Cannabis the changing landscape

MONIKA KOCH 2018

No conflicts of interest to disclose

Learning objectives

1) Use a clear algorithm to be able to assess the patients' use of cannabis.
2) Engage in a direct and scientifically backed conversation about the pros and cons of cannabis use and its effects on their patients' health.

What I will talk about

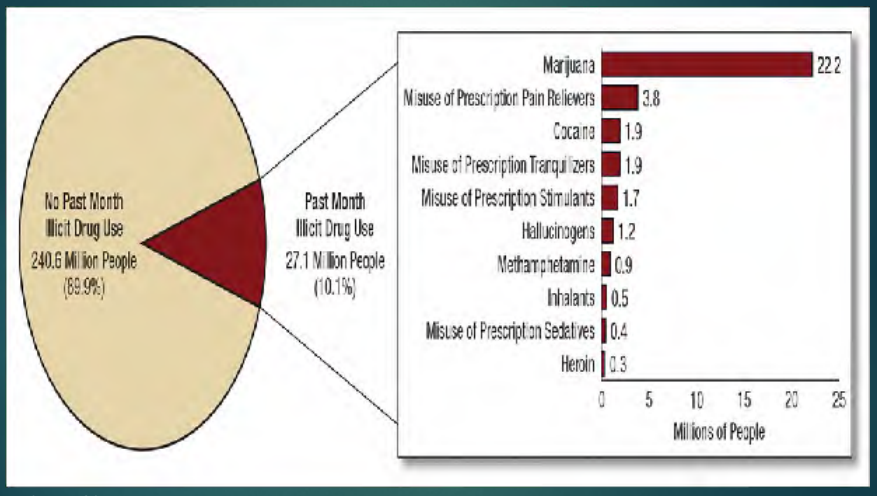
- What is it and how is it used
  - epidemiology/pharmacology
  - preparations
  - Selected Physiological effects
- Clinical Presentation
  - Cannabis use / cannabis use disorder
  - Comorbidity
  - Cannabis and psychiatric disorders
- Some comments on "medical cannabis"
- Policy issues

Epidemiology cannabis use

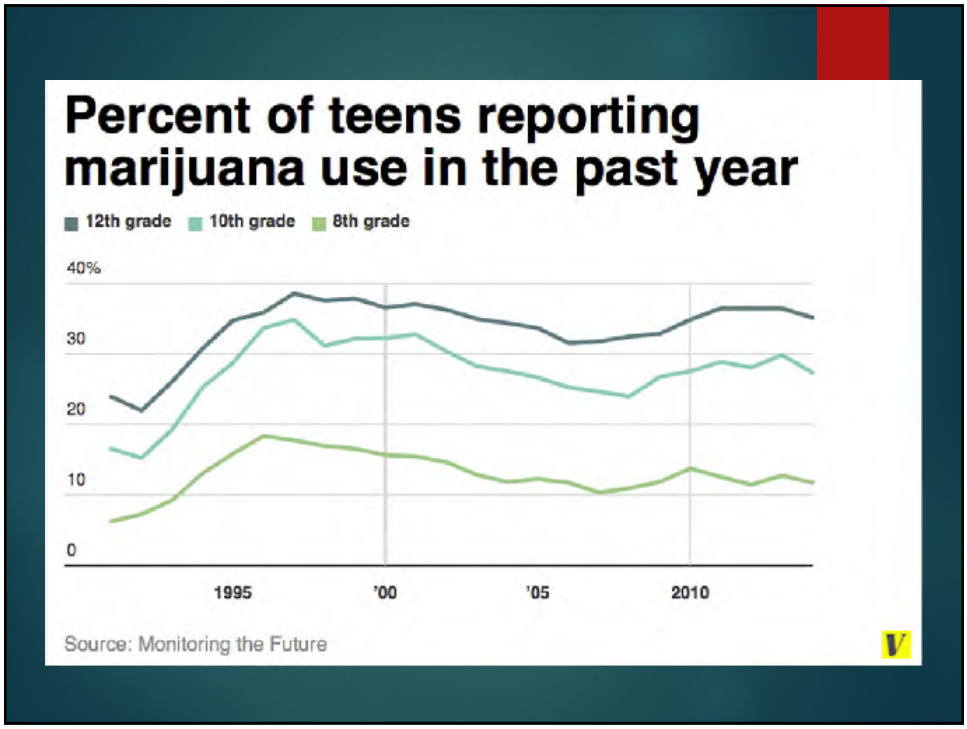
- Most commonly used illegal substance in the world
- Lifetime prevalence US 42-46%
- Past year use highest in young adults (18-25)
- Greater increase in use in MML states vs non-MML
- Greater use has not translated to higher CUD in adults from 2002 vs 2014

