More Americans are using marijuana, according to a new government report. About 8.4 percent of Americans ages 12 and older were current users of marijuana last year, up from 7.5 percent in 2013. The percentage of teens ages 12 to 17 who smoke, drink, or use prescription narcotics nonmedically has fallen, Health Day reports.

**US State Marijuana Laws in Effect as of January 2017**

- Prohibition
- Decriminalization only
- High CBD only law
- Medical marijuana law
- Medical marijuana law & Legalization
- Decriminalization & CBD only law
- Decriminalization & Medical marijuana law
- Medical marijuana law & Legalization
51 Medical Conditions For Which Marijuana Is Approved by a State

1. Alzheimer's Disease
2. Anorexia
3. Arnold-Chiari malformation
4. Arthritis
5. Ataxia
6. Cachexia
7. Cancer
8. Cardiopulmonary respiratory syndrome
9. Causalgia
10. Cervical dystonia
11. Crohn's disease
12. Decompensated cirrhosis
13. Dystonia
14. Epilepsy
15. Fibromyalgia
16. Glaucoma
17. Hepatitis C
18. HIV/AIDS
19. Huntington's disease
20. Hydrocephalus
21. Inflammatory autoimmune-mediated arthritis
22. Inflammatory bowel disease (IBS)
23. Inflammatory demyelinating polyneuropathy
24. Interscalene cysts
25. Lou Gehrig's disease (amyotrophic lateral sclerosis, ALS)
26. Lupus
27. Migraines
28. Multiple sclerosis
29. Myasthenia gravis
30. Myelosclerosis
31. Neuromyelitis optica
32. Neuropathy
33. Neuropathy
34. Neurofibromatosis
35. Nausea or vomiting
36. Neumonia atelectasis
37. Nystagmus
38. Pain
39. Pancreatitis
40. Peripheral neuropathy
41. Peripherical nerve lesion
42. Post-traumatic stress disorder (PTSD)
43. Post-traumatic stress disorder (PTSD)
44. Psychiatric disease
45. Rhabdomyolysis
46. Spinal cord injury
47. Spinal cord injury
48. Spinal cord injury
49. Stuttering
50. Tardive dyskinesia
51. Tourette's syndrome


Marijuana-12th
Cigarettes-12th
E-Cigs-12th
Alcohol-12th

SOURCES: University of Michigan, 2015 Monitoring the Future Study

What Are We Learning From the Legalization of Cannabis Products?

- MJ Use and Use Disorders
- MJ Attitudes/Perceptions
- MJ Availability/Accessibility
- Health Outcomes
- Other Drug Use
- Social Outcomes
**MJ Use and Use Disorders (1)**

**USE:**
- Adolescents: MJ use remained consistent while use of other drugs, alcohol and tobacco declined
- Adults: Increases in MJ use between 2001 and 2013
- Parent current MJ use increased likelihood of child past year MJ use

**Cannabis Use Disorders:**
- Density of dispensaries related to higher rates of MJ abuse and dependence
- BUT: 80% medical MJ patients use daily without cannabis use disorder symptoms

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**MJ Use and Use Disorders (2)**

**Product types and methods:**
- MMJ consumers use differently than recreational consumers
- Smoking is still predominant method in youth, but MMJ states more likely to consume in food or other ways than non-MMJ states
- Social media is source of information about novel forms of MJ – e.g. YouTube videos of dabbing
- Tweets related to edibles and dabs greater in states with medical and/or recreational MJ laws

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**Tweets About Edibles**

MJ Attitudes and Perceptions

- MMJ laws not associated with increases in MMJ states, however legislation may more broadly impact perceptions of harm.
- Even among parent users, strong opposition to teen use.

12th Graders’ Attitudes Regarding Marijuana Laws: What would you be most likely to do?

- Not use it even if it were legal and available
- Try it
- Use it more often than I do now

MJ Availability/Accessibility

- MM patients greater access to dispensaries and forms of use, more frequent and intensive use than non-patient marijuana users.
- Lack of understanding about age and possession limits.
- Medical marijuana programs vary in adherence to “good medical practice” with enrollment higher in “less medicalized” programs.
- No increase in perceived availability among youth.
Health Outcomes

- Increase in MJ dependent hospital discharges and poison center calls.
- Medical MJ patients reported reasons for MJ use as sleep, anxiety, pain.
- Persistent MJ use in young adulthood positively associated with generalized anxiety disorder, substance use (incl. alcohol and tobacco) disorders.

Other Drug Use

- Alcohol:
  - Evidence of both substitution and complementarity.
  - Concurrent use more common among recreational users and somewhat rare among medical users.
- Tobacco:
  - Teen smoking predicted later MJ use.
- Rx Opioids:
  - Trends towards less misuse of prescription opioids.

Social Outcomes

- Density of dispensaries related to higher violent and property crime, child neglect and abuse.
- Early adolescent use of MJ associated with lower education and economic outcomes.
- Driving/riding after MJ use common in underage MJ-using college students.
Percent of Students Reporting Daily Use of Marijuana, by Grade and Potency (%Δ-9 THC)

SOURCE: University of Michigan, 2013 Monitoring the Future Study; University of Mississippi Marijuana Project, NIDA 2013

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So What Does All Of This Mean to Healthcare Practitioners?

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NAS Report – released Jan 2017

PURPOSE: To provide a comprehensive review of the current evidence regarding the health effects of using cannabis and cannabis-derived products

Report made 4 recommendations.
1. Address Research Gaps

- Examine health effects of cannabis in at-risk or under-researched populations (e.g. youth, elderly, pregnant/breastfeeding women)
- Determine benefits & harms associated with understudied MJ products (e.g. edibles, topicals)
- Investigate economic impact of recreational/medical MJ use on health care systems, health insurance providers, & patients.

