

How Can Cannabis Improve Behavior Symptoms in Patients with Autism?



Michael Elice, MD.
AIM Integrative Medicine

History of Cannabis



- The plants cannabis sativa, indica and ruderalis have been cultivated for more than 10000 years
- Has been used for textiles, paper, oil, seeds for medicine and for psychotropic activity.
- Medical uses date back to 2737 BCE in China - treatment for malaria, female disorders and other illnesses
- 1794: used for coughs, venereal disease and urinary incontinence, rabies, rheumatism, epilepsy and tetanus
- 1850: cannabis added to the pharmacopeia in the U.S.
- 1941: cannabis removed from the U.S. pharmacopeia - its medical uses no longer recognized in America
- 1975: Nabilone, a synthetic cannabinoid is used for cancer chemotherapy-induced nausea and vomiting and adjuvant for neuropathic pain

History of Cannabis



- 1996: California becomes the first state to use medical marijuana legalized for people with AIDS, cancer and other serious illnesses
- To date: marijuana is still classified as Schedule I drug by FDA

Clinical Applications



- Inflammation: reductions on different cell types and on the immune system eg. Mast cells, T-lymphocytes, TNF-alpha, Interleukins, ROS and others
- Cannabis contains phytocannabinoids which contain antioxidants, Anti-inflammatory and neuroprotective effects
- Anxiety: the endocannabinoid system helps to modulate stress reactions, fear, emotion and reward
- Regulation of the HPA axis system via reduction of production and release of corticosteroids
- Seizures: CBD alone has no psychotropic effects, modulates neuronal excitability. It is effective against grand mal seizures, cortical focus seizures, complex partial seizures and temporal lobe epilepsy

Clinical Applications

- Pain: inflammatory and neuropathic
- Nausea and vomiting
- Arthritis

Hypothesis

Patients with ASD will have improved health conditions after use of cannabis.

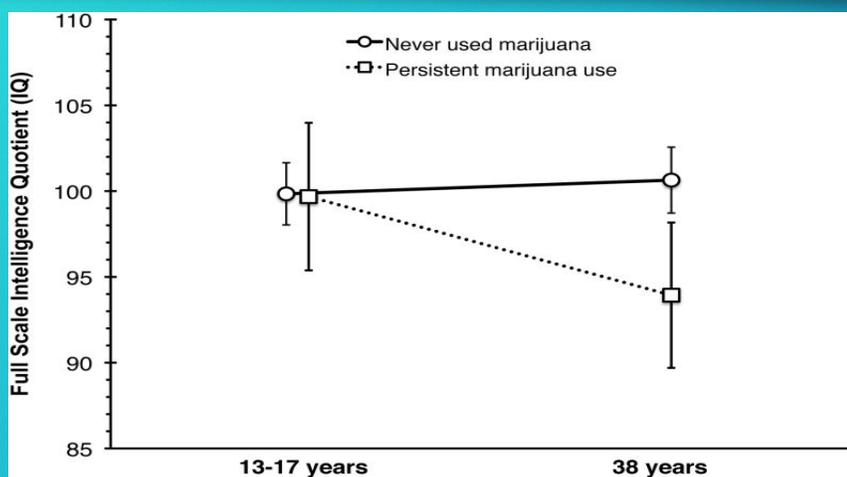
• RESEARCH

[Pediatrics](#). 2019 Feb;143(2). pii: e20180558. doi: 10.1542/peds.2018-0558. Epub 2019 Jan 4.
Ethical Implications for Providers Regarding Cannabis Use in Children With Autism Spectrum Disorders.
[Duvall SW](#)¹, [Lindly O](#)^{2,3}, [Zuckerman K](#)^{2,4,5}, [Msall ME](#)^{6,7}, [Weddle M](#)

- Children with autism spectrum disorder (ASD) are at risk for self-injurious behaviors that can be difficult to treat in the context of co-occurring low IQ and adaptive skills. Increased prevalence and decriminalization of cannabis in some states have led to more frequent questions for pediatricians about the use of cannabis for difficult-to-treat developmental and behavioral conditions.
- **What do we know about the possible benefits and risks of cannabis use in children with ASD? How should the clinician respond to a parent who expresses interest in cannabis to manage behavior in a child with ASD?**

[J Dev Behav Pediatr. Author manuscript; available in PMC 2016 Feb 1.](#) Published in final edited form as:

J Dev Behav Pediatr. 2015 Feb-Mar; 36(2): 115-123.



