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BRIEF REPORT

Study rationale and baseline data for pilot trial of dronabinol adjunctive treatment of agitation in Alzheimer's dementia (THC-AD)

Leah M. Cohen,[1] Eleanor Ash,[1] John D. Outen,[2] Ryan Vandrey,[2] Halima Amjad,[3] Marc Agronin,[4] M. Haroon Burhanullah,[2] Patricia Walsh,[5] James M. Wilkins,[1,6] Jeannie-Marie Leoutsakos,[2,7] Milap A. Nowrangi,[2] David Harper,[1,6] Paul B. Rosenberg,[2] and Brent P. Forester[1,6]

[1]*Division of Geriatric Psychiatry, McLean Hospital, Belmont, MA, USA*
[2]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[3]*Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[4]*Department of Mental Health and Clinical Research, Miami Jewish Health, Miami, FL, USA*
[5]*Department of Psychiatry, North Shore Medical Center, Salem, MA, USA*
[6]*Harvard Medical School, Boston, MA, USA*
[7]*Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*

Abstract

Agitation is a common complication of Alzheimer's dementia (Agit-AD) associated with substantial morbidity, high healthcare service utilization, and adverse emotional and physical impact on care partners. There are currently no FDA-approved pharmacological treatments for Agit-AD. We present the study design and baseline data for an ongoing multisite, three-week, double-blind, placebo-controlled, randomized clinical trial of dronabinol (synthetic tetrahydrocannabinol [THC]), titrated to a dose of 10 mg daily, in 80 participants to examine the safety and efficacy of dronabinol as an adjunctive treatment for Agit-AD. Preliminary findings for 44 participants enrolled thus far show a predominately female, white sample with advanced cognitive impairment (Mini Mental Status Examination mean 7.8) and agitation (Neuropsychiatric Inventory-Clinician Agitation subscale mean 14.1). Adjustments to study design in light of the COVID-19 pandemic are described. Findings from this study will provide guidance for the clinical utility of dronabinol for Agit-AD. ClinicalTrials.gov Identifier: NCT02792257.

Key words: Alzheimer's disease, dementia, agitation, neuropsychiatric symptoms, drug trials

Introduction

Agitation is a common and distressing neuropsychiatric complication of Alzheimer's dementia (AD), for which there are currently no FDA-approved treatments. Behavioral and other nonpharmacological interventions are recommended as a first-line therapy, but may be difficult to implement in routine clinical practice, and less efficacious for more acute, severe agitation. Antipsychotic medications, the most widely used class of medication to treat Agit-AD, appear to be only modestly effective and are associated with increased mortality in older adults with dementia (Schneider *et al.*, 2006). While antidepressant medications (i.e. citalopram) appear to have comparable efficacy to antipsychotics, there are also concerns about adverse side effects, particularly cognitive and cardiac ones (Porsteinsson *et al.*, 2014). There remains a critical need for safe, effective medications for treatment of Agit-AD. Cannabinoids such as tetrahydrocannabinol (THC) are a novel and promising class of medications for treatment of this indication. Ruthirakuhan *et al.*'s meta-analysis of six studies of natural and synthetic cannabinoids for agitation and aggression in AD found that while, on average, cannabinoids did not affect agitation, synthetic cannabinoids had a larger effect than natural cannabinoids (Ruthirakuhan *et al.*, 2019). Preliminary data suggest that FDA-approved synthetic cannabinoid dronabinol (Marinol) is a safe and effective treatment for severe agitation. Forester

Correspondence should be addressed to: Brent P. Forester, M.D., M.Sc., Division of Geriatric Psychiatry, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA. Office: 617-855-3622; Fax: 617-855-3246. Email: bforester@mclean.harvard.edu. Received 08 Apr 2021; revision requested 03 May 2021; revised version received 04 Aug 2021; accepted 05 Aug 2021. First published online 11 October 2021.

and colleagues published a retrospective case series of 40 inpatients at McLean Hospital, finding that Pittsburgh Agitation Scale (PAS) scores decreased significantly for patients with Agit-AD treated with dronabinol adjunctive to other psychotropics (Woodward *et al.*, 2013). Additionally, as a drug that is already FDA approved with a known safety profile, it is an attractive choice among cannabinoids. However, placebo-controlled trials are necessary to establish the efficacy of dronabinol as a treatment for Agit-AD.

