Highlight in Pediatric epilepsy treatment

Pongkiat Kankirawatana, M.D.
Professor & Medical Director,
Pediatric Epilepsy Program
UAB Department of Pediatrics
at Children’s of Alabama

Disclaimer

• I have never own or use or try any products that will be discussed in my talk

• Some (or most) of products discussed today are not FDA-approved or legally approved.
Outlines

• Medical marijuana treatment in pediatric epilepsy
• New treatment protocol in infantile spasm

Summary: Mechanisms of Neuromodulation

<table>
<thead>
<tr>
<th>AED</th>
<th>Na⁺ Channel Blockade</th>
<th>Ca²⁺ Channel Blockade</th>
<th>H-current enhancement</th>
<th>Glutamate Receptor Antagonism</th>
<th>GABA Enhancement</th>
<th>Carbonic Anhydrase Inhibition</th>
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Modified from White HS and Rho JM, Mechanisms of Action of AEDs, 2010.
Summary: Mechanisms of Neuromodulation

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<th>Ca** Channel Blockade</th>
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</table>

Modified from White HS and Rho JM, Mechanisms of Action of AEDs, 2010.

Summary: Mechanisms of Neuromodulation

* Excitatory synapse

* Inhibitory synapse

Case: VS

- A 14 yr-old girl s/p grid-based R frontal epilepsy surgery in 2006 with path dx: FCD-2B. Had seizure-free only 1 mo
- Was on 7 medications. Having 10 drop seizures every day (received 10 stitches from a drop about 3 weeks before they moved). 25-35 tonic clonic seizures everyday.
- Could not go to school for a full day. 10 or more severe temper tantrums a day. Would not sleep through the night. Gaining weight. When she moved out there she was 73.6kg. Did not interact with her surroundings.
- Could not/would not follow simple commands.
- Moved to Colorado in Nov 2013. Now on 240mg of CBD and Topamax & Tegretol
- Now ~ 3 seizures in ~ 3 weeks

the link to Charlottes web video is [www.theroc.us](http://www.theroc.us).

Also our site to our fundraising page is [Www.gofundme.com/5vnq2s](http://Www.gofundme.com/5vnq2s)
History of Cannabis: 麻

- Cannabis, má 麻 (hemp; ma-Spanish; numbness) or dàmá 大麻 (with "big; great")
- In Chinese, was used for fiber starting about 10,000 yrs ago
- 麻醉, má zui Chinese term for anesthesia
- Yanghai Tombs near Turpan, Xinjiang-Uighur Autonomous Region, China have recently been excavated the 2700-yr-old grave of a Caucasoid shaman whose accoutrements included a large cache (~2 pounds) of cannabis...
- The cannabis was presumably employed by this culture as a medicinal or psychoactive agent, or an aid to divination.
- These provide the oldest documentation of cannabis as a pharmacologically active agent, and contribute to the medical and archaeological record of this pre-Silk Road culture.


- Emperor Shen-Nung, also a pharmacologist, wrote a book (circa 2700 B.C), medical benefits of cannabis, including constipation, gout, rheumatism, and absent-mindedness.
- discovered its healing properties as other 2 other mainstays of Chinese herbal medicine, ginseng and ephedra.”
- Hua Tuo (c. 140–208) was a Chinese physician from the late Eastern Han Dynasty. The historical texts Records of the Three Kingdoms and Book of the Later Han record Hua Tuo as the first person in China to use anaesthesia during surgery. He used a general anaesthetic combining wine with a herbal concoction called ma-fei-san (麻沸散, lit. "cannabis boil powder").
Cannabis pollen is found on the mummy of Ramesses II, who died in 1213 BC. Prescriptions for cannabis in Ancient Egypt include treatment for the eyes (glaucoma), inflammation, and cooling the uterus, as well as administering enemas.

An Ancient Egyptian Herbal, 1989

• **1213 BC - Egyptians Use Cannabis for Glaucoma, Inflammation, and Enemas**

History of Cannabis: 麻

• **1000 BC - Bhang, a Drink of Cannabis and Milk, Is Used in India as an Anesthetic**

Bhang, a cannabis drink generally mixed with milk, is used as an anesthetic and anti-phlegmatic in India.

