Cannabinoids Overview: Medical Use, Abuse, Pharmacotherapy, and Assessment of Consequences <Fall 2015>

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Disclosure Statement

- Dr. Teter reports no real or perceived financial relationships or other conflicts of interest
- Dr. Teter will be discussing '*unapproved*' uses for cannabinoids

- PLEASE NOTE: the <u>intended purpose</u> of this lecture is to provide a *broad overview of many topics* related to cannabinoids:
  - Full references available at end of presentation

Commonly-used Abbreviations

- AE = adverse effect
- ***CB = cannabinoid***
- CNS = central nervous system
- DSM-5 = Diagnostic & Statistical Manual
- HR = heart rate
- **MJ = marijuana**
- NNH = number needed to harm
- NNT = number needed to treat
- NS = non-significant
- OR = odds ratio
- PD = pharmacodynamics
- PK = pharmacokinetics
- PLC = placebo
- SS = statistically significant
- **THC = ∆-9-tetrahydrocannabinol**
- UDS = urine drug screen

Cannabinoids (CB): Outline

- PART 1: CB Primer
  - Endogenous vs. exogenous
  - Mechanism of action
    - Including CNS regional effects
  - Potential interactions
- PART 2: Medical MJ Use (*state specific; focus on medical MJ vs. other formulations*)
  - Medicinal marijuana (MJ)
    - Data supporting use (*i.e., efficacy*)
    - **Focus on impact to nursing and pharmacy professions**
- PART 3: CB Use Disorders (*consistent with DSM-IV and DSM-5 approach*)
  - Acute intoxication (*focus on potent synthetic CBs such as "Spice"*)
    - Presentation and management
  - **CB Dependence**
    - **Novel pharmacotherapy**
- PART 4: Potential AEs in Adult Populations*
  - Cardiovascular/cerebrovascular
  - Pulmonary/respiratory
  - Cognition/neurologic
- ***NOTE: adolescent CB use impact beyond scope of current presentation**

Part #1: CB Primer

Cannabinoids (CB)

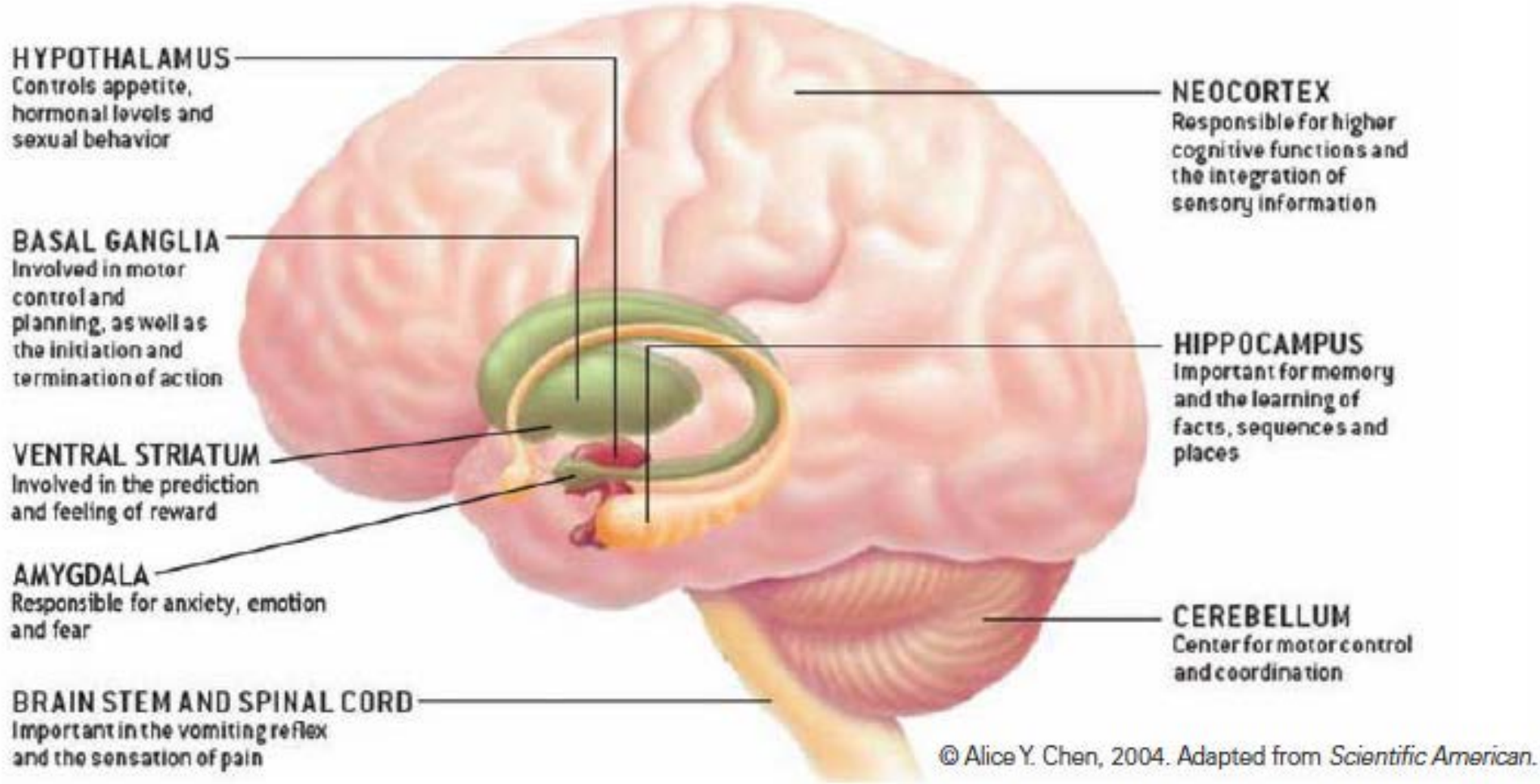
- Categorization:
  - Natural CBs
    - Endogenous ligand
      - Anandamide
    - Exogenous ligand (e.g., *CB sativa, CB indica*)
      - Δ-9-tetrahydrocannabinol
  - Synthetic CBs
    - Prescription medications
      - Dronabinol (Marinol); nabilone (Cesamet)
    - Recreational use
      - "Spice/K2" (*potent CB formulations*)

CB: Endocannabinoid System

- **CB1 Receptors**
  - CNS: Basal Ganglia, Cerebellum, Hippocampus, Hypothalamus, Limbic system, Neocortex
    - CB1 binding induces *dopamine release*
    - G-protein activity
      - Signal transduction pathways
      - Neuronal stabilization
- CB2 Receptors
  - Periphery: immune cells and tissue
  - CB2 binding effects in CNS not well-understood

Borgelt et al. Pharmacotherapy 2013;
www.cnsforum.com

Marijuana's Effects on the Brain



Source (public domain): National Institute on Drug Abuse

http://www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects

CB: Pharmacodynamics

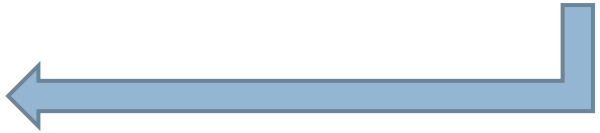
- MJ is a complex plant
  - Numerous compounds
    - **60(+) CBs**
  - Various strains
    - Differing CB concentrations
- Lack of correlation between drug concentrations and physiologic effect
- Highly variable drug administration
  - Concerns with self-titration and dosing

