Cannabis: The Good, The Bad & The “Mad”

By:
Dr. Shahla Modir, M.D.
American Board of Psychiatry and Neurology:
Addiction Psychiatry & General Psychiatry
Question 1

How many states have enacted laws to legalize medical marijuana?

A. 13
B. 29
C. 32
D. 24
Question 2

What are the following common uses of medical marijuana?

A. Spasticity
B. Nausea
C. Peripheral Neuropathy
D. Cachexia
E. All of the above
Results

Spasticity 0%  Nausea 0%  Peripheral Neuropathy 0%  Cachexia 0%  All of the above 0%
Medical Marijuana’s safety profile is the same in adolescents as it is in adults?

1. True
2. False
There are 3 drugs derived from the plant:

- **Marijuana** - refers to leaves/stems (THC 0.5%-5%) & flowers (sinsemilla THC 7-14%) smoked as reefers, joints, roach, etc.
- **Hashish** - potent resinous substance from dried plant usually smoked in pipes; THC 2%-8%
- **Hash oil** - very potent, viscous liquid extract usually dropped onto normal cigarettes; THC 15%-50%
- Plant contains **400 chemicals** and over 60 cannabinoids. The smoke contains more than **2000 chemicals**.
- **Delta 9 THC** isolated in 1965: is the chemical responsible for producing the psychoactive effect.
- Others such as cannabidiol and cannabinol may modify the effects of THC.
Delta 9 THC
Distribution of Receptor Sites Radiolabeled CP-55,940

CB1 Receptors - 1988
- Hippocampus – Memory and Learning
- Amygdala – Novelty, Emotion, Appetites
- Basal Ganglia – Motor
- Cerebellum – Real Time Coordination, Selective Attention and Time Sense
- Nucleus Accumbens - Reward Mechanism (Addiction)
- Cortex (Anterior > Posterior) – Frontal Lobe Executive Functions

CB2 Receptors - 1993
- Macrophages
- Spleen, Intestines
Endogenous Cannabinoids

- Anandamide (arachidonolylethanolamide, AEA, or AnNH)
- 2-AG (2-arachidonylglycerol)
- 2-AGE (Noladin ether, or 2-arachidonyl glyceryl ether)
Evolutionary Perspective

Anandamide and receptor sites are present in all mammals

Anandamide and receptor sites are also present in:

birds, amphibians, fish, sea urchins, leeches, mussels, and most primitive animal with a nerve network, the Hydra
Neurotransmitter vs. Neuromodulator

1.) The role of our endocannabinoid system is largely to regulate activity of other neurotransmitters

2.) "There is barely a physiological system in which endocannabinoids are not involved. Hence its importance is far beyond that of THC… “
Amygdalar Endocannabinoid Effects on Appetite and Bonding

- Cannabinoid stimulation increases appetite and blockers decrease appetite
- Clinical trial of 20 mg of the CB1 antagonist rimonabant (Acomplia, from Sanofi-Synthelabo) showed an average 20 pound weight loss (and a positive impact on smoking cessation)
- The cannabinoid blocker SR141716A given to rat pups within 24 hours of birth stops suckling and causes death in 4-8 days
Effects of Cannabinoids

Cannabinoid Agonists
- Reduce spontaneous activity – catalepsy (Basal Ganglia)
- Incoordination

Driving Research:
- Slowed reaction time and diminished reflexes not as severe as alcohol; however synergistic with alcohol

CNS Effects: Effects last 1-4 hours (depends on tolerance/ptcy/route of administration)
- Alteration in short term memory, sense of time, sensory perception, attention span
- Decreased psychomotor control
- Mild euphoria, relaxation/anxiety, panic, paranoia
Medical Marijuana

- **1937** Medicinal use was abolished by the MJ Tax Act in California
- **1970** Controlled Substance Act
  - Marijuana classified Schedule 1 drug
  - Reduced the research possibilities for medicinal marijuana
- **1999** the Institute of Medicine determined cannabinoids have therapeutic value, but route other than smoking should be used
- **1996** California, passed the Compassionate Use Act
- **2003** The Medical MJ program was established in CA
  - System in CA is highly abused and “defacto legalization”
  - No regulation of conditions for which it is prescribed: any condition
  - There are no controls over amount given/I.D. cards are not mandatory
  - THC: uncertain potency/consistency/pestacides/microbes
  - No taxation but de facto legalization
  - Not a Schedule II drug and only a note is written; poor verification
Pending Legislation to Legalize Marijuana

