MARIJUANA AND PEDIATRICS

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Disclosures

- CDPHE Med MJ Grant RFA acceptance
- CDPHE committees:
  - Retail advisory
  - Edible work group
  - Educational campaign

Objectives

- Pathophysiology
- Epidemiology
- Pediatric Exposures
  - Locally
  - Nationally
- Prevention Measures
  - Child Resistant Packaging
  - Current Regulations
- Use of CBD for pediatric seizures

Cannabis

- Cannabis
  - Sativa, Indica, Ruderalis
- Many known cannabinoids
  - Cannabinols, cannabidiols
  - Delta 9 tetrahydrocannabinol (THC)
- Smoke, Vaporize, Ingest, Topical
- Various terms:
  - Pot, Grass, dope, MJ, mary jane, doobie, hooch, weed, hash, reefer, ganja,

Various forms of Cannabis

- Marijuana: dried plant matter that is smoked
- Hashish: dried plan resin that is either smoked or mixed in edibles
- Hash oil: liquid thick oil, usually smoked or mixed in edibles.
- Shatters/Budders/waxes: concentrated wax/paste, usually smoked

Extraction Methods

- Various solvents
  - Butane, hexane, IPA, ETOH
- Solvents then removed
- Product purified
- Directly used, or mixed with butter, margarine, oil
2 G-protein linked receptors
- Inhibit adenylyl cyclase and stimulate potassium conductance
  - CB1
    - Basal ganglia, substantia nigra, cerebellum, hippocampus, cerebral cortex
    - Presynaptic, inhibits release of Ach, L-glutamate, GABA, NE, DE, 5-hydroxytryptamine
  - CB2
    - Peripherally in immune system tissues, splenic macrophages, B lymphocytes, peripheral nerve terminals, and vas deferens
    - Regulation of immune responses and inflammatory reactions
- Endogenous cannabinoid receptor ligands
  - Anandamide, palmitoylethanolamide

**Kinetics**
- Absorption
  - Inhalation: onset of psychoactive effects within minutes (peak coma 3-10 min)
  - Ingestion: unpredictable, onset 1-3 hours (unstable in gastric pH and first pass metabolism), peak 2-4 hours
- Distribution
  - Vd 2.5-3.5 l/kg
  - Lipid soluble
- Metabolism
  - CYP 2C9 and 3A4
- Elimination
  - 1/2 life IV/inh 1.57 hrs,
  - Urine and fecal

**Pathophysiology**
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**Fig. 5. Mean plasma concentrations of Δ⁹-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) of six subjects during and after smoking a cannabis cigarette containing about 5mg of THC**

**Fig. 6. Mean plasma concentrations of Δ⁹-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) after ingestion of one oral dose of THC 15mg (estimated from single graph for each patient of Fytena et al. with permission). The plasma curve of THC showed considerable interindividual variation (see figure 8 for the individual courses of THC plasma concentrations of three patients).**

**Fig. 10. Time course of subjective effects following three modes of administration of Δ⁹-tetrahydrocannabinol. A rating of the degree of high was made by subjects on a 0-10 scale.**
**Symptoms**
- Desired: relaxation, well being, increased appetite
- Adverse effects: dysphoria, fear, and panic reactions, vomiting.
- Objective signs: tachycardia, hypertension, lethargy, sedation, slowed reaction times, postural hypotension, slurred speech, ataxia

**Treatment**
- Supportive care
- Benzodiazepines
- Antipsychotics
- Capsacin Cream
- Respiratory support

**Confirmatory testing?**
- Standard Urine Drug Assay
  - ELISA
  - THC cutoff
  - False Positives
  - May not represent acute ingestion (except in children)
  - Difficult to interpret and relate to level of intoxication
  - ? Second hand smoke

**HOSPITAL VISITS**

Graphs showing:
- Marijuana-Related Emergency Room Visits
- Hospitalizations Related to Marijuana
A case series of marijuana exposures in pediatric patients less than 5 years of age

