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, 2017.
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.
- ☐ 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, the Review Panel will provide the Commissioner of Health its written report of findings.
- ☐ The Commissioner will approve or deny the petition by December 1.

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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.*

Autism Spectrum Disorder

See attached Section B.

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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 C.

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 Section D.

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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 E.

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)*

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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] 07/31/2017

SIGNATURE 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

Authors and Co-petitioners:

[redacted]

[redacted]

Section B: Medical Condition You Are Requesting Be Added

Clinical Information:

- **Autism Spectrum Disorder (ASD)** begins in childhood and is marked by the presence of abnormal or impaired development in social interaction, communication, and restricted repertoire of activity and interest. Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual.[1]

- ASD is characterized by impairments in social interaction and communication accompanied by a pattern of repetitive, stereotyped behaviors and activities. Developmental delays in social interaction and language surface early on, prior to age 3 years.

- Autism Spectrum Disorder is typically diagnosed in early childhood. The hallmark characteristics of ASD involve impairments in communication, social interactions and presence of repetitive behaviors.

    - For example: Children with autism might have problems talking with you, or they might not look you in the eye when you talk to them. They may spend a lot of time putting things in order before they can pay attention, or they may say the same sentence or words over and over in an effort to calm themselves down. They often seem to be in their "own world."

- Autism is considered a "spectrum disorder" because those with autism can have very different features or symptoms and varying degrees of functional deficit.

- Autism is a lifelong condition for which there is no cure.

- There are myriad of treatments option which range from biologically-based therapies such as nutritional supplements, special diets, chelation, oxygen therapies, and pharmacologic therapies; to behaviorally-based, intentional recreational therapies, including music, pet, auditory integration, sensory integration, drama, dance, acupuncture, massage, yoga, and chiropractic care.[2] Initiating treatment as early as possible is important to achieving successful outcomes.

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

Diagnostic Criteria and Symptomology

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by 3 of 3 symptoms:

A1. Deficits in social-emotional reciprocity; ranging from abnormal social approach, failure of normal back and forth conversation; through reduced sharing of interests, emotions, and affect and response; to total lack of initiation of social interaction.

- Abnormal social approach: unusual social initiations like touching or licking; or use of others as tools.
- Failure of normal back and forth (reciprocal) conversation.
- Reduced sharing of interests.
- Reduced sharing of emotions/affect: lack of responsive smile, failure to share enjoyment, excitement or achievements with others, failure to respond to praise or show pleasure in social interactions, failure to comfort others, indifference/aversion to physical contact.
- Lack of initiation of social conversation.
- Poor social imitation: failure to engage in simple social games.

A2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated-verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

- Impairment in social use of eye contact (early detector).
- Impairment in the use and understanding of body postures (facing away from speaker).
- Impairment in understanding and use of gestures.
- Abnormal volume, pitch, intonation, rate, rhythm, stress, and prosody of speech.
- Abnormal use and understanding of affect: impairment in use of facial expressions, lack of warm/joyful expression to others, limited communication of own affect, inability to recognize or interpret others' nonverbal expressions.
- Lack of coordinated verbal or non-verbal communication: eye contact or body language with words.

- Lack of coordinated non-verbal communication; eye contact with body language.

A3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people.

- Difficulty in developing and maintain relationships appropriate to developmental level: (Lack of "theory of mind"/ to take another's perspective)
- Difficulty adjusting behavior to suit social contexts: (does not notice another's lack of interest in an activity, lack of response to contextual cues, in appropriate expression of emotions, unaware of appropriate social behavior, does not notice another's distress or disinterest, does not notice when not welcomed in play or conversation; limited recognition of social emotions such as being teased, or how their behavior impacts others.
- Difficulty in sharing in imaginative play: (no imaginative play with peers when > 4 years old).
- Difficulty making friends: (does not try to establish friendships, lack of cooperative play, does not play in groups, does not play with others of same age or developmental level, has interest in friendships but lack understanding of conventions of social relationships, does not respond to the social approaches of children.

<u>Severity is based on social communication impairments and restricted, repetitive patterns of behavior.</u>

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history.

B1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrase

- Stereotyped or repetitive motor movements, use of objects, or speech (pedantic or unusually formal speech, echolalia, jargon or gibberish > 24 months, use of rote language, idiosyncratic or metaphorical language, pronoun reversal, refers to self by name vs "I", perseveration, repetitive vocalizations).

B2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).

- Adherence to routine: (specific unusual multi-step sequences, insistence in rigidity, unusual routines
- Ritualized patterns of verbal and non-verbal behaviors: (repetitive questioning on a particular topic, verbal rituals, compulsions –movement, lining up toys, etc)
- Excessive resistance to change: (difficulty with transitions, over-reactive to trivial changes)
- Rigid thinking: (inability to understand humor, inability to understand nonliteral speech, rigid and inflexible or rule-bound behaviors)

B3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

- Preoccupations; obsessions • Interests that are abnormal in intensity • Narrow range of interests • Focused on the same few objects, topics or activities • Preoccupation with numbers, letters, symbols • Being overly perfectionistic • Interests that are abnormal in focus • Excessive focus on nonrelevant or nonfunctional parts of objects • Preoccupations (e.g. color; time tables; historical events; etc.) • Attachment to unusual inanimate object (e.g., piece of string or rubber band) • Having to carry around or hold specific or unusual objects (not common attachment objects such as blankets, stuffed animals, etc.) • Unusual fears (e.g. afraid of people wearing earrings).

B4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

- High tolerance for pain
- Poking own eyes
- Preoccupation to texture or touch
- Unusual visual exploration or activity: (close visual observation of objects or self with no purpose, looks at objects from corner of eyes, unusual squinting of eyes, extreme fascination with watching movement of things)
- In all sensory domains consider: (odd responses to sensory input or atypical, persistent focus on sensory input)
- Unusual sensory exploration with objects (sound, smell, taste, vestibular): licking or smelling objects out of context

<u>Severity is based on social communication impairments and restricted, repetitive patterns of behavior.</u>

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities

Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.[1]

Section D: Availability of Conventional Medical Therapies

Autism has no cure and treatments vary based on patient.[3]

Pharmacological therapies

Pharmacological therapies are used to treat severe and sustained behaviors that negatively impact a child's ability to participate in daily activity. They may also be used when other treatment approaches have failed to adequately improve symptoms or behaviors. In some cases, medications are used to treat comorbid conditions that exist within the child with Autistic Spectrum Disorder. The FDA has approved two medications for the treatment of ASD associated behavioral: Risperidone and Abilify. These medications are classified as atypical antipsychotic medications that carry significant side effects. Parents are often forced to choose between giving their child and medication that has serious side effects or watch their child suffer through multiple "take downs" and physical holds (non-violent crisis intervention) in an effort to keep everyone safe.

*Atypical Antipsychotic Agents

- **Sedation**
    - Sedation is common with antipsychotic medications and is dose related. It can be a cause of poor compliance and, if persistent, can interfere with social and vocational

functioning. Many patients become tolerant to the sedative effect over time. Low-potency first generation antipsychotics (FGAs) and clozapine are the most sedating, with some effect from olanzapine (Zyprexa) and quetiapine (Seroquel).[4]

- **Hypotension**
  - Orthostatic hypotension can occur with all antipsychotic medications, depending on the degree of α_1-adrenoreceptor antagonism, particularly with low-potency FGAs and clozapine. It can also occur with risperidone (Risperdal) and quetiapine, especially with rapid titration. This effect is more common in older adults (with risk of falls), those on blood pressure medications, and those who have other cardiovascular diseases.[4]

- **Anticholinergic Effects**
  - Anticholinergic effects include constipation, urinary retention, dry mouth, blurred vision and, at times, cognitive impairment. These symptoms can lead to other problems such as tooth decay, falls, or gastrointestinal obstruction. Low-potency FGAs and clozapine are highly likely to cause anticholinergic effects; olanzapine and quetiapine have been shown to do so at high dosages.[4]

- **Extrapyramidal Symptoms**

  - Antipsychotic medications cause four main extrapyramidal symptoms: pseudo parkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The first three usually begin within a few weeks of starting a new medication (or increasing the dosage). These symptoms may cause discomfort, social stigma, and poor compliance. They are more likely to occur with higher dosages of high-potency FGAs, such as haloperidol (formerly Haldol), and are less likely with FGAs that have weaker dopamine blockade. Several meta-analyses, most comparing second generation antipsychotics (SGAs) with haloperidol, have shown that SGAs are less likely to cause extrapyramidal symptoms. However, recent studies comparing SGAs with lower potency FGAs have not shown this difference.[4]