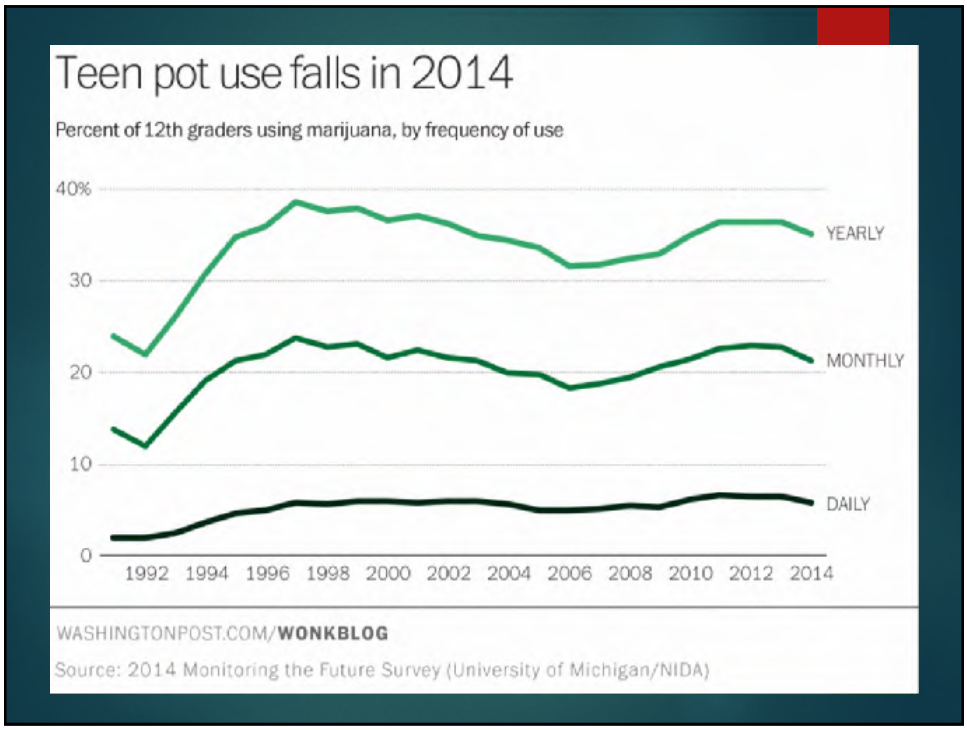
- Hasin JAMA 2017, DuPont 2014 Up to date, Compton 2016