2. Improve Research Quality

- Develop minimum dataset for observational & clinical studies, standards for research methods & designs, guidelines for data collection methods
- Adapt existing research reporting standards to needs of MJ research
- Develop uniform terminology for clinical & epidemiological MJ research
- Develop standardized & evidence-based question banks for clinical research & public health surveillance tools

3. Improve Surveillance Capacity

- Develop question banks on beneficial & harmful effects of therapeutic & recreational MJ use & incorporate them into major public health surveys such as NHANES, NHIS, BRFSS, NSDUH, YRBS, NVSS, MEPS, NSFG.
- Strategies for surveillance of harmful effects of MJ for therapeutic use
- Develop novel diagnostic technologies for rapid, accurate, non-invasive assessment of MJ exposure & impairment.
4. Address Research Barriers

- Propose strategies for expanding access to research-grade MJ.
- Identify nontraditional funding sources & mechanisms to support comprehensive national MJ research agenda.

Physician Prescribing Background

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

440 pages | 6 x 9 | PAPERBACK

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana.
After careful consideration, the committee chose not to attempt to review basic, non-human research in order to attempt to bolster evidence for identified health outcomes from cannabis exposure.

Given the methodologic variation in the studies reviewed, as well as potential deficiencies in study design and execution, the committee focused its attention and energy on identifying high quality studies with the best information and lowest risk of bias as the way to ensure that report findings and conclusions were as informative and relevant as possible.

Exposure measurement is always an additional concern when evaluating comprehensive reviews of observational studies.

Assessment of cannabis exposure is particularly challenging because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific type of cannabis product used, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure.

Risk of poly substance use

The Federation of State Medical Boards (September 2016) recommendations set forth some basic ground rules for doctors who choose to prescribe or make a referral for medical marijuana:

• The doctor should adhere to current stands of practice and comply with state laws, rules and regulations, which may specify conditions for which a patient may qualify.

• The doctor’s office should not be located at a marijuana dispensary or cultivation center. The doctor should not receive financial compensation from or hold a financial interest in marijuana-related businesses or be affiliated with them in any way.

• The physician should not use marijuana either medically or recreationally while actively engaged in the practice of medicine.

GUIDELINES ON PRESCRIBING MARIJUANA

GUIDELINES ON PRESCRIBING MARIJUANA

GUIDELINES ON PRESCRIBING MARIJUANA

GUIDELINES ON PRESCRIBING MARIJUANA

Will I Get Arrested for Prescribing (Recommending) Medical Cannabinoids?

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Will I Get Arrested for Prescribing (Recommending) Medical Cannabinoids?
What Should A Prescriber Know About Medical Cannabinoids?

Terms

Pharmacokinetics – what the body does to a drug. Refers to the movement of a drug into, through, and out of the body.
ADME (Absorption, Distribution, Metabolism, and Elimination)
Absorption – after taking a drug, it must cross one or more biological membranes before it reaches the systemic circulation.
Exception: Drugs administered IV enter the systemic circulation directly – no absorption step.
Distribution – the passage of drug molecules from blood to tissues.
Metabolism – chemically changing drug components into metabolites.
Excretion – the passage of molecules from the blood to the outside of the body through urine, bile, or other routes.

Terms

Bioavailability - amount of drug absorbed compared to the drug dose.
Example: a fraction of the dose may be metabolized during the early passage through the gastrointestinal tract or liver.
Half Life - amount of time required for the concentration or amount of drug in the body to be reduced by 50%.
Cmax - peak concentration of drug.
Pharmacodynamics - the study of the action or effects of drugs on the body.
Psychoactive (Personal) vs Non-Psychoactive (Medical)

Cannabinoids

Delta-9-THC
“PSYCHOACTIVE”

CBD
“NOT PSYCHOACTIVE”

Are You Familiar With THC Medications You Can Prescribe?

Marinol (Dronabinol)

- Chemically as (6αR-trans)-6a,7,8,10a-tetrahydro-6,6,9-
  trimethyl-5-pentyl-6H-dibenzo[b,d]pyran-1-ol.
- Is synthetic delta-9-tetrahydrocannabinol (delta-9-THC)**
- Available in round soft gelation capsules in 2.5mg, 5mg, or
  10mg capsules
- Pharmacodynamics: primarily central sympathomimetic
  activity
- Onset: 0.5-1.0 hours
- Peak: 2-4 hours
- Duration: 4-6 hours with appetite stimulation lasting up to
  24 hours after administration
**Marinol (Dronabinol)**

**Pharmacokinetics**
- Absorption and Distribution: 93% absorbed after single dose but only 10-20% reaches systemic circulation, large volume (Vd) of distribution due to high lipid solubility.
- Metabolism: Undergoes first pass hepatic metabolism, yielding both active and inactive metabolites. Primary metabolite is 11-OH-delta-9-THC which concentrations peak at 0.5 to 4 hours after oral dosing; clearance average is 0.2L/kg but varies and declines over several days.
- Elimination: Initial half-life is 4 hours and terminal half-life is 25-36 hours due to large Vd. Marinol is excreted at low levels for prolonged periods of time. Excreted in feces and urine (low levels of Marinol detected in urine after 5 weeks).

**Syndros (Dronabinol) Oral Solution**
- FDA Approved in 1985
- Oral Solution 5mg/ml
- Syndros is a cannabinoid indicated in adults for the treatment of: anorexia associated with weight loss in patients with AIDS (1); nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
- Dosing: Calibrated oral syringe with 5mg Syndros max if more than 5mg necessary must give in divided doses with 6-8 ounces of water
- Updated 2016 Guidelines: Starting dose of 2.1mg orally twice daily, one hour before lunch and dinner.
- ADEs: Dizziness, Euphoria, Paranoid Reaction, Abnormal Thinking, Abdominal Pain, Nausea, and Vomiting
- FDA CenterWatch 2016

**Other THC Medications Being Considered for FDA Approval**
- Sativex (THC and CBD): Oral mucosal spray formulation used for the treatment of moderate to severe spasticity of MS
- Epidiolex (CBD): is plant-derived CBD, in development for the treatment of a number of rare pediatric epilepsy disorders.
So What Is All of the Controversy About Prescribing THC/CBD Medications?

The Use of Leaf Marijuana as a Medication !!!!!

