

Medical Marijuana: What We Know and Don't Know

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Medical Marijuana: The “Big” Questions



- Is marijuana harmful/addictive?
- Does medical marijuana work for medical conditions?
- Why is marijuana a Schedule 1 drug?
- What should I tell my patients who are asking me to recommend medical marijuana?

Educational Objectives



1. Describe the mechanism of action of marijuana.
2. Discuss marijuana's effects on health and its potential for addiction.
3. Explain the problems with the current system of medical marijuana.
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Marijuana Use is Common



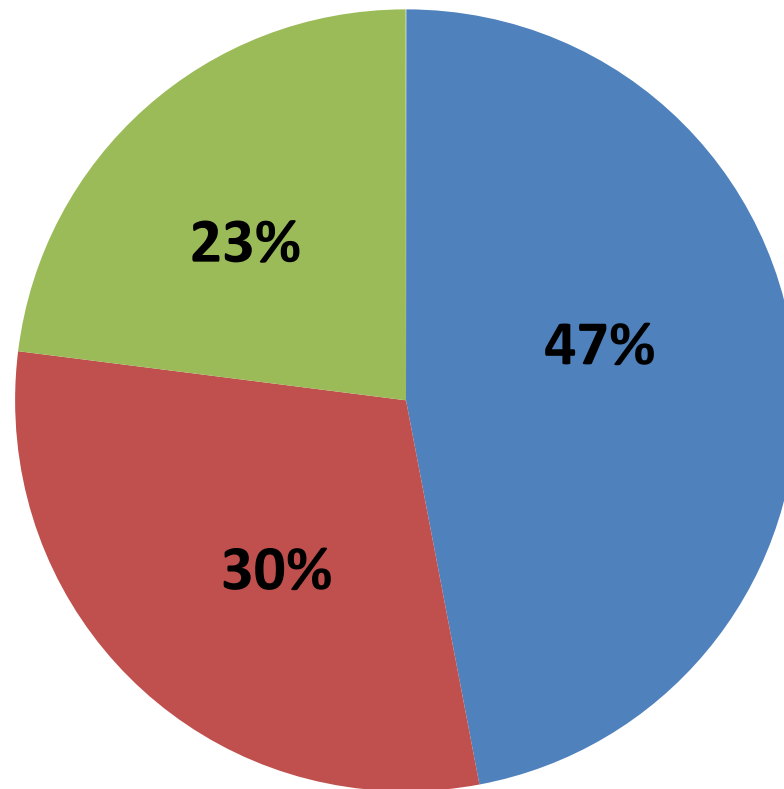
- Marijuana is the most commonly used illicit drug in the U.S.
- Any use among general population age 12+ in past month:
 - 2011: 7%
 - 2008: 5.8%
- Use is most common among people age 18-25 (19% of population)
- 48% of adults in the US report having used marijuana at some time in their life

Why Do People Use Marijuana?



Among people who used marijuana in the past year:

■ For Fun ■ For Medical Reasons ■ For Fun and for Medical Reasons



Marijuana: What is it?



- Dry, shredded mix of leaves, flowers, stems, and seeds, usually from *Cannabis sativa* or *Cannabis indica* plant
- Both are common subspecies of the hemp plant, which is common throughout the world
- Contains over 400 chemical compounds
- Common names: grass, weed, pot, reefer, Mary Jane, ganja



How is Marijuana Used?



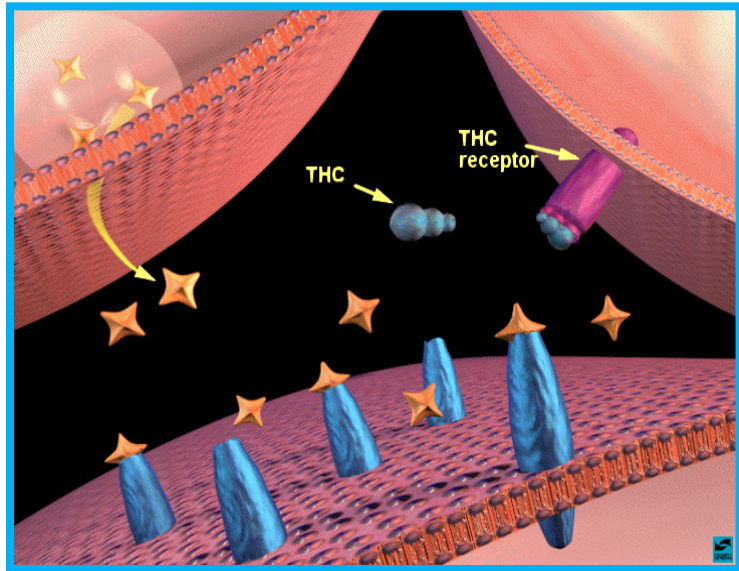
| SMOKED | VAPORIZED | EATEN/DRUNK |
|---|--|---|
| Smoked in a pipe, bowl, cigarette | Inhaled through machine that converts active compounds into inhalable form | Consumed as ingredient in baked goods, candies, sodas |
| Rapid effects | Rapid effects | Takes time to reach brain, so effects are delayed |
| Burning marijuana releases toxins that can cause pulmonary problems | Does not release toxins that cause pulmonary problems | Does not release toxins that cause pulmonary problems |

Marijuana: Other Forms



- Hashish
 - Compressed resin of cannabis plant
 - More concentrated and potent than marijuana plant
- Hash Oil (“Wax”)
 - Psychoactive chemicals extracted from cannabis plant with butane
 - Three to four times as potent as marijuana plant
- Synthetic Marijuana (“Spice”, “K2”)
 - Herbal and chemical mixtures that produce experiences similar to marijuana
 - The five most common active chemicals in synthetic marijuana are now illegal in the U.S.

Marijuana: How Does it Work?

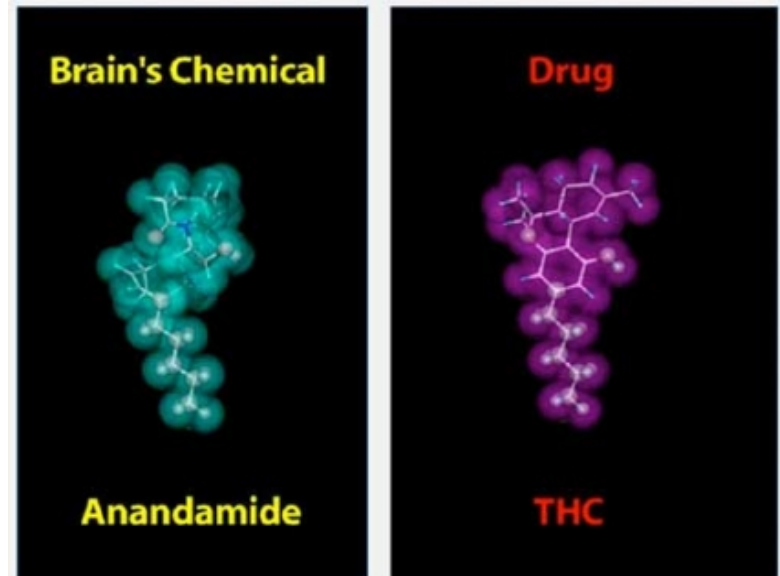


- Contains over 60 cannabinoids: main active chemical is Δ -9-tetrahydrocannabinol (THC)
- Stimulates “high” by triggering receptors in parts of brain that influence pleasure, memory, thinking, concentration, coordination
- THC’s molecular structure is similar to that of neurotransmitters that affect cannabinoid receptors (affect pain, appetite, vomiting reflex)
- Effects generally last 1-4 hours

How Does Marijuana Affect the Brain?



- When marijuana is smoked, THC rapidly passes from the lungs into the bloodstream, which carries the chemical to the brain and other organs throughout the body
 - It is absorbed more slowly when ingested in food or drink.
- THC acts on specific molecular targets on brain cells, called cannabinoid receptors. These receptors are ordinarily activated by chemicals similar to THC that naturally occur in the body (such as anandamide) and are part of a neural communication network called the endocannabinoid system.
 - This system plays an important role in normal brain development and function.