- In 2014: **3 states** passed legislation
  - Maryland
  - Minnesota
  - New York
- In 2014: **15 states** failed legislation
- Currently, **24 states including Washington DC** have enacted laws to legalize medical marijuana
Routes of Administration

- **Smoked**: typical joint 0.5 mg-1 gram
- Delivering 20-70% THC within 14 sec
- Only need 2-3 mg THC
- **Oral**: tinctures, marinol, hash oil, baked goods, lollipops: slow and erratic but prolonged
- **Vaporizers**: deliver THC to smoked without burning the cannabis leading to less smoke related adverse events
- **Sublingual delivery**: Whole cannabis plant extract: use metered spray device delivering measured doses of THC (2.7 mg) and Cannabidiol (2.5 mg)-undergoing trials US but licensed elsewhere for cancer pain/MS as nabiximols “Sativex”
Marinol/Medical MJ

• In 1985 the synthetic THC drug Marinol® was approved to treat nausea and vomiting in Cancer patients.
• In 1992 Marinol was approved for the treatment of appetite loss and subsequent severe anorexia in AIDS patients.
• In 1960 the average potency of smoked marijuana was around 1-2%,
• Currently the THC potency average is around 6%-10%
• Marinol ® has controlled doses at 2.5, 5, and 10 mg
• Newer drugs include: Sativex
• Medical MJ in California is not regulated for THC, pesticides, or micro-organisms
Therapeutic Potential of Cannabinoids
“The Good”

• Antipyretic
• Bronchodilator
• Anticonvulsant
• Muscle relaxant
• Hypnotic
• Analgesic
• Antiemetic
• Appetite stimulant
Medical MJ and Pain

- 9 randomized “quality” studies done to evaluate effect of marijuana on pain

- Single dose studies: compared oral synthetic THC to codeine or placebo
  - Oral cannabinoids THC 10 mg outperformed placebo and analgesically equivalent to codeine 60 mg
  - Higher doses of THC 20 mg were comparable to codeine 120 mg but more adverse effects: sedation
Studies on Pain and MJ

• Series of clinical trials: CA Center for Medicinal Cannabis Research
• Study of HIV peripheral neuropathy:
  Pts allowed to continue pain regimes and either:
  -Added Smoked THC 1%-8% potency: smoked THC reaches brain immediately and peak concentration is 10 min
  -Added cigarettes with THC removed
Neuropathy and MJ

• Results:
  – Cannabis significantly reduced pain intensity with patients reporting 34%-40% reduction compared to 17%-20% placebo
  – 30% reduction in pain is associated with improved quality of life in studies
  – NNT to achieve this 30%=3.5-4.5 a number achieved by standard non-opioid analgesics
  – Medium dose 3.5% were as effective as high dose 7.5%

Fourth study: examined dose response for pain relief in an experimental model where capsaicin was intradermally injected in healthy volunteers.

- Low dose 2% THC had no effect.
- High dose 8% associated with increased pain.
- Medium dose 4% provided significant analgesia.

Oral Preparations for Pain

Marinol: Synthetic THC

• Absorption from gut slower to delay peak effect compared to smoking: peak concentration from 1-6 hours after ingestion with a magnitude 10% of that achieved from smoking

• Summary of evidence for neuropathic pain and spasticity associated with Multiple Sclerosis:
  – Marinol reduces pain significantly compared to placebo (50 % reduction in pain compared to 30 % with placebo)

Sativex

- Sativex is sold in Europe, Canada and Mexico to treat muscle spasticity/pain caused by multiple sclerosis. 1:1 combination of THC and CBD in a metered spray
- The spray is not currently approved for use in the U.S. for any condition.
- FDA “Fast Tracked Sativex” last year and currently studies are in Phase III clinical trials.
- A study of Sativex in 2012 on cancer pain non-responsive to other treatments found:
  - 26% improvement in pain among cancer patients who received a low dosage of nabiximols.
  - Patients receiving low and medium doses of nabiximols slept better.
  - No significant improvement in pain in a high dosage group.
  - Side effects included nausea and loss of cognitive function.

