

## Petition to add a Qualifying Condition to the Iowa Medical Cannabidiol Program

Condition: Alzheimer's Disease, unspecified ICD-10-CM G30.9

Alzheimer's disease (AD) is a progressive neurodegenerative condition. It is one of the most common forms of dementia, a group of symptoms that lead to a decline in mental function severe enough to disrupt daily life. Alzheimer's causes problems with a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities.<sup>i</sup> Alzheimer's disease is a brain disorder that begins in late-middle age or old age, and gradually worsens over time. AD is a degenerative disease that is characterized by the onset of dementia. Dementia, or a group of intellectual or social symptoms affecting brain functions (i.e. memory loss, judgment), that affects a person's ability to perform daily tasks or activities. Alzheimer's disease is the most common form of dementia, and slowly affects the parts of the brain that control thought, memory, and language. Early onset of symptoms can begin between the ages of 40 and 60. The late onset form of AD begins with onset of symptoms after the age of 60. Age and family history of the disease are risk factors for developing AD. No current treatments can cure the disease, and patients with AD will eventually require total care.<sup>ii</sup>

Alzheimer's disease causes many different symptoms which lead to a decreased quality of life. Patients can become aggravated, confused, depressed, apathetic, and withdrawn. AD damages and kills brain cells. The endocannabinoid system plays an active role in the mediation of the symptoms and progression of Alzheimer's disease, suggesting therapeutic benefits of cannabis use in patients living with AD. Cannabis has been shown to alleviate behavioral symptoms of AD, as well as removing plaque-forming proteins from brain cells – protecting nerve cells from cell death and inhibiting the progression of the disease. Cannabis has also shown its ability to block amyloid proteotoxicity initiated inflammatory response in patients with AD. As AD is incurable, cannabis shows therapeutic potential as a treatment for patients living with AD.<sup>iii</sup>

Attached is the Alzheimer's disease petition that was used for the Minnesota Cannabis Program. The petition contains excellent resources, summaries, and letters of recommendation. Accompanying the petition is the brief that the Minnesota Department of Health wrote in response to the petition. After reviewing the petition, the Minnesota Medical Cannabis program added Alzheimer's disease to the list of qualifying conditions. It is recommended that Alzheimer's disease be added as a qualifying condition in Iowa's Medical Cannabis Program to increase the quality of life for Iowans with Alzheimer's disease.

Thank you for your time and consideration.

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<sup>i</sup> <https://www.psychiatry.org/patients-families/alzheimers>

<sup>ii</sup> ICD-10-CM diagnostic guidelines

<sup>iii</sup> MN Medical Cannabis Program Petition to Add a Qualifying Medical Condition (Alzheimer's disease)



BEFORE THE IOWA MEDICAL CANNABIDIOL BOARD

Caitlin Anderson

Petition by (Your Name)

for the (addition or removal) of

Alzheimer's disease

}

PETITION FOR ADDITION or REMOVAL (Circle one)

(medical condition, medical treatment or debilitating disease) to the list of debilitating medical conditions for which the medical use of cannabidiol would be medically beneficial.

|   |  |   |   |
|---|--|---|---|
| Petitioner's Information  |  |   |   |
| Name (First, Middle, Last or Name of Organization):<br>Caitlin E Anderson                   |  |   |   |
| Home Address (including Apartment or Suite #):<br>6721 W 140th St N                         |  |   |   |
| City:<br>Mingo  |  | State:<br>IA                                    | Zip Code:<br>50168  |
| Telephone Number:<br>515-988-2618   |  | Email Address:<br>cat.anderson@medpharmiowa.com |   |
| Is this the person/ organization to whom information about the petition should be directed? |  |   | Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> |

|   |  |        |  |
|---|--|--------|--|
| Representative's Information (If applicable)  |  |        |  |
| Name (First, Middle, Last):   |  |        |  |
| Mailing Address (including Apartment or Suite #):   |  |        |  |
| City:   |  | State: | Zip Code:  |
| Is this the person/ organization to whom information about the petition should be directed? |  |        | Yes <input type="checkbox"/> No <input type="checkbox"/> |



|   |  |                      |  |
|---|--|----------------------|--|
| Telephone Number:   |  | Email Address:       |  |
| 1. Please provide the name of the specific medical condition, medical treatment, or debilitating disease you are seeking to add to or remove from the list of debilitating medical conditions for which patients would be eligible to receive a medical cannabidiol registration card. <i>Please limit to ONE condition, treatment, or debilitating disease per petition.</i> |  |                      |  |
| Recommended Action  |  | Condition or Disease |  |
| <input checked="" type="checkbox"/> Add<br><input type="checkbox"/> Remove  |  | Alzheimer's disease. |  |

2. Please provide a brief summary statement that supports the action urged in the petition. *Attach additional pages as needed.*

see attached



3. Please provide a brief summary of any data or scientific evidence supporting the action urged in this petition. *Attach additional pages as needed*

see attached

4. Please provide a list of any reference material that supports your petition.

see attached



5. Please provide a list of subject matter experts who are willing to testify in support of this petition (if any). The list of subject matter experts must contain names, background, email addresses, telephone numbers, and mailing addresses. *Attach additional pages if needed.*

| Name             | (1) | (2) | (3) |
|------------------|-----|-----|-----|
| Background       |     |     |     |
| Email address    |     |     |     |
| Telephone number |     |     |     |
| Mailing address  |     |     |     |

6. Please provide the names and addresses of other persons, or a description of any class of person, known by you to be affected by or interested in the proposed action which is the subject of this petition. *Attach additional pages if needed.*

See attached

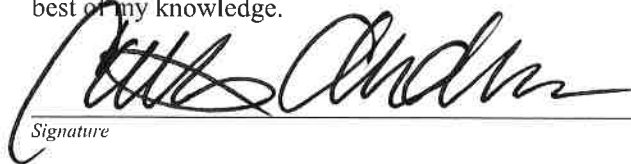


|  |  |                                |
|--|--|--------------------------------|
| 7. Please indicate whether you have attached a brief in support of the action urged in the petition. | Yes<br><input checked="" type="checkbox"/> | No<br><input type="checkbox"/> |
|--|--|--------------------------------|

|   |  |                                |
|---|--|--------------------------------|
| 8. Please indicate whether you are asking to make an oral presentation of the contents of the petition at a board meeting following submission of the petition. | Yes<br><input checked="" type="checkbox"/> | No<br><input type="checkbox"/> |
|---|--|--------------------------------|

9. Acknowledgement and Signature

By signing this document I certify that the information provided in this petition is true and accurate to the best of my knowledge.

