



Regular Research Article

A Randomized Controlled Trial of the Safety and Efficacy of Dronabinol for Agitation in Alzheimer's Disease

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ABSTRACT

Importance: Agitation in Alzheimer's disease (AD) is a great source of distress for patients and caregivers and a major public health burden. Current treatments are only modestly effective and many have safety issues including mortality risk. Novel therapeutic options are needed. There is preliminary evidence for the safety and efficacy of dronabinol (tetrahydrocannabinol, THC) for agitation in AD. **Objective:** Assess the safety and efficacy of dronabinol (THC) to decrease agitation in AD. **Design:** THC-AD was a 3-week randomized parallel double-blind placebo-controlled clinical trial, conducted between 2017 and 2024. **Setting:** 5 inpatient and outpatient academic clinical research centers in the Eastern U.S. **Participants:** Volunteer sample of 75 participants meeting inclusion

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*criteria for agitation of AD (International Psychogeriatric Association Provision Criteria) with Neuropsychiatric Inventory Clinician Version Agitation or Aggression (NPI-C A/A) domains total score of 4 or greater. Major exclusion criteria included seizure disorder, delirium, and non-AD dementia. **Interventions:** 3 weeks dronabinol vs. placebo titrated up to target dose of 10 mg daily in divided twice-daily. **Main Outcomes and Measures:** Prespecified co-primary agitation outcomes were the Pittsburgh Agitation Scale (PAS) and NPI-C A/A total score. **Results:** The majority of participants were female and were taking concomitant psychotropic medications (antidepressants and antipsychotics) at baseline. Study participants were moderately agitated at baseline, were diverse in ethnic background (9% Black, 11% Hispanic/Latina/Latino), and had severe cognitive impairment evidenced by MMSE or SIB-8. 84% completed the 3-week trial. Dronabinol decreased agitation on both primary outcomes greater than placebo to a clinically relevant extent. The fitted between-arm difference in PAS decline/week was -0.74 (SE 0.3, $p = 0.015$, effect size = 0.53) and for NPI-C A/A the decline was not significant at -1.26 (SE 0.67, $p = 0.094$, effect size = 0.36). No secondary outcomes differed between treatment arms including sleep, activities of daily living, Cohen-Mansfield Agitation Inventory (CMAI), cognition, intoxication, or use of 'as-needed' lorazepam or trazodone. Dronabinol treatment was not associated with greater intoxication nor with other adverse events (AEs) except for somnolence. **Conclusions and Relevance:** Adjunctive dronabinol treatment was safe and effective for treating agitation in AD. **Clinical Trials Registration:** NCT02792257 (Am J Geriatr Psychiatry 2026; 34:167–179)*

Editorial accompaniment, please see page 180.

Highlights

- **What is the primary question addressed by this study?**

Is dronabinol (synthetic THC) a safe and effective treatment for reducing agitation in individuals with Alzheimer's disease?

- **What is the main finding of this study?**

In a 3-week randomized, placebo-controlled trial of 75 participants with moderate to severe Alzheimer's disease, dronabinol significantly reduced agitation as measured by the Pittsburgh Agitation Scale (effect size = 0.53) and showed a trend toward improvement on the NPI-C Agitation/Aggression domain. The medication was well tolerated, with somnolence as the only notable side effect and no increased risk of delirium, falls, or intoxication.

- **What is the meaning of the finding?**

These results suggest that dronabinol may be a relatively safe and effective pharmacologic option for managing agitation in Alzheimer's disease.

KEY POINTS

Questions: Is dronabinol (tetrahydrocannabinol, THC) safe and effective for treating Agitation in Alzheimer's Disease (AD)?

BACKGROUND

Alzheimer's disease (AD) is a neuropsychiatric disorder impacting cognition, functioning, and behavior, with a wide array of neuropsychiatric symptoms

(NPS). NPS are near-universal throughout the course of AD¹ and agitation is associated with increased caregiver burden^{2,3} and more rapid institutionalization.^{4,5} A consensus group convened by the International Psychogeriatric Association has defined criteria for agitation in AD, including at least 2 weeks' change from baseline and not caused by non-AD psychiatric disorders or by delirium.^{6,7} Behaviors can include excess motor behavior (i.e., pacing), verbal aggression (i.e., yelling or cursing), and/or physical aggression.