- **Pseudo parkinsonism**
  - Pseudo parkinsonism is a reversible syndrome that includes tremulousness in the hands and arms, rigidity in the arms and shoulders, bradykinesia, akinesia, hyper salivation, masked facies, and shuffling gait. The presence of bradykinesia or akinesia can create a diagnostic dilemma, with symptoms resembling depression or even the negative symptoms of schizophrenia (i.e., an inability to pay attention, the loss of a sense of pleasure, the loss of will or drive, disorganization or impoverishment of thoughts and speech, flattening of affect, and social withdrawal).[4]

- **Akathisia**

- Akathisia is described subjectively as a feeling of inner restlessness that can be manifested as excessive pacing or inability to remain still for any length of time. It can be difficult to differentiate akathisia from psychiatric anxiety and agitation[4]

- **Dystonic reactions**
  - Dystonic reactions are spastic contractions of the muscles, including oculogyric crisis, retrocollis, torticollis, trismus, opisthotonos, or laryngospasm. These reactions are uncomfortable and can be life threatening if left untreated.[4]

- **Tardive dyskinesia**
  - Tardive dyskinesia is an involuntary movement disorder that can occur with long-term antipsychotic treatment, and may not be reversible even if the medication is discontinued. Tardive dyskinesia usually involves the orofacial region, but all parts of the body can be involved. Abnormal movements can include myoclonic jerks, tics, chorea, and dystonia. They become most evident when patients are aroused, but ease during relaxation and disappear during sleep.[31] Risk factors for developing tardive dyskinesia include long-term therapy with higher dosages, older age, female sex, and concurrent affective disorders. Attempts to treat tardive dyskinesia usually begin by discontinuing the offending agent or switching to one with a lower risk, but evidence is insufficient to show that this or any other treatment markedly reduces symptoms after onset.[4]

- **Hyperprolactinemia**
  - Antipsychotics cause high prolactin levels by blocking the normal tonic inhibition on pituitary mammotropic cells of dopamine produced in the hypothalamus. Hyperprolactinemia is common with the use of any FGA, as well as with the SGA risperidone (up to 60 percent of women and 40 percent of men), and is dose dependent. It appears to be much less common with other SGAs, but has been reported with the use of olanzapine and ziprasidone (Geodon) at high dosages.[4]

  - Hyperprolactinemia can be asymptomatic, but may cause gynecomastia, galactorrhea, oligo- or amenorrhea, sexual dysfunction, acne, hirsutism, infertility, and loss of bone mineral density. Symptoms often appear within a few weeks of beginning the antipsychotic or increasing the dosage, but can also arise after long-term stable use.[4]

  - There is growing evidence that chronic hyperprolactinemia from antipsychotics can cause osteoporosis and an increased risk of hip fracture. A recent case-control analysis of a large general practice database in the United Kingdom showed that the risk of hip fracture was 2.6 times higher in patients taking prolactin-raising antipsychotics compared with the general population.[4]

- **Sexual Dysfunction**

- Up to 43 percent of patients taking antipsychotic medications report problems with sexual dysfunction, a distressing adverse effect that can lead to poor medication adherence. Use of antipsychotics can affect all phases of sexual function, including libido, arousal, and orgasm. Both FGAs and SGAs can impair arousal and orgasm in men and women. FGAs especially have been found to cause erectile and ejaculatory dysfunction in men, including spontaneous, painful, or retrograde ejaculation, as well as priapism.[4]

- **Agranulocytosis**
  - In rare cases, clozapine may cause neutropenia (absolute neutrophil count [ANC] of less than 1,500 cells per mm^3 [1.50×10^9 per L]) and agranulocytosis (ANC of less than 500 cells per mm^3 [0.50×10^9 per L]) that can lead to potentially fatal infections. Agranulocytosis occurs in slightly less than 1 percent of patients, almost always within three months of starting treatment (84%). Risk increases with older age, female sex, and Asian race. The U.S. Food and Drug Administration (FDA) requires that clozapine be available only through programs that monitor white blood cell counts weekly for the first six months, every two weeks for the next six months, and monthly thereafter. According to FDA guidelines, the medication should be stopped if the white blood cell count drops below 3,000 cells per mm^3 (3.00×10^9 per L) or the ANC level below 1,500 cells per mm^4.

- **Cardiac Arrhythmias**
  - All antipsychotics can contribute to prolongation of ventricular repolarization (prolonged QT interval), which can in turn lead to Torsades de Pointes (a specific type of abnormal heart rhythm) and sudden cardiac death. This effect is most marked with the low-potency FGA thioridazine and the SGA ziprasidone, and is dose dependent. The incidence of sudden cardiac death among patients taking antipsychotics is about twice that of the general population.[4]

- **Seizures**
  - All antipsychotics can lower the seizure threshold. They should be used with caution in patients who have a history of seizures and in those with organic brain disorders. Generally, the more sedating the antipsychotic, the more it lowers the seizure threshold. Seizures are most common with low-potency FGAs and clozapine, especially at higher dosages. Depot (long acting, injectable) antipsychotics should not be used in patients with epilepsy because they cannot be quickly withdrawn.[4]

- **Metabolic Syndrome Issues**
  - Weight gain is a common adverse effect of using anti-psychotic medications, and can be rapid and difficult to control. Weight gain does not seem to be dose dependent within the normal therapeutic range. The effect is worse with clozapine and olanzapine; minimal with aripiprazole and ziprasidone; and intermediate with other antipsychotics, including low-potency FGAs.[4]

- Antipsychotic medications can contribute to a wide range of glycemic abnormalities, from mild insulin resistance to diabetic ketoacidosis, as well as worsening of glycemic control in patients with preexisting diabetes. Although FGAs and SGAs can cause these problems, risk is variable—the greatest risk is with clozapine and olanzapine. The magnitude of risk is difficult to quantify because so many other diabetes risk factors are present in this population. Although the weight gain associated with antipsychotics clearly contributes, there appear to be other independent effects as well.[4]

- Dyslipidemia is also associated with several antipsychotic medications, with increases noted primarily in triglyceride levels. Low-potency FGAs and the SGAs clozapine, olanzapine, and quetiapine are associated with a higher risk of hyperlipidemia. Overall, metabolic disturbances appear to be greatest with clozapine and olanzapine, intermediate with quetiapine and low-potency FGAs, and lowest with aripiprazole, risperidone, ziprasidone, and high-potency FGAs.[4]

***Stimulant meds**

Stimulant medications are used to treat symptoms of hyperactivity, inattention, and impulse control in children with Autism Spectrum Disorder. Clinical studies show a mean improvement in symptoms of 20-25 percent vs mean improvement of 50 percent in children with ADHD.[5]

Alteration of appetite is a great concern for children with ASD. The restrictive patterns characteristic of ASD apply to dietary choices as well. The potential for causing poor dietary intake and subsequent growth implications are high with the use of stimulant medications.

In addition to loss of appetite, increases in agitation, irritability, onset of tics, and sleep disturbances have been reported in children with Autism Spectrum Disorders.

***Selective Serotonin Re-Uptake Inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of conditions often comorbid with ASD such as depression, anxiety, and obsessive-compulsive behaviors. Antidepressants were the most commonly prescribed medications for ASD, and the fastest growing therapeutic class for this indication through the early 2000s, the trend has changed with recent studies finding neuroleptics and even stimulants are prescribed more often.

Children with Autism are 28 percent more likely to attempt suicide than the general population[6] yet use of SSRIs in in persons with ASD had shown to be of little benefit. Since the FDA warnings in 2004, studies have been conducted to explore the relationship between initiation of antidepressant treatment and suicidal events. Suicide continues to be a significant side effect of SSRI use although patient characteristics play an important role in the evaluation of risk.[7]

The most significant concern of using SSRIs in the treatment of ASD is the risk of activation which includes irritability, anger outbursts, excitability, manic symptoms, hyperactivity, agitation, nervousness, sleep disturbances, lability, and hostility.

***Antiepileptic Medications**

Several reasons occur for the use of antiepileptic drugs in autistic spectrum disorders, including the high incidence of epilepsy in these individuals, anecdotal reports suggesting an improvement of communication and behavior in autistic subjects with epileptic discharges, and increased awareness that some disruptive behaviors may be manifestations of an associated affective disorder. There is evidence that autism, epilepsy, and affective disorders commonly co-occur, and that they may share a common neurochemical substrate which is the common target of the psychotropic mechanism of action of different antiepileptic drugs; although the role of antiepileptic drugs for ASD is not well established.