Borgelt et al. Pharmacotherapy 2013

CB: Pharmacokinetics

- THC
  - Half-life = 30 hours (*wide variability*)
  - Smoked THC
    - Absorption: rapid (*within minutes*)
    - Bioavailability: wide range (**10-25%**)
  - Oral THC
    - Absorption: variable
    - Peak concentrations: **1-3 hours**
  - Other formulations: vaporized, "edibles"
- **Teter CJ: [Variability (PD) x Variability (PK)] = [Variability]**
  - (*i.e. lack PK/PD standardization*)

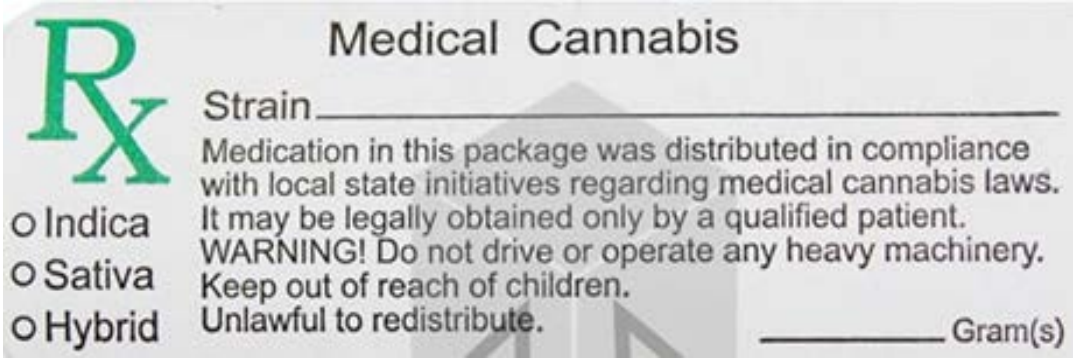
Delay has contributed to AEs



Borgelt et al. Pharmacotherapy 2013

CBs: Interaction Potential

- Drug-Demographic
  - Gender:
    - Females (higher estrogen levels; sensitivity)
- Drug-Disease:
  - Cardiovascular:
    - CB causes *hemodynamic* effects
  - Psychiatric:
    - Changes in mood/ behavior
    - DSM-5 (*signs & symptoms*)



- Drug-Drug (*Rx or illicit*):
  - Increased heart rate:
    - *Tobacco*, anticholinergics, CNS stimulants
  - Decreased cognitive function:
    - Benzodiazepines, alcohol, opioids

Borgelt et al. Pharmacotherapy 2013

Part #2: Focus on Medical MJ

Question for Audience

- Where do health professionals "fit" into the current medical MJ scheme?
  - Is it dispensed via a *valid prescription* with clear instructions?
  - Is pharmacy, nursing, and other health care professionals circumvented in the process?
  - Who is responsible for tracking and monitoring the use of medical MJ?
- What conditions are *appropriately* treated with medical MJ?

Medicinal MJ: Indications & Efficacy

- Indications for use (…*geographical variation!*)
  - Pain, Nausea, Seizure-activity, Muscle spasms, Wasting syndrome, Cancer, Irritable Bowel Syndrome, Glaucoma, HIV/AIDS, Hep-C, ALS, Alzheimer's disease, nail patella syndrome, PTSD
  - Petition to add an indication
    - "*reputable*" and "*sufficient*" evidence
  - Focus of today's presentation: non-terminal illnesses

Medicinal MJ: Indications & Efficacy

- Many controlled trials have been conducted using CBs for various conditions
  - Focus of this presentation: the use of <u>medical MJ</u>
    …particularly for non-terminal conditions
    - Literature search*
      - MS: **spasticity** and **pain**
      - Neuropathic **pain** (*central and peripheral*)
- Please refer to reference list

*Research trainees (*Nicole Chasse, PharmD Candidate & Nicholas McGlinchey, PharmD Candidate*) performed a literature review and discussion of trials that met minimum pre-determined criteria (e.g., randomized, placebo-controlled, sufficient sample size, CB, etc.).

Medicinal MJ: Indications & Efficacy

- Study considerations
  - Many study limitations:
    - Small sample sizes
    - Various dosage formulations
    - Varying THC concentrations
    - Difficulty randomizing to placebo
      - Psychoactive substance
- EXAMPLE studies (*let us discuss*)
  - Multiple sclerosis
  - Neuropathic pain

Medicinal MJ: Multiple Sclerosis

- Study design:
  - Randomized, placebo-controlled, cross-over trial
  - **N=30** patients with treatment-resistant spasticity
- Methods:
  - Control group (*placebo cigarette*)
  - Intervention group (**4% THC cigarette**)
  - Drug administration: *Foltin Uniform Puff Procedure*
  - Evaluations:
    - Prior to, 45 minutes after drug administration

Corey-Bloom et al. CMAJ 2012

Medicinal MJ: Multiple Sclerosis

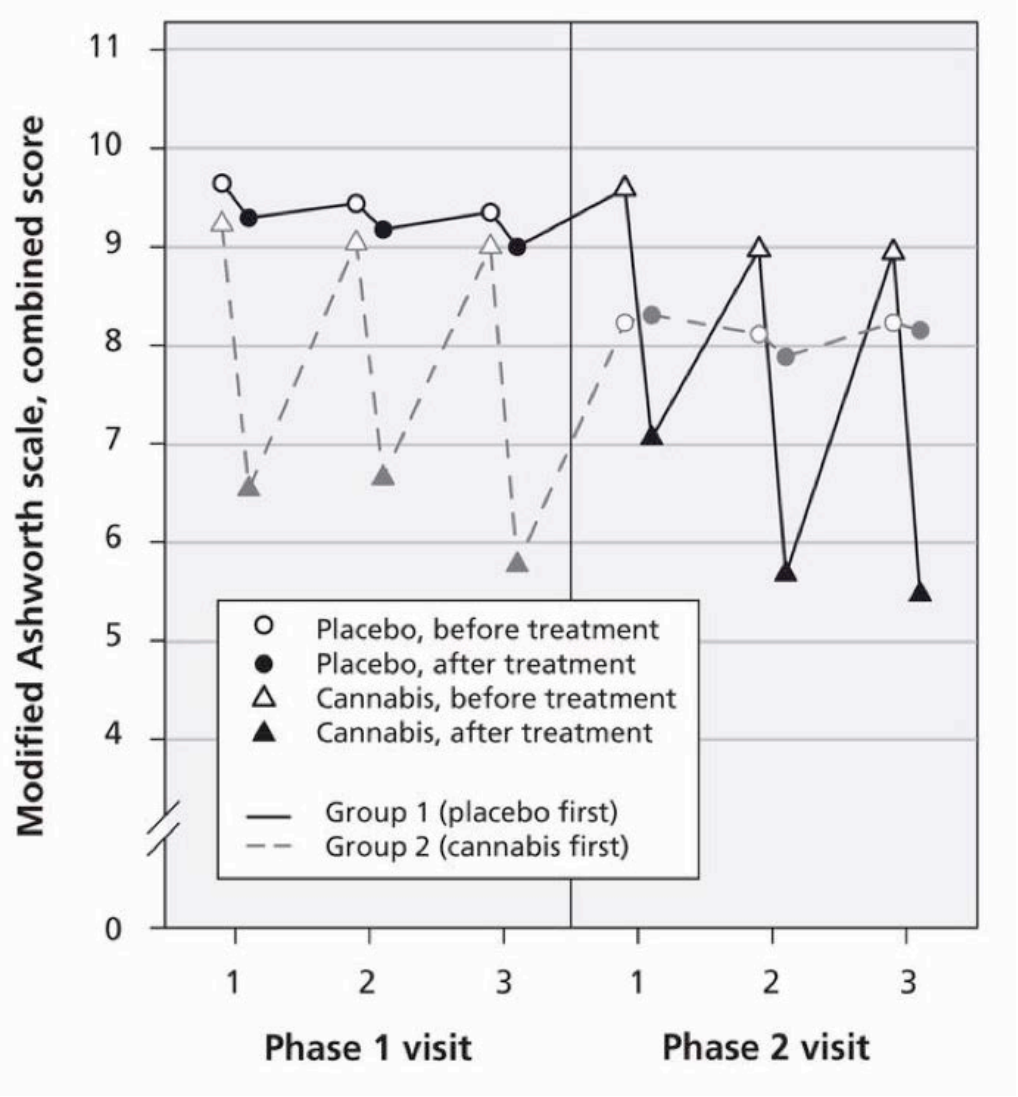
- Primary objective:
  - Spasticity (*modified Ashworth Scale*)
- Secondary objectives:
  - Pain (*visual analogue scale*), walking time, cognition
- Results:

Objective	Mean Change	CI	P-value
Spasticity	**2.74**	**2.20 to 3.14**	**< 0.001**
Pain	5.28	2.48 to 10.01	= 0.008
Walking time	1.20	0.15 to 4.31	= 0.2
Cognition	8.67	4.10 to 14.31	= 0.003

Corey-Bloom et al. CMAJ 2012

Medicinal MJ: Multiple Sclerosis

- Results:
  - Decrease in spasticity
  - Combined Ashworth scores:
    - **2.74 point decrease** (vs. placebo)
    - **P < 0.001**
- Conclusions:
  - MOA possibly related to glutamate modulation or neuronal stabilization



Corey-Bloom et al. CMAJ 2012

Medicinal MJ: Neuropathic Pain

- Study design:
  - N=39, placebo controlled, cross-over study
  - Analgesic efficacy: *vaporized* CB
  - Participants experiencing neuropathic pain despite traditional treatment
- Primary outcome:
  - VAS (*pain intensity*)
  - 0 (*none*) to 100 (*worst pain*)
- Comparison groups:
  - Placebo
  - Low dose (**1.29% THC**)
  - Medium dose (**3.53% THC**)

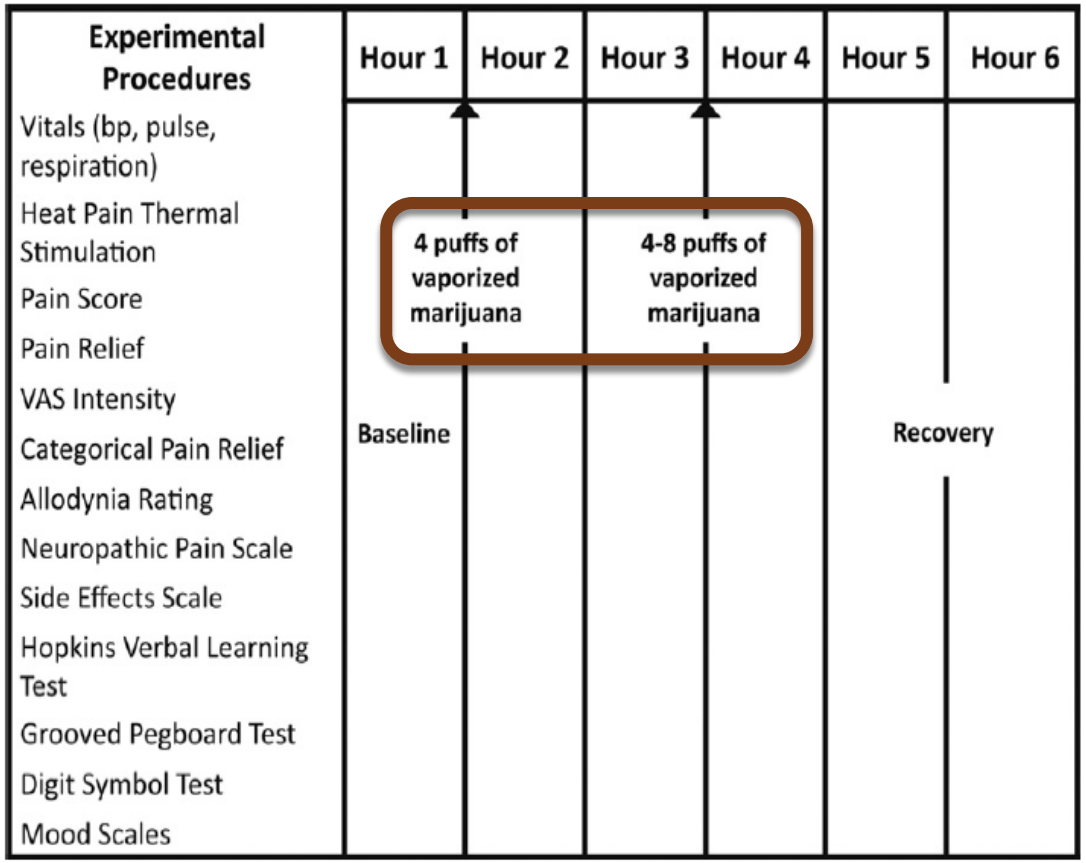


Figure 1. Experimental procedures and timing of cannabis vaporization sessions.

Wilsey et al. J Pain 2013

Medicinal MJ: Neuropathic Pain

- Results:
  - THC doses equi-analgesic
  - Statistical separation from placebo (*120 minutes through 300 minutes*)
  - NNT (*30% pain reduction*)
    - **3.2** (PLC vs. low-dose)
    - **2.9** (PLC vs. medium dose)
  - Multiple AEs commonly reported
    - "high", "stoned", "liked the drug effect"
- Conclusions:
  - AEs vs. efficacy balanced?