  
Signature

9/30/2019  
Date (mm/dd/yyyy)

- Please fill out each section that is applicable to your petition. Failure to conform to what is required in this petition may result in a denial of consideration by the board.
  - You do not need to fill out sections asking for your representative's information if you do not have one.
  - For section 2, please provide a short, essay-like summary of your argument.
  - For section 3, please provide a short, essay-like summary of the articles and evidence that supports your position (if any).
  - For section 4, please provide a list of articles that are in support of your position (if any).
  - For section 5, please provide a list of experts that would be willing to testify in support of your position (if any). In the background section, please provide the reasons why they should be considered experts in the area: education, credentials, field of study, occupation, etc. This section is optional but will greatly aid in helping the board consider your petition.
  - For section 6, please provide information about groups of people that will be affected if the petition were approved. This could include people suffering from a specific disease, advocacy groups, local government officials, etc.
  - Sections 7 and 8 are optional but may aid the board in considering this petition.
- Please be aware:
  - The board may request that you submit additional information concerning this petition. The board will notify you of the requested materials in the event that more information is needed.
  - The board may also solicit comments from any person on the substance of this petition. The board may also submit this petition for a public comment period where any interested person may comment.
  - The board has six months after you submit this form to either deny or grant the petition. If approved, you will be notified in writing that the board has recommended the addition or removal of the medical condition, treatment, or debilitating disease to the board of medicine. If denied, the board will notify you in writing the reasons for denial.



- If the board denies your petition for failure to conform to the required form, you will be allowed to correct the errors and resubmit for consideration.
- **After you have completed this petition, please make sure that you sign, date it, and email, mail, or hand deliver to:**

**Iowa Department of Public Health  
Office of Medical Cannabidiol  
Lucas State Office Building  
321 E. 12th Street  
Des Moines, IA 50319-0075  
Email: [medical.cannabidiol@idph.iowa.gov](mailto:medical.cannabidiol@idph.iowa.gov)  
Phone: (515) 281-7996**

## Minnesota Medical Cannabis Program Petition to Add a Qualifying Medical Condition

### *Making your petition*

- Any person may petition the Minnesota Department of Health ("the department" or "MDH") to add a qualifying medical condition to those listed in subdivision 14 of Minnesota Statutes section 152.22.

**Petitions will be accepted only between June 1 and July 31, 2018.  
Petitions received outside of these dates will not be reviewed.**

**Petitions must be sent by certified U.S. mail to:**

Minnesota Department of Health  
Office of Medical Cannabis  
P.O. Box 64882  
St. Paul, MN 55164-0882

- You must mail the original copy of the petition with an original signature.
- Complete each section of this petition and attach all supporting documents. Clearly indicate which section of the petition an attachment is for.
- Each petition is limited to one proposed qualifying medical condition. If your petition includes more than one medical condition, it will be dismissed.
- If you are petitioning for the addition of a medical condition that was considered but not approved in a prior year's petition process, you **must include** new scientific evidence or research to support your petition or describe substantially different symptoms. Please refer to our website to see which medical conditions were reviewed in prior years (<http://www.health.state.mn.us/topics/cannabis/rulemaking/addconditions.html>).
- If the petition is accepted for consideration, MDH will send the petition documents to the Medical Cannabis Review Panel ("Review Panel"). MDH staff will also provide information to the Review Panel about the proposed qualifying condition, its prevalence, and the effectiveness of current treatments.
- You may *withdraw* your petition any time before the Review Panel's *first public meeting of the year* by submitting a written statement to the Department stating that you want to withdraw it.

### **Petition review process**

- An appointed citizens Review Panel will meet to review all eligible petitions and supporting documentation.
- MDH will post notice of the public meetings of the Review Panel on its medical cannabis website.
- After the public meeting and by November 1, 2018 the Review Panel will provide the Commissioner of Health a written report of findings.
- The Commissioner will approve or deny the petition by December 3, 2018.



Minnesota Medical Cannabis Program  
Petition to Add a Qualifying Medical Condition

| Section A: Petitioner's Information                          |  |                               |                         |
|--|--|-------------------------------|-------------------------|
| Name (First, Middle, Last): [REDACTED]                       |  |                               |                         |
| Home Address (including Apartment or Suite #):<br>[REDACTED] |  |                               |                         |
| City:<br>[REDACTED]  |  | State:<br>MN                  | Zip Code:<br>[REDACTED] |
| Telephone Number:<br>[REDACTED]                              |  | E-mail Address:<br>[REDACTED] |                         |

| Section B: Medical Condition You Are Requesting Be Added  |
|---|
| Please specify the name and provide a brief description of the proposed qualifying medical condition. Be as precise as possible in identifying the condition. <b>Optional:</b> Include diagnostic code(s), citing the associated ICD-9 or ICD-10 code(s), if you know them. <i>Attach additional pages as needed.</i> |
| Alzheimer's disease<br><br>ICD-10-CM G30.9<br><br>* see attached  |

Minnesota Medical Cannabis Program  
Petition to Add a Qualifying Medical Condition

**Section C: Symptoms of the Proposed Medical Condition and/or Its Treatment**

Describe the extent to which the proposed qualifying medical condition or the treatments cause suffering and impair a person's daily life. *Attach additional pages if needed.*

\* see attached

**Section D. Availability of conventional medical therapies**

Describe conventional medical therapies available and the degree to which they ease the suffering caused by the proposed qualifying medical condition or its treatment. *Attach additional pages if needed.*

\* see attached

Minnesota Medical Cannabis Program  
Petition to Add a Qualifying Medical Condition

**Section E: Anticipated benefits from Medical Cannabis**

Describe the anticipated benefits from the medical use of cannabis specific to the proposed qualifying medical condition. *Attach additional pages if needed.*

\* see attached

**Section F (optional): Scientific Evidence of Support for Medical Cannabis Treatment**

It will strengthen your petition to include evidence generally accepted by the medical community and other experts supporting the use of medical cannabis to alleviate suffering caused by the proposed medical disease or its treatment. This includes but is not limited to full text, peer-reviewed published journals or other completed medical studies. Please attach complete copies of any article or reference, not abstracts.