George Sun Wang, Sanderip K. Niyang, Kathrynn Wells, Ryan Chiang

Table 1: Incident marijuana exposures

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Presenting symptoms</th>
<th>Presence of medical marijuana use</th>
<th>Auxiliary use</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>7 year</td>
<td>Male</td>
<td>Seizures</td>
<td>Yes</td>
<td>THC, Xanax</td>
</tr>
<tr>
<td>2</td>
<td>5 year</td>
<td>Male</td>
<td>Seizures</td>
<td>No</td>
<td>THC, Xanax</td>
</tr>
<tr>
<td>3</td>
<td>10 month</td>
<td>Male</td>
<td>Seizures</td>
<td>Yes</td>
<td>THC, Xanax</td>
</tr>
<tr>
<td>4</td>
<td>10 month</td>
<td>Male</td>
<td>Seizures</td>
<td>Yes</td>
<td>THC, Xanax</td>
</tr>
<tr>
<td>5</td>
<td>4 year</td>
<td>Male</td>
<td>Seizures</td>
<td>Yes</td>
<td>THC, Xanax</td>
</tr>
</tbody>
</table>
Association of Unintentional Pediatric Exposures With Decriminalization of Marijuana in the United States

Georg S. Hong, MD, Gene Rassmussen, MD, MPH; Marsha D. Cai, MD; Erin R. Mahoney, MD; Brian B. Baram, MD, MPH; Nita C. Blumenthal, MD, MPH; Jennifer A. Healy, MD

Objective: We compared data trends in unintentional pediatric marijuana exposures, as measured to call volume to 20 poison centers, by state marijuana legislation status.

Methods: We conducted a retrospective analysis of the American Association of Poison Control Centers National Data System from January 1, 2004, to December 31, 2013. Data were collected monthly by states that have not passed legislation to allow marijuana use. Data were analyzed using chi-square tests and multivariate analyses. Data were compared by state marijuana legislation status.

Results: There were 862,953 total marijuana exposures reported from 2004 through 2013 in children aged 0 to 19 years. The states with marijuana decriminalization saw an increase in the number of marijuana exposures per 100,000 children. The number of exposures per 100,000 children was higher in states with marijuana decriminalization compared to states with no marijuana legislation. More exposures were reported in decriminalized states, and more children had major/moderate effects and were admitted to critical care units. The rate of exposure per 100,000 children did not change from 2004 to 2013. The call rate in marijuana states increased by 30.5% per year, and transitional states had a mean linear trend of an increase of 13.7% per year.

Conclusions: Although the number of pediatric exposures to marijuana reported to the National Poison Data System was lower than the data for heroin (6,450 to 20,363) in states that had passed marijuana legislation. (J Emerg Med. 2016)

Please see page 18 for the Editor's Capsule Summary of this article.

US Pediatric Exposures
- 985 unintentional exposures
- Median age 1.7 (52%M)
- 60-74% seen in health care facility
- 78% reported ingestion
- 20-37% Drowsiness/Lethargy
- 10 patients with respiratory depression, bradycardia, or hypotension
- Most symptoms lasted 2-24 hrs
- No deaths

Decriminalized states
- More patients evaluated in health care facility (OR 1.9; 1.5,1.6)
- More patients with major/mod effects (OR 2.1; 1.4, 3.1)
- Admission to critical care units (OR 3.4; 1.8, 6.5)
**Ataxia**

**Somnolence,**

**CNS Depression**

**Seizure like activity or hyperkinetic activity**

**Apnea/Bradyapnea**

**Prolonged Symptoms**
1950’s: Safety cap for Aspirin

1960’s: Palm-N-Turn Vial

Introduction of the Palm-N-Turn cap was associated with large declines in childhood poisoning from medication in two large population studies:

- A decline of 95% at Madigan General Hospital in 1968 – 1970 (Scherz R, NEJM, 285:1361-2; 1971)

- A decline of 91% in Essex County, Ontario in 1967-1972 (Breault, Clin Toxicol 7:91-95; 1974)
The Poison Prevention Packaging Act (15 U.S.C. 1472), enacted by Congress in 1970, requires child-resistant packaging for household products that present a risk of “serious injury or illness to children under five” who may drink, eat or handle the contents. It applies to numerous household chemicals, cosmetics, and medications, including most prescription drugs in oral dosage form, and all controlled drugs. For a detailed guide, visit [http://www.cpsc.gov/cpscpub/pubs/384.pdf](http://www.cpsc.gov/cpscpub/pubs/384.pdf).