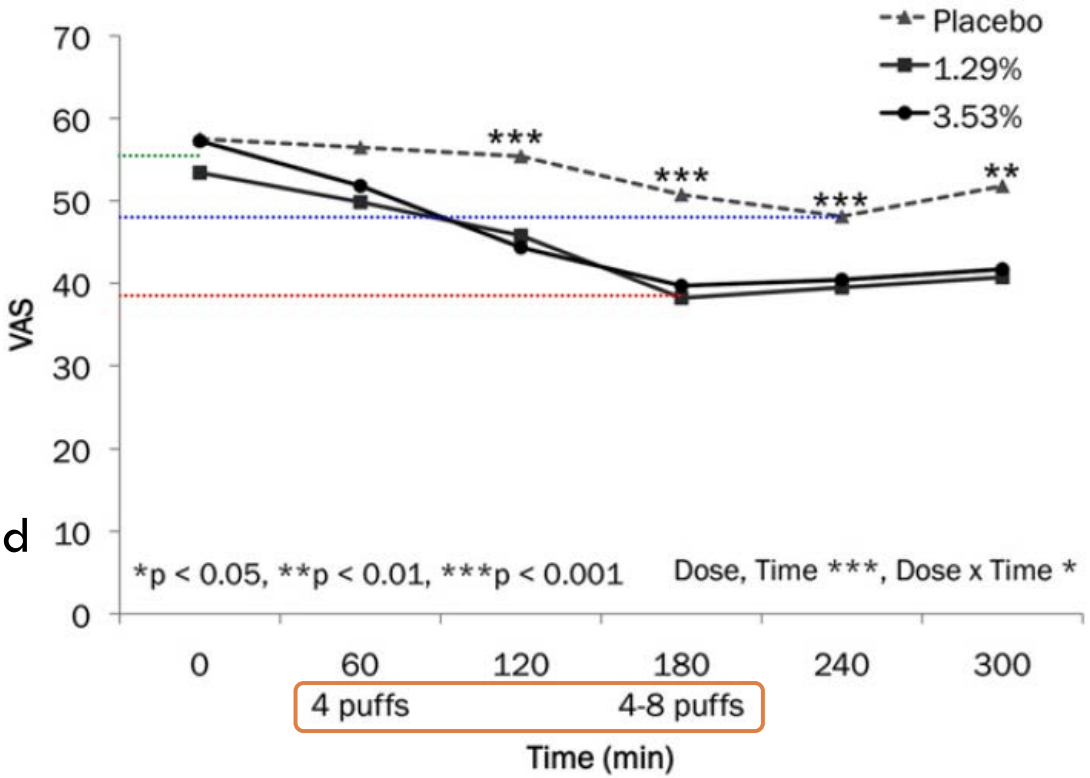
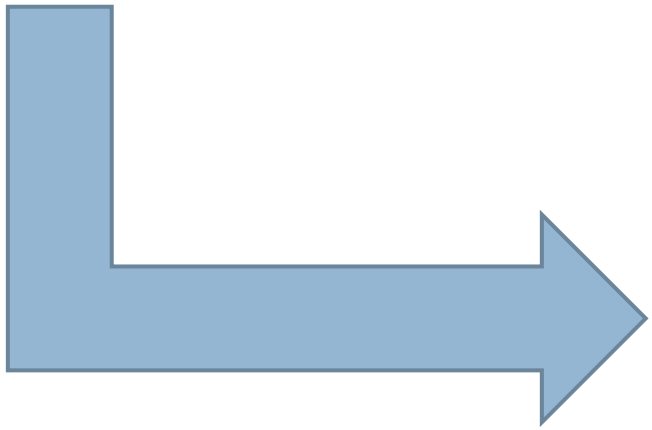


Figure 3. VAS pain intensity.

Wilsey et al. J Pain 2013

Controlled vs. Natural Environments

- Dosing methodology:
  - Studies have attempted to standardize the MJ dosage (i.e., within individual studies)
  - HOWEVER, standardization is not evident in the current medical MJ model:
    - Model: "*patient-determined*"; "*self-titrated*"



Medicinal MJ: Logistics

- Background
  - First state with enacted laws: 1996
  - Approximately 20(+) states and D.C.
    - Many tables available
- Patient considerations (*examples*):
  1. Condition eligible?
  2. Dispensary vs. caregiver distinction
  3. Know the allowable limits
     - *e.g., 24 'usable' ounces, 6 mature/18 immature plants*

Medicinal MJ: Logistics

- Qualifying patient
  - Documentation from a physician
    - Medical MJ *benefit to patient*
  - Application
    - *Fee ($)* and clinician certification
    - Submitted to state government

"bona fide" relationship

- Caregiver
  - Designated by patient
    - Includes: *nursing facility* or hospice
  - Register with government (*exceptions*)
- Clinicians
  - Medical license (*good standing*)
  - Controlled substance registration
  - Monitor patients & maintain records

MMMP, 2013

Medicinal MJ: Logistics

- Dispensary
  - Sell medical MJ
  - Registered with government
  - May undergo inspections
- Monitoring
  - Local registry (*in Maine, voluntary for patient*)
  - NOT currently identified in the state PDMPs!
  - Physician agrees to monitor patient

MMMP, 2013

Medical MJ: Questions to Consider

- Are there any "*directions*" for the patient?
  - Similar to a prescription
  - Certification/card is received
    - Self-directed care (*in many cases*)
    - Model: "patient-determined"; "self-titrated"
- 'Medical' MJ?

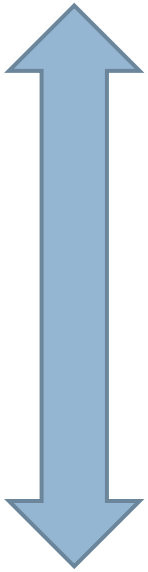
- What is the future of medical MJ?
- Example:
  - www.ct.gov
    - Licensed dispensary = pharmacist "*who the Department of Consumer Protection determines to be qualified to acquire, possess, distribute and dispense marijuana*"

Part #3: Substance Use Disorders

NIDA Research Report (2012)

[public domain]

Predictable (e.g., DSM-5 criteria)



Limited/growing understanding

Consequences of Marijuana Abuse

Acute (present during intoxication)

- Impairs short-term memory
- Impairs attention, judgment, and other cognitive functions
- Impairs coordination and balance
- Increases heart rate
- Psychotic episodes

Persistent (lasting longer than intoxication, but may not be permanent)

- Impairs memory and learning skills
- Sleep impairment

Long-term (cumulative effects of chronic abuse)

- Can lead to addiction
- Increases risk of chronic cough, bronchitis
- Increases risk of schizophrenia in vulnerable individuals
- May increase risk of anxiety, depression, and amotivational syndrome*

*These are often reported co-occurring symptoms/disorders with chronic marijuana use. However, research has not yet determined whether marijuana is causal or just associated with these mental problems.

CB: Epidemiology

- Prevalence
  - Current (*i.e., past month*) MJ use: approximately **7.0%**
- Co-ingestion
  - MJ is the most common drug co-ingested with nonmedical use of Rx medications (*e.g., opioids*)
  - Recent change in drug use patterns
    - **MJ > Etoh** as most common co-ingested drug
- CB Use Disorder
  - **9%** transition from use to dependence

Lopez-Quintero et al, 2011; McCabe et al 2012; SAMHSA, 2013

CB: DSM-5 Criteria (*intoxication*)

- Recent CB use.
- Clinically significant problematic *behavioral or psychological changes* (developed during/shortly following CB use):
  - Includes: impaired motor coordination, *euphoria*, *anxiety*, sensation of slowed time, *impaired judgment*, and social withdrawal.
- Two (or more) following signs/symptoms develop within 2 hours of CB use:
  - Conjunctival injection
  - Increased appetite
  - Dry mouth
  - *Tachycardia*
- Must rule-out another medical condition, mental disorder, and other substance-related signs & symptoms.

DSM-5, 2013

CB: DSM-5 Criteria (*withdrawal*)

A. Cessation of heavy/prolonged CB use.

B. Three (or more) of the following signs and symptoms develop within approximately 1 week after Criterion A:

1. *Irritability*, anger, or aggression
2. Nervousness or *anxiety*
3. *Sleep difficulty* (e.g., insomnia, disturbing dreams)
4. Decreased appetite or weight loss
5. Restlessness
6. Depressed mood
7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache

C. Signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. Signs or symptoms not attributable to another medical condition and not better explained by another mental disorder, including intoxication or withdrawal from another substance.