**I have attached relevant articles.** *(check box if you have attached scientific articles or studies)*

**Section G (optional): Letters in Support of Adding the Medical Condition**

Attach letters of support for the use of medical cannabis from persons knowledgeable about the proposed qualifying medical condition, such as a licensed health care professional.

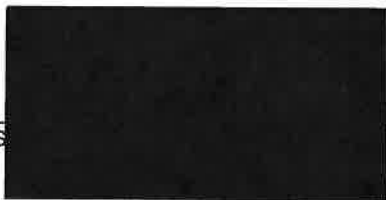
**I have attached letters of support.** *(check box if you have attached letters of support)*

Minnesota Medical Cannabis Program  
Petition to Add a Qualifying Medical Condition

**Section H: Acknowledgement and Signature**

*Please Note: Any individually identifiable health information relating to any past, present, or future health condition or health care contained in this Petition is classified as a health record under Minnesota Statutes §144.291, and is not subject to public disclosure.*

**I certify that the information provided in this petition is true and accurate to the best of my knowledge.**

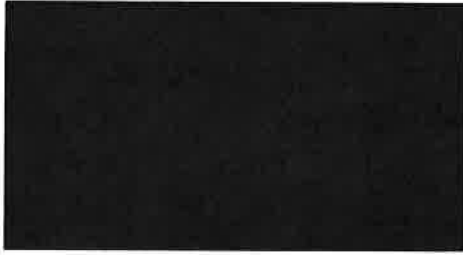


07/29/2018

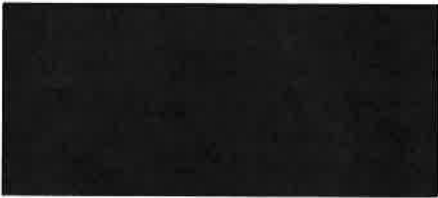
DATE (mm/dd/yyyy)

*To obtain this information in a different format, call:  
(651) 201-5598 in the Metro area and (844) 879-3381 in the Non-metro.*

## Section A: Petitioner's Information



### Co-petitioners:



## Section B: Medical Condition You Are Requesting Be Added

### Clinical Information: Alzheimer's Disease

- Condition: **Alzheimer's Disease, unspecified ICD-10-CM G30.9<sup>i</sup>**
- Alzheimer's disease (AD) is a brain disorder that begins in late-middle age or old age, and gradually worsens over time. AD is a degenerative disease that is characterized by the onset of dementia.<sup>i</sup>
- Dementia, or a group of intellectual or social symptoms affecting brain functions (i.e. memory loss, judgement), that affects a person's ability to perform daily tasks or activities. Alzheimer's disease is the most common form of dementia, and slowly affects the parts of the brain that control thought, memory, and language. Early onset form of AD, usually, begins with the onset of symptoms between the ages of 40 and 60 years old. The late onset form of AD begins with the onset of symptoms after the age of 60 years. Age and the family history of the disease are risk factors in developing AD. No current treatments can cure the disease, and patients with AD will eventually require total care.<sup>i</sup>
- Diagnostic criteria: three stages of Alzheimer's disease:
  1. Preclinical – changes in the brain that includes the buildup of extracellular amyloid plaques, intracellular neurofibrillary tangles, and other changes to nerve cells, AD may be in progress, but significant clinical symptoms are not yet evident.
  2. Mild Cognitive Impairment (MCI) – a pre-dementia stage characterized by evident symptoms of memory and/or thinking deficits that are more progressed than by normal standards for a person's age and education, but do not interfere with the person's independence. People with MCI may or may not progress to stage three/ dementia.
  3. Alzheimer's Dementia – the final stage of the disease in which symptoms, such as memory loss, word-finding difficulties, and visual/spatial

problems, significantly impair a person's ability to function independently.<sup>ii</sup>

- The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) provides three criteria for Alzheimer's disease:
  1. The diagnostic criteria for major or minor neurocognitive disorder is fulfilled:  
Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains\*:
    - i. Learning and memory
    - ii. Language
    - iii. Executive function
    - iv. Complex attention
    - v. Perceptual-motor
    - vi. Social cognition
  - b. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required 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).

\*Evidence of decline is based on: concern of the individual, a knowledgeable informant, or the clinician who have observed that there has been a significant decline in cognitive function; and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment<sup>iii</sup>

2. Onset and gradual decline of cognitive function in one or more areas for mild neurocognitive disorder, or two or more areas for major neurocognitive disorder.
  3. The diagnostic criteria for either possible or probable Alzheimer's dementia are fulfilled:
    - a. Presence of causal AD genetic mutation based on family history or genetic testing.
    - b. The following three indicators are present:
      - i. Decline in memory or learning, and one other cognitive area – based on history or trials of neuropsychological testing.
      - ii. Steady cognitive decline, without periods of stability.
      - iii. No indicators of other psychological, neurological, or medical issues responsible for cognitive decline.<sup>iv</sup>
- According to Mayo Clinic, when examining for potential AD, a doctor will perform a physical and neurological exam to test for overall neurological health by testing: reflexes, muscle tone and strength, ability to get up from a chair and walk across the room, sense of sight and hearing, coordination, and balance. Lab tests will be conducted to rule out other potential causes of memory loss and confusion. Brain imaging is utilized to identify visible abnormalities related to conditions other than AD that may cause cognitive

change; new imaging applications may enable doctors to identify specific brain changes caused by AD. Brain-imaging technology includes: magnetic resonance imaging (MRI), computerized tomography (CT), positron emission tomography (PET), and the testing of cerebrospinal fluid for biomarkers that indicate the likelihood of AD.<sup>v</sup>

