



Neuropsychiatric Aspects of Marijuana Use

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3/23/18

Disclosures

My spouse is employed by Denali Therapeutics and he is a stockholder

Objectives

- ▶ Participants will be able to:
 - ▶ Discuss the relative potency of different forms of marijuana
 - ▶ State ways in which risks are different for adolescent users vs adult users of marijuana
 - ▶ Discuss the risks vs benefits of using different forms of marijuana and tailor patient education based on the unique characteristics of the patient.
 - ▶ State the literature findings regarding IQ and psychosis for marijuana users
 - ▶ State several medical conditions where there is some evidence for the beneficial effects of marijuana



When a patient says they smoke Marijuana what image comes to mind?

When a patient says they smoke Marijuana what image comes to mind?





300+ TYPES OF EDIBLES



MARIJUANA HASH & CONCENTRATES



HASH



BUBBLE HASH



HASH OIL



WAX



SHATTER



LIQUID THC

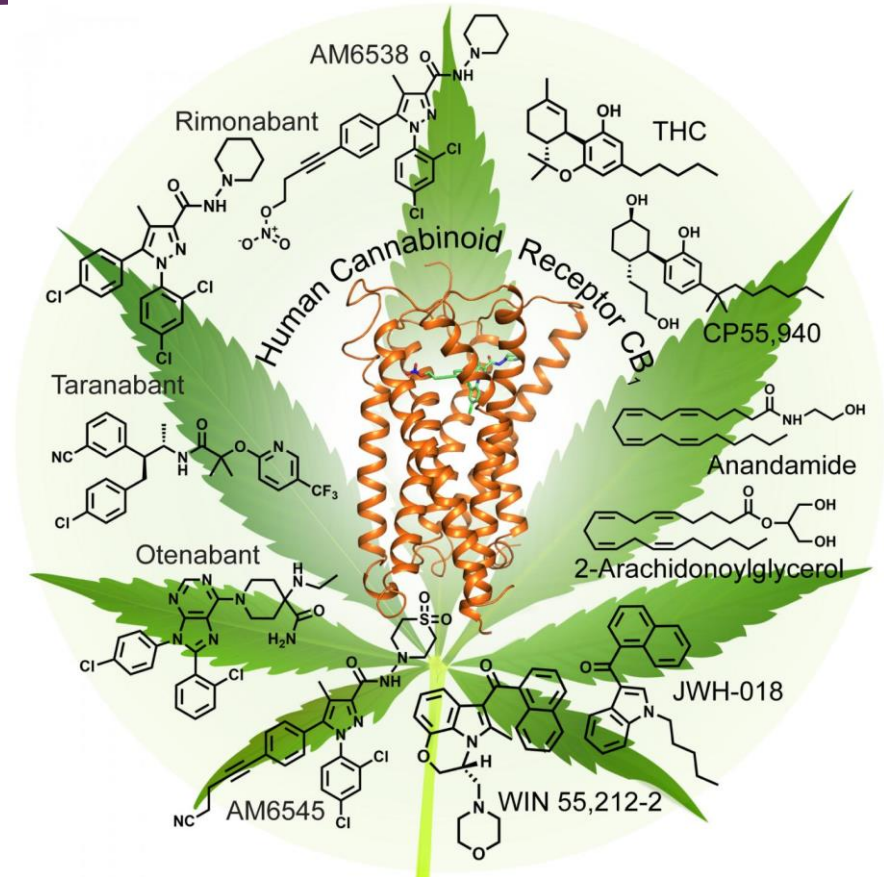
Routes of Administration

- ▶ Smoking (joint, blunt)
 - ▶ Immediate onset, lasts 1-3 hours
- ▶ Vaporizing – heat to ~200 degrees C (below point of combustion)
 - ▶ Near immediate onset
- ▶ Oral ingestion
 - ▶ Delay in onset 30 – 60 minutes, lasts up to 4 hours, variable 1st pass metabolism
- ▶ “Blasting dabs”



Marijuana is complex from a pharmacological point of view

- ▶ “Cannabinoids” – General term for all compounds from the cannabis plant
- ▶ THC is the major psychoactive component
- ▶ Cannabis/Hemp plant makes ~400 chemicals
 - ▶ ~ 70 of these are true “cannabinoids” (structurally)
 - ▶ Some psychoactive and some not
 - ▶ Notable nonpsychoactive compounds include cannabitol and cannabidiol



Different THC Concentration in Various Parts of the Cannabis Plant

Cannabis Anatomy



- ▶ Potency in descending order:
 - ▶ Flowers
 - ▶ Upper leaves
 - ▶ Lower leaves
 - ▶ Stems
 - ▶ Seeds

Different THC Concentration in Various Parts of the Cannabis Plant

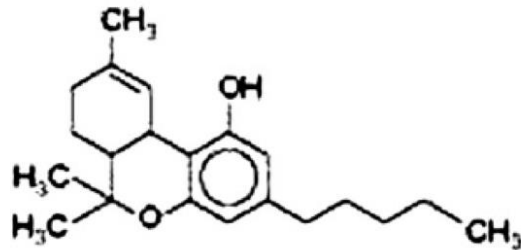
Cannabis Anatomy



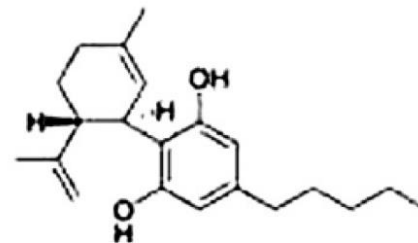
- ▶ Percentage by weight of THC content:
 - ▶ **0.5%-5% THC:** MJ containing mostly leaves and stems
 - ▶ **2%-8% THC:** Hashish, dried cannabis resin and compressed flowers
 - ▶ **7%-30% THC:** Flowering tops of female plants ("sinsemilla")
 - ▶ **15%-80% THC:** Hash Oil, organic solvent used to extract THC from Hashish or MJ
 - ▶ "Fiber type" cannabis, has low THC content **<0.4%** but higher cannabidiol content

