

# Alzheimer's Disease

## ISSUE BRIEF ON ALZHEIMER'S DISEASE

### Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

### Definition

Alzheimer's disease (AD) is a neurodegenerative disorder that is distinct from normal aging and is the most common cause of dementia. Dementia refers to a decline in cognition (compared to a previously attained level of cognition) – to the point where it affects day-to-day life and social functioning. This decline is observable as memory loss, diminished reasoning skills and executive functioning (decision-making, planning), and changes to personality/mood and behavior. Neuropathological characteristics of the disease include deposition of  $\beta$ -amyloid ( $A\beta$ ) into what are called amyloid plaques (amyloidosis) and accumulation of tau protein into neurofibrillary tangles – both of which are implicated in neurodegenerative processes observed in AD brains (Alzheimer's Association).

## Diagnosis

The National Institute on Aging and the Alzheimer’s Association (NIA-AA) recently updated their clinical guidelines for diagnosing AD in 2011. These guidelines generally mirror the typically observed progression of AD, which is: 1) preclinical AD (individual may be undergoing amyloidosis, neurodegeneration, or both processes concurrently, but person is asymptomatic for AD; Sperling et al., 2011), 2) mild cognitive impairment (MCI) due to AD (patient shows signs of cognitive impairment but at levels below a dementia diagnosis; Albert et al., 2011), and 3) clinical AD (McKhann et al., 2011).

NIA-AA’s preclinical AD guidelines are a framework for advancing research into identifying preclinical states of AD rather than providing diagnostic criteria for the clinician. Due to research indicating that there are biomarkers for AD (a measurable indicator that may be found within the brain/body (e.g, a substance) that indicates the presence of a particular disease) in the absence of any observable changes, NIA-AA recommends further advancing this area of research to find biomarkers that best predict AD. In addition, they also recognize that there may be subtle cognitive changes in preclinical AD patients—they emphasize the need to develop more sensitive neurocognitive tools to capture these changes to lead to earlier diagnosis.

NIA-AA’s criteria for diagnosing mild cognitive impairment (MCI) due to AD include concern being brought to the attention of a clinician regarding a patient’s observed change in cognition (either from the patient, someone who knows the patient well, or the clinician). The patient must also show impairments in at least one cognitive domain that would be greater than what one would expect for someone that age and of their educational background. Furthermore, these impairments cannot be attributed to some other systemic or brain disease. These individuals must still be functioning at a relatively independent level, and they must not fit criteria for a dementia diagnosis.

Diagnosis of clinical AD has two main requirements which are to 1) meet core criteria for a dementia diagnosis, and 2) satisfy criteria that would indicate that the cause of dementia is either probably AD (probable AD) or possibly AD (possible AD). Criteria for dementia includes interference in ability to function at usual activities or work, a decline from a previously-attained level of functioning, impairments in cognition as indicated in the patient’s history and through cognitive assessments, and impairments in at least two cognitive domains (acquiring and remembering new information, reasoning/judgment, visuospatial skills, language skills, or changes to personality/behavior). Probable AD criteria includes the observation that symptoms have worsened gradually (months to years as opposed to over a few hours/days) as well as a historical record of this worsening trend, and that cognitive deficits either fall into an amnesic presentation (memory impairments) or non-amnesic presentation (language, visuospatial, executive functioning impairments).

## Prevalence

According to one model of AD prevalence, 6.08 million Americans had AD in 2017 (includes those with mild cognitive impairment due to AD, early clinical AD, and late clinical

AD). Those numbers are predicted to rise to 15.0 million cases in the US by 2060. According to the same model, 46.7 million Americans were in a preclinical AD state (asymptomatic individuals experiencing amyloidosis, neurodegeneration, or both amyloidosis and neurodegeneration). Preclinical AD cases are expected to rise to 75.68 million by 2060 (Brookmeyer et al., 2018).

