Complementary and Alternative Medicines (CAM)

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Objectives

• Complementary and Alternative Medicines (CAM)
• Herbal medicines
• Cannabinoids
• Research studies
**CAM**

- Definition of complementary and alternative medicine
  - National Center for Complementary and Alternative Medicine (NCCAM)
    - “A group of diverse medical and health systems, therapies, and products that are not presently considered to be part of conventional medicine”

- CAM facts in the United States
  - CAM use among pediatric population
    - Approximately 12% of child population uses CAM
    - Children whose parents are regular users of CAM are more likely to use CAM (24%) compared to children whose parents are not regular users of CAM (5%)

**Sources**
Epidemiology of CAM

• CAM facts in the United States
  • Retrospective study of children 2-5 years with Autism (ASD) and developmental disabilities (DD)
    • CAM use: 39% of ASD patients; 30% of DD patients

Sources:
Epidemiology of CAM

• CAM facts in the United States – survey data
  • 2007 National Health Interview Survey (NHIS)
  • CAM use among pediatric patients with and without neurological disorders
    • Ages 3-17; children with headaches, migraines, seizures
    • CAM use:
      • 24% of patients with neurological diseases
      • 12.6% of children without neurological diseases (p<0.0001)

Sources:
CAM - Examples

- Website of Comprehensive Epilepsy Center at NYU Langone Medical Center
  - Relaxation therapy and biofeedback
  - Acupuncture
  - Chiropractic therapy
  - Self-control of seizures
  - Herbal therapies

Sources:
- http://epilepsy.med.nyu.edu/diagnosis-treatment/alternative-therapies/relaxation-therapy-biofeedback#sthash.jaM0MfeQ.dpbs
- http://epilepsy.med.nyu.edu/diagnosis-treatment/alternative-therapies#sthash.4jcJ3ywy.dpbs
CAM Use In Epilepsy

• Other examples
  
  • Melatonin
  
  • Study population: 13-32 year-old; failed 3 AEDs; 4 seizures in prior three weeks; N=10
  
  • Study design: randomized, double-blind, cross-over, placebo-controlled study
  
  • Dose: melatonin 10 mg or placebo po qhs for three weeks; one week of washout period
  
  • Results
    
    • Seizure frequency (three weeks)
    
    • Placebo: 7.75 vs. melatonin: 4.6 (p=0.034)
    
    • Responder rate: 30%
    
    • Better efficacy among patients with partial seizures

Sources

Efficacy of CAM

• Efficacy
  • Current issues of CAM
    • Limited number of evidenced-based analysis
  • Study design
    • Small sample size
    • Duration of clinical study
    • Limitations
    • Generalizability

• Bias
  • Sponsorship
  • Interventions
    • Skilled practitioners vs. amateurs
      • e.g., acupuncture, massage
CAM Therapies

• Other therapies can help promote wellbeing, as well as reduce stress
• Such therapies may be used alongside any anti-epileptic drugs (AEDs)
• CAM therapies include:
  • Homeopathy
  • Herbal remedies
  • Massage
  • Aromatherapy
  • Acupuncture
• It is **important** not to change/stop medication without consulting the epileptologist

Sources:
• Epilepsy Society: http://www.epilepsysociety.org.uk/complementary-therapies#.VRixCKNgISo
CAM Therapies

Homeopathy
• Holistic therapy, which investigates a person’s health, life, and feelings in great detail
• May prescribe small doses of natural substances

Massage and Aromatherapy
• Types of massage
  • Indian head massage (head shoulders and arms)
  • Holistic massage (whole body)
  • Swedish massage (neck down)
  • Shaitsu (using acupressure on acupuncture joints)
• Usage of pure essential oils that are extracted from plants
• Oils have a calming and relaxing effect
• Certain oils are **not recommended** for use in epilepsy as it might trigger seizures
  • Rosemary, fennel, sage, eucalyptus, hyssop, camphor and spike lavender

Sources:
• Epilepsy Society: http://www.epilepsysociety.org.uk/complementary-therapies#.VRixCKNgiSo
CAM Therapies

Herbal Medicine
• Herb use for epilepsy treatment
  • Single herb – e.g., medical marijuana, hemp oil
  • Multiple herbs – e.g., Herbal cocktails or combinations
    • Sometimes unable to identify active ingredients
      • e.g., names of active ingredients are written in foreign language or are not blatantly listed.

