



Investigating the safety and efficacy of nabilone for the treatment of agitation in patients with moderate-to-severe Alzheimer's disease: Study protocol for a cross-over randomized controlled trial

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ABSTRACT

Agitation is a prevalent and difficult-to-treat symptom in patients with moderate-to-severe Alzheimer's disease (AD). Though there are nonpharmacological and pharmacological interventions recommended for the treatment of agitation, the efficacy of these are modest and not always consistent. Furthermore, the safety profiles of currently prescribed medications are questionable. Nabilone, a synthetic cannabinoid, has a distinct pharmacological profile that may provide a safer and more effective treatment for agitation, while potentially having benefits for weight and pain. Additionally, emerging evidence suggests nabilone may have neuroprotective effects. We describe a clinical trial investigating the safety and efficacy of nabilone for the treatment of agitation in patients with moderate-to-severe AD. This will be a double-blind, randomized cross-over study comparing 6 weeks of nabilone (0.5–2 mg) and placebo, with a 1-week washout preceding each phase. Study outcomes will be measured at baseline and end of treatment for each treatment phase. The primary outcome measure will be agitation as assessed by the Cohen-Mansfield Agitation Inventory. The secondary outcomes include safety, behaviour (Neuropsychiatric Inventory), cognition (standardized Mini Mental Status Exam and either Severe Impairment Battery or Alzheimer's disease Assessment Scale-Cognitive subscale) and global impression (Clinician's Global Impression of Change). Exploratory outcomes include pain (Pain Assessment in Advanced AD), nutritional status (Mini-Nutritional Assessment-Short Form), caregiver distress (NPI caregiver distress), and blood-based biomarkers. A safe and efficacious pharmacological intervention for agitation, with effects on pain and weight loss in patients with moderate-to-severe AD could increase quality-of-life, reduce caregiver stress and avoid unnecessary institutionalization and related increases in health care costs.

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Abbreviations: AD, Alzheimer's disease; CB, cannabinoids; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CGIC, Clinician's Global Impression of Change; CMAI, Cohen Mansfield Agitation Inventory; EC₅₀, half maximal effective concentration; FDA, Food and Drug Administration; IPA, International Psychogeriatric Association; LTC, long-term care; MAR, Medication Administration Record; MNA-SF, Mini-Nutritional Assessment-Short form; NPI-NH, Neuropsychiatric Inventory-Nursing home version; NPS, neuropsychiatric symptoms; PAINAD, Pain Assessment in Advanced AD; RCT, randomized controlled trial; SIB, Severe Impairment Battery; sMMSE, standardized Mini-Mental Status Examination; THC, tetrahydrocannabinol

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1. Introduction

Agitation is one of the most challenging neuropsychiatric symptoms (NPS) to treat in Alzheimer's disease (AD), and has an increased likelihood of occurrence in the advanced stages of AD [1,2]. In community-dwelling AD patients, the prevalence of agitation is 20%, with rates increasing to 50% in AD patients residing in long-term care facilities (LTC) [3–7]. This is a particular problem in LTC, as 90% of residents have a diagnosis of moderate-to-severe AD [2,8,9]. Furthermore, agitation is associated with mortality, decreased quality of life, and increased caregiver burden and rates of institutionalization [10–13]. Though there has previously been a lack of consensus on the definition of agitation, the Food and Drug Administration (FDA) has accepted the provisional definition and criteria set out by the International Psychogeriatric Association (IPA). The IPA criteria define patients as having clinically significant agitation when they have symptoms accompanied by distress that fall into one or more of the following categories, for at least two weeks: 1) physical nonaggression, 2) physical aggression, and 3) verbal aggression [14].