Common side effects of antiepileptic drugs are dizziness, drowsiness, and mental slowing, weight gain, metabolic acidosis, nephrolithiasis, closed angle glaucoma, skin rash, hepatotoxicity, colitis, and movement and behavioral problems. The behavioral side effects of antiepileptic medications are of most concern to the ASD community. Common behavioral side effects are aggression (1.9-81.0%), psychoses (0.3-18.9%), hyperactivity or restlessness (0.0-42.0%) and behavioral disorder, NOS (0.0-43.8%).[8] Side effects of antiepileptic drugs vary and depend on the medication, dose, other medications in use, and host or patient factors.

In addition, the frequent laboratory monitoring required for some antiepileptic medications with narrow therapeutic windows can be extremely distressing for children with ASD requiring the addition of sedatives.

***Other Medications**

Alpha-2 agonists have been studied as possible alternatives to stimulants for managing hyperactivity and impulsivity in this patient population. A recent randomized, double-blind, placebo-controlled trial examined the efficacy of extended-release guanfacine in children and adolescents (aged 5 to 14 years) with autistic disorder, Asperger's disorder, or pervasive developmental disorder, not otherwise specified.[9] The 8-week trial showed extended-release guanfacine to be superior to placebo in lowering scores on the ABC-hyperactivity subscale and on global improvement measures (CGI-I) scores.[9] The findings were similar to another trial in which guanfacine was compared to placebo in children (aged 5 to 9 years) with autism, intellectual disability, and comorbid ADHD; guanfacine effects were superior to placebo on measures of hyperactivity and global improvement.[10]

Two small double-blind, placebo-controlled studies and one retrospective open-label study have examined clonidine for the treatment of hyperactivity and impulsivity in children and adolescents with autism spectrum disorders.[11 12 13] All three studies found clonidine to be at

least modestly effective for symptoms of hyperactivity. Some of the studies found it to be helpful for other symptoms, such as social relationships, sensory responses, irritability, sleep and aggression.[14]

Adverse effects of the guanfacine studies included drowsiness, fatigue and decreased appetite. Blood pressure decreased slightly early in the study, but returned to baseline by study endpoint. Adverse effects reported from the clonidine studies were sedation or drowsiness but the medication was otherwise well-tolerated.

***Polypharmacy concerns in children with Autism Spectrum Disorder**

A retrospective study of medication use in children with Autism Spectrum Disorder was conducted using medical claims and pharmacy data from a large country-wide health insurer. A total of 33,565 records were selected for review from claims dated in 2001-2009. The primary objective was to determine how many children had been prescribed at least one psychotropic medication for 30 days or longer, then how many children were prescribed medications from multiple classes for 30 days or more. The results revealed that over 64 percent of the children had received a psychotropic medication for ASD and greater than 33 percent were prescribed multiple psychotropic medications over an average length of 3 years. Differences were observed between age groups, genders, and availability of private insurance. Researchers concluded that despite minimal evidence of the effectiveness or appropriateness of multidrug treatment of ASD, psychotropic medications are commonly used, singly and in combination, for ASD and co-occurring conditions.[15]

Non-pharmacological Therapies

Several different types of non-pharmacologic therapies are used in the treatment of autism including behavior and communication therapies, educational therapies, and family therapies.

Behavioral and communication therapies address the range of social, language, and behavioral difficulties associated with ASD. These programs may focus on reducing problem behavior and teaching new skills. Other therapies focus on learning how to act in social situations or communicate with others.

ASD patients often need highly structured educational programs. These programs include a team of specialists equipped with a variety of activities to improve social skills, communication, and behavior in addition to appropriate academic education.

Parents and other family members receive benefit from family therapies that teach them how to play and interact with children who have ASD in a way that promotes social interaction, manages problem behaviors, and teaches daily living and communication skills.

Complementary and Alternative Medicine (CAM)

Alternative therapies are used in the treatment of ASD, either as an alternative to conventional treatment or as a complement to established treatment protocols. CAM treatments include creative and sensory-based therapies that attempt to reduce the child's sensitivity to touch or sound; chelation therapy to remove mercury and other heavy metals from the body believed to be interfering with normal neuropsychiatric function, and highly-controlled, special diets that target the fatty acid and inflammatory pathways in the body; and acupuncture to improve the flow of energy within the body to decrease inflammation and open blocked neuropathways. Many CAM treatments have not undergone the rigor of scientific investigation supporting their value in the treatment of Autism Spectrum Disorder, and some therapies are considered dangerous.

A comprehensive review of studies focusing on complementary and alternative therapies for Autism Spectrum Disorder was completed in 2015 by Brondino et al. who searched 2687 clinical publications from MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CINAHL, Psychology and Behavioral Health Sciences Collection, Agricola and Food Science Resource for studies regarding the use of CAM in the treatment of ASD. A total of 80 studies were included for review.[16]

Section E: Anticipated Benefits from Medical Cannabis

The limbic system is essential for the development of emotional attachment, social behaviors, parenting, learning and language development. Autopsy and MRI studies have revealed an immature development of many structures of the limbic system, including amygdala, gyrate nucleus, and hippocampus, but no damage or loss of neurons in persons with Autism Spectrum Disorder. Stimulation of the existing, limbic and autonomic systems is believed to improve social, emotional, and behavioral characteristic associated with Autism Spectrum Disorders.

The endocannabinoid system has been implicated in psychoses, dysregulation in Autism Spectrum disorders, circadian rhythm disorders, mood disorders and inflammatory disorders. Cannabidiol activates the limbic systems and down regulates the effect of endocannabinoid system deregulation thereby decreasing anxiety, psychotic-like behavior, and aggression while improving social-emotional regulation and response, mental flexibility, eating and mood regulation. THC is more effective outside the limbic system.

A third of the children with autism are subject to polypharmacy and two thirds have been prescribed at least one psychotropic medication. Many of the medications target one behavior or one symptom or cause a new symptom or behavior that requires additional medications. Medical cannabis has the potential to decrease the overall medication load in persons with Autism Spectrum Disorder.

The summaries below provide an overview of related research.

Endocannabinoid Signal Dysregulation in Autism Spectrum Disorders: A Correlation Link between Inflammatory State and Neuro-Immune Alterations (2017)

The endocannabinoid system is a complex network of lipid signaling pathways comprised of arachidonic acid-derived compounds (**anandamide**, AEA) and 2-arachidonoyl glycerol (2-AG), their G-protein-coupled receptors (cannabinoid receptors CB1 and CB2) and associated enzymes. The endocannabinoid system is involved **in** several other psychiatric **disorders in addition to autism** (i.e., anxiety, major depression, bipolar disorder and schizophrenia). This system is a key regulator of metabolic and cellular pathways involved **in autism**, such as food intake, energy metabolism and immune system control. Early studies **in autism** animal models have demonstrated alterations **in** the brain's endocannabinoid system. Endocannabinoid system dysfunction **in** a monocyte and macrophagic cellular model of **autism** has been demonstrated by showing that the mRNA and protein for CB2 receptor and endocannabinoid enzymes were significantly dysregulated, further indicating the involvement of the endocannabinoid system **in autism**-associated immunological disruptions. Together, these new findings offer a novel perspective **in autism** research and indicate that the endocannabinoid system could represent a novel target option for **autism** pharmacotherapy.[17]

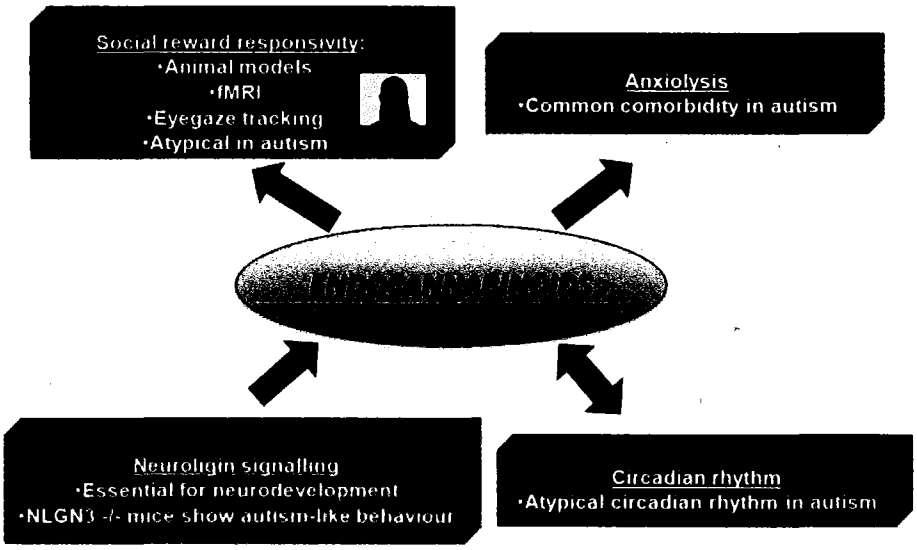
Cannabinoid Receptor Type 2, but not Type 1, is Up-Regulated in Peripheral Blood Mononuclear Cells of Children Affected by Autistic Disorders (2013).

