Cannabis & Autism: Piecing it All Together

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Scope of the Problem

• Over the last 30 years, there has been a 3-fold increase in number children dx with ASD worldwide. 1 in 68 8 year old children dx, 4:1 Male:Female, siblings 15-25% higher incidence

• No specific treatments are currently available

• Interventions Focus on:
  Decreasing disruptive behaviors
  Training and teaching self-help skills for greater independence

• Previous observations have shown that cannabidiol effects might include alleviation of psychosis, anxiety, facilitation of REM sleep and suppressing seizure activity
History of Cannabis Through the Ages

- Used as medicine for 5000 years all over the globe, its presence is documented ~10,000 years ago in Taiwan
- Referenced in the Old Testament
- Used as an anticonvulsant in Middle East and India for 4000 years
- Used heavily in women’s health, for migraines, menstrual disorders, etc.
- Hemp required crop in 13 original colonies—Food, cloth, robe
- US Pharmacopeia 1850, Eli Lilly, Park Davis and others produced it
- Opium, cocaine in Coca-Cola, heroin developed, tablets (ASA and MSO4) made cannabis tinctures obsolete
POISON
No. 100
969
CHOCOLATE-COATED TABLETS
CHLORODYNE
HALF STRENGTH
MORPH. HYDROCHL.
1-12 gr.
Ext. Cannabis 1-8 gr.
Nitroglycerin 1-600 gr.
Oleores. Caps. 1-20 gr.
Peppermint Oil q.s.
Dose 1 to 4 Tablets

SHARP & DOHME
BALTIMORE

872196A
• Dupont (nylon), Mellon (financier), Hearst (journalism) and Harry Anslinger (Federal Bureau of Narcotics), alcohol prohibition ended in 1933 → criminalization of drugs (cannabis new target)

• 1944 La Guardia organized a study on cannabis. Interestingly, users were more often what would now be described as Asperger’s. Cannabis is safe, low side effects, effective, does not lead to MSO4 or heroin addiction, does not contribute to crimes or juvenile delinquency

• Nixon’s war on drugs. Ignoring new evidence that marijuana users were “timid, drowsy, and passive”, pushed for criminalization
1970
- Classified as schedule 1 drug 1970
  - High potential for abuse
  - No currently accepted medical use in treatment in the United States
  - There is a lack of accepted safety for use under medical supervision

1985
- Marinol (Dronabinol or synthetic THC) approved

1996
- Medical cannabis legal in CA 1996, Compassionate Use Act

2003
- US Government received patent 6,630,507
  - Cannabinoids as antioxidants and neuroprotectants
Perspective

- CDC reports 6 million deaths annually from tobacco
- WHO reports 3.3 million deaths annually from alcohol
- 480,000 tobacco deaths a year in the US
- 88,000 alcohol deaths a year in the US alone
Total U.S. Drug Deaths

More than 72,000 Americans died from drug overdoses in 2017.
Cannabis deaths annually?

Zero

There are no receptors in the brainstem, therefore no overdose potential.

You can take too much and feel like you are dying, but it is not terminal, and is self-limited.
Current Statistics

- 2014 JAMA states with legal cannabis have 24.8% decrease in opioid related overdoses
- Effect increases over time
Approved Conditions in Maryland:

- Cachexia, anorexia, chronic pain, severe nausea, seizures, severe and persistent muscle spasms, glaucoma, PTSD and other condition that might benefit from cannabis
- Autism not specifically listed. It is an approved condition in Pennsylvania, Delaware, Georgia
Patient Statistics 04.21.2020

Number of Registered Providers by Board Type & Total Number of Providers:

<table>
<thead>
<tr>
<th>Board Type</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Podiatry</td>
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<tr>
<td>Nursing</td>
<td>749</td>
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<tr>
<td>Physicians</td>
<td>927</td>
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<tr>
<td>Dental</td>
<td>121</td>
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<tr>
<td>Total Providers</td>
<td>1,818</td>
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</table>

Patient Information:

Certified Patients 98,309
Maryland Medical Cannabis Sales
1st Calendar Year

<table>
<thead>
<tr>
<th>Month</th>
<th>Sales</th>
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<tbody>
<tr>
<td>JAN.18</td>
<td>$2,639,660</td>
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<tr>
<td>FEB.18</td>
<td>$3,808,153</td>
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<tr>
<td>MAR.18</td>
<td>$5,470,822</td>
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<tr>
<td>APR.18</td>
<td>$6,393,472</td>
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<td>MAY.18</td>
<td>$7,811,690</td>
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<tr>
<td>JUN.18</td>
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<tr>
<td>JUL.18</td>
<td>$9,629,944</td>
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<td>AUG.18</td>
<td>$10,928,756</td>
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<td>SEPT.18</td>
<td>$11,574,526</td>
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<td>OCT.18</td>
<td>$12,884,159</td>
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<td>NOV.18</td>
<td>$13,919,951</td>
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<tr>
<td>DEC.18</td>
<td>$15,727,579</td>
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</table>

2018

0 | $5,000,000 | $10,000,000 | $15,000,000 | $20,000,000
Medical Cannabis Dispensary Sales ($)

December 2018 - December 2019
Total Retail Sales = $268,251,313

<table>
<thead>
<tr>
<th>Month</th>
<th>Sales</th>
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<tbody>
<tr>
<td>Dec. 18</td>
<td>$16,023,781</td>
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<tr>
<td>Jan. 19</td>
<td>$15,113,702</td>
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<td>Feb. 19</td>
<td>$15,582,994</td>
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<td>Mar. 19</td>
<td>$16,283,010</td>
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<td>Apr. 19</td>
<td>$16,924,176</td>
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<tr>
<td>May 19</td>
<td>$19,525,539</td>
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<td>Jun. 19</td>
<td>$20,694,427</td>
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<td>July 19</td>
<td>$22,477,947</td>
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<td>Aug. 19</td>
<td>$24,367,816</td>
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<td>Sept. 19</td>
<td>$23,065,282</td>
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<tr>
<td>Oct. 19</td>
<td>$23,034,389</td>
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<td>Nov. 19</td>
<td>$25,624,003</td>
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<td>Dec. 19</td>
<td>$27,354,247</td>
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Endocannabinoid System

- ECS is a link between the mind and body
- 1940 Roger Adams extracted CBD from cannabis
- 1988 Allyn Howlett and William Devane found CB1 in the brain of a rat, 1993 CB2 discovered
- 1992 Raphael Mechoulam et al. discovered anandamide, having discovered THC in 1964
- ECS found all across the body in tissues, organs, cells, glands
- Promotes homeostasis and health, “Relax, Eat, Sleep, Forget & Protect”
Cannabinoids. What are they?

Therapeutic compounds and the active ingredients found in cannabis.

- **Phytocannabinoids** plant based cannabinoids, produced by cannabis
- **Endogenous Cannabinoids** Produced in humans and other animals
- **Synthetic Cannabinoids** Produced in the lab
  - Marinol, Nabilone, Sativex
CBD has been used to treat pain (chronic and neuropathic), diabetes, cancer, and neurodegenerative diseases, such as Huntington's disease. Animal studies indicate that a high dose of CBD inhibits the effects of lower doses of THC. Some studies suggest that oral or oromucosal CBD may prolong and/or intensify the effects of THC, though this has been disputed.

Data to suggest that high-dose oral CBD (150–600 mg per day) may exert a therapeutic effect for epilepsy, insomnia, and social anxiety disorder.

- Cannabidiol in humans-the quest for therapeutic targets.Zhornitsky S, Potvin S
THC is the major psychoactive (intoxicating) component of cannabis and acts on CB₁ receptors in the central nervous system. Stimulates serotonin synthesis, inhibits its reuptake and promotes its release. May also modulate dopamine imbalances in headaches (Russo).

THC and cannabinoids inhibit prostaglandin E2 synthesis.

THC oral potency as anti-inflammatory is 20x ASA and 2x HC (inhibits cyclooxygenase and lipoxygenase).

Opioids, cannabinoids & eicosanoids signal through common NO gap coupling.

THC promotes downregulation of inflammation.
THC and CBD are neuroprotective antioxidants that exceed the potency of Vit C & E.

CBD is non-intoxicating and does not act directly on CB1 and CB2 receptors. It is thought to be a negative allosteric modulator at CB1.

CBD in combination with THC has received regulatory approvals in several European countries and is under study in registered trials with the FDA.

Epidiolex 25mg/kg showed a 50% reduction in sz, SEs somnolence and decreased appetite.
What is the Entourage Effect?