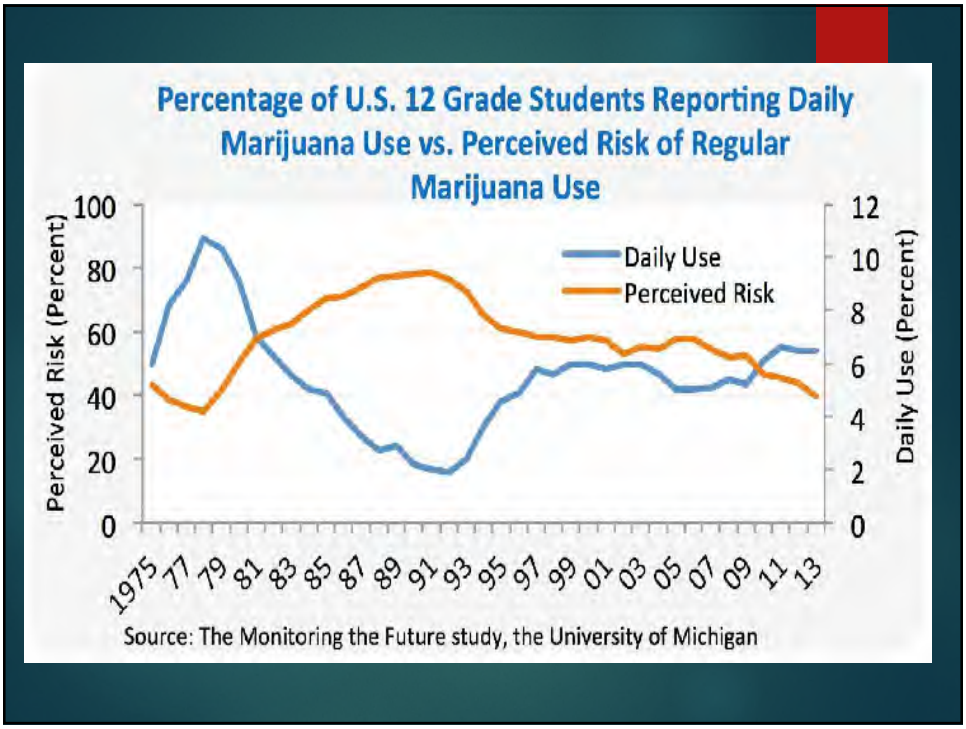
Epidemiology



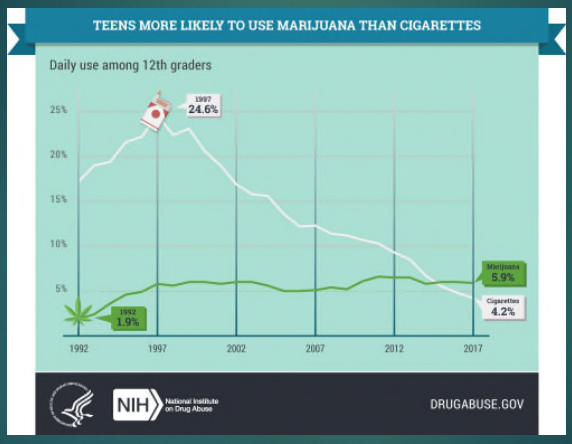
NSDUH 2015
https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.htm#fig1


Percent of teens reporting marijuana use in the past year
12th grade
10th grade
8th grade
40%
30
20
10
0
1995
'00
'05
2010
Source: Monitoring the Future


Teen pot use falls in 2014
Percent of 12th graders using marijuana, by frequency of use
40%
30
20
10
0
YEARLY
MONTHLY
DAILY
1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014
WASHINGTONPOST.COM/WONKBLOG
Source: 2014 Monitoring the Future Survey (University of Michigan/NIDA)



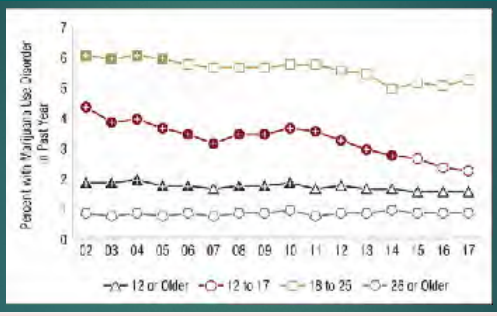
NIH: Teens more likely to use marijuana than cigarettes



+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.

FFR1.34

Marijuana Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: Percentages, 2002-2017



Monitoring the future 2017

Age Group	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
12 or Older	1.8+	1.8+	1.9+	1.7+	1.7+	1.6	1.7+	1.7+	1.8+	1.6	1.7	1.6	1.6	1.5	1.5	1.5
12 to 17	4.3+	3.8+	3.9+	3.6+	3.4+	3.1+	3.4+	3.4+	3.6+	3.5+	3.2+	2.9+	2.7+	2.6	2.3	2.2
18 to 25	6.0+	5.9+	6.0+	5.9+	5.7	5.6	5.6	5.6	5.7	5.7	5.5	5.4	4.9	5.1	5.0	5.2
26 or Older	0.8	0.7	0.8	0.7	0.8	0.7	0.8	0.8	0.9	0.7	0.8	0.8	0.9	0.8	0.8	0.8

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.

