1. **Medical condition proposed:**

   Autism.

2. **Provide justification for why this medical condition should be included as a qualifying debilitating medical condition for the use of medical marihuana.**

   Autism is neither a listed qualifying condition under the Michigan Medical Marihuana Act nor does it routinely exhibit any of the qualifying symptoms under the Act, though mild cachexia or wasting syndrome is seen in some cases. However, medical marihuana has been used successfully in Michigan to treat the symptoms of autism in patients who also suffer from epilepsy, and its use in treatment is supported by several Michigan physicians who specialize in treating autism.

   This petition was approved by the Medical Marihuana Review Panel on July 31, 2015, but denied by LARA Director Mike Zimmer in the department's final determination of August 27, 2015.

   The MMMA was retroactively amended effective December 20, 2016 to allow the use of extracts and products infused with medical marihuana. Director Zimmer's conclusion included a detailed analysis of the law and case law regarding these alternate forms, which has been retrospectively nullified by the actions of the Legislature. Please reconsider this petition.

3. **Provide a summary of the evidence that the use of medical marihuana will provide palliative or therapeutic benefit for this medical condition or is a treatment for this condition.**

   1) There exist few effective treatments for autism, and cannabis is less toxic than those other treatments. Currently FDA approved treatments include clonopin, rispiridone, and Abilify.

   2) As shown in the attached research, it is certain that modulation of the endocannabinoid system effects the symptoms of the condition, and may possibly create conditions more conducive for other development to occur. Treating autistic patients with cannabis has shown to increase appetite, stimulate better bonding, reduce compulsive or ritualistic behaviors, and reduce self-injurious behavior.

   3) Parents and caretakers should be protected for making the choice to treat autism with cannabis if they have physician approval and monitoring, both requirements under the Act. Many doctors who specialize in treating autism will approve and monitor the use of cannabis, should the panel approve the condition. Today, it is impossible for a doctor to protect either patient or parent for making this choice.
4) Dronabinol (synthetic THC capsules, trade name Marinol) is being used off-label as a treatment, but does not include CBD or any other likely beneficial cannabinoids, and is less effective than botanical extract.

5) Despite the early onset of the condition, the long-term prognosis of autism minimizes concerns of any unknown risks possibly posed by cannabis use on the developing brain. Note that the approved FDA treatments for autism also have unknown long-term effects. Only a small percentage of autistic adults can achieve a level of independence.

6) The MMMA allows the use of medical marihuana to treat any condition approved by the panel. The approval of autism will not cause a radical increase in participation; just protection for the patients, their parents, and their doctors. By voting in favor of adding autism to the list of qualifying conditions under the act, this panel is not recommending marihuana for every person with autism in the state. The panel is merely ensuring that doctors, their patients and parents may not be punished for recommending or trying the treatment.

To put it another way, the panel is not recommending medical marihuana for this condition. The panel is only recommending that autism should be added to the qualifying conditions list in order to protect patients from arrest for trying a non-toxic treatment.

7) NIDA research contradicts older research showing IQ decline:

Dr. Isen says, “We suspect that children's delinquent proclivities, and the family-level characteristics that underlie them, drive IQ decline.” For most of these young people, marijuana use is one deviant behavior among others, and their generally under-socialized behavior and delinquency, rather than marijuana use, affects their IQ trajectory.

Taken singly, those findings indicate that a teen’s overall substance use, rather than marijuana use, is a more significant contributor to IQ trajectory.

The researchers say that although their evidence indicates that marijuana exposure does not cause persistent loss of intellectual function up to age 20, prolonged regular exposure for decades might do so.


Pigs “might” fly, but until NIDA has some evidence of flying pigs, they should stop suggesting the possibility. It is a shame that an organization requiring scientific evidence, downplays the evidence, and promotes the propaganda and completely unfounded theories of marihuana prohibitionists.
4. Provide articles published in peer-reviewed scientific journals reporting the results of research on the effects of marihuana on the medical condition or treatment of the medical condition and supporting why the medical condition should be added to the list of debilitating medical conditions under the Medical Marihuana Act.