- Mother nature does it best
- Why the “one note” of synthetic THC doesn’t work all that well
- Cannabinoids (108 or more) in cannabis and terpenes (over 100) work synergistically to give a variety of effects. The terpenes appear to modulate the cannabinoids’ effects.
Terpenes

A-PINENE
- Anti-inflammatory
- Bronchodilator
- AIDS memory
- Anti-bacterial
- Also found in pine needles

LINALOOL
- Anesthetic
- Anti-convulsant
- Analgesic
- Anti-anxiety
- Also found in lavender

CARYOPHYLLENE
- Anti-inflammatory
- Analgesic
- Protects cells lining the digestive tract

MYRCENE
- Contributes to sedative effect of strong indicas
- Sleep aid
- Muscle relaxant
- Also found in hops

LIMONENE
- Treats acid reflux
- Anti-anxiety
- Antidepressant
- Also found in citrus
### Ingestion Options

<table>
<thead>
<tr>
<th>Vaporization</th>
<th>Sublingual</th>
<th>Oral</th>
<th>Topical</th>
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<tbody>
<tr>
<td>Flower</td>
<td>Tinctures</td>
<td>Elixirs</td>
<td>Balms/Lotions</td>
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<tr>
<td>Concentrates</td>
<td>Tablets</td>
<td>Edibles</td>
<td>Patches</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Bath Soaks</td>
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</tbody>
</table>
VAPORIZATION
SMOKING OR COMBUSTION
TINCTURES AND TABLETS
ELIXIRS AND EDIBLES
Drug Interactions

- Approximately 60% of clinically Rx drugs are metabolized by CYP3A4

- Hepatic cytochrome 450 (CYP450) isoenzymes 2C9 and 3A4 play a significant role in the primary metabolism of THC and CBN, whereas 2C19 and 3A4 may be responsible for metabolism of CBD

- Separate cannabis doses by at least 2 hours from other Rx
Cannabidiol Based Medical Cannabis in Children with Autism—A Retrospective Feasibility Study (2018 Neurology Aran et al)

- Retrospective study on 60 children
- CBD enriched cannabis oil
- Behavior outbreaks improved in 61%
- Communication improved in 47%
- Anxiety improved in 39%
- Stress in 33%
- Disruptive behavior in 33%

- 188 ASD patients treated with medical cannabis 2015-2017
- 30% CBD, 1.5% THC oil (20:1)
- Symptoms inventory, global assessment, side effects at 6 months
- After 6 months, 82.4% in active treatment, 60% assessed:
  - 30.1% significant improvement
  - 53.7% moderate improvement
  - 6.4% slight improvement
  - 8.6% no change
  - 25.2% experienced at least one SE, most common was restlessness (6.6%)
Patient Population

• Mean age 12.9 yrs, 7.4% less than 5, 37.2% 6-10, 38.2% 11-18
• 81.9% male
• 14.4% suffered from epilepsy
• 3.7% ADHD
Quality of Life

• Quality of Life, mood, ability to perform ADLs assessed before treatment at 6 months
  • Good quality of life reported by 31.3% prior to treatment, 66.8% at 6 months
  • Ability to dress and shower independently 26.4% to 42.9%
  • Good sleep (3.3%) and good concentration (0%) increased to 24.7% & 14%

• Seizures
  • 84.6% reported disappearance of sx, 2 patients reported improvement
  • Restlessness and rage attacks improved in 91% and 90.3% respectively
Key to Success

• Slow titration of dose—up to 2 months.
• Wide dosage range from one to 20 drops TID
• Every patient is different, so don’t compare your results to others
Why does it work?

• ASD may result from a dysregulation of endocannabinoid system

• CBD enhances oxytocin and vasopressin release, important in bonding and social interaction

• Anandamide levels lower in ASD  Karhson et al “Plasma anandamide concentrations are lower in children with autism spectrum disorder” Molecular Autism, (2018) 9:18

• ASD 3-9 year olds have high levels of CB2 receptors Sinascalco “Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders” J Autism Dev Disord 2013
Endocannabinoid System Chakrabarti et al  
“Endocannabinoid Signaling in Autism” Neurotherapeutics (2015)

• Controls emotional responses
• Behavioral reactivity to context
• Social interaction, social reward responsivity
• Densely wired throughout our bodies
• Altered in several neurodegenerative diseases and inflammatory states
• Influences circadian rhythms
• Mediates anxiety
• Involved with seizure activity including epilepsy
Importance of SAFE Medication

• Not all CBD is safe
• Insist on seeing COAs, buy from someone reputable
• Not regulated (yet) so amount listed may not be accurate, it may or may not contain THC
• I like Social brand out of Oregon. Biggest CBD company in US.
• Hemp vs. Cannabis. By definition, hemp must contain < 0.3% THC
• MMCC.Maryland.gov for more information