Cannabis Plant Anatomy

- Cannabinoid Concentration
  - 30,000 cannabis preparations confiscated in the U.S. between 1980 and 1997 were
  - Average Concentrations
    - 3% THC
    - 0.3% CBD

- Influencing Factors
  - Plant sex, age/developmental stage, environment, genetic makeup
  - Medical species are grown to produce similar levels of THC and CBD
  - Sinsemilla is derived from the unpollinated female cannabis plant
    - preferred for its high THC content (up to 17% THC)
  - Concentrations of cannabinoids in the body (parent or metabolite) are
    dependent on use and dose
Classifying Marijuana

- Marijuana produces some **excitatory** effects but it is not generally regarded as a stimulant.
- Marijuana produces **sedative** effects, but a person faces no risk of slipping into a coma or dying.
- Marijuana produces mild **analgesic** effects (pain relief), but it is not related pharmacologically to opiates like drugs.
- Marijuana produces **hallucinations** at high doses, but its structure does not resemble LSD or any other drug formally categorized as hallucinogen.

Chemistry was established over 100 years ago by two chemists, the Smith Brothers.

50 cannabinoid-based compounds, with 4 major cannabinoids in the plant:

- 2 isomers, a trans-**delta-9-THC** and a delta-8-THC
- A cannabidiol (CBD) (the 2nd most abundant psychoactive ingredient after THC)
- A cannabinol is a decomposition product of THC that accumulates as cannabis samples age.

After ingestion, delta-9 is converted in the liver to **11-Hydroxy THC** which is equally as potent and active.

**Delta-9-tetrahydrocannabinol (THC)** is the active ingredient of marijuana

major metabolites OH-THC (inactive) and THC-COOH (carboxylic acid, inactive)

Levo is the more active isomer
Chemical constituents of Cannabis

Chemical classes
- Cannabinoids (66)
- Nitrogenous compounds (27)
- Amino acids (18)
- Proteins/enzymes (11)
- Sugars (34)
- Hydrocarbons (50)
- Simple alcohols (7)
- Simple aldehydes (12)
- Simple ketones (13)
- Simple acids (21)
- Fatty acids (22)
- Simple esters/lactones (13)
- Steroids (11)
- Terpenes (20)
- Non-cannabinoid phenols (25)
- Flavonoids (21)
- Vitamins (1)
- Pigments (2)
- Elements (9)

Total known compounds (483)

Endocannabinoid System

CB1 and CB2: presynaptic receptors
Depending on site, inhibit neurotransmitter release
(GABA, glutamate, 5HT, DA, ACh)

Sites of Action
*affects nearly every major organ system*

<table>
<thead>
<tr>
<th>CB1:</th>
<th>CB2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Immune cells (T cells, B cells, monocytes)</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Liver</td>
</tr>
<tr>
<td>Heart</td>
<td>Spleen</td>
</tr>
<tr>
<td>GI Tract</td>
<td>Tonsils</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Heart</td>
</tr>
<tr>
<td>Adipose</td>
<td>Liver</td>
</tr>
<tr>
<td>Muscle</td>
<td>Lungs</td>
</tr>
<tr>
<td>Reproductive organs</td>
<td>Other?</td>
</tr>
<tr>
<td>Other?</td>
<td>As-of yet unidentified receptors?</td>
</tr>
<tr>
<td>Activity on non-cannabinoid receptors?</td>
<td></td>
</tr>
</tbody>
</table>
The Ubiquitous CB1

- Endogenous CBs are a major class of neuromodulators, acting through receptors, CB1 and CB2
- CB1 receptors are primarily located on CNS neurons
  - Levels exceed those of nearly all neurotransmitter receptors
- Exogenous CBs exert their effects by driving this innate system, often mimicking and enhancing its natural functions
The Ubiquitous CB1

- The omnipresent central distribution of CB1, has led to the term, Omnineuromodulator, to describe CB action
- Therapeutic effects are primarily due to agonist action in brain regions that mediate nausea/vomiting, appetite, and neuropathic pain

Endocannabinoids are the body’s endogenous cannabinoids. “The Bliss Molecules”

Anandamide (Sanskrit ananda inner bliss) is one endocannabinoid. It is found in chocolate (though there is some controversy over whether the small quantity has any effect on the body). It is about as potent as THC.

Typical Marijuana Preparations

<table>
<thead>
<tr>
<th>No.</th>
<th>Form</th>
<th>Source</th>
<th>Methods of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Marijuana/Cannabis</td>
<td>Dried flowers, stems, leaves and hash</td>
<td>Washed by water</td>
</tr>
<tr>
<td>2</td>
<td>Hash</td>
<td>Fresh flowers and stalk</td>
<td>Mixed with food items and consumed orally</td>
</tr>
<tr>
<td>3</td>
<td>Hashish</td>
<td>Leaves, seeds, stems and flowers soaked in alcoholic solvent</td>
<td>Washed by water or consumed orally</td>
</tr>
</tbody>
</table>
Marijuana

- Cheaper and less potent substance.
- Prepared from the leaves and flowering tops of the plant.
- Average THC concentration in marijuana is 1-5%.
- THC Dose = 10-40 mg usually.
- <100 mg per cigarette.
- How do you dose this formulation?

Hashish

- Resin extracted from the flower clusters and top leaves of the hemp plant, Cannabis sativa and C. indica.
- Most potent grade of cannabis.
- Obtained from cultivated plants grown in hot, moist climates.
- Hash oil is an extract of hashish that can be smoked or added to the tobacco.
- Produces euphoria and exaggerations of sensations.
- [THC] = 8-12 % by weight.
- Hash oil [THC] = 25-60% by weight.

