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CME Outfitters

Master Class for Neuroscience Professional Development

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CME Outfitters

Patients Keep Asking About Cannabis: The Data Behind Its Use in Neurology and Psychiatry

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Learning Objective 1

Evaluate the potential effect of cannabinoids in neuropsychiatric disorders.

Learning Objective 2

Assess the latest evidence on the use of cannabis in neurology.

Learning Objective 3

Examine the politics/advocacy of cannabis use in patients and the community.

The drug has certain remarkable properties and **if its chemical structure were determined and synthetic variations developed**, some of these might prove to be particularly valuable, both as therapeutic agents and as experimental tools.

Dr. Robert Walton, 1937

Professor and Head of the Department of Pharmacology and Therapeutics at the Medical College of South Carolina

US in 19th and Early 20th Centuries

Marijuana Has Been Used As Homeopathic Medicine Throughout History

Ancient History

- Used in Chinese medicine dating back 10,000 years, still basic herbal in Traditional Chinese Medicine
- Ancient Egypt: Hemorrhoids and other inflammatory conditions
- India: Used for insomnia, pain, digestive problems
- Ancient Greece: Extensive veterinary uses, also in humans (nosebleeds, tapeworms)
- Middle East: Used as antiemetic, diuretic, antiepileptic, anti-inflammatory

Western Medicine

- Europe: Muscle spasms, stomach cramps
- America: Widespread use in “patent medicines”

Modern Times Advocates Support Use In

- Insomnia
- Pain
- Anxiety
- Depression
- Nausea and vomiting
- Appetite with weight loss
- Crohn’s disease
- Muscle spasms
- Epilepsy
- Glaucoma
- Many others

Ultra-High Potency *Cannabis* Facts
Edibles and Hashish Oil Extracts

Marijuana Edibles
• Marijuana "edibles are food products (eg baked goods, candy, drinks) that contain *Cannabis*
• Edibles can contain significantly more THC compared with average smoked marijuana, although advertised potencies have been found to be inaccurate.
• Slow gastrointestinal absorption can result in a longer time to achieve a "high," with accumulation of more *Cannabis* than intended, difficulty predicting dosing effects, potentially serious AEs including death
• Edibles often attractively packaged to resemble popular brand-name products, with particular appeal to minors
Hash Oil Extracts
• Ultra-high potency hash oil extracts are also known as wax, dabs, crumble, budder, or shatter
• May contain as much as 80%-90% THC
• Compared to conventional marijuana, hashish oil may be associated with greater risk of tolerance/withdrawal, psychosis, an and burns associated with preparation

Average THC Content of Different Types of *Cannabis*

	THC 1995	THC 2004
Hemp	0.4%	0.4%
Marijuana	4%	6%
Semsimilla	10%	13%
Cannabis resin	< 5%	> 35%
Hash oil	< 15%	> 50%

THC = delta-9-tetrahydocannabinol

Chandra S, et al. *Eur Arch Psychiatry Clin Neurosci*. 2019 Jan 22. doi: 10.1007/s00406-019-00983-5. [Epub ahead of print].

What Ailments Qualify for Medical Cannabis in Pennsylvania?

Patients in Pennsylvania diagnosed with one of the following severe, debilitating, or life-threatening medical conditions, are afforded legal protection under the Pennsylvania Medical Marijuana Law

- Cancer
- Positive status for HIV/AIDS
- Amyotrophic lateral sclerosis (ALS)
- Parkinson's disease
- Multiple sclerosis
- Damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
- Epilepsy
- Inflammatory bowel disease (including Crohn's disease & ulcerative colitis)
- Neuropathies
- Huntington's disease
- Glaucoma
- Post-traumatic stress disorder (PTSD)
- Intractable seizures
- Sickle cell anemia
- Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain in which conventional therapeutic intervention or opiate therapy is contraindicated or ineffective
- Chronic inflammatory Demyelinating Polyneuropathy
- Autism
- Terminally ill, where a medical prognosis of life expectancy of approximately one year or less if the illness runs its normal course
- Neurodegenerative Diseases
- Dyskinetic & Spastic Movement Disorders
- Opioid-Use Disorder

Getting Medical Marijuana. Available at https://www.pa.gov/guides/pennsylvania-medical-marijuana-program/#HowtoGetMedicalMarijuana. Accessed February 1, 2019

Advocates Claim: Medical Marijuana

- Has anti-cancer effects
- Can slow the progression of Alzheimer's and Parkinson's diseases
- Reduces the debilitating seizures caused by epilepsy
- Reduces spasms experienced by chemotherapy and traditional HIV/AIDS treatments so that patients can more comfortably continue medical care.
- Minimizes the neurological damage caused by spinal cord and traumatic brain injuries

Medical Marijuna, Inc. https://www.medicalmarijuanainc.com/cbd-hemp-oil-frequently-asked-questions/

Unintended Consequences?

