Medical Marijuana: Not just for adults!!

JOHN A. VANCHIERE, M.D., PH.D. (LSUHSC-SHREVEPORT)

AND

KATELYN RAMSEY CASTLEBERRY

Evolution of medical marijuana treatment in Pediatrics and the law

KATELYN RAMSEY CASTLEBERRY

Disclosure

- John A. Vanchiere, M.D., Ph.D. and Katelyn Ramsey Castleberry have no financial disclosures.

The connection between autism and marijuana

Some doctors are starting to recommend marijuana for children for ailments other than physical ailments (e.g., Tourette syndrome, epilepsy, dystonia, seizures; Hadland et al., 2015). Anecdotal report suggests marijuana may increase sociability, heighten perception, give a sensation of slowing time, decrease aggression, and increase appetite (Hadland et al., 2015). Thus, on the surface, it appears marijuana may be appropriate for several behaviors typically associated with individuals with ASD (e.g., decreased appetite, severe problem behavior including aggression towards other or self, inappropriate social skills, inability to maintain attention;

Autism Support Network, 2016).

William Brooke O'Shaughnessy

O'Shaughnessy established his reputation by successfully relieving the pain of rheumatism and stilling the convulsions of an infant with cannabis. He eventually popularized its use back in England. His most famous success came when he quelled the wrenching muscle spasm of tetanus and rabies with resin. While he could not cure tetanus, he observed that the cannabis mixture reduced their symptoms of spasticity and their suffering.

Ongoing studies per ClinicalTrials.gov (01Aug2019)

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	Cannabinoids for Behavioral Problems in Children With ASD	• Autistic Disorder	• Drug: Cannabinoids - 99% pure cannabinoids mix • Drug: Placebo • Drug: Cannabinoids - whole plant extract	• Shaare Zedek Medical Center Jerusalem, Israel
2	☐	Recruiting	Cannabidivarin (CBDV) vs. Placebo in Children With Autism Spectrum Disorder (ASD)	• Autism Spectrum Disorder	• Drug: Cannabidivarin (CBDV) • Drug: Matched Placebo	• Montefiore Medical Center Bronx, New York, United States

Where Autism is a qualifying condition for medical marijuana

Why we want marijuana for our children

- Only two drugs are approved by the FDA and endorsed by the AMA for autism. Risoerdal and Abilify.
- Extreme long term and short term side effects. Some life threatening.
- Years of failed therapies and first fail protocols.
- Our children are getting older and we want to keep them out of institutions.

The problem with data

- Marijuana remains a Schedule 1 substance. Research with federal funding isn't possible.
- There are no double blind controlled studies in the U.S. where autism is treated with marijuana.
- There are no standardized medical products available in Louisiana.
- The science is "young".
- There is no standard animal model for autism.
- Autism is a huge category of varying disease states.

To do no harm

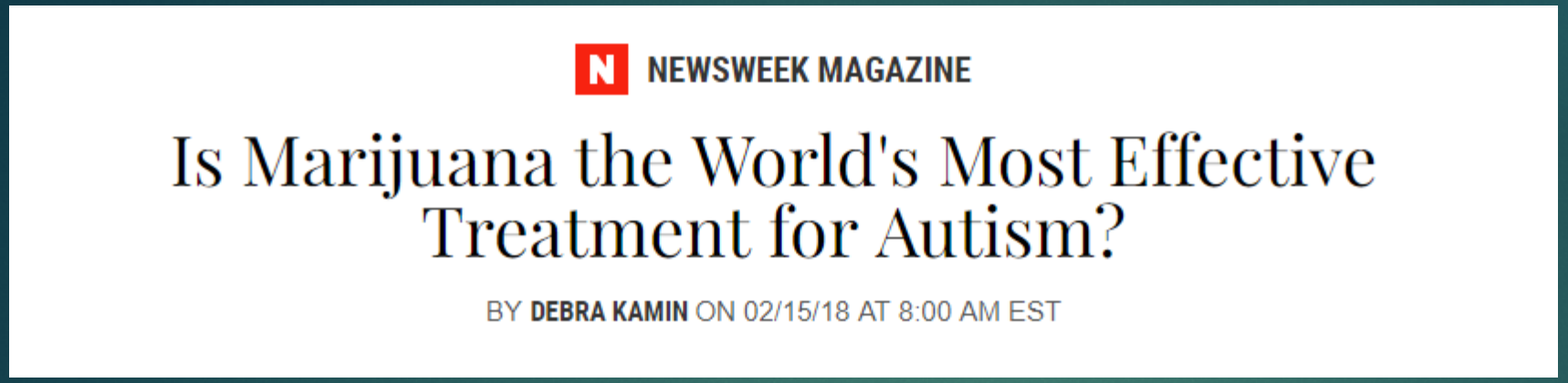
The Academy recognizes that anecdotal accounts have shown that certain marijuana compounds could benefit some children with chronic life-limiting, debilitating conditions. For this reason, the AAP strongly supports research and development of pharmaceutical cannabinoids and supports a review of policies promoting research on the medical use of these compounds. The AAP recommends changing marijuana from a Drug Enforcement Agency (DEA) schedule I to a schedule II drug to facilitate this research.