Cannabinoids

- **THC**
  - Psychoactive, euphoria, increased reaction time, loss of memory/cognitive functioning decreases, clearance half-life of less than 30 minutes and is not detectable in urine
- **CBN**
  - Pain relief, Anti-insomnia, Promotes growth of bone cells, Anti-bacterial, Anti-inflammatory, Anti-convulsive, Appetite stimulant
- **CBD**
  - May modify THC effects, inhibits conversion of THC to 11-OH-THC (CYP450), formation of CBD from THC does not occur by heat from smoking nor by human metabolism, blocks anxiety and psychological side effects produced by THC intake
- **THC-COOH**
  - Lipid soluble component (metabolite), can be stored in fat cells for weeks to months, found in blood and urine, typically appears in the urine within 60 minutes, but can take as long as 4 hours, presence of the major THC-COOH >LOQ indicates exposure to THC within 3 days after a single use, to approximately 30 days in heavy chronic users

THC: Pharmacodynamics

**Drug to Body**

- Causes disinhibition of dopamine (DA) neurons by presynaptic inhibition of GABA neurons in the VTA
- Causes euphoria and relaxation
- Feelings of well-being, grandiosity, and altered perception of passage of time
- Dose-dependent perceptual changes, disinhibition, impaired coordination, and memory impairment
- Hash (concentrated THC) may result in visual hallucinations, depersonalization, and fresh, psychotic episodes
THC: Pharmacodynamics

- a partial agonist at both CB1 & 2 receptors, has activity at non-CB receptors and other targets, and is responsible for the psychoactive effects of cannabis through its actions at the CB1 receptors.
- smoking route or by vaporization central nervous system and physiological effects occur within minutes
- The psychotropic effect or “high” occurs much more quickly by the smoking than by the oral route
- Physiological effects include rapid changes in heart rate and diastolic blood pressure, conjunctival suffusion, dry mouth and throat, vasodilatation, and decreased respiratory rate

THC: Pharmacokinetics

Body to Drug – Absorption

A. Inhalation/Smoking
- 90% of THC in blood circulates in plasma and rests in RBCs
- Delta-9-THC is detectable in plasma within seconds after the first puff
- Peak plasma concentration attained within 3 – 10 minutes
- Bioavailability varies according to depth of inhalation, puff duration, and breath-hold
- Systemic bioavailability is ~23 – 27% for heavy users and 10 – 14% for occasional users
- Maximum THC plasma concentration is observed 8 minutes after onset of smoking
- Delta-9-THC plasma concentration rapidly decreases to 1 – 4ng/mL within 3 – 4 hours

B. Oral Ingestion
- relatively slower systemic absorption: 1 to 2 hours but can be delayed by a few hours
- extensive liver metabolism reduces oral bioavailability of THC by 4 = 16%
- maximum THC plasma concentration 4.4011ng/mL for 20mg and 2.7 – 6.3ng/mL for 15mg
THC: Pharmacokinetics – Distribution

- Extensive tissue binding due to lipophilic nature of the THC
- Rapidly distributed into highly vascularized tissues and lipophilic tissues such as fat
- Slow redistribution due to its deep fat deposits
- Terminal phase is reached ~10 hours after intake

NOTE: This is why THC levels are maintained in the body for a long time following abuse! Ex) clinical study among 52 volunteers showed that THC-COOH was detectable in serum from 3.5 to 74.3 hours

THC: Pharmacokinetics – Metabolism

Active, Psychoactive component

Inactive; Diagnostic

Δ9THC → 11-OH-THC → THC-COOH

Peak 3-8 minutes
Peak 15-81 minutes
Peaks 81-240 minutes

*THC is metabolized in the liver by cytochrome P450s – 2C9, 2C19, and 3A

THC: Pharmacokinetics – Excretion/Elimination

>65% excreted in the feces (in the form of 11-OH-THC)
-20% excreted in urine
-80 - 90% of cannabis excreted within 5 days as hydroxylated and carboxylated metabolites
-Most metabolites form a conjugate with glucuronic acid to increase water solubility (THCCOOH is the primary glucuronide conjugate in urine)
-Low renal clearance due to reabsorption
-Clearance levels: 11.8±1.5 L/hr (women); and 14.9±3.1 L/hr for men
-Clearance for native cannabis users and 60 L/hr for regular users
-Half Life: Infrequent users: 1.3 days, frequent users: 3-5 days
Adverse Drug Effects of Leaf Marijuana

Psychological Effects

- Euphoria
- Relaxation
- Altered time and space perception
- Lack of concentration
- Impaired memory/learning
- Mood changes
- Disorientation
- Sense of well-being
- Drowsiness

Physiological effects

- Tachycardia
- Reddened conjunctiva
- Dry mouth and throat
- Increased appetite
- Vasodilation
- Bronchodilation
- Decreased respiratory rate
Duration of Effects on Driving

- Effects from smoking are felt within minutes
- Effects reach their peak in 10-30 minutes
- Most users experience a "high" that last about 2-3 hours
- Most behavioral and physiological effects last 3-6 hours after drug use
- Researchers have shown that some residual effects may last up to 24 hours
- Psychomotor impairment can persist after the perceived high has dissipated

Drug Interactions

- Marijuana combined with stimulants (cocaine, amphetamines, etc.) can lead to increased hypertension, tachycardia and possible cardiotoxicity
- Depressants (Benzodiazepines, barbiturates, muscle relaxants, etc.) can increase drowsiness and CNS depression
- Marijuana used in combination with ethanol leads to additive effects
- Marijuana and ethanol use makes the user more likely to be a traffic safety risk than when consumed alone

How much should a person use to get 25 mg of THC?

- 20% THC
- Net weight 1/8 oz or 3.5 gm
- Single serving 50 mg

http://bothcollective.com/page/6/?app-download=windowsphone
But Is THC Toxic??

• 2009 study from American Scientist on the relative toxicity of recreational drugs showed that using only 10 times the "effective" dose of alcohol could be fatal, whereas more than 1,000 times the effective dose of marijuana would have to be used to be possibly fatal.
• The toxic dose of THC in a 65kg adult would be 8.45kg.

But is THC Toxic??

• The tachycardia almost invariably produced in acute intoxication, combined with the sensory alterations and increased tremor commonly reported, probably contribute to the affective components of these reactions. CNS and respiratory depression are noted with high doses, which in severe overdose may be life-threatening (Rosencrantz, 1983). These effects are, of course, more dangerous to those with pre-existing cardiac irregularities. Because of the large effective to lethal dose ratio in humans (probably in excess of 1:1000 in non-tolerant users) the risk of experiencing severe toxic effects of cannabis is limited by the aversive psychotrophic effects of high doses, which usually lead to cessation of use before the onset of dangerous physical consequences.