[Life Sci. 2019 May 1;224:120-127. doi: 10.1016/j.lfs.2019.03.053. Epub 2019 Mar 22.](#)

Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment.

[Premoli M¹](#), [Aria F¹](#), [Bonini SA¹](#), [Maccarinelli G¹](#), [Gianoncelli A¹](#), [Pina SD¹](#), [Tambaro S²](#), [Memo M¹](#), [Mastinu A³](#)

- The pharmacological research on the Cannabis sativa-derived compounds has never terminated. Among the phytocannabinoids without psychotropic effects, the prevalent one in Cannabis is cannabidiol (CBD). **Recently, CBD has been authorized by the FDA to treat some rare forms of epilepsy and many trials have begun for the treatment of autism spectrum disorders.** This review aims to clarify the pharmacological activity of CBD and its multiple therapeutic applications. Furthermore, critical and conflicting results of the research on CBD are discussed with a focus on promising future prospects.

[Neuropsychopharmacology](#), 2019 Feb 6

Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder.

[Pretzsch CM](#)¹, [Freyberg J](#)¹, [Voinescu B](#)¹, [Lythgoe D](#)², [Horder J](#)¹, [Mendez MA](#)¹, [Wichers R](#)¹, [Ajram L](#)¹, [Ivin G](#)³, [Heasman M](#)³, [Edden RAE](#)⁴, [Williams S](#)², [Murphy DGM](#)¹, [Dalry E](#)¹, [McAlonan GM](#)⁵.

- There is increasing interest in the use of cannabis and its major non-intoxicating component cannabidiol (CBD) as a treatment for mental health and neurodevelopmental disorders, such as autism spectrum disorder (ASD).
- However, before launching large-scale clinical trials, a better understanding of the effects of CBD on brain would be desirable.
- Preclinical evidence suggests that one aspect of the polypharmacy of CBD is that it modulates brain excitatory glutamate and inhibitory γ -aminobutyric acid (GABA) levels, including in brain regions linked to ASD, such as the basal ganglia (BG) and the dorsomedial prefrontal cortex (DMPFC).
- However, differences in glutamate and GABA pathways in ASD mean that the response to CBD in people with and without ASD may not be the same.
- 34 healthy men (17 neurotypicals, 17 ASD).
- **Across groups, CBD increased subcortical, but decreased cortical, Glx. Across regions, CBD increased GABA+ in controls, but decreased GABA+ in ASD; the group difference in change in GABA+ in the DMPFC was significant. Thus, CBD modulates glutamate-GABA systems, but prefrontal-GABA systems respond differently in ASD.**

[Sci Rep](#), 2019 Jan 17;9(1):200.

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

[Bar-Lev Schleider L](#)^{1,2}, [Mechoulam R](#)³, [Saban N](#)², [Meiri G](#)^{4,5}, [Novack V](#)⁶.

- There has been a dramatic increase in the number of children diagnosed with autism spectrum disorders (ASD) worldwide. Recently anecdotal evidence of possible therapeutic effects of cannabis products has emerged. The aim of this study is to characterize the epidemiology of ASD patients receiving medical cannabis treatment and to describe its safety and efficacy.
- We analysed the data prospectively collected as part of the treatment program of 188 ASD patients treated with medical cannabis between 2015 and 2017. The treatment in majority of the patients was based on cannabis oil containing 30% CBD and 1.5% THC.
- Symptoms inventory, patient global assessment and side effects at 6 months were primary outcomes of interest and were assessed by structured questionnaires. After six months of treatment 82.4% of patients (155) were in active treatment and 60.0% (93) have been assessed;
- **28 patients (30.1%) reported a significant improvement, 50 (53.7%) moderate, 6 (6.4%) slight and 8 (8.6%) had no change in their condition. Twenty-three patients (25.2%) experienced at least one side effect; the most common was restlessness (6.6%). Cannabis in ASD patients appears to be well tolerated, safe and effective option to relieve symptoms associated with ASD.**

[Cannabis Cannabinoid Res.](#) 2016 Feb 1;1(1):81-89.

Enhancement of Anandamide-Mediated Endocannabinoid Signaling Corrects Autism-Related Social Impairment.