Researchers investigated the involvement of cannabinoid system in peripheral blood mononuclear cells of autistic children compared to age-matched normal healthy developing controls (age ranging 3–9 years; mean age: 6.06 ± 1.52 vs. 6.14 ± 1.39 in autistic children and healthy subjects, respectively). The mRNA level for cannabinoid receptor type 2 (CB2) was significantly increased in the peripheral blood mononuclear cells from subjects with Autism Disorders as compared to healthy subjects (mean ± SE of arbitrary units: 0.34 ± 0.03 vs. 0.23 ± 0.02 in autistic children and healthy subjects, respectively), whereas CB1 and fatty acid amide hydrolase mRNA levels were unchanged. Protein levels of CB-2 were also significantly increased in autistic children (mean ± SE of arbitrary units: 33.5 ± 1.32 vs. 6.70 ± 1.25 in autistic children and healthy subjects, respectively). The data suggest that CB2 receptor is potential therapeutic target for the pharmacological management of Autism Spectrum Disorders.[18]

Endocannabinoid Signaling in Autism (2015)

The Endocannabinoid (eCB) system controls emotional responses[20] behavioral reactivity to context[22] social interaction[20] work on endocannabinoid signaling provides an explanation of the alterations of neurochemical responses in the presence of Autism Spectrum Disorder. Chakrabarti (2015) reviewed previous work involving endocannabinoid signaling and neurobiology of Autism Spectrum disorder then presents an argument in favor of the use of cannabinoids in treating Autism Spectrum Disorder. The diagram below depicts four reasons why this author believes medical cannabis would be beneficial for Autism Spectrum Disorders. Any potential therapeutic approach is unlikely to involve a simple choice between activation *versus* inhibition of the eCB system to target specific features related to autism, as supported by the evidence presented by Chakrabarti in humans and animal models. Any such approach will need to be precisely tuned to the developmental timeline and to the specific

pathogenetic underpinnings of autism in the single patient. Chakrabarti concludes that, "it seems of major interest that preliminary data, showing consistency between changes in distinct eCB system elements (i.e., CB_2) in animal models of ASD[24] and in peripheral blood mononuclear cells from young patients with ASD[25] support a role for these elements in the (early) diagnosis of the disease.[19]



Circadian Rhythms and Sleep in Children with Autism (2009).

Sleep disturbances has been identified as one of the most distressing behaviors of the Autism Spectrum Disorders profile, by parents and patients alike. Developing good sleep hygiene practices and bedtime routines are the current recommendations for improving sleep for persons with ASD. Disturbed sleep–wake patterns and abnormal hormone profiles in children with autism suggest an underlying impairment of the circadian timing system.[20]

Entopeduncular Nucleus Endocannabinoid System Modulates Sleep–waking Cycle and Mood in Rats (2013).

Previous research has demonstrated that the **endocannabinoid system** (eCBS) is prominently involved in the **regulation** of the SWC, mood and its related disorders. Since cannabinoid receptor 1 (CB1R) is highly expressed in basal ganglia, in particular in the entopeduncular nucleus (EP), we believe that it is important to know what the role of the EP CB1R is on SWC, depression, and anxiety. It seems that activation of the CB1R in the EP is important to induce **sleep**, while its blockade promotes W, as well as anxiety and depression, somewhat resembling insomnia in humans. These results suggest that the EP CB1R is modulating **sleep** and mood.[21]

The endocannabinoid system (eCBS) is highly present in basal ganglia, particularly in the entopeduncular nucleus (EP).[22, 23] Two of the most studied cannabinoids endogenous (eCB) are

anandamide (AEA), and 2-arachydonyl-glycerol (2-AG); the enzymes involved in their biosynthesis and degradation, N-acyl phosphatidylethanolamine phospholipase-D (NAPE-PLD) and fatty acid amide hydrolase (FAAH), are responsible for AEA metabolism; diacylglycerol lipase (DAGL) and monoacylglycerol lipase (MAGL) are responsible for 2-AG metabolism, and finally, the sites of action of this eCB are cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R).

Menendez-Diaz et al. (2010) show that AEA administration in the EP facilitates the expression of NREMs and REMs due to an increase in frequency (Fig. 1 and Table 1), suggesting that the EP CB1R is involved in regulating the mechanisms that trigger sleep. The EP is not a brain structure widely recognized as crucial in the regulation of the sleep-wake cycle (SWC) but the authors of this study provide evidence regarding the importance of EP to the SWC. Remarkably, the eCBs in the EP also regulates mood and anxiety. Interestingly, sleep disorders predict depression and anxiety disorders, among other psychiatric entities, suggesting that sleep disorders might be considered an indicator of risk for these debilitating illnesses.[30, 24] In conclusion, we would say that the study of the role of the eCBs in the EP provides research opportunities that promise to yield new and exciting information on its role in the modulation of sleep and mood.[21]

Distinct Effects of {delt9}-tetrahydrocannabinol and Cannabidiol on Neural Activation During Emotional Processing (2009).

The purpose of this study was to evaluate the substrates THC and CBD on regional brain function during emotional process. Subjects were 15 adult males who had used marijuana less than 15 times during their life. The primary outcome measures were regional brain activation (oxygenation level response) and electrodermal activity (skin conductance response), objective and subjective ratings of anxiety. Researchers found that THC and CBD clearly had distinct effects on the neural, electrodermal, and symptomatic response to fearful faces. CBD caused activation of the limbic and paralimbic regions may contribute to its ability to reduce autonomic arousal and subjective anxiety, whereas the anxiogenic effects of THC may be related to effects in other brain regions.[25]

Effects of Δ9-Tetrahydrocannabinol, Synthetic Cannabinoids, and Fatty Acid Amide Hydrolase Inhibitors on Mood and Serotonin Neurotransmission (2016)

Little was known about the capacity of cannabis to modulate the transmission of serotonin (5-HT), despite evidence of its euphoric properties and ability to precipitate psychoses in persons with certain neuropsychic conditions. Serotonin is the primary neurotransmitter implicated in the regulation of mood and depression. Researchers have attempted to clarify how CB1 receptor (CB1R) agonists, CB1R antagonists, and fatty acid amide hydrolase (FAAH) inhibitors modulate the firing activity of 5-HT neurons located in the dorsal raphe nuclei. The results indicate that while the CB1R agonist WIN 55,212-2 produced a bell-shaped curve, increasing 5-HT firing at low doses and decreasing firing at higher doses, the FAAH inhibitor URB 597 produced a different curve, plateauing at the highest doses tested. Acute injection of delta 9-THC produces a mixed response on 5-HT firing activity; however, after 4 days of intraperitoneal

injections, delta9-THC produces a significant elevation in 5-HT firing. WIN 55,212 and delta9-THC evoke a robust decrease in 5-HT firing rate after long-term administration during adolescence precipitating the associated deficits in emotional reactivity. These data indicate that both natural and synthetic CB1R agonists and FAAH inhibitors modulate the 5-HT system, which may have implications for emotional behavior and mood disturbances.[26]

Abnormal Autonomic and Associated Brain Activities During Rest in Autism Spectrum Disorder. (2014).