### **Section C: Symptoms of Proposed Medical Condition and/or Its Treatments**

- Causations of Alzheimer's disease aren't yet fully understood yet, but its effect on the brain is clear: AD damages and kills brain cells.
- Symptoms of Alzheimer's disease: brain changes associated with AD lead to the progression of issues with memory, thinking and reasoning, making judgments and decisions, planning and performing familiar tasks, and changes in personality and behavior, such as depression, apathy, social withdrawal, mood swings, distrust in others, irritability and aggressiveness, changes in sleeping habits, wandering, loss of inhibitions, and delusions, such as believing something has been stolen. Many important skills aren't lost until late in the disease, such as the ability to read, dance and sing, enjoy music, engage in crafts and hobbies, tell stories, and reminisce.<sup>vi</sup>
- Alzheimer's disease damages and kills brain cells. As more and more brain cells die, AD leads to significant brain shrinkage. Two types of abnormalities are considered hallmarks of the disease: **plaques** (clumps of a protein called beta-amyloid may damage and destroy brain cells in several ways, including interfering with cell-to-cell communication – the collection of beta-amyloid on the exterior of brain cells is a prime suspect in brain-cell death), and **tangles** (threads of tau protein twist into abnormal tangles inside brain cells – leading to failure of the transport system – strongly implicated in the decline and death of brain cells).<sup>vi</sup>
- Cholinesterase inhibitor medications are used to treat early to moderate AD symptoms including memory, language, thinking, and judgement. The most common side effects of cholinesterase inhibitors are: most common are nausea, vomiting, and diarrhea. Other side effects may include: changes in vision or balance, dizziness/ fainting spells/ or falls, increase in frequency of passing urine or incontinence, nervousness/ agitation/ increased confusion, skin rash or hives, slow heartbeat/ or difficulty breathing, stomach pain, sweating, uncontrollable movements, unusual bleeding or bruising/ red or purple spots on skin, and weight loss. Other side effects may include: drowsiness, headache, indigestion or heartburn, loss of appetite, joint pain, muscle cramping, trouble sleeping, and fatigue. Benadryl (used for insomnia and allergies) and St. John's Wart (used to improve mood) have potential to interact with cholinesterase inhibitors. The following medical conditions require caution before beginning cholinesterase inhibitors: asthma or other lung disease, difficulty passing urine, head injury, heart disease, liver disease, kidney disease, low blood pressure, tobacco smoker, Parkinson's disease, seizures, severe headaches, stomach or intestinal disease (ulcers or stomach bleeding), a prior unusual or allergic reaction to donepezil, galantamine, rivastigmine, or other medicines, foods, dyes, or preservatives.<sup>vii</sup>
- Memantine side effects include: bloating or swelling of the face/ arms/ hands/ lower legs/ or feet, blurred vision, dizziness, headache, nervousness, pounding in the ears, slow or fast heartbeat, tingling of the hands or feet, unusual weight gain or loss, stomach pain, agitation, bleeding gums, black/ tarry stools, blistering/ peeling/ or loosening of the skin, blood in the urine or stools, chest pain, coma, constipation, continuing vomiting,

convulsions, dark-colored urine, decreased urine output, depression, fear, insomnia, fainting, fast/ pounding/ or irregular heartbeat or pulse, fatigue, high fever, high or low blood pressure, hostility, increased sweating, indigestion, itching, lethargy, light-colored stools, lip smacking or puckering, loss of consciousness, muscle twitching, no blood pressure, no breathing, no pulse, numbness or tingling in the arms or legs without any injury, pain/ tension/ and weakness upon walking, pinpoint red spots on the skin, puffing of the cheeks, rapid or worm-like movements of the tongue, recurrent fainting, red irritated eyes, skin lesions, seizures, severe constipation, severe headache, severe muscle stiffness, severe vomiting, sores/ ulcers/ or white spots in the mouth or on the lips, stupor, sudden severe weakness, total body jerking, trouble with speaking or walking, troubled breathing, uncontrolled chewing movements, unusual bleeding or bruising, unusually pale skin, loss of appetite, and jaundice (other side effects not listed may occur in some patients).<sup>viii</sup>

- Antidepressant medications are used to treat AD symptoms of depression, agitation, aggression, and mood disorders. Common side effects of antidepressants include: nausea, increased appetite, weight gain, reduced sex drive, difficulty reaching orgasm, erectile dysfunction, fatigue, drowsiness, insomnia, dry mouth, blurred vision, constipation, dizziness, agitation, restlessness, and anxiety; genetic variations in a person may determine whether or not an antidepressant will cause side effects or be an effective treatment. Side effects that may decrease as the patient's body adjusts to the medication including: More common: abnormal dreams, chills, constipation, decrease in sexual desire or ability, diarrhea, drowsiness, dry mouth, heartburn, increased sweating, loss of appetite, nausea, stomach pain or gas, stuffy or runny nose, tingling, burning, or prickly sensations, trembling or shaking, trouble sleeping, unusual tiredness or weakness, vomiting, and weight loss. Less commonly changes in taste, muscle tension, and yawning may subside. Rarely will night sweats subside.<sup>ix</sup>
- Namzaric (combination of a cholinesterase inhibitor and an NMDA receptor agonist) side effects include: muscle problems with anesthesia, slow heartbeat and fainting, increased stomach acid, nausea, vomiting, difficulty passing urine, seizures, and worsening of lung problems in people with asthma or other lung disease. Individuals taking Namzaric may see an improvement in cognition and overall mental function, and a temporary slowdown in the worsening of symptoms. However, there is no evidence that Namzaric prevents or slows the underlying disease process in patients with Alzheimer's disease.<sup>x</sup>
- Leukine (sargramostim) is a recombinant granulocyte-macrophage colony stimulating factor; a potent immune system stimulator used to "eat" the beta-amyloid plaques in the brain; side effects: most common include aching or pain in the bones and muscles, joint pain, chills, headache, nausea, vomiting, stomach pain, diarrhea, loss of appetite, fatigue, hair loss, weight loss, skin rash or itching, injection site reactions (redness, swelling, itching, lumps, irritation, or bruising; serious side effects include: chest pain, sudden weight gain, swelling of the hands or feet, shortness of breath, black stools, persistent stomach or abdominal pain, vomit that looks like coffee grounds (clotted blood from internal bleeding), fast or irregular heartbeat, vision problems, a sudden reddening of the face/ neck/ chest, severe dizziness, and fainting.<sup>xi</sup>