We present the study design for a double-blind, placebo-controlled, randomized trial of adjunctive dronabinol for the treatment of Agit-AD (THC-AD). We hypothesize that dronabinol will be 1) more effective than placebo in reducing agitation as evidenced by reductions on the Pittsburgh Agitation Scale (PAS) and the Neuropsychiatric Inventory-Clinician (NPI-C) Agitation subscale and 2) well tolerated with adverse events (AEs) not significantly different than placebo, including incident delirium.

Methods in brief

THC-AD is a three-week clinical trial of dronabinol (titrated to 10 mg daily, administered in divided doses) administered to 80 participants with severe Agit-AD (Figure 1). Study sites include Johns Hopkins University in Baltimore, Maryland, McLean Hospital in Belmont, Massachusetts, North Shore Medical Center in Salem, Massachusetts, and Miami Jewish Health in Miami, Florida.

Study design choices

Duration

We chose a duration of 3-week drug treatment based on a previous trial of citalopram for Agit-AD (Porsteinsson *et al.*, 2014) that reported placebo response plateauing at 3 weeks. Additionally, in our retrospective case series examining dronabinol use for Agit-AD (Woodward *et al.*, 2013), the mean duration of treatment was 16.9 days, further supporting the rationale for a 3-week trial duration.

Age range

The age range is 60–95 years. Clinical AD appears to be relatively uncommon prior to age 60 and often confounded with other dementia diagnoses (particularly frontotemporal dementia) or with autosomal dominant forms of AD. Additionally, as medical comorbidities advance with increasing age, our upper limit of 95 addresses IRB safety concerns.

Informed consent

Most participants lack cognitive capacity to consent for medical procedures. In these cases, informed consent is obtained from the legally authorized surrogate decision maker along with the assent of the participant. All study procedures, including informed consent, were approved by local ethics boards.

Inclusion criteria

Inclusion and exclusion criteria are chosen to include patients with advanced dementia and severe agitation. Inclusion criteria include a diagnosis of AD (major neurocognitive disorder, Alzheimer's type) (McKhann *et al.*, 2011), as well as the presence of Agit-AD, defined by criteria from the International Psychogeriatric Association (IPA) (Cummings *et al.*, 2015). The NPI-C subdomains of agitation or aggression must be ≥ 4 (i.e. clinically significant agitation or aggression). In order to complete study scales, participants must be fluent in English or Spanish. The study began recruiting only hospitalized inpatients, but expanded to recruit outpatients as well to improve feasibility and generalizability, particularly given the impact of COVID-19 on long-term care facilities.

Exclusion criteria

Exclusion criteria include serious or unstable medical illness, history of seizure disorder, and concurrent use of lithium, which might confound assessment of safety outcomes. Baseline delirium, assessed by the Short-Confusion Assessment Method (Short-CAM) and DSM-5 criteria, is also exclusionary, as treatment for underlying etiology of delirium and associated agitation takes precedence. Because we are compounding study drug by over encapsulating dronabinol pills (vs. placebo), inability to swallow a capsule is exclusionary.

Outcome measures

Coprimary outcome measures are the PAS and the NPI-C Agitation domain. The PAS captures fluctuation in agitation symptoms over the course of a day or week and rates the severity of agitation in four behavioral domains: aberrant vocalization, motor agitation, aggressiveness, and resisting care. We use the NPI-C because it provides a thorough assessment of neuropsychiatric symptoms, divides agitation and aggression into separate domains, and incorporates input from interview of the participant and informant, with the clinician ultimately making a clinical judgment of severity on each item. Secondary outcomes include the Cohen-Mansfield