A consensus is growing that the autonomic nervous system serves a key role in emotional processes, by providing physiological signals essential to subjective states. The authors hypothesized that altered autonomic processing is related to the socio-emotional deficits in autism spectrum disorders. The purpose of this study was to evaluate the relationship between non-specific skin conductance response and brain fluctuations during rest in high-functioning adults with autism spectrum disorder relative to neuro-typical controls. Skin conductance response is an objective index of sympathetic neural activity. Individuals with autism spectrum disorder showed less skin conductance responses overall when compared with control participants. Results also showed weaker correlations between skin conductance responses and frontal brain regions, including the anterior cingulate and anterior insular cortices. Additionally, skin conductance responses were found to have less contribution to default mode network connectivity in individuals with autism spectrum disorders relative to controls. Researchers concluded that the results suggest that autonomic processing is altered in autism spectrum disorders, which may be related to the abnormal socio-emotional behaviors that characterize this condition.[27]

Section F: Scientific Evidence of Support for Medical Cannabis Treatment

The following scientific literature is enclosed:

Eliam-Stock, T., Xu, P., Caio, M. Xiaosi, G. VanDam, N.T, Anagnostu, E., et al. (2014). "Abnormal Autonomic and Associated Brain Activities During Rest in Autism Spectrum Disorder." *Brain,* 137(1): 153-171. https://dx.doi.org/10.1093%2Fbrain%2Fawt294

Fusar-Poli P, Crippa JA, Bhattacharyya S, et al. (2009). "Distinct effects of {delta}9-tetrahydrocannabinol and Cannabidiol on Neural Activation During Emotional Processing." *Arch Gen Psychiatry,* 66:95–105.

Gobbi, G., Nuñez, N., Mclaughin, R., & Bambico, F. (2016). Effects of Δ9-Tetrahydrocannabinol, Synthetic Cannabinoids, and Fatty Acid Amide Hydrolase Inhibitors on Mood and Serotonin Neurotransmission. *Neuropathology of Drug Addictions and Substance Misuse,*815-826. doi:10.1016/b978-0-12-800213-1.00076-6

Marco, E. M., Rapino, C., Caprioli, A., Borsini, F., Maccarrone, M., & Laviola, G. (2011). Social encounter with a novel partner in adolescent rats: Activation of the central

endocannabinoid system. *Behavioural Brain Research,220*(1), 140-145. doi:10.1016/j.bbr.2011.01.044

Méndez-Díaz, M., Caynas-Rojas, S., Arteaga Santacruz, V., Ruiz-Contreras, A.E., Aguilar-Roblero, R., & Prospéro-García, O. (2013). "Entopeduncular Nucleus Endocannabinoid System Modulates Sleep–waking Cycle and Mood in Rats." Pharmacology, Biochemistry, and Behavior, 107, 29-30. doi: http://dx.doi.org/10.1016/j.pbb.2013.04.003

Onaivi, E. S., Benno, R., Halpern, T., Mehanovic, M., Schanz, N., Sanders, C., . . . Ali, S. F. (2011). Consequences of Cannabinoid and Monoaminergic System Disruption in a Mouse Model of Autism Spectrum Disorders. *Current Neuropharmacology,9*(1), 209-214. doi:10.2174/157015911795017047

Scahill, L., & Pachler, M. (2007). Treatment of Hyperactivity in Children with Pervasive Developmental Disorders. *Journal of Child and Adolescent Psychiatric Nursing,20*(1), 59-62.

Sciolino, N. R., Bortolato, M., Eisenstein, S. A., Fu, J., Oveisi, F., Hohmann, A. G., & Piomelli, D. (2010). Social isolation and chronic handling alter endocannabinoid signaling and behavioral reactivity to context in adult rats. *Neuroscience,168*, 371-386.

Siniscalco D, Sapone A, Giordano C, et al. (2013). "Cannabinoid Receptor Type 2, but not Type 1, is Up-regulated in Peripheral Blood Mononuclear Cells of Children Affected by Autistic Disorders." *Journal of Autism and Developmental Disorders*, 43:2686–2695. doi: 10.1007/s10803-013-1824-9

Section G: Letters in Support of Adding the Medical Condition

A letter of support is included from the following individuals:

Dr. Jacob Mirman
Dr. Gretchen A. Moen, DNP, APRN, CPNP-PC
Elizabeth Jefferson
Lisa Stock

Additionally, the following individuals indicated their support for the addition of Liver Disease as a qualifying condition to Sensible Minnesota and Marijuana Policy Project. Commentary is as sent, except for minor modifications for clarity.

[redacted]

Physician

[redacted]

[redacted]

Patients that need marijuana for their conditions face many difficulties obtaining it. This is unfair and hurts patients.

[redacted]
Physician, Patient's Spouse

[redacted]

[redacted]

[redacted]

[redacted]

I'm on the medical program for chronic pain here in Minnesota. And marijuana works best for everything without the harsh side effects that pharmaceuticals. But this program is lacking quality, variety, and the range of conditions! If someone has an ailment and marijuana helps them best, why should there be any question who gets treatment? When it's so easy for people to get opiates and Vicodin and Percocet that kill 10's of thousands a year and this natural, broad range of multiple reliefs, with extremely limited side effects, and 0 deaths ever is so hard to get! It's stupid and ridiculous that we're even still having to fight and beg for something today is so much better than anything that big Pharma and doctors are tying to do for us!

[redacted]

I have wide spread chronic pain (fibromyalgia, myofascial, muscle spasms, nerve pain, migraines) well as nausea from Mariners disease. I also have issues with anxiety, depression & PTSD. I've just started the medical cannabis program here about 1mo ago. I've noticed a major decrease in my nausea & anxiety I'm not as depressed my muscle spasms have lessened and I don't concentrate a lot on the pain but the pain is still there. I do not feel sick or lethargic like I did when I was on opiate medication. For the first time in 20 plus years I can actually sleep 4+ hours @ night. I've also noticed that I'm able to focus a better without all the anxiety of having to remember how to move and how to be around people in public. The major drawback to this program here in Minnesota for me is that I'm low-income and have a hard time paying for the products. I would also like to see other choices such as edibles or the plant as an option. In conclusion, I would like to add that this medication would be fabulous for all of the related conditions above especially for people with Alzheimer's and Dementia to alleviate their stress of anxiety when they can't remember or become disoriented. As well as for people with autism will help with their focus and minimize the cold symptoms of anxiety and depression. Thank you for your time.

[redacted]

I would like to see Minnesota add autism as a qualifying condition. All the research and testimonies ASD individuals deserve a quality of life. Aggression and anxiety and meltdowns prevent ASD individuals. From enjoying day to day activities for example not going into stores. Self-injuries behaviors. Some ASD have sensory issues and with textures food intake is limited.

Please allow these individuals a chance to prosper and grow and be part of a community.

[redacted]

[redacted]

My chronic pain and nausea caused by migraine headaches and lower back issues are relieved by medical marijuana. Opiates are not an option in my life as I am allergic.

[redacted]

[redacted]

My story is about my son's epilepsy and regressive autism. His story I have heard is not unique but I have figured out that often what triggers the episodes with many of our children with epilepsy and autism is varying types of inflammation and varying degrees of inflammation. The type of CBD my son needs is a high concentrated form of CBD that is cost-prohibitive to our family. I would advise the legalization of growing the product and providing facilities that educate the public in how to safely make their own CBD and providing labs to test what they make. Otherwise the monthly cost of CBD at the strength I need is about 500 dollars a month for my son who is utilizing OT, ST, and soon ABA. The cost of these services is also including equipment then you add the time it takes to understand and provide for someone of such need and the cost of food for the ketogenic diet which reduces inflammation and the cost of the organic reduced inflammatory food (decreasing exposure to herbicides and pesticides) and you see how it is out of reach for families with autism. We have a growing autism crisis made worse by adjuvants and environmental electromagnetic and radiation pollution, chemical pollutants, and more environmental industrial contaminants, drugs that do not consider the far-reaching effects and consequences when prescribed, outdated medical system with restrictive protocols that doesn't keep up with science and geopathic stress. To reduce the incidence of autism in our country we need to address these things and thus we have a healthier nation of people with reduced chronic health needs. In the meantime, to reduce the demand on the healthcare system we need to approve for the self-production of medicine in Minnesota. It is unfair that physicians cannot address these needs and must follow a protocol which further damages patients. Our worldly systems are often unethical for biological diversity of species, and what is going on in our country is unethical for systems of life and individual living organisms. We have polluted

land, air, water, ionosphere, electromagnetic field....it is no mystery why we are ill. Exome genetic sequencing will never tell the complete tale----- it is environment. We are chemo -(we have bio-chemical actions) photo- (we utilize photons)hetero (elemental beings that utilize nutrition from a variety of complex sources) trophic eukaryotic organisms. We are highly connected if we choose to see. The world needs to change and fast before the demand for care of this problem outpaces the individuals available to provide it.