Cannabis use disorder lifetime prevalence

- Whole population ca 1-5%
- Cannabis users -ca 9%
- Adolescent users – 17% CUD
- Daily users -> 25-50% CUD
- Start before age 18-> 4-7 x higher risk for CUD
- Past year CUD highest in age 21-26
- 2015 about 4 mill CUD and 138 000 sought treatment voluntarily

NIDA drug facts 2012

Cannabis preparations






Marijuana:
THC average 12% in 2014 (was 3-4% in 1995'

Kief (trisomes) – 20-60%
Hashish – up to 65%
Wax – 80-95%

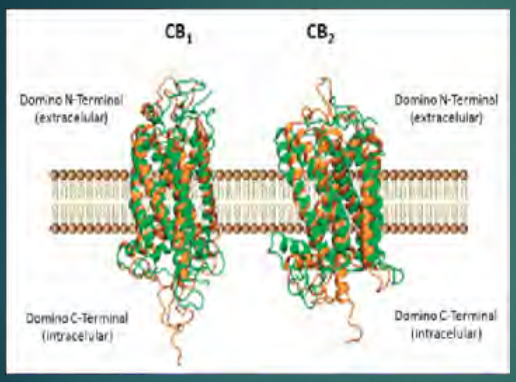
Cannabis products



Cannabis products

Cannabis products

Cannabis physiology



Cannabinoides: una prometedora herramienta para el desarrollo de nuevas terapias Anales de la Real Academia de Farmacia · June 2014

G-protein coupled
Also interact with other GPCR and ion channels

Endocannabinoids
- anandamide
- 2-arachidonoyl glycerol

THC – main psychoactive compound, binds to CB1 and CB2

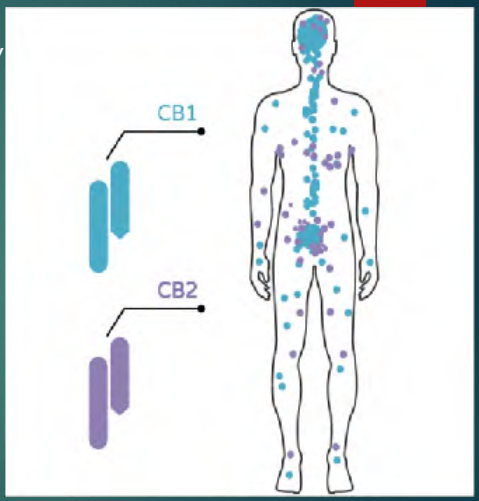
CBD – low affinity to CB1/CB2, not psychoactive, antiepileptic properties

Cannabis physiology

CB1 – most frequent, mostly in brain, presynaptic -> stimulation suppresses neuronal excitability and inhibits neurotransmission

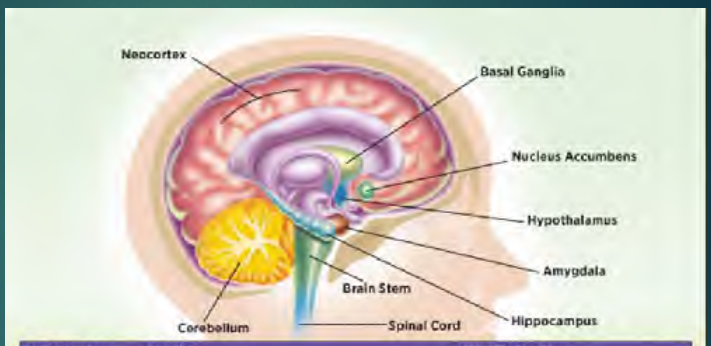
CB2 – less frequent and seems to be more in immune cells

Can be seen as neuromodulator more than usual neurotransmitter



https://spectrumcannabis.com/international/en/health-professionals

Cannabis physiology



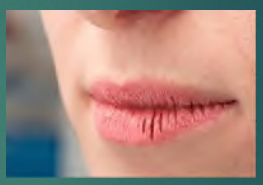
Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

The brain structures illustrated above all contain high numbers of CB receptors

http://headsup.scholastic.com/students/endocannabinoid

Cannabis intoxication:

psychological / behavioral impairment + 2 symptoms within 2 hours



Cannabis withdrawal - >=3 within first week

- Irritable
- Nervous
- Insomnia
- Reduced appetite
- Restless
- Depressed
- Physical sx






Treatment

- Gabapentin 1200 mg/d vs placebo -> reduced withdrawal symptoms and UA less + *(Mason BJ 2012 n=5-)*
- NAC 1200 mg bid vs placebo -> NAC less UA + *(Gray KM 2012 n=116 adolescents)*

Cannabis withdrawal scale

1. The only thing I could think about was smoking some cannabis
2. I had a headache
3. I had no appetite
4. I felt nauseous (like vomiting)
5. I felt nervous
6. I had some angry outbursts
7. I had mood swings
8. I felt depressed
9. I was easily irritated
10. I had been imagining being stoned
11. I felt restless
12. I woke up early
13. I had a stomach ache
14. I had nightmares and/or strange dreams
15. Life seemed like an uphill struggle
16. I woke up sweating at night
17. I had trouble getting to sleep at night
18. I felt physically tense
19. I had hot flashes