Cannabis begins to be used in India to treat a wide variety of human maladies. US National Commission on Marihuana and Drug Abuse "Marihuana, A Signal of Misunderstanding," druglibrary.org, 1972

• **700 BC - Medical Use of Marijuana in the Middle East Recorded in the Venidad**

"The Venidad, one of the volumes of the Zend-Avesta, the ancient Persian religious text written around the seventh century BC purportedly by Zoroaster (or Zarathustra), the founder of Zoroastrianism, and heavily influenced by the Vedas, mentions bhang and lists cannabis as the most important of 10,000 medicinal plants." Martin Booth Cannabis: A History, 2005
History of Cannabis:

- **600 BC - Indian Medicine Treatise Cites Cannabis as a Cure for Leprosy**

"Cannabis was used in India in very early medical applications. People believed it could quicken the mind, prolong life, improve judgment, lower fevers, induce sleep and cure dysentery... The first major work to lay out the uses of cannabis in [Indian] medicine was the Ayurvedic [a system of Indian medicine] treatise of Sushruta Samhita written in 600 BC... Within the Sushrita, cannabis is cited as an anti-phlegmatic and a cure for leprosy."  
  
  Jonathon Green  Cannabis, 2002

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Cannabis

- Annual herbaceous plant
- The flowers (and to a lesser extent the leaves, stems, and seeds) contain cannabinoids

- **C. sativa** – tall thin narrower leaves and grow a lighter green in color. They grow very quickly and can reach heights of 20 feet in a single season. They originally come from Colombia, Mexico, Thailand and Southeast Asia.

- **C. indica** originally come from the hash producing countries of the world like Afghanistan, Morocco, and Tibet. They are short dense plants, with broad leaves and often grow a darker green.

- **C. indica** has lower THC, higher CBN/CBD

- **C. ruderalis** has a lower THC content than either C. sativa or C. indica
Neurochemistry & Pharmacology

• Cannabinoids
• Phenoids
• Flavonoids

Cannabinoids

• Cannabis contain ~500 chemicals
• Compounds with a skeleton made of a resorcinol type ring with a terpene moiety derivative attached to it (around 70 identified)
• 70+ cannabinoids (21-carbon molecule)
• Among cannabinoids, THC and Cannabidiol (CBD) are the most abundant.
Some of the more prominent cannabinoids include:

- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Cannabinol (CBN)
- Tetrahydrocannabinvarin (THCV)
- Cannabichromene (CBC)
- Cannabicyclol (CBL)
- Cannabidivarin (CBDV)
- Yet still another est. 80-100 other cannabinoids!

THC (Delta-9-Tetrahydrocannabinol)

- 1964 - THC, Main Psychoactive Component of Cannabis, First Identified and Synthesized by Dr. Raphael Mechoulam, Professor of Medicinal Chemistry at the Hebrew University of Jerusalem,
- He is the first to identify delta-9-tetrahydrocannabinol (THC), as the main psychoactive component of cannabis.
- Effects of THC are included among the effects of marijuana, but not all the effects of marijuana are necessarily due to THC
- Delta-9-THC and Delta-8-THC are the only compounds in the marijuana plant that produce all the psychoactive effects of marijuana.
Pharmacological actions of THC

• Psychotropic
  • Initial euphoria and relaxation
  • Followed by a depressant period
  • Alterations memory and cognitive perceptual abilities
• Immuno-suppressive/ immuno-modulation
• Cardiovascular (tachycardia, orthostatic hypotension, peripheral vasodilation)
• Analgesic
• Anti-emetic
• Appetite stimulant

Pharmacological Effects of CBD

• Anticonvulsant
• Analgesic
• Anti-anxiety
• Anti-psychotic
• Anti-inflammatory
• Anti-arthritic
• Immunosuppressive
Milestones in Cannabinoid Pharmacology

