Pilot trial of dronabinol adjunctive treatment of agitation in Alzheimer's disease (AD) (THC-AD)

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Pilot trial of dronabinol adjunctive treatment of agitation in Alzheimer's disease (AD) (THC-AD)

Principal Investigators: Brent Forester, MD, MSc, McLean Hospital and Paul Rosenberg, MD, Johns Hopkins
Research Sites: McLean Hospital, Miami Jewish Health, and Johns Hopkins Hospital
Coordinating Center: Johns Hopkins University
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1. Background and Significance:

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of aging, affecting an estimated 5.2 million Americans and predicted to increase to 13.8 million by 2050 (1). AD affects both cognition and emotion. Neuropsychiatric symptoms (NPS) in AD are a major cause of burden to patients, caregivers, and society (2,3) and are near-universal at some point in the AD course with > 97% of AD patients having at least one symptom reported on the Neuropsychiatric Inventory (NPI) (4). The most common NPS are agitation, depression and apathy (2,5).

One of the most troubling of these symptoms is agitation (Agit-AD), typified by a variety of problem behaviors including combativeness, yelling, pacing, lack of cooperation with care, insomnia, and restlessness (4). In community-based samples, Agit-AD is common: in the Cardiovascular Health Study the prevalence of Agit-AD in the past month was 30% (5), and in the Cache County Dementia Progression study the 5-year prevalence was > 40% (4). Agit-AD tends to persist (6) with its prevalence increasing with dementia severity (7). Agit-AD is associated with greater caregiver burden (8) and shorter time to institutionalization (1,9), and there is a particularly acute need for interventions for severe Agit-AD in advanced dementia. One important question for treatment development is whether Agit-AD represents a specific target for intervention or a nonspecific syndrome shared with many other diseases.

Agit-AD is a specific syndrome and suitable target for intervention research

One of the major challenges in treating Agit-AD has been understanding the precise definition of the syndrome of agitation, as clinical manifestations may be varied and overlap with a number of other conditions including mood disorders and delirium. The International Psychogeriatric Association (IPA) recently addressed this issue with a consensus definition of Agit-AD derived from opinion leaders on the neuropsychiatry of Alzheimer's disease (10). The definition requires the presence of cognitive impairment, evidence of emotional distress, and one of three of observable behavior (excessive motor activity, verbal aggression, physical aggression). It requires that the behaviors cause excess disability, and that the behaviors not be solely attributable to another disorder such as psychiatric illness, medical illness, or substance use. The pharmaceutical industry has re-embraced Agit-AD as a target after several years hiatus, with are at least three controlled trials of novel medication interventions in the field for Agit-AD (clinicaltrials.gov NCT01922258 [brexpiprazole], NCT01584440 [Nuedexta (Dextromethorphan/quinidine)], and NCT01735630 [scylloinositol]). Nuedexta has recently reported positive results in a phase II trial but there are no peer-reviewed publications to date. This new definition allows for treating Agit-AD as a specific target rather than a non-specific symptom, addressing past concerns about "pseudospecificity" of target symptoms (11).

There is widespread agreement that behavioral therapies should be first-line treatment for Agit-AD given their inherent safety. These interventions are being increasingly incorporated into "user-friendly" algorithms (12). However, behavioral interventions are still not widely disseminated, may be less effective for the most severe cases of Agit-AD, and significant time and effort may be expended prior to observing response. While behavioral management strategies are inherently safer than medications and are being increasingly systematized for wider dissemination (12,13), there clearly remains a role for medications, particularly in more severe cases.

While there are currently no FDA approved medications for Agit-AD, psychotropic medications are widely prescribed "off-label" to treat Agit-AD. The most commonly used classes of medications prescribed for "off-label" treatment are antipsychotics and antidepressants. The evidence to date for efficacy remains mixed. Antipsychotics appear to have some degree of efficacy, but the effects are not highly replicable (3,8,14,15,16) and their use is associated with increased mortality in elderly patients with dementia (12,17,18). The latter has prompted an FDA "black-box" warning and caution in the field about their use. Antidepressants (particularly selective serotonin reuptake inhibitors, SSRIs) appear to have fewer and less severe adverse effects compared to antipsychotics, as well as no known mortality risks, but are not without limitation. In a recent multi-center RCT of citalopram for Agit-AD (CitAD), clinical benefit was observed in that study (reviewed in Preliminary Data), but cautions were raised about adverse effects (prolonged QTc intervals and cognitive decline) (19). CitAD participants were largely outpatients, and CitAD excluded patients taking antipsychotics and those with severe Agit-AD. Clinical response was not observed until 6-9 weeks following medication induction and response was poorer in more impaired participants. Also, only ~40% of patients were characterized as "responders," indicating a large unmet public health need. Therefore, exploration of alternative treatments for Agit-AD, particularly severe cases, is timely and warranted.

Dronabinol

Given modest efficacy and concerns about toxicity with current pharmacotherapies, there is a need to explore alternatives. Dronabinol (Marinol®) is FDA-approved for the treatment of anorexia/weight loss in AIDS and for nausea/emesis associated with chemotherapy, which is now being used off-label for Agit-AD. Dronabinol is a synthetic oral formulation of delta-9-tetrahydrocannabinol (THC), a psychoactive constituent of the cannabis plant that acts as a partial agonist at the Type 1 (CB1) and Type 2 (CB2) endocannabinoid receptors. This pharmacology is appropriate for targeting Agit-AD because CB1 receptor agonism can produce anxiolytic and antidepressant effects and CB2 receptor agonism can be anti-inflammatory.

Dronabinol (Marinol®) is an oral synthetic formulation of delta-9-tetrahydrocannabinol (THC), a partial agonist at the cannabinoid receptors (CB1 and CB2) and one of the major psychoactive constituents of the cannabis plant. The endocannabinoid system is widespread throughout the human body. The CB1 receptor is a G-coupled protein receptor primarily located on the spinal cord, peripheral nervous system, and in brain areas associated with learning/memory (hippocampus), movement (basal ganglia, cerebellum), mood (amygdala), higher-order cognition (frontal cortex), and appetite/reward (hypothalamus, nucleus accumbens) among others. The CB1 receptor modulates the release of most major neurotransmitters in the brain, most often inhibiting release. The CB2 receptor is primarily located in the immune system and in the gut, but also is present in the CNS. Significant first-pass metabolism and degradation of THC occurs with the oral route of administration resulting in bioavailability of about 10-20%. THC is metabolized to 2 primary metabolites: 11-OH-THC, a psychoactive metabolite of approximately equal potency as THC; and THC-COOH, a non-psychoactive metabolite. Subjective/physiological effects are dose dependent. Due to THC and its metabolites being highly lipid

soluble, blood cannabinoid levels are not necessarily reflective of acute drug effects, particularly following oral administration.