## **Section D: Availability of Conventional Medical Therapies**

- Treatments: drugs, creating a safe and supportive environment, exercise, and nutrition.
  - Drugs: Two types of drugs are currently used to treat cognitive symptoms: cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine in an attempt to slow the progression of symptoms of AD. A combination of donepezil and memantine (Namzaric). Sometimes, antidepressants are used to help control the behavioral symptoms associated with AD; sleeping medications, such as Ambien or Lunesta, may increase confusion and the risk of falls. Anti-anxiety medications, such as Klonopin and Ativan, increase the risk of falls, confusion, and dizziness. Treatment of inflammation may be required - Leukine (sargramostim). Alzheimer's Disease is found in middle to older adults who may also have other health conditions that limit the use of common AD treatments due to their side effects or interactions with other treatments.
  - Creating a safe and supportive environment: occupational therapy, music therapy, pet therapy, aromatherapy, massage therapy, art therapy; establish and strengthen routine habits and minimize memory-demanding tasks; remove clutter or excess furniture; mirrors can be confusing or frightening to people with AD.
  - Exercise: activities such as a daily walk can help improve mood and maintain the health of joints, muscles, and the heart; may also promote restful sleep and prevent constipation. Physical activity results in the production of endocannabinoids, and some studies have shown that exercise may slow the progression of AD.
  - Nutrition: offer high-calorie, healthy shakes and smoothies, water, juice, and other beverages (avoid caffeine as it can increase restlessness, interfere with sleep, and trigger a need for frequent urination) to prevent dehydration and constipation.<sup>v</sup>
- There is no cure for Alzheimer's disease.

## **Section E: Anticipated Benefits from Medical Cannabis**

- The following states allow patients with Alzheimer's disease access to medicinal cannabis: Arizona, Arkansas, California, Connecticut, Delaware, District of Columbia, Florida, Illinois, Maine, Massachusetts, Michigan, New Hampshire, North Dakota, Ohio, Oregon (degenerative or pervasive neurological condition), and Rhode Island.<sup>xii</sup>

## **Terpenoids as Potential Anti-Alzheimer's Disease Therapeutics**

This study investigated naturally occurring terpenoids and cannabinoids as anti-Alzheimer's Disease (AD) medication. Tetrahydrocannabinol is a widely-studied natural product with anti-emetic, anti-convulsive, anti-inflammatory, and analgesic effects. A protective effect of THC against AD has been reported. THC comparatively inhibits acetylcholinesterase (AChE) and increases the availability of acetylcholine (ACh). It also reduces the inhibition of AChE-induced A $\beta$  aggregation, and subsequently reduces A $\beta$ -induced toxicity. It is more efficient than commercially available AChE inhibitors, such as tacrine and donepezil, and reduced behavioral

and circadian disturbances in patients with severe dementia. Further, cannabidiol has neuroprotective effects against AD. The strong antioxidant effects of CBD provide neuroprotection by reducing oxidative damage such as lipid peroxidation. CBD also alleviates A $\beta$ -induced inflammatory signals. Further, Tau hyperphosphorylation, a pathological hallmark of AD, is also reduced by CBD treatment. The neuroprotective effects of CBD have been confirmed in an AD-mouse model induced with intrahippocampal injection of A $\beta$  by a reduction in glial activated pro-inflammatory mediators.<sup>xiii</sup>

### **The Role of the Endocannabinoid System in Alzheimer's Disease Facts and Hypotheses**

This research looked at various literature on the regulation and role of the endocannabinoid system in Alzheimer's disease, and the potential treatment of this disorder with cannabinoids and endocannabinoid-based drugs. The data review concluded that direct antagonists against the CB1 and CB2 receptors could prove beneficial for use in AD patients, but that indirect agonists might be as efficacious as, and safer than the direct antagonists. Additionally, endocannabinoids appear to also contribute to the cognitive symptoms of A $\beta$ -induced neurotoxicity and might be useful in late phases of the disorder to reduce the cognitive deficits of AD. Non-cannabinoid receptor-mediated mechanisms induced by the anti-inflammatory components of cannabis, for cannabidiol, might also be exploited in the future as relatively safe therapeutic strategies.<sup>xiv</sup>

### **The Potential Therapeutic Effects of THC on Alzheimer's Disease**

This study investigated the potential therapeutic qualities of tetrahydrocannabinol with respect to slowing or halting characteristics of Alzheimer's disease. N2a-variant amyloid- $\beta$  protein precursor cells (A $\beta$ PP) were incubated with THC and assayed for amyloid- $\beta$  levels at the 6, 24, and 48-hour time marks. Further testing was done on THC synergy with caffeine, which is not discussed in this summary. The study shows the proclivity to slow or halt Alzheimer's disease progression by dampening the synthesis of the major pathological marker of AD, A $\beta$ , at an extremely low dose of THC. The authors conclude that the multifaceted functions of THC will ultimately decrease downstream tau hyperphosphorylation and neuronal death, thereby halting or slowing the progression of Alzheimer's disease.