[redacted]

I myself have chronic pain from Fibromyalgia, RA and Polyarthritis . I am not allowed pain pills which are the only things that make me feel well enough to move. When I take my pain pills I get an energy boost and am free of pain. But the state has taken away my rights to be pain free that way. Most meds have caused me to gain tons of weight which only causes my problems to be worse.

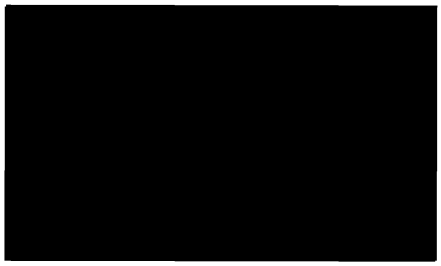
My son has Asperger's autism/ADHD and Anxiety. He has so much anxiety, he cannot hold still, does not stop talking or moving his body. His Autism causes him to be unable to shut his brain off at night to sleep, causes him to worry and panic, hit himself, and break things. He is on 6 different meds now and none seem to help or help very little. I only want to help him relax, slow down and enjoy life. He can't even sit to eat dinner :(

[redacted]

As a patient, I feel as though anyone who can be helped by Medical Marijuana should have the option to try to find a medicine that can help with their condition.

[redacted]

Though my condition is Asperger Syndrome, I'm still fall under the Autism Spectrum. As I've developed full interest and support of legal Cannabis, I've found benefits that would greatly help me. I get anxious about socializing, and depressed that I'm unsuccessful with trying to be relaxed and happy enough to enjoy life. Even when I'm happy, I can get so hyper sometimes that I can't stand or sit still, and I can't control it. I'm also not as verbal as I like to me in every day conversation. There might be some more problems to my condition, but I usually can't think of more at the top of my head when I try to remember (I guess that's another). I try to resolve these things naturally before moving on to medications, my last resort, but I don't think I can do it on my own. But after hearing about stories of other treatments from whomever about whatever condition and what the twisted side effects are, I'm really nervous about taking medications. I also hear that some meds don't work sometimes anyhow. I don't think I can handle my condition on my own anymore. I'm sure that Cannabis helps crush anxiety and depression more naturally, and I'm sure it could benefit me.



As an autistic person, I feel I would greatly benefit from the medicinal effects of marijuana. I'm frequently stressed out to the point of tears and breaking things, intense periods of frustration followed by even longer periods of guilt and sadness. Autistic adults are often plagued with anxiety and depression, even some having co-morbid conditions like PTSD, Generalized Anxiety Disorder, Depression, etc. I currently take Clonazepam 0.5mg, and while it works some of the time, it's not a guaranteed to even have an effect on me in times of dire crisis. It's a bit of a gamble as to whether or not it will do its job. I think marijuana is something that would invite more stability, which is essential for someone like me.

Physician Assistant, Personal Care Assistant

I work in multiple homes with high and frequent behaviors from individuals that suffer from these conditions. Some are nonverbal and some that can't go to the bathroom on their own because they forgot how to. They injure themselves and other clients and staff

and they don't even know why. I believe marijuana would help bring peace to many individuals on much more intense medicine with much worse side effects.

[redacted]

I have two children on the spectrum. Medication can only do so much and I would like to be able to try something different to see if that would be helpful. I'd also like to see medical cannabis expanded to include ADD and ADHD

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[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

[2] Brondino, N., Fusar-Poli, L., Rocchetti, M., Provenzani, U., Barale, F., & Politi, P. (2015). Complementary and Alternative Therapies for Autism Spectrum Disorder. *Evidence-Based Complementary and Alternative Medicine, 2015*. doi:10.1155/2015/258589

[3] Mayo Clinic, June 3, 2014. Autism Spectrum Disorder, Treatment and drugs. Retrieved July 2, 2017 from http://www.mayoclinic.org/diseases-conditions/autism-spectrum-disorder/basics/treatment/con-20021148

[4] Muench, J. & Hammar, A. (2010). "Adverse Effects of Antipsychotic Medication." *American Family Physician,* 81(5): 617-622. http://www.aafp.org/afp/2010/0301/p617.html

[5] Scahill, L., & Pachler, M. (2007). Treatment of Hyperactivity in Children with Pervasive Developmental Disorders. *Journal of Child and Adolescent Psychiatric Nursing,20*(1), 59-62.

[6] Soraya, L. (2013, March 17). New Research on Autism and Suicide. Retrieved July 30, 2017, from https://www.psychologytoday.com/blog/aspergers-diary/201303/new-research-autism-and-suicide

[7] Gibbons, R. D., & Mann, J. J. (2014, December 31). The Relationship Between Antidepressant Initiation and Suicide Risk. Retrieved from http://www.psychiatrictimes.com/special-reports/relationship-between-antidepressant-initiation-and-suicide-risk

[8] Thigpen, J., Miller, S.E., & Pond, B.B. (2013). "Behavioral Side Effects of Antiepileptic Drugs." *U.S. Pharmacist,* 38(11), HS15-HS20. Retrieved from: https://www.uspharmacist.com/article/behavioral-side-effects-of-antiepileptic-drugs

[9] Scahill L, McCracken JT, King BH et al. (2015). "Extended-release Guanfacine for Hyperactivity in Children with Autism Spectrum Disorder." *American Journal of Psychiatry*, 172(12):1197–1206.

[10] Handen BL, Sahl R, Hardan AY et al. (2008). "Guanfacine in Children with Autism and/or Intellectual Disabilities." *Journal of Developmental and Behavioral Pediatrics*, 29(4):303–308.

[11] Jaselskis CA, Cook EH, Jr, Fletcher KE, Leventhal BL. (1992). "Clonidine Treatment of Hyperactive and Impulsive Children with Autistic Disorder." *Journal of Clinical Psychopharmacology*, 12(5):322–327.

[12] Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD. (1992). "A Double-Blind Placebo-Controlled Study of the Efficacy of Transdermal Clonidine in Autism. *Journal of Clinical Psychiatry,* 53(3):77–82.

[13] Ming X, Gordon E, Kang N, Wagner GC. (2008). "Use of Clonidine in Children with Autism Spectrum Disorders." *Brain and Development*, 30:454–460.

[14] DeFillipis, M. & Wagner, K.D. (2014). "Treatment of Autism Spectrum Disorders in Children and Adolescents." *Psychopharmacological Bulletin*, 46(2):18-41. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5044466/

[15] Spencer, D., Marshall, J., Post, B., Kulakodlu, M., Azocar, F., & Jain, A. (2013). "Psychotropic Medication Use and Polypharmacy in Children with Autism Spectrum Disorders." Pediatrics, 132(5), 833-840. doi: 10.1542/peds.2012-3774

[16] Brondino, N., Fusar-Poli, L., Rocchetti, M., Provenzani, U., Barale, F., & Politi, P. (2015). Complementary and Alternative Therapies for Autism Spectrum Disorder. *Evidence-Based Complementary and Alternative Medicine,2015*. doi:10.1155/2015/258589

[17] Brigida, A.L., Schulz, S., Cascone, M., Antonucci, M., & Siniscalo, D. (2017). "Endocannabinoid Signal Dysregulation in Autism Spectrum Disorders: A Correlation Link between Inflammatory State and Neuro-Immune Alterations." *International Journal of Molecular Sciences,* 18(7). doi: 10.3390/ijms18071425

[18] Siniscalco D, Sapone A, Giordano C, et al. (2013). "Cannabinoid Receptor Type 2, but not Type 1, is Up-regulated in Peripheral Blood Mononuclear Cells of Children Affected by Autistic Disorders." *Journal of Autism and Developmental Disorders*, 43:2686–2695. doi: 10.1007/s10803-013-1824-9

[19] Chakrabarti, B., Persico, A., Battista, N., & Maccarrone, M. (2015). "Endocannabinoid Signaling in Autism." *Neruotherapeutics*, 12(4): 837-847. doi: https://dx.doi.org/10.1007%2Fs13311-015-0371-9

[20] Glickman G. "Circadian Rhythms and Sleep in Children with Autism." (2010). *Neuroscience Biobehavior Review*, 34:755–768. doi: 10.1016/j.neubiorev.2009.11.017.