Potential mechanisms for benefit of dronabinol in Agit-AD

The mechanism by which dronabinol exerts its effects on agitation and aggression in patients with dementia may occur through its action at the CB1 and/or the CB2 receptor. Agonists at the CB1 receptor in the brain improve anxiety and depression in humans as well as animal models (20,21). Dronabinol is an effective agonist at the CB1 receptor, which is generally specific to neurons and localized predominantly on the presynaptic terminal (22) where it inhibits glutamatergic, dopaminergic and other neurotransmitter release (23). The CB1 receptor effects has been observed to mediate the observed anxiolytic and antidepressant effects of THC (24). Dronabinol is also an agonist at CB2, a potent anti-inflammatory receptor localized on activated microglia. Patients with AD have increased central (7) and peripheral (25) inflammation, likely as a result of the accumulation of beta-amyloid. Increased inflammation may have a number of behavioral effects (26) that could drive the agitation and aggression in dementia patients. Dronabinol's effects at the CB2 receptor therefore could also produce changes in behavior in AD patients by reducing inflammation.

Dronabinol shows promise as a novel treatment for Agit-AD

Recently there has been renewed interest in potential alternative medical applications of cannabis/THC and medical marijuana is now legalized in 23 states and the District of Columbia. Acute effects of THC can include subjective feelings of euphoria, relaxation, and sedation, and clinicians noted that THC is well tolerated for its approved indications. Given these subjective effects and relatively benign safety profile, investigators have studied THC preparations for the treatment of Agit-AD and there are several promising small studies. Volicer et al (27) administered dronabinol 2.5 mg twice daily to 15 participants with advanced AD and anorexia in a crossover randomized controlled trial (RCT). They observed reduction in Agit-AD measured by the Cohen-Mansfield Agitation Inventory (CMAI) during dronabinol exposure. Adverse events (AEs) were few although one participant experienced a generalized seizure after a single dose of 2.5 mg. Patel et al performed a retrospective chart review of 48 residents of an assisted living dementia unit who had AD and anorexia (28). Following treatment with dronabinol 2.5 mg twice daily, agitation improved in 65%. No clinically significant AEs were attributed to dronabinol treatment. Walther et al (29) reported decreased nocturnal motor activity and reduced agitation in 6 participants with dementia in an open-label trial of dronabinol 2.5 mg daily with no AEs attributed to drug exposure. Forester and colleagues published a case series of 40 inpatients at McLean Hospital with Agit-AD of advanced severity treated for 7 days with dronabinol (mean dose 7 mg daily) adjunctive to other psychotropics (30). Pittsburgh Agitation Scale (PAS) scores decreased from a mean (SD) of 9.68 (3.91) to 5.25 (4.17) ($p<0.0001$), for an effect size of 1.09. Similar decreases were seen in PAS subscales including aberrant vocalization, motor agitation, aggressiveness, and resisting care. Adverse events were no more than mild in severity and dronabinol was well tolerated. At Johns Hopkins, Dr. Rosenberg had similarly positive initial clinical results on 11 inpatients with Agit-AD. However, a recent null trial from the Netherlands co-authored by Dr. Rosenberg suggests that dosing greater than 4.5 mg daily may be required for therapeutic efficacy (31). In laboratory studies with healthy adults, Dr. Vandrey, observed that oral cannabis containing 10 mg THC produced positive drug effects in the absence of cognitive impairment or spontaneously reported adverse events (AEs). These encouraging preliminary results support a proof-of-concept RCT of dronabinol for Agit-AD. Because a 4.5 mg/day dose was insufficient in a prior study, and 10 mg/day of THC appears to acutely maximize positive effects in healthy adults compared with 25 and 50mg, 10 mg daily is a good target dose for both tolerance and efficacy in frail elderly adults.

There is a great need for better interventions that target Agit-AD, a major source of patient disability as well as caregiver burden and stress, particularly in the case of moderate to severe agitation. This pilot trial could open the door to "repurposing" dronabinol as a novel and safe treatment for Agit-AD with significant public health impact.

2. Specific Aims:

We propose THC-AD: a three-week placebo-controlled, double-blind, randomized clinical trial of dronabinol (10 mg QD) in 80 patients with severe Agit-AD. Concomitant medications will be limited to currently used antipsychotics, antidepressants, benzodiazepines, as well as anticonvulsant therapy when not used for seizure disorder, with lorazepam 0.75 QD total daily allowed as rescue medication, and can be administered orally or intramuscularly. Additionally, these four categories of currently used concomitant medications are permitted to be used with PRN trazodone in doses up to 100 mg total daily dose for agitation and insomnia.

AIM 1: To compare the efficacy of three weeks of dronabinol adjunctive treatment to placebo in 80 patients with severe Agit-AD.
Hypothesis 1: Compared to placebo, dronabinol treatment will be associated with a greater reduction in symptoms of agitation as measured by co-primary outcomes of a) PAS b) NPI-C Agitation, Aggression, and the sum of Agitation and Aggression. The Cohen-Mansfield Agitation Inventory will be a secondary agitation outcome. Psychosocial function, cognition, and sleep will be assessed for potential benefit.

AIM 2: To compare the safety of three weeks of dronabinol adjunctive treatment to placebo in 80 patients with severe Agit-AD.
Hypothesis 2: Dronabinol treatment will be well tolerated with (AEs) not significantly different than placebo, including incident delirium as measured by the Confusion Assessment Method (CAM).

Outcomes:

The primary objective of this proposal is to assess dronabinol as a treatment for moderate to severe agitation in AD patients. The Pittsburgh Agitation Scale (PAS) includes the important elements of other agitation measures in a relatively short instrument developed for clinical and research settings. Based on our preliminary data demonstrating significant declines in PAS total and subscales, we have chosen the PAS to serve as one of two primary outcome measures in addition to the Neuropsychiatric Inventory, Clinician Version (NPI-C), an updated version of the original Neuropsychiatric Inventory which is the most widely used measure for Agit-AD. The Cohen-Mansfield Agitation Inventory (CMAI), a longer instrument providing a rich description of detailed agitation symptoms, will serve as a secondary outcome measure, along with measures of global function (CGI-C), sleep, cognition (MMSE and SIB-8), subjective and observer-rated drug effects, and adverse events.

3. Participant Selection:

We plan to screen approximately 160 patients ages 60-95 with a clinical diagnosis of Alzheimer's Dementia currently experiencing severe agitation symptoms. We estimate a screen failure rate of 50% for a total of 80 participants randomized. Enrolled participants who meet all inclusion and exclusion criteria

during the screening visit will proceed to the baseline visit as outlined below. We have included more information about recruitment strategies below.