### **Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study**

A study from Israel examined whether tetrahydrocannabinol (THC) is an effective treatment for Alzheimer's disease as an add-on to the patient's current pharmacotherapy, in relieving behavioral and psychological symptoms associated with dementia (BPSD). The researchers observed and treated eleven patients with Alzheimer's disease (who suffered from BPSD) for four weeks on an open label trial. The researchers note that many studies have indicated that THC directly interacts with amyloid- $\beta$  peptide – a group of amino acids that are crucially involved in Alzheimer's disease as the main component of the amyloid plaques found in the brains of Alzheimer patients – associating the endocannabinoid systems involvement on neuroinflammation, neurogenesis, and the pathological processes of Alzheimer's disease. The researchers note that the endogenous cannabinoid system is involved with the central nervous

system with regulation of psychomotor activation, mood, sleep-wake cycle, and eating behavior – all said functions are impaired in moderate and severe dementia. Eleven inpatients were recruited during February 2013 – July 2014, with their diagnosis' in accordance with DSM-IV criteria for Alzheimer's dementia accompanied by BPSD. A form of botanical cannabis (MCO) was utilized for the study. MCO is an oil extract from cannabis flowers with a 1.65% potency. MCO of 2.5mg of THC was added to the patients' medication regime (mainly antipsychotic medications). If no adverse side-effects or any minor improvements were noticed after two days, the patients received an increased dosage to 5 mg of THC (as MCO) twice daily. The maximal dosage a patient received during the four-week study was 7.5 mg THC twice daily, with the minimal dose being 2.5 mg. During the four weeks, patients' weight, glucose level, and both systolic and diastolic blood pressure were assessed. Ten patients completed the full trial. Eight patients' medication regime included antipsychotic medications: 5-Risperidone, 2-Olanzapine, and 1-Clozapine; four patients received acetylcholinesterase inhibitors – used to relieve neurological symptoms of dementia. Three patients suffered adverse events, two not associated with MCO ingestion, with the third patient reducing to the minimal dosage of 2.5 mg/day – and the patient's adverse side-effect of confusion improved. Results of the study indicate that no significant changes were obtained for weight, glucose level, and both systolic and diastolic blood pressure. The researchers concluded that significant decreases in symptomology were observed in delusions, agitation/aggression, apathy, irritability, aberrant motor behavior, sleep and night time behavior disorders, and Caregiver distress was reduced. The researchers state that “there is no FDA-approved treatment for BPSD, but antipsychotic drugs are frequently prescribed off-label yielding only modest improvements associated with increased mortality.”<sup>xvi</sup>

### **A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology**

A study from California in 2006 demonstrated that the active component of marijuana,  $\Delta^9$ -tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid  $\beta$ -peptide (A $\beta$ ) aggregation (plaque formation in the brain) - the key pathological marker of Alzheimer's disease – in mice models, with control experiment results that were identical to those used to assay A $\beta$  aggregation (plaque formation). Through the study, the researchers found that THC shows competitive inhibition of AChE, and completely blocks the AChE effect on A $\beta$  aggregation – one of the most effective aggregation inhibitors reported to date. The researchers state that “it is noteworthy that THC is a considerably more effective inhibitor of AChE-induced A $\beta$  deposition than the approved drugs for Alzheimer's disease treatment, donepezil and tacrine;” (Eubanks et. Al.) Therefore, THC and other cannabinoids may provide therapeutic benefits for dementia by preventing neurotransmitter degradation and reducing A $\beta$  aggregation, thereby simultaneously treating both the symptoms of dementia and progression of Alzheimer's disease.<sup>xvii</sup>

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## **Alzheimer's Disease; Taking the Edge Off with Cannabinoids?**

A review by scientists from the Department of Physiology and Trinity College Institute of Neuroscience, Trinity College Dublin, in Ireland investigated the known pathological hallmarks of Alzheimer's disease, which include: the deposition of  $\beta$ -amyloid protein and hyper-phosphorylation of tau – evoking neuronal cell death and impairing inter-neuronal communication, neuroinflammation, excitotoxicity, and oxidative stress. The scientists investigate the proclivity of cannabinoids ability to exert a neuroprotective influence, and the mitigation of the symptoms of neurodegenerative disease (such as dementia). The scientists state that neuronal damage increases the production of endocannabinoids – implementing cannabis use as protection against deleterious consequences of pathogenic molecules such as amyloid- $\beta$  peptides (A $\beta$ ). A $\beta$  has been shown to induce hippocampal degeneration, gliosis, and cognitive decline. It is surmised that cannabis can reverse the negative consequences of exposure to A $\beta$  based on research conducted on rodents. Cannabidiol (CBD) has been shown to prevent A $\beta$ -mediated neurotoxicity (neuronal cell death), reverse tau hyper-phosphorylation by reducing phosphorylation of glycogen synthase kinase-3 $\beta$  – a tau protein kinase responsible for hyper-phosphorylation in Alzheimer's disease, oxidative stress, neuro-inflammation, and apoptosis (a process of programmed cell death). In several mouse models of Alzheimer's disease, neurogenesis is reduced – targeting adult neurogenesis is a means to mitigate the symptoms of Alzheimer's disease. Cannabis has been shown to regulate neurogenesis in the dentate gyrus of the hippocampus and the subventricular zone of the brain – resulting in the presence of newly generated neurons in the adult brain. In conclusion, the authors state that “Alzheimer's disease is a devastating illness for which there is no cure. Current AD drugs, which serve as AChE inhibitors, have several unpleasant side effects such as hepato-toxicity and gastrointestinal disturbances” (Campbell et. Al.). The process of neurodegeneration cannot be reversed with current treatments. It's surmised that cannabinoids can reduce the oxidative stress, neuroinflammation, and apoptosis that is evoked by A $\beta$  – while promoting the brain's essential repair mechanisms. (The authors state no conflict of interest).<sup>xviii</sup>