Solutions

- the AAP recommended moving marijuana from Drug Enforcement Agency Schedule 1 to Schedule 2 in order to pave the way for future clinical trials. -2015

"Hopefully, it will be found to be effective, and hopefully, it will be found to be very safe for these individuals, but right now, we just don't have that knowledge.”

https://www.google.com/amp/s/amp.livescience.com/62455-can-marijuana-treat-autism.htmlDevinsky



Charlotte Figi, who lives in Colorado, has life-threatening epilepsy. Since infancy, she suffered up to 300 grand mal seizures a week. By the age of 5, her heart had stopped several times, and she couldn't walk or eat on her own. In 2013, her desperate parents convinced a Denver doctor to prescribe cannabis oil for their daughter. The compound, a special strain of cannabis with a 20-to-1 ratio of CBD to THC, saved her life.

Charlotte is now 11. Every day, she takes two doses of cannabis oil, with that same 20-to-1 ratio, in her food. Her seizures have nearly ceased. She is healthy and thriving. Her recovery is so remarkable that a special high-CBD and low-THC strain of medical cannabis produced in Colorado was named Charlotte's Web.

Dr. Adi Aran, an Israeli pediatric neurologist, who has used CBD to treat hundreds of children with severe autism
.

“As for Benjamin, within two weeks of filling the prescription from Aran, Sharon says, he was calmer. He responded when she spoke to him. He could sit still and make eye contact. If she took him with her to visit friends, she could sit with the adults drinking tea while he played quietly in the other room. Within months, he was doing so well that his teachers recommended he leave his special-needs school for a standard classroom. "It's like a miracle. I can leave the house and go out with him and not worry," says Sharon. "I can breathe.“”

Dr. Eric Hollander, director of the Autism and Obsessive Compulsive Spectrum Program at New York's Montefiore Medical Center: Hollander's patients are receiving a treatment that contains neither THC nor CBD. They will receive pure cannabidivarin, or CBDV, a cannabinoid derived from the cannabis plant that is very similar in chemical makeup to CBD.

What does marijuana do to humans?

- **Onset of physiologic and psychologic effects vary based on route of administration, with peak effects occurring 30 minutes after inhalation and two to four hours after ingestion.**
- **Acute effects include on the one hand relaxation, euphoria, heightened perception, sociability, sensation of time slowing, increased appetite and decreased pain, and on the other hand, paranoia, anxiety, irritability, impaired short-term memory, poor attention and judgement, and poor coordination and balance.**
- **Physiologic effects include tachycardia, hypertension, dry mouth and throat, and conjunctival injection, mostly due to sympathetic nervous system activity.**
- **Prenatal exposure to cannabis is associated with hyperactivity, impulsivity and inattention symptoms in childhood**

J Dev Behav Pediatr. 2015 ; 36(2): 115–123.