THC's chemical structure is similar to the brain chemical anandamide. Similarity in structure allows drugs to be recognized by the body and to alter normal brain communication

Endocannabinoid System Functions



- The neuron's “**volume control**” system: dials down neuron activity when too strong
- Regulates **neurotransmitters** that affect pleasure, mood, pain, appetite, motivation, memory



Endocannabinoid System



- Shapes brain development by...
 - guiding neurons to grow to the right places in the brain for correct function
 - controlling neuron activity, thereby affecting brain wiring (“neurons that fire together, wire together”)
 - supporting myelin growth on neurons

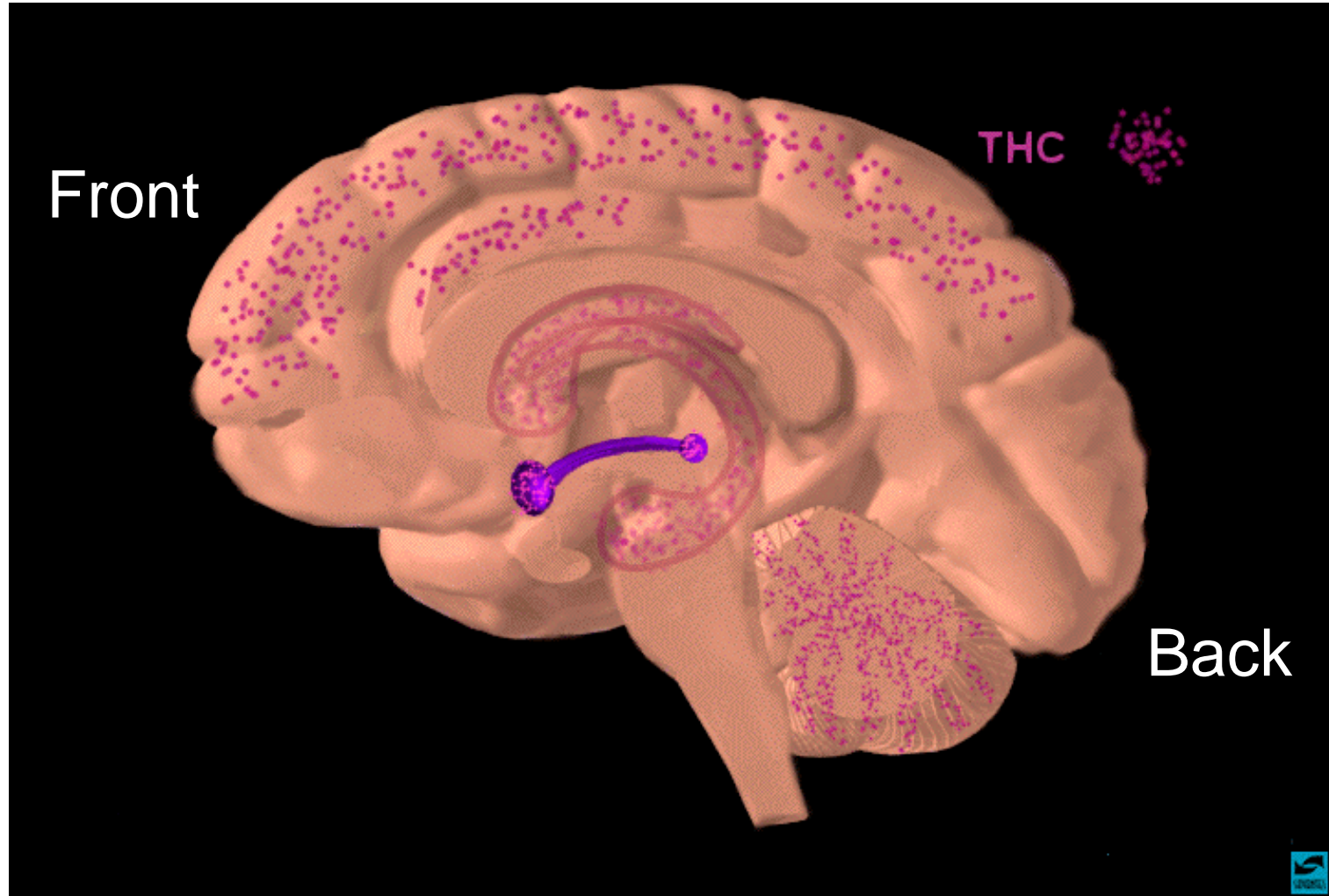
Source: Galve-Roperh I, Palazuelos J, Aguado T, Guzman M. Eur Arch Psychiatry Clin Neurosci. 2009;259:371-382.

THC vs. Anandamide



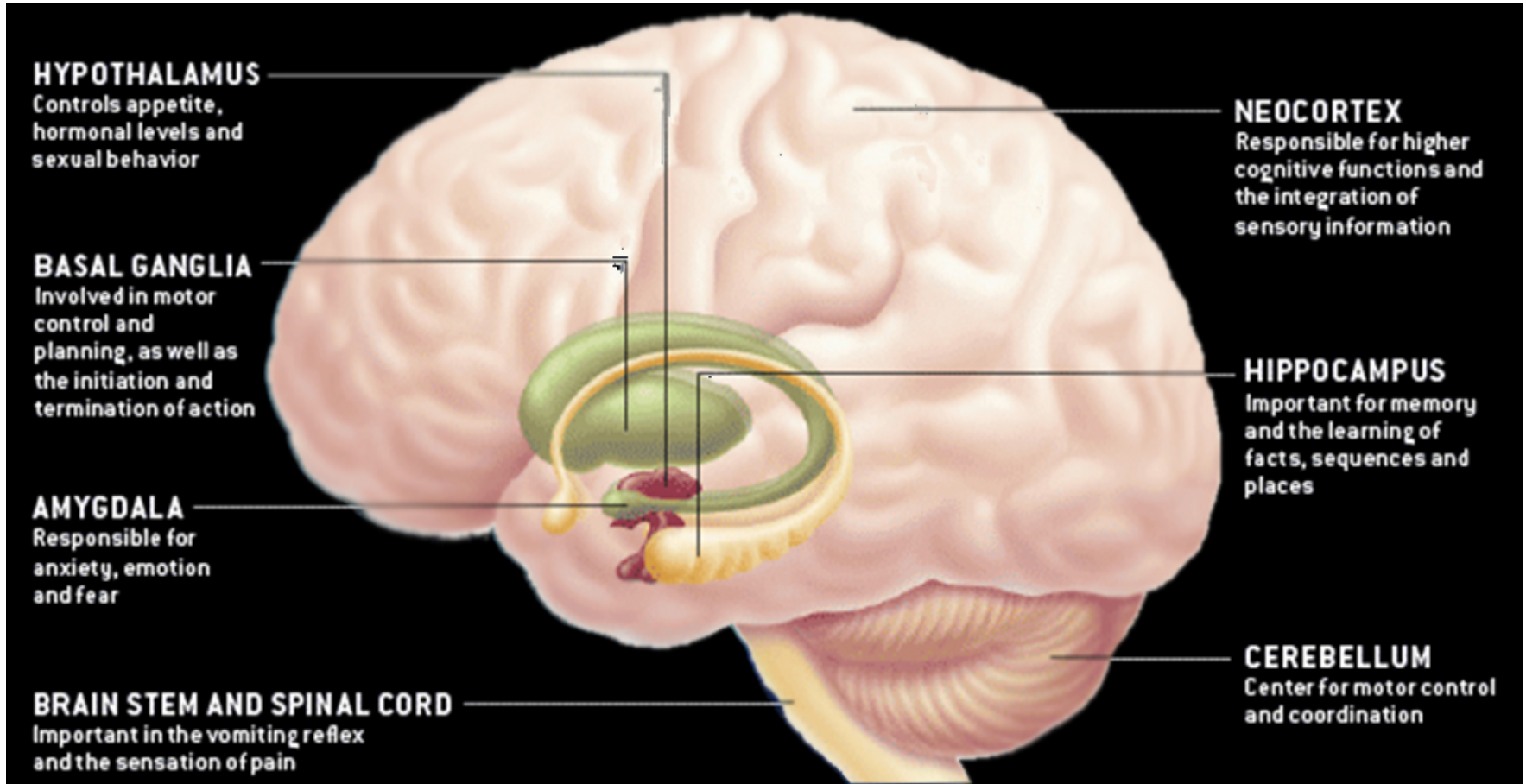
- Both dial down neuron activity to change neurotransmitter release
- THC has a **MUCH STRONGER, LONGER** effect than anandamide on brain cells
- THC interferes with anandamide function, **so it can't do its job to protect and balance cell activity**