1964  Δ⁹-THC synthesized and structure identified (Gaoni & Mechoulam)
1980s  Synthetic cannabinoids
1988  CB₁ receptor identified (Devane et al.)
1990  CB₁ receptor cloned (Matsuda et al.)
1992  CB₂ receptor (Kaminski et al.)
1992  Anandamide discovered (Devane et al.)
1993  CB₂ receptor cloned (Munro et al.)
1995  2-arachidonylglycerol identified (Mechoulam, Sigiura)
1994-7  Receptor antagonists (Rinaldi-Carmona et al.)
1998  Endogenous ligands shown to be analgesic (Walker et al.))
1998  CB₁ receptor “knock out” mice (Ledent et al., Zimmer al.)
2000  CB₂ receptor “knock out” mice (Buckley et al.)
2001  Noladin -ether identified
2001+  Synthetic cannabinoids, more on the endogenous system, biosynthesis and degradation, delivery systems etc.

Endocannabinoid

• “28yrs after discovering THC, in 1992, Dr. Mechoulam, Dr. William Devane and Dr. Lumir Hanus, identified the brain's first endogenous cannabinoid (or endocannabinoid) - the brain's natural version of THC -which they called ‘Anandamide,’ from the Sanskrit word 'ananda,' which means 'eternal bliss' or 'supreme joy.'
• ECS is a group of neuromodulatory lipids and their receptors in the brain that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory;
• It mediates the psychoactive effects of cannabis
## Endocannabinoid

- **1988** - Cannabinoid-binding sites in rat brains identified
- **1991** - Human cannabinoid receptor CB1 successfully cloned
- **1992** - Discovery of the first endocannabinoid, arachidonoyl ethanolamide, later named anandamide (a Sanskrit word for "internal bliss")\(^2\)
- **1993** - Peripheral CB2 receptor cloned
- **1995** - Discovery of a second endocannabinoid, 2-arachidonoyl glycerol (2-AG)

Vigorous exercise stimulates the release of anandamide, and the sense of euphoric well-being that comes with a healthy workout - what jogging enthusiasts refer to as a 'runner's high' - is due to elevated levels of endocannabinoids. The endocannabinoid system in the brain is also believed to help mediate emotions, consolidate memory, and coordinate movement.

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### Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
  - Feeding behavior
  - Energy balance, metabolism, and GI function
  - Pain perception
  - Motor control and posture
  - Learning, memory, and emotions
  - Immune and inflammatory responses
  - Cardiovascular function
  - Reproduction
  - Bone formation

Mechanism of Cannabinoid action

• G-protein coupled cannabinoid CB1 receptors

• Abundantly distributed in the BG, cerebellum, limbic system and cortex

• Endocannabinoids act as retrograde messengers at many central synapses causing inhibition of neurotransmitter release
Cannabinoid Receptors

- G-protein–coupled receptors
- \( \text{CB}_1 \) receptors highly expressed in the brain
  - \( \text{CB}_1 \) receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- \( \text{CB}_2 \) receptors are expressed primarily in immune cells
  - \( \text{CB}_2 \) receptor expression in neurons is being studied


Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter

<table>
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<tr>
<th>Presynaptic</th>
<th>Postsynaptic</th>
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</table>

Retrograde neurotransmitter

<table>
<thead>
<tr>
<th>Presynaptic</th>
<th>Postsynaptic</th>
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</table>

Classical Neurotransmitter (ie, acetylcholine)

- In a classical neurotransmitter system, for example, acetylcholine, an action potential invades presynaptically, thereby causing depolarization, which triggers the opening of calcium voltage-gated channels.
- Calcium ions flood in (they are at higher concentration in the extracellular solution) and interact with the synaptic vesicles, allowing for the release of stored neurotransmitter (exocytosis). Acetylcholine spills out into the synaptic cleft (exocytosis) and diffuses across the synaptic cleft.
- The neurotransmitter (acetylcholine) interacts with receptors at the postsynaptic membrane; these receptors tend to be ligand-gated channels, so they open when neurotransmitter binds.
- Ions flow through the ligand-gated channels, causing a change in the postsynaptic membrane potential. This is the critical step that initiates the cascade of downstream physiologic effects.
- The neurotransmitter is then degraded by the enzyme acetylcholinesterase.