There is a consensus among clinicians that behavioral interventions such as DICE (Describe, Investigate, Create and Evaluate) should be the primary interventional strategy.^{8,9} However, many patients do not improve with behavioral interventions alone and medications are widely used to attenuate agitation in AD in these cases. In 2023, the U.S. Food and Drug Administration (FDA) approved the first medication for agitation in AD (brexpiprazole), but with a boxed warning about mortality risk common to the class of antipsychotic medications.^{10–12} Other promising drugs include the SSRI citalopram,¹³ the alpha-1 antagonist prazosin,¹⁴ NMDA antagonist combinations (dextromethorphan-quinidine¹⁵ and dextromethorphan-bupropion¹⁵), and the alpha-2 agonist dexmedetomidine.^{16,17} However, given modest efficacy and safety concerns including risk of sedation, ataxia, and mortality, new approaches are clearly needed.^{18,19}

Cannabinoids, including delta-9-tetrahydrocannabinol (THC; the primary psychoactive constituent of cannabis), are being increasingly studied as medical therapies. Endogenous CB1 cannabinoid receptors mediate the anxiolytic effects of cannabinoids.²⁰ Agitation in AD may be an exaggerated behavioral reaction to fear and anxiety, and specific brain circuits may mediate these reactions.²¹ Dronabinol is an oral pharmaceutical formulation of synthetic THC FDA approved for the treatment of HIV/AIDS-induced anorexia and chemotherapy-induced nausea and vomiting. A case series of 40 patients with AD and agitation treated with dronabinol at a mean dose of 7 mg daily reported a significant decrease in agitation measured with the Pittsburgh Agitation Scale (PAS).²² An RCT using 4.5 mg daily THC in outpatients in the Netherlands reported no benefit,²³ but the synthetic THC analog nabilone reduced agitation in AD in a Canadian nursing home cohort.⁷ Since THC offers promise for the safe and effective treatment of agitation in AD, we aimed to determine the

safety and efficacy of dronabinol for treatment of agitation in AD in a rigorous 3-week randomized, double-blind, parallel group trial.

METHODS

Study subjects were recruited from inpatient and outpatient units of Johns Hopkins Bayview Medical Center, McLean Hospital, Miami Jewish Health, Salem Hospital, and Tufts Medical Center. The trial initially recruited inpatients at Johns Hopkins and McLean Hospital but broadened inclusion to outpatients midway through the trial in response to the COVID-19 lockdown and administrative changes. All study participants or their legally authorized representatives signed written informed consent prior to study participation and procedures. Ethics approval was obtained at all participating sites.

Details of the protocol have been previously published.^{24,25} Inclusion criteria included: 1) Diagnosis of Dementia due to AD (by most recent criteria from McKhann et al.²⁶) 2) Presence of agitation in AD as defined by the provisional criteria from the International Psychogeriatric Association (IPA).⁶ The definition requires the presence of cognitive impairment, evidence of emotional distress, one of 3 observable types of behavior (excessive motor activity, verbal aggression, physical aggression), requires that the behavior cause excess disability, requires a minimum of 2 weeks' symptoms, 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 Neuropsychiatric Inventory, Clinician Version (NPI-C) Agitation or NPI-C Aggression ≥ 4 , a cutoff used in prior trials of agitation in AD;¹³ 4) age 60–95 years. Exclusion criteria included: 1) serious or unstable medical illness, 2) seizure disorder, 3) baseline delirium as determined by Confusion Assessment Method (CAM)²⁷ and DSM-5 criteria,²⁸ 4) current use of lithium, or 5) inability to swallow a pill. Psychotropic medications including antipsychotics, antidepressants, and anticonvulsants were allowed at enrollment with a target of keeping these doses stable through the 3-week trial; we chose to allow these concomitant medications to enhance the generalizability of findings. Lorazepam in doses up to 0.75 mg daily (0.25 mg 3 times daily) 'as-needed' was allowed for the

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treatment of persisting agitation, as was trazodone in doses up to 100 mg daily for sleep.

Study Drug

We chose a relatively short duration of 3 weeks to accommodate recruitment of both inpatients and outpatients with agitation in AD. The study drug was supplied as capsules containing dronabinol or inert filler (for placebo). Study medication was administered at 8 A.M. and 2 P.M. Capsules of dronabinol contained 2.5 mg per dose (5 mg daily) during Week 1, then increased to 5 mg per dose (10 mg daily) for Weeks 2 and 3. Study physicians were allowed to decrease the dose or stop the study drug altogether if deemed necessary for safe management of adverse effects (AEs).