There are certain risk factors that have been associated with an increased risk of an AD diagnosis. Those who are 60 years old and older are more susceptible to AD (Centers for Disease Control and Prevention; CDC), with 95% of all AD cases identified in patients  $\geq 65$  years old (Reitz & Mayeux, 2014). The rate of those with AD doubles every 5 years beyond age 65 (CDC). There also seems to be an inherited risk of developing AD if there are biological family members with the disease (CDC). Other risks include having a cardiovascular disease, Type II diabetes, high blood pressure, excessive body weight, and decreased mental stimulation (Reitz & Mayeux, 2014; CDC)

## Current Therapies

There are currently four FDA-approved pharmacotherapies for treating cognitive and functional decline in AD patients, which are: donepezil, galantamine, rivastigmine, and memantine. The first three are acetylcholine esterase (AChE) inhibitors, while the last one (memantine) is an N-methyl-D-aspartate (NMDA)-receptor antagonist (Anand et al., 2014).

AChE inhibiting drugs work by inhibiting the activity of an enzyme (acetylcholine esterase) that breaks down the neurotransmitter acetylcholine (ACh). Dementia is associated with a dysfunctional cholinergic system; therefore, AChE inhibitors are prescribed to enhance ACh levels (by inhibiting AChE, this gives ACh a longer period of time to act on receptor targets). AChE drugs are relatively affordable treatments that are generally well-tolerated (Birks, 2006). While cholinesterase inhibitors appear to be moderately effective in improving cognitive and functional status, the clinical meaningfulness of those changes are sometimes debated in the literature (Livingston et al., 2017; Epperly et al., 2017). In other words, a statistically significant change in dementia symptom scores may not necessarily translate into an observable, clinically significant improvement in dementia.

Memantine, as an NMDA-receptor antagonist (NMDA receptor is a glutamatergic receptor), is prescribed due to evidence of glutamatergic excitotoxicity in AD patients. Essentially, too much glutamate release has neurotoxic effects on cells; therefore, memantine works to block NMDA-receptor mediated activity to inhibit the perpetuation of this excessive glutamate release. According to a Cochrane review of memantine on dementia, evidence points to moderate efficacy of this drug on cognition and agitation in moderate to severe Alzheimer’s disease patients and is well tolerated (McShane et al., 2009).

Neuropsychiatric symptoms associated with dementia (i.e., depression, agitation) have been treated with antipsychotics (primarily for agitation) and antidepressants (for depression and agitation). However, neuropsychiatric symptoms are poorly managed overall due to low evidence of efficacy (Bains et al., 2002; Nelson & Devanand, 2011) or harms when prescribed to dementia patients. For example, there has been evidence to suggest increased risk of mortality

and cerebrovascular events with antipsychotic use in dementia patients (Schneider et al., 2005; Schneider et al., 2006).

There has been some interest in investigating the benefits of physical exercise and cognitive engagement in dementia patients. According to Forbes et al. (2015), there is little evidence to suggest that incorporating regular, physical exercise will improve cognition or neuropsychiatric symptoms in dementia patients. However, exercise may improve the ability for dementia patients to perform daily activities (Forbes et al., 2015).

Interest in cognitive engagement in dementia patients operates under the general idea that being cognitively stagnant accelerates cognitive decline. A couple Cochrane Reviews suggest that while highly structured cognitive tasks (some which focused on training in a particular cognitive domain) showed little evidence of improving cognitive function, more generalized cognitive engagement that exposed patients to a wide range of activities improved cognitive and social functioning (Bahar-Fuchs et al., 2013; Woods et al., 2012).

## Preclinical Studies

Preclinical research on the effects of cannabis or cannabinoids on AD has focused heavily on influencing endocannabinoid (eCB) signaling for its potential to provide neuroprotective effects in AD. A review paper of this preclinical work is summarized below, followed by two preclinical studies that indicate reductions in some markers of AD pathology with the administration of  $\Delta$ -9-tetrahydrocannabinol (THC) or cannabidiol (CBD).