Retrograde Neurotransmitter (ie, endocannabinoid)

- ECS paradigm: in contrast to the classical paradigm, endocannabinoids are not stored in vesicles. An action potential that triggers the opening of calcium channels activates the synthesis of endocannabinoids from membrane-bound lipid precursors. This takes place postsynaptically.
- Endocannabinoids are released and diffuse freely into the synaptic cleft. The transport mechanism is currently unknown.
- Endocannabinoids then bind to and activate CB1 receptors located presynaptically. This reverse path is referred to as retrograde signaling. After binding to the CB1 receptors the G proteins are stimulated to relay the signals to regulate a number of cellular processes.
- The importance of this signaling paradigm is that the ECS is normally quiet until endocannabinoids are synthesized on demand, they are taken up back into cells rapidly, and degraded immediately. Thus, they act locally at the site of synthesis.
Cannabinoids act backwards

MacDonald J. Christie and Christopher W. Vaughan

Cannabis is useful for treating many ailments, but has unwanted side effects. Drugs that control signalling by cannabinoids found naturally in the body might be more useful.

• Cannabinoids are able to function as retrograde synaptic messengers
• Endocannabinoid synthesized and released from postsynaptic neurons
• Travels backwards across synapse activating CB1 on the presynaptic axon
• Resulting in suppression of neurotransmitter release

(Wilson & Nicoll, 2001; Ohno-Shosaku et al., 2001; Kreitzer & Regehr, 2001)

Signal transduction at the CB receptor

• CB receptors are linked to inhibitory G protein
  • Inhibit adenylyl cyclase ⇒ cAMP
  • Opening potassium channels: cell firing
  • Closing voltage dependent calcium channels: release neurotransmitters
• Overall effect is that of cellular inhibition
• Similar to opioids
Endocannabinoid system (ECS): Overview

Endocannabinoid ligands
- Produced on demand
- Act locally
- Inactivated rapidly
- Bind to transmembrane G-protein receptors, principally inhibiting neurotransmitter release

Cannabinoid receptor type 1 (CB₁)
Most widespread CB receptor
(brain, spinal cord; peripheral nervous system, organs, tissues)

Cannabinoid receptor type 2 (CB₂)
Immune cells

Key ECS Elements
Cannabinoid receptors are G-protein-coupled receptors

Endocannabinoids
- Anandamide
- 2-Arachidonoyl-glycerol

Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors


Central nervous system
- Hippocampus
- Basal ganglia
- Cortex
- Cerebellum
- Hypothalamus
- Limbic structures
- Brainstem

GI tract (myenteric neurons and epithelial cells)
Liver (hepatocytes)
Adipose tissue
Muscle
Pancreas (β-cells)

Immune cells and tissues
- T cells, B cells
- Macrophages
- Dendritic cells
- Spleen, thymus
- Adipose tissue

Implications of CB₁ receptor activation

**Central nervous system**
- Hypothalamus
- Limbic system
- Appetite
- Motivation to eat/smoke

**Peripheral tissue**
- Liver
- GI tract
- Adipose tissue
- Skeletal muscle
- Lipogenesis
- Altered glucose metabolism


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**Cannabidiol in Treatment-Resistant Epilepsy Efficacy**

- Data collected from 10 centers in the United States that have treated children and young adults with pure CBD
- N = 213 patients

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<th>Outcomes</th>
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<td>Dravet patients</td>
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<td>LG5 patients</td>
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<tr>
<td>Atonic seizure frequency</td>
<td>-52</td>
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Objective: To characterize the effects of cannabidiol (CBD) in a battery of well-established rodent seizure models.

Background: Previous investigations have reported anticonvulsant effects of CBD in various preclinical animal models (Jones et al., 2010, 2012), and suggest it is a promising candidate for the control of seizures warranting systematic investigation. Here, the anticonvulsant and tolerability profile of plant-derived CBD (GW Pharmaceuticals) was investigated in the Anticonvulsant Screening Program (ASP) to verify and further characterize CBD's effects in a battery of well-established rodent seizure models.

Methods: CBD was investigated in several rodent models of seizure: 6Hz “psychomotor” tests of therapy-resistant partial seizures, subcutaneous Metrazol seizure threshold test (scMET) of clonic forebrain seizures, and maximal electroshock test (mES) of generalized tonic-clonic seizures. Additionally, CBD's effect on minimal muscular and neurological impairment was assessed in mice using the rotarod test. Rats were examined in a battery of tests (gait and stance test, placing response test and righting reflex test) to determine any neurological deficits of CBD.