DSM-5, 2013

CB: DSM-5 Substance Use Disorder (*abuse/dependence*)

A. Problematic pattern of CB use leading to clinically significant impairment or distress; includes at least two of the following (within 12-month period):

1. CB often taken in larger amounts or over longer period than intended.
2. Persistent desire or unsuccessful efforts to cut down or control CB use.
3. Great deal of time spent in activities necessary to obtain/use/recover from CB use.
4. Craving, or a strong desire or urge to use CB.
5. Recurrent CB use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued CB use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of CB.
7. Important social, occupational, or recreational activities given up/reduced due to CB use.
8. Recurrent CB use in situations in which it is physically hazardous.
9. CB use continued despite knowledge of having persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by CB.
10. Tolerance (defined by either of the following):
    - A need for markedly increased amounts of CB to achieve intoxication or desired effect.
    - Markedly diminished effect with continued use of the same amount of CB.
11. Withdrawal (manifested by either of the following):
    - Withdrawal syndrome for CB (refer to Criteria A and B for CB withdrawal).
    - CB (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

DSM-5, 2013

CB (*acute*): Synthetic Formulations

- Incense/potpourri products
  - "K2", "spice", etc.
- Botanical ingredients
  - Sprayed with CB agonists (e.g., JWH-018)
- CB intoxication
  - (-) routine urine toxicology analysis
  - Sudden onset *anxiety* or *psychosis*
- Schedule I

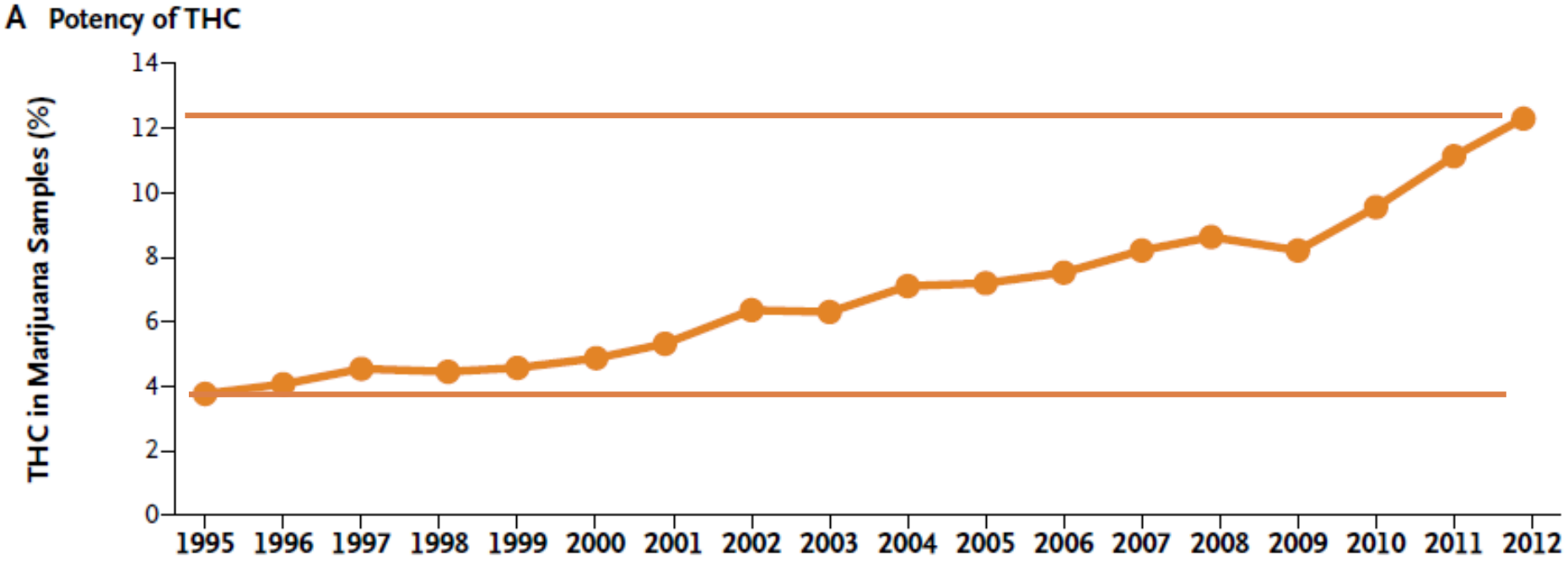
Castellanos & Thornton, 2012; Cohen et al, 2012; Schubart et al, 2011; Seely et al, 2012

CB (*acute*): Synthetic Formulations

- Proposed MOA for AEs:
  - Potent CB agonists
    - Intensified PD effects
  - Lack cannabidiol (?)
    - Example: higher cannabidiol concentrations may lessen psychotic experiences
- Management:
  - No specific antidote
  - Aggressive benzodiazepine use

Castellanos & Thornton, 2012; Cohen et al, 2012; Schubart et al, 2011; Seely et al, 2012

CB: THC Potency

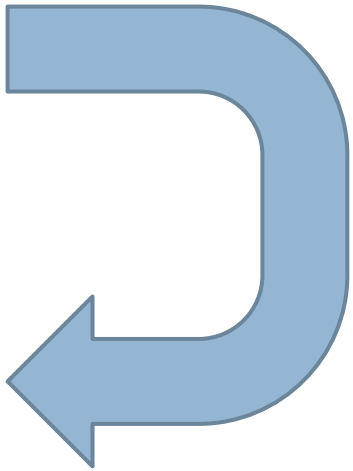


- DEA MJ samples seized
- Percentage of THC

Volkow et al. NEJM 2014

CB (*chronic*): Pharmacotherapy for Dependence/Relapse Prevention

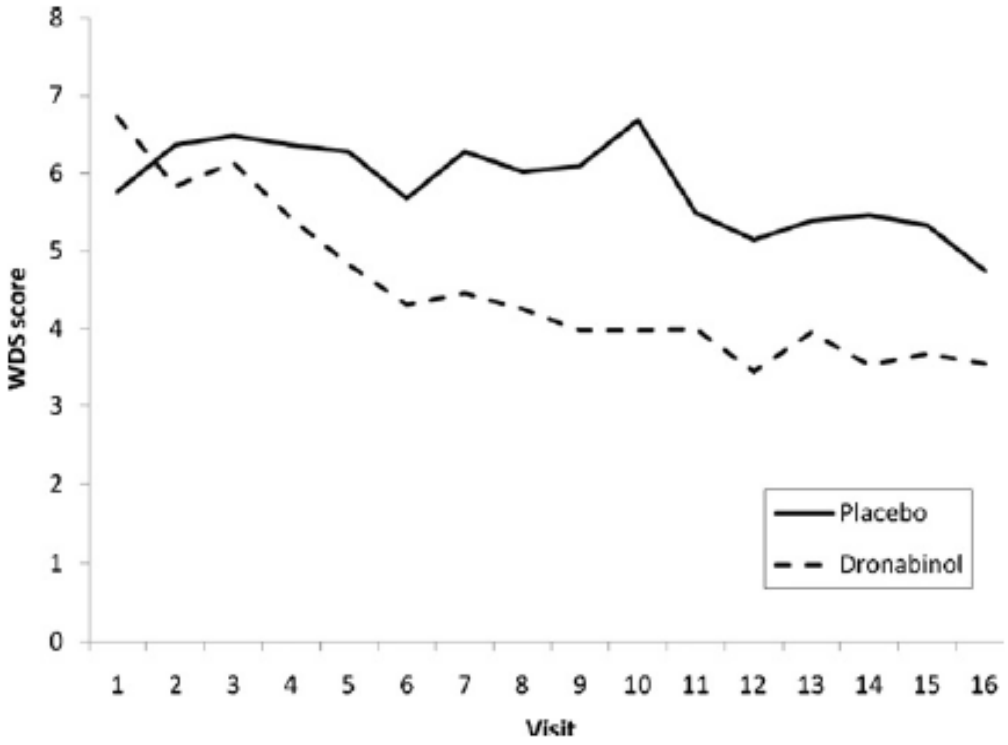
- Buspirone study
  - Study rationale: anxiolytic effect
    - Anxiety and MJ use relationships
  - Methods: 12-week, placebo-controlled
    - Sample size: n=50 (*modified ITT sample*)
    - Intervention: buspirone (*maximum 60 mg/day*)
  - Results: buspirone group with greater number of (-) UDS
    - **11% (PLC)** vs. **28.8% (buspirone)**
    - Risk difference = **17.8%; NS**
    - AEs: dizziness in buspirone group
    - Low "completer sample"
  - Conclusions:
    - Buspirone *numerically* superior
    - Larger sample size?