**Aso E, Ferrer I. Cannabinoids for treatment of Alzheimer’s disease: moving toward the clinic. *Front Pharmacol.* 2014; 5: 37. doi: 10.3389/fphar.2014.00037.**

The authors cite the lack of effectiveness of AD-modifying treatments and highlight the potential of the endocannabinoid (eCB) system as a potential target for AD-modifying outcomes, particularly if eCB signaling can be enhanced during the asymptomatic period of AD (when pathological changes in the brain are not yet influencing observable changes in behavior and cognition). The authors subsequently review the state of the evidence on the role of the eCB system in AD pathology, which is summarized below.

Endocannabinoids (naturally occurring compounds within the brain that interact with cannabinoid receptors and affect neuronal transmission) have been documented to increase as a function of neuronal damage, suggesting that they may have a role in repair. For example, there has been evidence of increased CB2 receptor expression in post-mortem samples of AD patient brains, and this increased expression has been correlated with increased  $\beta$ -amyloid ( $A\beta$ ) levels and plaque formation – both of which are associated with AD pathology. Other evidence has shown that AD brains have dysregulatory fatty acid amide hydrolase activity (FAAH; an enzyme that primarily breaks down anandamide, one of the most well-studied eCBs to date). FAAH appears to be overexpressed in AD brains which has the following consequences: 1) the eCB anandamide is metabolized more quickly in AD brains, which leads to decreased eCB signaling in AD patients than in neurologically healthy patients, and 2) increased FAAH activity

in AD brains then leads to increased accumulation of the metabolite arachidonic acid (AA; FAAH breaks down anandamide into AA). The metabolite AA has been implicated in pro-inflammatory responses within the brain and in the immune system; therefore, the overexpression of FAAH in AD brains has the consequence of contributing to inflammatory processes that are typically not found in neurologically healthy individuals.

The authors also cite evidence of cannabinoids providing neuroprotection against A $\beta$ . For example, in rodents injected with A $\beta$  and subsequently administered an eCB or exogenous cannabinoid showed a greater number of healthy neurons (cell viability) after a period of time compared to controls, with other evidence also pointing to a reduction in A $\beta$ -induced impairments in memory. There is also evidence of eCB signaling affecting tau hyper-phosphorylation. In AD, the tau protein gets abnormally phosphorylated which has been implicated in cell death and synapse loss. A handful of studies have implicated both CB1 and CB2 receptor agonism playing a role in reducing tau hyper-phosphorylation. Evidence is also provided for the role of the eCB system in reducing neuroinflammatory responses found in AD brains. Increased proliferation and activation of microglia (a type of cell that supports central nervous system functions) signal inflammatory responses in AD, and according to evidence cited in the paper, CB2 receptor agonists and Sativex (pharmaceutical drug with 1:1 ratio of THC to CBD) seem to reduce microglial response in rodent models of AD.

**Cao C, Li Y, Liu H, Bai G, Mayl J, Lin X, et al. The potential therapeutic effects of THC on Alzheimer’s disease. *J Alzheimers Dis.* 2014; 42(3): 973-984.**

These authors introduced the cannabinoid THC to N2a-variant amyloid- $\beta$  protein precursor cells (N2a/A $\beta$ PPswe) to observe for A $\beta$  aggregation in vitro. A $\beta$  is secreted at high levels in N2a/A $\beta$ PPswe cells; therefore, these cells were chosen as an exploratory target for THC action. A prior study by Cao et al. (2009) showed evidence that caffeine suppressed brain A $\beta$  levels, with long-term administration decreasing A $\beta$  deposits in hippocampal and cortical regions. Therefore, differences in A $\beta$  aggregation in N2a/A $\beta$ PPswe cells was measured in THC-only, caffeine-only, and THC+caffeine experimental conditions compared to control. Enzyme-linked immunosorbent assays (ELISA) were conducted to measure A $\beta_{40}$  levels (A $\beta$  isoform that is most abundantly found in the brain) after N2a/A $\beta$ PPswe cells were treated with THC or caffeine for 6 hours, 24 hours, and 48 hours.