Allsop 2011

Cannabis use disorder

Two within 12 months

- Larger amounts , longer than intended
- Persistent use / unsuccessful cut down
- A great deal of time spent
- Cravings
- Failure at major obligations
- Persistent social/ interpersonal impairment
- Important activities reduced
- Recurrent use in hazardous situations
- Use despite consequences
- Tolerance
- Withdrawal

DSM 5

CUDIT-R

Adamson SJ, Kay-Lambkin FJ, Baker AL et al. An improved brief measure of cannabis misuse: The cannabis use disorders identification test – Revised (CUDIT-R). Drug and Alcohol Dependence. 2010;110:137-143.

Have you used cannabis over past 6 months?

If YES:

1. How often do you use cannabis?
2. How many hours were you "stoned" on a typical day ...?

How often during the past 6 months ...

3. did you find that you were not able to stop using cannabis once you had started?
4. did you fail to do what was normally expected from you because of using cannabis?
5. have you devoted a great deal of your time to getting, using, or recovering from cannabis?
6. have you had a problem with your memory or concentration after using cannabis?
7. How often do you use cannabis in situations that could be physically hazardous, ...?
8. Have you ever thought about cutting down or stopping...?

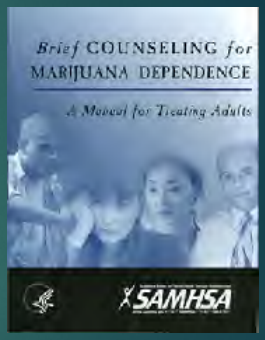
Cannabis use disorder treatment
Medication

- Levin FR 2011: RTC, n=156
  - Dronabinol (Delta – 9 THC) : 20 mg bid vs placebo -> higher retention and reduced withdrawal symptoms
- Allsop DJ 2014: RTC n=51
  - Nabiximols (Sativex - (ca 80mg THC:80mg CBD) vs placebo -> higher retention and reduced withdrawal symptoms

Levin 2011, Allsop 2014

Cannabis use disorder treatment
Behavioral interventions

- good evidence for
  - Cognitive Behavioral Therapy
  - Motivational Interviewing
  - Contingency Management
  - Group therapy



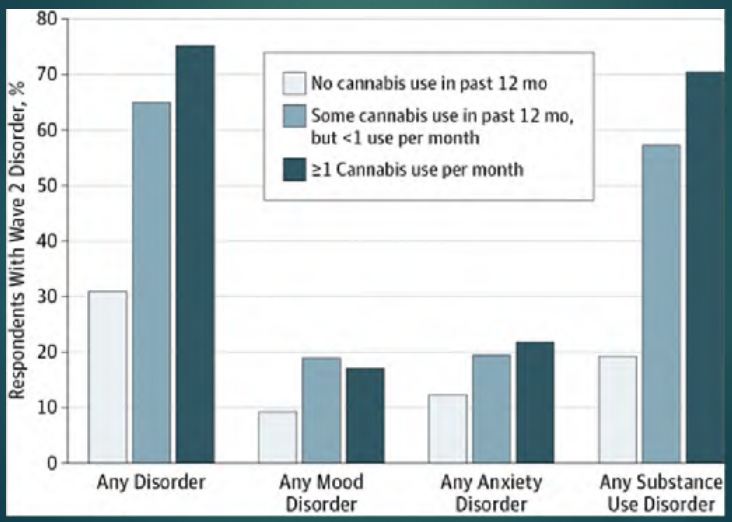
DuPont 2014 (up To Date)