- Not dying of overdose = safe?
- Medicinal vs recreational—honesty or expediency?
- Less psychiatry and psychiatric medications
- Less alcohol
- Learning to smoke tobacco
- Juul: e-cigarettes
- Cannabis
- Chasing the dragon
  - Crack
  - Meth
- Second hand effects
  - Drugged driving
- Third hand effects
  - Pregnancy exposures

As Americans Drink Less Alcohol, Booze Makers Look Beyond the Barrell – WSJ 2019

- Americans' consumption of ethanol, or pure alcohol, has declined sharply over the past couple of decades. Alcohol consumption stood at 8.65 liters per person in 2017—the most recent year for which data is available—compared with 10.34 liters in 1980
- Some in the industry worry that alcohol volumes could take a further hit as marijuana is increasingly legalized.
- Nonalcoholic drinks—including energy drinks and nonalcoholic beers—already make up more than 10% of the Bud brewer's volumes.

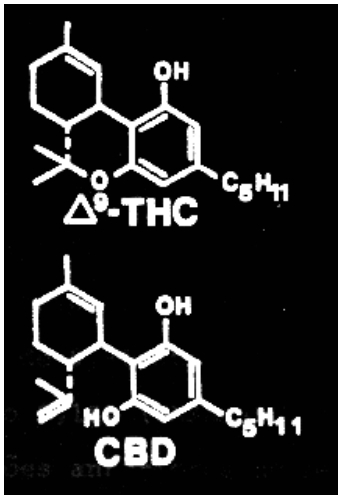
Chaudhuri S, Maloney J. The Wall Street Journal. Published January 17, 2019. Available at https://www.wsj.com/articles/americans-are-drinking-less-alcohol-11547733600.

Potential Effect of Cannabinoids in Neuropsychiatric Disorders

Igor Grant, MD, FRCP(C)
University of California,
San Diego
La Jolla, CA

Marijuana Compounds

+ 80 cannabinoids



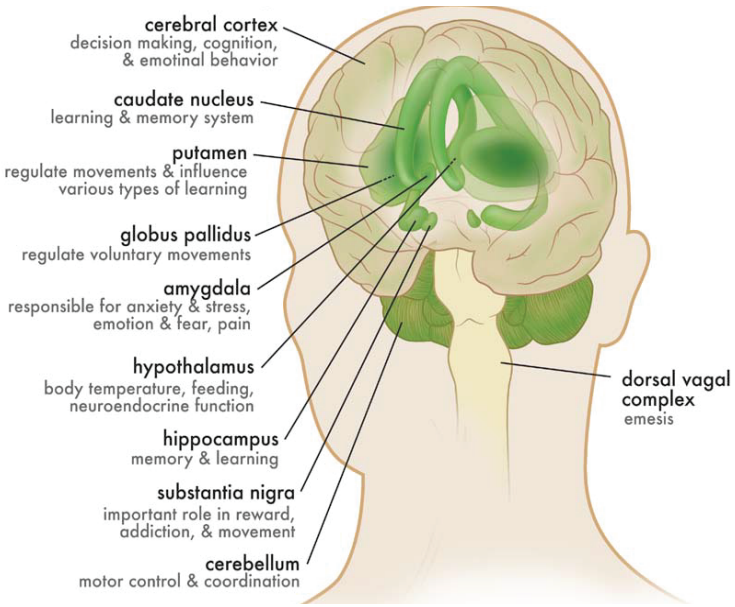
Isolation, structure, and partial synthesis of an active constituent of hashish.
Gaoni Y, Mechoulam R. *J Am Chem Soc*. 1964;86:1646.

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil.