Components of Cannabis

- ▶ Delta-9-tetrahydrocannabinol = THC
 - ▶ Main component of cannabis responsible for the high of smoking cannabis
 - ▶ Associated with psychosis
- ▶ Cannabidiol (CBD)
 - ▶ Does not produce a high
 - ▶ Anxiolytic, sedative, anticonvulsive, antiemetic, **antipsychotic**, anti-inflammatory and antitumor effects



Tetrahydrocannabinol
(Δ9-THC)



Cannabidiol (CBD)

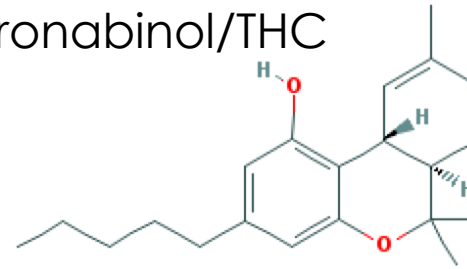
THC to CBD ratio

- ▶ Generally a THC-to-CBD ratio of 1:1 is thought to be clinically preferable for medical marijuana
- ▶ Street Cannabis THC/CBD ratio:
 - ▶ 1995 it was 14:1
 - ▶ 2014 it was 80:1

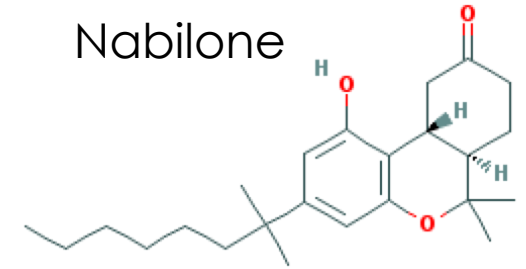
FDA Approved Medications Derived from Cannabis

- ▶ US FDA Cannabis-derived compounds approved for nausea/emesis associated with cancer chemotherapy and/or cachexia from wasting diseases:
 - ▶ Dronabinol (Marinol) – synthetic THC
 - ▶ Schedule III
 - ▶ Nabilone (Cesamet)
 - ▶ Schedule II
 - ▶ Syndros (liquid synthetic THC) – Schedule II

Dronabinol/THC



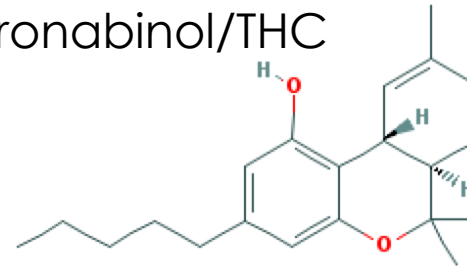
Nabilone



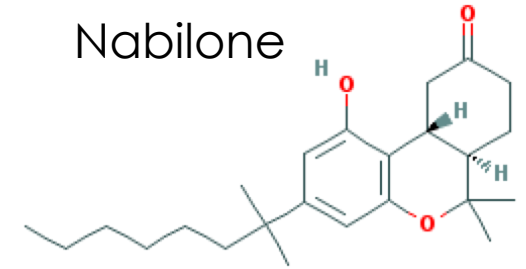
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 - ▶ Syndros (liquid synthetic THC) – Schedule II
- ▶ Nabiximols (Sativex) – THC/cannabadiol (1:1) spray (not approved in US yet) likely will be approved for cancer pain and spasticity in multiple sclerosis.
- ▶ Cannabidiol (Epidiolex) – Orphan drug status in US for the pediatric epilepsy syndromes of Dravet and Lennox-Gastaut syndromes

Dronabinol/THC

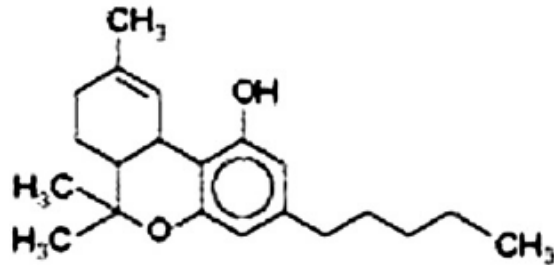


Nabilone

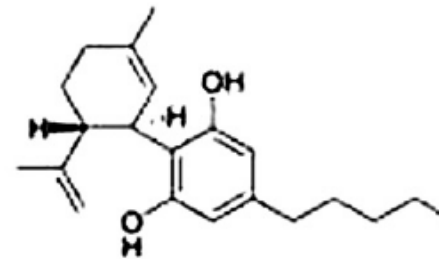


Plant Derived versus Endogenous Ligands for Human Cannabis Receptors

Exocannabinoids (plant-derived)