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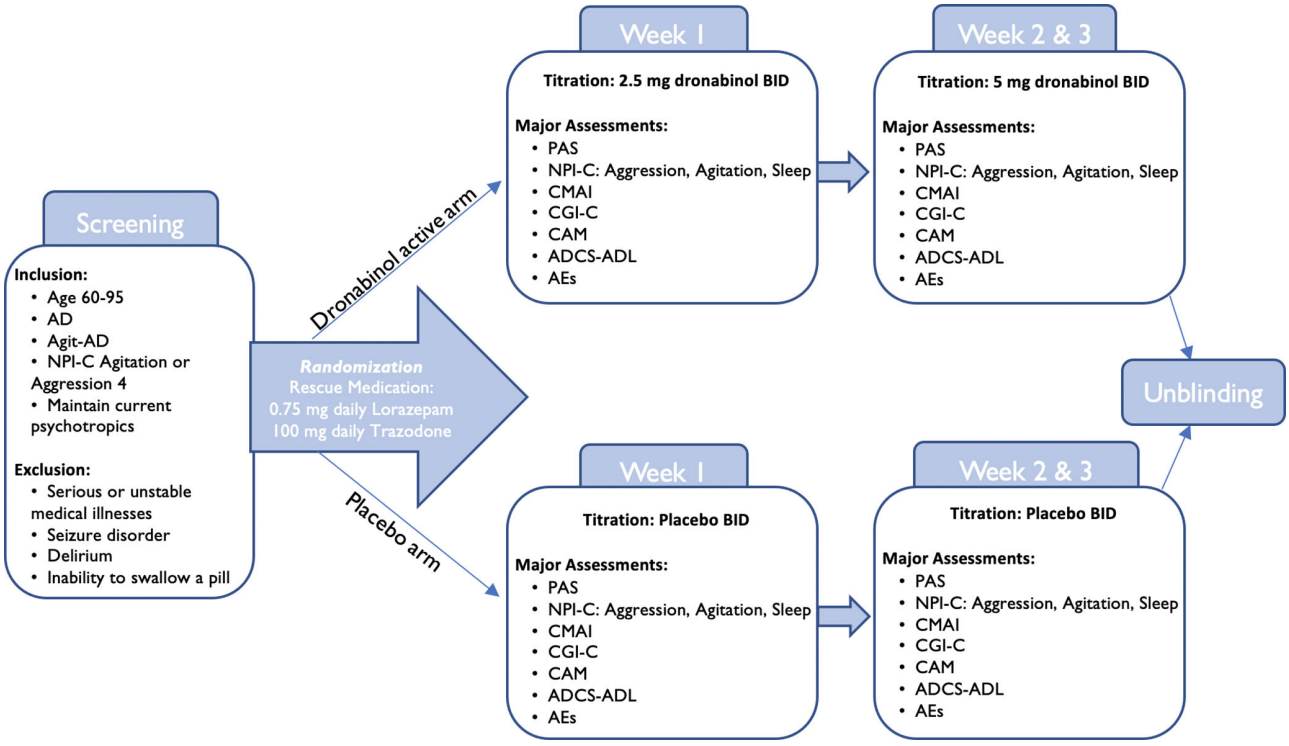

Figure 1. A flow diagram of the trial displaying the two randomization cohorts (treatment arm vs. control (placebo) arm. Notes: AD: Alzheimer's disease; Agit-AD: Agitation in AD; NPI-C: Neuropsychiatric Inventory-Clinician rating scale; PAS: Pittsburgh Agitation Scale; CMAI: Cohen Mansfield Agitation Inventory; CGI-C: Clinical Global Impression of Change-Clinician Version; CAM: Confusion Assessment Method; AEs: Adverse Events.

Agitation Inventory-Short Form (CMAI-SF), change in functioning (Clinical Global Impression of Change-Clinician Version, CGI-C and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)), sleep ("Sleep" subscale of the NPI-C), cognition (Mini-Mental State Exam (MMSE) and an abbreviated form of the Severe Impairment Battery (SIB-8)), and AEs. Figure 1 outlines the Study Workflow. Figure 2 lists the schedule of procedures.

Safety monitoring

The major risks of dronabinol in older adults include delirium, sedation, seizures, and changes in vital signs (e.g. blood pressure changes, increased heart rate). THC appears to be well tolerated, but we monitor for these risks as well as dizziness, red or irritated eyes, drowsiness, sedation, easy laughing, euphoria, dry mouth, jitters, headache, nausea, vomiting, increased appetite, perceptual difficulties, memory lapse, hallucinations, confusion, depression, paranoid reaction, depersonalization, and rash. Monitoring instruments include the Drug Effects Questionnaire (DEQ), and a customized Medication Side-Effects Questionnaire focusing on these symptoms. Additional safety monitoring includes ECG and laboratory testing, including complete blood count (CBC), comprehensive metabolic panel (CMP), and thyroid stimulating hormone (TSH). Cognition is monitored with the SIB-8 and MMSE. The Short-CAM is used to monitor for incident delirium.