[21] Méndez-Díaz, M., Caynas-Rojas, S., Arteaga Santacruz, V., Ruiz-Contreras, A.E., Aguilar-Roblero, R., & Prospéro-García, O. (2013). "Entopeduncular Nucleus Endocannabinoid System Modulates Sleep–waking Cycle and Mood in Rats." Pharmacology, Biochemistry, and Behavior, 107, 29-30. doi: http://dx.doi.org/10.1016/j.pbb.2013.04.003

[22] Giuffrida, A., & Seillier, A. (2012). New insights on endocannabinoid transmission in psychomotor disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,38*(1), 51-58. doi:10.1016/j.pnpbp.2012.04.002

[23] Svizenska, I., Dubovy, P., & Sulcova, A. (2008). Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures — A short review. *Pharmacology Biochemistry and Behavior,90*(4), 501-511. doi:10.1016/j.pbb.2008.05.010

[24] Siversten, B., Salo, P., Mykletun, A., Hysing, M., Pallesen, S., & Krokstad, S. (2012). The bidirectional association between depression and insomnia: the HUNT study. *Psychosom Med,74*, 758-765.

[25] Fusar-Poli P, Crippa JA, Bhattacharyya S, et al. (2009). "Distinct effects of {delta}9-tetrahydrocannabinol and Cannabidiol on Neural Activation During Emotional Processing." *Arch Gen Psychiatry*, 66:95–105.

[26] Gobbi, G., Nuñez, N., Mclaughin, R., & Bambico, F. (2016). Effects of Δ9-Tetrahydrocannabinol, Synthetic Cannabinoids, and Fatty Acid Amide Hydrolase Inhibitors on Mood and Serotonin

Neurotransmission. *Neuropathology of Drug Addictions and Substance Misuse,*815-826. doi:10.1016/b978-0-12-800213-1.00076-6

[27] Eliam-Stock, T., Xu, P., Caio, M. Xiaosi, G. VanDam, N.T, Anagnostu, E., et al. (2014). **"Abnormal Autonomic and Associated Brain Activities During Rest in Autism Spectrum Disorder."** ***Brain,*** **137(1): 153-171.** https://dx.doi.org/10.1093%2Fbrain%2Fawt294

SECTION G

Dakota Child and Family Clinic

Healthcare for People, Not for Profit

Dr. Gretchen A. Moen, DNP, APRN, CPNP-PC
Pediatric Nurse Practitioner
Executive Director

Michelle S. Christian, APRN, MAN, ANP-C
Adult Nurse Practitioner

Dr. Angie M. Grabau, DNP, APRN, CPNP-PC
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July 11, 2017

TO: Dr. Ed Ehlinger,MD, MPH,
Commissioner, Minnesota Department of Health
RE: Use of Medical Cannabis for treatment of Autism Spectrum Disorders

Dear Dr. Ehlinger,

I am writing in support of adding Autism Spectrum Disorders (ASD) to the list of approved diagnoses for treatment with Medical Cannabis. I have been certified through the MN Cannabis program since 2015 and provide health care to nine children with dual diagnoses of Tourette's syndrome and ASD who have been treated with medical cannabis for greater than six months.

Response to treatment/outcome data is subjectively reported by parents and directly observed by myself in clinic. Eight of the nine patients are male and all are between the ages of six to seventeen years old. Many of the children were taking multiple medications or had tried and failed multiple medications prior to starting medical cannabis. The results vary by individual but the themes include a decrease in raging and aggression, an increase in mental flexibility and ease of transitions, and a significant reduction of motor and verbal tics. To a lesser extent, I have observed a decrease in overall anxiety and a willingness to try new things, or allowing new situations to occur. The results I have observed are similar to those observed by Dr. Adi Aran in the Jerusalem Study (2017). *Please refer to the vignettes below for details.*

The pharmacologic interventions available today for the treatment of ASD and associated behaviors have significant side effects and can cause long term problems. Drug-induced insulin resistance and subsequent obesity is nearing crisis levels. Poly pharma is rampant as more medications are added to patient regimens to combat the side effects of primary treatments. Although medical cannabis is not appropriate for everyone, having another option for the management of children with Autism Spectrum Disorder allows providers and families to consider alternatives to the type of medications for treatment that are available today.

Thank you for your consideration regarding the addition of Autism Spectrum Disorder to the Medical Cannabis approved diagnosis list.

Sincerely,

[redacted]

Vignettes

7 year old male: ASD, Tourette's, aggression, rage episodes and anxiety. After starting medical cannabis there was a 60% reduction in tics and aggression, an increase in his tolerance of others and more rapid de-escalation and recovery from rages – by parent report.

8 year old male with ASD, Tourette's, aggression and anxiety. Once starting medical cannabis, and after a few adjustments in the combination of THC and CBD, there was a 70% reduction in tic behaviors, 40+% reduction in aggression, 50% reduction in anxiety, and a 40% improvement in his sleep, per his parents.

8 year old male with ASD, Tourettes, and anxiety: after starting cannabis there is a 50% reduction in raging episodes with a 40% increase in flexibility to transitions, and a 70% reduction in tics as reported by parents.

13 year old female with ASD, Tourette's self-injury, aggression, and anxiety: Picking and self-injury behaviors nearly resolved, vocal tics 90% improved, aggression symptoms were "less frequent" but, more importantly, "recovered much faster" from aggressive episodes, as reported by caregivers.

10 year old male with Tourette's and ASD on 8 medications to manage behaviors: initially an 80% reduction in tics, 30% reduction in anxiety, and 20% increase in willingness to try new things, increased flexibility. Parents report that he is continuing to show significant improvement in his anxiety and transitions and his tics have all but disappeared.

17 year old male with ASD, Tourette's, anxiety: Mom reports his "life has completely turned around". His tics were so severe he could not attend school, sit long enough to do homework or participate in family activity. I hardly recognized him at his last visit because he was transformed into a sociable, smiling, happy young man!

6 year old with Tourette's and ASD: prior to starting cannabis, this child actually broke the ceiling light in the office with a stuffed animal, tried to walk up the inside of the door, could not sit for more than a second and his vocal and movement tics were out of control. The family had tried a number of medications and had failed a recent trial of clonidine. After three months with medical cannabis he is able to sit through the visit, he is able to accomplish some study activities, is far less aggressive and is sleeping better than he had been for his whole life per MOM.

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07-20-2017

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 Dr. Jacob Mirman, I graduated from the University of Minnesota Medical School and completed my residency in primary care internal medicine at Illinois Masonic Medical Center in Chicago. I specialize in integrative medicine and I am the Medical Director of Life Medical, an integrative medicine clinic in St. Louis Park.

I write to you today in support of the petitions to add nausea, autism, dementia, Alzheimer's disease, liver disease, and chronic pain to Minnesota medical cannabis program. As a physician treating patients for all these conditions, I believe my patients who suffer from these conditions would benefit from being added to the state's program.

I am a primary care internist. I am a not a politician, a law enforcement officer or a cannabis policy expert. Yet, as an internist with 25 years of experience working with patients, I hope you will consider my views on whether to expand Minnesota's medical cannabis program.

I have been certifying patients for medical cannabis for over a year now, and have seen a tremendous benefit to patients when they return to me for follow-ups. Notably, in addition to the medical condition that qualifies them for the program, many patients who I have certified suffer from some other ailment — including several listed above — and have seen their conditions improved with medical cannabis use.

Patients come to me because they need help. I agree to see them and do my best to help them. The buck stops with me. If I send a patient to a specialist and he or she is unable to help, the patient comes back to me and their medical care is again my responsibility.. When standard approaches do not help the patient, my responsibility as their physician does not end.

For the last few months, around 20% of my practice has involved treating patients benefiting from medical cannabis. I certify on average two-three new patients per day. Notably, many patients are finding relief for not just the condition they have been certified for, but also secondary conditions. Further, my patients are happier, suffer from less anxiety (many have

ceased use of anti-anxiety medication), and are significantly reducing their pain. Quite a few have gotten off of narcotics and other pain killers altogether.

Practicing integrative medicine allows me to find the best treatment for my patients, and their success stories are what make my work so much fun. The beauty of integrative medicine is that it brings together different treatment methods to get the best effect for each individual patient. We use whatever modality we consider best for each patient's case. Our patients get the benefit of customized treatment plans that include conventional and complementary therapies. We combine all possible treatment options; whatever may help the patient in the most effective and safest way. And we are seeing great results using integrative approach.

Nausea is a common symptom of many conditions, or their treatments, including cancer and pain. Migraines are often accompanied by nausea, adding nausea to the program could significantly help my patients. Nausea is also often associated with PTSD, muscle spasms, and pain, all of which are currently covered by the program. Adding nausea to the program just makes sense.