McRae et al, 2009

CB (*chronic*): Pharmacotherapy for Dependence/Relapse Prevention

- Dronabinol Study
  - Study rationale: CB agonist approach
  - Methods: **n=156**, placebo-controlled, 12-week trial, with behavioral approaches
    - Intervention: **dronabinol 20 mg twice daily** vs. PLC
  - Results:
    - Primary outcome: **NS**
    - Study retention: **SS**
      - Greater with dronabinol
    - Significantly lower w/d
      - Time x treatment interaction (p=0.02)
  - Conclusions:
    - CB agonist approach promising (…in combination similar to NRT?)



Levin et al, 2011

CB (*chronic*): Pharmacotherapy for Dependence/Relapse Prevention

- N-acetylcysteine (NAC)
  - Study rationale:
    - Glutamate modulation
  - Methods:
    - Sample: Treatment seeking (ages 13 to 21)
    - Design: 8-week, RCT
    - Medication: NAC (1200 mg) given BID
      - (+) non-pharmacologic treatment
    - Primary outcome: Odds of (-) UDS for CB
  - Results:
    - **OR = 2.4 [1.1-5.2]** favoring NAC for (-) UDS
    - NAS was well-tolerated
  - Discussion
    - Primary outcome was SS!

Gray et al. Am J Psych 2012

Part #4: Selected Assessment of Adverse Events

(*…not including impact on adolescent development*)

Home stretch! I know your eyes are tired, but take a breath…and prepare for the upcoming heart-felt data review. (*Research Trainees*)

- *"Within a few minutes after inhaling marijuana smoke, an individual's **heart rate speeds up**, the **bronchial passages relax** and become enlarged, and **blood vessels in the eyes** expand, making the eyes look red."*

NIDA Research Report (public domain)

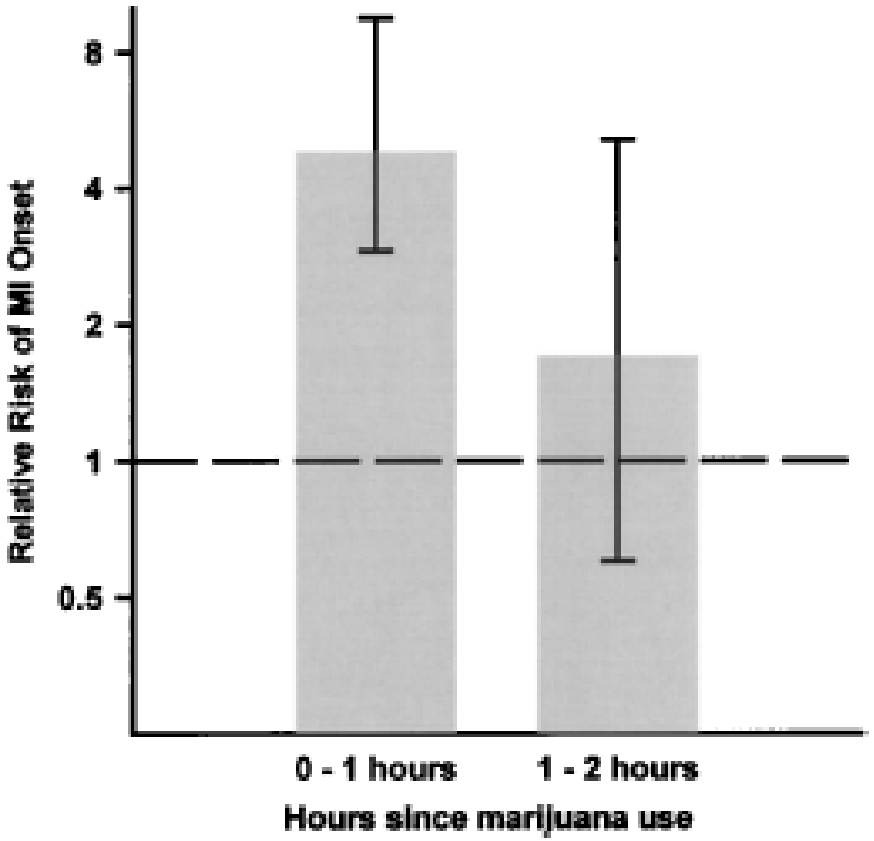
CB: Vascular Effects

- Cardiovascular effects
  - Increase: **HR**, BP, peripheral blood flow, catecholamine release
  - Decrease: coronary blood flow, cardiac oxygen delivery
- Cerebrovascular effects
  - Cerebral *vasoconstriction* and vascular resistance
- NOTE: must consider other confounding variables (e.g., tobacco use, obesity, and illicit drug use).

Thomas et al. Am J Cardiology 2014

CB: Risk for MI

- Study rationale:
  - Hemodynamic changes from CBs
- Methods:
  - Patient interviews following MI
  - N=3800(+)
- Results:
  - **RR: 4.8 (2.9 to 9.5)**
  - **P < 0.001**
- Conclusions:
  - Rare event
  - Vulnerable patients?