Inclusion Criteria:

1) Diagnosis of Dementia due to AD (by most recent criteria from McKhann et al (32))
2) Presence of Agit-AD as defined by the provisional criteria from the International Psychogeriatric Association (IPA) (10). The definition requires the presence of cognitive impairment, evidence of emotional distress, one of three observable types of behavior (excessive motor activity, verbal aggression, physical aggression), requires that the behavior cause excess disability, and notes that the behaviors cannot be solely attributable to another disorder such as psychiatric illness, medical illness, or effects of substance use.
3) Clinically significant severity of agitation defined by NPI-C Agitation or NPI-C Aggression ≥ 4. This cutoff has been widely used in Agit-AD trials as evidence of clinically significant agitation, for example in CitAD (19,33).
4) Able to give informed consent, or deemed to lack such capacity by clinical team and legally authorized representative consents. We anticipate that most participants will lack capacity to consent and surrogate consent will be obtained in accordance with local state law and hospital guidelines.
5) Must be fluent in English and/or Spanish (includes reading, writing, and speech)
6) Must be admitted to clinical sites associated with McLean Hospital, Johns Hopkins University, and Miami Jewish Health Services as an inpatient/long term care resident during the study duration (3 weeks) OR be able to travel to these locations to enroll as an outpatient.
7) Must be 60-95 years old
8) Must begin enrollment in study within one week of being determined eligible

Exclusion Criteria:

1) Serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic or hematologic disease, which might confound assessment of safety outcomes.
2) Seizure disorder
3) Baseline delirium as determined by Confusion Assessment Method (CAM) (34) and DSM-5 criteria (35)
4) Current use of lithium
5) Inability to swallow a pill

Delirium:

Delirium is a syndrome of transient cognitive and behavioral change caused by a medical illness or medication. Delirium is an important confound for studies of Agit-AD, as delirium is very common in dementia with an estimated lifetime prevalence of 56% (36) and dementia is the strongest risk factor for post-operative delirium (37). It would be poor medical practice to misdiagnose delirium as Agit-AD; the

proper treatment for delirium is to address the underlying medical etiology. We have four interventions to address this issue. As part of routine clinical care, participants will receive thorough medical evaluation and management. This will include physical exam, laboratory tests as appropriate, and management of medications. Given the large range of potential medical conditions that one might encounter, it is not possible to specify these interventions in advance; instead, we specify that participants will be stabilized medically (as judged by the internist or geriatrician) prior to randomization. Second, we will exclude patients diagnosed at baseline as meeting criteria for delirium using both a structured instrument (CAM) and clinical diagnostic criteria (DSM 5). Third, we will monitor incident delirium as a safety outcome using the CAM. Lastly, we will exclude participants with delirium at baseline, because the approach to agitation in these participants is fundamentally different and requires addressing causes of delirium itself.

Concomitant medications and rescue medication:

Participants may enter THC-AD taking antidepressants, antipsychotics, benzodiazepines, as well as anticonvulsant therapy when not used for seizure disorder. The dosages of concomitant medication will be maintained unchanged through the 3-week RCT unless dose adjustment is required for safety reasons. Lithium will not be allowed. Lorazepam (up to 0.75 mg QD; 0.25 mg TID) to be administered orally or intramuscularly will be allowed as "rescue medication" for uncontrollable agitation. A similar dose of lorazepam (0.25 mg BID) has been used in prior trials (CitAD) without creating undue bias in interpretation of outcomes (19). We have increased the dose to 0.25 mg TID in order to safely care for severely agitated participants. PRN trazodone in doses up to 100 mg total daily dose will be allowed for agitation and insomnia.

We propose to assess the effect of dronabinol on agitation in participants with AD. This is a population with high behavioral acuity and severely impaired cognition, as evidenced in our preliminary data. Given this acuity, it is neither safe nor ethical to impose a period of time to stabilize on current psychotropic medications, which might make for a more rigorous trial design and longer study duration. Mandating that patients with agitation in AD delay further changes in treatment is clinically unacceptable at the study site facilities. We elected to balance concomitant medications (antidepressants, antipsychotics, benzodiazepines, as well as anticonvulsants) in the two treatment groups prior to randomization using the process of "minimization" (38). This method allows for balancing important covariates between groups in relatively small samples. While minimization requires altering the 1:1 ratio of randomization to maintain balance in covariates, treatment assignment is still randomized and study staff is blinded to assignment. The alterations in the randomization ratio are usually small and we have used this method in several trials without any evidence of unblinding or bias.

Study screen fails:

Participants will be deemed Screen Failures if they fail to meet the inclusion criteria and/or meet any exclusionary criteria as outlined above. Participants may also be deemed Screen Failures if, during the course of the study, study staff learn that participants have misinformed study staff about the inclusion/exclusion criteria and, therefore, no longer meet study selection criteria.

All participants will complete the pre-screening and screening process detailed below. No participants will be excluded on the basis of race, ethnicity or sexual orientation.

Participants will be recruited at clinical sites associated with McLean Hospital, Johns Hopkins University, and Miami Jewish Health Services. Referrals will come from physicians on these units following standard IRB procedures and maintaining confidentiality per HIPAA standards. Specifically, referring physicians will obtain consent from participants or legally authorized representatives (i.e. family with power of attorney or who serve as the patient's health care proxy) to make the referral. Then participants and/or families will be approached by research staff per standard IRB-approved procedures.

4. Participant Enrollment:

At the informed consent/screening visit, a member of the study staff will go through the informed consent form with the participants, and if appropriate, delegates. The participants and/or legal authorized representative will be encouraged to ask any questions they may have regarding study related procedures before the consent form is signed. Study staff will provide adequate time for the potential participant to consider participation in the study. Study staff will continue to emphasize that participation is voluntary and may be stopped at any time after signing consent without affecting their ability to receive treatment at McLean Hospital, Johns Hopkins Hospital, Miami Jewish Health, or any other institute. Potential participants who decide to participate in the study will document their consent by signing and dating the consent. All consents will be obtained by trained study clinicians.

Before participants sign the consent form, an independent clinician will meet with the participants to assess their capacity to make informed decisions about participating in this study and complete the competency/capacity evaluation form. In the case the participant is deemed unable to give consent for the study, a legal representative may consent on their behalf.

While it is customary to include an assent signed by the participant when the participant lacks capacity to consent, in this study we will make that optional because many participants will be too impaired to give meaningful assent; i.e., they can "sign on the line" but their language skills are too impaired to meaningfully assess their comprehension, even to the limited degree required for assent. We will adhere to the crucial ethical principle that research procedures cannot and will not be forced on any participant, and point out that study drug must be swallowed and cannot be administered to an unwilling participant.

Once enrolled, participants will receive a copy of their signed consent form. Receipt of the signed consent form will be documented on the Documentation of Informed Consent Form. All participants are assigned an identification number, according to the chronological order of consent date, which will be used in place of their full name on research study documents. Copies of the informed consent form will be placed in the participant's medical record (at McLean, if applicable) with the participant's permission.

At McLean, participants will receive the "Partners Healthcare Notice for Use and Sharing of Protected Health Information" packet, and will be required to sign the "Acknowledgement of Receipt of Privacy Notice" form. Participants will be reminded that they can ask questions at any time and that the study is completely voluntary. Once consent is received, participants will begin the study assessment.

At Johns Hopkins and Miami Jewish Health, IRB-approved procedures for informing participants and their legally authorized representatives of their right to confidentiality of health care information will be

followed. At Johns Hopkins and Miami Jewish Health, the custom is to include this language in the informed consent.