Weight loss occurs in approximately one third of patients with AD [15], and the risk of weight loss increases as the disease progresses [16]. Weight loss has also been associated with a greater likelihood of rapid cognitive decline in AD patients [17]. Environmental and educational interventions have shown some effectiveness, however benefits were modest [18] and not investigated in a controlled environment [19]. Oral supplementation was shown to increase weight in AD patients at risk of malnutrition [20]; however, there seemed to be a large placebo effect, given that approximately 42% of patients on placebo also gained weight. Therefore, while studies have shown some effectiveness in improving weight in AD patients, none of the interventions have given reliable results, and weight loss in AD is still an important issue that needs to be addressed. Pain is another common symptom in AD patients, which is difficult to identify, associated with increased agitation and may be under-treated [21]. Approximately 50% of AD patients experience pain [22], with the prevalence increasing to 60–80% in institutionalized AD patients [23]. In the majority of these patients, pain is persistent [24], and has been associated with a reduced quality of life and increased NPS [23]. Furthermore, increased pain has been associated with appetite disturbances and poorer nutritional status [25,26]. As such, weight loss and pain in moderate-to-severe AD patients are important issues that need to be addressed.

Cannabinoids (CB) such as tetrahydrocannabinol (THC), which are agonists at CB receptors 1 and 2 (CB1/2), have psychotropic effects that may benefit AD patients with agitation. Though two double-blind randomized controlled trials (RCTs) with THC in AD patients, reported no significant improvements in NPS compared to placebo [27,28], studies with synthetic CB, such as dronabinol and nabilone [29–33] have demonstrated efficacy. CB have also been associated with appetite stimulating effects in patients with eating disorders and AIDS [34], while also demonstrating analgesic benefits in patients with neuropathic pain, rheumatoid arthritis and cancer pain [35]. Therefore, CB may benefit AD patients with agitation while also having therapeutic benefits for nutritional status and pain.

2. Methods

2.1. Study aims

2.1.1. Primary

To investigate the effect 6 weeks of nabilone treatment on symptoms of agitation, as assessed by the Cohen Mansfield Agitation Inventory (CMAI), compared to placebo.

The CMAI was chosen as the primary outcome measure because it has been shown to be reliable and sensitive to change in nursing home residents [36]. In a previous cross-over trial with AD patients, differences on CMAI scores were observed following 6 weeks with

dronabinol, compared to placebo [29]. Additionally, a 9-week double-blind cross-over RCT with sertraline in AD patients with agitation/aggression demonstrated responsiveness of the CMAI to drug treatment [37]. Changes in CMAI scores were also observed in other clinical trials with AD patients [38,39].

2.1.2. Secondary

- 1) To investigate whether nabilone treatment is associated with improvements in NPS as assessed by the Neuropsychiatric Inventory-Nursing Home version (NPI-NH), compared to placebo.
- 2) To investigate whether nabilone treatment is associated with improvements in caregiver distress as assessed by the NPI-NH total caregiver distress score.
- 3) To investigate whether nabilone treatment is associated with improvements in cognition as assessed by the standardized Mini Mental Status Examination (sMMSE) and Severe Impairment Battery (SIB) or Alzheimer's disease Assessment Scale – Cognitive Subscale (ADAS-Cog), compared to placebo.
- 4) To investigate whether nabilone treatment is associated with improvements on the Clinician's Global Impression of Change (CGI-C), compared to placebo.
- 5) To investigate whether nabilone treatment and placebo have comparable tolerability and safety.

2.1.3. Exploratory

- 1) To investigate whether nabilone treatment is associated with improvements in pain (Pain Assessment in Advanced AD (PAIN-AD)), weight, and nutritional status (Mini-Nutritional Assessment-Short Form (MNA-SF)), compared to placebo.
- 2) To investigate whether blood-based biomarkers of interest are associated with agitation severity, and whether they can predict treatment response to nabilone.
- 3) To determine whether patients met IPA criteria for agitation/aggression.

2.2. Study design

This is a randomized, double-blind, placebo-controlled crossover design study (Fig. 1), to determine the safety and efficacy of nabilone with the potential for a larger phase 3, multicenter trial. Following a 1-week placebo run-in, eligible patients will be randomized to receive either nabilone or placebo (1:1 assignment ratio) for 6 weeks each, with a 1-week placebo washout between phases. A 1-week washout was justified as this length of time was equivalent to 4.5 half-lives of nabilone's active metabolites.

2.3. Setting

This trial will recruit inpatients from Sunnybrook's Veterans' LTC Facility (Toronto, ON), and outpatients the Greater Toronto Area's outpatient psychiatry clinics. As all study visits will be completed at Sunnybrook Health Sciences Centre (Sunnybrook), this will be a single-site study.