THC Binding Sites



Source: NIDA

Marijuana Acts in Many Parts of the Human Brain



Marijuana: Immediate Effects



| | |
|---|---------------------------------|
| Altered Mood | Reduced Anxiety |
| Cognitive Impairment (Attention, Judgment) | Sedation/Drowsiness |
| Altered Perception | Sensory Intensification |
| Impaired coordination/balance | Increased heart rate |
| Hunger | Hallucinations (in large doses) |

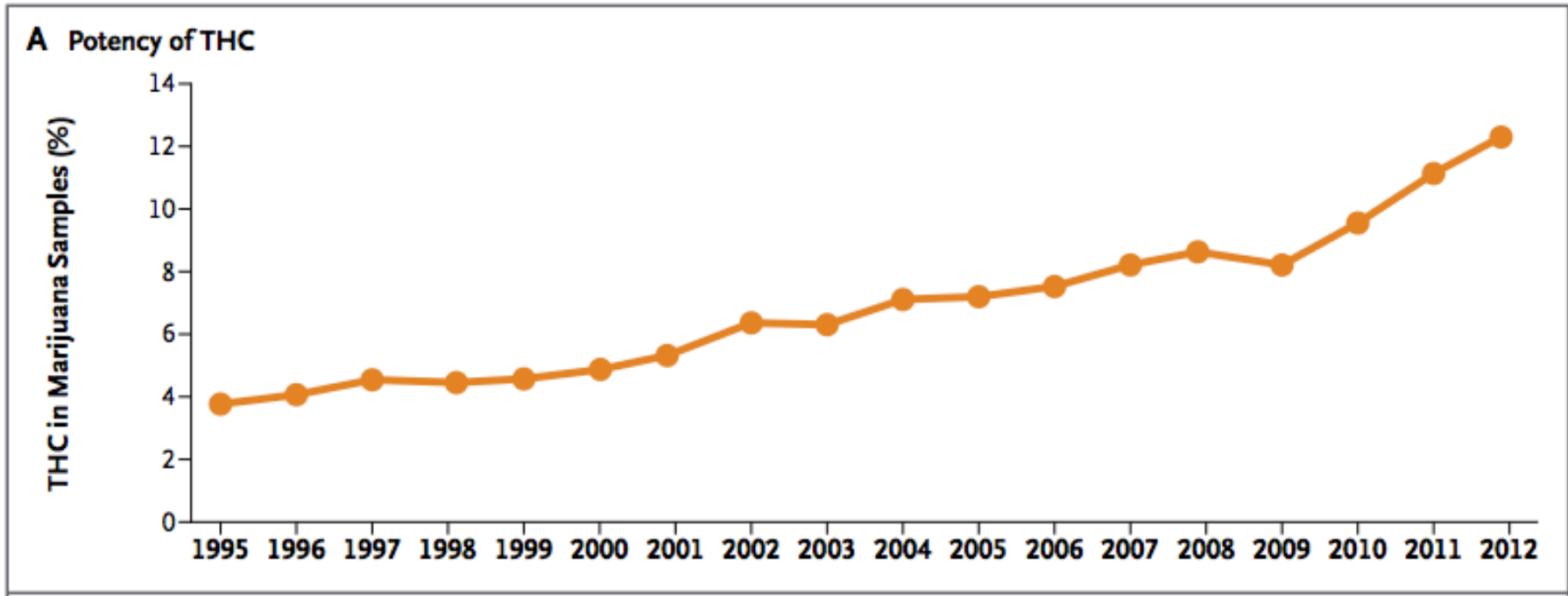
- Effects can vary by strains
 - *Sativa*: More euphoria, stress relief
 - *Indica*: Relaxation, physical (especially pain) relief
 - *Sativa* and *Indica* often combined, leading to variable effects

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Marijuana Potency is Increasing



- Marijuana growers have worked to make the drug as potent as possible.
- In 1960s-70s average THC concentrations were 1-2%. Today, they are as high as 20%

Marijuana: Negative Effects on Behavior and Mental Health



- Similar to alcohol/other drugs if misused (impairment)
- Long term use has negative impact on learning and memory
- Long term use reduces motivation (“amotivational syndrome”)
- Associated with mental health problems
 - Unclear if marijuana use is cause or effect
 - Heavy use is highly associated with serious mental illness – particularly among those with high risk (e.g., family history)

Marijuana: Negative Effects When Smoked



- Can lead to respiratory illness
 - One marijuana cigarette causes as many pulmonary problems as 4-10 tobacco cigarettes
 - Increased risk for bronchitis, emphysema, lung cancer
- Can cause cardiovascular complications
 - Raises blood pressure & heart rate 20-100%
 - 4.8 times risk of heart attack in hour after use

Marijuana: Negative Effects in Pregnancy

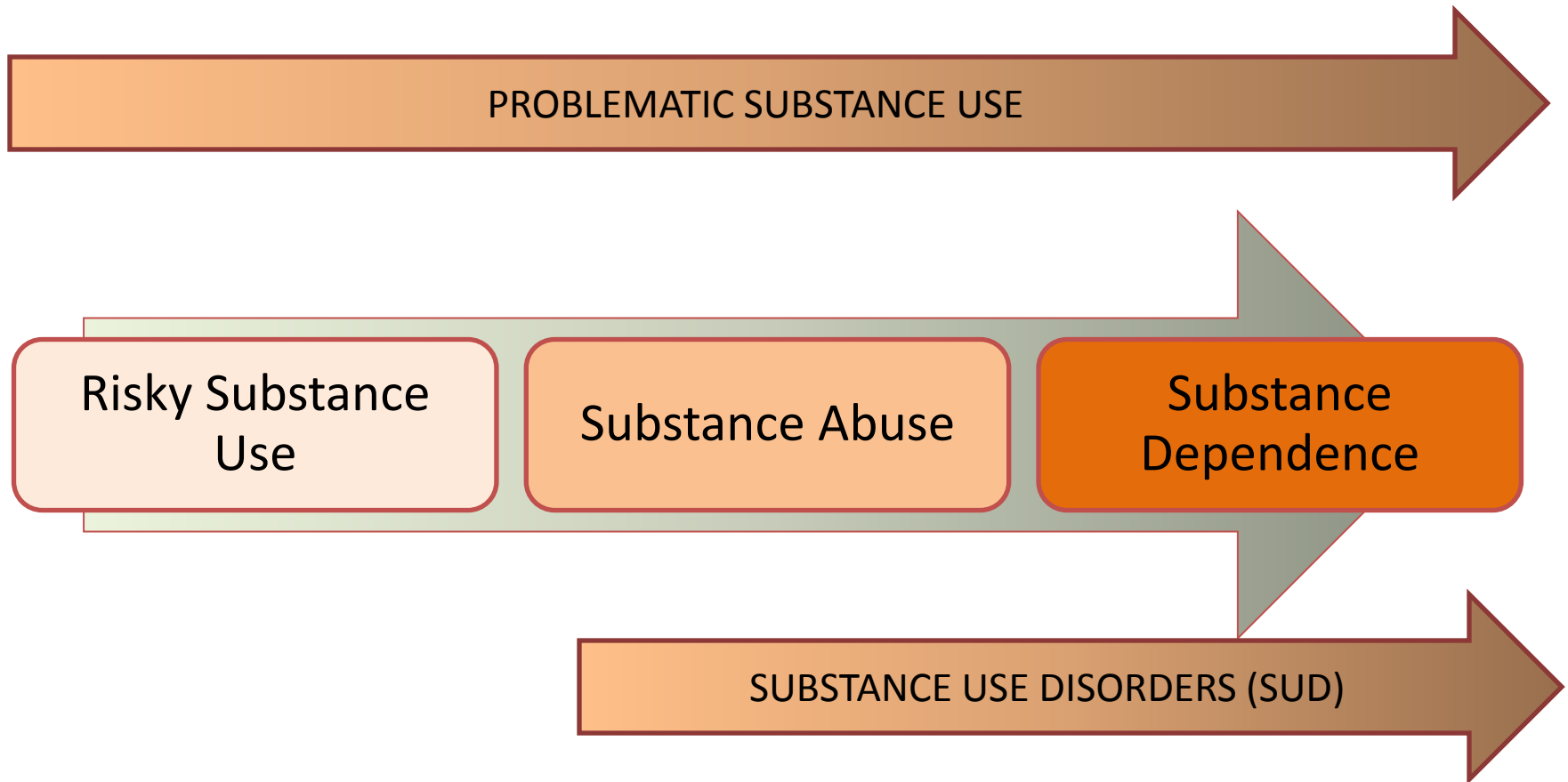


- There is increasing evidence that prenatal exposure may result in:
 - Increased risk of motor, social, and cognitive disturbances.
 - Higher rate of low birth weight infants, and childhood leukemia
- Marijuana has been found in breast milk although levels are generally considered subclinical.