Comorbidity: CUD and other SUD

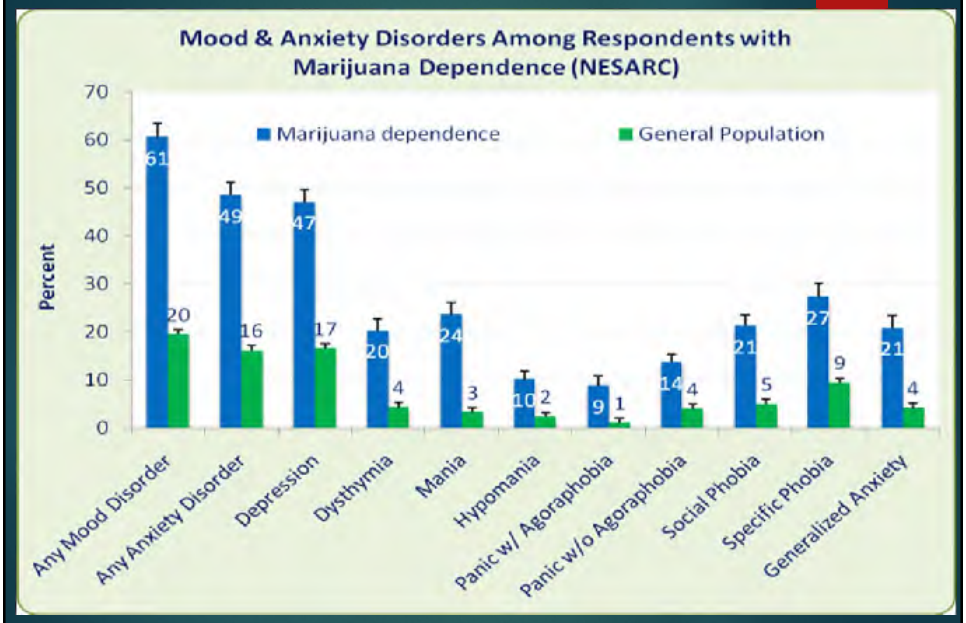
- N = 34653 respondents NESARC
- Prospective study , subjects > 18y/o interviewed 2001-02, 2004- 05
- Cannabis use associated with increase of
  - SUD (OR 6.2)
  - CUD (OR 9.5)
  - AUD (OR 2.7)
  - Nicotine dependence (OR 1.7)
- Cannabis use did not increase mood or anxiety disorder risk

Blanco 2016 - JAMA

Comorbidity: Mood and anxiety disorders



Blanco et al 2016



American College of pediatricians 2017

Co-morbidity: Social anxiety disorder (SAD) and cannabis use disorder (CUD)

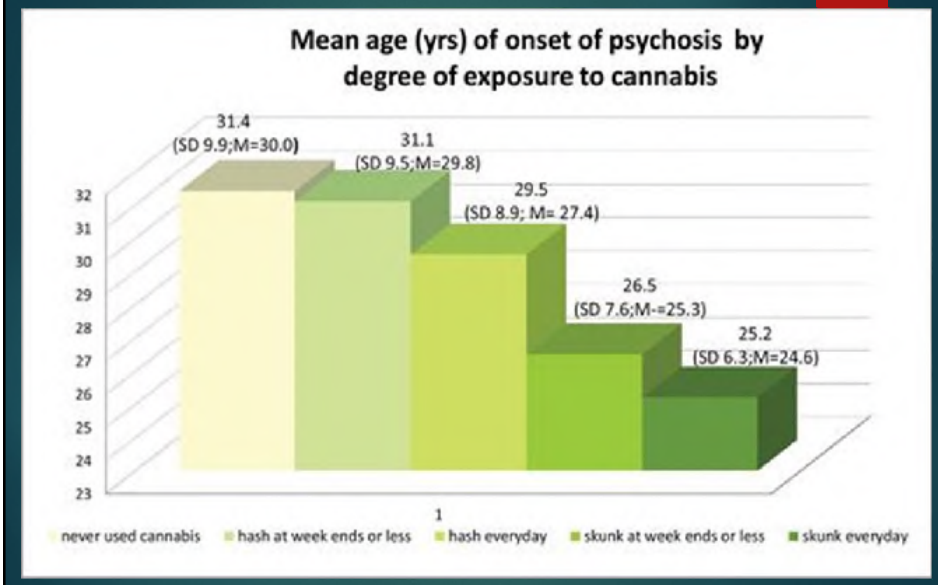
- Severe CUD -> 21% SAD
- Mild-moderate CUD – 8.6% SAD
- 80% SAD preceded CUD
  - "self medication"
  - Benefit from anxiety management tools and treatment
- 15% CUD preceded SAD
  - Cannabis related behaviors result in problems in social interactions
  - SUD treatment tools