2.4. Study participants

Patients who meet the current DSM-5 criteria for Major Neurocognitive Disorder due to AD, or both Major Neurocognitive Disorder due to AD and Major Vascular Neurocognitive Disorder (i.e., mixed AD and cerebrovascular disease), and who have clinically significant agitation will be considered for inclusion (Table 1). In this trial, “clinically significant agitation” will be defined as that for which a physician has determined that a medication is appropriate, and is rated as 1) occurring at least ‘frequently’ or 2) occurring ‘often’ with

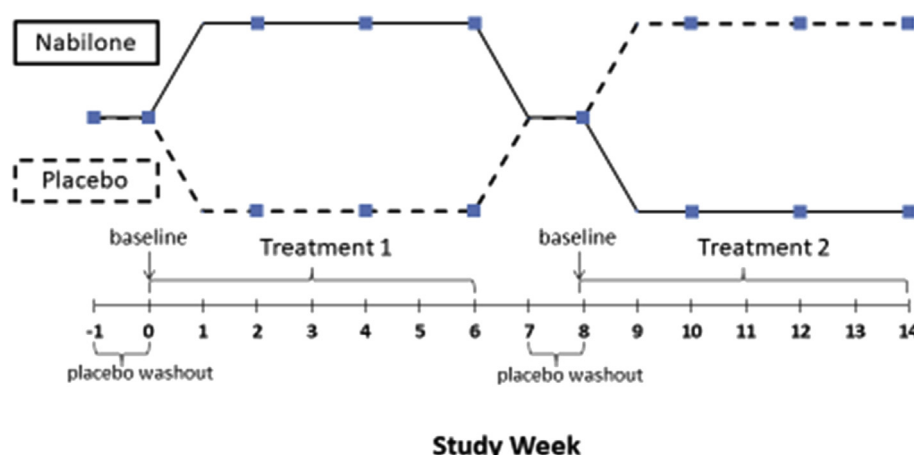


Fig. 1. Treatment schedule. Blue boxes correspond to scheduled assessments. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

‘moderate’ or ‘marked’ severity as assessed by the agitation/aggression subscale items of the NPI-NH.

2.5. Study intervention

Eligible and consented participants will begin with one week of placebo run-in (week -1). During baseline (week 0), 1 capsule (0.25 mg or placebo) will be given before bedtime for the first three nights, then tapered up to 1 capsule BID (0.5 mg/day total or placebo) for the next four days. Participants will then take 1 capsule (0.5 mg or placebo) daily during week 1. The study dose will be increased to 1 capsule BID (1 mg/day total or placebo) during week 2. Throughout weeks 3 and 4, the dose can be increased to a maximum of 2 capsules BID (2 mg/day total or placebo) or decreased based on tolerability. This dose will be maintained until down-titration in week 6. Following the first three maintenance days of week 6, there will be a taper phase for the remaining four days (days four-five will reduce to 1 mg/day total, and days six-seven will decrease to 0.5 mg/day total) in order to reduce the risk of potential withdrawal effects of active treatment. For patients receiving a maintenance dose lower than 2 capsules BID, they will maintain that dose during the titration until the next step in the titration would decrease their dose. This will ensure that all participants will end titration at the same time and with the same dose.

2.6. Study assessments

The following assessments will be carried out by a trained member of the research team at Sunnybrook. For those that require caregiver input, the primary nurse will complete the forms with the research team for inpatients, and a family caregiver who has regular contact with the

patient will complete the forms with the research team for outpatients.

2.6.1. Primary outcome measure

CMAI [40]: A 29-point scale that measures agitation in two dimensions, verbal and physical, each of which having two poles, aggressive and non-aggressive.

2.6.2. Secondary outcome measures

NPI-NH [41]: An assessment of behavioural disturbances in dementia, including: apathy, agitation, delusions, hallucinations, depression, euphoria, aberrant motor behaviour, irritability, disinhibition, anxiety, sleeping, and eating. The frequency and severity of these symptoms are judged on a 4-point and 3-point scale, respectively. A 5-point scale is used to evaluate caregiver distress.

sMMSE [42]: A measure of global cognition, which includes assessments of orientation to time and place, immediate recall, short-term verbal memory, calculation, language, and construct ability. Scored out of 30, the sMMSE is used to describe severity of cognitive impairment.