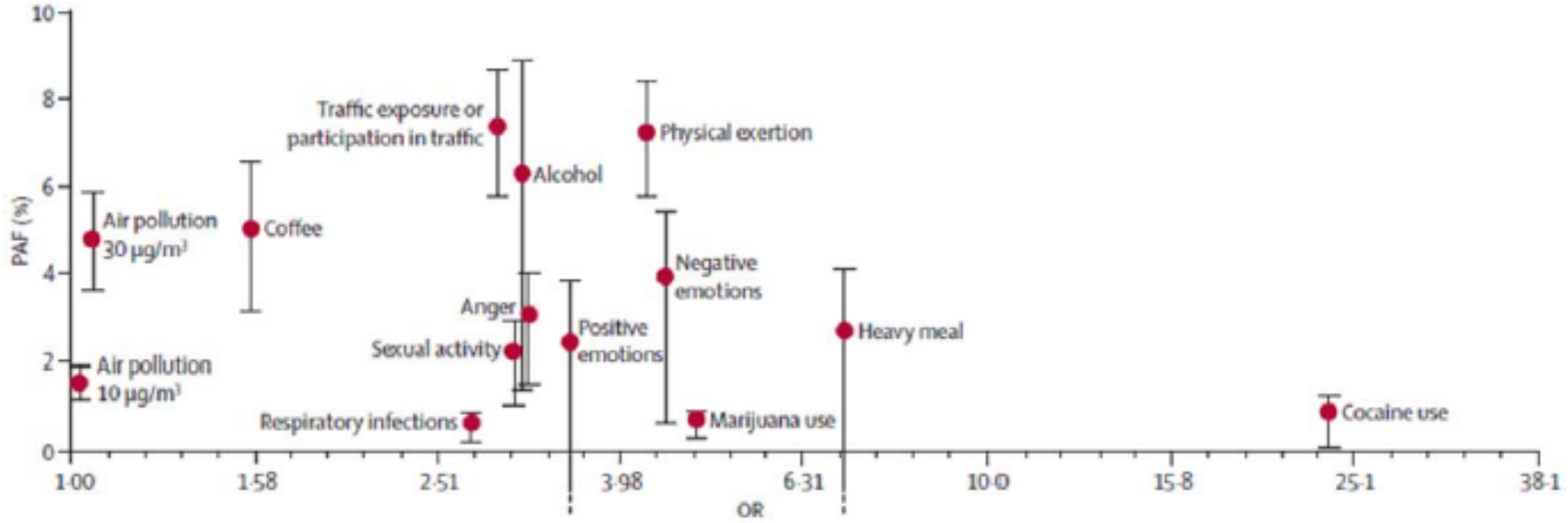


FIGURE 1. The relation between OR and PAF for each trigger of myocardial infarction.[56] OR indicates odds ratio; PAF, population attributable factor.

- The endocannabinoid system appears to play a significant role in normal neurodevelopment prenatally and extending throughout childhood and adolescence.
- Cannabinoid receptors, which are normally activated by endogenous compounds such as anandamide, appear to modulate axonal migration and long-range subcortical projections in the brain during early brain development, and affect synaptic connectivity throughout childhood and adolescence.
- Some of these developmental processes are known to occur throughout adolescence and into young adulthood, and alterations in these processes during critical windows are believed to result in permanent, irreversible deleterious effects.

J Dev Behav Pediatr. 2015; 36(2): 115–123.

- Positive effects reported by users include anxiolysis, euphoria, heightened perception, increased sociability, sensation of time slowing, increased appetite, and decreased pain.
- Negative effects of marijuana include paranoia, anxiety, irritability, worsened short term memory, poor attention, altered awareness of the passage of time, impaired judgement, decreased coordination and balance, and distorted spatial perception, all of which could arguably exacerbate symptoms in developmental and behavioral conditions.
- Over the long-term, adolescent cannabis use may be associated with a decline in intelligence quotient (IQ).
- Regular cannabis use during adolescence is also associated with adverse psychiatric outcomes, although these psychiatric outcomes have not been rigorously studied among patients with developmental or behavioral concerns.

J Dev Behav Pediatr. 2015; 36(2): 115–123.

Why would we consider giving marijuana to children with autism?