**Current regulations**

- Recreational
  - Each individual packaged edible retail product, even if comprised of multiple servings <= 100 mg THC
  - May not be designed to appeal to children (specifically targets individuals < 21 yo, including but not limited to cartoon or similar images)
  - Statement whether the container is child-resistant
  - Must leave with exit package that is child-resistant (meet PPFA/CPCS standards)
  - Warnings: “keep out of reach of children”
  - No mass market campaigns

- Medical
  - Recent legislation matches recreational regulations

**Edibles**

- “Multiple-Serving Edible Retail Marijuana Product” means an Edible Retail Marijuana Product unit for sale to consumers containing more than 120 mg of THC and no more than 1000 mg of THC.
- A Retail Marijuana Products Manufacturing Facility must ensure that each single Standardized Serving Of Marijuana of a Multiple-Serving Edible Retail Marijuana Product is physically demarked in a way that enables a reasonable person to intuitively determine how much of the product constitutes a single serving of active THC. Each demarked Standardized Serving Of Marijuana must be easily separable in order to allow an average person 21 years of age and over to physically separate, with minimal effort, individual servings of the product.
- If an Edible Retail Marijuana Product is of the type that is impracticable to clearly demark each Standardized Serving Of Marijuana or to make each Standardized Serving Of Marijuana easily separable, then the product must contain no more than 10 mg of active THC per unit of sale, and the facility manufacturing the product must ensure that the product complies with subparagraph (b)(2)(a) of rule R 1004.5.

**Other Recent Legislation**

- HB-1361: Limits purchasers of retail marijuana to the equivalent of up to 1-oz dry, loose-leaf MJ per transaction. (Previously it was ambiguous whether "marijuana" meant only the loose-leaf plant or, e.g., 1-oz THC concentrate, about a 90-fold difference in the amount of THC being sold.)
- HB-1366: The Dept of Revenue has until 1/1/16 to make sure edible products themselves (not just their packages) are “clearly identifiable” as marijuana products, in contrast to non-infused candy products; in many cases, these items now look exactly alike. (The more specific wording of “colored, stamped, shaped or otherwise marked” as containing THC was removed.)
Future Regulations
- Universal Symbol
- Potency Testing
- Safe Production
- Education and Best Practices

Pediatrics and CBD

Old studies
Newer studies
  - CBDV/CBD significant anticonvulsant effects in the penylenetetrazole and audiogenic seizure models, and suppressed pilocarpine induced convulsions

Recent Abstract

Real Oil (Charlotte’s Web) CBD ratio of 16:1
- 11 of 13 parents interviewed: 4 Doose, 2 Dravet, 1 Lennox-Gastaut, 1 metachromic leukodystrophy, 1 cortical dysplasia, 2 idiopathic epilepsy. Ave 10 AED’s.
  - 100% reported reduction in weekly frequency of motor type seizures, 5 of 11 are seizure free.

Parent Reports
  - Survey presented to parents belonging to a Facebook group dedicated to sharing info about the use of CBD for seizures.
  - 19 responses, 2 (11%) reported complete seizure freedom, 8 (42%) reported a 80% reduction, 16 (84%) reported a reduction in seizure frequency, 6 (32%) reported 25-60% reduction

Cochrane Review
- Searched Cochrane Epilepsy Group Specialized Register, controlled trials, medline, ISI web of knowledge, and clinicaltrials.gov
- RCT trials
- 4 randomized reports which included a total of 83 patients, each of which used cannabidiol as the treatment agent. One report was an abstract, and another was a letter to the editor. Anti-epileptic drugs were continued in all. Details of randomizations were not included in any study. There was no investigation of whether control and treatment groups were the same or different. All the reports were low quality. The four reports only answered the secondary outcome about adverse effects.
  - None of the patients in the treatment groups suffered adverse effects.
  - No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 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.

MARIJUANA AND ADOLESCENTS
Youth (ages 12 to 17 years) Past Month Marijuana Use, 2012

- Colorado average for youth was 10.47 percent.
  - In 2012, the Colorado average was 39 percent higher than the national average.
  - Colorado was ranked 4th in the nation.
  - In 2006, Colorado was ranked 14th in the nation for past month marijuana usage among youth.
**Adolescent Risk Use**

- More likely to have impaired cognitive and academic abilities after 28 days of abstinence
- Lower IQ score after short term abstinence
  - Fried 2005
- Less likely to graduate high school and less likely to attain college degree
  - Fergusson 2003, 2008, Horwood 2010
- More likely to be addicted to other illicit drugs after adolescent

**Adolescent Risk Use**

- Mixed evidence for depression
- More likely to develop schizophrenia after adolescence
- Quitting have lower risks of negative cognitive and mental health outcomes
  - Swift 2012

**Summary**

- Marijuana comes in all forms
- Recreational use and unintentional exposures are increasing
- Burden on hospitals are increasing
- Lots of on-going legislation
- Pediatric patients have more severe and prolonged symptoms
- Influx of patients using CBD for seizures and other ailments
- Adolescent population vulnerable
- Get involved

**Questions?**

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