• Possible issues of herbal medicine use among epilepsy patients
  • Poor medication compliance – rely on “natural” remedy
    • Need education
  • Unexpected drug-herb interaction
    • e.g., changes in metabolism – fluctuation in serum concentration of AED
    • e.g., increase risk of adverse outcomes – e.g., bleeding risk
  • Breakthrough seizures – e.g., stimulant-type herbs
  • Other serious adverse reactions
    • e.g., allergic reactions, abnormal liver/renal functions

Sources:
• Epilepsy Society: http://www.epilepsysociety.org.uk/complementary-therapies#.VRixCKNgis0
CAM Therapies

**Acupuncture**

- Involves inserting fine pins or needles into specific points on a person’s body
- Creates/stimulates energy pathways and natural healing processes
- Needles in body may be left for a few seconds to 30-40 minutes
- No evidence for directly improving a person’s epilepsy.
- However, found to be effective in reducing stress and anxiety, which may result in less seizures for some people with epilepsy

Sources:
- Epilepsy Society: http://www.epilepsysociety.org.uk/complementary-therapies#.VRixCKNgIso
Safety of CAM

• Safety

  • Can CAM therapy alter seizure threshold?
    • Peony and curcumin – increase seizure threshold; neuroprotective efficacy
    • Ginkgo – provokes seizures

  • Can CAM therapy interfere with pharmacokinetics of antiseizure medication(s)?
    • Absorption, distribution, metabolism, excretion
    • Chelating, protein binding, isoenzymes – substrate, inducer, inhibitor
    • Interactions with AEDs
    • Interactions with other medications

• Can CAM therapy interfere with overall health condition?
  • Liver function, renal function, blood pressure, etc.
Chemicals in Marijuana

• Cannabinoids are a class of diverse chemical compounds that activate cannabinoid receptors on cells that repress neurotransmitter release in the brain.
• Over 85 cannabinoids have been identified
• THC and CBD are the 2 main cannabinoids
  • THC is the main psychoactive component
  • CBD is the main nonpsychoactive component
    • Structure described 1963
    • Anticonvulsive, antianxiety, anti-inflammatory
    • Protective against epilepsy, anxiety, psychosis
    • Ameliorate basal ganglia disorder symptoms

Source:
Cannabinoids

THC is the primary psychotropic ingredient of Cannabis. It is a partial agonist at CB₁ and CB₂ receptors. It is therapeutically used as an antiemetic and to boost appetite in AIDS patients. A Cannabis-based extract with approx 1:1 ratio of Δ⁹-THC and CBD (Sativex®) is marketed in Canada for the symptomatic relief of neuropathic pain in adults with multiple sclerosis and as an adjunctive analgesic treatment for adult patients with advanced cancer.
Cannabinoids

CBD, a major non-psycotropict cannabinoid. It has been clinically evaluated in anxiety, psychosis, and movement disorders, and to relieve neuropathic pain in patients with multiple sclerosis (in combination with Δ⁹-THC as a 1:1 mixture, i.e. Sativex®)
Multiple cannabinoid compounds exist. Many of which the exact on to the body or brain is unknown:

- Cannabidivarin (CBDV)
- Cannabinol (CBN)
- Δ⁹-tetrahydrocannabivarin (Δ⁹-THCV)
- Cannabigerol (CBG)
- Cannabichromene (CBC)
- Δ⁹- tetrahydrocannabinolic acid (Δ⁹-THC)
- Cannabidiolic acid (CBDA)
Cannabinoid receptors

• 1990 discovery of a 7-transmembrane G protein-coupled receptor (CB1) found to be the endogenous receptor for Δ⁹-THC.
  • CB1 is primarily expressed in the nervous system
  • CB2 primarily expressed in immune cells
  • Probably others
Cannabinoid receptor activation

• Intracellular effects of ligand binding CB1
  • Inhibition of adenylyl cyclase leading to decreased levels of intracellular cAMP.
  • Stimulation of potassium channels leading to an increased efflux of potassium
  • Inhibition of voltage-gated calcium channels leading to a decreased calcium influx
• Modulates (decreases) presynaptic cell excitability

Source:
CB1 receptor expression

- CB1 receptors are expressed on GABAergic neurons at presynaptic sites
  - Activation results in decreased GABA release and thus increased excitability
- CB1 receptors also expressed on glutaminergic neurons
  - Reduced excitability
- Overall effect can be a reduction of both inhibitory and excitatory transmission.
Endogenous cannabinoids

• 1992 the first endogenous ligand for cannabinoid receptors identified and named anandamide
• Endocannabinoids are synthesized on-demand when neurons are stimulated, thereby regulating neuronal excitability.
“Spice”

• Synthetic cannabinoids of various types
• Potent CB1-receptor agonists
• Can cause:
  • Psychosis
  • Tachyarrhythmias
  • Seizures
Focus on Cannabidiol

