Dementia

ISSUE BRIEF ON DEMENTIA

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, 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

Dementia is a general term to describe 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 can manifest as memory loss, diminished reasoning skills and executive functioning, and changes in personality and behavior.

One assessment may not adequately diagnosis dementia; therefore, clinicians may perform a variety of assessments. For the purposes of this brief, diagnostic criteria from the most recent publication of the Diagnostic and Statistical Manual of Mental Disorders is presented here (DSM-5; American Psychiatric Association, 2013). According to the DSM-5, dementia is introduced by a new term: Major Neurocognitive Disorder. Diagnostic criteria for Major Neurocognitive Disorder is taken verbatim from the DSM-5 and presented below:
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
   2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications.

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

The section on Major Neurocognitive Disorder in the DSM-5 allows clinicians to further code by the origins of the neurocognitive disorder. These include: Alzheimer’s disease, Frontotemporal lobar degeneration, Lewy body disease, Vascular disease, Traumatic brain injury, Substance/medication use, HIV infection, Prion disease, Parkinson’s disease, Huntington’s disease, Another medical condition, Multiple etiologies, and Unspecified. Definitions/criterion for these diseases are further provided in the DSM-5.

For the purposes of this issue brief, the term Dementia will be used over Major Neurocognitive Disorder because of the wider public’s familiarity with the term and incorporation into common vernacular.

Prevalence

Approximately 47 million people were living with dementia worldwide according to 2015 estimates. Those numbers are expected to triple by 2050, with 9.9 million new cases projected to appear every year (Prince et al., 2015; World Health Organization, 2017). Patients with Alzheimer’s Disease (AD) account for 60-80% of all dementia cases followed by those with vascular dementia. Other less prevalent conditions associated with dementia are dementia with Lewy bodies and frontotemporal dementia (Ahmed, 2016; Stevens et al., 2002).

Dementia is most prevalent among the aging population (Ferri et al., 2005) and is a major cause of dependency and disability among the elderly. It has been estimated to cost society $818 billion annually (Prince et al., 2015).

Current Therapies

Currently there are both pharmacologic and non-pharmacologic therapies available for dementia patients. A review of some common therapeutic options will be discussed below.
**Pharmacological Interventions**

Cholinesterase inhibitors are commonly prescribed as pharmacotherapy in dementia patients with mild to moderate cognitive and functional decline, including Alzheimer’s dementia (Epperly et al., 2017), vascular dementia (Farooq et al., 2017), and Lewy body dementia (Velayudhan et al., 2017). This is because a dysfunctional cholinergic system often manifests in dementia patients. Cholinesterase inhibitors essentially slow the degradation of acetylcholine thereby allowing more of the neurotransmitter to be available for neuronal transmission. Common cholinesterase inhibitors include donepezil, rivastigmine, and galantamine, and these 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 is another treatment used to manage cognitive decline and, to a lesser degree, neuropsychiatric symptoms (e.g., agitation). Glutamatergic neurotransmission may have a role in dementia (too much glutamate release has neurotoxic effects on cells). Therefore, memantine inhibits glutamate release as an N-methyl-D-aspartate (NMDA) receptor antagonist. 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).

**Non-pharmacological Interventions**

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

There are a number of preclinical studies that suggest the role of the endocannabinoid system in dementia, particularly Alzheimer’s pathology. While clinical studies (which are discussed a later section) focus on managing dementia-related symptoms, a perusal of preclinical publications suggests great interest in manipulating the endocannabinoid system to control and even reverse the progression of dementia pathology. Since the focus of preclinical dementia research is quite variable – from methods to interfere with endocannabinoid metabolism to the development of a cannabinoid receptor knockout mouse model – this brief presents some studies that are most relevant to MN’s program. More precisely, the preclinical research below all investigate the role of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) specifically – the primary cannabinoids found in MN’s medical cannabis products.