Sample Size Determination

Statistical power was estimated using observational PAS data,²² where individuals declined from 9.68 (3.91) at pretreatment to 5.25 (4.17) post treatment; this 45% reduction corresponded to a treatment effect of 1.1. Using the formulae of Jung and Ahn,²⁹ and assuming a missing data pattern that increases monotonically to 15% by week 3, an exchangeable within-person correlation of 0.5, and no change in the placebo arm, we estimated that with 80 participants we would have 80% power to detect a 27% reduction. This would correspond to a difference in slope of -0.86 points/week or an effect size of 0.22. If instead we had missingness increase to 30% at week 3, we would have 80% power to detect a 29% reduction, which would correspond to a difference in slope of -0.94 points/week or an effect size of 0.24. We repeated those calculations with $n = 60$ and found that with 15% missingness we would have 80% power to detect a 30.3% decrease, corresponding to a difference in slope of 0.98 or an effect size of 0.25. With 30% missingness and $n = 60$ we would have 80% power to detect a 33% reduction, which would correspond to a difference in slope of 1.06 or an effect size of 0.27.

Randomization

The investigators and research teams were blinded to treatment assignments. Research pharmacists at each site over encapsulated dronabinol tablets or placebo, using inert filler to maintain identical appearance. We used 'dynamic minimization' to balance

characteristics of the treatment groups with respect to use of antidepressants and antipsychotics. This method is preferred over stratification for trials of small sample size.³⁰

Clinical Assessments (Performed at Baseline and Weeks 1, 2, and 3)

Co-primary outcomes

Pittsburgh Agitation Scale (PAS):³¹ 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 for a total range of 0–16. The PAS has been shown to have high interrater reliability.³²

Neuropsychiatric Inventory, Clinician Version (NPI-C):³³ The NPI-C expands upon the Neuropsychiatric Inventory (NPI)³⁴ to include separate subscales for "Agitation" and "Aggression" and input from the clinician's assessment of behavior. There is a scale that ranges from 0 to 3 for a total range of 0–144. We used clinically significant NPI-C Agitation or Aggression (≥ 4 on either domain) as entry criteria for the study.

Secondary Outcomes included the NPI-C Sleep Subscale, the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL),³⁵ the Cohen-Mansfield Agitation Inventory (CMAI),^{36,37} the Confusion Assessment Method (CAM) to measure delirium,²⁷ and the Clinical Global Impression-Clinician version (CGI-C) to assess overall response to treatment.³⁸

Cognitive assessments were performed at baseline and Week 3 and included the SIB-8,³⁸ designed to assess cognition in severely impaired individuals, and the Mini Mental State Exam (MMSE).³⁹

Nonpharmacologic strategies for addressing Agit-AD

We adapted a psychosocial intervention used previously in CitAD¹³ based on the DICE approach: 1) evaluation and clinical management of medical comorbidities that may be associated with behavioral disturbances (e.g., infection, pain, constipation, sensory problems); 2) reduction or elimination of medications with anticholinergic and/or sedative effects; 3) maximization of environmental supports and nonpharmacological treatments to reduce agitation using the DICE approach.³⁸

Drug effect monitoring

Drug Effect Questionnaire (DEQ) was implemented to collect observer ratings of cannabis intoxication at each study visit (baseline and weeks 1, 2, and 3). The observer was the caregiver or family member with closest knowledge of the participant's condition during that week, and they were asked to rate the participant's condition on the day of the rating.

Safety and Adverse Event (AE) Monitoring

All AEs occurring after randomization and during the 3-week treatment period, regardless of adherence to study treatment, were recorded at all contacts. Serious adverse events (SAEs) were defined per FDA guidelines and reported in a timely manner. We additionally added the following 'events of interest' to SAE reporting: 1) Delirium at 2 consecutive weekly assessments; 2) Seizures; 3) Fall resulting in injury.

Data Safety Monitoring Board (DSMB)

THC-AD used a 3-person DSMB with one expert in dementia trials, one expert in geriatric medicine, and one biostatistician experienced with clinical trial design and management. The DSMB met by videoconference prior to the first randomization and every 6 months thereafter, along with an NIA representative. The DSMB reviewed unblinded data supplied by the THC-AD statistician, and made recommendations about whether to alter study procedures based on safety considerations per NIH and local IRB policy.

Biostatistical Analyses

All analyses were conducted using STATA⁴⁰ and R⁴¹ under the supervision of the study statistician (Dr. Leoutsakos). Analyses were on an intention-to-treat basis including all participants who were randomized. To investigate sensitivity to missing values, those with and without missing values were compared by background covariates. Missing values were not imputed. Tests were two-sided and p-values <0.05 was considered significant. Multiple test corrections were applied as appropriate. All primary analyses were adjusted for site and the variables balanced through minimization (use of antidepressants and use of antipsychotics). To account for the inclusion of multiple sites, we included

site as a covariate. These analyses are considered exploratory as the study was not powered to detect these 3-way interactions. All participants were assessed either in-person at all visits (prior to March, 2020) or in-person at baseline and week 3, remotely at weeks 1 and 2 (March, 2020 and after).