Adjunctive treatment

Given the behavioral acuity of the study population, it is felt to be neither safe nor ethical to impose a period of time to stabilize on current psychotropic medications prior to randomization, which might make for a more rigorous trial design and longer study duration. Relevant categories of concomitant medications (e.g. antidepressants and antipsychotics) in the two treatment groups are balanced in the randomization process using minimization, a method of adaptive stratified sampling suitable to small trials (Scott *et al.*, 2002). Rescue medications include lorazepam up to 0.75 mg daily and trazodone up to 100 mg daily for inpatient and outpatient participants. Study participation does not impact participation in nonpharmacological interventions (e.g. group therapy).

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Procedure	Screening	Baseline	Week 1	Week 2	Week 3
Informed Consent	x				
Inclusion/Exclusion Criteria	x				
Demographics	x				
Coronavirus Impact Scale	x				
Randomization		x			
Study Medication Dispensing		x	x	x	
Unblinding					x
Clinical Instruments					
Pittsburgh Agitation Scale (PAS)		x	x	x	x
Neuropsychiatric Inventory, Clinician Version (NPI-C)		x	x	x	x
Cohen-Mansfield Agitation Inventory-Short Form (CMAI-SF)		x	x	x	x
Modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (CGI-C)		x	x	x	x
Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL)		x	x	x	x
Short-Confusion Assessment Method (Short-CAM)		x	x	x	x
Sleep Assessment (NPI-C Sleep Subscale)		x	x	x	x
Cognition					
Severe Impairment Battery-8 item (SIB-8)		x			x
Mini-Mental State Exam (MMSE)		x			x
Drug Effect					
Drug Effects Questionnaire (DEQ)		x	x	x	x
Medication Side-Effects Questionnaire		x	x	x	x
Safety and AE monitoring					
Physical and Neurological Exam	x				
General Medical Health Rating (GMHR)	x				
Initial Health Assessment	x				
Weekly Health Assessment		x	x	x	x
Vital Signs		x	x	x	x
Adverse Event Monitoring		x	x	x	x
ECG		x			x
Blood draw (DNA, Biomarker, CBC, CMP, TSH)		x			x

Figure 2. Weekly procedures including cognitive exams, safety assessments, and clinical outcomes.

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Choice of dose

A previous trial of low dose THC (4.5 mg daily) did not show significant benefit for neuropsychiatric symptoms of dementia (van den Elsen *et al.*, 2015), but our previous retrospective case series suggested clinical benefit of dronabinol for agitation in persons with dementia at a mean dose of 7 mg daily (Woodward *et al.*, 2013). Given concerns that a higher dose of THC may be needed for efficacy, we chose a target dose of 10 mg daily, starting with an initial dose of 2.5 mg twice daily (5 mg/day) increasing to a maximum of 5 mg twice daily (10 mg/day) after the first week. Given the 4-6 hour half-life of dronabinol, 8 a.m. and 2 p.m. dosing was chosen to address agitation in the daytime and the late afternoon/early evening.

Outpatient arm

Due to inpatient and ALF recruitment challenges posed by COVID-19, we broadened inclusion criteria to include outpatients. Outpatient participants attend a portion of each visit in-person. Safety protocols are employed to minimize the risk of COVID-19 exposure, including remote data collection through HIPAA-compliant telemedicine services when possible. Caregivers receive study medication, a schedule for medication administration, and a medication log. Study staff perform a pill count at weekly visits. All other procedures are identical in outpatients and inpatients.

Data analytic strategy

Analyses will be intention-to-treat. All primary analyses will be adjusted for site, use of antidepressants, and use of antipsychotics. Efficacy will be assessed by fitting a longitudinal linear regression model with both primary outcomes (PAS and NPI-C Agitation) and terms for treatment, time, their interaction, and adjustment for site and randomization variables; the correlation structure is assumed to be exchangeable. Though we have two primary outcomes, we opted not to use a Bonferroni correction. Such corrections are known to be over-conservative, particularly when the outcomes are correlated. Not imposing such a correction may have the potential to limit our analysis, but we will temper our interpretation accordingly, particularly if the two outcomes do not agree. The interaction term between time and treatment will be the coefficient of interest and will represent the mean difference in change over the 3-week period between the treated and placebo groups. Tests will be two-sided with $\alpha = .05$. We expect a moderate level of attrition, which may result in limitations to our analysis, but we will investigate sensitivity to missingness by comparing rates as a function of background covariates. We plan to compare retained vs. discontinued patients on baseline variables. Inpatient vs. outpatient will be included, secondarily, as a covariate in analyses.