Remember, not all marijuana is created equally....

- THC to CBD ratios differ
- The concentrations of nearly one hundred other cannabinoids in marijuana also vary widely.
- The leading cannabinoid preparations considered for use in children are: Cannabidiol (CBD), Cannabidivarin (CBDV) and 20:1 ratio of CBD to THC.
- Louisiana producers will be making pharmaceutical grade preparations with high reproducibility and well-characterized repertoires of cannabinoids.

Table 1 Participant characteristics

	Neurotypical control	Children with ASD
N	93	93
Age	11.8 ± 4.3	13.1 ± 4.1^
% male	79%	79%
BMI	21.0 ± 4.2	20.4 ± 5.5
Epilepsy comorbidity	0%	10%
High ASD symptoms severity		
ADOS comparison score = 8–10		77%
VABS standard score ≤ 70		88%
CARS total score ≥ 37		81%
SRS *t* scores ≥ 75		86%
Psychotropic medications*		
Any		80%
Antipsychotic		56%
SSRIs		23%
Stimulants		15%
Antiepileptic (mood stabilizers)		13%
Benzodiazepines		8%
Others		5%

^Significant age difference ($P = 0.040$). The BMI difference was not significant
*Medications were stable for at least 1 month before blood collection.

CB_1R and its endogenous ligands (AEA and 1-AG) regulate social play and anxiety in animal models and in humans.

AEA is N-arachidonoylethanolamine (anandamide)
2-AG is 2-arachidonoil-glycerol
OEA and PEA don't interact with CB_1R

<u>Prior research has shown:</u>

- **Decreased endocannabinoid "tone" in animal models of autism.**
- **Activation of the ECS in animal models "reversed" autistic symptoms.**
- **Decreased CB_1R in postmortem brains of patients with autism.**
- **Decreased AEA concentrations in plasma of children with autism.**