Results: The ASP demonstrated that CBD exerted significant anticonvulsant effects in the 6Hz (32 mA) test (ED_{50} = 144 (102-194) mg/kg), 6 Hz (44 mA) test (ED_{50} = 173 (136-213) mg/kg), mES (ED_{50} = 80 (65-96) mg/kg) and scMET (ED_{50} = 120 (99-146) mg/kg) models in mice, and the mES model (ED_{50} = 53 (39-67) mg/kg) in rats. Moreover, CBD was well tolerated by both mouse (TD_{50} = 272 (241-303) mg/kg) and rat (TD_{50} > 500 mg/kg) in toxicity tests.

Conclusions: CBD produces significant anticonvulsant effects in a number in vivo seizure models and is well-tolerated in both rodent species in the ASP. These data validate previous results from GW Pharmaceuticals’ preclinical program and suggest that CBD may be a novel therapeutic candidate for a diverse range of human epilepsies, with a potentially favorable tolerability profile.
S14.006 - Seizure Response to Cannabidiol in a State-Sponsored Open-Label Program

Objective:
To assess seizure response to pharmaceutical grade CBD formulation (Epidiolex) in patients with treatment-refractory epilepsy enrolled in an open-label safety study.

Introduction:
CBD use for seizure management through a State-sponsored program allowed us to follow longitudinally a group of patients who have failed at least 4 different AEDs, who were experiencing on average at least 4 countable seizures per month prior to enrollment, and who were referred to the study by their managing neurologist or epilepsy specialist.

Methods:
In all 51 patients, pre-CBD seizure frequency was averaged over 3 months prior to initiating CBD at 5mg/kg/day for seizure control with adjustments as tolerated q2 weeks by 5mg/kg/day up to a maximum of 25mg/kg/day. Bi-weekly seizure frequency was monitored via diary. Other AEDs were adjusted as needed (especially clobazam and valproate). Standard statistical measures were used for this non-normally distributed cohort.

Results:
51 patients (23 pediatric and 28 adults) had at least one follow-up visit (343 visits total); 25 (49%) were responders at the last visit (≥50% seizure reduction). There was no difference in responder rates between pediatric and adult groups (Chi-square p=0.55). 9/51 (18%) patients were no longer participating in the study at the last visit either due to lack of efficacy (7; 5 children and 2 adults) or intolerable side effects (2-diarrhea; 1 child and one adult). With up-titration of CBD, seizure control improved when compared to baseline (32, 45, 45, 43, 41% decrease when taking 5, 10, 15, 20, or 25mg/kg/d of CBD, respectively). Two patients were seizure-free at the last assessment. This trend was significant (Spearman rho=-0.316; p=0.000).

Conclusions:
This compassionate use open-label study indicates approximately 50% responder rate at the last visit with overall sustained improvement in seizure control over the 6-month duration of the study.

Systematic Review: Efficacy and Safety of Medical Marijuana (Cannabis) in Selected Neurologic Disorders

Medical Marijuana (Cannabis)
Clinical Question 1: Spasticity in MS

• Do cannabinoids relieve spasticity in patients with MS?

Conclusions

For patients with spasticity:

• Oral cannabis extract (OCE) is established as effective for reducing patient-reported scores (2 Class I studies\(^7\,^8\)). OCE is probably ineffective for reducing objective measures at 12 to 15 weeks (1 Class I study\(^7\)) but possibly effective at 1 year (1 Class II study\(^11\)).

• THC is probably effective for reducing patient-reported scores (1 Class I study\(^7\)). THC is probably ineffective for reducing objective measures at 15 weeks (1 Class I study\(^7\)) but possibly effective at 1 year (1 Class II study\(^11\)).

Medical Marijuana (Cannabis)
Spasticity in MS (continued).

Conclusions

For patients with spasticity:

• Nabiximols is probably effective for reducing patient-reported symptoms at 6 weeks (1 Class I study\(^6\)) and probably ineffective for reducing objective measures at 6 weeks (1 Class I study\(^6\)).