Marijuana Abuse/Dependence



- SUD fall on a continuum of alcohol and drug use

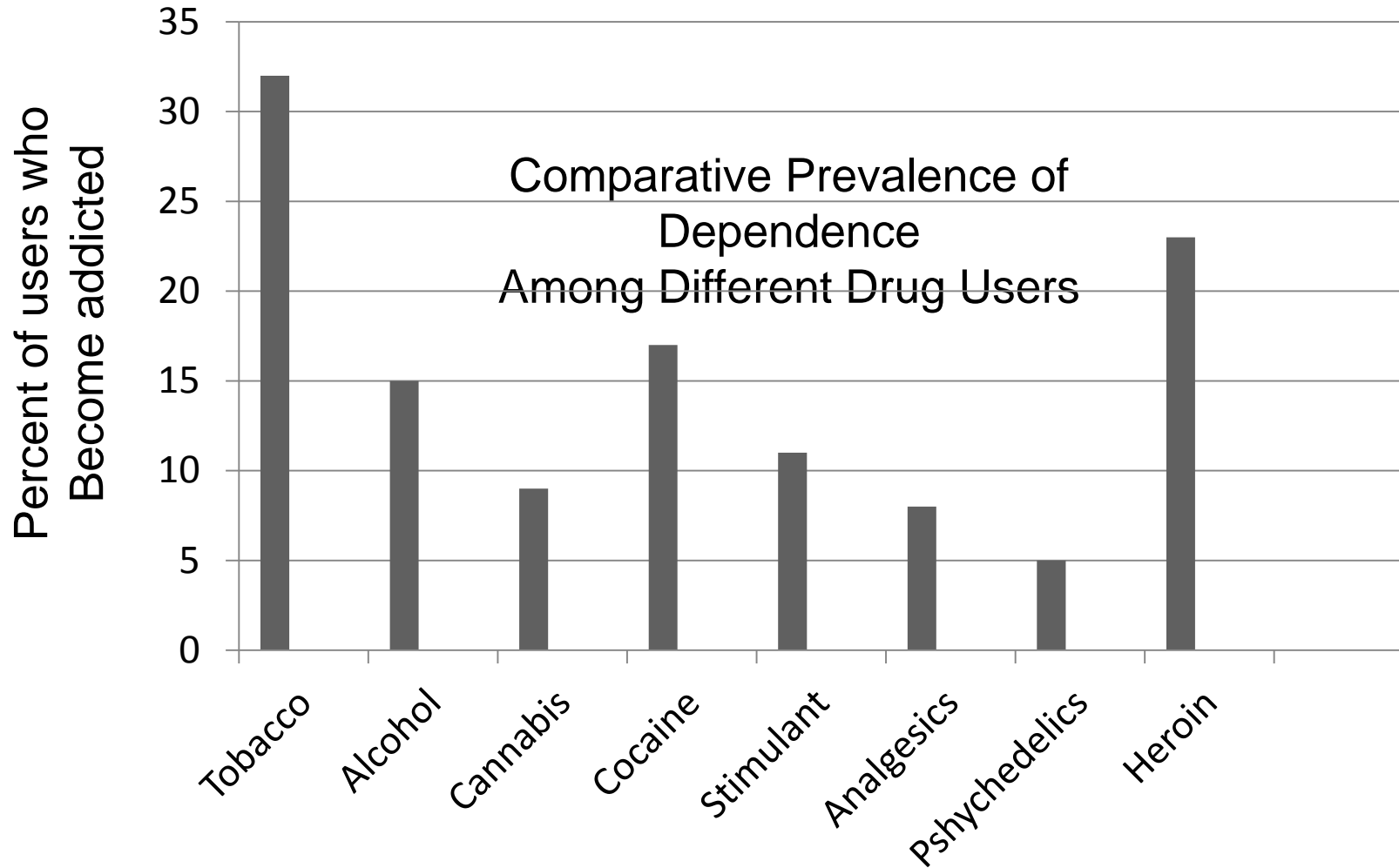


Marijuana: Potential for Abuse/Dependence



- Regular and prolonged use can change the way the brain works, leading to abuse or dependence
- Marijuana abuse/dependence most common among individuals with mental health disorders
- In 2011, 22.9% of people in US who received addiction treatment received treatment for marijuana use disorders
- Average adult entering treatment for marijuana abuse/dependence has used daily for ten years, tried to quit six times

Marijuana IS Addictive for SOME People



- Nonmedical Use

* *

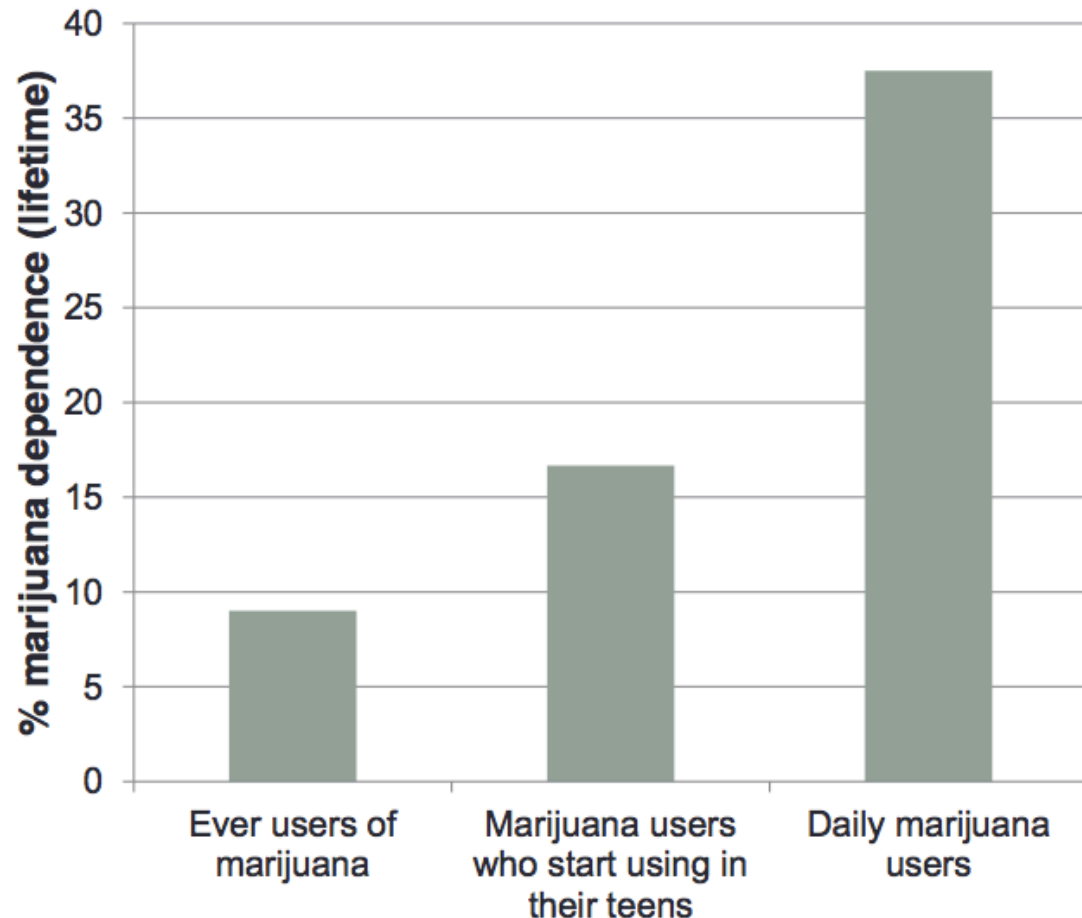
Marijuana is More Addictive for Teens



Addictiveness of marijuana

“Adolescents, especially troubled ones, and people with psychiatric disorders (including substance abuse) appear more likely than the general population to become dependent on marijuana... Some controlled substances that are approved medications produce dependence after long-term use; this, however, is a normal part of patient management and does not generally present undue risk to the patient”