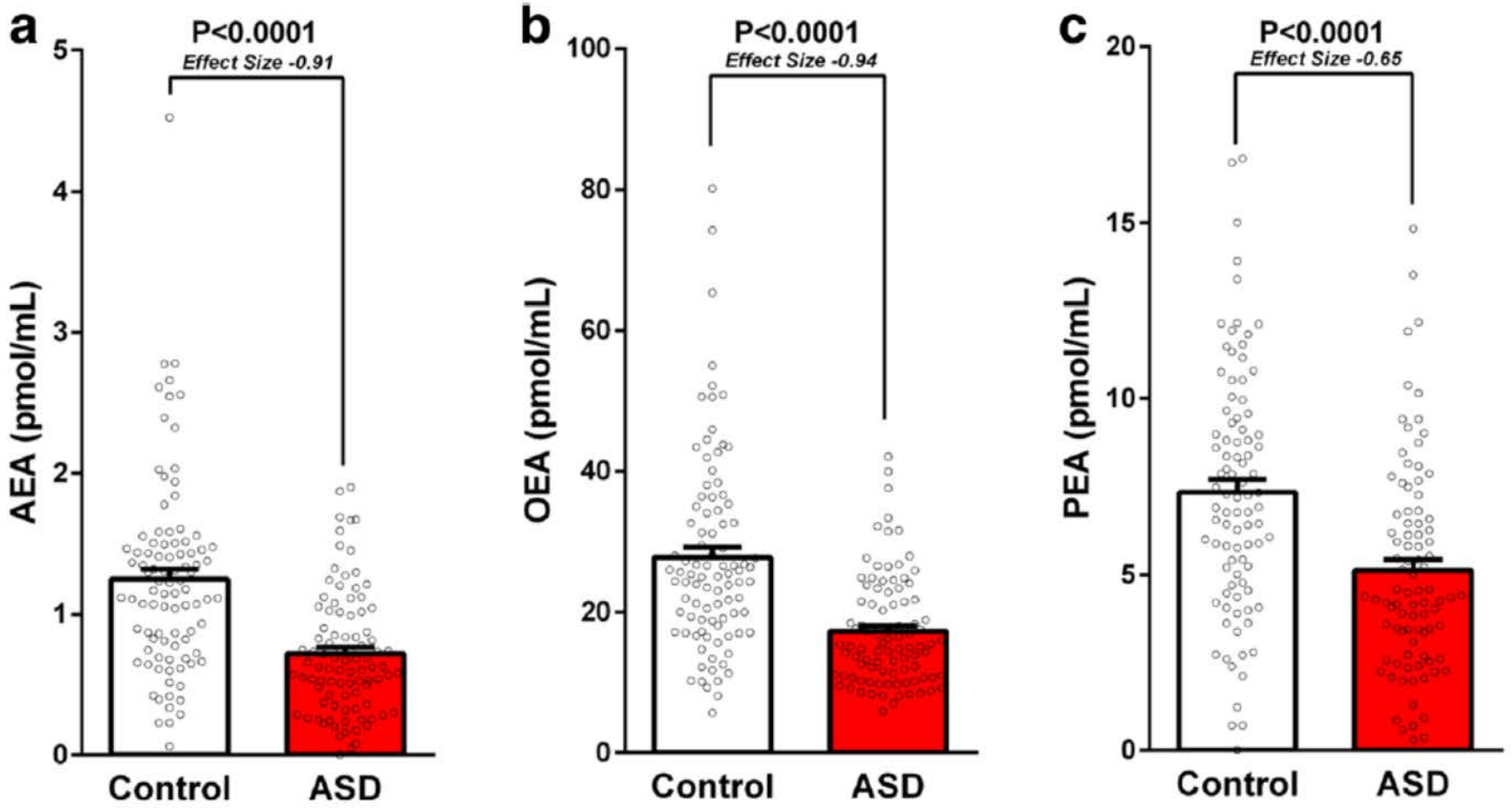


Fig. 1 Lower serum endocannabinoid levels in children with ASD. Legend: low endocannabinoid "tone" in serum samples of 93 children with ASD compared with 93 age- and gender-matched controls. Results of anandamide (AEA; panel **a**), oleoylethanolamine (OEA; panel **b**), and palmitoylethanolamide (PEA; panel **c**) are presented as mean, standard error, and distribution respectively

There was no correlation of AEA, OEA or PEA levels with age, gender, BMI, medications or level of functioning.

Does “supplementation” of Endogenous Cannabinoid System help children with ASD?

A retrospective study of 60 children with ASD who were treated with CBD showed:

- reduced behavioral outbursts in 61%
- improved communication in 47%
- reduced anxiety in 39%
- reduced stress in 33%
- reduced disruptive behavior in 33%

Small studies of Dronabinol (THC-based drug) showed improvements in hyperactivity, lethargy, irritability, stereotypy and inappropriate speech at 6 months.

Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy

Lihi Bar-Lev Schleider[1,2], Raphael Mechoulam[3], Naama Saban[2], Gal Meiri[4,5] & Victor Novack[1]

SCIENTIFIC REPORTS | (2019) 9:200 | DOI:10.1038/s41598-018-37570-y

	Total (188)
Mean age (SD)	12.9 (7.0)
Gender (male), No. (%)	154 (81.9)
Mean body mass index (SD)	29.0 (5.3)
Previous experience with cannabis (Yes), No. (%)	19 (10.1)
Comorbidities:	
Epilepsy, No. (%)	27 (14.4)
Attention Deficit Hyperactivity Disorder, No. (%)	7 (3.7)
Tourette syndrome, No. (%)	4 (2.1)
Celiac Disease, No. (%)	3 (1.6)
Anxiety Disorder, No. (%)	3 (1.6)