Compared to control, THC-treated and caffeine-treated N2a/A $\beta$ PPswe cells had lower concentrations of A $\beta_{40}$ . Furthermore, these reductions in A $\beta_{40}$  levels in both treatment conditions occurred in a dose-dependent manner; higher concentrations of THC and caffeine both lead to greater reductions in A $\beta_{40}$ . This was true for all incubation time periods (6 hrs vs. 24 hrs. vs 48 hrs). Data also showed that lower doses of THC was necessary to establish dose-dependent decreases in A $\beta_{40}$  accumulation compared to caffeine, suggesting greater efficacy of THC in inhibiting A $\beta$  production. Interestingly, incubation of both THC and caffeine in N2a/A $\beta$ PPswe cells did not further enhance A $\beta_{40}$  inhibition compared to THC treatment alone; this suggests the lack of a synergistic effect of both treatments to inhibit A $\beta$  production. Additional experimentation with a one-time treatment or repeated treatments of THC also demonstrated that repeated treatments were more effective in A $\beta$  inhibition, particularly at

higher THC doses. To establish that THC and caffeine did not have neurotoxic effects on N2a/A $\beta$ PPswe cells, a 3(4,5-dimethylthiazol-2-yl)2,5-diphenyl-2H-tetrazolium bromide (MTT) conversion assay was performed. MTT assay established that THC and caffeine were not neurotoxic to N2a/A $\beta$ PPswe cells indicating relative safety of these treatments. Additional study with THC-treated N2a/A $\beta$ PPswe cells in a fluorometric assay was indicative of decreased A $\beta$  aggregation as evidenced by decreased intensity of fluorescence in A $\beta$ . Furthermore, greater reductions of fluorescence in A $\beta$  was associated with higher THC concentrations. Lastly, because overexpression of glycogen synthase kinase 3 (GSK-3) and tau is associated with Alzheimer’s disease pathology, additional assays were performed to measure their expression with THC treatment. Data showed a dose-dependent effect of THC on GSK-3 and tau levels; greater THC concentrations decreased their expression. Overall, results suggest that THC and caffeine may be safe treatment options that can inhibit A $\beta$  production and other markers of Alzheimer disease pathology in vitro.

**Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis Sativa, on  $\beta$ -amyloid-induced toxicity in PC12 cells. *J Neurochem*. 2004; 89: 134-141.**

This study explored potential neuroprotective effects of the cannabinoid cannabidiol (CBD) on  $\beta$ -amyloid (A $\beta$ )-induced neurotoxicity. Alzheimer’s disease patients show accumulation of A $\beta$  peptide which induces oxidative stress on cells thus leading to an inflammatory response and apoptosis (programmed cell death). Therefore, these investigators examined whether the administration of CBD may reverse those effects. Cultured pheochromocytoma PC12 cells in rats were treated with A $\beta$  alone (A $\beta$ -only) or in conjunction with CBD (A $\beta$ +CBD). In the A $\beta$ +CBD condition, CBD was administered immediately before A $\beta$ . A third experimental condition included the administration of a CB1-receptor antagonist (SR141716A) 10 minutes prior to CBD administration (A $\beta$ +CBD+SR141716A). Cell viability was measured via 3(4,5-dimethylthiazol-2-yl)2,5-diphenyl-2H-tetrazolium bromide (MTT) conversion assay. Reactive oxygen species (ROS) formation and malondialdehyde (MDA) accumulation (respectively indicators of cellular oxidation and lipid peroxidation) were also measured. Investigators also observed for presence of caspase 3 protein as well as any evidence of DNA fragmentation (both are markers of apoptosis).