SIB [43]: The SIB is directed towards individuals who are too impaired to complete standard neuropsychological tests. This test allows for non-verbal and partially correct responses, as well as for simpler response modes such as matching. The SIB is scored out of 100, with lower scores indicating greater severity. In the proposed study, this test will be administered to patients who have an sMMSE ≤ 15.

ADAS-Cog [44]: The ADAS-Cog is a validated assessment of cognitive performance in mild to moderate AD patients [44]. This instrument is the most widely used primary outcome measure of treatment efficacy in clinical trials of AD [45–47]. The ADAS-Cog is scored out of 70, with greater scores indicating greater impairment. In the proposed study, this test will be administered to patients who have an sMMSE > 15.

Table 1
Inclusion/Exclusion criteria.

Inclusion	Exclusion
• Males or females ≥ 55 years of age • DSM-5(72) criteria for Major Neurocognitive Disorder due to AD. Patients with both Major Neurocognitive Disorder due to AD and Major Vascular Neurocognitive Disorder (i.e., mixed AD and cerebrovascular disease) will also be included. • sMMSE ≤ 24 • Presence of clinically significant agitation (Neuropsychiatric Inventory-agitation subscale ≥ 3) • If treated with cognitive-enhancing medications (cholinesterase inhibitors (ChEIs) and/or memantine), dosage must be stable for at least 3 months. If the ChEI and/or memantine has been discontinued, they may enroll after 1 month.	• Change in psychotropic medications less than 1 month prior to study randomization (e.g., concomitant antidepressants) • Contraindications to nabilone (history of hypersensitivity to any cannabinoid) • Current significant cardiovascular disease (e.g. uncontrolled hypertension, clinically significant ischemic heart disease, clinically significant arrhythmia or severe heart failure) • Presence or history of other psychiatric disorders or neurological conditions (e.g. psychotic disorders, schizophrenia, epilepsy), previous or current abuse of/dependence on marijuana • Clinically significant delusions and/or hallucinations (NPI-NH-delusions/hallucinations subscale ≥ 4)

CGI-C [48]: The CGI-C is a clinician's rated scale of global deterioration to assess clinically significant change. This scale uses a 7-point Likert scale to rate each participant along a continuum from (1 = marked improvement, 2 = moderate improvement, 3 = minimal improvement, 4 = no change, 5 = minimal worsening, 6 = moderate worsening and 7 = marked worsening).

2.6.3. Exploratory outcome measures

PAINAD [49]: The PAINAD is a 5-item observer-rated scale conducted after a 5-min observation. The scale examines breathing, vocalizations, facial expression, body language, and consolability. This scale is already extensively used in the LTC facility at the hospital in which this study will be conducted.

MNA-SF [50]: The MNA-SF is a structured interview consisting of 6 items that categorizes patients as malnourished, at risk of malnutrition, or of normal nutritional status. This scale is considered to be the most suitable scale to use in a LTC facility as it contains items which have been shown to reflect characteristics associated with nursing home facilities that other scales do not [51].

2.7. Study schedule

Assessments will be conducted on the following weeks: -1 (screening; placebo run-in), 0 (baseline, start of treatment 1), 2, 4, 6 (end of treatment 1; start of placebo washout), 8 (start of treatment 2), 10, 12, 14 (end of treatment 2; final assessment) and 15 (safety follow-up). All assessment will be conducted within a three-day window of the visit date. Demographic data, as well as cognitive and behavioural measures will be collected during screening. Measures of behaviour, nutrition, vital signs and adverse events (AEs) will be conducted at all study visit days. Comprehensive cognitive and behavioural assessments, as well as serum samples for biomarkers of interest will additionally be collected from each patient at the beginning and end of each treatment phase (weeks 0, 6, 8, and 14) (Table 2).

2.8. Randomization and masking

A block randomization code will be independently computer-generated by the Pharmacy Department at Sunnybrook. All study personnel will remain blind to the randomization code, block size and treatment allocation until the final patient has completed his/her follow-up check and the database is "locked". The randomization code will remain locked in a secure location in the Pharmacy Department at Sunnybrook. Unblinding will not be allowed unless there exists exceptional clinical circumstances that justify it (i.e., necessary for acute medical management of serious adverse events (SAE)) and only after approval by the principal and/or qualified investigator (PI or QI).