## **Amyloid Proteotoxicity Initiates an Inflammatory Response Blocked by Cannabinoids**

In this study from 2016, a proteotoxicity model based upon the inducible expression of beta amyloid (A $\beta$ ) in a human central nervous system nerve cell line to determine a distinct form of nerve cell death caused by the intracellular development of A $\beta$ . Intracellular A $\beta$  has been shown to induce a toxic inflammatory response – leading to cell death. A $\beta$  induces multiple proinflammatory genes and an increase in both arachidonic acid and eicosanoids, including prostaglandins that are neuroprotective and leukotrienes that potentiate cell death. The study concluded that cannabinoids have shown the ability to remove intraneuronal A $\beta$ , block the inflammatory response, and are neuro-protective. Early form of proteotoxicity can be blocked by the activation of cannabinoid receptors.<sup>xix</sup>

## **Cannabinoids Remove Plaque-forming Alzheimer's Proteins from Brain Cells**

Scientists from Salk Institute have found evidence, from the study mentioned above (*Amyloid Proteotoxicity Initiates an Inflammatory Response locked by Cannabinoids*), that tetrahydrocannabinol (THC) and other compounds found in cannabis can promote the cellular removal of amyloid beta (A $\beta$ ) – a toxic protein associated with Alzheimer's disease. A $\beta$  accumulates within the nerve cells of the aging brain well before the appearance of Alzheimer's disease symptoms and plaque formations. A $\beta$  is a major component of plaque deposits in Alzheimer's. High levels of A $\beta$  are associated with cellular inflammation and nerve cell death. It was found that exposing cells to THC reduced A $\beta$  levels and eliminated the inflammatory response, initiated by A $\beta$ , which allowed the nerve cells to survive.<sup>xx</sup>

## **Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease**

Quality of life and daily functioning are affected by common symptoms of aggression in patients living with Alzheimer's disease (AD), including: shouting, verbal insults, hitting, biting others, and throwing objects. Common symptoms of agitation include: excessive fidgeting, restlessness, pacing, shouting, screaming, and motor activities associated with anxiety (i.e. hand wringing). The first resource for treatment of aggression and agitation is person-centered care or behavioral therapy techniques. Antipsychotics may be prescribed for dangerous aggression and agitation, but it is not recommended any longer due to serious adverse events from side-effects of antipsychotics (i.e. stroke, mortality). New therapies that reduce the risk of adverse effects are needed for treatment of agitation and aggression in patients living with AD. The endocannabinoid system has shown great potential as a therapeutic target to treat AD pathology and symptomology. Previous studies have shown cannabis may have a beneficial impact on neurodegenerative and neuroinflammatory diseases, as well as being a neuroprotectant. Studies have shown that the use of a synthetic THC medication, dronabinol, significantly reduced aberrant vocalization, motor agitation, aggressiveness, and resistance to care. In patients with mild cognitive impairment, the presence of agitation and irritability was associated with abnormal concentrations of A $\beta$  plaque. Cannabis has been shown to remove or prevent the formation of A $\beta$  plaque-forming proteins in the brain. Also, aggression has not been associated with the medical use of cannabinoids in AD. Cannabis may offer patients with AD a better quality of life by reducing agitation, aggression, and other behavioral symptomology.<sup>xxi</sup>

### **Section F: Evidence of Support for Medical Cannabis Treatment**

Discussed literature:

*Terpenoids as Potential Anti-Alzheimer's Disease Therapeutics*

*The Role of the Endocannabinoid System in Alzheimer's Disease Facts and Hypotheses*

*The Potential Therapeutic Effects of THC on Alzheimer's Disease*

*Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study*

*A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology*

*Alzheimer's Disease; Taking the Edge Off with Cannabinoids?*

*Amyloid Proteotoxicity Initiates an Inflammatory Response Blocked by Cannabinoids*

*Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease*

## **Conclusion:**

The endocannabinoid system plays an active role in the mediation of the symptoms and progression of Alzheimer's disease, suggesting therapeutic benefits of cannabis use in patients living with AD. Cannabis has been shown to alleviate behavioral symptoms of AD, as well as removing plaque-forming proteins from brain cells – protecting nerve cells from cell death, and inhibiting the progression of the disease. Cannabis has also shown its ability to block amyloid proteotoxicity initiated inflammatory response in patients with AD. As AD is incurable, cannabis shows therapeutic potential as a treatment for persons living with AD. It is recommended that Alzheimer's disease be added as a qualifying condition in Minnesota's Medical Cannabis Program to increase the quality of life in patients with Alzheimer's disease.

## **Section G: Letters in Support of Adding the Medical Condition**

**\*see attached.**

### **Citations and research:**

<sup>i</sup>ICD-10-CM code.

<sup>ii</sup>Alzheimer's disease diagnostic guidelines.

<sup>iii</sup>DSM-5.

<sup>iv</sup>Alzheimer's disease/ dementia diagnostic criterions.

<sup>v</sup>Mayo Clinic AD diagnostic procedures and treatments.

<sup>vi</sup>AD symptomology.

<sup>vii</sup>Cholinesterase inhibitors side effects.

<sup>viii</sup>Memantine side effects.

<sup>ix</sup>Antidepressant side effects.

<sup>x</sup>Namzaric side effects.

<sup>xi</sup>Leukine side effects.

<sup>xii</sup>States allowing medicinal cannabis access for patients with AD.

<sup>xiii</sup>Terpenoids as Potential Anti-Alzheimer's Disease Therapeutics.

<sup>xiv</sup>The Role of the Endocannabinoid System in Alzheimer's Disease Facts and Hypotheses.

<sup>xv</sup>The Potential Therapeutic Effects of THC on Alzheimer's Disease.

<sup>xvi</sup>Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study.

<sup>xvii</sup>A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology.

<sup>xviii</sup>Alzheimer's Disease; Taking the Edge Off with Cannabinoids?

<sup>xix</sup>Amyloid Proteotoxicity Initiates an Inflammatory Response Blocked by Cannabinoids.

<sup>xx</sup>Cannabinoids Remove Plaque-forming Alzheimer's Proteins from Brain Cells.

<sup>xxi</sup>Cannabinoids for the Treatment of Agitation and Aggression in AD.

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<sup>iii</sup> *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, American Psychiatric Association, Arlington, VA 2013.