• Smoked marijuana is of uncertain efficacy (insufficient evidence).

• More improvements were seen in subjective measures than objective measures, possibly explained in part by the overall improvements in “feelings” or well-being provided by marijuana, or by pain relief allowing improved mobility.
Medical Marijuana (Cannabis)
Clinical Question 2 : Pain in MS

• What is the efficacy of using cannabinoids to treat central pain or painful spasms in MS?

Conclusions
• For patients with MS with central pain or painful spasms, OCE is effective for reduction of central pain (2 Class I studies\(^7,^8\)).
• THC or nabiximols (1 Class I study each\(^7,^24\)) are probably effective for treating MS-related pain or painful spasms.
• Smoked marijuana is of unclear efficacy for reducing pain (2 Class III studies that examined different issues\(^14,^15\)).

Medical Marijuana (Cannabis)
Clinical Question 3: Bladder Dysfunction in MS

• Do cannabinoids help treat bladder dysfunction in MS?

Conclusions
• Nabiximols is probably effective for reducing the number of bladder voids per day at 10 weeks (1 Class I study\(^26\)).
• THC and OCE are probably ineffective for reducing bladder complaints (1 Class I study\(^7\)).
• Nabiximols is of unknown efficacy in reducing overall bladder symptoms (contradictory Class I studies).
Medical Marijuana (Cannabis)
Clinical Question 4: Tremor in MS

• Do cannabinoids help treat tremor in MS?

Conclusions
• THC and OCE are probably ineffective for treating MS-related tremor (1 Class I study⁷).
• Nabiximols is possibly ineffective (1 Class II study¹⁰).

Medical Marijuana (Cannabis)
Clinical Question 5: Movement disorders

• Do cannabinoids reduce symptoms in involuntary movement disorders?

Conclusion- Huntington Disease
• Whereas 1 Class I study³¹ and 1 Class III study³⁵ suggest lack of benefit, both were underpowered to detect differences, and thus no reliable conclusions can be drawn.

Conclusion- Parkinson Disease
• OCE is probably ineffective for treating dopa-induced dyskinesias in patients with Parkinson disease (1 Class I study³⁶).

Conclusion- Tourette syndrome
• For patients with Tourette syndrome, data are insufficient to support or refute efficacy of THC for reducing tic severity (1 Class II study, 1 Class III study³⁹,⁴⁰).
Medical Marijuana (Cannabis)
Clinical Question 6: Epilepsy

- Do cannabinoids decrease seizure frequency in epilepsy?

**Conclusion (as of 2014 AAN)**

- For patients with epilepsy, data are insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency (no Class I–III studies).

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Medical Marijuana (Cannabis)
Clinical Question 6: Epilepsy (continued)

**Clinical Context**

- Neither the present review, nor a Cochrane review which includes abstracts, non–peer-reviewed literature, and anecdotal reports of smoked cannabis use by patients with seizure disorders, concluded there is sufficient evidence to prescribe CBDs or recommend self-treatment with smoked marijuana.
Medical Marijuana (Cannabis)
Clinical Question 6: Epilepsy (Adverse Effects)

- Overall, 1,619 patients were treated with cannabinoids for less than 6 months.
- Simple meta-analysis yielded 6.9% who stopped the medication because of adverse effects (AEs). Of the 1,118 who received placebo, 2.2% stopped because of AEs.
- Data on the symptom(s) that caused medication withdrawal were often incomplete.
- Psychosis, dysphoria, and anxiety are associated with higher concentrations of THC, which were not typical of the studies analyzed.
- There was 1 death "possibly related" to treatment (a seizure, followed by fatal aspiration pneumonia).\(^\text{18}\)

Medical Marijuana (Cannabis)
Adverse Effects, cont.

- Among patients treated with cannabinoids, the following symptoms appeared in at least 2 studies:
  - Nausea
  - Increased weakness
  - Behavioral or mood changes (or both)
  - Suicidal ideation or hallucinations (or both)
  - Dizziness or vasovagal symptoms (or both)
  - Fatigue
  - Feelings of intoxication
Medical Marijuana (Cannabis) Adverse Effects (continued).

