The Effects of Medical Cannabis in Children With Autistic Spectrum Disorder

0281-17-ASF ver. 5.2 23.08.20

Treatment with medical cannabis

Cannabinoids are defined as compounds acting on the cannabinoids receptors CB1 and CB2. When referring to cannabis treatment, there is not a specific, well defined treatment but a variety of compounds with different activity between them, all of them acting on the cannabinoids receptors.

There are three groups:

- Endocannabinoids, produced endogenously from phospholipids in the cell membrane, such as Anandamide and Arachidonoylglycerol.
- Phytocannabinoids: terpeno-phenols found mainly in Cannabis plants
- Synthetics

Cannabis was already known in China, before some 5000 years ago. In the Middle ages, it was used against vomits, epilepsy and inflammations, much as today.

During the 20 th century, Cannabis was less used because of the discovery of new drugs. During the '70s it became illegal as part of the war against dangerous drugs in the US.

In the sixties, Prof. Mechoulam and his team isolated and reported the chemical composition of the 2 main compounds: cannabidiol (CBD) and 19-tetrahydrocannabinol (THC). Both of them are neuro-active, THC is responsible for euphoria feeling and CBD has a calming effect. Today, more than 110 compounds are known in Cannabis plants.

In the meantime, case reports of its benefits in the treatment of refractory diseases began to accumulate and there was public pressure to allow it for medical needs. Canada in 2003 was the first country to permit medical use and many countries followed after.

A meta-analysis published in 2015 by JAMA reported 79 studies.

Some studies have tested the efficacy and safety of cannabinoids in a vast array of indications: epilepsy, chronic pain, spasticity, chemotherapy side-effects.

Knowledge re. long term safety and risks is mainly from experience in recreational cannabis use.

The conclusion is that the risks are linked to THC concentration. The higher THC, the higher risk.

CBD has a protective effect.

Additional risks are: alcohol and tobacco consumption, family history of schizophrenia.

Treatment of children with cannabis

Most of the experience with Cannabis treatment in children comes from refractory epilepsy treatment. In some of the cases, these children were also diagnosed with ASD and show an improvement of some of the autism comorbidities. The drug used was THC:CBD 1:20 oral drops.

Treatment of children with autism (ASD) with medical cannabis.

US figures report an increase in the prevalence of ASD with current numbers around 1 in 59 children and rates are similar in developed countries. Prevalence has a ratio of ~4:1 male-to-female

Children with ASD commonly exhibit co-morbid symptoms such as hyperactivity, self-injury, aggressiveness, restlessness, anxiety and sleep and eating disorders. Conventional medical treatment includes various psychotropic medications such as atypical anti psychotics, selective serotonin reuptake inhibitors (SSRI's), stimulants and anxiolytics. These drugs have many side-effects.

Several studies are being conducted worldwide on the use of cannabidiol in children with ASD to treat comorbid symptoms. However, there is limited published data on the use of cannabinoids in this population A recent review by Poleg, 2019, has suggested cannabidiol as a candidate for treatment of ASD.

A study by Barchel et al, 2019, reported benefits of T:C 1:20 treatment in 53 children with ASD. The results show an improvement in the severity of the symptoms for between 40-70% of the patients.

The aim of the present study is to assess efficacy and safety of medical cannabis oil CBD:THC 20:1 in children and young adults with ASD.

Population of the trial

Children and young adults from all over Israel diagnosed with ASD based on DSM IV (American Psychiatric Association, 2000) or DSM V (American Psychiatric Association, 2013) criteria, between 5 and 25 years of age will be included.

PURPOSES

Main

To assess the effect of medical cannabis oil treatment on the comorbidities of ASD

To compare between 2 products with same CBD:THC ratio

To assess the effect of treatment on cognitive function

To measure levels of cannabinoids in the blood of the participants

Secondary

To detect side-effects and reasons for failure

To assess if high CBD conc. oil is effective in treating sleep and behavior problems in patients with ASD.

To detect changes in biochemical and hormonal profile during treatment

Methods

Parents of children and young adults with ASD will be interviewed at the Clinical Pharmacology Unit, Shamir MC. If recruited, they will sign ICF and will fill in questionnaires. Medical history and concomitant drugs will be recorded.

There will be 3 visits with the patients: before treatment, after 3 months and after 6 months of treatment.

The treatment length will be of 6 months for each participant. A group of specialists including a pediatrician, a pediatric neurologist specialized in ASD, a psychologist and a speech therapist,

will assess the effects of the treatment using specific tools such as ADOS and questionnaires.

Efficacy and adverse effects will be recorded during the phone follow-ups.

ASD comorbid symptoms to be evaluated are: hyperactivity, aggression, anxiety,

sleep problems, eating problems, communication problems and social problems.