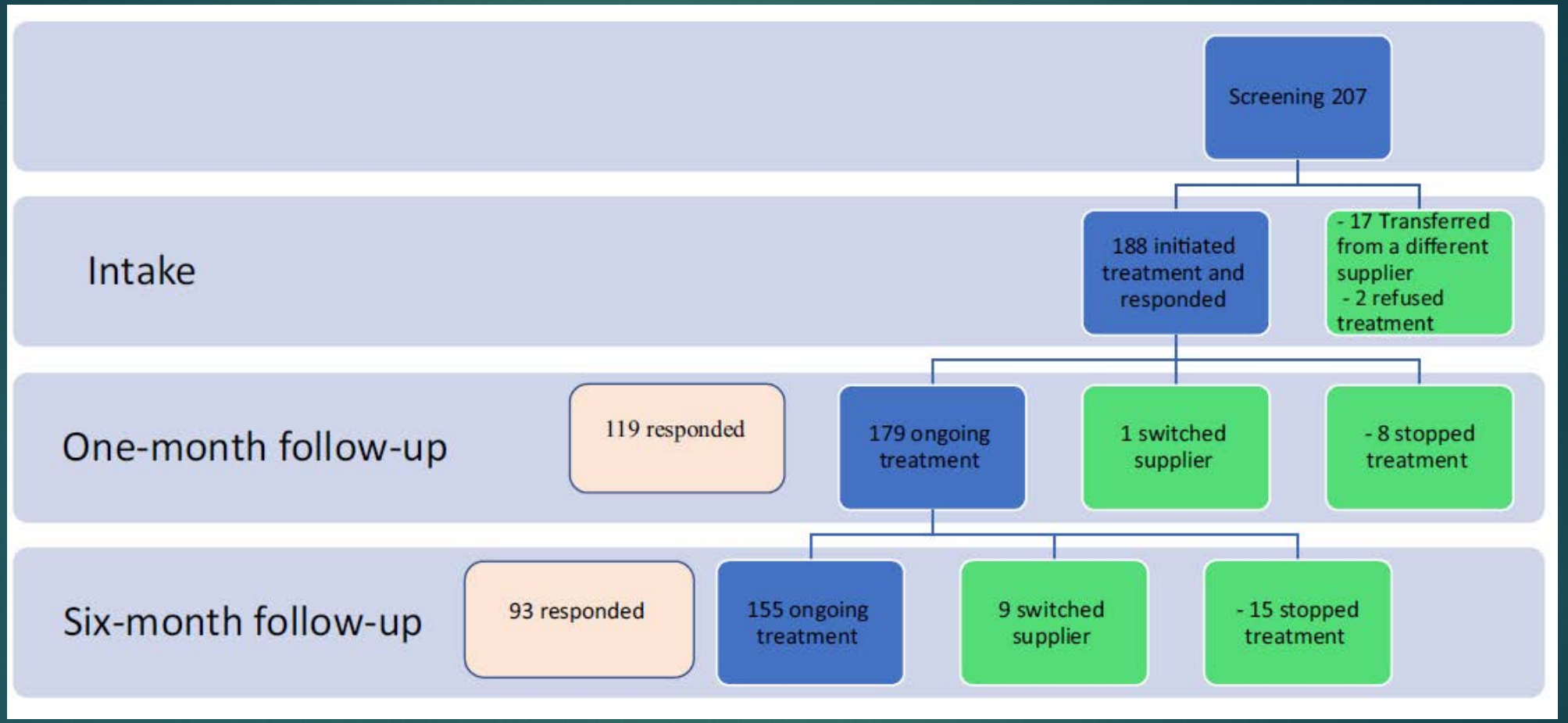
Table 1. Demographic and clinical characteristics of patients at intake.

Treatment Regimen:

- Cannabis oil dissolved in olive oil with THC:CBD of 1:20 (30% CBD and 1.5% THC)
- Starting dose was one drop (50ul) 3x per day sublingually
- The dose was increased gradually for each patient depending on the effect on targeted symptoms, as per individual treatment plan.
- Optimal dosing took up to 2 months, with final doses of 1-20 drops 3x per day.