-- Institute of Medicine

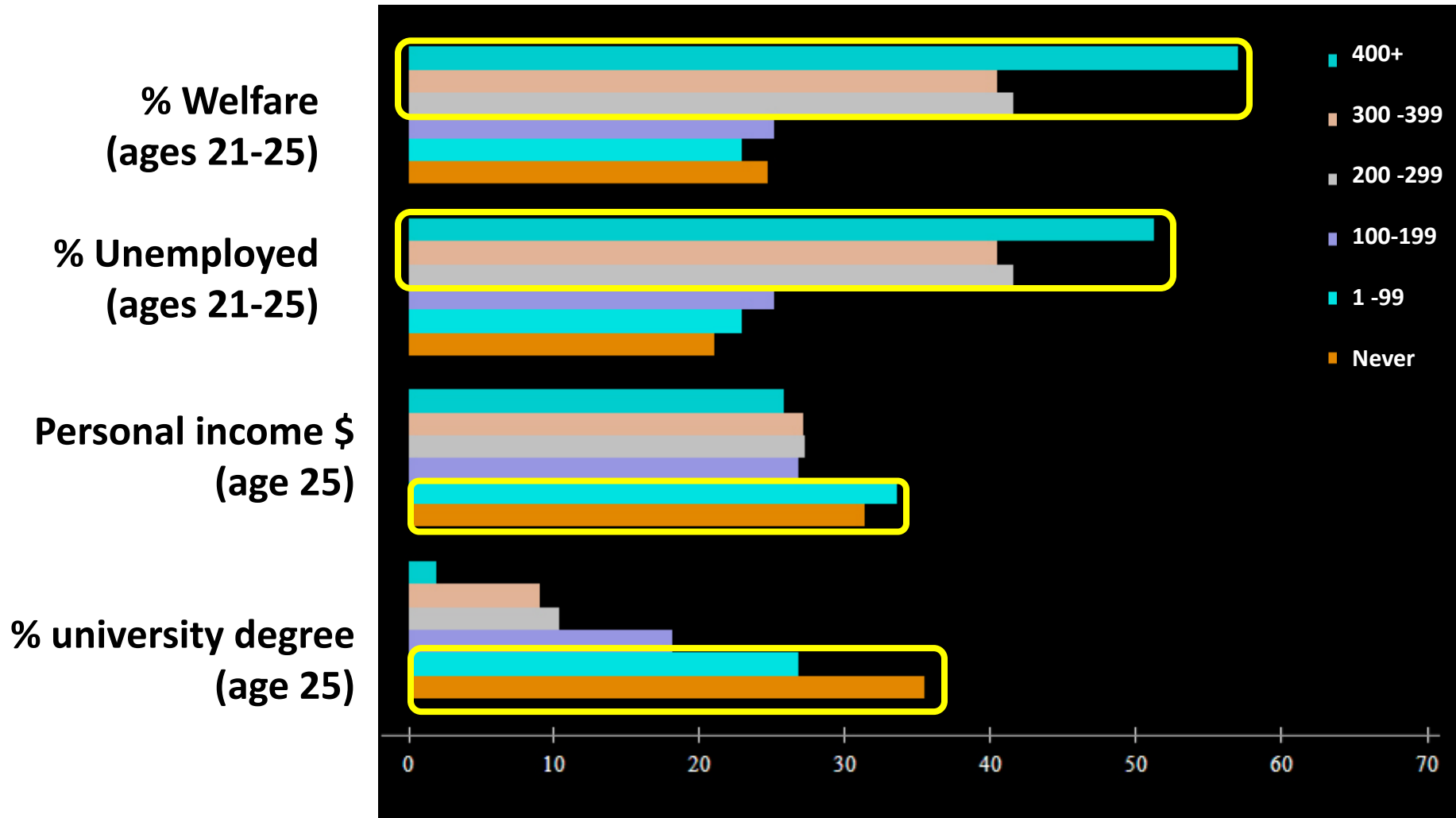


Anthony, J.; Warner, L.A.; and Kessler, R.C. *Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey*. *Exp Clin Psychopharmacol* 2:244–268, 1994;

Hall, W.; and Degenhardt, L. *Adverse health effects of non-medical cannabis use*. *Lancet* 374:1383–1391, 2009;

Hall, W. *The adverse health effects of cannabis use: What are they, and what are their implications for policy?* *Int J of Drug Policy* 20:458–466, 2009

Amount of Marijuana Used between 14-21 yrs Associated With Poorer Outcomes Later in Life



Pope and Yurgelun-Todd, 1996; Solowij et al. 2002, Fletcher et al., 1996,McHale and Hunt,2008; Solowij et al. 2002, Fletcher et al., 1996,McHale and Hunt,2008 ; Porter, & Frampton, 2007 et al., 2002; Solowij & Pesa, 2010; Pope HG Jr, et al.? Drug Alcohol Depend. 2003 Apr 1;69(3):303-10; Crean Rdet al., J Addict Med. 2011 Mar;5(1):1-8

Marijuana: Signs of Abuse/Dependence



- Tolerance/withdrawal
 - Anger or Aggression
 - Decreased Appetite / Weight Loss
 - Irritability
 - Nervousness / Anxiety
 - Restlessness
 - Sleep Difficulties / Strange Dreams
- Preoccupation
- Loss of control
- Continued use in the face of adverse consequences
- Cognitive distortions/denial

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Different Kinds of Marijuana-Based Medicine



- Botanical cannabis (plant): “Medical Marijuana”
- Synthetic THC medications available in U.S. for nausea/appetite stimulation:
 - Dronabinol (Marinol®) (FDA approved for HIV)
 - Nabilone (Cesamet®) (FDA approved for cancer; HIV off-label)
- Other medications not available in U.S.:
 - Nabiximols (Sativex®) THC/cannabidiol mouth spray for pain relief, muscle spasms; currently being investigated by FDA
 - Rimonabant (Accomplia®, Zimulti®) for treatment of obesity and nicotine dependence (selective cannabinoid receptor-1 blocker)

FDA Approval Process



- Medicines have to go through a rigorous process of testing in human subjects for
 - safety
 - efficacy
 - long term effects
 - side effects
 - *Testing for a single medical condition,*
 - many other standards, including:
 - measuring shelf life, gauging manufacturing and labeling practices, inspections of the cleanliness of the facilities in which the drug is manufactured, etc.

More Detailed FDA Criteria



Is it pure compound, predictable chemistry, production?

Are production methods validated?

Toxic effects in animals, in humans?

How much gets into human bloodstream. How much gets to target?

Is it contaminated with microbes, chemicals?

Safe dose range? Is it effective AND safe for ...?

What are side effects? Acceptable?

Follow-up case reports, safety updates

The Elephant in the Room Regarding Smoked Marijuana



- ***The science to support its effectiveness and safety, the dual standards for an approved medicine, does not yet exist.***
- Medical marijuana has been “legalized” by voting on a ballot, not by scientifically testing whether it meets standards for medicinal use.

Medical Marijuana is **NOT** FDA Approved



- FDA approval assures that medications are effective, safe, and properly labeled
- FDA cannot evaluate medical marijuana as a drug since it is a plant, not a standardized medical formulation
- Medical marijuana is different everywhere, depending on how it is bred, under what conditions it is grown, etc.
- No way to know if medical marijuana is pure. Can be contaminated by pesticides, mold, fungus.