[Wei D¹](#), [Dinh D¹](#), [Lee D¹](#), [Li D^{1,2}](#), [Anguren A¹](#), [Moreno-Sanz G¹](#), [Gall CM¹](#), [Piomelli D](#)

- We recently uncovered a signaling mechanism by which the endocannabinoid anandamide mediates the action of oxytocin, a neuropeptide that is crucial for social behavior, to control social reward. Oxytocin signaling has been implicated in autism spectrum disorder (ASD), and social reward is a key aspect of social functioning that is thought to be disrupted in ASD. Therefore, as a proof of principle for the core component of ASD-social impairment-we tested an endocannabinoid-enhancing compound on two widely studied mouse models of ASD
- **Methods:** We used the established three-chambered social approach test. We specifically increased the activity of anandamide by administering the compound URB597, a selective inhibitor of fatty acid amide hydrolase (FAAH), the hydrolytic enzyme for anandamide.
- **Results:** Remarkably, we found that FAAH blockade completely reversed the social impairment in both mouse models. CB₁ receptor blockade prevented the prosocial action of FAAH inhibition in mice. These results were likely independent of effects on anxiety, as FAAH inhibition did not alter the performance of mice in the elevated plus maze.
- **Conclusions:** The results suggest that increasing anandamide activity at CB₁ receptors improves ASD-related social impairment and identify FAAH as a novel therapeutic target for ASD.

[Drugs Today \(Barc\).](#) 2019 Mar;55(3):177-196

Cannabidiol as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.

[Lattanzi S¹](#), [Trinka E²](#), [Russo E³](#), [Striano P⁴](#), [Citraro R³](#), [Silvestrini M⁵](#), [Brigo F⁶](#).

- Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) are severe, refractory epilepsy syndromes with onset in early childhood. Currently available interventions fail to control seizures in most cases, and there remains the need to identify new treatments.
- **Cannabidiol (CBD) is the first in a new class of antiepileptic drugs. It is a major chemical of the cannabis plant, which has antiseizure properties in absence of psychoactive effects.**

[F1000Res.](#) 2019 Feb 28;8.

Epidiolex as adjunct therapy for treatment of refractory epilepsy: a comprehensive review with a focus on adverse effects.

[Sekar K¹](#), [Pack A¹](#).

- Medically refractory epilepsy remains an area of intense clinical and scientific interest since a significant porportion of patients continue to suffer from debilitating seizures despite available therapies.
- Recent studies have focused on assessing the benefits of cannabidiol (CBD)-enriched cannabis, a plant based product without psychoactive properties which has been shown to decrease seizure frequency in animal models.
- More recently, several randomized controlled and open label trials have studied the effects of Epidiolex, a 99% pure oral CBD extract, on patients with refractory epilepsy.
- **This in turn has led to the FDA approval of and more recently, to the Drug Enforcement Administration's placement of Epidiolex into schedule V of the Controlled Substances Act (CSA)**

[Perm J.](#) 2019;23:18-041. doi: 10.7812/TPP/18-041.

Cannabidiol in Anxiety and Sleep: A Large Case Series.

[Shannon S¹](#), [Lewis N²](#), [Lee H³](#), [Hughes S⁴](#).

- Cannabidiol (CBD) is one of many cannabinoid compounds found in cannabis. It does not appear to alter consciousness or trigger a "high." A recent surge in scientific publications has found preclinical and clinical evidence documenting value for CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points toward a calming effect for CBD in the central nervous system. Interest in CBD as a treatment of a wide range of disorders has exploded, yet few clinical studies of CBD exist in the psychiatric literature.
- A large retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients.
- Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment.
- The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25)
- **Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients.**
- **Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.**

[Epilepsia](#). 2019 Jan;60(1):6-19

Cannabis-based products for pediatric epilepsy: A systematic review.

[Elliott J](#)^{1,2}, [DeJean D](#)³, [Clifford T](#)^{1,4}, [Coyle D](#)¹, [Potter BK](#)¹, [Skidmore B](#)⁵, [Alexander C](#)⁶, [Repetski AE](#)⁶, [Shukla V](#)², [McCoy B](#)^{7,8}, [Wells GA](#)^{1,2}.