Aim 1: Efficacy was 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 is the coefficient of interest and represents the mean difference in change over the 3-week period between the treated and placebo groups. Within-person correlations were handled via the method of generalized estimating equations (GEE),⁴² with inferences on model coefficients made via a Wald test assuming the test statistic follows a Z-distribution. Secondary outcomes were assessed with similar models.

Aim 2: We modeled 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 also scrutinized counts of each specific type of AE as a function of treatment assignment to determine if there were specific AEs which we should power ourselves to detect in future, larger-scale trials. Special attention was paid to new-onset delirium, seizures, falls, and arrhythmias.

RESULTS

Study Conduct

Between March 21, 2017 and May 31, 2024 we randomized 75 participants at 5 clinical research sites (Table 1). Most of the recruitment was at 3 sites (Johns Hopkins, McLean, and Miami). 63 of 75 participants (84%) completed the trial. Participant flow is presented in a CONSORT diagram (Fig. 1).

FIGURE 1. CONSORT flowchart.

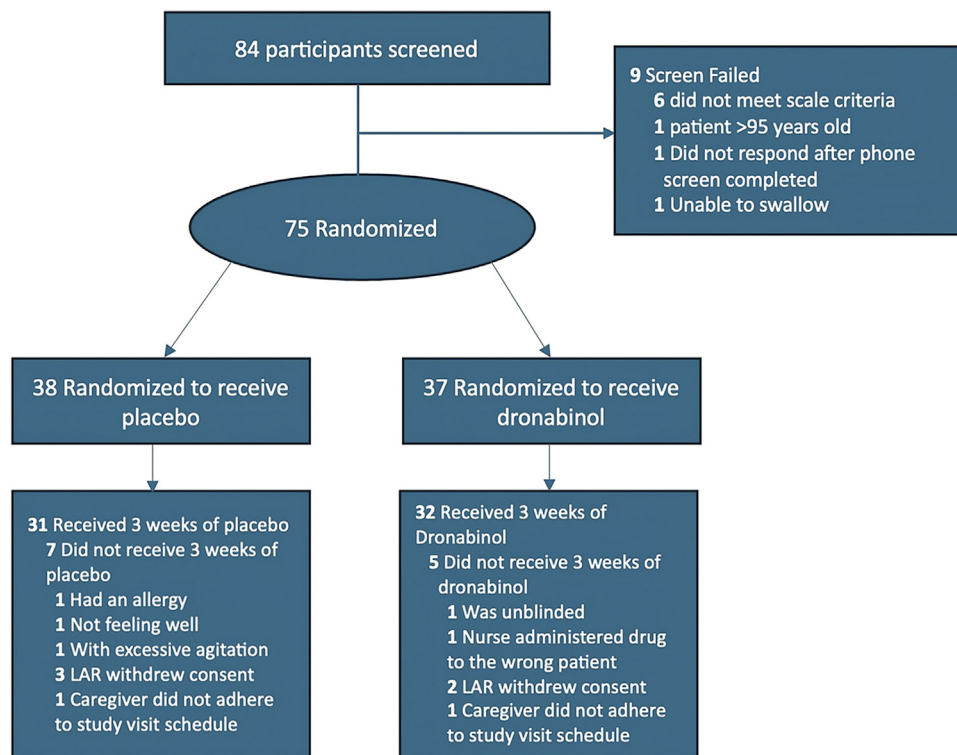


TABLE 1. Baseline Characteristics of Participants

Variable	Total	Placebo	Dronabinol
N	75	38	37
Age, mean (SD)	78.5 (7.5)	79.1 (7.3)	77.9 (7.7)
Sex			
Male	26 (35%)	11 (29%)	15 (41%)
Female	49 (65%)	27 (71%)	22 (59%)
Race			
Black	7 (9%)	5 (13%)	2 (5%)
White	67 (89%)	32 (84%)	35 (95%)
Asian	1 (1%)	1 (3%)	0 (0%)
Ethnicity			
Hispanic/Latina/Latino	8 (11%)	4 (11%)	4 (11%)
Not Hispanic/Latina/Latino	67 (89%)	34 (89%)	33 (89%)
Education, mean (SD)	13.8 (3.2)	13.6 (3.6)	14.1 (2.9)
Current Antidepressant	55 (73%)	25 (66%)	30 (81%)
Current Antipsychotic	38 (51%)	18 (47%)	20 (54%)
NPI-C Total, mean (SD)	76.5 (41.8)	76.4 (48.6)	76.7 (34.2)
NPI-C Agitation/Aggression, mean (SD)	20.4 (10.5)	19.0 (11.2)	21.9 (9.7)
NPI-C Sleep, mean (SD)	3.5 (5.0)	3.6 (4.9)	3.3 (5.1)
ADL Total, mean (SD)	23.2 (19.8)	21.1 (19.2)	25.4 (20.3)
SIB-8 Total, mean (SD)	12.3 (6.8)	12.6 (6.3)	11.9 (7.4)
MMSE Total, mean (SD)	8.6 (6.8)	8.2 (5.7)	9.1 (7.8)
CMAI Total, mean (SD)	29.7 (8.5)	28.9 (9.1)	30.5 (7.9)
PAS Total, mean (SD)	6.3 (4.2)	5.6 (4.2)	7.1 (4.1)