- In regard to Sativex and spasticity, recent meta-analysis combining 3 trials in over 600 patients noted the mean intensity of patient rated spasticity was significantly reduced compared to placebo
  - The proportion of responders (ie 30% reduction) was also significantly greater with about 37% on sativex compared to 26% on placebo
  - Those reporting relief of spasticity seemed to maintain their gains over 1 year follow up
Anorexia/Nausea

- Meta-analysis indicates **marinol and nabilone** are more effective than **metoclopramide and neuroleptics** for control of acute and delayed nausea/emesis due to cancer chemotherapy.

There are no head to head comparing 5 HT3 receptor or Substance P/NK-1 receptors antagonists

- Trials in AIDS patients with severe weight loss showed that **dronabinol 5 mg per day significantly outperformed placebo** for short term appetite enhancement (38% vs. 8% at 6 weeks) and these effects persisted for up to 12 months
Cannabidiol and Epilepsy

Cannabidiol is the major non-psychoactive component of *C. Sativa*.

Little evidence is available to prove or disprove the efficacy and safety of CBD in patients with epilepsy.

Gloss and Vickrey conducted a Cochrane systemic review of CBD and epilepsy: 4 randomized controlled studies with total number of subjects =48.

There were several limitations to all of these studies.

The studies did report NO meaningful changes in seizure frequency.

Cunha et al reported a 2 phase pilot of CBD vs placebo in normal volunteers and pts with refractory epilepsy on AEDs:

Phase one normal volunteers CBD or placebo at 3 mg/kg x 30 days to establish safety and tolerability.

Phase 2: Double blinded in 15 pts with TR-epilepsy receiving 200-300 mg CBD or placebo per day x 135 days.

- All subjects tolerated CBD well.
- 4/8 CBD arm almost seizure free for duration of study.
- 3/8 CBD arm had a partial reduction and 1/8 CBD arm had no response.
- 7 pts in placebo arm: seizure frequency unchanged in 6 and 1 improvement.
American Academy of Neurology released guidelines 2014 on efficacy and safety Medical MJ for selected Neurological disorders: examine 1729 abstracts and rigorous criteria for inclusion: only 34 studies met criteria

- **Multiple Sclerosis**: Oral cannabis extract (OCE) is effective and nabiximols and THC probably effective at reducing patient centered measures; at 1 year OCE and THC are effective for both patient and objective measures.

- **Central Pain**: OCE is effective; THC and nabiximole probably effective.
Summary of the AAN Guidelines

- **Urinary dysfunction**: nabiximols is probably effective for reducing # bladder voids per day’ THC and OCE ineffective for bladder complaints
- **Tremor**: THC and OCE likely ineffective; nabiximol possibly ineffective
- **Huntington’s/Tourette’s/Cervical Dystonia**: likely ineffective; insufficient data for all to draw conclusions
- **Leva dopa induced dyskinesia’s**: OCE ineffective
“The Bad”
Marijuana’s Impact on the Frontal and Prefrontal Cortex: “The Bad”

- Decreased Blood Flow and Glucose Metabolism
- Decreased EEG Energy
- Neuropsychological Impairment
  - Diminished Executive Functions
  - Temporal Disorganization (Altered Perception of Time)
  - Impaired Planning
  - Altered Self-Awareness
Endocannabinoids in the Nucleus Accumbens

• Cannabinoid agonists increase the efflux of dopamine seen with other drugs of addiction and a cannabinoid blocker will “block” this effect
• NA plasticity in response to endocannabinoid induced dopamine increase
• Infusion of cannabinoid blocker leads to withdrawal symptoms after 8 days of THC administration
• Increase in dopamine levels is blocked by naloxone
• Animals will self administer THC : monkeys, rats, rabbits
Neuroanatomy of Addiction
Addiction Circuits

- The brain’s sensation of “reward” is signalled in the NA.
- Activated by pleasureable events, relationships, food.
- Hijacked by drugs and alcohol to simulate pleasureable events.
Rates of Cannabis Dependence