2.9. Compliance

Administration of the study medication will be supervised by a caregiver. For inpatients, the caregiver will be the primary nurse and capsules administered will be entered in the Medication Administration Record (MAR) binder and narcotics log. For outpatients, caregivers will be instructed to enter administration into a capsule diary, and return unused medications at each visit. Adherence to the study medication will be measured by information from the MAR/narcotics log/capsule diary and capsule counts.

2.10. Biomarker analyses

Serum samples for biomarkers of interest will be collected from serum at four time points; the start and end of each treatment phase, and will be frozen (-80°C) immediately and batched for analysis.

2.11. Safety monitoring plan

All emerging AEs that are clinically significant based on QI or designated qualified physician's assessment will be noted and followed-up until resolution. All SAEs will be reviewed by Drs Lanctôt and Herrmann, and will be reported to the research ethics board as per their reporting criteria. Dr. Herrmann will be reviewing all serious adverse events. Any patient who has greater than minimal deterioration on the CGI-C, or shows a clinically significant increase in behavioural symptoms (NPI total increases by $\geq 50\%$ [52,53]) at any point during the trial will be considered for discontinuation from the study medication. This will be the decision of the double-blinded investigator. Furthermore, if the attending physician has any concern about the patient throughout the trial, the patient will be flagged for possible removal from the study. At the end of the treatment period, the attending physician will be unblinded and will have the choice to continue nabilone off-study. Subjects will be withdrawn from the study if consent is withdrawn, and will be considered for study withdrawal for any of the following reasons: significant non-compliance or protocol deviation, SAEs, clinically significant global deterioration, or lack of efficacy of study drug.

2.12. Data collection, retention and management

Data will be collected on printed source documents/case report forms (CRFs). Source documents/CRFs include physical, cognitive, nursing/caregiver and clinician assessments. Source documents, CRFs, and other records pertaining to the conduct of this study will be retained for 25 years, as per Health Canada regulations.

Anonymised data will be entered into a central database, with data entry in agreement with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use standards for good clinical practice. Database lock, unblinding and subsequent data analysis will be conducted only once recruitment and patient follow-up data entry and data verification are completed.

2.13. Statistical analyses

Analyses will be performed according to intention-to-treat procedures. Outcomes will be summarized using mean $\pm$ standard deviation and tests will be two-tailed with a significance level of 0.05. For continuous outcomes, linear mixed models will be used. For dichotomous outcomes, McNemar's test will be used. These results can inform the design of a larger trial using additional analyses as appropriate. Treatment order and carry over effects will be examined using paired t-tests. Treatment order effects would occur when the order of receiving nabilone or placebo may affect the outcome. Carry-over effects would occur when receiving nabilone from phase 1 would affect the response in phase 2. Exploratory analyses will be performed to determine predictors of response including demographics, biomarkers and compliance, using logistic regression.

2.14. Sample calculation

Sample size calculations were determined using SPSS SamplePower (IBM Corp., Armonk, NY, USA), which uses Cohen's calculations [54]. A paired t-test with a total of 30 subjects and an alpha of 0.05 is powered (0.89) to detect medium to large effect sizes for CMAI change scores between treatment and placebo. In the earlier placebo-controlled crossover trial [29], improvements in CMAI scores favoured cannabinoid treatment in 15 patients. In order to account for likely attrition rates (5% [37], 14% [55] and 27% [56] in our previous trials), we will randomize 40 subjects (10 drop-outs = 25% attrition). As a pilot study, the data collected will be used to confirm the feasibility of testing and refine sample size calculations for larger, future grants.

Table 2
Schedule of assessments.