**Highlights of Attached Research**

Direct Links:
- NL3 mutations inhibit tonic secretions of endocannabinoids
- ECS is suggested target for fragile X treatment
- CB2 upregulated and is suggested target for ASD treatment
- PPAR alpha/gamma and GPR55 downregulated
- CB1 is key element of perception of basic emotions (like happy faces)

Correlations:
- Modulation of GABA efflux via CB1 and CB2
- ECS and 5-HT system closely interrelated o eCBs via CB1 modulate 5-HT release
  - 5-HT regulates the release of eCBs via 5-HT2a
  - AEA reduces 5-HT binding
  - THC, THCA, CBD, CBDA are all 5-HT1a agonists
  - THC increases 5-HT1a receptor expression and function
  - Cannabinoid agonists inhibit 5-HT3
  - CBD tryptophan degradation suppressor
- Cannabinoid signaling suppresses cytokine proliferation/release via CB1/CB2 dependent and independent mechanisms
- CB1 regulates synaptic plasticity at synapse onto Purkinje cells
- ECS target for modulating neuronal and glial cell function in epileptogenic developmental pathologies
- Tonic eCBs regulate GI functions (including metabolism)

The ECS plays a functional role in a number of symptoms and associated diseases of autism. The ECS is a potential target of therapeutic exploitation. We’re confident that if you’re willing to review the available data that you might be able to lead the way in an attempt to increase the quality of life for those in MI suffering from truly debilitating forms of autism.

**The Endocannabinoid System as it Relates to Autism**

Joe Stone; Christian Bogner, M.D.

The importance of the discovery and continued elucidation of the crucial role that the endocannabinoid system (ECS) plays in human health and disease cannot be understated. Cannabinoid receptors are the most highly expressed of any GPCR.
They’re the only ones to play a direct role in virtually every aspect of the human body (CNS and immune systems, throughout the periphery, presynaptic, and postsynaptic). (Alger 2013)

The growing body of data in regards to this aspect of physiology continues to lead to the further elucidation of the physiological basis in a growing number of diseases (including psychiatric) (Pacher 2006). One reason that this is important is because one such pathogenesis is for that of autism (ASD). There are a number of direct correlations between ASD and the ECS. Some will be outlined in this paper.

**NL3 Mutations Inhibit Tonic Endocannabinoid Secretions**

“Rare mutations in neuroligins and nerexins predispose to autism” (Földy 2013). Neuroligin-3 is the only known protein required for tonic secretion of endocannabinoids that include AEA and 2-AG (Földy 2013). Neuroligin-3 mutations have been shown to inhibit tonic endocannabinoid secretion (Földy 2013). These alterations in endocannabinoid signaling may contribute to autism pathophysiology (Földy 2013, Krueger 2013, Onaivi 2011, Siniscalco 2013). These finding have in part prompted researchers to apply to conduct research with nonhuman primates in order to further elucidate this link (Malcher-Lopes 2013).

Endocannabinoid system deficiencies are suggested to be involved in the pathophysiology of a growing number of diseases (Marco 2012, Russo 2003). Pacher and Pertwee both cover the endocannabinoid system in detail (Pacher 2006, Pertwee 2010). The number of functions that endocannabinoid signaling regulate in the human body is extensive and beyond the scope of this paper (Pertwee 2010). For sake of brevity only a few potentially relevant aspects will be listed:

- “Endocannabinoids are key modulators of synaptic function” (Castillo 2012).
- Tonic secretions of endocannabinoids regulate GI functions (including metabolism) (Di Marzo 2011, Li 2011).
- Endocannabinoids (and exogenous cannabinoids) suppress proliferation and cytokine release (Cencioni 2010).
- Endocannabinoids regulate stress responses, in part via the modulation of the 5-HT system (Haj-Dahmane 2011).
- CB2 is expressed in Purkinje cells (Gong 2006). “In the cerebellar cortex, CB1Rs regulate several forms of synaptic plasticity at synapses onto Purkinje cells, including presynaptically expressed short-term plasticity and, somewhat paradoxically, a postsynaptic form of long-term depression (LTD) (Carey 2011).”
- “CB1 variations modulate the striatal function that underlies the perception of signals of social reward, such as happy faces. This suggests that CB1 is a key element in the molecular architecture of perception of certain basic
emotions. This may have implications for understanding neurodevelopmental conditions marked by atypical eye contact and facial emotion processing, such as ASC” (Chakrabarti 2011).