This study explored potential neuroprotective effects of the cannabinoid cannabidiol (CBD) on β-amyloid (Aβ)-induced neurotoxicity. Alzheimer’s disease patients show accumulation of Aβ 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 Aβ alone (Aβ-only) or in conjunction with CBD (Aβ+CBD). In the Aβ+CBD condition, CBD was administered immediately before Aβ. A third experimental condition included the administration of a CB1-receptor antagonist (SR141716A) 10 minutes prior to CBD administration (Aβ+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 Aβ for 24 hours had died (Aβ-only condition), supporting Aβ’s neurotoxic effects. Administration of CBD immediately before Aβ (Aβ+CBD) significantly reduced cell death compared to the Aβ-only condition, with administration of higher concentrations of CBD leading to greater neuroprotection (fewer cell deaths). ROS accumulation had increased in Aβ-only cells compared to untreated cells, and Aβ+CBD cells showed significantly reduced ROS accumulation. The concurrent administration of CB1-receptor antagonist SR141716A in Aβ+CBD-treated cells (Aβ+CBD+SR141716A) showed similar levels of ROS attenuation as Aβ+CBD-treated cells, suggesting that CBD’s neuroprotective effects are not mediated via CB1 receptors. MDA levels were significantly higher in Aβ-only treated cells compared to untreated cells, with Aβ+CBD treated cells showing fewer MDA accumulation compared to Aβ-only cells. Higher concentrations of CBD in Aβ+CBD treated cells showed greater reductions in MDA accumulation. The apoptosis assay (via appearance of caspase 3 band in PC12 cells) showed that Aβ-only cells showed significant apoptosis within 6 hours of Aβ.
administration; administration of Aβ+CBD reversed those effects. Results also showed that untreated cells showed no DNA fragmentation while Aβ-treated cells showed fragmentation. Concurrent CBD administration (Aβ+CBD), especially at higher concentrations, appeared to decrease signs of DNA fragmentation. Lastly, while intracellular calcium levels were significantly elevated in Aβ-treated cells, calcium levels were comparatively lower in Aβ+CBD-treated cells. Results suggest to the authors that CBD may have neuroprotective, anti-apoptotic, and anti-oxidative effects against Aβ peptide toxicity.


This study examined the role of acetylcholinesterase (AChE) – an enzyme that metabolizes (breaks down) the neurotransmitter acetylcholine (Ach) – in β-amyloid (Aβ) accumulation. One of the hallmarks of Alzheimer’s disease is cholinergic dysfunction, specifically a decrease in cholinergic transmission in Alzheimer’s patients. Previous research has shown that AChE may actually induce and accelerate Aβ formation in Alzheimer’s disease and that AChE activity may be inhibited by compounds that can bind to the AChE peripheral anionic site (PAS; located on surface of AChE). This suggests that PAS of AChE may be a possible therapeutic target to inhibit AChE activity and, thereby prevent further Aβ formation. For example, propidium, a ligand that can bind to PAS of AChE has been shown to decrease human AChE activity and further prevent Aβ accumulation in vitro (Bartolini et al., 2003). Based on the chemical and structural characteristics of the cannabinoid THC, the authors hypothesized that THC may also be able to bind to PAS of AChE to inhibit AChE activity and prevent Aβ accumulation. AChE activity was measured via colorimetric determination assay, and Aβ peptide aggregation was measured via the thioflavin T-based fluorometric assay (more Aβ aggregation manifests as greater fluorescence in this assay).

Results revealed a proposed docking site of THC to mouse AChE. More importantly, THC was shown to inhibit AChE, with greater concentrations of THC associated with greater AChE inhibition. Additional experiments mixing AChE with THC + propidium revealed that the addition of propidium (a PAS ligand like THC is proposed to be) doesn’t lead to greater inhibition than mixing AChE with THC only. This suggests that THC and propidium cannot bind to AChE simultaneously (PAS binding can occur for either compound but not at the same time). Lastly, the fluorometric assay analysis suggested that THC – like propidium – can inhibit AChE-induced Aβ aggregation; mixing AChE with THC showed decreased Aβ staining/fluorescence compared to controls.