Modifying Concentrations

• Why
  – Seeking better high
  – More THC and less CBD
    • CBD limits psychoactive effects of THC
    • terpenes, delay or modulate the onset of effects of cannabinoids
      – anti-inflammatory terpenes that protect the lungs from irritation
• What
  – Honey Oil, Wax, Hash Oil
• How
  – Using burning techniques and solvents to rid plant and plant resins of CBD
  – pure THC preparations may be the presence of residual solvents (e.g., ethanol) that are needed to solubilize the sticky pure THC
Evolving Cannabis Administration

• What?
  – New routes

• Why?
  – Provide more direct delivery

• Considerations:
  – Mathematical models have been developed to estimate the time of marijuana exposure within a 95% confidence interval based on blood concentrations
  – Marijuana has been shown to impair performance on driving simulator tasks and on open and closed driving courses for up to approximately 3 hours

Medical Marijuana Standards

What is in medical cannabis?

[Image of a medical marijuana standards chart]

[Image of a website link: www.fullspectrumlabs.com]
Recent Clinical Trials of Cannabinoids for the Treatment of CNS Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Target Symptoms</th>
<th>Therapeutic Cannabinoid</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Spasticity</td>
<td>Oral THC, CBD</td>
<td>In progress</td>
</tr>
<tr>
<td>Neurogenic pain</td>
<td></td>
<td>Sublingual THC, CBD</td>
<td>Phase II trial in progress</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
<td></td>
<td>Sublingual THC, CBD</td>
<td>Phase II trial in progress</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Dystonia</td>
<td>Nabilone</td>
<td>No effect</td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td>Nabilone</td>
<td>↓ Dystonia</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td>60-THC</td>
<td>No effect</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td>Sublingual THC, CBD</td>
<td>Phase III trial in progress</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>Pain</td>
<td>IM levonantradol</td>
<td>↓ pain, but less effective than existing therapies</td>
</tr>
</tbody>
</table>

CBD = cannabidiol
THC = tetrahydrocannabinol

Recent Clinical Trials of Cannabinoids for the Treatment of CNS Disorders (cont’d)

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<th>Therapeutic Cannabinoid</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury</td>
<td>Pain</td>
<td>Sublingual THC, CBD</td>
<td>Phase II trial in progress</td>
</tr>
<tr>
<td>All tract pain</td>
<td>Pain</td>
<td>THC</td>
<td>↓ Morphine requirement</td>
</tr>
<tr>
<td>Traumatic Brain Injury / Stroke</td>
<td>Neurodegeneration</td>
<td>5V dexanabinol (HU-211)</td>
<td>↓ Intracranial pressure, ↓ mortality, phase III trial in progress</td>
</tr>
<tr>
<td></td>
<td>Neurodegeneration</td>
<td>CBD</td>
<td>In progress</td>
</tr>
<tr>
<td>HIV wasting syndrome</td>
<td>Appetite loss, nausea</td>
<td>Smoked cannabis</td>
<td>In progress</td>
</tr>
<tr>
<td></td>
<td>Appetite loss, nausea</td>
<td>Dronabinol</td>
<td>↑ appetite, ↓ nausea</td>
</tr>
<tr>
<td>Tourette’s syndrome</td>
<td>Behavioural disorders</td>
<td>THC</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>

Croxford, JL. CNS Drugs 2003; 17(3)

Pharmacology

https://biomedical.net/wp-content/uploads/2014/05/tumblr_mmt475oMxO1s85ojqo1_500.png
Pharmacology

- **Marinol**
  - Reduction of nausea and vomiting in chemotherapy
  - Increase appetite in HIV-wasting disease
  - Potential New Indications
    - Reduction of spasticity, analgesia, agonist-replacement in cannabis dependency

  **Kinetic Profile after a single oral dose (10mg of THC)**
  - Mean peak conc found 1-2 hours post dose
    - THC: 3.8 ng/ml (1.1-12.7 ng/ml)
    - 11-OH-THC: 3.4 ng/ml (1.2-5.6 ng/ml)
    - THC-COOH: 26 ng/ml (14-46 ng/ml)


Pharmacology

- Cultivation methods have been developed to reproducibly produce plants with defined THC or CBD concentrations. **GW Pharmaceuticals** has produced two standardized extract preparations, *Tetranabinex®,* which is high in THC, and *Nabidiol®,* which is high in CBD. *Sativex®* contains equal proportions of *Tetranabinex®* and *Nabidiol®*, and, hence, almost equal amounts of THC and CBD.

Drug Interactions

• Stimulants
  – Cocaine, Amphetamines, etc
    • increased hypertension
    • tachycardia
    • cardiotoxicity.

• Depressants
  – Benzodiazepines, Barbiturates, Ethanol, Opioids, Antihistamines, muscle relaxants, etc.
    • increase drowsiness
    • CNS depression

• Alcohol
  • greater impairment
  • decreases in function
  • less likely to react appropriately
  • increased reaction times

But What About Cannabis Oil?

Cannabinoids for epilepsy: Cochrane Review

Objective

• the treatment of people with epilepsy

Inclusion

• 4 randomized reports including a total of 48 patients, each of which used cannabidiol as the treatment agent

Results

• No reliable conclusions on efficacy but 200 – 300 mg daily of cannabidiol was safely administered to a small number of patients for a short period of time

Gloss D, Vickrey B. Cochrane Database of Systematic Reviews 2012, Issue 6

American Academy of Neurology

Conclude that “for patients with epilepsy, data are insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency.”

There is NOT sufficient evidence to prescribe CBD or recommend self-treatment with smoked marijuana.

Why are parents using cannabis?

Anecdotal cases of children successfully treated with medical marijuana (CBD enriched preparations).

Prominent internet and national media attention.

Belief that treatments derived from natural products are safer or more effective is common and potentially dangerous.

Charlotte

1. Charlotte is a little girl from Colorado with Dravet syndrome.
2. Frequent bouts of febrile and afebrile status epilepticus.
3. Failed multiple medications: levetiracetam, oxcarbazepine, topiramate, zonisamide, valproate, clobazam, clonazepam, and diazepam.
4. At 5 years of age, had significant cognitive and motor delays, required a feeding tube, and needed full assistance with activities of daily living.
5. 50 generalized tonic-clonic seizures per day.