Baseline Characteristics

Demographics and baseline clinical variables for the cohort are listed in [Table 1](#). The majority of participants were female and were taking concomitant psychotropic medications (antidepressants and antipsychotics) at baseline. Study participants were moderately agitated at baseline (baseline CMAI~30), were diverse in ethnic background (9% Black, 11% Hispanic/Latina/Latino), and had severe cognitive impairment evidenced by mean MMSE 8.6 (6.8) or SIB-8 score 12.3 (6.8). The treatment arms were well balanced on demographic and baseline clinical variables. There were no statistically significant differences in demographics and baseline clinical variables stratified by site except for ethnicity, with 7 of 8 Hispanic participants coming from the Miami site (data not shown). The only significant difference in these variables between participants who completed and who did not complete data collection was that the SIB-8 was higher in completers (12.9) than noncompleters (7.4).

Primary Outcomes

The co-primary outcomes were PAS Total and NPI-C Agitation/Aggression (NPI-C A/A) total. The coefficient of interest was the treatment by week interaction, which represents the difference in rate of change between the 2 study arms. For PAS and NPI-C A/A, the difference in rate of change was statistically significantly different from 0 (for PAS) and trended different than 0 (for NPI-C A/A), and in the expected direction (with participants randomized to the dronabinol arm becoming less symptomatic compared to placebo). The effect sizes, calculated as the fitted between-arm difference in change over 3 weeks divided by the baseline standard deviation, were 0.53 and 0.36 for PAS and NPI-C A/A, respectively ([Fig. 2](#)).

Secondary Outcomes

There were no significant differences in secondary outcomes (NPI-C Sleep, NPI-C Total, CMAI, Caregiver Distress, ADCS-ADL, NPI-C Disinhibition, NPI-C Irritability or CGI-C) between treatment arms ([Supplementary Table 1](#)). Similarly, there were no differences in MMSE or SIB-8 between treatment arms ([Supplementary Table 1](#)).

Drug Effect Questionnaire (DEQ)

There were no differences between the treatment arms in DEQ items for an informant report of evidence of 'drug effect', 'relaxed', 'sleepy', 'restless', or 'increased appetite' ([Table 2](#)).

Lorazepam and Trazodone Usage

We analyzed the dosage effects of Trazodone and Lorazepam, administered as needed, using regression analysis and found no significant differences by treatment assignment. This suggests that the overall effects observed are more likely attributed to dronabinol rather than as-needed medication usage of Lorazepam and Trazodone.