<sup>iv</sup> Major or Mild Neurocognitive Disorder Due to Alzheimers Disease DSM-5 331.0 (G30.9). (n.d.). Retrieved from [https://www.theravive.com/therapedia/major-or-mild-neurocognitive-disorder-due-to-alzheimers-disease-dsm--5-331.0-\(g30.9\)](https://www.theravive.com/therapedia/major-or-mild-neurocognitive-disorder-due-to-alzheimers-disease-dsm--5-331.0-(g30.9))

<sup>v</sup> <https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/diagnosis-treatment/drc-20350453>

<sup>vi</sup> Alzheimer's disease. (2017, December 30). Retrieved from <https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447>

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<sup>viii</sup> Memantine (Oral Route) Side Effects. (2017, March 01). Retrieved from <https://www.mayoclinic.org/drugs-supplements/memantine-oral-route/side-effects/drg-20067012>

<sup>ix</sup> Antidepressants: Get tips to cope with side effects. (2016, December 17). Retrieved from <https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20049305>

<sup>x</sup> [https://www.alz.org/national/documents/topicsheet\\_treatments.pdf](https://www.alz.org/national/documents/topicsheet_treatments.pdf)

<sup>xi</sup> Common Side Effects of Leukine (Sargramostim) Drug Center. (n.d.). Retrieved from <https://www.rxlist.com/leukine-side-effects-drug-center.htm>

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P.O. Box 18741  
Minneapolis, Minnesota 55418

Sensible policies, safer communities.

July 25, 2018

Commissioner Jan Malcolm  
Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882  
St. Paul, MN 55164-0882

Re: Petition to add Alzheimer's Disease as a Qualifying Condition for Medical Cannabis

Dear Commissioner Malcolm:

I write today to urge you to approve Alzheimer's Disease as a qualifying condition for medical cannabis in Minnesota. In 2016, Alzheimer's Disease was the primary cause of death for 2,220 Minnesotans according to data from the Minnesota Department of Health. That's 2,220 families who lost a loved one to this disease.

Typically, the Commissioner of Health looks to available conventional medical therapies for the treatment of the proposed condition. Medication therapy for Alzheimer's disease is limited to a handful of medications that treat cognitive symptoms, slow the progression of symptoms, or are used to control behavioral symptoms like insomnia, depression, and anxiety.

Anticipated benefits from medical cannabis are also examined. Research suggests the endocannabinoid system plays an active role in treating Alzheimer's disease, and that medical cannabis alleviates behavioral symptoms of the disease and is physiologically beneficial.

Alzheimer's disease is a progressive condition that does not get better, and patients and their families deserve the option of medical cannabis in the treatment regimen for this condition. Minnesota would join over fifteen other states that allow medical cannabis as a therapeutic treatment in palliative care for patients with Alzheimer's disease.

On behalf of Sensible Minnesota, I urge you to approve Alzheimer's disease as a qualifying condition for medical cannabis in Minnesota.

Sincerely,





July 23, 2018

Minnesota Department of Health Office of Medical Cannabis  
P.O. Box 64882  
St. Paul, MN 55164

To the Minnesota Department of Health,

My name is [REDACTED] I graduated with a PhD in Neuroscience from the University of Texas Southwestern Medical Center at Dallas, and my research has focused on neurogenesis and brain repair. I am a professor with the Holistic Cannabis Academy, author of *Vitamin Weed: A 4-Step Plan to Prevent and Reverse Endocannabinoid Deficiency*, and CEO of Infused Health, a technology platform for certified cannabis coaches.

I strongly support adding Alzheimer's disease as a qualifying condition to the Minnesota medical cannabis program, due to strong published and anecdotal evidence of both the safety and efficacy of cannabis for Alzheimer's. The U.S. government holds patent #6630507 on "Cannabinoids as Antioxidants and Neuroprotectants."<sup>1</sup> The abstract of the patent specifically states "the cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke or trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease..."

Several clinical trials have completed or are in progress on the role of cannabinoids in treating behavioral aspects of Alzheimer's disease. One study that is currently recruiting at John Hopkins University is investigating synthetic THC (Marinol) as a treatment for agitation in Alzheimer's disease.<sup>2</sup> This follows up on the small pilot study that found Marinol increased appetite and reduced severity of disruptive behavior in Alzheimer's patients.<sup>3</sup> One case study found Marinol stopped treatment-resistant dementia-associated sexual disinhibition that was disruptive in a nursing home.<sup>4</sup> Another study at Sunnybrook Health Sciences center is recruiting patients for a study on nabilone, a THC analogue, in reducing agitation, sleep issues, and other symptoms of dementia.<sup>5</sup>

In addition to the clinical research, there is extensive rodent research suggesting the cannabinoid system is involved in protecting the brain against the development of Alzheimer's disease. CBD reduces inflammation and gliosis in a mouse model of Alzheimer's disease, as well as promotes neurogenesis and neuron survival by increasing the endocannabinoid anandamide in the brain.<sup>6-8</sup>

In my personal experience as a cannabis educator and health coach, patients with Alzheimer's have responded well to cannabis products contain THC, CBD, or both. In fact, in Denver, Colorado, where I previously worked for the last four years, several nursing homes allowed the

use of cannabis to relieve anxiety and pain in patients as well as reduce violence towards caretakers. It is impossible to die from respiratory depression or other causes from cannabis, making it safer to use than any other prescription or over-the-counter drug.

In sum, I strongly urge you to add Alzheimer's disease as a qualifying condition for medical cannabis in Minnesota.

Sincerely,



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# 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 $\beta$ <sub>40</sub> 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 $\beta$ <sub>40</sub>. Furthermore, these reductions in A $\beta$ <sub>40</sub> levels in both treatment conditions occurred in a dose-dependent manner; higher concentrations of THC and caffeine both lead to greater reductions in A $\beta$ <sub>40</sub>. 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 $\beta$ <sub>40</sub> 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 $\beta$ <sub>40</sub> 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).