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Lola Polianski, Research coordinator

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Aviad Schnapp, MD – (Student)
Grant/Research Support: BOL pharma, National Institute of Psychobiology in Israel

Consultant: BOL pharma

I will be discussing “off-label” uses of medical cannabis
Research Interests

1. Cannabinoids & endocannabinoid system in autism spectrum disorder

2. Biomarkers & Early Diagnosis of Autism in Risk-groups (CEDAR/ אטר"ה)
Medical cannabis & Autism – clinical studies
“The plural of anecdote is not evidence! “

1972 – Dr. Archie Cochrane
Evidence for the Risks and Consequences of Adolescent Cannabis Exposure.

Levine A. et al. 2017 Mar;56(3):214-225

Phytocannabinoids- compounds unique to the cannabis plant

- Δ9 – tetra-hydro-cannabinol - THC
- Cannabidiol - CBD
- THC is the main psychoactive substance (anxiety, psychosis)
- CBD is non-psychoactive, anti-psychotic, anxiolytic.
Different strains—completely different impact

Most medical strains are high THC low CBD

For ASD we try high CBD low THC strains
Medical cannabis & Autism – Pre-clinical studies
The endocannabinoid system and ASD

- Regulation of:
  - Social and emotional reactivity
  - Motivation
  - Learning and memory processes
  - Epilepsy
  - Circadian rhythm regulation
The endocannabinoid system and ASD

- Alterations of the EC system have been found in several animal models of ASD

- **Monogenic**: Fragile X (Fmr1 knockout), Neuroligin-3 (mutation & knockout)

- **Polygenic** (idiopathic ASD): BTBR model

- **Environmental**: prenatal VPA exposure,
Lower circulating endocannabinoid levels in children with autism spectrum disorder

Adi Aran¹, Maya Eylon², Moria Harel¹, Lola Polianski¹, Alina Nemirovski², Sigal Tepper³, Aviad Schnapp¹, Hanoch Cassuto¹, Nadia Wattad¹ and Joseph Tam²
2-Arachidonoylgllycerol (2-AG)
Anandamide (AEA)
Arachidonic Acid
Palmitoylethanolamide (PEA)
Oloeylethanolamide (OEA)
Lower endocannabinoid levels in serum samples of 93 children with ASD compared with 93 age- and sex-matched controls. 

Anandamide (AEA)  Oleoylethanolamine (OEA)  Palmitoylethanolamide (PEA)
PPARs

Nucleus

TRPV1

CB1

R

PEA

OEA

AEA

FAAH

Ethanolamine

NAPE

- PLD

NAP

Postsynaptic neuron (Dendrite)

2-AG

DAGL

Presynaptic neuron (Axon)

PEA

OEA

AEA

TRPV1

CBD

Ananda = extreme happiness in Sanskrit

Others

CB1

ASD

Adi Aran¹ © · Hanoch Cassuto² · Asael Lubotzky¹ · Nadia Wattad¹ · Esther Hazan¹
Patients and treatment

- Children age 5-18 years with ASD
- Severe behavioral problems (CGI-S = 6 or 7)
- Failure of proper medical and behavioral treatments
- Whole plant extracts of CBD-rich cannabis strains
Results - patients

- **60 children:** age 11.8 ± 3.5 (5.5-17.5 years), 77% low cognitive functioning; 83% boys

- **Follow-up:** 7-13 months
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No of patients (%)</th>
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</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>29 (51%)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Unexplained laugh</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Mood changes</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Gain of appetite</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Confusion</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td><strong>No of patients (%)</strong></td>
</tr>
<tr>
<td>Psychotic event</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
Overall improvement in behavior as rated by parents on the CGIC scale

- **Improvement in behavior:**
  - 21%– None or worse
  - 17%– slightly improved - 25-50% reduction
  - 34%– much improved- 50-75% reduction
  - 28%– Very much improved- 75-100% reduction
Overall improvement in communication as rated by parents on the CGIC scale

- **Improvement in communication:**
  - 35%– None or worse
  - 17%– slightly improved
  - 25%– much improved
  - 23%– Very much improved
Overall improvement in anxiety as rated by parents on the CGIC scale

- **Improvement in anxiety:**
  - 40%—None or worse
  - 20%—slightly improved - 25-50% reduction
  - 25%—**much improved**- 50-75% reduction
  - 15%—**Very much improved**- 75-100% reduction
Improvement in disruptive behavior (HSQ) and parental stress (APSI) following cannabis treatment

![Improvement Graph]

- **All (n=57)**
- **Boys with 'idiopathic ASD' (n=39)**

<table>
<thead>
<tr>
<th></th>
<th>HSQ-ASD</th>
<th>APSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>Boys</td>
<td>25%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Uncontrolled trials should be interpreted cautiously.
Phase 2- Too many questions

- Should we use THC?
  - which CBD:THC ratio?
- Pure cannabinoids vs. whole plant extracts (the entourage effect)
- Total daily dose
- Target population (age, function, syndromic ASD, environmental risk factors)
- Treatment targets (core symptoms, disruptive behavior)
You can never ask too many questions, but you can ask too many questions in a row.
Whole plant extract (n=50)

Treatment period 1 (12 Weeks)

Washout 4 Weeks

Whole plant extract

Treatment period 2 (12 Weeks)

Placebo

Pure cannabinoids

Placebo

Pure cannabinoids

Baseline evaluations

ADOS-2
Vineland-II
CARS-2
SCQ

Primary outcome measures

Clinical Global Impression-Improvement
Home Situation Questionnaire

Secondary outcome measures

Social Responsiveness Scale
Autism Parenting Stress Index
Adverse events
Interventional controlled trial

- 150 participants
- Double-blind, randomized, placebo controlled trial
- Three arms and cross over

**Arm A**
Whole plant extract
20:1 ratio of CBD: THC

**Arm B**
Placebo

**Arm C**
Pure cannabinoids
20:1 ratio of CBD: THC
I am not at liberty to discuss
Can cannabinoids expand our tool box for treating children with ASD?
Are We There Yet?
Cannabinoids in Children with ASD – A multi-center phase III Study

Evdokia Anagnostou
Bloorview Research Institute
SickKids

Xavier Castellanos
NYU Child Study Center

Ann Neumeyer
Massachusetts General Hospital
Harvard Medical School
Early Biomarkers in ASD
Thank you