Close to 40% of PC12 cells incubated with A $\beta$  for 24 hours had died (A $\beta$ -only condition), supporting A $\beta$ ’s neurotoxic effects. Administration of CBD immediately before A $\beta$  (A $\beta$ +CBD) significantly reduced cell death compared to the A $\beta$ -only condition, with administration of higher concentrations of CBD leading to greater neuroprotection (fewer cell deaths). ROS accumulation had increased in A $\beta$ -only cells compared to untreated cells, and A $\beta$ +CBD cells showed significantly reduced ROS accumulation. The concurrent administration of CB1-receptor antagonist SR141716A in A $\beta$ +CBD-treated cells (A $\beta$ +CBD+SR141716A) showed similar levels of ROS attenuation as A $\beta$ +CBD-treated cells, suggesting that CBD’s neuroprotective effects are not mediated via CB1 receptors. MDA levels were significantly higher in A $\beta$ -only treated cells compared to untreated cells, with A $\beta$ +CBD treated cells showing fewer MDA accumulation compared to A $\beta$ -only cells. Higher concentrations of CBD in A $\beta$ +CBD treated cells showed greater reductions in MDA accumulation. The apoptosis assay (via appearance of caspase 3



band in PC12 cells) showed that A $\beta$ -only cells showed significant apoptosis within 6 hours of A $\beta$  administration; administration of A $\beta$ +CBD reversed those effects. Results also showed that untreated cells showed no DNA fragmentation while A $\beta$ -treated cells showed fragmentation. Concurrent CBD administration (A $\beta$ +CBD), especially at higher concentrations, appeared to decrease signs of DNA fragmentation. Lastly, while intracellular calcium levels were significantly elevated in A $\beta$ -treated cells, calcium levels were comparatively lower in A $\beta$ +CBD-treated cells. Results suggest to the authors that CBD may have neuroprotective, anti-apoptotic, and anti-oxidative effects against A $\beta$  peptide toxicity.

## Clinical Trials

In contrast to the preclinical research’s emphasis on manipulating the eCB system to reverse or slow down AD progression, the clinical literature has primarily investigated the role of cannabinoids in altering mood or behavior in AD patients. Therefore, there currently is a gap in the clinical literature to address whether cannabinoids can reverse or slow down the neurocognitive dysfunction that is found in AD patients.

There are some limitations in how much interpretive power the following clinical trials can provide. Firstly, sample sizes are quite small across the studies. Secondly, not all clinical trials that were found specifically focused on AD patients. Of the four clinical trials reviewed below, two of them specifically focused on AD patients (with one of those two studies only including two patients in their trial). The remaining two clinical trials focused on a broader group of dementia patients, including those diagnosed with vascular dementia or mixed dementia. Nevertheless, the justification for including these two studies is based on the composition of AD patients in the sample (majority of patients in both studies were composed of AD patients).

**Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer’s disease. *Int J Geriatr Psychiatry*. 1997; 12: 913-919.**

This was a double-blind, placebo controlled crossover study where the primary objective was to investigate the effects of dronabinol (synthetic THC) on anorexia in Alzheimer’s disease patients. In this 12-week study, patients were randomly assigned to one treatment arm (dronabinol capsule or placebo) for the first half (6 weeks) and were switched to the other treatment in the second half of the study (6 weeks). 5 mg of dronabinol was administered daily in two doses (2.5 mg each). Body weight, caloric intake, and skin-fold measures were dependent measures in this study. In addition, agitation (Cohen Mansfield Agitation Inventory; CMAI) and mood measures (Lawton Observed Affect Scale) were also collected in this study. A total of n = 12 patients were included in the analysis. While the amount of calories consumed did not change over the course of the study (nor were there any differences in caloric intake between treatment groups), body weight increased over the 12-week period with greater gains found in the patients who started on dronabinol first. Tricep skin fold thickness also showed an increase over the 12-week study and was not affected by treatment order. More importantly,

for the purposes of this research brief, there was a decrease in agitated behavior compared to baseline during the dronabinol treatment phase as measured by the CMAI. In addition, for patients who received dronabinol first, the decrease in agitated behavior persisted during the placebo phase that followed (authors do not explain what may underlie this persistence in the absence of any active treatment). Lastly, there was a decrease in negative affect over the 12-week study with this decrease being more pronounced during dronabinol treatment. Those who received dronabinol first showed a greater decrease in negative affect than those receiving placebo first.