For each comorbid symptom, the evaluations will mark improvement, no change, or worsening of symptoms, as compared to the baseline, according to the parent's reports.

Parents will received a license for pediatric use of medical cannabis oil from the Israeli

Ministry of Health.

The cannabinoid oil solutions will be manufactured at Nextar for Seach Sarid LTD and at Panaxia for Canndoc Ltd. at concentration of 30% and 1:20 ratio of CBD and THC for each of the 2 arms.

Treatment and dosage

Treatment will start at one drop/day and dose will increase as per physician or CRA instructions (titration) until improvement is seen in at least one of the symptoms or until failure is decided upon.

Recommended daily dose of CBD is 16 mg/kg (maximal daily dose 600 mg), and for

THC- daily dose of 0.8 mg/kg (maximal daily dose of 40 mg).

Sample size

One of the symptoms of ASD is self- aggression. Supposing 65% reporting self-aggression before treatment started, and 40% during treatment, 65 participants will be needed (5% significance, 80% power). Taking into account dropout, 100 participants will be recruited into each arm (total of 200 participants) in order to attain significant results.

Visits

- First visit before treatment start (may be divided into 2 different days)

Patients will undergo weight and height measurements, Cognitive evaluation, 1 hour EEG test, Social and communication evaluations ADOS, adaptive behavior, blood tests.

Parents will fill in questionnaires and have teacher fill in Conners questionnaire

At the end of the visit, parents will receive cannabis oil and instructions about their use.

- Middle-term visit

Patients will undergo weight and height measurements, neurologist evaluation, blood tests.

Parents will fill in questionnaires and have teacher fill in Conners questionnaire

- Third visit(end of treatment)

Patients will undergo weight and height measurements, Cognitive evaluation, 1 hour EEG test, Social, skills and communication evaluations

Parents will fill in questionnaires and have teacher fill in Conners questionnaire

In-between the 3 visits, there will be biweekly phone follow-up.

Early termination visit

Patients not willing to complete the 6 months of the trial will be asked to be present at a conclusion visit, in the format of third visit.

Dosage reducing will be gradual and take 1 week.

Sleep quality

Sleep quality will be measured using electronic devices and questionnnaires.

Video filming of the participants

Participants will be taped during ADOS test for later analysis of repetitive behavior and facial movements.

Other aspects

Female of bearing age will be asked to use contraceptives or to declare they will not have sexual activity during the time of the trial.

Participants taking other drugs will be asked not to make any changes without prior consent of the trial team.

Criteria for participation ceasing

Significant side-effects, Psychosis or depression, pregnancy

Contraindications

Primidone, Phenobarbital, Carbamazepine, Rifampicin, Rifabutin, troglitazone, Hypericum perforatum

Total trial length: 3 years

Bibliography

1. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. Jama. 2015;313(24):2456-2473.

2. Mechoulam R, Shvo Y. Hashish. I. The structure of cannabidiol. Tetrahedron. 1963;19(12):2073-2078.

3. Mechoulam R, Gaoni Y. Hashish. IV. The isolation and structure of cannabinolic cannabidiolic and cannabigerolic acids. Tetrahedron. 1965;21(5):1223-1229

7. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016;15(3):270-278.

8. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav. 2015;45:49-52.

9. Savage SR, Romero-Sandoval A, Schatman M, et al. Cannabis in Pain Treatment: Clinical and Research Considerations. J Pain. 2016;17(6):654-668.

10. Jensen B, Chen J, Furnish T, Wallace M. Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence. Curr Pain Headache Rep. 2015;19(10):50.

11. Chohan H, Greenfield AL, Yadav V, Graves J. Use of Cannabinoids for Spasticity and Pain Management in MS. Curr Treat Options Neurol. 2016;18(1):1.

12. May MB, Glode AE. Dronabinol for chemotherapy-induced nausea and vomiting unresponsive to antiemetics. Cancer Manag Res. 2016;8:49-55.

13. Patti F. Health Authorities Data Collection of THC:CBD Oromucosal Spray (L'Agenzia Italiana del Farmaco Web Registry): Figures after 1.5 Years. Eur Neurol. 2016;75 Suppl 1:9-12.

14. Barchel D, Stolar O, De-Haan T, Ziv-Baran T, Saban N, Fuchs DO, Koren G, Berkovitch M.

Front Pharmacol. 2019 Jan 9;9:1521. doi: 10.3389/fphar.2018.01521. eCollection 2018.

PMID: 30687090

15. Poleg S, Golubchik P, Offen D, Weizman A.

Prog Neuropsychopharmacol Biol Psychiatry. 2019 Mar 8;89:90-96. doi: 10.1016/j.pnpbp.2018.08.030. Epub 2018 Aug 29. PMID: 30171992