Medical Marijuana Has Not Been Thoroughly Tested



- Gold standard: double-blind, placebo-controlled clinical trials
- Few exist for smoked marijuana
- Clinical trials have been small, largely unsuccessful

JAMA Article in June 2015



Original Investigation

Cannabinoids for Medical Use A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PhD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

STUDY SELECTION Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

79 RCTs were included (No. of reports [No. of patients])^b

- 28 Nausea and vomiting due to chemotherapy (37 [1772])
- 28 Chronic pain (63 [2454])
- 14 Spasticity due to multiple sclerosis or paraplegia (33 [2280])
- 4 HIV/AIDS (4 [255])
- 2 Sleep disorder (5 [54])
- 2 Psychosis (9 [71])
- 2 Tourette syndrome (7 [36])
- 1 Anxiety disorder (1 [24])
- 1 Glaucoma (1 [6])
- 0 Depression

Most Trials Were Flawed...



Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings (continued)

| Indication ^a | No. of Studies (No. of Patients) | Cannabinoid (No. of Studies) | Comparator | Outcome ^b | Summary Estimate | Favors | I ² , % | GRADE Rating ^c |
|-------------------------|----------------------------------|------------------------------|------------|---|--|-------------|--------------------|---------------------------|
| Depression | 1 (66) | Nabiximols | Placebo | Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks | Mean difference (95% CI), 0.15 (-1.0 to 1.31) | Placebo | NA | Very low |
| | 1 (182) | Nabiximols | Placebo | Depression assessed using the Montgomery-Åsberg Depression Scale (0-54) Follow-up 9 weeks | Mean difference (95% CI), 1.90 (-0.22 to 4.02) | Placebo | NA | Very low |
| | 1 (160) | Nabiximols | Placebo | Depression Beck Depression Inventory Scale (0-63) Follow-up 6 weeks | Mean difference (95% CI), 0.69 (-0.76 to 2.14) | Placebo | NA | Very low |
| Anxiety disorder | 1 (24) | Cannabidiol | Placebo | Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes | Mean difference, -16.52 P value = .01 | CBM | NA | Very low |
| Sleep disorder | 1 (22) | Nabilone | Placebo | Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks | Mean difference, -19.64 P value = .02 | CBM | NA | Low |
| | 8 (539) In other indications | Nabiximols (7), THC/CBD (1) | Placebo | Sleep quality NRS (0-10) Follow-up 2-15 weeks | WMD (95% CI), -0.58 (-0.87 to -0.29) | CBM | 33 | Very low |
| | 3 (1637) In other indications | Nabiximols (3) | Placebo | Sleep disturbance NRS (0-10) | WMD (95% CI), -0.26 (-0.52 to 0.00) | CBM | 64 | Very low |
| Psychosis | 1 (35) | | | | | CBM | NA | Low |
| | 1 (35) | | | | | Amisulpride | NA | Low |
| Tourette syndrome | 1 (17) | | | | | THC | NA | Low |
| | 1 (17) | | | | | THC | NA | Low |
| | 1 (18) | | | | | THC | NA | Low |
| | 1 (17) | | | | | THC | NA | Low |

GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. The GRADE ratings of very low-, low-, moderate-, or high-quality evidence reflect the extent to which we are confident that the effect estimates are correct.

Most Trials Were Flawed...



- Used the Cochrane risk of bias tool to assess RCTs, which highlighted a number of methodological weaknesses:
 - failure to appropriately handle withdrawals
 - selective outcome reporting
 - inadequate description of methods of randomization, allocation concealment, and blinding
 - very small sample sizes; glaucoma (N = 6), Tourette syndrome (average N = 18), sleep disorder (average N = 27), and anxiety disorder (N = 24)
- Only 4 trials were considered at low risk of bias

Flaws aside, what did the article show?



- Moderate-quality evidence to support the use of cannabinoids for the treatment of **chronic pain and spasticity**.
- Low-quality evidence suggesting that cannabinoids were associated with improvements in **nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome**.
- Cannabinoids were associated with an increased risk of short-term AEs (dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination).

This is not to say there are no advantages to smoked marijuana...



- Safety:
 - Has little effect on major physiological functions
 - There is no known case of a lethal overdose
 - On the basis of animal models, the ratio of lethal to effective dose is estimated as 40 000 to 1. By comparison, the ratio is between 3 and 50 to 1 for secobarbital and between 4 and 10 to 1 for ethanol.
- Addictiveness:
 - Marijuana is less addictive than many drugs now used as muscle relaxants, hypnotics, and analgesics.

Take-Home



- Unfortunately, there is little evidence that smoked marijuana works for any medical condition
- Doctors have a hard time recommending that their patients smoke marijuana
- However, most doctors recognize that there may be continuants of marijuana that may be therapeutic
- More research needs to be done...

How do patients get access to
smoked marijuana?



Medical Marijuana and Federal Law



- Supreme Court ruled that medical necessity is no excuse to break federal law (2001)
- FDA affirmed smoked marijuana is not considered medicine (2006)



Marijuana and its Derivatives as Medicine: Federal Law



- Investigational New Drug Program
 - Individuals could apply for marijuana from the federal government
 - Under 100 patients given marijuana in program
 - Large numbers of people with HIV/AIDS applied
 - Program shut to new enrollees in 1992 due to high demand
 - Handful of people still getting drug through program today
- Dronabinol (Marinol®) approved by FDA for cancer chemotherapy (1985) and HIV/AIDS (1992)
- Nabilone (Cesamet®) approved by FDA 1985, became available for cancer chemotherapy in 2006

Medical Marijuana and State Law



- 23 states and the District of Columbia allow for the use of marijuana medically
 - Through votes in state legislatures
 - Through ballot measures
- An unconventional approach to making decisions about medicine
 - Only drug approved for medical use through political process rather than scientific trials and research
- Over 200,000 individuals in California obtain marijuana through medical marijuana dispensaries
 - In 2010, 69% of medical marijuana users in US were in California



- California Compassionate Use Act (1996)
 - Approved as Proposition 215 by 56% of California voters; amended in 2003 by SB 420
 - First medical marijuana law and the most open to interpretation
 - Legalized for treatment of many medical conditions (including HIV/AIDS) and “*any other illness for which marijuana provides relief*” (open to broad interpretation)

Medical Marijuana and State Law: California (continued)



- Unlike other medications, doctors do not prescribe amount of marijuana, number of refills, content of medication, or route of administration
 - Dispensary staff often recommend specifics
- Doctor simply recommends the drug after one visit
 - Cost of a visit generally \$40-\$100
 - Patients obtain a “recommendation” for medical marijuana
 - Grow marijuana personally, or purchase it at marijuana dispensaries
- Doctor does not have to monitor patient progress (e.g., response to medicine, changes in symptoms)

Obtaining Medical Marijuana in MA



- Individual must have one or more ‘qualifying’ conditions
- A physician must document that the individual has one of these qualifying conditions and sign a form that is submitted to the state
- The state will then provide a card as verification that a patient qualifies to possess medical marijuana
- The patient can then either grow marijuana or obtain it from a dispensary.

Effects of Medical Marijuana Legalization



- Marijuana use is more common in states that have medical marijuana laws
 - It is unclear if higher rates of use are cause or effect of medical marijuana laws
- Rates of marijuana abuse and dependence are higher in states that have medical marijuana laws
 - Higher rates of abuse/dependence due to increased rates of use
 - No increase in rate of dependence among users

Who Uses Medical Marijuana?



- People who have a history of non-medical marijuana use
 - 95% of California medical marijuana patients were using the drug even before they got physician approval
 - Use can evolve from recreational to medical

Why do People Use Medical Marijuana?



| REASON FOR USE | % REPORTING REASON |
|-----------------------|--------------------|
| Pain Relief | 82.6% |
| To Sleep | 70.6% |
| To Relax | 55.6% |
| Muscle Spasms | 41.3% |
| Anxiety | 38.1% |
| To Stimulate Appetite | 38.0% |
| Nausea | 27.7% |
| Depression | 26.1% |

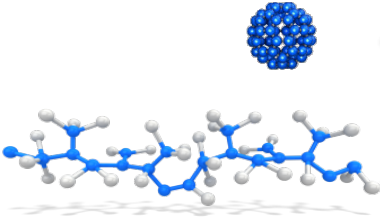
Why do People Use Medical Marijuana?



| DISORDER THAT REQUIRES TREATMENT | % CITING AS REASON FOR MJ USE |
|----------------------------------|-------------------------------|
| Chronic Pain | 58.2% |
| Mental Health Disorders | 22.9% |
| Sleep Disorders | 21.3% |
| Neurological Disorders | 16.6% |
| HIV | 1.6% |
| Cancer | 1.5% |
| Glaucoma | 1.3% |

DRUG SCHEDULING

Any drug with stimulant, depressant, hallucinogenic effect is considered to have abuse potential



Scientific knowledge regarding the drug

Immediate precursor of a controlled substance



Scientific evidence of pharmacological effects

Risk to public health?