	Intake prevalence Total (188)	Change at six months		
		Symptom disappeared	Improvement	No change or deterioration
Restlessness, No. (%)	170 (90.4)	1 (1.2)	71 (89.8)	7 (8.8)
Rage attacks, No. (%)	150 (79.8)	1 (1.3)	65 (89.0)	7 (9.5)
Agitation, No. (%)	148 (78.7)	1 (1.4)	57 (83.8)	10 (14.7)
Sleep problems, No. (%)	113 (60.1)	9 (19.5)	27 (58.6)	10 (21.7)
Speech Impairment, No. (%)	113 (60.1)	—	15 (30)	35 (70)
Cognitive impairment, No. (%)	91 (48.4)	—	15 (27.2)	40 (72.7)
Anxiety, No. (%)	69 (36.7)	—	24 (88.8)	3 (11.1)
Incontinence, No. (%)	51 (27.1)	2 (9.0)	7 (31.8)	13 (59.0)
Seizures, No. (%)	23 (12.2)	2 (15.3)	11 (84.6)	—
Limited Mobility, No. (%)	17 (9.0)	2 (18.1)	—	9 (81.8)
Constipation, No. (%)	15 (8.0)	1 (12.5)	6 (62.5)	2 (25)
Tics, No. (%)	15 (8.0)	1 (20.0)	4 (80.0)	—
Digestion Problems, No. (%)	14 (7.4)	1 (12.5)	5 (62.5)	2 (25.0)
Increased Appetite, No. (%)	14 (7.4)	1 (33.3)	1 (33.3)	1 (33.3)
Lack of Appetite, No. (%)	14 (7.4)	2 (40.0)	1 (20.0)	2 (40.0)
Depression, No. (%)	10 (5.3)	—	5 (100.0)	—

Table 2. Symptom prevalence and change. Symptom prevalence at intake in 188 patients assessed at intake and change at six months in patients responding to the six-month questionnaire.


Screening 207
Intake
188 initiated treatment and responded
- 17 Transferred from a different supplier
- 2 refused treatment
One-month follow-up
119 responded
179 ongoing treatment
1 switched supplier
- 8 stopped treatment
Six-month follow-up
93 responded
155 ongoing treatment
9 switched supplier
- 15 stopped treatment

	Sleep			Eating with Appetite			Concentration on daily tasks			Bowel Activity		
	Before	During	p value	Before	During	p value	Before	During	p value	Before	During	p value
Severe difficulty	44 (47.3)	2 (2.2)		2 (2.2)	1 (1.1)		75 (80.6)	21 (22.6)		3 (3.2)	2 (2.2)	
Moderate difficulty	18 (19.4)	27 (29.0)		6 (6.5)	13 (14.0)		11 (11.8)	41 (44.1)		13 (14.0)	17 (18.3)	
No difficulty	28 (30.1)	39 (41.9)	<0.001	59 (63.4)	47 (50.5)	0.751	2 (2.2)	11 (11.8)	<0.001	71 (76.3)	54 (58.1)	0.242
Good	2 (2.2)	15 (16.1)		10 (10.8)	16 (17.2)		0	10 (10.8)		5 (5.4)	13 (14.0)	
Very Good	1 (1.1)	8 (8.6)		16 (17.2)	14 (15.1)		0	3 (3.2)		1 (1.1)	4 (4.3)	

Medication family	Intake	Change at six months follow-up				
	Total	Stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	New medication
Antipsychotics, n (%)	55	11 (20)	3 (5)	41 (75)	0	0
Antiepileptics, n (%)	46	6 (13)	0	35 (76)	2 (4.5)	3 (6.5)
Antidepressants, n (%)	10	3 (30)	0	4 (40)	1 (10)	2 (20)
Hypnotics and sedatives, n (%)	10	2 (20)	1 (10)	7 (70)	0	0
Anxiolytics, n (%)	7	2 (28)	0	5 (72)	0	0

Table 4. Concomitant medications. Concomitant medications use at the baseline and six months follow up in patients responding to the six-month questionnaire.

Summary and Conclusions

- The consideration to use cannabinoids for the treatment of behaviors related to ASD is complex… involving parents, physicians and others who want the best for children.
- The anecdotes and limited data that is currently available supports the hypothesis and hope that CBD and/or other cannabinoid preparations may be beneficial for children with severe ASD who have aggressive and/or disturbing behaviors.
- Pediatricians who care for children with ASD should keep abreast of developments in this exciting area.
- All of us have a role to play in advocacy and policy-development related to the availability and use of cannabinoids in children.