Randomization and blinding:

The investigators will be blind to treatment assignment. The Research Pharmacy will prepare blind medication using opaque capsules and randomly assign eligible participants to dronabinol vs. placebo treatment. We will use minimization to ensure that treatment groups are balanced with respect to use of antidepressant and antipsychotics. This method is preferred over stratification for trials of small sample size (38). The goal is have a ratio of drug:placebo close to 1:1 but adjust over time to achieve balance of antidepressant and antipsychotic use between the dronabinol and placebo groups. To address concerns that future or past randomizations could be predicted based on knowledge of treatment assignment of any one participant (relevant to unblinding at the end of the study for ethical reasons), we will use dynamic, non-deterministic probabilities of treatment assignments (39). User-friendly software to perform this type of minimization has already been developed and used by our research group in several R01-supported clinical trials including "Pilot Trial of Carvedilol in AD" and "Venlafaxine for depression in AD". Note that although the odds of assignment to treatment group may vary across the course of the study, treatment assignment still remains a randomized process and the investigators remain blind to treatment assignment. The Research Pharmacy will keep treatment assignment confidential but have access to treatment assignment available on a 24-hour basis. In the event of medical emergency where knowledge of treatment assignment is essential to providing safe patient care, the Research Pharmacy will inform treating physicians of the treatment assignment. The investigators will be kept blind to treatment assignment except in extreme cases. In the event of unmasking, the Research Pharmacist will make a report to the DSMB.

Methods for maintaining blinded rating of primary outcomes Frail elderly demented patients are notoriously prone to AEs including mood, attention, and subjective effects, and dronabinol is no exception to these concerns. Additionally, the subjective effects may in fact be central to therapeutic benefit. But observation of these effects could lead to inadvertent unmasking of treatment assignment and thus to bias in assessing outcomes. To minimize these issues, we have separated members of the study team rating primary outcomes from those rating AEs. Although all members of the team are blinded to treatment assignment, this minimizes the possibility that raters of primary outcomes will guess or suspect treatment assignment based on AEs, and therefore minimizes the possibility that the rating of primary outcomes will be biased by knowledge of AEs. This is a standard procedure used widely in industry-sponsored AD trials.

Study drug titration schedule:

Study drug will be supplied as capsules containing dronabinol or inert filler (for placebo). Study medication will be administered at 8 a.m. and 2 p.m. Capsules of dronabinol will contain 2.5 mg per dose (5mg QD) during Week 1, then increase to 5 mg per dose (10mg QD) for Weeks 2 and 3. Commercial dronabinol will be overencapsulated and topped off with inert filler to preserve the blind.

The study physicians will remain blinded to treatment assignment. However, if the study physicians opine that the study drug has led to adverse events, the study physicians have the option of reducing the dose of study drug at his/her discretion.

Rationale for dosing:

The recently published results of van den Elsen et al (31) reporting null effect of 1.5mg THC TID (4.5mg QD) suggest that if THC is to be effective for Agit-AD, this dose is too low. We observed benefit in our observational data with twice daily dosing for a mean total of 7mg QD, but the retrospective, uncontrolled study design did not allow a fine-grained look at dose effectiveness. Our preliminary data in younger adults suggests that an acute dose of 10 mg produces mild to moderate positive subjective effects with few adverse effects whereas higher doses do not increase positive subjective effects and are associated with cognitive impairment and mild-moderate AEs. Because our target population is frail and likely to be more sensitive to drug effects, we believe that a targeted 10 mg (5mg BID) daily dose will to maximize both efficacy and maintenance of safety. The half-life of dronabinol is ~ 4 hours. Dr. Ryan Vandrey is a consultant on the study at Johns Hopkins who specializes in pharmacologic research on controlled substances including THC. Although Dr. Vandrey's work in younger persons demonstrates subjective effects last 6-8 hours total; we propose to dose 6 hours apart to maximize daytime coverage for agitation, with dosing at 8 a.m. and 2 p.m. The morning dose is standardly used in our clinical practice; the afternoon dose is timed to target late-afternoon/early evening agitation, a very common cycle in Agit-AD (often inappropriately termed "sundowning"). Kevin Hill M.D. will also serve as a consultant on the study. Dr. Hill is a national expert on marijuana treatment and policy.

Outpatient Enrollments and Remote Assessments:

Participants who enroll as outpatients will be required to attend a portion of each visit in-person. Due to the COVID-19 pandemic, we will minimize physical interaction between participants and study team members by reducing the number of assessments that are completed in-person. In-person visits will include the following precautions: a telephone screening prior to the visit to assess possible COVID-19 symptoms, minimizing the number of staff members and caregivers involved, wearing personal protective equipment, maintaining physical distance, and thorough cleaning of all clinical spaces and instruments used during the visit. Assessments that do not require in-person interaction will be completed remotely in order to decrease the length of in-person visits and to enhance safety for all involved, including remote consent (see Table 1 below). Caregivers will be provided instructions on how to complete the remote assessments with study clinicians through a HIPAA compliant telemedicine software at a mutually agreed upon schedule. The study team will provide a packet with all necessary information for remote assessments during the Baseline visit. This packet will also include the DICE approach (Describe Investigate Create Evaluate) to educate caregivers with techniques to help manage behavioral symptoms of AD. DICE is an algorithmic, evidence-based approach to NPS that includes the following four steps: *Describe* the behavior to derive an accurate characterization and the context of the emergent NPS; *Investigate* possible underlying causes of the NPS; *Create* and implement a treatment plan for the behavior; *Evaluate* what parts of the treatment and plan were effective (61).

During remote assessments, caregivers will provide information to study clinicians as requested and allow them to interact with participants via video. The study team will complete all assessments shown below in Table 1. The contact format will remain the same for each subject (either in-person or remote for each visit during the 3 week enrollment duration). Caregivers will receive study medication, a schedule for medication administration, and a medication log during in-person outpatient visits. For outpatient participants, study staff will also perform a pill count at weeks 1-3 visits. Study clinicians will continue to prescribe rescue medications if needed, carefully monitor drug effects, and provide clinical referral or

schedule additional visits if AEs develop. Study clinicians will provide their contact information and will be in frequent communication with caregivers and participants throughout the enrollment duration. Caregivers will be well-informed of the possible side effects of dronabinol and will promptly inform study clinicians of all observations.

Inpatient Enrollments and Remote Assessments:

As described in the above section on remote assessments for outpatients, research team members will also have the option to remotely interview healthcare providers for inpatient enrollments. For both outpatient and inpatient enrollments, study clinicians will have the option to remotely interview subjects and their caregivers to discuss the criteria for study enrollment, review the risks and benefits, determine capacity, and complete consent. Interviews will be completed through a HIPAA compliant telemedicine software. Only the contact format will change to remote, but the assessment forms will remain the same (remote assessments will be identical to in-patient assessments). The contact format will remain the same for each subject (either in-person or remote for each visit during the 3 week enrollment duration).

Table 1. Outpatient Study Procedures by Visit

Procedure	Screening	Baseline	Week 1	Week 2	Week 3
Informed Consent Process	X				
Review of inclusion/exclusion criteria	X				
Demographics	X				
Medical History	X				
Other Medications	X				
Randomization		X			
Study medication dispensing		X			
Coronavirus Impact Scale (CIS)		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 (CMAI)		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
Confusion Assessment Method (CAM)		X	X	X	X
Sleep Assessment (NPI-C Sleep Subscale)		X	X	X	X
Cognition					
SIB-8		X			X
Mini Mental State Exam (MMSE)		X			X
Drug Effect					

Drug Effect Questionnaire (DEQ)		X	X	X	X
Medication Side-Effects Questionnaire		X	X	X	X
Safety and AE monitoring					
Physical Exam		X			
Neurological Exam		X			
Vital Signs		X	X	X	X
General Medical Health Rating (GMHR)	X				
Adverse Event Monitoring		X	X	X	X
ECG		X			X
Blood draw (DNA, Biomarker, CBC, CMP, TSH)		X			X

*Only done after all other study procedures are complete.