• Most common illicit drug used: In the US, 42% of persons over 12 have used MJ at least once

• 11.5% have used in the past 1 year and 1.8% meet criteria for cannabis use disorder

• 9% for anyone 18 years and older who ever experiments and 25%-50% of daily users become dependent

  - 3 times more likely to lead to dependency for those who first smoke before 18 years old with a dependency rate near 17% within 2 years of smoking

• Between 2007-2010, past month use among youth aged 12-17 increased from 6.7% to 7.4 % with a decrease in perceived risk leading to 6,600 new users of MJ every day in the U.S. 1 in 6 adolescents
A problematic pattern of using alcohol or another substance resulting in impairment in daily life or noticeable distress. The person must have at least two of the following for a given substance within the same 12-month period:

- Worrying about cutting down or stopping; or unsuccessful efforts to control use.
- Spending a large amount of time using a substance, recovering from it, or doing whatever is needed to obtain it.
- Common use of a substance resulting in (1) failure to take care of things at home, work, school (or to fulfill other obligations); and/or (2) giving up once-enjoyed recreational activities or hobbies.
Substance Use Disorder: DSM V Criteria

• Craving, a strong desire to use alcohol or another substance.
• Continuing the use of a substance despite problems caused or worsened by it — (1) in areas of mental (e.g., blackouts, anxiety) or physical health; or (2) in relationships (e.g., using a substance despite people’s objections or it causing fights or arguments).
• Recurrent alcohol/substance use in a dangerous situation (such as driving or operating machinery).
• Building up “tolerance” as defined by either needing to use noticeably larger amounts over time to get the desired effect or noticing less of an effect over time after repeated use of the same amount.
• Experiencing withdrawal symptoms (e.g., anxiety, irritability, fatigue, nausea/vomiting, hand tremor or seizure in the case of alcohol) after stopping use.
Severity and Specifiers

Severity is ranges from mild to severe based on the number of symptoms:

- **Mild**: two to three symptoms
- **Moderate**: four to five
- **Severe**: six or more

Course Specifiers:

- “in early remission”
- “in sustained remission”
- “on maintenance therapy”
- “in a controlled environment”
Rising strength of Cannabis contributes to addictive properties

- Skunk, or sinsemilla, has a huge share of the market and is squeezing out other types of cannabis
- Cannabis resin now accounts for 20 percent of use, compared with 60-70 per cent in 2002
- “Traditional” herbal cannabis now accounts for only 5 per cent, compared with 15 per cent six years ago
- The amount of THC in skunk has doubled in the last 10 years

David Potter et al, 2008
High Risk Populations

• Children and Adolescents
• Pre-existing Chemical Dependence and Family History (+) for CD
• Pre-existing or latent Psychiatric Illness
Brain Development
Ages 5-20 years

- MRI scans of healthy children and teens compressing 15 years of brain development (ages 5–20).

- Red indicates more gray matter, blue less gray matter.

- Neural connections are pruned back-to-front.

- The prefrontal cortex ("executive" functions), is last to mature.

Source: Paul Thompson, Ph.D.
UCLA Laboratory of Neuroimaging

Information taken from NIDA's Science of Addiction
http://www.drugabuse.gov/ScienceofAddiction/
Continuing Brain Development

Early in development, synapses are rapidly created and then pruned back. Children’s brains have twice as many synapses as the brains of adults.

Shore, 1997
The interaction between the developing nervous system and drugs of abuse leads to:

- Difficulty in decision making
- Difficulty understanding the consequences of behavior
- Increased vulnerability to memory and attention problems

This can lead to:

- Increased experimentation
- Addiction

Feillin, 2009
Early Reactions to Cannabis Predict Later Dependence

Positive Subjective Responses:
- Got Really High
- Felt Happy
- Felt Relaxed
- Did Silly Things
- Laughed a Lot

5 Positive responses to initial marijuana use increased odds of later dependence by 28.5 times

Negative responses were unrelated to later dependence:
- Felt ill, dizzy
- Felt Frightened
- Passed Out