- **OBJECTIVE:** To assess the benefits and harms of cannabis-based products for pediatric epilepsy.
- **METHODS:**
- We identified in this living systematic review randomized controlled trials (RCTs) and nonrandomized studies (NRSs) involving children with epilepsy treated with cannabis-based products. The primary outcome was seizure freedom; secondary outcomes were seizure frequency (total, $\geq 50\%$ reduction), quality of life, sleep, seizure status, death, gastrointestinal adverse events, and visits to the emergency room. Data were pooled by random-effects meta-analysis.
- **RESULTS:**
- Four RCTs and 19 NRSs were included, primarily involving cannabidiol. All RCTs were at low risk of bias, whereas all NRSs were at high risk. Among RCTs, there was no statistically significant difference between cannabidiol and placebo in seizure freedom (relative risk [RR] = 6.77, 95% confidence interval [CI] = 0.36-128.38; 1 RCT), quality of life (mean difference = 0.6, 95% CI = -2.6 to 3.9; 3 RCTs), sleep disruption (mean difference = -0.3, 95% CI = -0.8 to 0.2; 3 RCTs), or vomiting (RR = 1.00, 95% CI = 0.51-1.96; 4 RCTs). There was a statistically significant reduction in the median frequency of monthly seizures with cannabidiol compared with placebo (-19.8%, 95% CI = -27.0% to -12.6%; 3 RCTs) and an increase in the number of participants with at least a 50% reduction in seizures (RR = 1.76, 95% CI = 1.07-2.88; 1 RCT) and diarrhea (RR = 2.25, 95% CI = 1.38-3.68; 3 RCTs). Death and status epilepticus were infrequently reported.
- **SIGNIFICANCE:**
- Evidence from high-quality RCTs suggests that cannabidiol probably reduces seizures among children with drug-resistant epilepsy (moderate certainty). At this time, the evidence base is primarily limited to cannabidiol, and these findings should not be extended to all cannabis-based products.

[Drugs](#). 2018 Nov;78(17):1791-1804.

Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis.

[Lattanzi S](#)¹, [Brigo F](#)^{2,3}, [Trinka E](#)^{4,5,6}, [Zaccara G](#)⁷, [Cagnetti C](#)⁸, [Del Giovane C](#)⁹, [Silvestrini M](#)⁸.

- Approximately one-third of patients with epilepsy presents seizures despite adequate treatment. Hence, there is the need to search for new therapeutic options. Cannabidiol (CBD) is a major chemical component of the resin of *Cannabis sativa* plant, most commonly known as marijuana. The anti-seizure properties of CBD do not relate to the direct action on cannabinoid receptors, but are mediated by a multitude of mechanisms that include the agonist and antagonist effects on ionic channels, neurotransmitter transporters, and multiple 7-transmembrane receptors. In contrast to tetra-hydrocannabinol, CBD lacks psychoactive properties, does not produce euphoric or intrusive side effects, and is largely devoid of abuse liability.
- The aim of the study was to estimate the efficacy and safety of CBD as adjunctive treatment in patients with epilepsy using meta-analytical techniques.
- Randomized, placebo-controlled, single- or double-blinded add-on trials of oral CBD in patients with uncontrolled epilepsy were identified. Main outcomes included the percentage change and the proportion of patients with $\geq 50\%$ reduction in monthly seizure frequency during the treatment period and the incidence of treatment withdrawal and adverse events (AEs).
- Four trials involving 550 patients with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) were included. The reduction in all-types seizure frequency by at least 50% occurred in 37.2% of the patients in the CBD 20 mg group and 21.2% of the placebo-treated participants

Adjunctive CBD in patients with LGS or DS experiencing seizures uncontrolled by concomitant anti-epileptic treatment regimens is associated with a greater reduction in seizure frequency and a higher rate of AEs than placebo.

[Eur Neuropsychopharmacol](#). 2019 Apr 8. pii: S0924-977X(19)30198-1. doi: rint] **Acute effects of Δ 9-tetrahydrocannabinol (THC) on resting state brain function and their modulation by COMT genotype.**

[Bossong MG](#)¹, [van Hell HH](#)², [Schubart CD](#)³, [van Saane W](#)⁴, [Iseger TA](#)⁵, [Jager G](#)⁶, [van Osch MJ](#)⁷, [Jansma JM](#)⁸, [Kahn RS](#)⁹, [Boks MP](#)¹⁰, [Ramsey N](#)