Charlotte's Web

A high concentration CBD/THC strain of cannabis produced by a medical marijuana group in Colorado.

Charlotte's Web, supplied by Realm of Caring, is based out of Colorado and parents and families are moving there to attempt treatment.

Parents began giving Charlotte low doses of plant extract and slowly increased the dose over time.

Month 3: >90% reduction in generalized tonic-clonic seizures and weaned from other AEDs.

Month 20: 2-3 nocturnal generalized tonic-clonic seizures per month, feeds and drinks by mouth, behaviors have improved, walking and talking.


Parent Survey of Cannabidiol-Enriched Cannabis Use

- Stanford University
- Survey of 24 questions
- Diagnosis and seizure types
- Parental-reported effect of cannabidiol-enriched cannabis on the child's seizure frequency and side effects
- Administered to Facebook group of 150 parents supporting the use of cannabidiol-enriched cannabis to treat children with treatment-resistant epilepsy

• Age range: 2 – 16 years old
• Seizure Types:
  • Dravet syndrome = 13
  • Doose syndrome = 4
  • Lennox-Gastaut syndrome = 1
  • Idiopathic early-onset epilepsy = 1
• 18/19 patients experienced treatment resistant epilepsy for more than 3 years before trying CBD
• Unsuccessful trials included other antiepileptics
• Seizure frequency pre-CBD 1 per week to 250 per day

Population Demographics

- Dose Ranges: 0.5 mg/kg/day to 28.6 mg/kg/day
- THC: 0 to 0.8 mg/kg/day

Intervention

- 16/19 (84%) reported a reduction in their child's seizure frequency
- 2/16 reported to be seizure free
- 8/16 reported a greater than 80% reduction in seizure frequency
- 3/16 reported a greater than 50% reduction in seizure frequency
- 12/19 patients weaned their child from another AED

Other effects:

- Better mood (15/19, 79%)
- Increased alertness (14/19, 74%)
- Better sleep (13/19, 68%)
- Drowsiness (7/19, 37%)
- Fatigue (3/19, 16%)

Results

- Child's seizure frequency
  • 18/19 reported to be seizure free
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  • Better sleep (13/19, 68%)
  • Drowsiness (7/19, 37%)
  • Fatigue (3/19, 16%)
Cannabidiol (CBD) versus THC

- THC and CBD molecules present in largest amounts in cannabis. Most recognized and studied.
- Classed as phytocannabinoids (as opposed to endocannabinoids and cannabinoids that are manufactured artificially), both CBD and THC interact with specific cells in our brains.
- THC – Psychoactive cannabinoid, THC is responsible for the “high” from smoking marijuana so production and usage are strictly regulated (even in WA, OR, CO and AK).
- CBD – naturally occurring cannabinoid, and the second most abundant molecule in Cannabis plant.
- CBD is legal and safe to consume, yet has long been in the shadow of THC.

CBD: Pharmacodynamics

- Lacks detectable psychoactivity and does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations.
- Affects the activity of a significant number of other targets including ion channels, receptors, and enzymes.
- May have anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects.
CBD: Pharmacokinetics

Absorption
- Oral Bioavailability: 13–19% due to marked first-pass effect
- IV preferable

Distribution
- Like THC, it is highly lipophilic - rapidly distributed and easily passes the blood brain barrier (BBB)

CBD: Pharmacokinetics

Metabolism
- undergoes multiple hydroxylations, oxidations to carboxylic acids, beta-oxidation, conjugation, and epoxidation

Excretion / Elimination
- prolonged due to lipophilicity (stays in system longer)
- excreted from urine, both in free state and as its glucuronide
- ****Half life = 9 hours

Cannabidiol (CBD) Absorption

- Smoked/inhaled
  - Average Bioavailability: 31.13%
  - Intravenous Administration (up to 72 hours post dosing)
    - Plasma Clearance: 960-1560 ml/min
- Oral Application (40mg of CBD)
  - Blood Concentration: 1.1–11 mg/ml
  - 1 h after dose chocolate cookies
  - CBD concentrations of 0.30–2.57 ng/ml
  - 1 h after oral intake of 5.4 mg of CBD , remained detectable for 3–4 h after
- Following administration of equivalent amounts of THC and CBD, lower plasma concentrations of CBD were always observed
- Studies suggest:
  - Identification and quantification of CBD could be an additional proof of cannabis exposure
  - Could improve interpretation of THC effects considering the potential ability of CBD to modify THC effects

Hueskes, M. 2009, Human Cannabidiol Pharmacokinetics, Institute of Health Sciences, 302, p. 170-180
### Cannabidiol (CBD) Metabolism

- Significant first-pass effect
  - Unlike THC, a large proportion is excreted unchanged in the feces
- Co-administration of CBD with THC did not significantly impact THC or THC metabolite kinetics, including:
  - the total clearance,
  - volume of distribution
  - terminal elimination half-lives
- CBD only partially inhibited the hydroxylation of THC to 11-OH-THC catalyzed by CYP 2C
  - Study based on concentration vs time curves, ratios of max. average concentrations, and AUC values of:
    - 11-OH-THC/THC
    - THC-COOH/THC
    - THC-COOH/11-OH-THC

### Cannabis Elimination

- 5 days post dose: 80–90% of THC is excreted
  - 65% is excreted in the feces
- Primary fecal metabolite: 11-OH-THC
- 20% being eliminated in the urine
  - primary urinary metabolite: acid-linked THC-COOH glucuronide conjugate
  - Urine concentration drops rapidly until reaching a concentration of 20–50 ng/ml, then begins decrease at a much slower rate
- Long terminal half-life of THC in plasma
  - Reported to be greater than 4.1 d in chronic cannabis users
- Mean plasma THC-COOH elimination half-lives:
  - Frequent Users: 5.2±0.8
  - Infrequent Users: 6.2±6.7d
- However, no significant pharmacokinetic differences between chronic and occasional users have been substantiated