Fergusson, et al., *Archives of General Psychiatry, Vol. 60, October 2003* pp. 1033-1039
In 2010, more than 46,000 8th, 10th, and 12th graders, enrolled in nearly 400 secondary public and private schools, participated in the study. Marijuana use rose for ALL prevalence periods this year (lifetime, past year, past 30-days, and daily in the past 30-days) in all three grades under study. Lloyd Johnston, the principal investigator of the study, said, “Perhaps the most troublesome part of it is that daily use of marijuana increased significantly in all three grades in 2010.” Daily or near-daily use is defined as use on 20 or more occasions in the prior 30 days; the rates for grades 8, 10, and 12 were 1%, 3%, and 6% in 2010. One in sixteen 12th graders today uses marijuana on a daily or near-daily basis.
Marijuana Use in U.S.
Nat’l Household Survey on Drug Use - 2010

• In 2010, more than 46,000 8th, 10th, and 12th graders, enrolled in nearly 400 secondary public and private schools, participated in the study.

• One possible explanation for the resurgence in marijuana use is that in recent years fewer teens report seeing much danger associated with its use, even with regular use.

• Possibly as a result, fewer teens have shown disapproval of marijuana use over the past two or three years.

• Both perceived risk and disapproval continued to decline in all three grades this year.
“Gateway Drug”

• This is a controversial subject. A drug that has been shown to increase the chances of using other more harmful drugs is nicotine

• That said, a concise appraisal of international multidisciplinary evidence:
  – Cannabis is more strongly assoc’d with other illicit drug use than tobacco or alcohol; the earliest and most frequent users are more likely to use illicit drugs (Room et al, 2010)

• Kandel study showed use of MJ precedes the use of heroin (5x more likely) and cocaine (2x more likely)
Educational Achievement

- Early use more damaging than later onset of use
- Lower GPA’s, negative attitudes toward, and reduced satisfaction with school, increased absenteeism, expulsions, suspensions, dropouts and unemployment
- Those who have smoked more than 100 times:
  - Rates of leaving school - 5.8 times higher
  - Rates of entering college - 3.3 times lower
  - Rates of college degree - 4.5 times lower

Cannabinoids and Cocaine

- The synthetic cannabinoid agonist, HU210, provokes relapse to cocaine seeking after prolonged withdrawal periods.

- Furthermore, the selective CB1 receptor antagonist, SR141716A, attenuates relapse induced by re-exposure to cocaine-associated cues or cocaine itself.

Cannabinoids and Alcohol

• Rats bred to voluntarily ingest alcohol reduce consumption when given the cannabinoid blocker SR141716A
• Cannabinoid agonists increase alcohol consumption by these rats
• Chronic alcohol consumption down-regulates CB1 receptors and increases production of anandamide
• Cannabis with ETOH greatly increases the risk of MVA due to combined effect on cognition and coordination
Impact of Marijuana Smoke on the Respiratory System

• Each inhalation:
  2/3 larger
  Inhaled 1/3 deeper
  Held 4 times longer
  50% higher in tar
• Acute and Chronic Bronchitis
• Local Immunological Impairment
• Precancerous Changes
The ability to focus attention and filter out irrelevant information, measured by frontal processing negativity to irrelevant stimuli, was impaired progressively with number of years of use.

The speed of information processing, measured by the latency of parietal P300, was delayed with increasing frequency of use.

Adolescents with daily MJ use show deficits in learning up to 6 weeks after stopping MJ use.

Solowij, Michie and Fox: “Differential Impairments of Selective Attention Due to Frequency and Duration of Cannabis Use,” Biological Psychiatry, Vol 37 #10, 731-9, May 15, 1995
Cognitive functioning of long-term heavy cannabis users seeking treatment

- On 9 standard neuropsychological tests that assessed attention, memory, and executive functioning
  - Impaired Learning
  - Impaired Retention
  - Impaired Retrieval
- Impairments endure beyond the period of intoxication and are worse with increasing years of regular cannabis use

Solowij et al., *JAMA, Vol. 287, No. 9, pp. 1123-31, Mar 6, 2002*
59% of frequent cannabis users report experiencing 1 or more Sxs, 44% report 2 or more and 34% report 3 or more