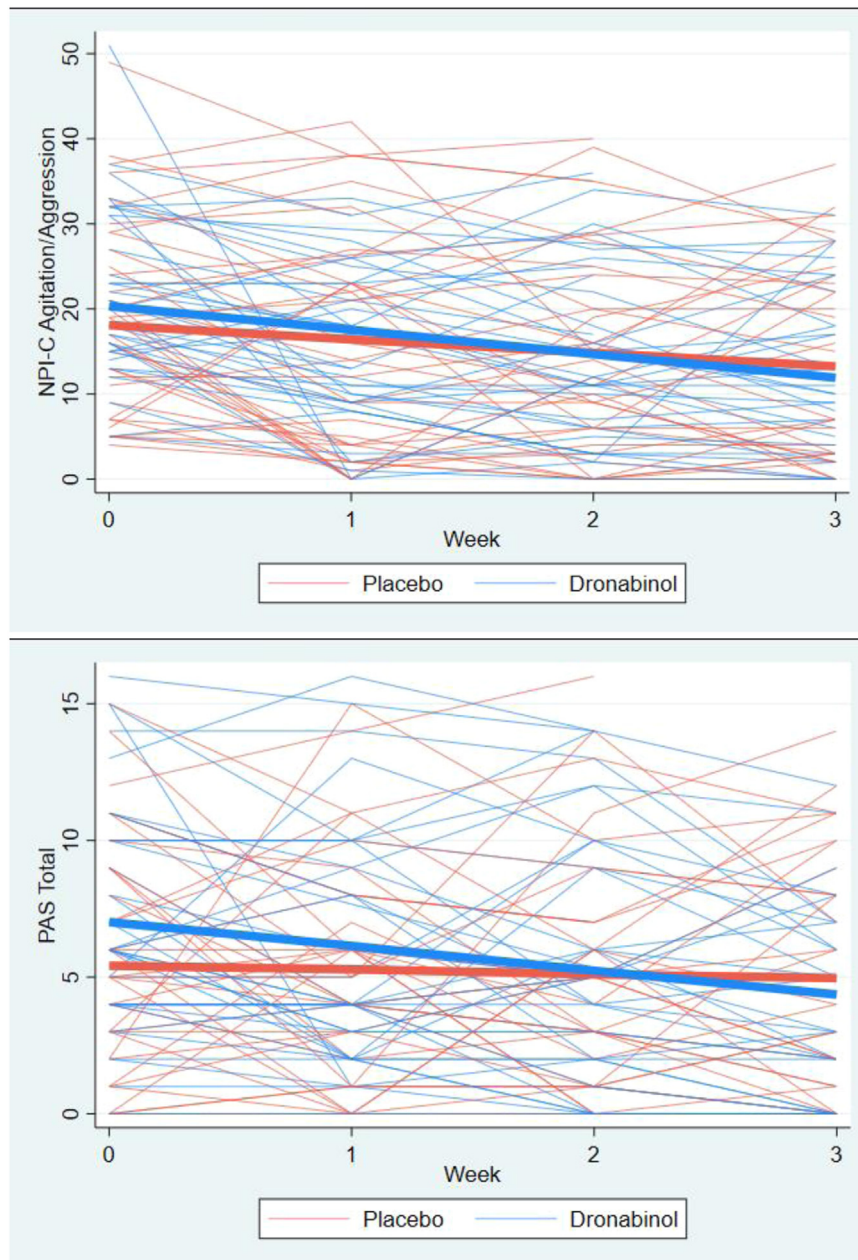
Adverse Events

There was no significant difference in AE incidence between the treatment arms (adjusted IRR 1.14 [0.26] $p = 0.57$). There were 3 episodes of delirium on dronabinol and 1 on placebo. There were 6 falls on dronabinol compared to 4 on placebo. There were 3 postrandomization SAEs experienced by 2 participants randomized to dronabinol, and 1 SAE that occurred prior to randomization. There were no SAEs in the placebo group. There were 7 reports of somnolence in dronabinol versus 2 reports of somnolence in placebo, and 7 episodes of diarrhea on placebo versus none on dronabinol. There were 4 falls in 3 people randomized to placebo, and 6 falls in 5 people randomized to dronabinol. There was 1 episode of delirium in 1 person randomized to placebo, and 3 episodes of delirium in 2 people randomized to dronabinol ([Table 3](#)).

CONCLUSIONS

The THC-AD trial demonstrates that dronabinol appeared safe and showed promise reducing agitation in AD, as evidenced by statistically significant benefit of the drug over placebo on one of two co-primary outcomes (PAS) but not on the other co-primary outcome (NPI-C A/A). This points to potential benefit of THC treatment of agitation in AD. Secondary outcomes were null (no statistically significant difference between dronabinol and placebo), but all but

FIGURE 2. Pittsburgh agitation scale total score over time, adjusted fit with 5 sites and NPI-C A/A over time, adjusted fit with 5 sites.



sleep was in the direction of benefit of drug. There was no evidence of a safety signal and no cognitive difference between drug and placebo, the latter most relevant as a safety outcome (i.e., dronabinol treatment was not deleterious to cognition). Additionally, there was no evidence for 'intoxication' from THC. There is the possibility of increased sedation,

delirium, and falls but none of these safety issues was significantly different between drug and placebo. Thus, dronabinol may be a relatively safe treatment alternative for agitation in AD.