### Pharmacodynamics of Other Cannabinoids

- Δ8-THC (an isomer of Δ9-THC): partial agonist at both CB receptors and shares relatively similar efficacy and potency with Δ9-THC. More potent anti-emetic than Δ9-THC.
- Cannabimol (a product of Δ9-THC oxidation): has 1/10 of the activity of Δ9-THC. Appears to have some possible immunosuppressive properties.
- Cannabigerol: partial CB1/CB2 receptor agonist. May have some anti-inflammatory and analgesic properties. It may also block 5-HT1A receptors and act as an α2-adrenoceptor agonist.
- Tetrahydrocannabivarin: acts as a CB1 receptor antagonist and CB2 receptor partial agonist. It may have anti-epileptiform/anti-convulsant properties.
Pharmacology (2015)

Cultivation methods have been developed to reproducibly produce plants with defined THC or CBD concentrations. GW Pharmaceuticals has produced two standardized extract preparations, Tetranabinex®, which is high in THC, and Nabidiolex®, which is high in CBD. Sativex® contains equal proportions of Tetranabinex® and Nabidiolex®, and, hence, almost equal amounts of THC and CBD.

Different Routes of Administration and the Effect on Plasma Concentrations

A. Intravenous Route
B. Oral Route
C. Vaporization/Inhalation
D. Dabbing

Intravenous Route: Research primarily
How Cannabis Causes Paranoia: Using the Intravenous Administration of Δ⁹-Tetrahydrocannabinol (THC) to Identify Key Cognitive Mechanisms Leading to Paranoia

Edibles

- Gelatin capsules, glycocholate, sesame oil: improved bioavailability
  - Considerable variations in peak concentrations and rates of absorption
    - Occurred even when administered in the same vehicle more than once
  - Sesame Oil based Administration
    - Oral THC bioavailability: 10-20%
      - Men ingested 20 mg
      - Women ingested 15 mg
    - Plasma Peak at 4-6 hours, but were considered overestimated because of radioactive labeling not being subject to only THC and extending to its metabolites

Oral Administration – Clinical Study Example

- Ingestion of brownies containing a low dose of Δ9-THC (9 mg Δ9-THC/brownie) → mean peak plasma Δ9-THC levels of 5 ng/mL
- Ingestion of brownies containing a high dose of Δ9-THC (~13 mg Δ9-THC/brownie) → mean peak plasma Δ9-THC levels of 6 to 9 ng/mL

NOTE: only 10 - 20% of the administered dose enters blood stream due to extensive first pass effect.
### Inhalation and Smoking

- **Absorption**
  - Rapid and efficient delivery from lungs to brain
  - Exposure of drug to the CNS (mainly via lungs)
  - Slightly lower peak concentrations than IV administered THC
  - Bioavailability: 2-56%

- **Due to variability in smoking dynamics/ability**
  - Number, duration, spacing between puffs, hold time, inhalation volume, smoking topography, and expectoration

- **Formation of 11-OH-THC and THC-COOH occurred later and with much lower concentrations**

- **Technique and Study Design**
  - THC disposition followed for 7 days after smoking a single cannabis cigarette containing 1.75% or 3.55% THC
  - Immediately following first cigarette puff
    - Mean THC conc 1.75% (16 mg): 7.0 ± 8.1 ng/ml
    - Mean THC conc 3.55% (34 mg): 18.1 ± 12.0 ng/ml
  - Peak THC conc 1.75% (16 mg): 84.3 ng/ml (range 50-129)
  - Peak THC conc 3.55% (34 mg): 162.2 ng/ml (range 76-267)
  - Within 2 hours of cessation all levels fell below 5 ng/ml
  - Dose detection (level above 0.5 ng/ml)
    - 1.75% (16 mg): 3 to 12 hours
    - 3.55% (34 mg): 6 to 27 hours

- **Thoughts on safety/delivery**
  - All subjects using hashish-based cigarettes experienced higher THC concentrations in plasma
  - THC concentrations typically peak during the act of smoking, while peak 11-OH THC concentrations occur approximately 9-23 minutes after the start of smoking

### Vaping

- **Absorption**
  - Vapers report the onset of effects more rapidly with pure THC (mean 2.5 min) than herbal cannabis (mean 6.5 min)
  - Vaping resulted in higher plasma concentrations of THC compared to smoked marijuana at 30 and 60 min at each strength

- **Technique**
  - Heating cannabis to a temperature between 180 and 200°C, it is possible to vaporize the cannabinoids that reside on the trichomes on the surface of cannabis flowers and leaves, while avoiding combustion

- **Thought on safety/delivery**
  - Volatilizes components such as THC, CBD, and terpenes, but with significant reduction of pyrolytic byproducts
  - Release substantial
  - Amounts of the THC while producing no measurable amounts of the benzene, toluene, and naphthalene, which are generated when marijuana is smoked
  - Vapors to inhale some form of pure THC (likely dissolved in alcohol or another solvent)

### Vaporization-clinical study example

**32 Adult cannabis smokers drank placebo or low-dose alcohol to min before inhaling 50 mg placebo, low-dose (1.56%) THC, or high-dose (6.75%) THC vaporized cannabis.**

**Blood and plasma concentrations were obtained before and up to 8.3h after ingestion.**


http://www.clinchem.org.proxy-remote.galib.uga.edu/content/61/6/585.full
Dabbing

- Inhalation of a concentrated tetrahydrocannabinol (THC) product created through butane extraction.
- Blasting
  - Pass butane through a steel or glass tube packed with dried cannabis trimmings
  - THC and other hydrophobic compounds in the plant's trichomes dissolve into the butane
  - Butane-THC solution leaves the tube through filter and is collected in a dish or tray
  - Butane evaporates and leaves resins that can have THC concentration up to 80%

So What Is the Problem With Medical Marijuana For Prescribers?
New Types of Concentrates

• Kief
• Water Hash
• CO2 Oil
• Butane Hash Oil (BHO)
• Rosin

Concentration: Kief

• Also known as dry siev (sometimes "dry sift") hash, kief is the simplest of concentrates. Kief is composed of the trichomes (the crystalline structures coating the outside surface of the flowers) broken away from the dried plant material, usually via specialized filtering screens and a little elbow grease. Kief is generally considered a lower-quality extract, but some top-flight extractors can produce an extremely clean and flavorful product using this method. THC content can range from 20 percent to 60 percent. This process at its highest level yields nothing but the largest, most perfect trichome gland heads and none of the gland stems, plant matter, etc. that generally clouds the quicker, lower-quality kief extractions. While it is certainly available in Colorado dispensaries, compared to three years ago, it is much harder to find because of the prevalence of solvent extracts and the low return that it provides to commercial growers.