Outpatient Enrollment – Procedures Color Legend:
Completed in-person
Completed remotely via HIPAA compliant video software
Completed via optional location (in-person or remote)

Unmasking:

Every effort will be made to maintain the masked nature of the trial while taking precautions to optimize participant safety. Unmasking of treatment assignment before 3 weeks ("emergency unmasking") will be limited to medical situations in which withholding knowledge of the identity of the drug will lead to unreasonable danger or suffering, and will not be necessary for routine management of potential side effects. The Research Pharmacy will have 24-hour access to treatment unmasking information. In an emergency situation, the study physician may elect to unmask a participant's treatment assignment. All participants will undergo treatment unmasking at the endpoint of the study. This will either be at the Week 3 visit, or earlier if study treatment is discontinued prior to the third week. Participants and their referring physicians will be informed of treatment assignment after unmasking.

5. Participant Procedures:

Following the informed consent process, each participant will complete assessments conducted by the study coordinator and the principal investigator or delegated study staff member. The specific assessments conducted are detailed below. The participant's participation will be comprised of 4 visits spanning their 3-week study enrollment. The study procedures per visit are outlined in Table 2.

- **Coronavirus Impact Scale (CIS)**: The CIS is a short, 12-item scale that rates the influence of the Coronavirus (COVID-19) pandemic on multiple health factors, including employment, access to healthcare, and stress. The CIS was developed by Joel Stoddard, MD MAS, and Joan Kaufman, Ph.D.

Clinical Assessments

- **Pittsburgh Agitation Scale (PAS)** (40) (Co-primary outcome): The PAS was developed for both

clinical and research settings to monitor symptoms of agitation that may fluctuate during the course of a day or week and to assess the response to therapeutic interventions. The PAS rates the severity of agitation in four behavioral domains: Aberrant Vocalization, Motor Agitation, Aggressiveness, and Resisting Care, on a scale ranging from 0 to 4. Anchor points guide the rater to assign the highest possible score within each behavior group so that the score reflects the most aberrant behavior during a period of observation. The PAS takes less than 1 minute to complete. Reliability and validity were assessed in an acute-care psychogeriatric unit and a chronic-care nursing facility. The intra-class correlation for four nurses using the PAS during their work on the inpatient unit was +0.82 for the PAS Total Score.

- **Neuropsychiatric Inventory, Clinician Version (NPI-C)** (41) (Co-Primary Outcome)The NPI-C is an improved version of the Neuropsychiatric Inventory (NPI) (42) that has been expanded to have separate subscales for "Agitation" and "Aggression". We will use clinically significant NPI-C Agitation or Aggression as entry criteria for the study and as co-primary outcomes. There is a training DVD available for the NPI-C. The validation study (41) not only reported good inter-rater reliability but better convergent validity than the NPI with other agitation instruments such as the Cohen-Mansfield Agitation Inventory (CMAI). We propose to use NPI-C Agitation, Aggression, and the sum of Agitation and Aggression as co-primary outcomes.
- **Sleep assessment (NPI-C Sleep Subscale):** Sleep is an important outcome in on its own and additionally may be associated with Agit-AD. Sleep will be quantified by using the Sleep Disorders subdomain of the NPI-C. The NPI-C collects information on eight domains of sleep quality and behavior. Information is collected on frequency and severity of sleep problems that patients commonly experience. We will use the NPI-C Sleep Disorders subdomain score as a secondary outcome.
- **Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL):** a 27-item instrument assessing participant's ability to perform activities of daily living (ADLs) (43). THC-AD staff will assess the ADCS-ADL by chart review and, where necessary, interview clinical staff who interact daily with the participant. The ADCS-ADL has been used to assess ADLs as an outcome measure in clinical trials targeting moderate-to-severe dementia (44)
- **Cohen-Mansfield Agitation Inventory (CMAI)** (45,46) (Secondary Outcome) CMAI is one of the most widely used agitation indicators for dementia-related clinical trials. We will use the 14-item CMAI short form, which rates 14 behaviors associated with agitation according to frequency from 1 'never' to 7 'several times an hour'. It was developed by directly observing behavioral disturbances in dementia patients and examines several agitated behaviors including verbal and physical agitation and aggression. Most dementia agitation trials have included CMAI, including CitAD.
- **Delirium (Confusion Assessment Method, CAM:** {Inouye et al. 1990 (34)}: The CAM was developed for both clinical and research settings to accurately and quickly identify delirium in older patients. The CAM can be used to diagnose delirium using four key criteria including acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM has excellent inter-rater reliability and validity confirmed in a recent meta-analysis (47).

Cognitive assessments

The major function of assessing cognition in this proposal is as a safety evaluation, to determine whether dronabinol adversely affects cognition. Alternatively, dronabinol might improve cognition, but the

literature and preliminary data do not point in this direction. We propose to use SIB-8 (targeted for advanced dementia) and MMSE (to anchor the assessments in the larger world of dementia research).

- **SIB-8** (48): The SIB-8 is designed to assess cognition in severely impaired individuals, and consists of 8 items chosen from the original SIB (see Preliminary Data above). We have shown that the SIB-8 score has a strong correlation with SIB in the proposed patient population at Johns Hopkins, and given the short duration of administration is preferable to the full SIB.
- **Mini Mental State Exam (MMSE)** (49): The MMSE is the most widely used instrument for assessment of general cognition, and widely used in dementia research. It consists of 30 items assessing orientation, immediate recall, concentration, delayed recall, repetition, ideomotor praxis, reading, writing, and visuoconstructional ability.

Drug effect monitoring

Traditional measures of drug effect and medication side effects are often designed to be administered directly to participants. Given that THC-AD participants will have dementia and in many cases severe dementia, we propose to rate the following two questionnaires on the basis of "all evaluable data" including participant interview, chart review, and discussion with clinical staff.

- **Drug Effect Questionnaire (DEQ) (Appendix 2):** The subjective ratings of cannabis intoxication will be determined using the Drug Effect Questionnaire (DEQ). The individual items of the DEQ include ratings of drug effects (e.g. drug effect, pleasant effect, unpleasant effect) and behavioral/mood states often associated with cannabis intoxication (e.g. relaxed, paranoid, hungry/have munchies). Each item will be rated using a 100mm visual analog scale (VAS) anchored with "not at all" at one end and "extremely" at the other end. We have shown this method is sensitive to detecting dose effects of cannabis and dronabinol. There are few data reflecting the validity and reliability of the DEQ in persons with cognitive impairment, and most neuropsychiatric measures in this field require the use of an informant. Dr. Vandrey, our substance abuse specialist and co-I, has developed an informant version of the DEQ (Appendix 2). The items are similar but worded to be administered to an informant.
- **Medication Side-Effects Questionnaire:** Research staff will interview participants and clinical staff and will rate on a 4-point scale (none, mild, moderate, strong) their impression of potential side effects of dronabinol. Based on the list of potential side effects from clinical trials with dronabinol, items will include nausea, diarrhea, dry mouth, upset stomach, vomiting, vivid or abnormal dreams, anxiety, dizziness, fatigue, confusion, depersonalization, hallucination, paranoia, depression, rapid heart rate/palpitations, flushing in the face or body, tinnitus, speech difficulty, blurred vision, headache, sweating, runny nose, and coughing.