Reassuringly, we did not observe an excess of AEs in the dronabinol arm. The numbers of AEs are too small for meaningful statistical comparison but do

TABLE 2. Drug Effect Questionnaire Results (Informant Version)

DEQ Question	TX by Week Interaction	p-Value	Effect Size
“Is the participant experiencing a drug effect?”	1.23 (2.67)	0.646	0.18
“Does the participant appear relaxed?”	-3.55 (2.9)	0.222	-0.34
“Does the participant appear sleepy or tired?”	2.88 (2.45)	0.241	0.30
“Does the participant appear restless?”	-3.31 (2.84)	0.245	-0.27
“Has the participant increased food intake?”	-1.32 (2.08)	0.524	-0.24

These are estimates from a longitudinal GEE model with terms for treatment, week, and their interaction and have adjusted estimates for site and for use of antidepressants and antipsychotics at baseline. Inferences for model coefficients are via Wald test assuming that the test statistic follows a Z-distribution. The Wald statistic is calculated as the quotient of the model coefficient and its standard error.

TABLE 3. Adverse Events

Adverse Event	Placebo	Dronabinol
Delirium	1	3
Fall	4	6
Seizure	0	1
Anemia	0	1
Leukopenia	1	0
Vertigo	0	1
Abdominal Pain	0	1
Constipation	1	0
Diarrhea	7	0
Urine Incontinence	0	1
Edema	1	0
Fatigue	0	1
Gait Disturbance	1	0
Neuroleptic Malignant Syndrome	0	1
COVID-19	1	0
Conjunctivitis	0	1
Prostatitis	0	1
UTI	1	1
Pressure Ulcer	1	0
Skin Tear	1	0
Foot Pain	1	0
Required Pain Management	0	1
Weakness	1	0
Appetite, Decreased	0	1
Appetite, Increased	0	1
Dehydration	1	0
Hypokalemia	0	2
Hyponatremia	1	0
Weight Loss	1	0
Dysarthria	1	1
Somnolence	2	7
Agitation	4	2
Anxiety	0	1
Confusion	3	2
Insomnia	0	2
Paranoia	0	1
Nosebleed	1	0
Ingrown Toenail	0	2
Hypotension	1	1
Total	37	43

not point to a notable increase in delirium or fall risk on dronabinol. There may be a trend towards more somnolence on dronabinol, similar to that observed

in a prior nabilone trial,²⁹ but no participants dropped out due to somnolence. Similarly, SAEs were too few for valid statistical comparison with 3 in dronabinol group and none on placebo. Furthermore, there was no evidence for a greater decline in cognition in the dronabinol arm, an important safety outcome given that many of the participants had moderate or severe dementia at study baseline.

The effect sizes were in the moderate range (0.36–0.53) for the co-primary outcomes (PAS and NPI-C A/A). For comparison with recent trials of other drug interventions for agitation in AD, the effect size for CMAI in the brexpiprazole phase 3 trial was 0.35.²⁹ While the primary outcome measures differed between studies, and we did not observe a statistically significant benefit of dronabinol on CMAI, this data suggests that dronabinol’s effect on agitation was comparable to brexpiprazole which is FDA-approved for agitation in AD. However, all 3 brexpiprazole studies were 12 weeks in duration and this study was 3 weeks in duration. It is possible that the effect size of dronabinol may have been larger or smaller if the study duration had been longer. A recent trial of citalopram for agitation in AD did not report effect sizes and demonstrated a different mix of statistically significantly positive findings.¹³

There are many strengths to this study design that point to potential impact on clinical care. The overall design was oriented toward a ‘real-world’ cohort and intervention. We had no exclusions for dementia severity and the cohort was quite severely impaired with mean baseline MMSE of 8.6 (6.8) and SIB-8 of 12.3 (6.8). The SIB-8 was administered only to participants deemed too impaired for a valid MMSE.⁴³ Retention (84%) was very good considering that most participants had advanced dementia and very substantial care needs. Most patients were

taking concomitant antidepressants and/or anti-psychotic medications which is typical for agitation in AD. Demographics were reasonably representative of U.S. dementia cohorts with diverse ethnic backgrounds. The majority were female as would be expected in an elderly cohort, mean age was 78 (7.5) years, and they had on average 13.8 (3.2) years of education. Thus, THC-AD represented a test of a 'real-world' intervention on a 'real-world' population. It is important to note that the THC-AD cohort was, on average, moderately to severely cognitively impaired with MMSE mean of ~8 and many participants evaluated with SIB-8 because they were too impaired for valid MMSE. Thus, our results may be more relevant to the treatment of patients with advanced dementia and agitation than those in earlier stages. Two factors may have enriched the cohort for severe stage dementia: 1) we started out as an inpatient trial 2) there is a strong association of agitation with dementia severity.⁴⁴

We chose dronabinol for this study because it is FDA approved in the U.S. and is generic and thus cheaper and more readily available to us for use. In other countries, nabilone is an alternative medication to consider if dronabinol is not an option or if it is cheaper/easier to get. Both dronabinol and nabilone are agonists at the CB1 receptor, so they are pharmacologically comparable. Nabilone has the advantage of better and more reliable absorption and is also more potent, so lower doses would be recommended. There are no data comparing nabilone and dronabinol's tolerability.