	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14 ^a	Week 15
Demographics										
DSM-V criteria for dementia	X									
Age	X									
Gender	X									
Height	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	
Date of diagnosis	X									
Outcomes										
CMAI (primary)	X	X	X	X	X	X	X	X	X	
NPI	X	X			X	X			X	
sMMSE	X	X			X	X			X	
SIB (if sMMSE ≤ 15)		X			X	X			X	
ADAS-Cog (if sMMSE > 15)		X			X	X			X	
CGI/CGI-C ^b		X	X	X	X	X	X	X	X	
PAINAD	X	X	X	X	X	X	X	X	X	
MNA-SF		X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	
BMI		X	X	X	X	X	X	X	X	
Blood biomarkers		X			X	X			X	
Safety outcomes										
Physical Examination, Vitals	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Blood panel review ^c	X								X	
ECG ^d	X									
Other										
Blindness check										X

CMAI = Cohen-Mansfield Agitation Inventory; NPI-NH = Neuropsychiatric Inventory - Nursing Home; BMI = Body Mass Index; MNA-SF = Mini Nutritional Assessment - Short Form; sMMSE = standardized Mini-mental State Examination; SIB = Severe Impairment Battery; ADAS-Cog = Alzheimer's Disease Assessment Scale of Cognition; PAINAD = Pain Assessment in Advanced Dementia; CGI = Clinician's Global Impression; CGI-C = Clinician's Global Impression of Change.

^a This visit will also take place if patient withdraws from study, or will need to end the study early.

^b The CGI and CGI-C are two components of one scale. The CGI will be completed at baseline. The CGI-C will be completed at weeks 2, 4, 6, 8, 10, 12 and 14.

^c Blood panel will be reviewed if it has been completed 3 months prior to the screening visit. If this is not available, the QI will order a blood panel for review. During the study, the QI will order blood work should they feel that it is clinically necessary.

^d An ECG will be ordered when the QI feels that it is necessary to rule out cardiac conditions.

3. Discussion

There are both advantages and disadvantages involved in the design of a cross-over RCT. One advantage is that each cross-over patient serves as their own control, limiting the influence of confounding covariates. Secondly, fewer patients are required compared to parallel group designs, which is advantageous in an advanced AD psychiatric population that may be difficult to recruit. Finally, in a cross-over trial, randomized patients receive all treatment allocations. This may be advantageous for recruitment purposes as this guarantees that all patients will have some exposure to the experimental medication. Limitations that may arise due to the design of a cross-over RCT include the potential for treatment-order and carry-over effects. However, in order to diminish the impact of a carry-over effect, we have included a 1-week washout period. Furthermore, as indicated in the statistical analysis plan, treatment order and carry-over effects will be examined using paired t-tests. Finally, a strong placebo effect can complicate the interpretation of placebo-controlled trials of agitation in AD [57]. In this trial, a 1-week, single blind placebo run-in before the baseline measurements will be made to mitigate this anticipated effect.

One of the major operational difficulties encountered included passing the regulatory requirements necessary to run this trial. As with all clinical studies, this trial required approval from our institution's Regulatory Ethics Board. However, since this trial aims to investigate the efficacy and safety of nabilone for a purpose different from its current indication as an antiemetic, we also required a No Objection Letter from Health Canada. Finally, as nabilone is registered as a Schedule II drug due to its potential for abuse, this study required approval from the Office of Controlled Substances. Though seeking regulatory approval from multiple governing bodies delayed our timeline for recruitment and study completion, Sunnybrook's Quality Assurance

and Education team and the PI/QI worked closely with study staff to ensure that we met regulatory standards.

To date, there have been five trials with dronabinol, a synthetic THC, which have reported efficacy data on agitation/aggression in AD [27–29,31,32]. A six-week cross-over RCT investigated the efficacy of dronabinol on food-intake in patients with AD [29]. As an exploratory outcome, that group also investigated agitation, as assessed by the CMAI, and reported that dronabinol treatment significantly reduced agitation over time. However, that may be due to a carry-over effect as there was no placebo washout period included in this study. Another cross-over RCT with dronabinol in 2 patients with AD reported a reduction in night-time agitation during the active treatment phase. However, that effect was not long-lasting as it did not persist for longer than 2–3 weeks [32]. A two-week placebo-controlled RCT reported that dronabinol reduced nocturnal motor activity in 24 agitated patients with AD [30]. An open-label study with dronabinol in agitated patients with AD reported a relative reduction in nocturnal motor activity during the first two days of treatment only [31]. A retrospective study with dronabinol reported clinically significant reductions in aberrant vocalization, motor agitation, aggressiveness, and resistance to care in patients with dementia and NPS [33]. There has been only one study (case report in one AD patient) with nabilone, a synthetic THC analogue. Though there was a significant reduction in the severity of agitation when treated with nabilone, that study involved a single patient and open label administration, and thus efficacy cannot be confirmed [58].