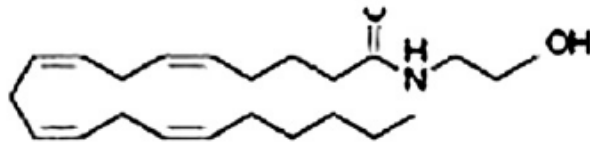


Tetrahydrocannabinol
(Δ9-THC)

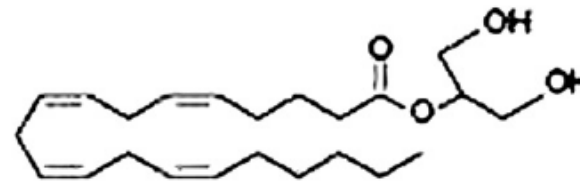


Cannabidiol (CBD)

Endocannabinoids



Anandamide
(AEA)



Arachidonoylglycerol
(2-AG)

Brain's Chemical



Anandamide

Drug



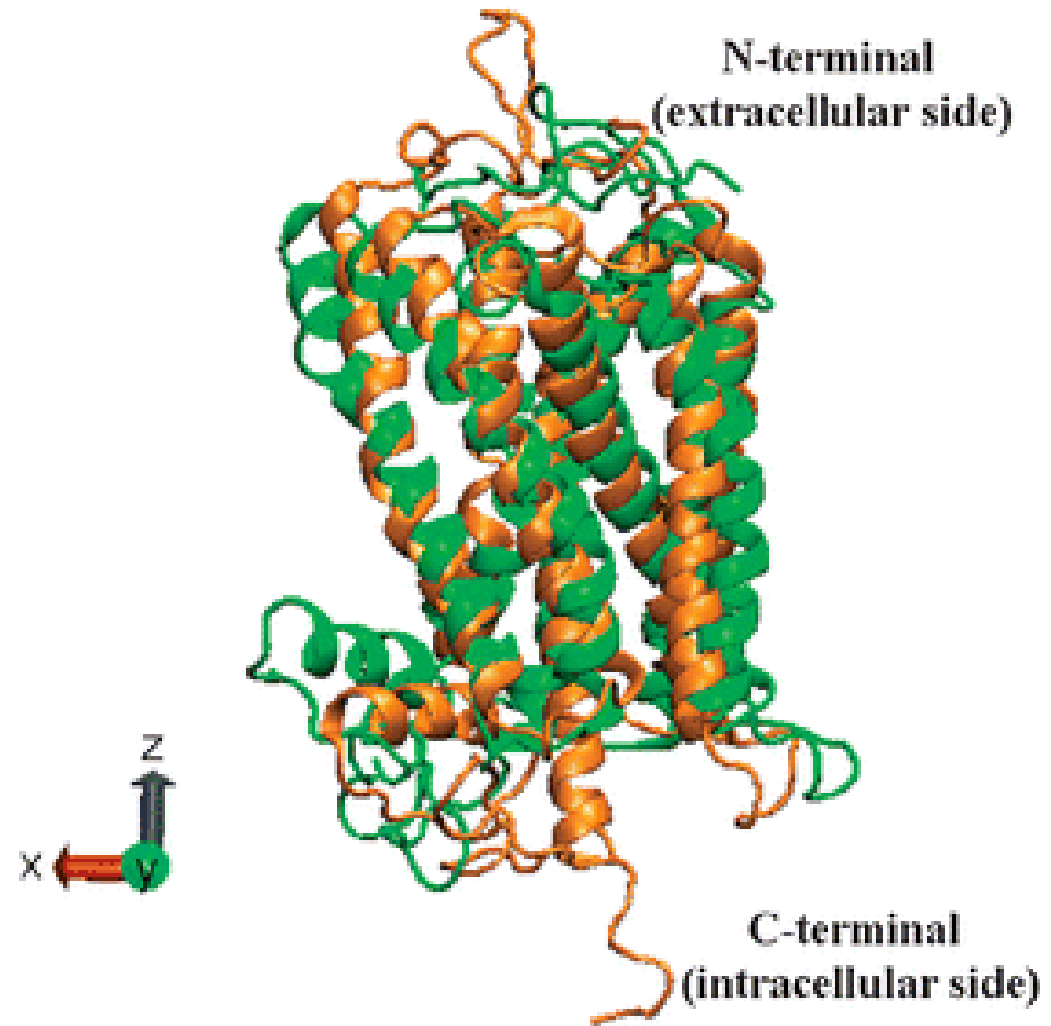
THC



CB1



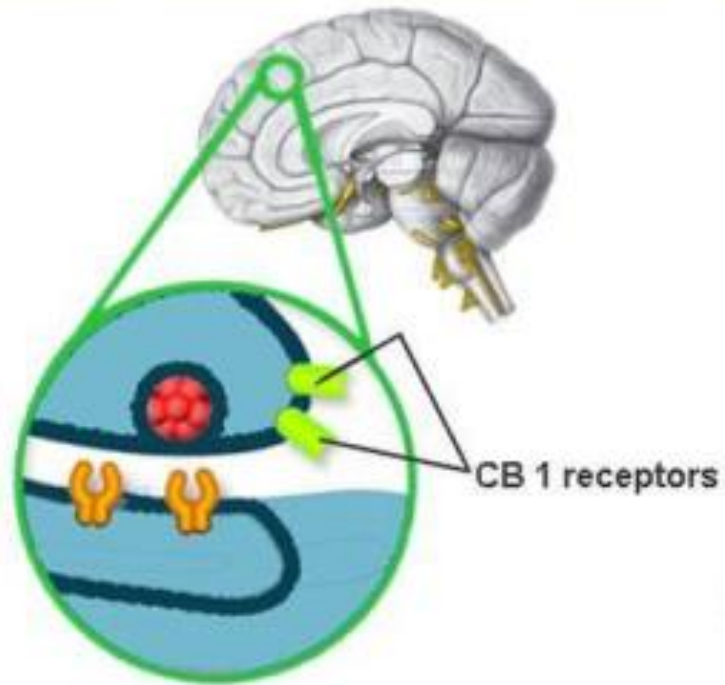
CB2



Mode of action

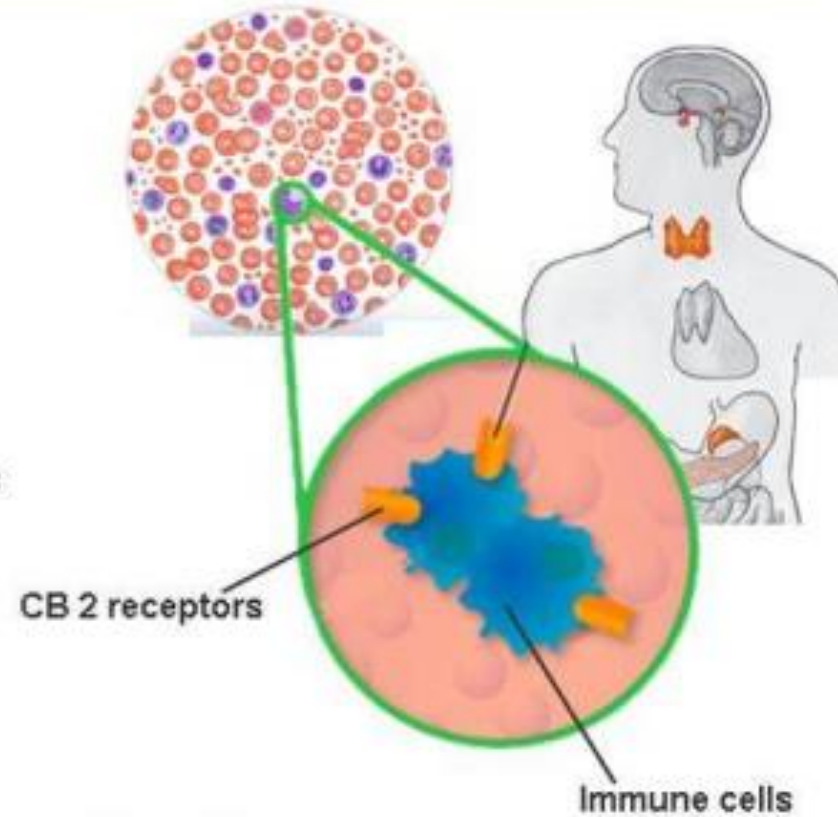
CB1 receptors

mainly localized in the brain
(hippocampus, cerebellum and cerebrum)



CB2 receptors

mainly situated in the periphery