Actual or relative potential for abuse



Scope, duration, significance of abuse



History and current pattern of abuse



Psychic or physiological dependence liability

Five Drug Schedules



Schedule I

no currently accepted medical use, high abuse potential

Heroin, LSD, MARIJUANA, MDMA, Peyote

Schedule II

high potential for abuse, severe psychological or physical dependence,

Cocaine, Methamphetamine, Methadone, Hydromorphone (Dilaudid), Meperidine Oxycodone (Oxycontin), Fentanyl, Dexedrine, Adderall, Ritalin

Schedule III

moderate to low potential for physical psychological dependence

< 15 mg Hydrocodone, < 90 mg Codeine per dose (Tylenol with codeine), Ketamine, Anabolic Steroids, Testosterone

Schedule IV

low abuse, addiction potential

Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien

Schedule V

lowest potential for abuse

Antidiarrheal, Antitussive, Analgesics, Cough preparations, Lomotil, Motofen, Lyrica, Parepectolin

Criteria for Currently Accepted Medical Use in Treatment in the United States (CSA)



a. Drug's chemistry

- must be known and reproducible

b. Evidence of Safety

- must be adequate

c. Evidence of efficacy

- must be adequate, well-controlled

d. Qualified experts

- must accept the drug

e. Scientific evidence

- must be widely available

57 Fed. Reg. 10499, 10504-10506 (1992). Failure to meet any of these five prongs precludes a finding that the drug has a currently accepted medical use in treatment in the United States for purposes of the Controlled Substances Act.

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a. Reproducible, Known Chemistry of Marijuana



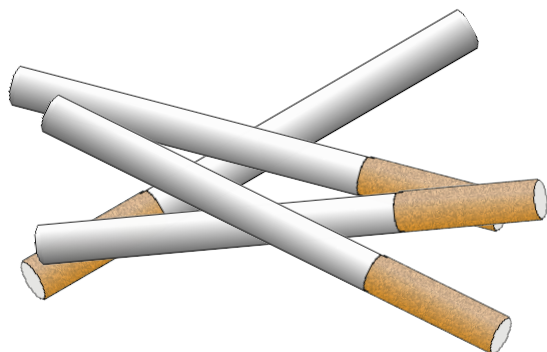
>400 Chemicals in Marijuana Smoke Similar to Tobacco



| Chemical | TOBACCO | MARIJUANA |
|-----------------------|---------|-----------|
| Pyridine | 59 | 93 |
| Quinoline | 2.2 | 2.68 |
| Toluene | 169 | 199 |
| Benzene | 94 | 84 |
| Styrene | 28 | 44 |
| Acrylonitrile | 24 | 67 |
| Isoprene | 540 | 132 |
| Hydroquinone | 299 | 71 |
| <i>m + p</i> -cresols | 51 | 46 |

| Extreme | | |
|-------------------------|-------------|--------------|
| Chemical | TOBACCO | MARIJUANA |
| <u>tar (mg/cig)</u> | <u>80.3</u> | <u>103</u> |
| pH | 5.47 | 7.73 |
| <u>NO (µg/cig)</u> | <u>151</u> | <u>685</u> |
| <u>NOx (µg/cig)</u> | <u>158</u> | <u>693</u> |
| CO (mg/cig) | 41.5 | 35.3 |
| nicotine (mg/cig) | 5.2 | 0.002–0.007* |
| <u>ammonia (µg/cig)</u> | <u>67</u> | <u>1315</u> |
| <u>HCN (µg/cig)</u> | <u>320</u> | <u>1668</u> |
| NNN | 160 | <1.49* |
| NAT | 125 | <1.87* |
| NAB | 8.26 | 0.063–2.00* |
| NNK | 158 ± 15 | <3.72* |
| Mercury | 5.35 | 3.51 |
| Cadmium | 284 | 14.6 |
| Lead | 43.8 | 7.7–25.7* |
| Chromium | 11.9–39.6 | 11.9–39.6 |
| Nickel | 12.9–43.1 | <12.9 |
| Arsenic | 12.7 | 2.25–7.49* |
| Selenium | 4.42–14.7 | 4.42–14.7 |

| Chemical | TOBACCO | MARIJUANA |
|--------------------------|---------|-----------|
| naphthalene | 4908 | 4459 |
| 1-methylnaphthalene | 4888 | 4409 |
| 2-methylnaphthalene | 3666 | 2917* |
| acenaphthylene | 711 | 459* |
| acenaphthene | 309 | 213* |
| fluorene | 1369 | 659* |
| phenanthrene | 515 | 476 |
| anthracene | 162 | 136* |
| fluoranthene | 171 | 117* |
| pyrene | 154 | 82.3* |
| benzo(a)anthracene | 52 | 43.1* |
| chrysene | 61.7 | 56.3 |
| benzo(b)fluoranthene | 21.9 | 16.2* |
| benzo(k)fluoranthene | 7.45 | 4.54* |
| benzo(e)pyrene | 19.2 | 12.6* |
| benzo(a)pyrene | 25.1 | 15.5* |
| perylene | 10.8 | 6.10* |
| indeno(1,2,3,-cd)pyrene | 10.1 | 8.65 |
| dibenz(a,h)anthracene | 4.84 | 2.83* |
| benzo(g,h,i)perylene | 7.17 | 6.03 |
| 5-methylchrysene | <0.071 | <0.071 |
| benzo(b)fluoranthene | 19.1 | 17.6 |
| benzo(j)fluoranthene | 13.3 | 12.2 |
| dibenz(a,h)acridine | <0.628 | <0.628 |
| dibenz(a,j)acridine | <0.519 | <0.519 |
| 7H-dibenzo(c,g)carbazole | <0.278 | <0.278 |
| dibenz(a,l)pyrene | <0.634 | <0.634 |
| dibenz(a,e)pyrene | <0.313 | <0.313 |
| dibenz(a,i)pyrene | 2.55 | <0.329* |
| dibenz(a,h)pyrene | <0.354 | <0.354 |



Moir et al, A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions. *Chem. Res. Toxicol.*, 2008, 21 (2), pp 494–502 Standard conditions employed a puff volume of 35 ml, a puff duration of 2 s, and a puff interval of 60 s. These conditions are termed “ISO” throughout. Conditions more reflective of marijuana smoking employed a puff volume of 70 ml, a duration of 2 s, and a 30 s interval. These conditions are referred to as “extreme” and differ from the Health Canada “intense” tobacco smoking conditions, which employ a puff volume of 55 ml

Pure Compound, Predictable Chemistry? Manufacturing? Composition? Amount in Blood? Tissues?



Contents

THC varies from 0.5 % to 15 % (3 - 30 mg)

Smoked

**delivery is
10 - 50%
efficient**

**Peak levels within
minutes - 1 hour**

Ingested

**delivery is
about 6%
efficient**

**Peak levels felt 30 -
120 minutes**

Criteria for Currently Accepted Medical Use in Treatment in the United States (CSA)



a. Drug's chemistry

- must be known and reproducible

b. Evidence of Safety

- must be adequate

c. Evidence of efficacy

- must be adequate, well-controlled

d. Qualified experts

- must accept the drug

e. Scientific evidence

- must be widely available

57 Fed. Reg. 10499, 10504-10506 (1992). Failure to meet any of these five prongs precludes a finding that the drug has a currently accepted medical use in treatment in the United States for purposes of the Controlled Substances Act.

b. Evidence of Safety For Use of Marijuana Under Medical Supervision?



Indications for marijuana are for chronic conditions. Marijuana clinical trials (RCT, others) have not interrogated whether:

- it interferes with normal daily function?
- it can be safely used daily for chronic medical conditions?
- patients progress to addiction?
- it is associated with high accident, (other) rates?
- its use extends to family members, children?