Mittleman et al. Circulation 2001

CB: Vascular Effects

- Background
  - CB associated with cardio/cerebrovascular events
- Methods
  - Sample: n=48, < 45 years of age, ischemic stroke
  - Urine drug screen, laboratory analyses, questionnaire
  - Imaging: multiple techniques
    - Single vs. multi-focal intracranial stenosis (MIS)
  - Dependent variable: **MIS**
  - Follow-up: 3 to 6 months

Wolff et al. Stroke 2011

CBs: Vascular Effects

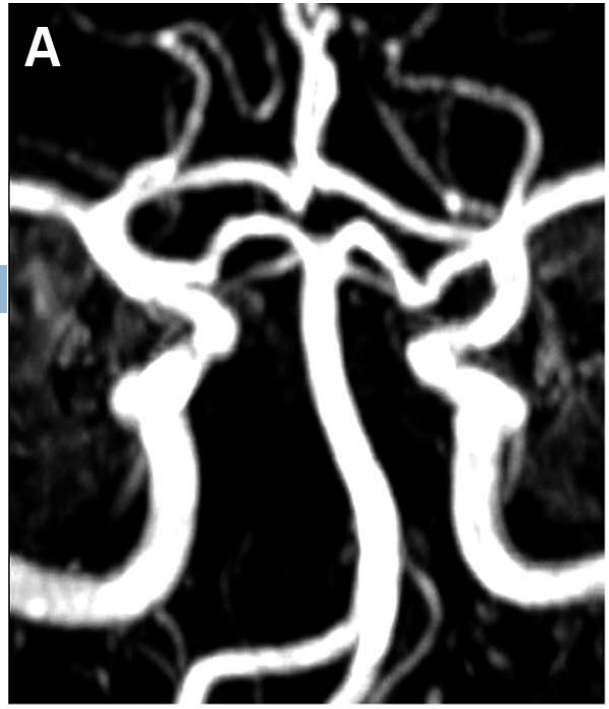
- Results
  - N=13 positive UDS and admitted to CB use
    - All smoked tobacco
  - N=10 CB users displayed clear MIS pattern
    - Total n=11 with MIS pattern
  - MIS and CB significantly related
    - ***OR = 113 [95% CI: 9 –5047]; P<0.001***
  - Reversibility among CB abstainers at follow-up
    - N=9 follow
      - N=6 abstained (partial/full recovery)
      - N=3 used (no reversibility)

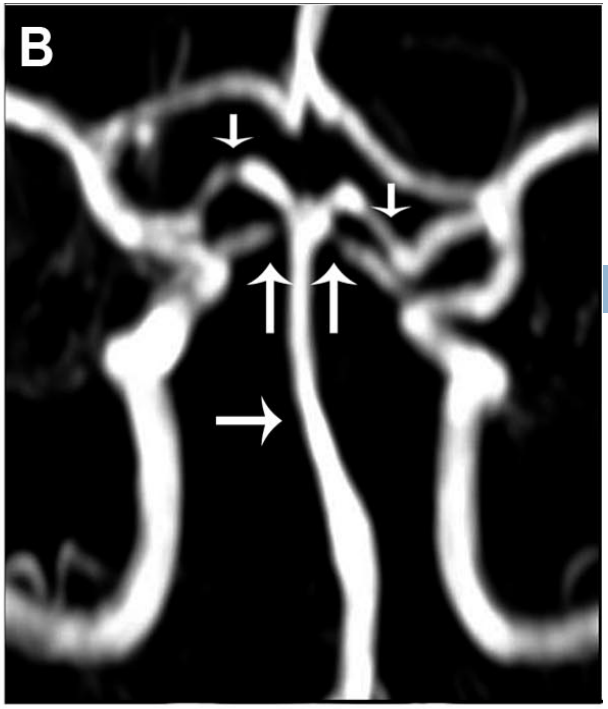
Wolff et al. Stroke 2011

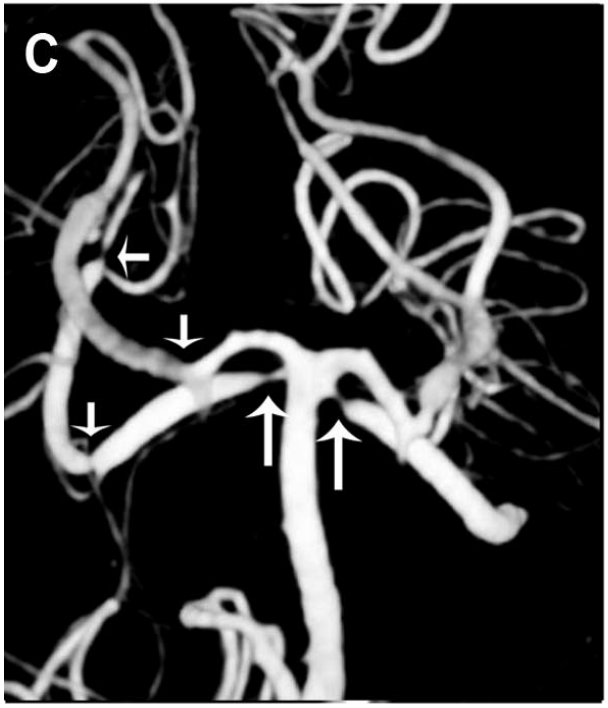
CBs: Imaging Findings

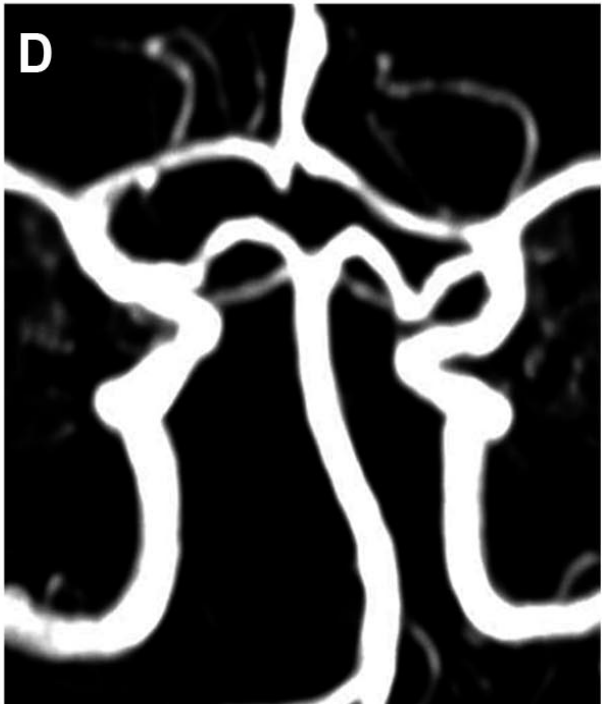
- Patient with repeated brain imaging procedures
  - Family history of aneurysm

- Images demonstrate:
  - A: Prior to CB use
  - B/C: Following CB use
  - D: Reversal (3 months)







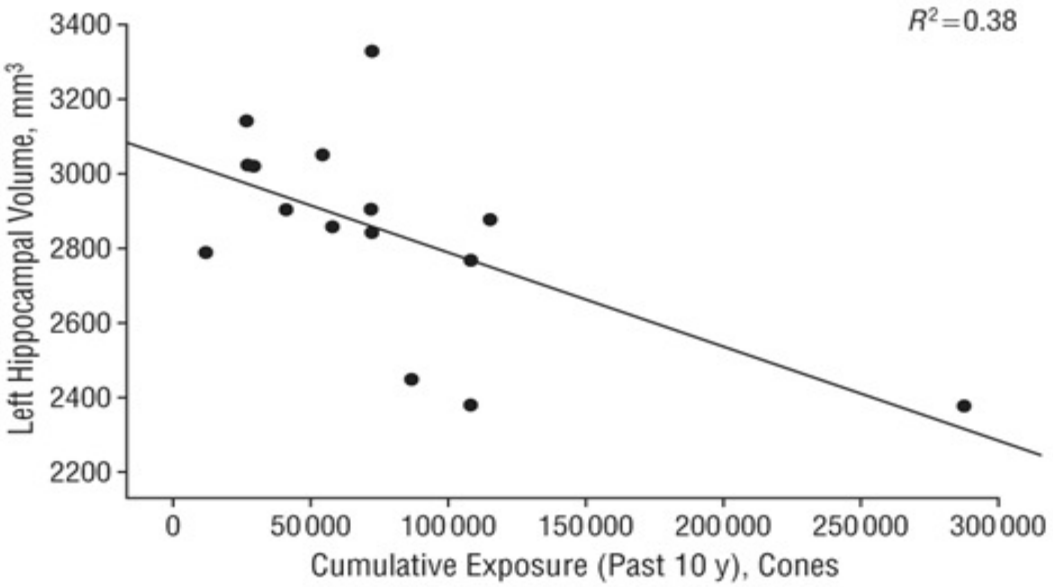


Wolff et al. Stroke 2011

CBs: Structural Changes in the Brain

<u>Long-term, Heavy Use</u>
(*10 years, 5 joints daily, mean age = 39 years of age*)