Buckner 2012
Comorbidity of SAD and CUD

Cannabis and psychosis

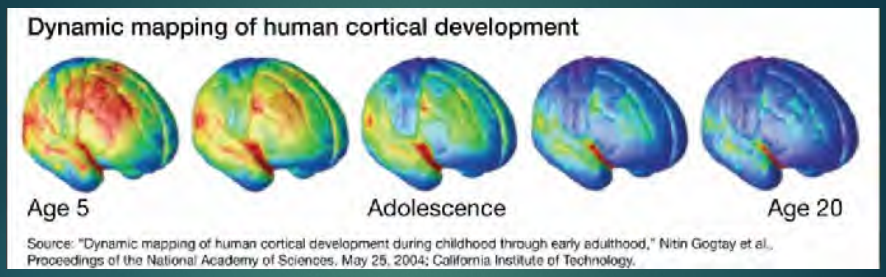
- Increased Risk of psychosis developing – causal relationship unclear
- Dose / frequency of use dependent risk
  - High potency users had onset up to 6 y earlier
- Cannabis users have onset of psychosis about 3 y earlier
- Cannabis use onset < 15 y/o earlier onset of psychosis than cannabis use onset > 15 y/o

Moore 2017, DiForti 2013



DiForti 2014

Cannabis and adolescence



Examples:
Endocannabinoids involved in
development of nerve tracts
maturation of other neurotransmitter systems
Users need to recruit more areas of brain for cognitive tests

https://www.csam-asam.org/sites/default/files/impact_of_marijuana_on_children_and_adolescents.pdf

Cannabis and adolescence

- Heavy Cannabis use in adolescence associated with (? causal)
  - Poor school performance (enter college 3.3x less often), higher HS drop out rate (x 5.8)
  - Increased welfare dependence and unemployment
- Dunedin Study , age 13-38, most persistent users reduced neuropsychological results equivalent to drop in IQ of about 6 points
- Structural changes in brain
- Higher risk of CUD
  - **Therefore: Deter, Delay, detect**

https://www.apa.org/monitor/2015/11/marijuana-brain.aspx
https://www.csam-asam.org/sites/default/files/impact_of_marijuana_on_children_and_adolescents.pdf

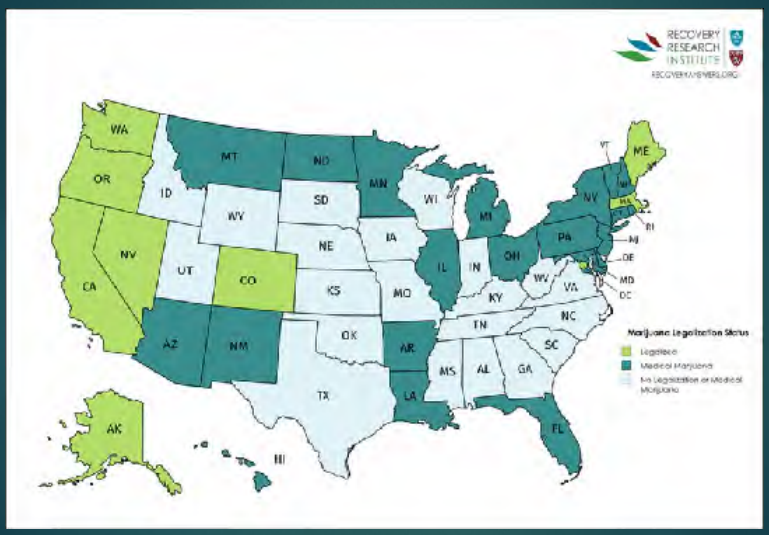
Cannabinoids as medication

- **Cannabidiol (Epodiolex®)**
  (FDA News Release June 25, 2018)
  - **oral preparation**
  - **Indicated for** Lennox-Gastaut syndrome and Dravet syndrome, in patients > 2 y/o
  - **Estimated cost $32,500 per year**
- Dronabinol (Marinol ®) (Delta – 9 THC)
  - Schedule III
  - anorexia associated AIDS, nausea/vomiting associated with chemotherapy
  - Wasting syndrome with HIV

Cannabinoids as medication

- Nabilone (Cesamet®)
  - Schedule II
  - Synthetic cannabinoid – similar to Delta 9 THC
  - indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

Legal status of marijuana in USA



https://geostar.info/us-marijuana-legalization-map.html#

"Medical" Marijuana

- Psychiatric
  - APA 2013 : no current psychiatric indications but more study warranted
- Non-psychiatric
  - Nausea/vomiting related to chemotherapy
  - Anorexia/Wasting related to HIV

