MDH Minnesota Department *of* Health

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.

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Minnesota Medical Cannabis Program
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Section A: Petitioner's Information		
Name (First, Middle, Last): [redacted]		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: MN	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [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. **Optional:** Include diagnostic code(s), citing the associated ICD-9 or ICD-10 code(s), if you know them. *Attach additional pages as needed.*

Alzheimer's disease

ICD-10-CM G30.9

* See attached

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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

MDH Minnesota Department *of* Health

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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)*

MDH Minnesota Department of Health

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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.

[redacted]

S

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

[redacted]

Co-petitioners:

[redacted]

Section B: Medical Condition You Are Requesting Be Added

Clinical Information: **Alzheimer's Disease**

- Condition: **Alzheimer's Disease, unspecified ICD-10-CM G30.9**[i]
- 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.[i]
- 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.[i]
- 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.[ii]

- The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) provides three criterions 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[iii]
    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.[iv]
- 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.[v]

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.[vi]
- 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).[vi]
- 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.[vii]
- 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).[viii]

- 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.[ix]
- 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.[x]
- 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.[xi]

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.[v]

- 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.[xii]

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 Aß aggregation, and subsequently reduces Aß-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 Aß-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 Aß by a reduction in glial activated pro-inflammatory mediators.[xiii]

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 Aß-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.[xiv]

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-ß protein precursor cells (AßPP) were incubated with THC and assayed for amyloid-ß 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, Aß, 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-ß 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."[xvi]

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, Δ9-tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid â-peptide (Aß) 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 Aß aggregation (plaque formation). Through the study, the researchers found that THC shows competitive inhibition of AChE, and completely blocks the AChE effect on Aß 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 Aß 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 Aß aggregation, thereby simultaneously treating both the symptoms of dementia and progression of Alzheimer's disease.[xvii]

Corresponding Researcher:

Kim D. Janda: Department of Chemistry, The Scripps Research Institute and the Skaggs Institute for Chemical Biology.

Phone: 858-784-2515

Fax: 858-784-2595

Email: kdjanda@scripps.edu

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 ß-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-ß peptides (Aß). Aß has been shown to induce hippocampal degeneration, gliosis, and cognitive declined. It is surmised that cannabis can reverse the negative consequences of exposure to Aß based on research conducted on rodents. Cannabidiol (CBD) has been shown to prevent Aß-mediated neurotoxicity (neuronal cell death), reverse tau hyper-phosphorylation by reducing phosphorylation of glycogen synthase kinase-3B – 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 Aß – while promoting the brain's essential repair mechanisms. (The authors state no conflict of interest).[xviii]

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 (Aß) in a human central nervous system nerve cell line to determine a distinct form of nerve cell death caused by the intracellular development of Aß. Intracellular Aß has been shown to induce a toxic inflammatory response – leading to cell death. Aß 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 Aß, block the inflammatory response, and are neuro-protective. Early form of proteotoxicity can be blocked by the activation of cannabinoid receptors.[xix]

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 (Aß) – a toxic protein associated with Alzheimer's disease. Aß accumulates within the nerve cells of the aging brain well before the appearance of Alzheimer's disease symptoms and plaque formations. Aß is a major component of plaque deposits in Alzheimer's. High levels of Aß are associated with cellular inflammation and nerve cell death. It was found that exposing cells to THC reduced Aß levels and eliminated the inflammatory response, initiated by Aß, which allowed the nerve cells to survive.[xx]

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 Aß plaque. Cannabis has been shown to remove or prevent the formation of Aß 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.[xxi]

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:

[i]ICD-10-CM code.
[ii]Alzheimer's disease diagnostic guidelines.
[iii]DSM-5.
[iv]Alzheimer's disease/ dementia diagnostic criterions.
[v]Mayo Clinic AD diagnostic procedures and treatments.
[vi]AD symptomology.
[vii]Cholinesterase inhibitors side effects.
[viii]Memantine side effects.
[ix]Antidepressant side effects.
[x]Namzaric side effects.
[xi]Leukine side effects.
[xii]States allowing medicinal cannabis access for patients with AD.
[xiii] Terpenoids as Potential Anti-Alzheimer's Disease Therapeutics.
[xiv] The Role of the Endocannabinoid System in Alzheimer's Disease Facts and Hypotheses.
[xv] The Potential Therapeutic Effects of THC on Alzheimer's Disease.
[xvi] Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study.
[xvii] A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology.
[xviii] Alzheimer's Disease; Taking the Edge Off with Cannabinoids?
[xix] Amyloid Proteotoxicity Initiates an Inflammatory Response Blocked by Cannabinoids.
[xx] Cannabinoids Remove Plaque-forming Alzheimer's Proteins from Brain Cells.
[xxi] Cannabinoids for the Treatment of Agitation and Aggression in AD.

[i] ICD-10-CM Codes. (n.d.). Retrieved from https://www.icd10data.com/ICD10CM/Codes/G00-G99/G30-G32/G30-/G30.9

[ii] Alzheimer's Disease Diagnostic Guidelines. (n.d.). Retrieved from https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines

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

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Sensible Minnesota

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,

[redacted]

INFUSED HEALTH

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."[1] 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.[2] This follows up on the small pilot study that found Marinol increased appetite and reduced severity of disruptive behavior in Alzheimer's patients.[3] One case study found Marinol stopped treatment-resistant dementia-associated sexual disinhibition that was disruptive in a nursing home.[4] 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.[5]

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.[6-8]

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,

[redacted]

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