(spleen, tonsillar and immune cells)



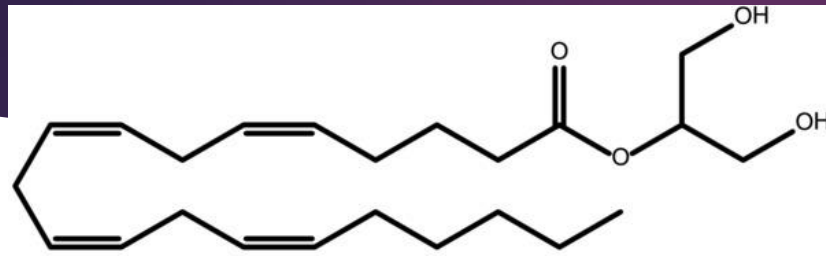
Natural versus Synthetic Ligands for CBRs

- ▶ Spice
- ▶ K2
- ▶ Kush
- ▶ Potpourri
- ▶ Skunk
- ▶ Moon Rocks
- ▶ Genie
- ▶ Aroma
- ▶ Krypton
- ▶ Bonzai
- ▶ Rapidly evolving other names

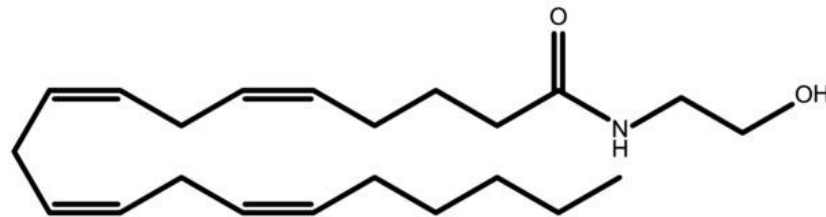
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- ▶ Bonzai
- ▶ Rapidly evolving other names
- ▶ “Probationer’s weed” (does not show on standard Utox)
- ▶ Variety of chemical structures
- ▶ UNTESTED FOR SAFETY IN HUMANS!!!!