- MRI: compared volumetric changes in hippocampus and amygdala
- Showed reduction in hippocampal and amygdala volume (**12% and 7.1%, respectively)**



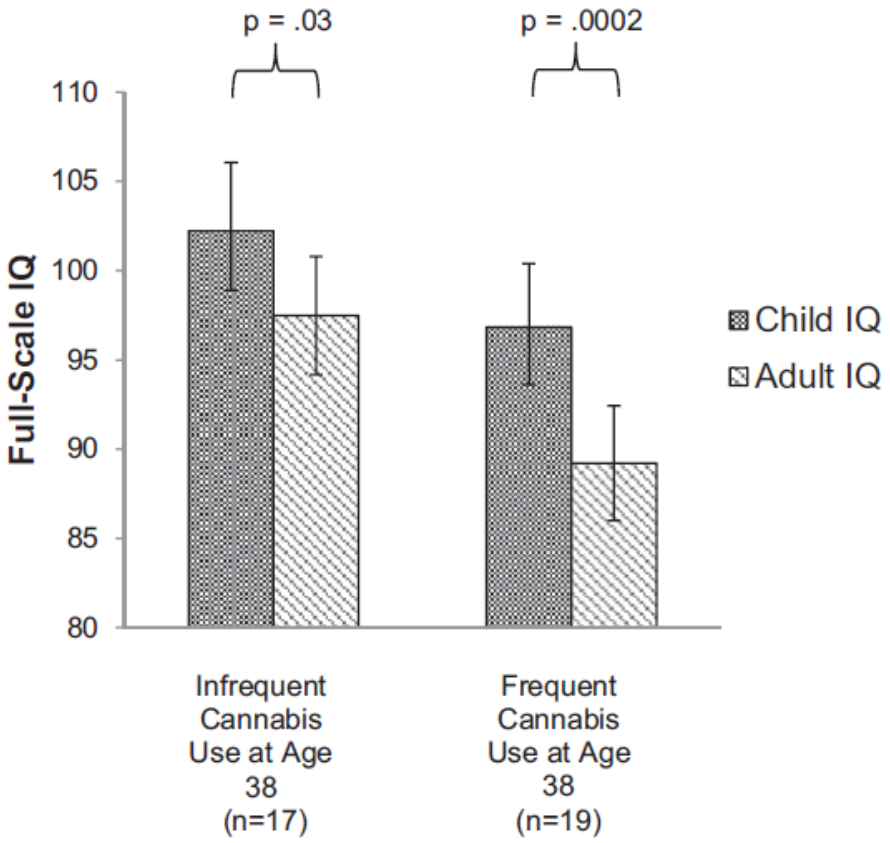
Yucel M et al. Archives of General Psychiatry 2008

CBs: Neurologic Effects

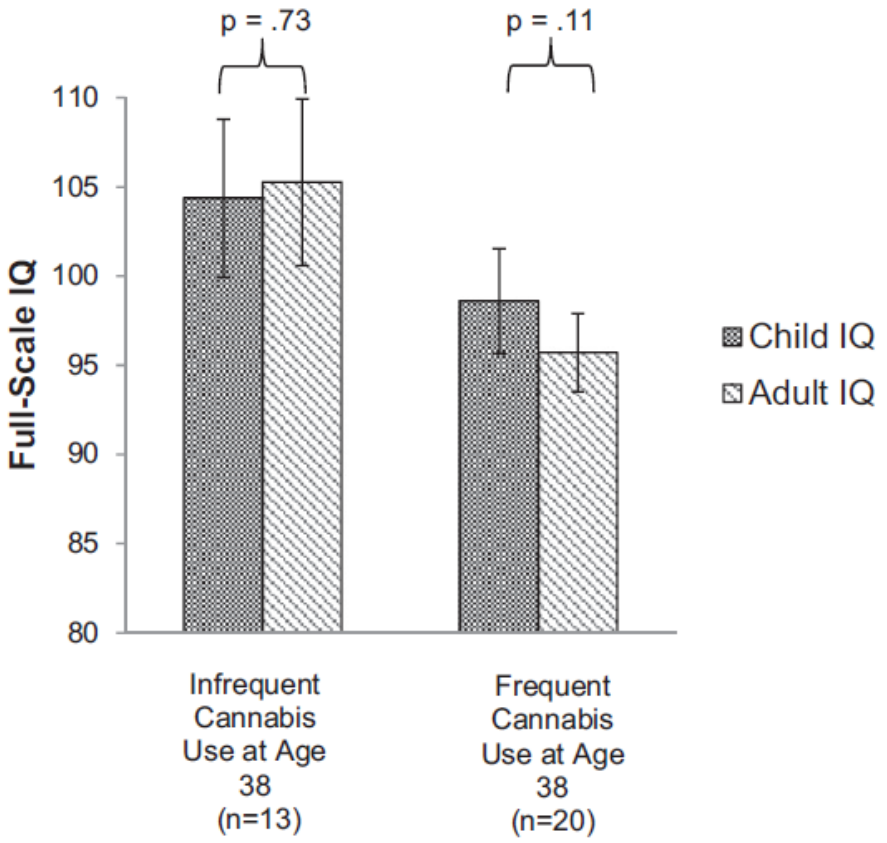
- Impact of persistent CB use on IQ
  - Methods:
    - Study design: prospective, longitudinal (*birth to 38 years*)
    - Sample size: **1000(+)** individuals
    - Study setting: New Zealand
    - Assessments:
      - CB use (*over time*)
      - Neuropsychological testing
  - Results:
    - Neuropsychological decline
    - Early onset associated with greatest decline

Meier et al. PNAS 2012

CBs: Neurologic Effects



Adolescent-Onset (Used Cannabis Weekly Before Age 18)



Adult-Onset (Did Not Use Cannabis Weekly Before Age 18)

Meier et al. PNAS 2012

CBs: Confidence in Evidence for AEs of MJ

Overall Effect	Level of Confidence
Addiction (*marijuana/other substances*)	**High**
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	**High**
Motor vehicle accidents	**High**
Symptoms of chronic bronchitis	**High**
Lung cancer	Low

Volkow et al. NEJM 2014

Part #5: Concluding Remarks

Conclusions

- CB primer
  - Much to be learned
- Medical MJ
  - Efficacy data still needed for many conditions
  - Medical community needs to be integrated
  - Reserve for treatment-resistance (?)
- SUDs
  - Risk for addiction in vulnerable individuals
  - Pharmacotherapy for CB dependence being investigated
    - Initial promising results (e.g., N-A-C)
- AEs
  - CB use not without risks (e.g., hemodynamic changes)

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