2 homogeneous sets of symptoms:
- Weakness (weakness, hypersomnia, psychomotor retardation, yawning)
- Anxiety/Depression (anxiety, depression, sweating, nausea, muscle aches, restlessness, tremors, insomnia)

Significant relationship found between use of a substance to relieve/reduce both sets of withdrawal symptoms
Cannabis Withdrawal Syndrome Criteria (Common Symptoms)

- Anger or Aggression
- Decreased Appetite / Wt. Loss
- Irritability
- Nervousness / Anxiety
- Restlessness
- Sleep Difficulties / Strange Dreams

Treatment / Recovery 2006:
220,000 (12-13%) Admissions
Reasons for Admission

- Loss of control of use
- Cognitive and Motivational Impairment, with Impact on
  Occupational and Academic Performance
- Decreased self-esteem
- Depression
- Complaint of a partner
- 525,000 users in CA met criteria for abuse or dependence in
  CA in 2009 (Pacula, 2010)
- In 2009, >32,000 treatment admissions in CA with MJ as the
  primary drug of abuse (HHS, 2009)
- Those under 21 y/o, represent 62% of all MJ primary tx
  (SAMSHA)
“The Mad”
Marijuana and Mental Disorders

- Among those with MDD, co-morbid MJ use is associated with increased rates of both SUICIDAL IDEATION AND ATTEMPTS.
- In those with family h/o psychotic disorders, MJ hastens the emergence of both positive and negative psychotic sx.
- The use of higher potency MJ for longer periods of time and frequency is also associated with increased risk of psychosis.
- In teens with weekly MJ use, predicted a 2x increase in risk of later depression/anxiety and is associated with increased depression, suicidal ideation, and risky behavior (Degenhardt, Hall et al 2003; Patton, Coffey et al, 2002).
Cannabis and Psychosis

- Cannabis use is associated with a dose dependent increased risk of developing schizophrenia (~ x 2)

- There is a strong association between use of cannabis and earlier age at first psychotic episode in male schizophrenics.
  Castle and Murray, Ed. Marijuana and Madness, Cambridge Univ. Press, 2004

- Marijuana can cause psychosis in high doses (Moore, Ammit, et al 2007)
Cannabis use in psychosis is associated with:

- Early psychotic breakdown
- Exacerbation or precipitation of symptoms
- Poor adherence to treatment
- Increased rates of hospitalization
- Increased duration of hospitalization
- Increased duration of psychotic episode


- Poor social functioning
- Increased rates of violence
- Increased rates of suicide
- Increased rates of victimization
- Homelessness
- Criminal behavior
- Poorer physical health
- Heavy burden on health services
Cannabis Effects

- Schizophrenics using cannabis lose more brain volume over 5 years than those who abstain.

- Long term cannabis use (at least twice monthly for an average of 19 years) produced 6-12% reductions in volume of hippocampus and amygdala.
  Murat Yücel, et al, “Regional Brain Abnormalities Associated with Long-term Heavy Cannabis Use,” Arch Gen Psychiatry/VOL 65 (N). 6), June 2008

- Rodents have a 44% decrease in hippocampal synapses 7 months after last exposure to THC – learning and memory effects into adulthood.
Cannabis and Bipolar Disorder

• Recent naturalistic study of 151 patients with bipolar I and II evaluated the impact of excessive alcohol versus cannabis use:
  – Patients with excessive MJ use showed EARLIER onset Bipolar disorder whether it preceded or followed bipolar disorder onset (after adjusting confounders)
  – Lifetime use of cannabis predicted an earlier onset and alcohol predicted a later onset relatively (Lagerburg, et al Jan 2011)
Treatment of MJ Dependence

- Few RCT trials
- Anecdotes with fluoxetine, nefazadone. Bupropion worsened wd sx's
- CB1 Antagonists
- Marinol worsened dependence
- Naltrexone some effect
- N-acetyl cysteine reduced craving
- CBT, MET and CM have the best evidence
In conclusion, there are risks and benefits associated with the medicinal use of MJ and great future medicines may develop from understanding the cannabinoid system: the current system in CA is a great danger and needs to be regulated.