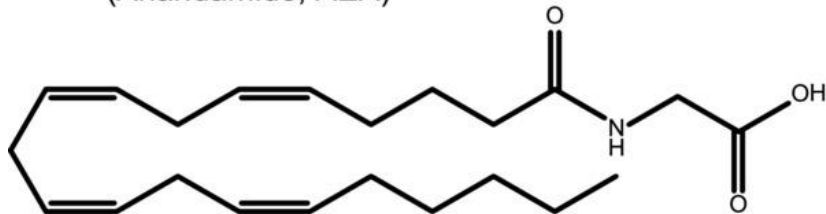
4 General Structural Classes of Cannabinoids



2-arachidonoyl glycerol
(2-AG)



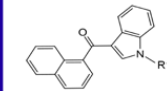
N-arachidonoyl ethanolamine
(Anandamide; AEA)



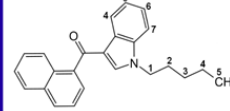
N-arachidonoyl glycine
(NAGly)

Aminoalkylindoles

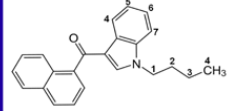
Naphthylindoles



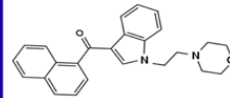
JWH-018*



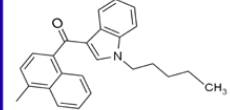
JWH-073*



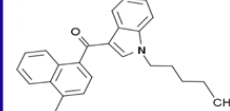
JWH-200*



JWH-122

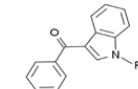


JWH-210

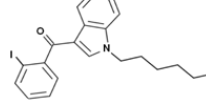


AM-2201

Benzoylindoles

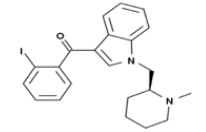


AM-694

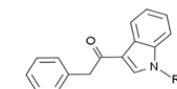


Pravadoline
(WIN-49,098)

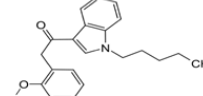
AM-2233



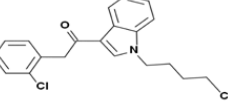
Phenylacetylindoles



JWH-250



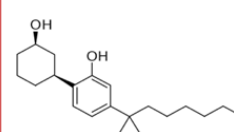
JWH-203



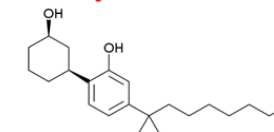
RCS-8

Cyclohexylphenols

CP-47, 497*

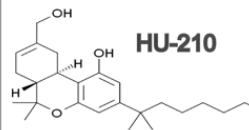


Cannabicyclohexanol*

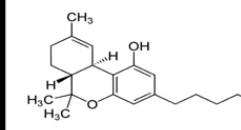


Classical Cannabinoids

HU-210



THC





In the late 2000s, two of Huffman's cannabinoid compounds began being sold in Germany as marijuana alternatives known as K2 and Spice.

"I figured once it got started in Germany it was going to spread. I'm concerned that it could hurt people," Huffman said. "I think this was something that was more or less inevitable. It bothers me that people are so stupid as to use this stuff".

Natural versus Synthetic Ligands for CBRs

- ▶ First introduced in 2004
- ▶ Generally full agonists (vs THC partial agonist)
- ▶ Binding affinities 5-10,000 times higher than THC at human CB-1/CB-2 receptors

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- ▶ Binding affinities 5-10,000 times higher than THC at human CB-1/CB-2 receptors
- ▶ Users describe as “intense and trippy”, higher doses lead to hallucinations/paranoia
- ▶ Herbs often used as carrier, “hot spots” can lead to huge batch to batch variations in potency.
- ▶ More likely to cause psychosis and adverse effects