Safety and Adverse Event (AE) monitoring

All AEs occurring after randomization and during the 3-week treatment period, regardless of adherence to study treatment, will be recorded at all contacts. AEs will be assessed by using all available data to determine if new symptoms or medical events have occurred. A list of common side effects of dronabinol will be used to monitor for adverse events. At scheduled visits, participants and clinical staff/family caregivers will be interviewed about whether the participant experienced any symptoms or side effects on the list since the last visit. Adverse events, other than what is listed as common side effects, will still be recorded. If adverse events are noted, they will be rated as mild, moderate, or severe based on their clinical severity and frequency. Finally, medical transfers to outside general hospitals (McLean) or to a medical/surgical unit in the same hospital (Johns Hopkins and Miami Jewish Health) will be monitored. The PIs and designated study physicians will be responsible for monitoring the safety of participants. They will be responsible for appropriate medical care of participants during the study in connection with

study procedures. Safety assessments will include physical exams, vital signs, ECGs, monitoring of adverse events, and monitoring and maintenance of concurrent medication records. AEs will be reported to the local IRBs per local policy. Serious adverse events (SAEs) will be defined per FDA guidelines and reported in a timely manner as is standard in clinical trials (with the initial report being next business day). In addition, we will add the following DSMB-agreed upon SAEs to the SAE definition:

1) Death (already defined as an SAE per standard FDA guidelines)
2) Delirium at two consecutive weekly assessments
3) Seizures
4) Fall resulting in injury

In accordance to FDA reporting requirements, any serious adverse events (SAEs) that occur at Johns Hopkins, Miami Jewish Health, and McLean Hospital will be reported to Johns Hopkins and Dr. Paul Rosenberg, M.D., the Sponsor-Investigator. Expected SAEs include delirium, intoxication, sedation, and increased appetite. Such reporting will adhere to the following process:

1) Sponsor-Investigator will be notified of the SAE and will be given a report
2) Sponsor-Investigator will notify the FDA of the SAE and a report will be submitted to the Regulatory Project Manager (RPM)/ FDA reviewing division within 7 calendar days via telephone, fax or email
3) Following the Sponsor-Investigator's initial receipt of the SAE, any relevant observations from animal or epidemiological studies suggesting significant risk to human subjects will be reported within 15 calendar days to the FDA in a written Safety Report via MedWatch Form 3500A
4) Any relevant additional information obtained by the Sponsor-Investigator that pertains to the previously submitted Safety Report will be submitted as a Follow-up Safety Report, within 15 calendar days following the Sponsor-Investigator initially receiving the information

- Collection of vital signs
- General medical health rating (GMHR) (50): this is a valid and reliable 4-point global rating of the severity of medical co-morbidity in patients with AD that our center has used in previous AD trials (51,52)
- Adverse events monitoring: All adverse events occurring after randomization will be recorded. AEs will be assessed by using all available data to determine if new symptoms or medical events have occurred
- Observation of ECG changes
- Observation of changes in laboratory values.
- Neurological and physical Exams

Rationale for duration:

The average length of inpatient stay in our observational data was ~16 days, and to cover this time period 3 weeks should be sufficient. Additionally, in CitAD we observed that the placebo response largely reached its maximum after 3 weeks. We are proposing a trial of dronabinol for patients with Agit-AD; there are practical and ethical limitations on the duration of such a trial given available resources and the ongoing stress that families and caregivers are experiencing. If we demonstrate efficacy, there will likely be a role for dronabinol as a relatively rapidly acting agent for Agit-AD; for example, the full response to citalopram in CitAD was observed after 9 weeks (53). More rapid response should be beneficial for reducing family/caregiver stress. Since placebo response is largely complete by 3 weeks, we argue that 3 weeks will be sufficient to distinguish drug from placebo response and to address whether dronabinol achieves a rapid response in that timeframe.

Non-pharmacologic strategies for addressing Agit-AD:

All participants will be provided with evidenced-based standard treatment for individuals with dementia complicated by agitation. This is an individualized approach and includes a combination of the following elements: 1) evaluation and clinical management of all medical co-morbidities that may be associated with behavioral disturbances (e.g., infection, pain, constipation, sensory problems); 2) reduction or elimination of all medications with anticholinergic effects that may adversely impact cognitive functioning and exacerbate behavioral symptoms; 3) maximization of environmental supports and non-pharmacological treatments to reduce agitation using the DICE approach (12) including but not limited to 1:1 staffing for ADL (activities of daily living) care in quiet setting and assessing environmental antecedents to behavioral agitation; 4) permission to continue and monitor all concomitant psychotropic medications; 5) incorporation of relevant elements of the psychosocial intervention used to address agitation in CitAD (33).

Exploratory biomarkers:

1) We propose to collect DNA specimens at baseline to explore the possibility that cannabinoid receptor polymorphisms may affect response to dronabinol. There has been preliminary work on the association between CB1 receptor polymorphisms and addiction (54) but none to date in AD.

While quantification of cannabinoid receptor density with neurochemical imaging could be very enlightening as to potential mechanism, it is neither practical nor ethically advisable to perform such imaging in advanced dementia and we do not propose it for this trial.

Inflammatory Markers (Cytokines):

We propose that participants will have blood drawn (approximately 42mL) to collect serum samples at Baseline and Week 3 to assay pro-inflammatory cytokines Interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α, and Interleukin-6 (IL-6) among others. The aforementioned serum samples will be collected to examine the association of peripheral markers of inflammation with agitation and response to dronabinol. Serum will be separated within ½ hour following the draw. The sample will stored at -80 degrees Celsius until ready ice until ready to ship. The assays will be performed at an outside laboratory.

Table 2. Study Procedures by Visit

Procedure	Screening	Baseline	Week 1	Week 2	Week 3
Informed Consent Process	X				
Review of inclusion/exclusion criteria	X				
Demographics	X				
Medical History	X				
Other Medications	X				
Randomization		X			
Study medication dispensing		X	X	X	
Coronavirus Impact Scale (CIS)		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 (CMAI)		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
Confusion Assessment Method (CAM)		X	X	X	X
Sleep Assessment (NPI-C Sleep Subscale)		X	X	X	X
Cognition					
SIB-8		X			X
Mini Mental State Exam (MMSE)		X			X
Drug Effect					
Drug Effect Questionnaire (DEQ)		X	X	X	X
Medication Side-Effects Questionnaire		X	X	X	X
Safety and AE monitoring					
Physical Exam	X				
Neurological Exam	X				
Vital Signs		X	X	X	X
General Medical Health Rating (GMHR)	X				
Adverse Event Monitoring		X	X	X	X
ECG		X			X
Blood draw (DNA, Biomarker, CBC, CMP, TSH)		X			X