Limitations of the study included a relatively short study duration of 3 weeks, chosen initially for feasibility of inpatient participation. A longer study duration would be preferable to assess durability of response and possible AEs that might not appear early in treatment. Additionally, we observed a statistically significant benefit of drug on the PAS but not on several secondary outcomes including the CMAI. This may be due to the limitations of current measurement tools, including the limited adoption of the NPI-C subscale and the lack of a gold standard for assessing agitation and aggression, underscoring the challenges in accurately capturing symptom changes. The fluctuating nature of these symptoms, combined with the reliance on weekly assessments, introduces potential

variability in our findings. The study may not have been sufficiently powered to detect differences in secondary outcomes. Importantly, the results reflect the effect of a pharmacologic synthetic THC preparation, and are not generalizable to 'medical' or 'recreational' cannabis preparations which are widely available in the U.S. There may have been unintentional unblinding due to perception of adverse effects such as sedation, and another limitation is that we did not assess potential unblinding of caregivers or study staff. Finally, this study was limited to the Alzheimer's type of dementia accounting for approximately two thirds of all dementias. Future research should include a more heterogeneous sample of individuals with mixed dementias, vascular dementia and frontotemporal dementias to increase the generalizability of study findings and determine efficacy in other dementia types.

Future studies should explore the use of digital tools for real-time assessment of behavioral symptoms, which could provide deeper insights into the phenotypic characteristics of agitation and aggression in dementia. Additionally, implementing daily data collection may enhance the ability to track symptom fluctuations more accurately, leading to a better understanding of outcomes and the overall effectiveness of interventions such as THC.

In summary, this study demonstrates that dronabinol (THC) may be relatively safe and effective in reducing agitation symptoms in individuals with moderate to severe AD but given limited sample size and short duration clinicians should view these conclusions as tentative meriting more robust replication including longer duration. These findings may potentially shape future clinical practice for the treatment of agitation symptoms that are a major part of the growing public health burden of AD and adversely impact quality of life for patients and their family care partners.

FINDINGS

Dronabinol was safe and effective in decreasing agitation in 75 participants with AD significantly more than placebo in a 3-week double-blind trial. There were no emergent safety issues with the possible exception of sedation.

MEANING

Dronabinol has potential for safely improving agitation in AD, and thus adds to clinicians' choices for treatment of this prevalent and disabling complication of dementia

DISCLOSURES

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AUTHOR CONTRIBUTIONS

Paul B. Rosenberg— Co-Principal Investigator; conceived the study idea, developed the methods, and contributed to drafting the manuscript. **Halima Amjad**— Contributed to data collection, data analysis, and drafting the manuscript. **Haroon Burhanullah**— Contributed to data collection and drafting the manuscript. **Milap Nowrangi**— Contributed to data collection and drafting the manuscript. **Mersania Jn. Pierre**— Contributed to data collection and drafting the manuscript. **John Outen**— Contributed to data collection, data analysis, and drafting the manuscript. **Christopher Marano**— Contributed to

data collection. **Marc Agronin**— Contributed to data collection, data analysis, and drafting the manuscript. **Ryan Vandrey**— Contributed to study design, data analysis, and drafting the manuscript. **James Wilkins**— Contributed to study design, data collection, data analysis, and drafting the manuscript. **David Harper**— Contributed to study design, data collection, data analysis, and drafting the manuscript. **Todd Laffaye**— Contributed to data collection and drafting the manuscript. **Eilis Reardon**— Contributed to drafting the manuscript. **Kathryn Turner**— Contributed to data collection and drafting the manuscript. **Rosain Ozonsi**— Contributed to data collection and drafting the manuscript. **Tuna Hasoğlu**— Contributed to data collection and drafting the manuscript. **Julia Cromwell**— Contributed to data collection and drafting the manuscript. **Meghan Schultz**— Contributed to data collection and drafting the manuscript. **Mia Drury**— Contributed to data collection and drafting the manuscript. **Andre Nguyen**— Contributed to data collection and drafting the manuscript. **Jeannie Marie Leoutsakos**— Contributed to method design, data analysis, and drafting the manuscript. **Brent P. Forester**— Contributed to study design, data collection, data analysis, and drafting the manuscript.

DATA STATEMENT

All data supporting the findings of this study are made publicly available. The full dataset can be accessed on ClinicalTrials.gov under the identifier NCT02792257.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.jagp.2025.10.011>.

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