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February 23, 2021

State Medical Board of Ohio
30 E Broad Street, 3rd Floor
Columbus, OH 43215

Re: Opposition to Inclusion of Autism and Anxiety as Qualifying Conditions or Diseases for Treatment with Medical Marijuana

President Bechtel and members of the State Medical Board of Ohio:

On June 4, 2019 and February 28, 2020, we, the undersigned, submitted the letter below to the State Medical Board of Ohio for consideration. We respectfully request the Board's consideration of our letter below detailing our opposition to adding autism and anxiety to the list of qualifying conditions for treatment with medical marijuana, as well as updated comments to address the new petitions.

Letter to State Medical Board

We, the physicians at the divisions of Child and Adolescent Psychiatry, Pediatric Neurology and Developmental Behavioral Pediatrics at Nationwide Children's Hospital are writing in opposition to a 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. In our view, there is little rigorous evidence that marijuana or its derivatives is of benefit for patients with autism and anxiety, but there is a substantial association between cannabis use and the onset or worsening of several psychiatric conditions.

We provide clinical care to hundreds of children with autism spectrum disorder (ASD), anxiety and intellectual delay every year. Some are highly aggressive towards themselves and others, leading to poor quality of life for themselves and their families. We appreciate the focus of the Medical Board on these chronic illnesses, and we applaud research attempts to look at the clinical effectiveness of medical marijuana in treating anxiety disorders and disruptive behaviors in children with ASD. However, we are also deeply concerned by the consideration of marijuana as a treatment for these conditions without the presence of any gold standard trials (randomized double-blind placebo-controlled trial) establishing the efficacy and safety of THC in this clinical population.

The development of pharmacological agents typically involves several rigorous steps, including several pre-clinical, clinical and post-clinical studies across multiple phases before consideration by the FDA for approval in clinical use. The studies cited in the petition to support the ordinance, however, meet few if any of these rigorous requirements. In fact, every other study we can find in the literature has serious methodological limitations and no placebo arm. One of the studies cited in the petition to support the use of THC in ASD is an open label trial of only 10 children with ASD and self-injurious behavior using dronabinol as an intervention.(1) In the second study cited by the ordinance, a group of 53 children with ASD (diagnosis not confirmed by the researchers) were treated with oral CBD oil, with improvement

reported by parents at follow-up after 63 days. It is important to note that the authors themselves discuss important limitations of this study including use of subjective report of parents to measure response, limited duration of the study of 60 days and unconfirmed diagnosis of ASD.(2)

In a retrospective study completed by Aran et al 2018, about 61% children with ASD showed improvement in disruptive behaviors. About half of the children in this study reported significant side effects from treatment and 23% discontinued the agent due to intolerable side effects.(3) In another open labelled cannabis study by Schleider et al, we were encouraged by a larger sample size of 188. However, only 30% patients with autism in this study showed significant improvement and a significant proportion (40%) of patients were excluded from this analysis leading to concerns for validity of results.

In contrast to these methodologically questionable studies, a great deal of current evidence supports a strong association of cannabis use with unwanted outcomes:

- The onset or worsening of several psychiatric disorders, most notably psychosis and mood disorders. This is of particular concern in patients with ASD, as emotional and communication deficits can make it difficult to report symptoms.

- A negative impact of long-term marijuana use on cognitive functions, including overall intelligence quotient, short-term memory, concentration and problem solving. These negative impacts can be devastating in a population with already-existing neurodevelopmental deficits. (5)

- A potentially higher risk of obesity, in an ASD population already at risk because of picky eating habits, motor skill delays and lack of insight into making lifestyle changes.

- A gradual and persistent decline in pro-social engagement (or “amotivation syndrome”), especially problematic in an ASD population already struggling with social skills.

- A higher risk of emergency department visits due to fear and panic as a result of cannabis use (though current literature does not allow us to differentiate between anxiogenic and non-anxiogenic responses). (6)

- Increased risk of significant elevation in liver enzymes with similar products. (8)

Updated Comments

According to the study *Cannabinoids for People with ASD: A Systematic Review of Published and Ongoing Studies*, “this review found low-level evidence for the use of cannabis and nabiximols in a variety of disorders. Despite our comprehensive literature search, only a few RCTs related to the disorders of interest were found. These RCTs were marred by a number of limitations, most importantly failure to blind the outcome assessor, participants, and research personnel (in the open-label trials). In addition, most RCTs had a small sample size, critically reducing the power of the study to draw robust conclusions. The findings of the RCTs reviewed here need to be validated via a series of larger, well planned, randomized, double-blinded, and placebo-controlled studies. The present report can be used to design and plan further studies; however, at present the use of CBD and nabiximols in clinical practice cannot be recommended with confidence due to the drawbacks noted above.”

"One open-label trial suggested favorable evidence for the use of cannabinoids CBD and Δ9-THC for hyperactivity, self-injurious behaviors, and anxiety symptoms in patients with ASD."

Using methodology for the U.S. Preventive Services Task Force (USPSTF), this level of data equals "there is insufficient evidence to recommend for or against the inclusion of the condition in a periodic health examination". Using another sound methodology used in the United States publications, the evidence for use of medical cannabis in autism would be considered "any estimate of effect is very uncertain."

Therefore, more scientifically sound research is needed and perhaps the state could support such research efforts to ensure the safety and well-being of the citizens of Ohio.