*Only done after all other study procedures are complete

*6. **Biostatistical Analysis:***

All analyses will be conducted using STATA (55) and R (56) under the supervision of the study statistician (Dr. Leoutsakos). Descriptive analyses will be conducted and measures checked for outliers and to ensure that distributional assumptions of the planned analyses are appropriate. If not, analogous non-parametric methods will be used. Analyses will be intent-to-treat. We expect minimal missing data, but if there is a significant amount of missing data, multiple imputation may be used if appropriate (57). To investigate sensitivity to missing values, those with and without missing values will be compared by background covariates. Tests will be two-sided and p-values <0.05 will be considered significant. Multiple test corrections will be applied as appropriate. All primary analyses will be adjusted for site as well as the variables balanced through minimization (use of antidepressants and use of antipsychotics). To account for the inclusion of multiple sites, we will include site as a covariate, with individuals being seen on an outpatient (largely remote) basis being treated as its own site. Secondarily, we will fit models with site, site x time, and site x treatment x time to determine if there are any effects of site on treatment effect over time. These analyses must be secondary as the study was not powered to detect these 3 way interactions. Importantly, no participants were stopped during their participation and all participants will have the same mode of assessment (either in-person or remote) throughout.

Aim 1: Efficacy will be assessed by fitting a longitudinal linear model with the co-primary outcomes (PAS and NPI-C Agitation/Aggression/Sum of Agitation and Aggression) and with time, treatment assignment and interaction between time and treatment. The latter term 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. Within-person correlations will be handled via the method of generalized estimating equations (58).

Aim 2: We will model risk of a severe adverse event as a function of treatment assignment using logistic regression, and counts of total adverse events using ordinal logistic regression or poisson regression as appropriate. We will also scrutinize counts of each specific type of AE as a function of treatment assignment to determine if there are specific adverse events which we should power ourselves to detect in future larger-scale trials. Special attention will be paid to new-onset delirium, seizures, and arrhythmias. Additionally we will specifically look at the effect of dronabinol on cognition using the SIB-8, and a regression model analogous to that in Aim 1. We will stratify adverse events by site and assess whether rates of particular AEs vary by site. In particular, we will assess whether outpatients differ in their rates and types of AEs (either favorably, due to being less acute, or unfavorably, due to a less controlled environment where falls might be more likely, for example).

Secondary Analyses: We will model change in additional outcomes (e.g., CMAI, MMSE, sleep, DEQ) using models analogous to that of Aim 1. We will also look at predictors of dronabinol response, including cannabinoid receptor polymorphisms and other patient characteristics. We will also model change in IL1β, TNF α, and IL6 as a function of treatment assignment. All secondary analyses will be conducted with site as a covariate, and additional analyses which include site x treatment and site x treatment by time will be performed.

Sample size and Power analysis

We observed a large effect in our observational study that used PAS as outcome. PAS is one of the co-primary outcomes and we will estimate power to detect change in PAS. There are no pilot data to estimate power to detect change in NPI-C which has not been used in prior trials of dronabinol. The PAS declined in our observational study from 9.68 (3.91) pre-treatment to 5.25 (4.17) post-treatment for a treatment effect of 1.1 and 45% reduction in PAS score.

We propose to use a more conservative estimate of 30% reduction in PAS score and calculated statistical power using the formulae of Jung and Ahn (59). A 30% reduction translates to decreasing from 9.68 PAS points to 7.26 points after 3 weeks, which means a slope of -0.81 points/week. This translates to an effect size of 0.206. It is essential to account for missing data including those from dropouts. Assuming first a missing data pattern that increases monotonically to 15% by week 3, with N= 80, a within-person correlation of 0.5 and an exchangeable correlation structure, we will have 80% power to detect a treatment effect of size 0.22, which translates to a decrease in PAS from 9.68 to 7.1 over 3 weeks; this is a 26.7% decrease. Assuming next a missing data pattern that increases monotonically to 30% by week 3, then with 80 people and a within-person correlation of 0.5 and an exchangeable correlation structure, we would have 80% power to detect a treatment effect of size 0.24, which translates to a decrease in PAS from 9.68 to 6.87 over 3 weeks; this is a 29.1% decrease. Thus, THC-AD is well-powered to detect a clinically plausible and conservatively estimate decrease in PAS which is a co-primary outcome.

We repeated the above power analysis assuming a sample size of 60 in the event that we do not meet our original recruitment goals. With a missing data pattern that increases monotonically to 15% by week 3, with N=60, a within-person correlation of .5 and an exchangeable correlation structure we will have 80% power to detect a treatment effect of size .25, which translates to a decrease in PAS from 9.68 to 6.75 over 3 weeks; this is a 30.3% decrease. With a missing data pattern that increases monotonically to 30% by week 3, and identical conditions otherwise, we would have 80% power to detect a treatment effect of size .27, which translates to a decrease in PAS from 9.68 to 6.51 over 3 weeks; this is a 33 % decrease.

*7. **Risks and Discomforts:***

Study medication side effects:

Based on the list of potential side effects from clinical trials with dronabinol, items will include nausea, diarrhea, dry mouth, upset stomach, vomiting, vivid or abnormal dreams, anxiety, dizziness, fatigue, confusion, depersonalization, hallucination, paranoia, depression, rapid heart rate/palpitations, flushing in the face or body, tinnitus, speech difficulty, blurred vision, headache, sweating, runny nose, and coughing.

Potential substance abuse:

Dronabinol is a Schedule III substance indicating moderate abuse liability relative to other drugs. Given the low doses to be administered, close monitoring of participants and medication administration, and relatively short duration of exposure proposed in the present study, we believe the risk of participants misusing the study medication or becoming dependent on dronabinol to be very low. Outcomes obtained from the DEQ patient-based and informant-based questionnaires will provide outcomes relevant to examining the abuse liability of the study doses in this population (e.g. subjective ratings of pleasant drug effect) that will be valuable for future studies. We will also evaluate whether participants or families of non-responders to dronabinol request to continue medication after the trial is completed.

Risk of Treatment Limitations:

It is possible that enrolling in this study will limit administration of medications typically used to treat agitation in AD. For example, this study allows participants to receive lorazepam up to 0.75 mg per day as a rescue medication, but some patients might have received higher dosages if they were not enrolled in this study. The study clinician will monitor these circumstances on a case-by-case basis and determine the best course of action in his professional judgement. By enrolling in this study, participants acknowledge this possible limitation of treatment.

Risks associated with blood draw:

When blood is drawn, some discomfort may be associated with it at the time of the blood draw. Bruising and/or bleeding at the needle site may occur. Occasionally a person feels faint. Rarely, an infection may develop. If an infection does occur, it can be treated. All McLean, Miami Jewish Health, and Johns Hopkins employees who may draw blood for this protocol will be phlebotomy trained and certified.

Risks associated with clinical assessment/rating scales:

Due to the nature of the clinical assessment and rating scales, participants may become distressed or frustrated when answering questions and/or recalling periods of their lives or their current mood state. In addition, some participants may feel fatigued while completing study assessments, such as the neuropsychological testing, due to the length of administration. Study staff will provide opportunities for participants to take breaks or, if requested, reschedule testing for another time.