Marinol — which is pure, synthetic THC — has been approved as a prescription drug since 1985 for nausea and vomiting associated with cancer chemotherapy in patients. Like other medications, Marinol can also be prescribed for off-label uses. However, Marinol is an inadequate substitute for many nauseated patients because, as a pill it is slow-acting. Also, unlike vaporized cannabis, a patient cannot precisely titrate their dosage and many end up overly intoxicated.

Autism, dementia, and Alzheimer's disease, are all marked by anxiety. Cannabis causes people to calm down. I have seen this many times with children in particular. For example, I had a young patient with seizures who, upon being placed on cannabis, changed her behavior drastically, she became better in school, improved in gymnastics, and had a higher quality of life. Offering cannabis to patients suffering from autism, dementia, and Alzheimer's disease, will result in a reduction in their anxiety and likely benefit these patients as to other symptoms they suffer from as well.

In addition, cannabis has been helpful at reducing self-injurious and aggressive behavior in autistic individuals who have not responded to other treatments. In Texas and Georgia, parents have talked to the media about their decision to break state law to help their autistic children, who were engaging in self-harm.

Liver disease often results in decreased appetite and nausea. Granting access for patients who suffer from this condition to medical cannabis, will likely help them battle these afflictions tremendously. Cannabis's alleviation of a decreased appetite is well-documented, and it is in the interest of my liver disease patients to have access to this important treatment option.

In my opinion, medical cannabis is the best pain medication of any pain medication available today either prescription or over the counter. It is much safer than opioids, and even safer than over-the-counter drugs like ibuprofen and Tylenol. Not only is cannabis incredibly effective, but there are few if any side effects and no risk of fatal overdose. Indeed in all my years of practicing

medicine, I have never seen a drug that has such a remarkable effect on patients with almost zero side effects.

Please add nausea, autism, dementia, Alzheimer's disease, liver disease, and chronic pain, to Minnesota medical cannabis program.

Sincerely,

Jacob I. Mirman, MD

July 24, 2017

Hello,

I am writing to share our family's experience with medical cannabis and express how important it is for Autism spectrum disorder to be added as a qualifying condition for the MN medical cannabis program.
Our journey with cannabis began in 2015, when we first heard about CBD oil. We began using it for our son [redacted]. [redacted] has both an ASD and a Tourettes diagnosis. We started with the CW brand and switched to the HH brand 3 mos later (we feel the HH brand is a high-quality and reliable product). This initial test with CBD oil proved extremely successful for [redacted]. [redacted] had been having extremely aggressive meltdowns reguarly. They occurred most often from going out into the community and having sensory overload. The meltdown would occur once he returned home. He would attack me and my husband (as well as therapists and school staff) when overwhelmed. We stopped going anywhere except routine places (basically school and therapy) to lessen these fits. However, they would happen randomly as well. The fits also terrified his little sister [redacted] (who also has ASD and Tourettes), causing much anxiety in her.

When we began CBD oil, the aggression during fits stopped. He no longer hit, kicked, or attacked us when upset. He still had meltdowns, but they were much shorter and the removal of the aggression was a huge improvement.

We also saw an increase in focus during ABA sessions, more eye contact, an increase in his wanting to and trying to communicate with us ([redacted] is semi-verbal, only able to make short requests or use learned phrases - he cannot hold a conversation or answer a question). When he started school again in the fall that year, staff were blown away by the changes in him. His FBA had to be rewritten after only one year due to the behavior improvements.

As a family, we were able to attend movies and go to Disney on Ice productions. [redacted] began ice-skating lessons and participated in Special Olympics basketball that winter. He was happier and visibly more comfortable. The CBD has helped his leaky gut issues as well, reducing inflammation and pain.

In 2016, [redacted] became registered with the MN Medical cannabis program under his Tourettes diagnosis. We tried a variety of different options with the guidance of the MN Med company. We did not see a lasting improvement in [redacted]'s tics however, after almost a year of trying the MN Med products. Currently, [redacted] is only taking the HH product, but we will keep trying to help him through the state cannabis program in future. It is very important to note how many of my son's ASD based symptoms - the aggressive meltdowns, lack of communication and eye contact, anxiety and sensory overload - all reduced due to CBD oil.

Our daughter [redacted] became registered with the MN Medical cannabis program in Aug 2016, with Tourettes being her qualifying condition. We saw initial improvement with tic reduction right upon starting the MN Med green product. This remained for about 4 mos until we purchased a new bottle of this product. For some reason, the new bottle did not have the same effects and stopped working. We switched companies and the Leafline product is working better, in combination with the HH product.

My daughter's ASD symptoms improved as well with both MN cannabis products. She became calmer, happier, and less anxious. Her speech improved and her spontaneous language increased. Her ability to answer questions also improved.

Being able to help my children by using the MN Cannabis program has made a huge difference in their lives and our family's life. There are many children out there with only an Autism diagnosis who would surely benefit from having the same access to this program. Medical cannabis has proven to help with so many of the symptoms and side effects that go with ASD - inflammation, speech/communication improvements, gut and digestive issues, sleep issues, behavior issues including aggression and self-injury, anxiety, depression, and other mental illnesses - just to name a few.

Why should these children and their families continue to suffer each day when there is an option that is safe and may help them? Please consider adding Autism as a qualifying condition for the MN medical cannabis program.
Thank you for reading our story.

Sincerely,

[redacted]

July 25, 2017

To Whom It May Concern,

My name is [redacted], my husband and I are sending this letter to share our family's personal experience with our daughter [redacted]. We are praying that the diagnosis of Autism Spectrum Disorder will be added to the list of Qualifying Conditions to the Medical Cannabis Program.

Our daughter's name is [redacted], she is 13 years old and is an exceptional artist, writer, illustrator, and has a heart of gold. She inspires us each day to be the best parents that we can be, to protect her, and nurture her in any every way possible. One of the challenges of parenting that we have is watching her struggle on a daily basis.

[redacted] was diagnosed with Autism Spectrum Disorder when she was 10 years old after many years of trying to figure out what was causing her to struggle severely in many areas of her life. [redacted] struggles with social communication; she has difficulty with peers and adults, and lacks skills in social settings. As she is in adolescence these deficiencies are more noticeable and upsetting to her. She also struggles with repetitive patterns of behavior and interests. Her focus on subjects and intensity are admirable, but they truly impede her happiness and success in areas of her life. She struggles with transitioning from one item to another and has difficulty engaging with others when she is hyper-focused on a subject or object. [redacted] also struggles with her behavior; she has rages daily when it comes to transitioning and carrying out her activities of daily living. She has anxiety, depression, and has also been diagnosed with Disruptive Mood Dysregulation Disorder (DMDD). [redacted] will self-injure as well as hurt others when she is unable to manage her emotions and is having sensory overload.

Due to her challenges she has been hospitalized multiple times. These hospitalizations have been to stabilize her as well as to attempt to manage her medications. We have had so many challenges with pharmaceutical medications that have been harmful immediately and over time. [redacted] currently is pre-diabetic, has high tri-glycerides, as well as high cholesterol. The medication that causes her to have these side effects also causes her to have insatiable hunger and has affected her self-esteem as she does not look like her peers. She is on an additional medication to help curb some of these side effects as well. We have tried many types of medications and have had major side effects with each one. A combination of medications prescribed caused her to be hospitalized due to aggression and extreme confusion where she struggled to speak. Another medication caused [redacted] to start lactating at age 11. We have recently been referred to a new Psychiatrist specializing in Autism Spectrum Disorder to hopefully come up with a plan that will keep her stable, functioning, safe, and not cause more serious health concerns due to side effects.

As [redacted]'s parents we struggle to make careful and informed choices about her medications. We have the best and most knowledgeable providers for her and they are running out of options to help [redacted]. As parents we want to protect her and ensure that as she is moving through life, she is safe, and able to realize her goals and aspirations. At the rate we are going many of these will not happen for [redacted] and as parents it breaks our hearts.

We have heard of many success stories from other families who use Medical Cannabis for their children who have qualifying conditions. The changes in these families' lives have been extraordinary. The ability to move away from pharmaceutical medications that can cause damaging side effects has been a blessing for so many people. As parents we would move heaven and earth for our child and truly need to have other options to treating her. We are asking to please allow Autism Spectrum Disorder to be added to the list of Qualifying Conditions in the Medical Cannabis program. The addition would allow families options for treating their children's illnesses and allow stability and safety without the fear of damage.

Thank You

[redacted]