Clinical Context
• AEs are a significant concern with marijuana use.
• It is especially concerning that a medication that may have an AE of suicide may be prescribed in a population such as patients with MS who already are at increased suicide risk.$^7$

International Collaborative Infantile Spasms Study (ICSSS) comparing hormonal therapies (prednisolone or tetracosactide depot) and vigabatrin versus hormonal therapies alone in the treatment of infantile spasms: Early clinical outcome

• Objective: To compare hormonal therapies (Prednisolone or tetracosactide depot) and vigabatrin versus hormonal therapies alone in the treatment of infantile spasms.

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• Methods

• Between March 2007 and May 2014, infants with IS and a compatible EEG were enrolled in a multicenter treatment trial. Infants were randomized to receive either hormonal therapy and vigabatrin or hormonal therapy alone. A second stage randomization allowed hormonal treatment to be allocated as either prednisolone or tetracosactide depot. Minimum doses were: vigabatrin 100 mg/kg/day, prednisolone 40 mg per day, or IM tetracosactide depot 0.5 mg on alternate days. The early primary outcome measure was cessation of spasms on and between days 14 and 42. Analysis is by intention to treat.

• Results

• 377 children were enrolled and early clinical outcome data will be available on 376 (1 case withdrew). 185 were allocated hormonal therapy and vigabatrin and 191 were allocated hormonal therapy alone. 133/185 (71.9%) on combination therapy versus 108/191 (56.6%) on hormonal therapy alone achieved a primary clinical response: treatment difference 15.3% (95% CI 5.4% to 25.2%, p=0.002). The treatment effect favouring combination therapy remained highly significant in a logistic regression analysis controlling for underlying aetiology, country of enrollment, whether hormonal therapy was randomized or not, and gender (Odds ratio 2.03, 95% CI 1.3 to 3.2, p=0.002). Treatment response was also significantly faster on combination therapy (median response time = 2 days, IQR 2–4 days) than hormonal therapy alone (median response time = 4 days, IQR 3–6 days, p<0.001). The electroclinical response will also be reported at the meeting.

• Conclusion

• The ICISS trial shows that combination therapy of hormonal therapy + vigabatrin is associated with a more rapid clinical response and greater proportion of infants achieving spasm cessation than on hormonal therapy alone.
**Entry Criteria**
- Age 2-14 months
- Clinical Diagnosis of infantile spasms
- EEG shows hypsarrhythmia or similar compatible with clinical infantile spasms
- Total screened 749
- Total recruited 377
- Total analyzed 377

**Randomization**
- Combination therapy (pred or synthetic ACTH + VGB)
  vs
- Hormonal therapy alone (pred or syn ACTH)

- Minimal doses
  - Prednisolone 40 mg/kg/d
  - Synthetic ACTH depot 0.5mg (40 IU) on alternate days
  - Vigabatrin 100 mg/day

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**Vigabatrin + Hormonal Therapy Efficacy in Infantile Spasms**

<table>
<thead>
<tr>
<th>Treatment difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Clinical Response</td>
<td>15.3%</td>
</tr>
<tr>
<td>71.9</td>
<td>56.6</td>
</tr>
<tr>
<td>Electro-clinical Response</td>
<td>11.5%</td>
</tr>
<tr>
<td>66.5</td>
<td>55</td>
</tr>
</tbody>
</table>

- Treatment response faster on combination vs hormonal therapy alone
- Median response time: 2 vs 4 days (P < 0.001)

Primary clinical response = cessation of spasms on and between days 14 and 42
Electro-clinical response = cessation of spasms on and between days 14 and 42 plus resolution of hypsarrhythmia on EEG

O’Callaghan F, et al. AES 2015; Abstract 2.255.
International Collaborative Infantile Spasms Study (ICSSS) comparing hormonal therapies (prednisolone or tetracosactide depot) and vigabatrin versus hormonal therapies alone in the treatment of infantile spasms: Early clinical outcome

Conclusion

• Increased proportion of patients achieving spasm cessation
• Increased proportion of patients achieving electroclinical response
• A faster clinical response

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