Conclusion

While we strongly support research and development of pharmaceutical cannabinoids and THC products for the treatment of chronic debilitating conditions, interpreting current research as indicative of clinical effectiveness and safety of cannabis in treating conditions such as autism and anxiety disorders is concerning and raises several medical, ethical and legal questions. As aforementioned, there is not a single published randomized, double-blind, placebo-controlled trial to specifically study the safety and efficacy of cannabis in ASD, which is the gold standard for FDA-approval of medications for use in the clinical setting. Almost every published study reviewed reports that there is lack of strong evidence to support the use of cannabinoids in ASD and that further randomized, double-blind, placebo-controlled trials are necessary to validate the efficacy and safety of cannabinoids in ASD (3,4,10,11). We request the Board oppose the inclusion of autism spectrum disorder and anxiety as qualifying conditions or disease for treatment with medical marijuana in Ohio.

We continue to support and hope for high quality unbiased research on this topic, however, do have significant concerns about prematurely approving medical cannabis for treatment of serious developmental and psychiatric conditions. We are closer than ever in our ability to systematically study the benefits vs. risks of these products on the brains of our kids. There are several well designed, randomized, double-blind placebo-controlled trials currently underway at several leading institutions including University of California San Diego, University of Colorado, and Montefiore Medical Center to investigate the efficacy and safety of cannabidiol (CBD) and other related plant products in children with Autism Spectrum Disorder (13,15,17). An additional larger size study at Shaare Zedek Medical Center in Israel with 150 children and adolescents is assessing the long-term effects of CBD (12). An open-label phase II trial at New York University is in process to assess the optimal dosing of CBD in ASD (14). There has been no comparison of cannabinoids to the current standard of care to date.

It would be, not only negligent but also unethical to approve medical cannabis as an indication of ASD and anxiety prior to the completion of these studies which is the standardized process to seek approval for drugs. We strongly request that the State of Ohio wait for solid, reliable information from these studies to make decisions on what products are safe for our children to be exposed to, instead of utilizing information which is being pushed by biased stakeholders.

Respectfully,

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1. Kruger T et al. “An Open Label Study of the Use of Dronabinol (Marinol) in the Management of Treatment-Resistant Self-Injurious Behavior in 10 Retarded Adolescent Patients.” Annual Meeting of the Society for Developmental and Behavioral Pediatrics 2006.

2. Kuester G et al. “Oral cannabis extracts as a promising treatment for the core symptoms of autism spectrum disorder: Preliminary experience in Chilean patients.” Journal of Neurological Sciences. 2017.

3. Aran A et al. “Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Programs – A Retrospective Feasibility Study.” Journal of Autism and Developmental Disorders. 2018

4. Schleider LB et al. “Real Life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy.” Nature. 9:200, 2019.

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7. Turna et al (2017). Is cannabis treatment for anxiety, mood and related disorders ready for prime time? Depress Anxiety. 2017 Nov; 34 (11):1006-1017.

8. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med 2018;378:1888-1897.

9. Poli et al. Cannabinoids for people with ASD: a systematic review of published and ongoing studies. Brain Sciences. 2020. 10, 572. doi:10.3390/brainsci10090572.

10. Fleury-Texiera et al. (2019). Effects of CBD-enriched cannabis sativa extract on ASD symptoms: an observational study of 18 participants undergoing compassionate use. Frontiers in Neurology. 10:1145. doi: 10.3389/fneur.2019.01145

11. Barchel et al. (2019). Oral Cannabidiol use in children with ASD to treat related symptoms and co-morbidities. 2019. Frontiers in Pharmacology. 9:1521. doi: 10.3389/fphar.2018.01521.

CBD trials in ASD

12. phase 2, randomized, double-blind, placebo-controlled trial at the Shaare Zedek Medical Center in Israel in 150 children and youth with ASD assessing long term effects of CBD
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT02956226. Cannabinoids for Behavioral Problems in Children With ASD. November 6, 2016. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02956226.

13. Single center, investigator sponsored phase 2 trials of Epidiolex in children with autism:
-UCSan Diego (Randomized, double blind, placebo controlled crossover study in 30 children aged 7-14)
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04517799. Trial of Cannabidiol to Treat Severe Behavior Problems in Children With Autism. August 18, 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04517799.

14. NYU (Open label, dose-finding phase 2 study in 30 children aged 7-17):
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03900923. Cannabidiol for ASD Open Trial. April 3, 2019. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03900923.

15. University of Colorado (Randomized, double blind, placebo controlled crossover study in 70 children aged 5-17):
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04520685. Cannabidiol Study in Children with Autism Spectrum Disorder (CASCADE). August 20, 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04520685.

16. An exploratory phase 2 trial (randomized, double-blind, placebo controlled) to investigate the safety and efficacy of cannabidiol in autism spectrum disorder in 160 children aged 6-17
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04745026. Trial to Investigate the Safety and Efficacy of Cannabidiol Oral Solution in Children and Adolescents with Autism Spectrum Disorder. February 9, 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04745026.

Cannabidivarin trials in ASD - GW also has 2 additional trials/research collaborations of another cannabinoid compound (cannabidivarin; CBDV) evaluating efficacy and/or safety in ASD

17. Randomized, double-blind, placebo controlled phase 2 trial of CBDV in patients with ASD aged 5-18:
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03202303. Cannabidivarin (CBDV) vs placebo in Children with Autism Spectrum Disorder (ASD). June 28, 2017. Available from: https://clinicaltrials.gov/ct2/show/NCT03202303.

18. Open-label phase 2 safety study of CBDV in 30 patients with ASD aged 4-18
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03849456. Safety and Tolerability of Cannabidivarin (CBDV) in Children and Young Adults with

Autism Spectrum Disorder. February 21, 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03849456.