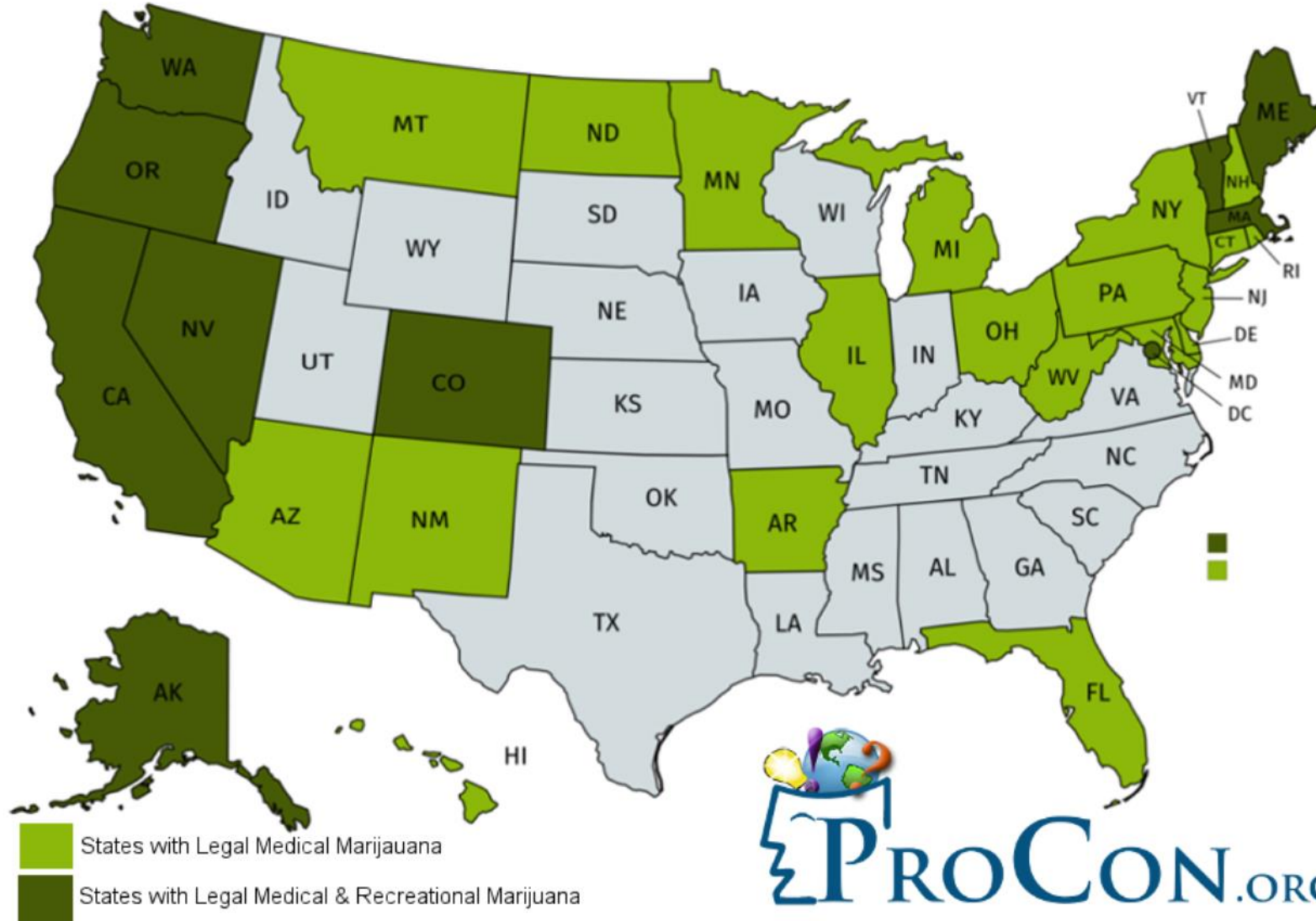
The Last Chemical Structure...I Promise



Clinical Uses of Medical Marijuana

- ▶ Conditions with multiple positive RCTs for Medical Marijuana:
 - ▶ Chronic Pain
 - ▶ Multiple Sclerosis
 - ▶ Neuropathic Pain
- ▶ Other conditions: epilepsy, ALS, Parkinson Disease, HIV/AIDS, Huntington Disease
- ▶ FDA approved Cannabis derived medications:
 - ▶ Dronabinol (Marinol) & Nabilone (Cesamet) are useful for nausea and cachexia
- ▶ In HIV + patients with cachexia, both smoked MJ and dronabinol (5mg) increased body weight in a dose dependent manner.
 - ▶ MJ caused intoxication
 - ▶ Dronabinol did not cause intoxication

29 Legal Medical Marijuana States & DC 9 Legal Recreational Marijuana States & DC



Clinical Aspects of Recommending Medical MJ

- ▶ Marijuana remains a Schedule I drug which has impeded research
- ▶ American Academy of Pediatrics has called for it to be rescheduled as a Schedule II substance to facilitate research
- ▶ Little research into efficacy, dosage, adverse effects and drug interactions for medical marijuana

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- ▶ Little research into efficacy, dosage, adverse effects and drug interactions for medical marijuana
- ▶ State laws generally suggest patients must have:
 - ▶ Debilitating condition
 - ▶ Multiple failed trials of FDA approved cannabinoids
 - ▶ Lack of substance use d/o, psychosis or unstable mood/anxiety d/o
 - ▶ Residence in a state where medical marijuana is legal
- ▶ Warn re psychiatric risk, operating a vehicle

Clinical Aspects of Recommending Medical MJ

- ▶ Clinicians may be hesitant to certify patients to receive medical MJ due to concerns over variability in dosing once at the dispensary
 - ▶ Clinicians who were eligible to certify patients for access to marijuana were less likely to recommend it than those who were not eligible to certify (85% vs 92%)
- ▶ Clinicians cited lack of knowledge of state vs federal laws, lack of education, and lack of evidence based research as the key barriers to certifying patients to receive MJ

Clinical Aspects of Recommending Medical MJ

- ▶ “And with the current system, I have no control. I would certify it, and then my patients would go to a [dispensary] that has nothing to do with me, yet decides which brand to give, which strain to give, whether to go up or go down in dosage.”
- ▶ Stefan Friedrichsdorf, MD, medical director of the Department of Pain Medicine, Palliative Care and Integrative Medicine at Children’s Minnesota

Cannabinoid Dose and Label Accuracy in Medical Cannabis Products

- ▶ Studies suggest improved clinical benefit and fewer adverse effects with a THC:CBD ratio of 1:1.
- ▶ Purchased 75 different products from dispensaries in Seattle, LA, SF sent them for chemical analysis
- ▶ **Accurately labeled** was considered to be THC and CBD content within 10% of the labeled values, **underlabeled** if the content was more than 10% above the labeled values, and **overlabeled** if the content was more than 10% below the labeled values

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- ▶ With respect to THC content:
 - ▶ 17% were accurately labeled
 - ▶ 23% were underlabeled
 - ▶ 60% were overlabeled
- ▶ The **median THC:CBD ratio** of products with detectable CBD was **36:1**, 7 had ratios of less than 10:1, and **only 1 had a 1:1 ratio**

