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State of Ohio Medical Board
30 East Broad
Columbus, Ohio 43215

Dear Medical Board,

As Ohio experts in the diagnosis and clinical care of autism spectrum disorder we are writing in response to the petition pursuant to Ohio Administrative Code 4731-32-05 to add autism as a qualifying condition or disease for treatment with medical marijuana in the State of Ohio.

First, we want to make it clear to the Board that no rigorous scientific evidence exists to date supporting marijuana (cannabis) use in persons with autism. While a few studies of cannabis for treatment of autism have been published, they are seriously flawed. First, they are all open-label studies, meaning that no placebo control was utilized. The gold standard for assessing clinical effectiveness of any drug is the randomized, placebo-controlled study. Studies that are open label are more likely to report positive response rates due to placebo effect where the caregiver desires positive outcomes of the treatment in question.

Looking more specifically at the few studies of cannabis for treatment of autism, in a recent paper written by Schleider et al. (2019), 30.1% of patients with autism were described as significantly improved and 53.7% moderately improved after open-label treatment with cannabis at a variety of doses and formulations. However, of the 188 patients treated with cannabis, only 60% (n=93) were evaluated, meaning 40% (n=62) were excluded from analysis. This is not how rigorous, systematic open-label drug studies are done and has the potential to result in biased and/or misleading findings. Further, the outcome measures utilized in the Schleider paper to assess treatment effectiveness are not standardized for use in individuals with autism and likely have little clinical utility. The authors themselves note that their results are based on subjective caregiver reports and may be reflective of "inflated expectations of the novel treatment 'miracle' effect." Finally, the Schleider paper was rejected for publication at autism-focused journals with editors who were aware of the shortcomings and weaknesses of this study.

A second open label study of cannabis for treatment of autism found some behavioral improvements but a high rate of side effects. Specifically, in a retrospective review of clinical treatment with cannabis in 60 youth with autism and severe behavior, Aran et al. (2019) reported 61% of patients exhibited significant behavioral improvement. However, 51% of the patients reported a significant adverse event including sleep disturbance, worsening irritability, and one girl who developed a severe cannabis-associated psychotic reaction. During the study, 27% of the patients stopped the treatment due to lack of efficacy and side effects.

Very few pre-clinical studies looking at the effects of cannabis in autism have been published. However, in contrast to the above studies, in the high impact journal

Translational Psychiatry, Guennewig et al. (2018) reported that THC exposure in induced pluripotent stem cell-derived neurons results in blunted brain cell responses from persons with schizophrenia. They also found that gene expression changes induced by THC in these neurons mimics the genetic alterations characteristic of autism. The conclusion from Guennewig et al. (2018) is one of caution when considering use of cannabis in autism as THC may actually *exacerbate* the core symptoms and brain features of autism, rather than having a beneficial treatment effect.

We recognize that autism is a lifelong disorder associated with significant communication, social and behavioral challenges that can greatly impact daily life for children and their families. We also recognize there is need to develop additional treatments that target these challenges. Cannabis is one of innumerable treatments proposed and discussed among autism researchers and families of children with autism each year. To determine the true clinic impact of cannabis for children with autism, a well-designed clinical investigation utilizing placebo-control approach and validated outcome measures is needed. Further, autism is a heterogeneous condition with significant individual variation in quality and severity of symptoms. Treatment studies of autism should more systematically aim to determine what subgroups or specific characteristics of autism are best targeted by the treatment in question. In Ohio, there is clear opportunity to rigorously study the clinical effectiveness of cannabis for children with autism. Our signatories include Schedule 1 DEA license holders at academic centers with autism specialty clinics who are in a position to conduct the studies required to evaluate the efficacy of cannabis for children with autism. Adding autism as an indication for medical marijuana use without compelling scientific evidence will undermine any efforts of autism researchers in Ohio to rigorously study efficacy of cannabis for children with this disorder. This, in turn, will prevent providers and families from obtaining accurate, scientifically-based information from which to make clinical decisions about cannabis use for children with autism.

Lastly, the psychoactive effects of THC pose significant threats for our population of persons with autism, in particular, those with communication deficits who cannot self-report internal states of displeasure, confusion, or psychosis induced by THC. Given this, it is of paramount importance to study cannabis use in autism in a controlled clinical trial setting with sufficient observation for safety and tolerability. There is no available understanding of how to dose cannabis in autism or what the impact combining THC containing cannabis and prescribed drugs will have in this vulnerable population. Many youth and adults with autism take other psychoactive FDA-approved drugs to treat interfering and symptoms such as anxiety, irritability, and ADHD and the impact of combining cannabis with such medications in this population is unknown.

We appreciate the efforts and interests of family and other stakeholders who are seeking to expand treatment options in autism. We appreciate the potential medical benefits of cannabis for certain indications. With that said, there is no compelling, scientifically sound evidence to support general use of marijuana in persons with autism. This is a topic that requires more study. Autism researchers in Ohio and nationwide are poised to rigorously study the potential role cannabis may have for treatment of autism. This work needs to be done before the State of Ohio Medical Board

can confidently say that there is sufficient safety and efficacy data supporting autism as an indication for medical marijuana use in Ohio.

References:

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