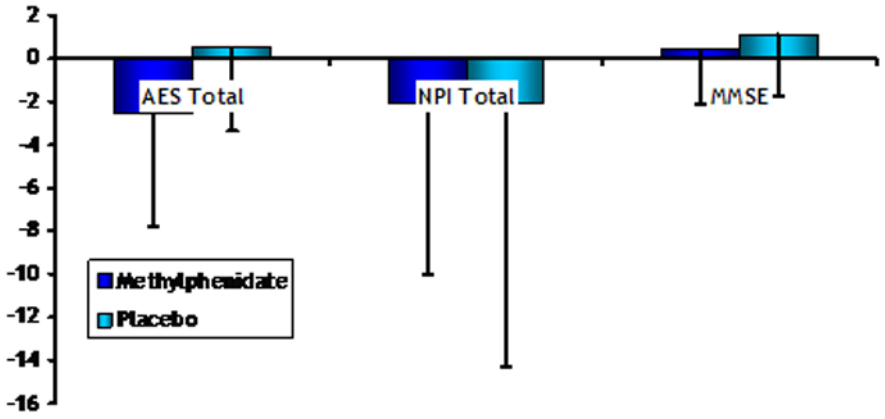

Figure 1. Change scores for methylphenidate versus placebo in 13 patients

Data from preliminary, randomized, cross-over study of 13 patients on cholinesterase inhibitors. The shaded bars are the mean change (end of treatment minus baseline) such that negative change values indicate improvement, and the lines indicate the standard deviation of the change.

Table 1

Data collection schedule

	Assessment visits and contacts (weeks from baseline)*						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Procedures							
Review of consent	✓	✓	✓	✓	✓	✓	✓
Review inclusion/exclusion	✓	.	✓	.	✓	.	✓
Collect demographic information	✓						
Review history	✓	.	✓	.	✓	.	✓
Perform ongoing medical monitoring	✓	.	✓	.	✓	.	✓
Review of medication use	.	✓	✓	✓	✓	✓	✓
Dispense of study drug	✓	.	✓	✓.	✓	.	.
Patient assessments							
AES	✓	.	✓	.	✓	.	✓
ADCS-CGI	✓	.	✓	.	✓	.	✓
Digit span	✓	.	✓	.	✓	.	✓
MMSE	✓	.	✓	.	✓	.	✓
NPI	✓						✓
Safety measures							
Review of adverse events	.	✓	✓	✓	✓	✓	✓
Blood collection for electrolyte panel	✓	.	✓	.	✓	.	✓
Review ECG	✓	.	✓	.	.	.	✓
Study partner intervention							
Psychosocial intervention	✓	.	✓	.	✓	.	✓

AES, Apathy Evaluation Scale, ADCS-CGI, Alzheimer's Disease Cooperative Study - Clinical Global Impression; NPI, Neuropsychiatric Inventory; MMSE, Mini-mental State Examination

*In-person clinic visits occur at baseline and weeks 2, 4 and 6 following baseline. Telephone contacts occur at weeks 1, 3, and 5following baseline.

Table 2

Design Summary

Apathy in dementia methylphenidate trial (ADMET)
Objectives
Primary objective
To examine in a masked, randomized trial the efficacy of methylphenidate for the treatment of clinically significant apathy, without depression, in patients with Alzheimer's dementia
Secondary objectives
To examine the effects of methylphenidate treatment on cognition of patients
To examine the safety of methylphenidate
To examine predictors of response to methylphenidate therapy
Type of trial
Randomized, multicenter phase II clinical trial
Two parallel treatment groups
Double masked
1:1 assignment ratio
Setting
Clinical centers
Johns Hopkins School of Medicine, Baltimore
Medical University of South Carolina, Charleston
Sunnybrook Health Sciences Centre, Toronto
Chair's office
Medical University of South Carolina, Charleston
Coordinating center
Johns Hopkins Bloomberg School of Public Health, Baltimore
Primary outcome measures
Change in apathy from baseline to 6 weeks as measured by AES
Change in apathy from baseline to 6 weeks as measured by ADCS-CGIC
Other outcomes
Change in apathy from baseline to 6 weeks as measured by NPI
Global cognition as assessed by MMSE
Attention as assessed by Digit Span
Adverse events (including delusions, hallucinations, weight loss and abnormal ECGs)
Serious adverse events (requiring hospitalization)
Study population
60 patients who meet the ADMET criteria for clinically significant apathy
Power calculations
AES:
Power greater than 80%

Two-sided alpha = 0.05

Standard deviation of AES = 4.5

Detectable difference in change in apathy severity is 3.3

ADCS-CGIC apathy:

Power greater than 80%

Two-sided alpha = 0.05

Assuming 20–30% of placebo patients improve

Detectable difference in proportion of patients improving is 35%

Treatment groups

Methylphenidate, target dose 20 mg per day (range 10–20 mg per day), given orally + standardized psychosocial intervention

Placebo + standardized psychosocial intervention

Stratification of randomization

By clinical center

Masking

Double-masked (treatment assignment masked to participants, study partners and all clinical center personnel, including physicians, nurses, and neuropsychologists)

Inclusion criteria

Possible or probable Alzheimer's disease (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria), with Mini-Mental State Exam (MMSE) score of 10–26 inclusive; MMSE scores above 26 in those who nevertheless meet criteria for AD may be allowed with Steering Committee approval on a case by case basis

Clinically significant apathy for at least four weeks for which either

1. the frequency of apathy as assessed by the NPI is 'Very frequently', or
2. the frequency of apathy as assessed by the NPI is 'Frequently' or 'Often' AND the severity of the apathy as assessed by the NPI is 'Moderate', or 'Marked'

Medication for apathy is appropriate, in the opinion of the study physician

Provision of informed consent for participation in the study by patient or surrogate (if necessary) and study partner

Availability of a study partner, who spends several hours a week with the patient and supervises his/her care, to accompany the patient to study visits and to participate in the study

No change to AD medications within the month preceding randomization, including starting, stopping, or dosage modifications

Treatment with stable doses of selective serotonin reuptake inhibitor antidepressants (SSRIs) is appropriate if stable for 3 months prior to randomization. Other psychotropics (with the exclusion of antipsychotics), if stable for 3 months, may be allowed only with Steering Committee approval on a case by case basis.

Exclusion criteria

Meets criteria for Major Depressive Episode by DSM-IV (TR) criteria

Clinically significant agitation/aggression for which either

1. the frequency of agitation/aggression as assessed by the NPI is 'Very frequently', or
2. the frequency of agitation/aggression as assessed by the NPI is 'Frequently' AND the severity of the agitation/aggression as assessed by the NPI is 'Moderate', or 'Marked'

Clinically significant delusions for which either

1. the frequency of delusions as assessed by the NPI is 'Very frequently', or
2. the frequency of delusions as assessed by the NPI is 'Frequently' AND the severity of the delusions as assessed by the NPI is 'Moderate', or 'Marked'

Clinically significant hallucinations for which either

1. the frequency of hallucinations as assessed by the NPI is 'Very frequently', or

2. the frequency of hallucinations as assessed by the NPI is 'Frequently' AND the severity of the hallucinations as assessed by the NPI is 'Moderate', or 'Marked'

Treatment with psychotropic medications in the 2 weeks prior to randomization with the exception of approved treatments for dementia (ChEIs and memantine), selective serotonin reuptake inhibitor antidepressants, and trazodone (if used as an aid to facilitate sleep and not as an antidepressant); other psychotropics (with the exclusion of antipsychotics), if stable for 3 months, may be allowed only with Steering Committee approval on a case by case basis. Note that antipsychotics are expressly prohibited.

Treatment with methylphenidate is contraindicated in the opinion of the study physician

Failure of treatment with methylphenidate in the past for apathy after convincing evidence of an adequate trial as judged by study physician

Treatment with a medication that would prohibit the safe concurrent use of methylphenidate, such as monoamine oxidase inhibitors and tricyclic antidepressants

Need for psychiatric hospitalization, or is suicidal

Uncontrolled hypertension (medication non-compliance or past 3 months with a diastolic reading of 105 as verified by compartment pressure of the rectus sheath [CPRS])

Symptomatic coronary artery disease deemed to be significant by study physician at the time of screening

Lack of appetite that results in significant unintentional weight loss as determined by the study physician in the last three months

Significant communicative impairments

Current participation in a clinical trial or in any study that may add a significant burden or affect neuropsychological or other study outcomes

Hyperthyroidism, advanced arteriosclerosis, symptomatic cardiovascular disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or a family history of sudden death or death related to heart problems

Glaucoma, pheochromocytoma, or known or suspected hypersensitivity to methylphenidate or its excipients

CNS abnormalities (e.g., cerebral aneurysm) and/or other vascular abnormalities such as vasculitis or pre-existing stroke, motor tics or a family history or diagnosis of Tourette's syndrome, seizures (convulsions, epilepsy), or abnormal EEGs

Any condition that, in the opinion of the study physician, makes it medically inappropriate for the patient to enroll in the trial

Duration of follow-up

6 weeks

Data collection schedule

Scheduled in-person visits (baseline and weeks 2, 4, and 6 after randomization)

Telephone contacts (weeks 1, 3, and 5 after randomization)