Results

To date (03/11/2021) we have screened 47 participants, with 3 screen failures (one due to exceeding the previous age limit of 90; the other two due to insufficient agitation at the time of screening). A total of 44 participants were enrolled across all sites, with 9 early discontinuations. Causes of early discontinuation included family withdrawal after request for more active medication management [1], family withdrawal after an apparent failure to improve [3], incorrect dosing [1], excessive agitation [1], somnolence and slurred speech [1], allergy to medication filler [1], and inability to swallow medication [1].

Baseline data and symptom severity

Demographics

The study sample enrolled thus far (n = 44) has a mean age of 78.0 years, standard deviation (SD) ± 7.1 [spread of 65–94], is predominately female (72.7%), white (86.3%) with a mean education of 13.5 years, SD ± 3.4 [spread of 3–19]; 43.0% have a known family history of dementia.

Baseline clinical status

The mean NPI-C Agitation subtotal was 14.1, SD ± 7.0 [spread of 0-30] and the mean NPI-C Aggression subtotal was 6.1, SD ± 5.5 [spread of 0-21]. The mean PAS score was 6.3, SD ± 4.1 [spread of 0–15]. The mean CMAI-SF score was 27.4, SD ± 9.1 [spread of 16–50]. Short-CAM results showed 83.3% of the participants as alert, 7.1% as vigilant, and 9.5% as lethargic. Mean MMSE score was 7.8, SD ± 6.1 [spread of 0-21], and mean SIB-8 score was 11.6, SD ± 7.1 [spread of 0–21].

General Medical Health Rating (GMHR)

About 11.4% rated Excellent, 50.0% rated Good, 38.6% rated Fair, and 0% rated Poor.

Concomitant medications

Totally, 56.1% of patients were taking medication for AD (24.4% taking memantine, 34.1% taking donepezil, 9.8% taking rivastigmine, and 0.0% taking galantamine), along with 90.2% taking

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antidepressants, 65.9% taking antipsychotics, and 53.8% taking any other class of psychotropics (including anticonvulsants not used for seizure disorder; benzodiazepines; and other medications defined as psychotropics by their ability to impact behavior, such as melatonin).

Discussion

Preliminary data suggest that dronabinol is an effective and safe adjunctive therapy for Agit-AD, but randomized control trials are necessary to establish the drug's impact. Benefits observed in this trial could motivate a definitive hypothesis-testing phase 3 trial and support further research into cannabinoid receptors as a potential target in treating the behavioral symptoms of dementia. This trial examines the acute effect of the drug, but future trials in outpatient populations should assess a longer time period, such as 12 weeks, in order to further reduce placebo response and better assess tolerance issues.

Conflicts of interest

R. Vandrey received compensation as a consultant or advisory board member from Canopy Health Innovations, FSD Pharma, and Present Life Corporation in the past year. J. Wilkins is supported by grant funding from the Alzheimer's Association. D. Harper is supported by grant funding from the National Institute on Aging, the Spier Family Foundation, The Rogers Family Foundation, Eli Lilly and Biogen. P. Rosenberg is supported by grant funding from the National Institute on Aging, Alzheimer's Association, Lilly, Functional Neuromodulation, Vaccinex, the Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Trials Research Institute (ATRI), and the Alzheimer's Clinical Trials Consortium (ACTC); he has served as a consultant to GLG, Leerink, Otsuka, Avanir, ITI, IQVIA, Food and Drug Administration, Cerevel, Bioxcel, Sunovion, and Acadia. B. Forester is supported by grant funding from the National Institute on Aging, the Spier Family Foundation, The Rogers Family Foundation, Eli Lilly, Eisai and Biogen; he serves as a consultant to Biogen and Acadia Pharmaceuticals. The remaining authors only declare the National Institute on Aging grant R01AG050515 that supported the conduct of this trial.

Description of authors' roles

L. Cohen and E. Ash and drafted the manuscript. J. Outen performed the data analysis. P. Rosenberg and B. Forester formulated the research question, designed the study, and supervised the data collection. All authors contributed to data collection and substantively revised and contributed to the manuscript.

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