- Additional targets of endocannabinoids (and exogenous cannabinoids), PPARα, PPARγ, and GPR55 expression levels have shown reductions in a valproic acid model of autism in rats (Kerr 2013) (Servadio 2016).

- Endocannabinoids and CB1 agonists increase cerebrocortical blood flow (Iring 2013).

- “The expression patterns in malformations of cortical development highlight the role of cannabinoid receptors as mediators of the endocannabinoid signaling and as potential pharmacological targets to modulate neuronal and glial cell function in epileptogenic developmental pathologies” (Zurolo 2010).

- The endocannabinoid signalosome is “a molecular substrate for fragile X syndrome, which might be targeted for therapy” (Jung 2012).

- Endocannabinoid signaling mediates oxytocin-driven social reward. (Wei 2015)

Exogenous cannabinoids from cannabis display similar pharmacological characteristics to that of endogenous cannabinoids (Pertwee 2010). The potential therapeutic value of systemic administration of phytocannabinoids has been suggested in the treatment of a number of diseases with suspected underlying endocannabinoid deficiencies (Russo 2003). Documentation of their safety and clinical efficacy in a variety of treatments continues to grow (Hazekamp 2013). Some similar characteristics include:


- Neuroprotection (Hampson 2003, Lara-Celador 2013, Sanchez 2012)


Based on their relative safety, the similar pharmacological characteristics to endocannabinoids that are inhibited in ASD, and the significant role those endogenous cannabinoids play in human health, it’s possible that cannabinoids from cannabis could prove therapeutic value in treatments.
Increased Expression of CB2 Receptors Associated with ASD

The second direct link, of possibly equal or greater relevance for treatment, is the upregulation of CB2 receptors in the brains of those with ASD (Siniscalco 2013). This is believed to be part of an endogenous neuroprotective role of the endocannabinoid system:

- “CB2 receptors have been identified in the healthy brain, mainly in glial elements and, to a lesser extent, in certain subpopulations of neurons, and that they are dramatically up-regulated in response to damaging stimuli, which supports the idea that the cannabinoid system behaves as an endogenous neuroprotective system. This CB2 receptor up-regulation has been found in many neurodegenerative disorders including HD and PD, which supports the beneficial effects found for CB2 receptor agonists in both disorders. In conclusion, the evidence reported so far supports that those cannabinoids having antioxidant properties and/or capability to activate CB2 receptors may represent promising therapeutic agents” (Fernández 2011).

- CB2 “expression is increased by inflammatory stimuli suggests that they may be involved in the pathogenesis and/or in the endogenous response to injury… receptors may be part of the general neuroprotective action of the ECS by decreasing glial reactivity. Neuropathological findings in human brains suggest that the upregulation of CB2 receptors is a common pattern of response against different types of chronic injury of the human CNS. In addition, their selective presence in microglial cells is highly suggestive of an important role in disease-associated neuroinflammatory processes. The anti-inflammatory effects triggered by the activation of the CB2 receptor make it an attractive target for the development of novel anti-inflammatory therapies” (Benito 2008).

Given that CB2 is upregulated, and that it’s believed to play a neuroprotective role in the human brain, CB2 activation is believed to be a potential target for treatment of ASD (Siniscalco 2013). Endocannabinoids (AEA, 2-AG) and the most prominent cannabinoids in cannabis (including THC) are CB2 agonists (Izzo 2009).

Elevated Cytokine Levels Associated with ASD

Elevated cytokine levels are associated with ASD (Napolioni 2013). Whether this is a direct result of inhibited tonic secretion of endocannabinoids remains uncertain. However, endocannabinoids (AEA, 2-AG) have been shown to play key roles inhibiting cytokines via CB2 activation (Cencioni 2010, Panikashvili 2006). “Both THC and CBD have been shown to decrease cytokine production” via CB1/CB2 dependent and independent mechanisms (Juknat 2012, Kozela 2010). The majority of cannabinoids are PPAR gamma agonists (Izzo 2009), which have been shown to inhibit cytokine production (Jiang 1998).
Clinically Diagnosing ASD

A team of researchers recently discovered and patented a process that claims that it’s possible to clinically diagnose ASD, and susceptibility to it, via observation of the degree of modulation that acetaminophen has on endocannabinoid levels (Schultz 2012).