**Walther S, Schüpbach B, Seifritz E, Homan P, Strik W. Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia. *J Clin Psychopharmacol*. 2011; 31(2): 256-257.**

This was a very small (n=2; both diagnosed with probable AD) randomized, double-blind crossover study investigating the effects of dronabinol on nighttime agitation and circadian disturbances. The study period was for 4 weeks in which one of the patients was randomly assigned to receive dronabinol for the first half (first 2 weeks) followed by placebo (second 2 weeks). The second patient had the opposite treatment order as the first patient. For the active treatment arm, a daily 2.5 mg evening dose of dronabinol was administered to patients. Patients wore a device on their wrist (worn like a wristwatch) to monitor nighttime agitation and circadian disturbances (continuous wrist actigraphy). Actigraphy was monitored from 9 pm to 6 am. In addition, the neuropsychiatric inventory (NPI) was administered weekly for patients to measure behavioral disturbances. The patient who received dronabinol first showed decreases in nocturnal motor activity (as measured by continuous wrist actigraphy) from baseline but saw a rebound to baseline levels by the 4th week (2nd week of placebo arm). The patient who received dronabinol last (3rd week of study, 1st week on dronabinol) saw a decrease in nocturnal activity in that 1st week but then saw an increase in nocturnal activity again. Nonparametric circadian rhythm analysis (NPCRA) showed that dronabinol improved circadian rhythms; both patients showed decreased fragmentation in circadian rhythms, stronger rhythms, and more stable interdaily rhythms during dronabinol treatment. Lastly, while NPI scores showed some decline during the study period (more apparent in the patient receiving dronabinol first), the authors noted that behavioral changes were very small clinically speaking across all NPI subdomains. The authors do not discuss results specifically on the agitation subdomain of the NPI. The major limitation of this study is the sample size which prevents results being analyzed statistically (conclusions based on descriptive analysis). Compared to the preceding clinical studies discussed above, it is also important to note that agitation as defined here is conceptually different from the studies above (nocturnal motor activity = agitation at night). Overall, apart from a potential signal of dronabinol having a regulatory role in circadian rhythms, the conclusions that can be drawn in this study are minimal due to study limitations.



**van den Elsen GA, Ahmed AI, Verkes R-J, Kramers C, Feuth T, Rosenverg PG, et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: a randomized controlled trial. *Neurology*. 2015; 84(23): 2338-2346.**

This was a randomized, double-blind, placebo-controlled multi-center study with dementia patients exhibiting neuropsychiatric symptoms (n=50; AD: n=34; Vascular dementia: n=7; Mixed dementia: n=9). The authors explored the idea that THC may be a pharmacological alternative to treating neuropsychiatric symptoms. Participants were randomly assigned to one of two treatment arms (parallel design)—either 4.5 mg THC tablet (Namisol) daily (split into three 1.5 mg doses at specific times of the day) or placebo tablet. The primary measure was scores on the Neuropsychiatric Inventory (NPI), which was measured at baseline, 14 days, and 21 days after the start of treatment. Participants diagnosed with Alzheimer’s disease, vascular dementia, or mixed dementia were eligible for the trial as long as they had an NPI score of at least 10 and also experienced agitation/aggression, and atypical motor behavior at least a month before the screening. NPI scores had decreased in both treatment groups at day 14 and 21, but these scores between the THC (n = 24) and placebo (n = 26) groups were not statistically different from each other. Therefore, THC did not improve neuropsychiatric symptoms over placebo. The authors concluded that the lack of a treatment effect would likely not have changed had they been able to recruit the initial target number of patients (design goal was 130 patients) by way of conditional power analysis. Lastly, results indicated that a 4.5 mg daily dose was well tolerated in this patient group, encouraging the authors to suggest further study with increased dosing in this patient population.