- Cannabis produces a broad range of acute, dose-dependent psychotropic effects. Moreover, how genetic variation influences the acute effects of cannabis on resting state brain function is unknown. Here we investigated the acute effects of Δ 9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, on resting state brain neurophysiology, and their modulation by catechol-methyl-transferase (COMT)
- Thirty-nine healthy volunteers participated in a pharmacological MRI study, where we applied Arterial Spin Labelling (ASL) to measure perfusion and functional MRI to assess resting state connectivity. THC increased perfusion in bilateral insula, medial superior frontal cortex, and left middle orbital frontal gyrus. This latter brain area showed significantly decreased connectivity with the precuneus after THC administration. THC effects on perfusion in the left insula were significantly related to subjective changes in perception and relaxation.
- These findings indicate that THC enhances metabolism and thus neural activity in the salience network. Furthermore, results suggest that recruitment of brain areas within this network is involved in the acute effects of THC. **Resting state perfusion was modulated by COMT genotype**, indicated by a significant interaction effect between drug and genotype on perfusion in the executive network, with increased perfusion.
- **This finding suggests that prefrontal dopamine levels are involved in the susceptibility to acute effects of cannabis.**

[Dig Dis Sci](#). 2019 Mar 2. doi: 10.1007/s10620-019-05556-z. [Epub ahead of print]

Association Between Cannabis Use and Complications Related to Crohn's Disease: A Retrospective Cohort Study.

[Mbachii C](#)^{1,2}, [Attar B](#)³, [Wang Y](#)³, [Paintsil I](#)³, [Mba B](#)³, [Fugar S](#)⁴, [Agrawal R](#)³, [Simons-Linares RC](#)⁵, [Jaiswal P](#)⁶, [Trick W](#)³, [Kotwal V](#)

- The anti-inflammatory effect of cannabis in intestinal inflammation has been shown in several experimental models; it is unknown whether this correlates with fewer complications in Crohn's disease patients.
- To compare the prevalence of Crohn's disease-related complications among cannabis users and non-users in patients admitted with a primary diagnosis of Crohn's disease or a primary diagnosis of Crohn's related complication and a secondary diagnosis of Crohn's disease between 2012 and 2014.
- **CONCLUSION:**
- **Cannabis use may mitigate several of the well-described complications of Crohn's disease among hospital inpatients. These effects could possibly be through the effect of cannabis in the endocannabinoid system**

Int J Mol Sci. 2018 Jul 8;19(7). pii: E1992. doi: 10.3390/ijms19071992.

In Vitro Model of Neuroinflammation: Efficacy of Cannabigerol, a Non-Psychoactive Cannabinoid.