If Marijuana Used for Medical Problems, Potential Risks:



| <u>Immediate</u> | <u>Long Term</u> |
|---|--|
| Intoxication: Changed perceptions, thinking, memory, judgment (impaired driving, etc). | Addiction |
| Intoxication: Risks for accidents, injuries, falls | Problems with academics, work, social |
| Psychological effects: Anxiety, panic | Withdrawal symptoms |
| Cardiovascular effects: Increased heart rate, blood pressure, increased risk of heart attack, stroke, injury to blood vessels. | Impaired learning, memory |
| Pulmonary effects: May worsen symptoms of asthma, other pulmonary conditions. | Psychosis, schizophrenia other psychiatric disorders |
| | Bronchitis, asthma symptoms, heart attack, testicular cancer |

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c. Evidence of Efficacy Adequate, Well Controlled?



CALIFORNIA

Cancer, glaucoma, HIV/AIDS, AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms, including spasms associated with multiple sclerosis, seizures, including seizures associated with epilepsy, severe nausea; Other chronic or persistent medical symptoms.

ARIZONA

Cancer, glaucoma, HIV/AIDS, Hepatitis C, ALS, Crohn's disease, Alzheimer's disease, cachexia or wasting syndrome, severe, and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms (including multiple sclerosis), PTSD

ILLINOIS

40 chronic diseases and conditions: cancer, glaucoma, positive status for HIV/AIDS, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, Rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and post concussion syndrome, Multiple Sclerosis, Arnold-Chiari malformation and Syringomyelia, Spinocerebellar Ataxia (SCA), Parkinson's Disease, Tourette Syndrome, Myoclonus, Dystonia, Reflex Sympathetic Dystrophy, RSD (Complex Regional Pain Syndromes Type I), Causalgia, CRPS (Complex Regional Pain Syndrome Type II), Neurofibromatosis, Chronic inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy, Sjogren's Syndrome, Lupus, Interstitial Cystitis, Myasthenia Gravis, Hydrocephalus, nail-patella syndrome or residual limb pain; or the treatment of these conditions."

CONNECTICUT

Cancer, glaucoma, positive status for HIV/AIDS, Parkinson's disease, multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, wasting syndrome, Crohn's disease, posttraumatic stress disorder, or... any medical condition, medical treatment or disease approved by the Department of Consumer Protection..

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Key Medical Associations Do Not Endorse Marijuana



- American Medical Association
- American Society for Addiction Medicine
- American Cancer Society
- American Glaucoma Society; American Academy of Ophthalmology
- American Academy of Pediatrics
- National Multiple Sclerosis Society
- British Medical Association
- Florida Medical Association

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Does Marijuana Meet This Criteria?



Purity: NO

- Over 400 chemicals, other cannabinoids. may be biologically active ; varies from plant to plant

**Dosage forms,
Standard doses: NO**

- No defined, measured ingredients consistent from batch to batch

**Quality control:
NO**

- No difference between “medical-grade” marijuana and “street” marijuana.

**Clinical trials:
LIMITED**

- Insufficient evidence that marijuana benefits outweigh risks for patients

**Safety, side effects
VERY LIMITED**

- Marijuana is proposed for chronic conditions. No long term research of marijuana use for chronic conditions

Rescheduling Marijuana will Enable Clinical Trials?



- 111 researchers registered with DEA: marijuana, marijuana extracts, non-tetrahydrocannabinol marijuana derivatives e.g. cannabidiol and cannabiniol
- 508 studies listed at clinicaltrials.gov
- FDA, HHS recently approved study of marijuana in PTSD
- FDA recently approved study of cannabidiol (CBD) to treat drug-resistant epilepsy in children, young adults 1-18 years
- 305 NIH funded studies on marijuana

Rescheduling Marijuana will Enable Clinical Trials?



The FDA Has Approved, and is Considering, Purified Products From Marijuana Plant:

| Compound | Administration | FDA Status | Approved Locations | Purposes |
|----------------------|------------------|--|--------------------------------------|---|
| Dronabinol (Marinol) | Oral capsule | FDA-approved (1985) | USA, Germany | Nausea & vomiting related to cancer chemotherapy and wasting associated with AIDS |
| Nabilone (Cesamet) | Oral capsule | FDA-approved (1985) *Marketed in the US in 2006 | USA, Canada, UK, Mexico | Nausea & vomiting related to cancer chemotherapy |
| Nabiximols (Sativex) | Oromucosal spray | Almost FDA-approved; late-stage clinical trials | Canada, UK, other European countries | Multiple sclerosis spasticity, cancer pain, neuropathic pain |

Marijuana Site Reclamation and Restoration Cost Analysis." U.S. Department of Interior, National Park Service. December 9, 2010 (unpublished data). <http://www.whitehouse.gov/ondcp/frequently-asked-questions-and-facts-about-marijuana#difference>

Only small proportion of MM cardholders report a serious illness



- ~ 5% report cancer, HIV/AIDS, glaucoma, MS, as their reason for using medical marijuana.
- **Profile:** 32-year old white male; history of alcohol and cocaine use; no history of life-threatening illnesses



Colorado Department of Public Health and Environment, 2011;
Oregon Public Health Authority, 2011

Poor Regulation



The Colorado State Auditor concluded that:

- 50% of ALL recommendations made by only TWELVE physicians



Colorado Office of the State Auditor, 2013

Conclusions



- Strong evidence of medicinal effects of smoked marijuana remains elusive.
- This is not to deny that marijuana may actually confer therapeutic benefit in specific cases, only that we currently *don't have rigorous evidence* that:
 - smoking marijuana has clinically significant medical benefits,
 - these benefits outweigh potential risks of addiction/cognitive side effects/mental health vulnerabilities
- *If patients have a medical problem, chances are, there are far more effective treatments than smoked marijuana*, treatments that have undergone meticulous testing procedures to minimize risk.

Educational Objectives



1. Describe the mechanism of action of marijuana.
2. Discuss marijuana's effects on health and its potential for addiction.
3. Explain the problems with the current system of medical marijuana.
4. Discuss alternatives to using medical marijuana.

Strategies to Address Neuropathy and Pain



- Pain relief is the most common reason for medical marijuana use for among general population
- Non-pharmacological options:
 - Physical therapy
 - Exercise
 - Relaxation techniques
 - Guided imagery
 - Massage
 - Biofeedback
 - Acupuncture
 - Hot/cold compresses
 - Deep breathing
 - Meditation
 - Hypnosis
 - Distraction

Strategies to Address Sleep Difficulties



- Sleep is the second most common reason for medical marijuana use for among general population
- Tips to help with sleep:
 - Go to bed and wake up the same time every day
 - Avoid caffeine and nicotine
 - Avoid alcohol, large meals, and beverages before bed
 - Don't exercise late in the day
 - Relax before bed (hot bath)
 - Create a good sleeping environment without distractions (avoid noise, bright lights, TV/computer in bedroom)

Additional Strategies to Address Anxiety/Depression



- Psychotherapy and group therapy
 - Talk to learn about mental health conditions, moods, thoughts, and behavior
 - Learn better coping and stress-management skills
- Medications
 - Antidepressants and anti-anxiety medications
 - Work by altering neurotransmitter activity

If Patients are Using Marijuana



- Screen for signs of abuse/dependence
 - Tolerance/withdrawal
 - Anger or Aggression
 - Decreased Appetite / Weight Loss
 - Irritability
 - Nervousness / Anxiety
 - Restlessness
 - Sleep Difficulties / Strange Dreams

If Patients are Using Marijuana



- Other signs of abuse/dependence
 - Preoccupation
 - Loss of control
 - Continued Use in the face of adverse consequences
 - Cognitive Distortions/Denial

Take-Away Points



- Medical marijuana provides real relief for some patients (question is WHY?)
- However, marijuana is not clearly superior to other, safer treatments
- Providers should educate patients about the risks associated with medical marijuana, and alternatives to its use

3/11/15: NYT editorial in favor of rescheduling marijuana; Response:



- As a scientist and a psychiatrist from across the pond, I, like many of my colleagues outside the US, am uncertain what “medical” marijuana actually is, other than physician-endorsed supply of recreational cannabis to patients with existing health problems. I have not seen any good quality evidence in the form of randomised-controlled trials in medical journals describing the benefits of “medical” marijuana over placebo. The proposed re-scheduling of cannabis in your country may allow this research to be conducted with less difficulty in the future but, until such research is conducted, reviewed and published, it seems not sensible that American physicians are being apparently used to circumvent prohibition.

Questions????