**van den Elsen GA, Ahmed AI, Verkes R-J, Feuth T, van der Marck MA, Rikkert MGM. Tetrahydrocannabinol in behavioral disturbances in dementia: A crossover randomized controlled trial. *Am J Geriatr Psychiatry*. 2015; 23(12): 1214-1224.**

This was a randomized, double-blind, placebo-controlled repeated crossover study with dementia patients exhibiting neuropsychiatric symptoms (n=22; AD: n=18; Vascular dementia: n=1; Mixed dementia: n=3). The primary objective of the study, similar to the research paper listed directly above, was to examine the efficacy of THC (in tablet form; Namisol) in treating neuropsychiatric symptoms. Participants underwent 6 treatment blocks in which each block consisted of an active treatment arm for 3 days and placebo for 3 days, followed by a 4-day washout period. Within each block, the order of treatment was randomized. THC dosage for blocks 1-3 was 1.5 mg split into two doses (0.75 mg twice daily), with an increase in dosage in blocks 4-6 to 3 mg (1.5 mg twice daily). Participants with Alzheimer’s disease, vascular or mixed dementia were eligible for the study if they scored at least a 10 on the Neuropsychiatric Inventory (NPI) and also experienced agitation or aggression. A total of 20 participants completed the study. Results showed no improvements in neuropsychiatric symptoms over placebo at both the low (1.5 mg daily) and high doses (3 mg daily). Neuropsychiatric symptoms, as measured by the NPI, had worsened for both placebo and THC groups over the 12-week study period. In addition, THC did not lead to decreases in agitated behavior or caregiver burden compared to placebo. Adverse events were similarly distributed across THC and placebo arms and were of mild to moderate severity.

## Ongoing Clinical Trials

As of early October 2018, two ongoing clinical trials were identified via ClinicalTrials.gov that investigated the effects of cannabis or cannabinoids on AD. They are discussed below to the extent information is available through the ClinicalTrials.gov website.

### **Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease (AD) (THC-AD) (THC-AD)**, <https://clinicaltrials.gov/show/NCT02792257>

This is a randomized, parallel assignment in-patient study of Dronabinol or placebo to Alzheimer’s patients (age 60-90) exhibiting agitation (Agit-AD). Investigators state that there are no FDA-approved meds for Agit-AD—“off-label” meds commonly given for Agit-AD (i.e., antidepressants, antipsychotics). Study purpose is to see how agitation in AD patients is affected by Dronabinol vs. placebo, with hypothesis that agitation will be decreased with Dronabinol. Treatment duration is for 3 weeks, with patients in the 1st week receiving 5 mg daily (split into two doses), then increasing to 10 mg daily (split into two doses) for the 2nd and 3rd week. Primary measures are: 1) Pittsburgh Agitation Scale, and 2) Neuropsychiatric Inventory (NPI). Secondary measure is 1) adverse events. Principal investigators are Drs. Paul Rosenberg and Brent Forester respectively of Johns Hopkins University and Mclean Hospital. Estimated study completion date is currently listed as December 2020.

### **Safety and Efficacy of Nabilone in Alzheimer's Disease**

<https://clinicaltrials.gov/show/NCT02351882>

This is a randomized, double blind, crossover study of Nabilone vs. placebo and its effects on agitation in AD patients (long-term care patients or outpatients, ≥55 years old). Participants will be in one treatment arm for 6 weeks followed by a one-week washout period, followed by the other treatment arm for 6 weeks (dosages not stated). Primary measure is 1) Cohen-Mansfield Agitation Inventory (CMAI). Secondary measures are: 1) Neuropsychiatric Inventory (NPI), 2) Standardized Mini-mental State Examination (xMMSE), 3) Severe Impairment Battery (SIB), 4) Alzheimer’s Disease Assessment Scale – Cognitive (ADAS-Cog), 5) Alzheimer’s Disease Cooperative Study – The Clinician Global Impression (ADCS-CGIC). They will also monitor pain, nutritional status, heart rate, blood pressure, and monitor specific biomarkers. Principal investigators are Drs. Krista Lanctot and Nathan Herrmann respectively of Sunnybrook Research Institute and Sunnybrook Health Sciences Centre. Estimated study completion date is currently listed as March 2019.