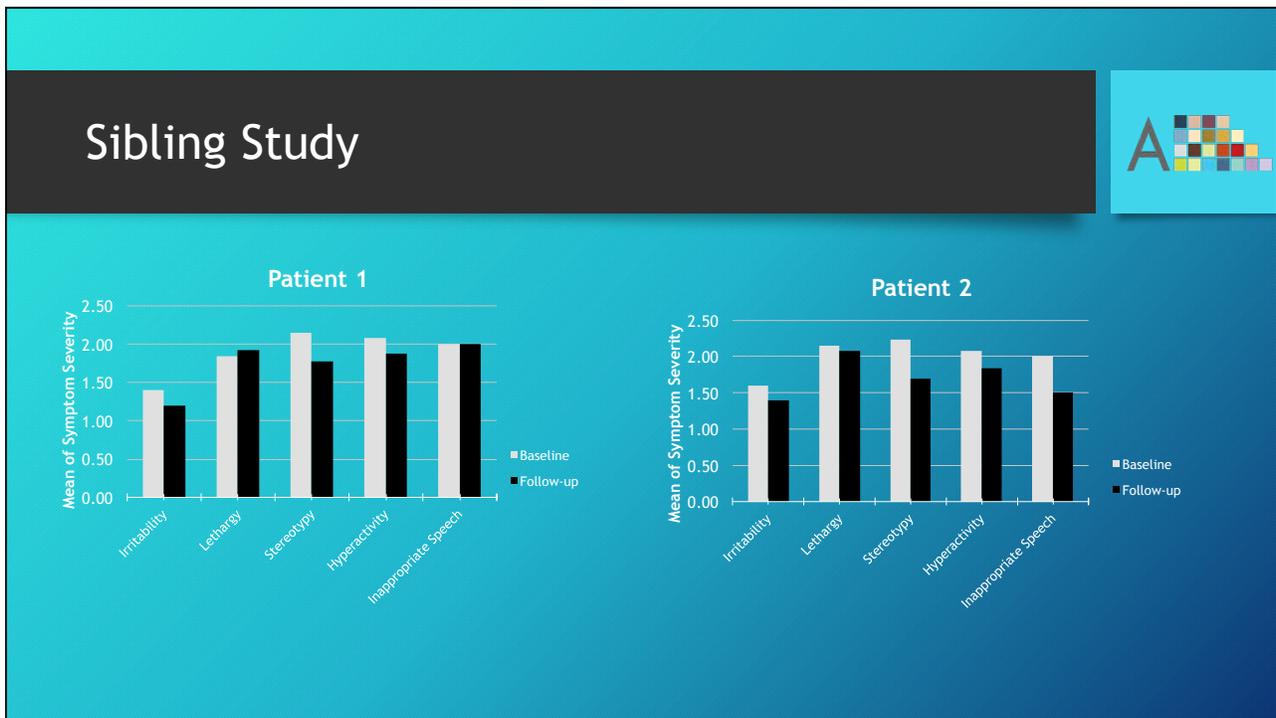
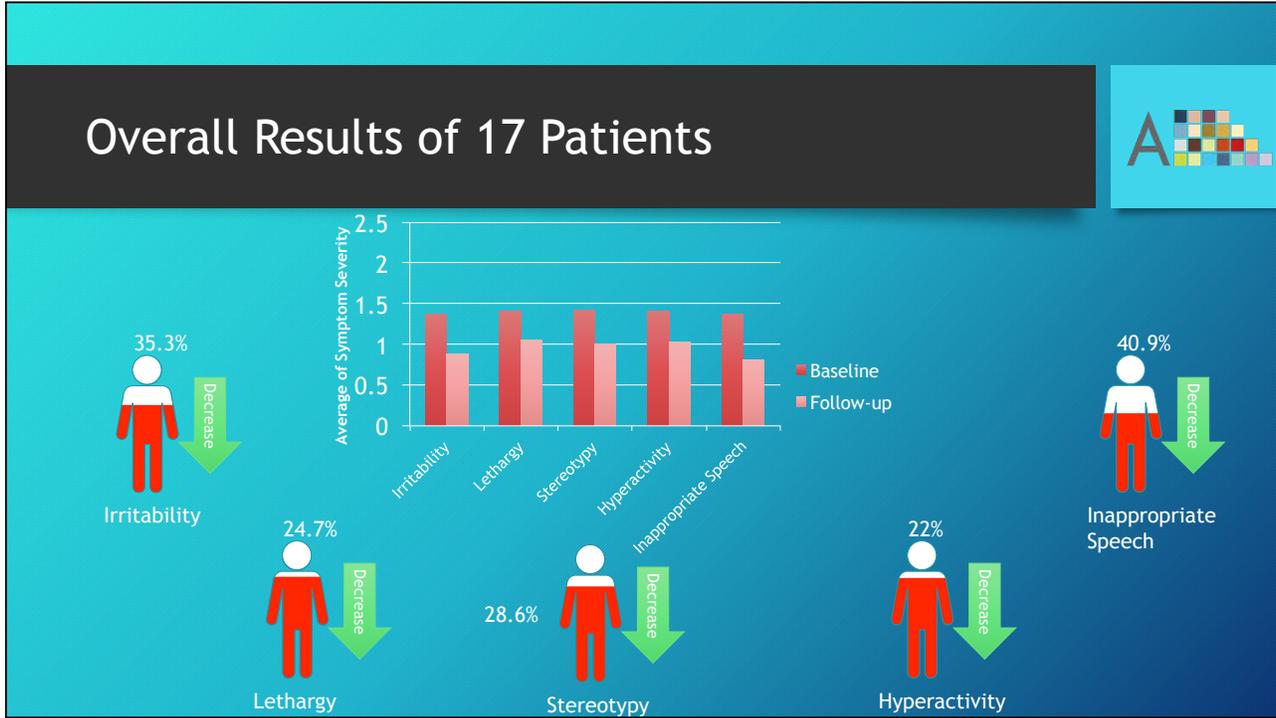
[Gugliandolo A](#)¹, [Pollastro F](#)², [Grassi G](#)³, [Bramanti P](#)⁴, [Mazzon E](#)⁵