Medical Marijuana for Neuropathic Pain

- ▶ They looked at 16 studies with 1750 participants
 - ▶ Plant or synthetic THC, THC/CBD spray, herbal cannabis
- ▶ Primary Outcome: Cannabis-based medicines may increase the number of people with 50% or greater pain relief c/t placebo. NNT 20
- ▶ Secondary Outcome: 30% or greater reduction in pain c/t placebo. NNT 11

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- ▶ Secondary Outcome: 30% or greater reduction in pain c/t placebo. NNT 11
- ▶ Cannabis-based medicines may increase nervous system adverse events c/t placebo with NNH of 3
- ▶ Psychiatric disorders occurred in 17% of participants using cannabis-based medicines and in 5% of those using placebo with a NNH 8

Multiple Sclerosis

- ▶ Clinicians might offer oral cannabis extract for spasticity symptoms and pain (excluding central neuropathic pain) (Level A)
 - ▶ The subjective benefit is possibly maintained for 1 year
- ▶ Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols) for spasticity symptoms, pain, and urinary frequency (Level B)
- ▶ No evidence for efficacy with tremor
- ▶ “After cannabis treatment, the subjects consistently showed reduced cognitive performance (Paced Auditory Serial Addition Test)”
- ▶ Patients with MS fared worse on measures of posture and balance 10 minutes after smoking 1 marijuana cigarette (but control patients did not experience these effects)

Medical Marijuana and Epilepsy

- ▶ Cannabidiol has moderate anticonvulsive effects
- ▶ Starting in the 1940s it was used for children with treatment resistant epilepsy
- ▶ CB1 receptor plays a critical role in neuronal firing, being studied for treatment of epilepsy
- ▶ American Academy of Neurology has published a systematic review stating the evidence for **medical MJ (not CBD)** in controlling epilepsy is undetermined “data neither support nor refute”
- ▶ American Academy of Neurology goes on to say weigh risks/benefits carefully as the rate of serious psychiatric side effects was 1%

CBD and Epilepsy

- ▶ 2018 Systematic Review of CBD (and other MJ products) as an adjunctive medication for treatment resistant epilepsy
- ▶ CBD doses were 2.5 - 20 mg/kg/day
- ▶ Pharmaceutical grade CBD
- ▶ *Insufficient evidence for cannabis sativa, CBD:THC combinations, or oral cannabis extracts*

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- ▶ CBD doses were 2.5 - 20 mg/kg/day
- ▶ Pharmaceutical grade CBD
- ▶ *Insufficient evidence for cannabis sativa, CBD:THC combinations, or oral cannabis extracts*
- ▶ CBD was more likely to produce > 50% reduction in seizures c/t placebo (n = 291) with a NNT = 8
- ▶ 48% of patients achieved > 50% reduction in seizures
- ▶ ~ 5 % became seizure free
- ▶ NNT for improved quality of life was 5
- ▶ NNH 164 for pt to withdraw due to adverse effects
- ▶ NNH 3 for any adverse side effect

Schizophrenia and Marijuana Use

- ▶ Numerous large, prospective, longitudinal studies suggest that use of cannabis is associated with an increase in risk for schizophrenia, worsening symptoms, and is associated with a poorer prognosis (even after controlling for other substance use)
- ▶ THC can cause acute, transient and dose-dependent psychosis

Schizophrenia and Marijuana Use

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- ▶ THC can cause acute, transient and dose-dependent psychosis
- ▶ Risk factor but causality not established:
 - ▶ use of cannabis increases the risk of non-affective psychotic illness three- to seven fold
 - ▶ High potency cannabis daily use increases risk to 5-12 fold in various studies

Risk for Psychosis

- ▶ Bechtold et. al. found that for each additional year adolescent boys used cannabis, their frequency of subclinical paranoia and hallucinations rose 133% and 92% respectively.
 - ▶ Followed prospectively over about 20 years
 - ▶ Level of symptomatology persisted even after at least 1 yr of abstinence
- ▶ Bourque et. al. found the trajectory of increasing psychotic experiences was associated with steeper growth of cannabis use from age 13 to 16 (N = 2566)

Use or Symptom Measure	Odds Ratio
Years of weekly marijuana use	
0 years	—
1–2 years	0.85
≥3 years	3.63*
Test of linear trend	1.61
Years with paranoia	
0 years	—
1–2 years	3.63*
≥3 years	4.69**
Test of linear trend	2.21***
Years with hallucinations	
0 years	—
1–2 years	1.67
≥3 years	7.50***
Test of linear trend	2.43***

Bechtold, J., Hipwell, A., et. al. (2016) AJP vol 173, #8, p. 781-789.

Bourque, Afzali, O'Leary-Barrett J. Child Psychology and Psychiatry July 2017

Synthetic Cannabinoids

- ▶ Case reports of patient using spice who experience psychotic catatonia.
- ▶ Some reports of temporary Parkinson-like symptoms
- ▶ Synthetic Drug Abuse Prevention Act (2012), synthetic MJ products Schedule 1
- ▶ Review of 4000 cases (26 deaths) found most common side effects: tachycardia (33-77%), agitation (16-41%) and nausea (13-94%). Most people tolerate them fairly well actually.



Most individuals who use cannabis do not develop schizophrenia...