## Observational Studies

Two observational studies were identified that investigated the role of cannabis or cannabinoids in AD patients. These two studies specifically investigated the effects of THC or dronabinol on behavioral symptoms. Both studies had small sample sizes as well as lacking a comparator group(s) for statistical comparison, which puts the evidence here as lower quality

compared to more rigorously controlled studies with larger sample sizes. It should also be noted that, while the last of the two observational studies was not restricted to AD patients, it is included in this brief since the majority were AD patients.

**Shelef A, Barak Y, Berger U, Paleacu D, Tadger S, Plopsky I, et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an open-label, add-on pilot study. *J Alzheimers Dis.* 2016; 51(1): 15-9.**

This was an uncontrolled, open-label study looking at the effects of THC in oil form on neuropsychiatric symptoms, mental state, and global improvements in Alzheimer’s patients. Patients (n=11) in this study underwent a 4-week treatment with 1.65% potency THC oil derived from cannabis flowers (cannabinoid profile verified via laboratory testing). Patients were started on a daily 5 mg THC dose split into two doses (8 am and 8 pm). Patients’ daily dose was increased to 10 mg THC (5 mg twice daily) after two days if they experienced no adverse events or experienced minimal improvements. If the patient still experienced no adverse events or minimal improvements, patients could max out at 15 mg THC (7.5 mg twice daily). During the study, only 3 patients tolerated a dose increase while the others (n=7) remained at the minimal dose during the 4-week treatment period. The following primary measures were collected at baseline and at the end of the second and fourth week of treatment: the neuropsychiatric inventory (NPI), Mini-Mental State Examination to measure cognitive impairment (MMSE), Clinical Global Impression Improvement (CGI-I), and Clinical Global Impression Severity (CGI-S). A total of 10 patients were included in the analysis (n=1 discontinued treatment). Total NPI scores showed improvements in neuropsychiatric symptoms as a function of treatment. Compared to baseline, total NPI scores had decreased in the second and fourth week indicating improvements in neuropsychiatric symptoms. Analysis of NPI subdomains showed overall improvements in the following: agitation/aggression, disinhibition, irritability/lability, aberrant motor behavior, caregiver distress, delusions, and sleep and nighttime behavior disorders.

**Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl).* 2006; 185(4): 524-528.**

This was an uncontrolled, open-label study investigating the effects of dronabinol on nighttime agitation and neuropsychiatric behavior in dementia patients (n=6). Preceding the Walther et al. (2011) randomized control trial discussed previously in the “Clinical Trials” section of this brief, this was a relatively short-term study involving dronabinol treatment for 2 weeks. Patients diagnosed with dementia (5 Alzheimer’s dementia, 1 vascular dementia) and experiencing circadian rhythm disturbances and nighttime agitation were recruited for this study. A wrist actometer was worn by patients for the duration of the study to measure changes in nighttime motor activity (monitored activity counts) compared to baseline. In addition, the neuropsychiatric inventory (NPI) was measured at baseline and once again at the end of treatment. Dronabinol was administered as a 2.5 mg daily evening dose for 2 weeks. Motor activity counts were aggregated daily within 3 different data collection periods for the duration of the study: evening (3 pm-9 pm), nighttime (9 pm-6 am), and the diurnal period (6 am-9 pm). Motor activity counts during the last 5 days compared to baseline was the primary

outcome measure. Overall results showed that activity counts had decreased by the end of the treatment period and was observed for the 3 different data collection periods (evening, nighttime, diurnal). Nocturnal motor activity had, on average, decreased by 59% compared to baseline levels. Total NPI scores had also decreased by the end of the study with the following NPI subscores showing decreases by end of treatment: agitation, nighttime behaviors, aberrant motor behavior, irritability, and appetite disturbances. The numeric change in NPI scores was not provided in the paper to assess whether this decrease fell in a clinically meaningful range.

## **National Medical Organization Recommendations**

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of Alzheimer’s Disease were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. This report included a review of evidence on the effects of cannabinoids on dementia, including Alzheimer’s Disease. The committee for this report concluded that “there is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia” (see Conclusion 4-13; National Academies of Sciences, Engineering, and Medicine, 2017).

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