- *Cannabis sativa* represents a reservoir of compounds exerting beneficial properties, including cannabigerol (CBG), whose antioxidant properties have already been demonstrated in macrophages.
- Here, we aimed to evaluate the ability of CBG to protect NSC-34 motor neurons against the toxicity induced from the medium of LPS-stimulated macrophages.
- we observed that CBG pre-treatment was able to reduce the loss of cell viability induced by the medium of LPS-stimulated macrophages.
- Indeed, CBG pre-treatment inhibited apoptosis
- CBG pre-treatment counteracted not only inflammation, as demonstrated by the reduction of IL-1 β beta; TNF- α alpha; IFN- γ gamma; and PPAR γ gamma; protein levels assessed by immunocytochemistry, but also oxidative stress in NSC-34 cells treated with the medium of LPS-stimulated RAW 264.7. Indeed, immunocytochemistry showed that CBG pre-treatment reduced nitrotyrosine, SOD1 and iNOS protein levels and restored Nrf-2 levels.
- All together, these results indicated the neuroprotective effects of CBG, that may be a potential treatment against neuroinflammation and oxidative stress.

Methodology



- Eligibility
- Prescription
- ABC Checklist
- Record Results
- Three month usage of medical marijuana
- ABC Checklist
- Record Results

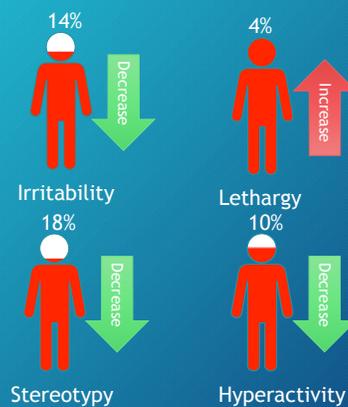
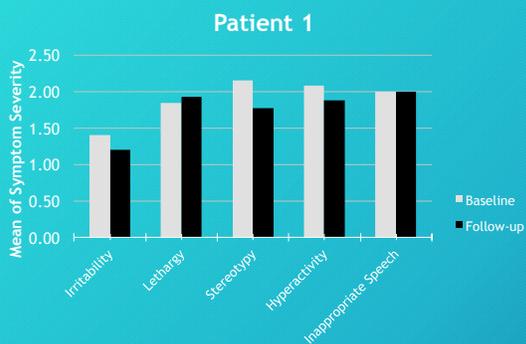


Patient KK 15 y/o male



- PANDAS/PANS
- OCD
- ADHD
- Environmental allergies
- Meds: Strattera, Cyproheptidine
- Multiple antibiotics
- THC:CD = 1:20
- Doing well now off antibiotics

First Sibling (KK)

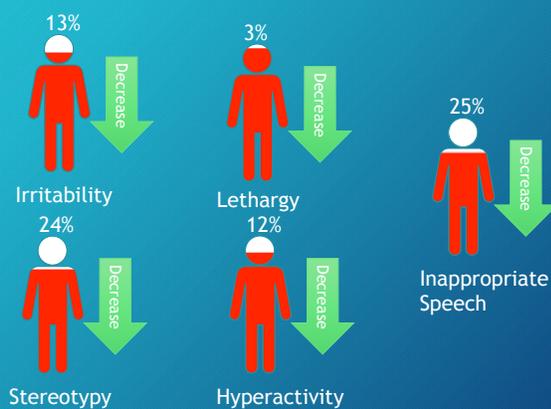
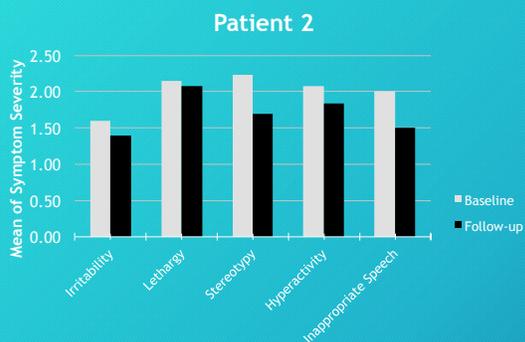


Patient TK 12 y/o white male



- PANDAS/PANS
- Babesia
- Environmental allergies - elevated Histamine
- OCD
- Multiple antibiotics, antihistamine
- THC:CBD = 1:20
- Doing well now off antibiotics

Second Sibling (TK)