During study participation, study staff may ask participants to answer sensitive and personal questions (such as previous substance use and psychiatric history) in order to evaluate study eligibility, appropriateness, and monitor for potential safety concerns. Although it is preferred that participants answer all questions, they have a right to not answer any questions.

Risks associated with protection of participant confidentiality:

Protected health information will be collected as part of this protocol and study staff take serious measure to preserve participant privacy. However, it is possible that confidentiality may be breached, despite the precautions.

Confidentiality will be maintained with the assignment of an identification number or code, which will be used in place of participant names in all data analyses and reports. All documents that contain confidential information that cannot be replaced with an identification code (such as a signature) will be stored in locked filing cabinets and offices, separately from the research scales, as an additional protection against potential loss of confidentiality. The principal investigator, the research staff, and the study collaborators may have access to the data that is collected, in addition to the parties listed on the ICF (i.e., federal or state agencies that oversee research, the McLean IRB, the Johns Hopkins IRB, the Miami Jewish Health IRB etc.).

Stored confidential information on the computer will be password protected. Keys showing the assignment of identification numbers to participant names will be stored with participant files in a room under lock and key. All of the data that is collected will be kept for a minimum of seven years once the study has been completed per federal guidelines. After the seven years, the research information is

destroyed appropriately. We will cease to use identifiable data collected for this protocol once the protocol has been closed out with the McLean, Miami Jewish Health, and Johns Hopkins IRBs.

All participants or legally authorized representatives will be required to give informed consent and must understand all procedures prior to the participant's participation in the study A member of the research staff will explain the consenting procedure and be available for any questions that arise from the consent form.

Participants are informed of their confidentiality and privacy rights in the informed consent form and receive information about the Privacy Rule, Partners Privacy/HIPAA policies at screening. To ensure that participants' rights and safety are protected during the conduct of this research study, participants consent to the inspection of their medical records by specifically authorized monitors. Such monitoring may be performed by the Human Research Protection Program of McLean Hospital, Miami Jewish Health, and Johns Hopkins, or by the FDA or other involved federal agency.

Participants are informed that all the information obtained in this study will be used for research investigational purposes only. Name of participants will never be publicly disclosed at any time. Participants will not be identifiable in any publication that may arise from this research.

Participants will receive a copy of the consent document to keep as well as a copy of the "Partners Healthcare Notice for Use and Sharing of Protected Health Information" for McLean Hospital, and the "Authorization for Release of Health Information" for Johns Hopkins or Miami Jewish Health. Participants will be informed that this research will be conducted and administered in compliance with all state and federal laws.

Release of information to the participants:

Participants may request that clinically-relevant information collected through the research study be shared with others. In order for staff to comply with such a request, participants must request the sharing of research information by completing an "Authorization for Release of Medical Records" form for McLean Hospital and an "Authorization for Release of Health Information" form for Johns Hopkins or Miami Jewish Health. Information most typically shared from the research study includes blood laboratory results, physical examination, and vital signs. Likewise, participants must also complete this form to give staff permission to obtain information, on behalf of the participant, from outside sources, such as the participant's psychiatrist.

Unknown risks and discomforts:

In addition to the risks described above, study procedures may have other risks that are not yet recognized or delayed.

8. Potential Benefits:

Participants may benefit from knowing that the results of this study could improve future care of patients with Alzheimer's disease by contributing to knowledge in the field and potentially providing benefits to treatment and management as a result of this increased understanding. This could result in improving the quality of life, safety, and possibly daily functioning of patients with Alzheimer's disease, which could allow for a transition to a more independent level of care.

The study medication, dronabinol, may also reduce agitation thereby improving the participants' quality of life, safety, and possibly daily functioning. This could allow for the transition to a more independent level of care.

9. Monitoring and Quality Assurance:

Potential participants are presented with information about possible risks during the consent process. The informed consent document contains all the known risks and warnings associated with participating in the research study. If any new changes in scientific knowledge alter our understanding of the condition or the proposed treatment, the consent form and the study clinician's instructions will be adjusted accordingly.

Data Safety Monitoring Board (DSMB):

THC-AD will use a three-person DSMB described in detail under "Protection of Human Subjects". This board will be constituted with one expert in dementia trials, one expert in geriatric medicine, and one biostatistician experienced with clinical trial design and management. The DSMB will meet by videoconference prior to the first randomization and every 6 months thereafter, along with the NIA program officer. The DSMB will review unblinded data supplied by the THC-AD statisticians, and will make recommendations about whether to alter study procedures based on safety considerations. The PIs of THC-AD will have the final responsibility about implementing such changes and will do so in accordance with IRB procedures, NIH policy, and full attention to the need to protect the safety and rights of research participants.

Adverse Event reporting:

All adverse events will be systematically recorded and reported to the McLean Hospital, Miami Jewish Health, and Johns Hopkins University IRBs, to the DSMB, and to the FDA via the Annual Report per 21 CFR 312.33. In the event that a participant becomes ill or injured as a direct result of participation in the research study, necessary medical care will be made available. The NIH Project Officer will be informed of any actions taken by the McLean, Miami Jewish Health, and Johns Hopkins IRBs as a result of such adverse events. All possibly related and unexpected adverse effects will be reported per current IRB guidelines. Unrelated or expected AEs will be reported at continuing review per current IRB guidelines. Serious adverse events will be followed to resolution or stabilization and reported per current reporting guidelines.

A participant may be discontinued from the study at any time as a result of adverse event, PI discretion, or participant non-compliance with protocol. All the information about participants will be treated confidentially. Overall, the principal investigator (AG) will be responsible for the execution of these protocol procedures and will monitor adverse events and participant safety throughout the study. The principal investigator will be informed of all adverse events that occur in the study.

Minimizing discomforts:

All procedures have been designed to minimize participant discomfort.
No participant will be asked to engage in research procedures not outlined in the consent form. We will follow and adhere to all guidelines as defined and outlined on the IRB websites of McLean Hospital, Miami Jewish Health, and Johns Hopkins.

Inter-rater reliability:

Prior to any data collection activities, THC-AD will have an in-person Investigator's Meeting for study initiation. Training will occur for all primary and secondary outcome measures and inter-rater reliability will be assessed for the PAS and NPI-C Agitation and Aggression domains by rating videotaped interviews and assessments. To prevent rater drift over time, this training and assessment of inter-rater reliability will be performed annually by videoconference with the goal of achieving intra-class coefficient (ICC[3,1]) of .75 or greater (60).

Blind maintenance plan:

In any drug study there is the risk that the study team will obtain data that might be interpreted as hinting at treatment assignment particularly due to observation of AEs, and that the observation of outcomes will become biased due to this awareness. This is a common issue in AD pharmaceutical industry trials. We will adopt the strategy of splitting up the members of the team who assess primary outcomes from those who assess AEs. Primary outcomes will be assessed by research assistants and/or coordinators. Outcomes that encompass subjective effects of drug exposure and/or AEs will be assessed by study physicians and/or nurses. These two teams will not exchange any information obtained and thus will be blinded to each other's findings. Combined with the fact that all study/clinical staff are blind to treatment assignment, this will ensure that observation of outcomes will remain unbiased.

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