• One of the 2 major phytocannabinoids
• The major nonpsychotropic phytocannabinoid
• Protects against memory-impairing and psychotomimetic effects of THC
CBD mechanisms of action

• Very low affinity for CB1 and CB2
• Antagonist of the GPR55 receptor (basal ganglia)
• 5-HT1A receptor agonist
  • Antidepressant, anxiolytic, neuroprotective
• Role in maintaining intracellular calcium homeostasis
• Activate transient receptor potential (TRP) channels
• Inhibits cytochrome P450 enzymes

Sources:
Research Studies-Animals

There is evidence that cannabinoids can reduce seizure severity and frequency in animal studies

  - No animal was protected from having a seizure (i.e., CBD had no effect on percentage of animals being seizure-free)
    - Does not affect mAChR activation
  - All CBD doses significantly reduced the % of animals having grade 4 or higher seizures
  - Reduced mean seizure severity
  - Reduced mortality with 10,100 mg/kg CBD
  - No significant effect on preventing seizures

*Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ et al. (2010)*
  - In vitro
    - Magnesium-free and 4-AP models of epileptiform activity in hippocampal brain slices
      - CBD decreased local field potential (LFP) burst amplitude and duration (Mg-free)
      - CBD decreased LFP burst amplitude, duration, and frequency (4-AP)
  - In vivo
    - Pentylenetetrazole model of generalized seizures
      - Reduced seizures severity
      - Reduced mortality

**Sources:**
In vitro
- 4-aminopyridine
- Mg-free conditions

In vivo
- Maximal electroshock
- Audiogenic seizures in mice
- Pentylenetetrazole-induced
- Pilocarpine-induced
Research Studies-Humans

**Mechoulam R, Carlini EA (1978):**
- 9 patients randomized to either 200 mg/day CBD or placebo
- In 3 months, 2/4 CBD patients became seizure-free.
- Seizure frequency unchanged in all 5 placebo patients

- 15 patients with temporal lobe epilepsy, all with secondary generalized seizures; double-blinded
- 8 treated with 200-300 mg CBD daily for up to 18 weeks. No change in routine antiseizure medications
- 4/8 “marked reduction in seizures”; 3/8 “partial improvement; 1/7 placebo patients improved

**Ames FR, Cridland S. (1986)**
- 12 institutionalized patients with uncontrolled seizures treated with 200 mg pure CBD daily
- No change in seizure frequency was noted.

Sources:
AUTHORS' CONCLUSIONS:
No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients, for generally short periods of time, and so the safety of long term cannabidiol treatment cannot be reliably assessed.

Source:
Stanford University

Survey of 24 questions presented to a Facebook group of 150 parents who support use of CBD-enriched cannabis in their children

Posted for 2 weeks, reposted another 2 weeks

20 parents responded, 19 met inclusion criteria (one child did not have epilepsy)
• 13 children with Dravet syndrome
  • 4 with Doose, 1 with LGS
• Age range 2-16 years
• Variety of seizure types
  • Focal, tonic-clonic, myoclonic, atonic, spasms
• Intractable seizures for >3 years in most all
• Average of 12 other AEDs tried
• CBD doses range <0.05 mg/kg/day – 28.6 mg/kg/day
• Pre-CBD seizure frequency range 2/week – 250/day
• Duration of CBD treatment range 2 weeks to >1 year
• 16 of 19 (84%) reported a reduction in seizure frequency
  • 2 (10%) became seizure-free
  • 8 (53%) had >80% - <100% seizure reduction
  • 3 had 50-80% seizure reduction
  • 3 had 25-50% seizure reduction
  • 3 (16%) had no change
• 12 weaned child from another AED
• Other beneficial effects
  • Better mood in 80%
  • Increased alertness in 75%
  • Improved sleep in 70%
  • Decreased self-stimulation behaviors in 30%

• Negative effects
  • Drowsiness in 40%
  • Fatigue in 15%
  • Other typical AED SE’s like rash, vomiting, irritability, dizziness, confusion, aggressive behavior not seen.
Where are we now?

• Some positive evidence from animal models of epilepsy that CBD and other cannabinoids have antiseizure effect.
• Limited and low-quality evidence of antiseizure effect in humans
• Appears to be well tolerated in short term use.
Where do we go from here?
Questions still unanswered.

• Who will respond?
• What dose is optimal?
• How do varying proportions of cannabinoids affect outcome or response?
• Are there additive or adverse effects when combined with other antiseizure medications?
• Does tolerance develop?
• Are there long-term adverse effects?
References

References