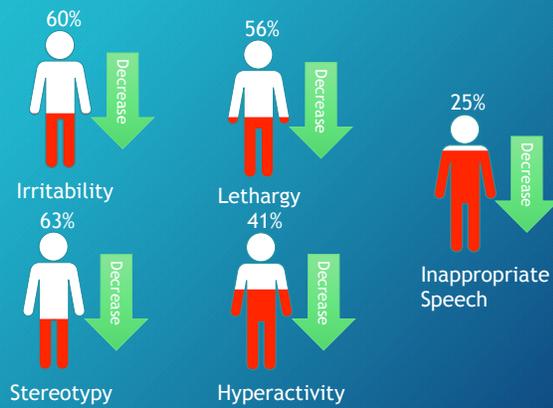
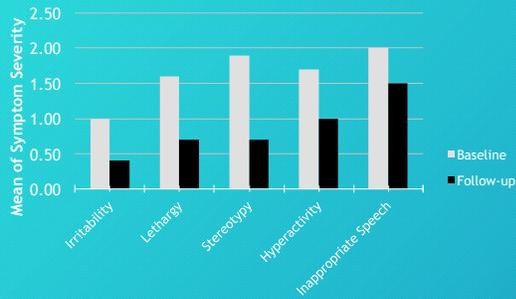


Patient DM: 10 y/o white male



- Extremely hyperactive/ADHD
- OCD
- Chronically constipated - only poops in the bathtub by squatting in warm water!
- Biofilm protocol, IV chelation
- Language improved
- Still very hyperactive
- THC:CBD = 1:20
- Significant improvements

Greatest Improvement (DM)

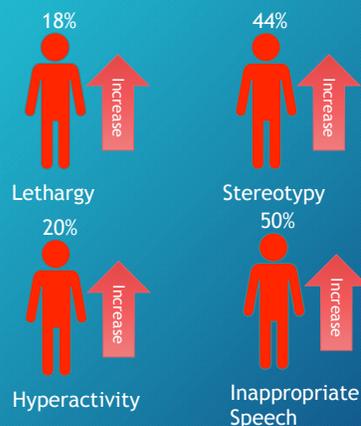
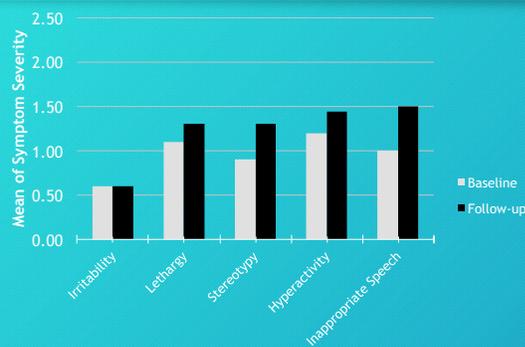


Patient DD: 12 y/o white male



- Fatty acid metabolism problems; low cholesterol (<145)
- Language is good but receptive language is off
- Every medication and supplement appears to have the opposite effect
- Continues to have gut issues, nocturnal enuresis, processing problems
- Started cannabis with no positive and questionably negative effect
- Initial genetic testing: endocannabinoid system is mutated
- Whole exome sequencing in progress

Worsened (DD)



Conclusion



Overall, looking at 17 patients:
35% decrease in irritability
25% decrease in lethargy
29% decrease in stereotypy
22% decrease in hyperactivity
41% decrease in 'inappropriate' speech

Considering these clinical observations
Treatment with medical cannabis using higher concentration of CBD:THC seems to be effective in reducing aberrant behaviors compared with supplements and antimicrobials. The regulatory effects: the H-P-A axis are manifested in calmer more focused and less 'anxious' patients.



References

- Hicks, J. MD. The Medicinal Power of Cannabis. 2015
- Hadland, SE etal, Medical marijuana: review of the science and implications for developmental-behavioral pediatric practice. J Dev Behav Ped 2015 Feb
- Wei, D., etal. Enhancement of Anandamide-Mediated Endocannabinoid Signaling Corrects Autism-Related Social Impairment. Cannabinoid Res, 2016 Feb
- Kaplan JS., etal. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc Natl Acad Sci USA 2017 Oct.
- Porcan GS. Etal. Efficacy of artisanal preparations of cannabidiol for the treatment fo epilepsy: Practical expereinces in tertiary medical center. Epilepsy Behav 2018, Feb