These authors introduced the cannabinoid THC to N2a-variant amyloid-β protein precursor cells (N2a/AβPPswe) to observe for Aβ aggregation in vitro. Aβ is secreted at high levels in N2a/AβPPswe 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 Aβ
levels, with long-term administration decreasing Aβ deposits in hippocampal and cortical regions. Therefore, differences in Aβ aggregation in N2a/AβPPswe 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 Aβ40 levels (Aβ isoform that is most abundantly found in the brain) after N2a/AβPPswe cells were treated with THC or caffeine for 6 hours, 24 hours, and 48 hours.

Compared to control, THC-treated and caffeine-treated N2a/AβPPswe cells had lower concentrations of Aβ40. Furthermore, these reductions in Aβ40 levels in both treatment conditions occurred in a dose-dependent manner; higher concentrations of THC and caffeine both lead to greater reductions in Aβ40. 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 Aβ40 accumulation compared to caffeine, suggesting greater efficacy of THC in inhibiting Aβ production. Interestingly, incubation of both THC and caffeine in N2a/AβPPswe cells did not further enhance Aβ40 inhibition compared to THC treatment alone; this suggests the lack of a synergistic effect of both treatments to inhibit Aβ production. Additional experimentation with a one-time treatment or repeated treatments of THC also demonstrated that repeated treatments were more effective in Aβ inhibition, particularly at higher THC doses. To establish that THC and caffeine did not have neurotoxic effects on N2a/AβPPswe cells, a 3(4,5-dimethylthiazol-2-y1)2,5-diphenyl-2H-tetrazolium bromide (MTT) conversion assay was performed. MTT assay established that THC and caffeine were not neurotoxic to N2a/AβPPswe cells indicating relative safety of these treatments. Additional study with THC-treated N2a/AβPPswe cells in a fluorometric assay was indicative of decreased Aβ aggregation as evidenced by decreased intensity of fluorescence in Aβ. Furthermore, greater reductions of fluorescence in Aβ 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 Aβ production and other markers of Alzheimer disease pathology in vitro.

**Clinical Trials**

A small handful of clinical trials were identified for dementia with all of them focusing on management of neuropsychiatric symptoms, particularly agitation. Overall safety profile of cannabinoids appears favorable in the treatment of dementia patients. However, the lack of consistent results across studies limits the strength of the evidence (Krishnan et al. 2009). Future studies would benefit by increasing sample sizes, greater efforts to standardize across study protocols, increasing treatment duration, and possibly increasing cannabinoid dosing in dementia patients.

This was a randomized, double-blind, placebo-controlled multi-center study with dementia patients exhibiting neuropsychiatric symptoms (n=50). 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.


This was a randomized, double-blind, placebo-controlled repeated crossover study with dementia patients exhibiting neuropsychiatric symptoms. 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.

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.


This was a very small (n=2) 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.

**Ongoing Clinical Trials**

As of mid-August 2017, two ongoing clinical trials were identified via ClinicalTrials.gov that investigated the effects of cannabis/cannabinoids on dementia, particularly dementia-related agitation. 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](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 December 2020.

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

[https://clinicaltrials.gov/show/NCT02351882](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 December 2017.
Observational Studies

Two observational studies examining the effects of cannabinoid administration on behavioral and neuropsychiatric symptoms were identified in dementia patients. These studies had small sample sizes limiting statistical power in addition to lacking a control group for comparative analysis. Authors from both papers suggest further study utilizing higher quality double-blind, randomized control trials with increased sample sizes.


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, 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 measures 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.


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.

**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 dementia were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. The committee for this report concluded that the evidence for cannabis/cannabinoids improving dementia-related symptoms is “limited due to the small number of patients enrolled, limits in the study design and reporting, and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabinoids” (see Conclusion 4-13; National Academies of Sciences, 2017).
References


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