Botanical Extracts > Dronabinol

Of equal relevance to this issue is the substantial data, including clinical studies, suggesting that the combined administration of CBD along with THC (and possibly other cannabinoids/terpenes present in cannabis) exhibit additive and synergistic effects resulting in greater clinical efficacies when compared to either cannabinoid alone (McPartland 2001, Izzo 2009, Russo 2011). The second most prominent cannabinoid in cannabis is CBD (Gertch 2010). CBD has been shown to inhibit intoxication, sedation, and tachycardia associated with THC (Russo 2006). It’s been shown to increase the clinical efficacy of THC, while adding therapeutic value in its own right (Russo 2006) (Iseger 2015).

● “CBD is demonstrated to antagonize some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported” (Russo 2006).

● “Several studies suggest that CBD is non-toxic in non-transformed cells and does not induce changes on food intake, does not induce catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature), does not affect gastrointestinal transit and does not alter psychomotor or psychological functions. Also, chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans” (Machado 2011).

An argument could be made that botanical extracts with CBD present offer safer options for patients, with greater clinical efficacy, when compared to THC (Dronabinol) alone (Russo 2006). CBD offers more than simply increasing the safety and efficacy of THC (Izzo 2009).
“CBD has been shown to have an inhibitory effect on the inactivation of endocannabinoids (i.e. inhibition of FAAH enzyme), thereby enhancing the action of these endogenous molecules on cannabinoid receptors, which is also noted in certain pathological conditions. CBD acts not only through the endocannabinoid system, but also causes direct or indirect activation of metabotropic receptors for serotonin or adenosine, and can target nuclear receptors of the PPAR family and also ion channels” (Campos 2012).

Here are some of the demonstrated pharmacological characteristics of CBD that may be relevant:

- CB1/CB2 agonist blocker (can inhibit overstimulation of CB1 by THC)
- FAAH inhibition increases endocannabinoid levels (including AEA, 2-AG)
- AEA reuptake inhibitor
- 5-HT1a agonist
- Suppressor of tryptophan degradation
- PPAR alpha and gamma agonist
- Positive allosteric modulator at glycine receptors
- TRPV1 and TRPV2 agonist
- Adenosine uptake competitive inhibitor
- Antagonist at abnormal-CBD receptor
- Regulator of intracellular Ca 2+
- T-type Ca 2+ channel inhibitor (Izzo 2009)

If we accept that tonic secretions of AEA and 2-AG are inhibited via NL3 mutations in ASD (both of which being CB1 and CB2 agonists), then it might be possible to suppose the potential benefits of low doses of THC in treatments as well. This seems especially true when the striking pharmacological similarities between THC and AEA are reviewed (Pertwee 2010). The majority of the research conducted thus far with ASD and cannabinoids has been with THC alone. Dronobinal has indicated potential in a single adolescent case study of autism (Kurz 2010). This might suggest that THC along with CBD might offer increased clinical efficacy (Russo 2006).

**Treating Symptoms Associated with ASD**
A considerably greater body of data can be gathered in regards to aspects of the involvement (and targeting for treatment) of the endocannabinoid system in a number of the symptoms, and diseases, associated with ASD (in comparison to the pathophysiology of ASD itself):

- Seizures (Jones 2012, Porter 2013, van Rijn 2011)
- Sleep Dysfunction (Murillo-Rodriguez 2011, Ware 2010)
- Tuberous Sclerosis (Krueger 2013, Shu, Hai-Feng 2013, Zurolo 2010)
- Cerebral Ischemia (Schmidt 2012, Choi 2013, Murikinati 2010, Garcia-Bonilla 2014)
- Depression/Anxiety (Hill 2009, Almeida 2013, Campos 2013, Schier 2012)
- Cachexia (Engeli 2012, Gamage 2012, Marco 2012)

**Conclusion**

Given the known role of the endocannabinoid system in ASD it seems entirely possible, if not likely, that cannabinoid rich botanical extracts from cannabis can be utilized as useful agents targeting the pathophysiology of ASD, as well as the many debilitating symptoms and conditions associated with it. We believe that families and physicians should have the legal right to explore these options on an individual basis without fear of prosecution.

**Works Cited**


94. Parent Ratings of Behavioral Effects of Biomedical Interventions The following data have been collected from the more than 27,000 parents who have completed our questionnaires designed to collect such information.

95. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4922773/ Aggression in autism spectrum disorder: presentation and treatment options