As agonism at CB1 has been associated with increased feeding behaviour, food craving, and energy deposition of fat into adipose tissue, nabilone may improve nutritional status in AD patients with agitation. Furthermore, as weight loss has been recognized as a common occurrence and is associated with rapid cognitive decline in AD, identifying

an intervention that demonstrates efficacy in improving nutritional status and weight is of clinical importance.

Pain is also a common symptom in AD patients with agitation, and has been associated with poorer nutritional status, reduced quality of life and function, and increased NPS. Current pharmacological treatments for pain management, such as acetaminophen, non-selective non-steroidal anti-inflammatory drugs, opioids, and morphine, have been associated with limited to modest efficacy and an increased risk of side-effects in patients with AD [59]. Preclinical and clinical evidence suggests that targeting the ECS may offer benefits for pain through inflammatory processes. Therefore, nabilone may also offer benefits for pain in AD.

Compared to the synthetic CBs, THC has a shorter time to maximum concentration, and a faster absorption period. Furthermore, the THC maximal concentration is 2–5 times smaller than that of dronabinol [60]. Given the positive preliminary data and potentially better pharmacological profile of synthetic CBs, this may provide rationale for why THC has not demonstrated efficacy in the treatment of persistent NPS in AD, such as agitation/aggression. While dronabinol and nabilone both act on CB1/2 receptors, the former is a full agonist and the latter a partial agonist. Dronabinol (synthetic THC) has a fast onset of action (approximately 30 min), and strongly binds to CB1/2 receptors, but is a weak agonist at CB2. Additionally, dronabinol has a half maximal effective concentration (EC_{50}) of 17 nM at CB1, and 1.5 nM at CB2. Nabilone (synthetic THC analogue) is a partial agonist at CB1/2 receptors and has a lower EC_{50} at CB1 (4 nM) and a greater EC_{50} at CB2 (16 nM). In addition to having better bioavailability [61], and being a stronger agonist at CB1 and CB2 [62], nabilone has a longer duration of action (approximately 8–12 h), and half-life (approximately 35 h for active metabolites) compared to dronabinol (duration of action: approximately 4–6 h, half-life: approximately 4 h). For these reasons, nabilone may be preferred over dronabinol in this patient population.

This is one of the first studies to examine the effects of cannabinoids in the AD population. Agitation is frequently observed in institutionalized patients with AD and is associated with increased caregiver burden, decreased quality of life, more rapid disease progression and increased weight loss. Clinical trials with atypical antipsychotics, antidepressants, anticonvulsants, benzodiazepines and cognitive enhancers have demonstrated little to modest efficacy in AD patients with agitation, and have also been associated with harmful side effects. However, due to a lack of efficacious alternatives, clinicians are limited in their options to treat patients with pharmacological agents that are both safe and effective. Cannabinoids have a distinct pharmacologic profile that may offer an alternative approach to pharmacotherapy of agitation, as well as having benefits for weight and pain. Though trials with THC have not demonstrated any significant benefits for agitation, trials with synthetic cannabinoids have reported some benefits with comparable safety between drug and placebo. However, those trials had small sample sizes and short trial durations, and as such, need to be validated. The proposed study will provide an initial signal for efficacy and information regarding the feasibility of a larger, multicentre trial of the synthetic cannabinoid nabilone. A safe and efficacious treatment for agitation in AD could increase quality-of-life, reduce caregiver burden, and avoid the negative impact of untreated agitation on health care costs.

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The remaining authors have no conflicting interests to declare.

Authors' contributions

KL and NH designed the study. KL, NH and MR contributed to the protocol development. The Neuropsychopharmacology Research Group, co-directed by KL and NH, will be responsible for recruitment, assessments, data management, analysis interpretation of data, and publication of results. All authors read and approved the final manuscript.

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