APA 2013, Abramowicz 2017 JAMA

"Medical" Marijuana

- Non-psychiatric
  - Pain syndromes
    - Chronic pain : 6 studies , n=325
    - Neuropathic pain: 6 studies, n=396
  - spasticity related to Multiple Sclerosis
    - 12 studies, n=1200

Abramowicz 2017 JAMA, Hill 2015 JAMA

Medical cannabis recommendation rules

- Guidelines for recommending Medical cannabis Medical Board April 2018
  - ***Qualifying Conditions:*** At this time, there is a lack of evidence for the efficacy of cannabis in treating certain medical conditions. Recommending cannabis for medical purposes is at the professional discretion of the physician.
  - If recommending medical cannabis, monitor treatment like any other medication

https://www.mbc.ca.gov/Publications/guidelines_cannabis_recommendation.pdf

Medical cannabis considerations

- Considerations for patient with chronic pain and on opioids using cannabis
  - Not same mechanism for analgesia
  - Concurrent use similar to other concurrent use of potentially addiction substances, e.g. alcohol
  - Can test in UA longer – harder to hide
  - Case by case, would avoid when you can

https://www.mbc.ca.gov/Publications/guidelines_cannabis_recommendation.pdf

Cannabis use considerations

- Metabolism
  - THC is metabolized by CYP2C9 and CYP3A4
  - CBD, but not THC, is metabolized by CYP2C19
  - THC is a CYP1A2 inducer
  - CBD is a potent inhibitor of CYP3A4 and CYP2D6
- Alcohol - Alcohol may ↑ THC levels (Hartman 2015)
- CNS depressants - Cannabis has additive CNS depressant effects with alcohol, barbiturates and benzodiazepines. In a small study, cannabis did not have additive CNS effects when combined with opioids (Abrams et al 2011).

https://doh.dc.gov/sites/default/files/dc/sites/doh/publication/attachments/Medical%20Cannabis%20Adverse%20Effects%20and%20Drug%20Interactions_0.pdf

TPMG policy

- What is KP policy on Cannabis use in our members (if any)?
  - Policy for not allowing it with opioids is revisited in TPMG
  - No policy for concurrent use of BZD and stimulant medication
  - Policy of not giving medical cannabis recommendation not changed
- What is KP policy on Cannabis use in our providers?
  - No policy in TPMG

Summary

- Cannabis
  - remains the most commonly abused drug and is most harmful in youth and young adults.
    - -> DETER, DELAY, DETECT
  - Causes syndromes of intoxication and withdrawal
- CUD
  - CUD has not increased, 1-5% in population and 17% in adolescent users
  - diagnosis requires open conversation and ratings scales are useful
  - Treatment focus is behavioral and medication use for withdrawal

Summary *(continued)*

- Cannabis use is associated with
  - higher risk for SUD but not anxiety or mood disorder
  - Worse outcome of psychotic disorder
- CUD is associated with higher risk of mood and anxiety disorders
- Cannabinoid medication approved for nausea/vomiting, wasting syndrome, specific seizure disorders
- No evidence based psychiatric indication for cannabinoids at this time
- If you recommend "medical marijuana" monitor it as any other medication

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SELF-ASSESSMENT QUESTIONS

SA-Q#1: Past year cannabis use is highest among which age group?

A. Age 12-17
B. Age 18-25
C. Age 26-35
D. Age 36-45

SA-Q#2. Risk of use disorder shown to be associated with which of the following? *(Select all that apply)*

A. Parental attitudes towards use
B. Early onset (adolescent) use
C. Route of administration
D. Regular/daily use

SA-Q#3. Cannabis is NOT legal for recreational use in which one of the following states as of 2018?

A. Washington
B. Massachusetts
C. California
D. Nevada
E. New York

SA-Q#4. FDA approved indications for cannabinoids include which of the following? *(select all that apply)*

A. Insomnia related to PTSD
B. Glaucoma
C. Seizure disorder
D. Nausea/vomiting related to chemo/HIV
E. Chronic pain/spasticity

SA-Q#5. In Buckner's study in 2012, Social Anxiety Disorder preceded Cannabis use disorder in what percentage of patients?

A. 20%
B. 40%
C. 60%
D. 80%


Thank
You