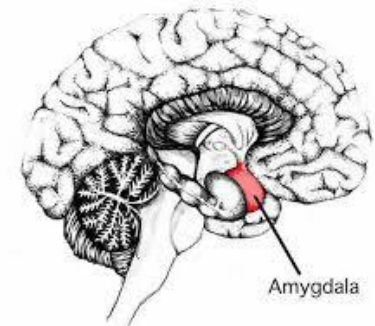
The strongest risk factor for schizophrenia remains having a close family member with schizophrenia

CBD as an adjunct for psychosis?

- ▶ RDBPC parallel group study of CBD 1000 mg/day as an adjunctive treatment for schizophrenia (N ~ 40 in each arm)
- ▶ Patients receiving CBD had significantly ($p = 0.02$) lower levels of positive psychotic symptoms but the effects were modest
- ▶ CBD treatment led to very few adverse effects
- ▶ Mechanism of attenuating psychosis unknown
 - ▶ Proposed that CBD inhibits the breakdown of anandamide, the endogenous ligand for CB1

Long-Term Cognitive Effects of Marijuana Use

- ▶ Although it is well established that acute use of cannabis impairs memory, executive functioning and attention, studies show varying effects on long term functioning (when not acutely intoxicated)
- ▶ After chronic use, most users do just as well as controls on simple tests of attention, memory, and executive functioning
- ▶ MRI functional imaging studies suggest people are able to compensate by recruiting other areas of the brain on simple and moderate complexity tasks.
- ▶ Impairment does seem to emerge in studies under complex and demanding situations



Cognitive Effects of Marijuana Use

- ▶ Exposure to cannabis during the adolescent period may induce long term cognitive impairments
- ▶ All stages of memory, including encoding, consolidation, and retrieval, are altered.
- ▶ Persistent users and dependent users lost about six IQ points, while nonusers gained about one IQ point (Meier et. al. (2012) PNAS, 109 # 40 p. 2657)
- ▶ Adolescent onset -8 IQ points
- ▶ The longer that cannabis is used, the more pronounced is the cognitive impairment



At what age is it safe to begin using Cannabis?

- ▶ Brain development is an ongoing process thought to continue until age 25
- ▶ Endocannabinoid system is involved in brain development
 - ▶ Axon elongation
 - ▶ Synaptic pruning
 - ▶ Neuronal migration
 - ▶ Neuronal differentiation/maturation
- ▶ Unlike endogenous ligands for the cannabinoid receptors which are short acting, cannabis activates receptors in a prolonged nonphysiological manner

Driving while using Marijuana

- ▶ The higher the blood THC concentration the higher the variability in speed and lane position.
- ▶ In driving simulators higher TCH levels are correlated with **decreased reaction time**
- ▶ Altered sense of time
- ▶ Decreased eye-hand coordination
- ▶ Use of MJ and Alcohol together get impairment at lower doses



Fatal Traffic Crashes and Marijuana

- ▶ Authors hypothesized that the “High Holiday” might be associated with an increase in traffic crashes
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- ▶ 25 years of data 1992-2016

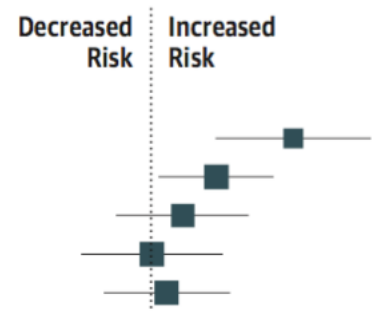
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Subgroup	Drivers in crashes on April 20	Drivers in crashes on control days
Age, y		
≤20	207	300
21-30	353	610
31-40	265	494
41-50	223	446
≥50	287	554



Cognitive Effects: American College of Obstetrics and Gynecology

- ▶ When Cannabis is used during pregnancy the following have been noted in children:
 - ▶ Cognitive delays/deficits
 - ▶ Impaired executive function
 - ▶ Low birth weight
 - ▶ Intrauterine growth restriction
 - ▶ Stillbirth
- ▶ Counsel and offer treatment to patients thinking of becoming pregnant or who are pregnant



Remission of Cannabis Use Disorder

- ▶ Of people who try cannabis 9% will develop a problem with cannabis use disorder
 - ▶ Majority of people are able to stop on their own
 - ▶ Females are more likely than males to develop dependence
 - ▶ Tolerance develops in both animals and humans
- ▶ Treatments
 - ▶ Psychotherapeutic approaches – MI, Family Structural Therapy, CBT-Relapse Prevention, Contingency management
 - ▶ N-Acetylcysteine – 1200mg BID, trial by Gray et. al. (2012) AJP showed 2.4 x more negative utox for MJ
 - ▶ Gabapentin – 1200 BID, reduced use by self report
 - ▶ Nabilone – in clinical trials
 - ▶ Combination therapies possibly promising– in clinical trials

Conclusions

- ▶ Explore what marijuana use means for your particular patient
- ▶ Help patients understand the risks of synthetic cannabinoids
- ▶ If you do certify patients for medical marijuana document:
 - ▶ Advised patient not to drive when using marijuana
 - ▶ Advised patient not to mix marijuana with other substances
 - ▶ Advised patient regarding psychiatric risks
- ▶ Encourage adolescents to avoid marijuana
- ▶ Aggressively refer adolescents and pregnant women for treatment
- ▶ Cannabis compounds are potentially promising treatments for myriad illnesses but further high quality research is needed



Thank You!!!