Concentrates of Water Hash

• There are various techniques used in the production of water hash, and the resulting products have many forms (bubble hash, solventless wax, ice wax, among others). The basic principle is this: plant material (either dry or fresh-frozen generally) is mixed with cold water and ice, then agitated manually or mechanically in order to break off the now-brittle trichome heads. This solution is then filtered through specifically-sized screens to remove anything undesirable, leaving behind a relatively pure finished product that typically tests between 50 percent and 80 percent THC. The most common way that water hash is extracted is using a series of microscreen fabric bags (generally referred to as "bubble bags") which remove various grades of product according to the size of particles they allow through.
Concentrates of CO2 Oil

- This variety of extract is created using carbon dioxide compressed at high pressures until it becomes what is known as a "supercritical fluid," which then is able to strip the essential oils of the cannabis plant much like hydrocarbon solvents. CO2 oil is generally a loose, orange-tinted oil that can be either clear or opaque depending upon the finishing processes used after extraction, and THC content tests between 50 percent and 75 percent. The appeal of this method for many is that it is non-flammable and contains no chemical solvents. The machines required to do CO2 extractions at any kind of commercial scale can cost hundreds of thousands of dollars.

Concentrates of Butane Hash Oil (BHO)

- Perhaps the most common type of extract on the market, BHO has a variety of names (wax, shatter, crumble, oil, etc., honeycomb, moon rock, nectar, etc.) but like water hash, the basic principles of extraction are the same across all of them, with the variations in appearance and texture mostly coming in finishing processes. To make a butane concentrate, butane is pressurized in a vessel and washed over plant material (usually dry, but sometimes fresh-frozen — more on that below), then the resulting solution is collected. The hashmaker must remove any residual solvent from this solution, so the next step generally is applying heat (butane has a low boiling point) and vacuum (which lowers the boiling point further) in order to make this process easier and faster while retaining the highest amount of flavorful terpenes and cannabinoids in the finished product. BHO generally tests between 60 percent and 90 percent THC, making it perhaps the strongest concentrate on the mainstream market.

Concentrates of Rosin

- The newest and hottest type of extract on the scene right now, rosin is extracted from either dried buds, trim, or lower-grade water hash/kief. What is unique about rosin is that it can be made with nothing more than a standard hair straightener, parchment paper and some hand-applied pressure. When the material is smashed and heated quickly between the parchment sheets, it extrudes some of the essential oils present in the plant, resulting in a golden shatter or oil-like extract that looks similar to pressed high-quality water hash or even solvent-extracted shatter. Rosin is a fairly recent development, so its availability in dispensaries is still somewhat limited, as is data about its potency; but early reports on some rosin extracts have showed numbers between 50 percent and 70 percent THC, similar to that of high-quality water hash.
Inhalation and Smoking

- Absorption
  - Rapid and efficient delivery from lungs to brain
  - Exposing drug effects to CNS (abuse potential)
  - Slightly lower peak concentrations that IV administered THC
  - Bioavailability: 2-56%
    - Due to variability in smoking dynamics/ability
      - Number, duration, spacing between puffs, hold time, inhalation volume, smoking topography, and expectation
  - Formation of 11-OH-THC and THC-COOH occurred later and with much lower concentrations

Colorado Marijuana Analysis – March 2015

- Denver lab analyzed more than 600 samples of bud provided by certified growers and sellers
- Average THC level was 18.7%, and some retail pot contained 30+% THC or more
- Little or no cannabidiol (CBD) — the average CBD amount: 0.11%
  - Recall: CBD lacks detectable psychoactivity and instead has anti-inflammatory, analgesic, anti-nausea, anti-psychotic, anti-convulsive, and anti-epileptiform effects - the "medical" in medical marijuana.

Other Administrations

- Routes
  - Oromucosal
    - Sativex® is administered sublingually to avoid first-pass metabolism by the liver. Sativex® is approved in Canada for the treatment of neuropathic pain associated with multiple sclerosis, and in three European countries for a number of indications.
  - Rectal
    - THC-hemisuccinate provided the highest bioavailability of 13.5% (Marinol® suppository)
    - Bioavailability of the rectal route was approximately twice that of the oral route
    - THC did not accumulate in the blood following 10–15 mg daily doses
    - Administration of 2.5–5 mg of THC produced maximum plasma concentrations of 1.1–4.1 ng/ml within 3–4 h.
  - Transdermal
    - Mean steady-state plasma concentration of Δ9-THC was 4.4 ng/ml within 1.4 h, and was maintained for at least 48 h.
    - Permeabilities of CBD and CBN were found to be 10-fold higher than for Δ9-THC
    - Low abuse potential due to slow delivery of THC to the brain
  - Intravenous
    - THC produced schizophrenia-like positive and negative symptoms and euphoria, and altered aspects of cognitive function
      - Acute paranoia, psychosis, hypotension, withdrawal, behavior and cognitive defects (endogenous psychosis)
Impact of Addiction

MARIJUANA:

2 year history of daily abuse

underside surface view of prefrontal and temporal lobe activity

© 2006 Amen Clinics Inc

Withdrawal According to the DSM 5

- A. Cessation of cannabis use that has been heavy and prolonged
- B. 3 or more of the following develop within several days after Criterion A
  - 1. Irritability, anger or aggression
  - 2. Nervousness or anxiety
  - 3. Sleep difficulty (insomnia)
  - 4. Decreased appetite or weight loss
  - 5. Restlessness
  - 6. Depressed mood
  - 7. Physical symptoms causing significant discomfort: must report at least one of the following: stomach pain, shakiness/tremors, sweating, fever, chills, headache

Questions???????