Cannabis Comes in from the Cold: A Tale of Science and Politics

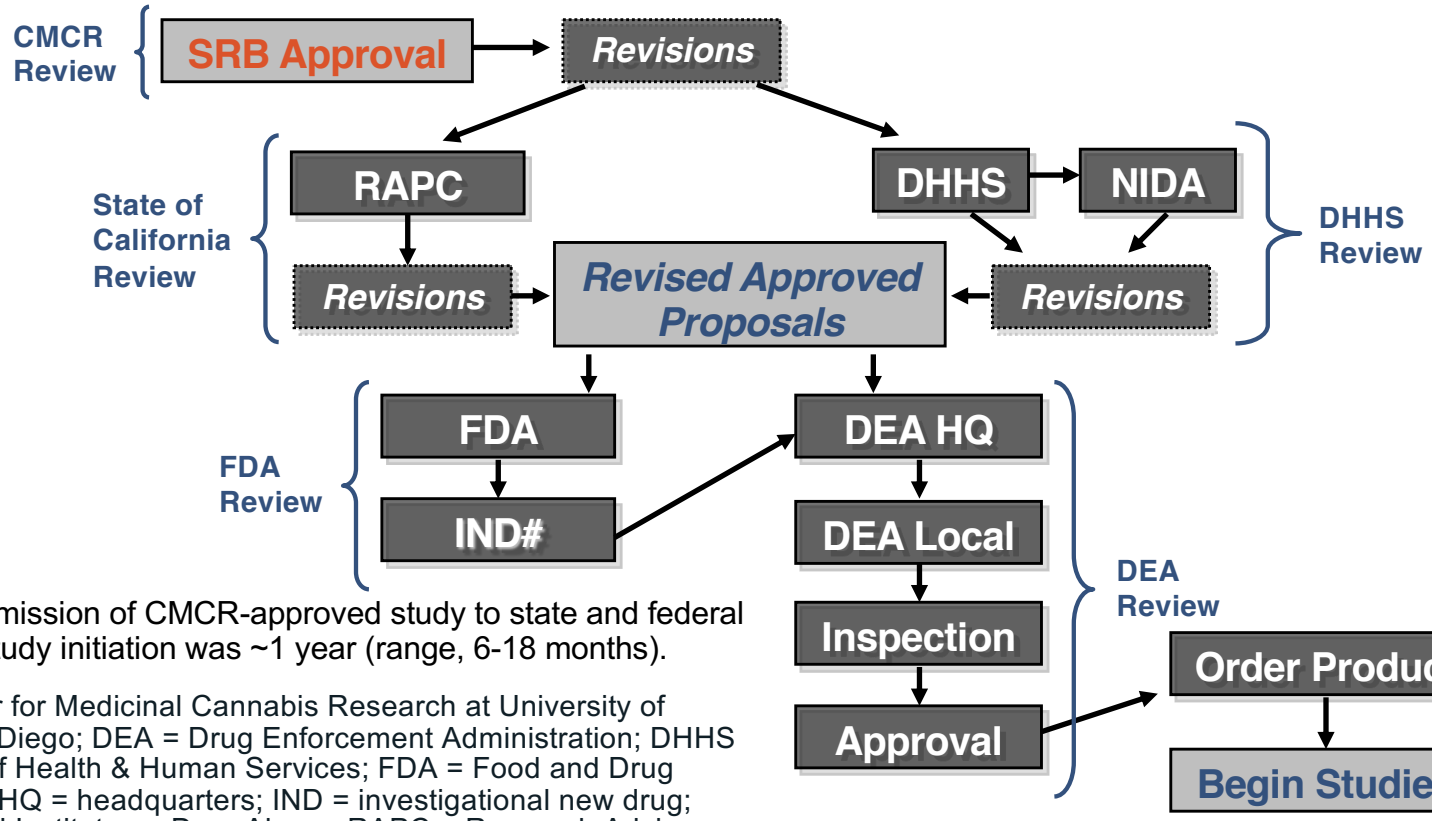
- Persistent anecdotal reports of benefits
- Political shifts favoring medicinal access (in the United States, most states now provide for some measure of access)
- Discovery of the endocannabinoid system
  - CB1 and CB2 receptors
  - Anandamide[1]
  - 2-arachidonoylglycerol[2,3] and other signaling molecules
  - Development of synthetic molecules: agonists, partial agonists, antagonists, and other modifiers (e.g., inhibitors of fatty acid amide hydrolase [FAAH]. FAAH breaks down anandamide)

Distribution of CB1 Receptors



1. Devane, et al. *Science*. 1992;258(5090):1946-1949. 2. Sugiura, et al. *Biochem Biophys Res Commun*. 1995;215:89-97.
3. Mechoulam R. *Biochem Pharmacol*. 1995;50:83-90.

Because Cannabis Is a Schedule 1 Drug, and the Only Legal Source Is the Federal Government, Medical Studies Are Challenging



Time from submission of CMCR-approved study to state and federal regulators to study initiation was ~1 year (range, 6-18 months).

CMCR = Center for Medicinal Cannabis Research at University of California, San Diego; DEA = Drug Enforcement Administration; DHHS = Department of Health & Human Services; FDA = Food and Drug Administration; HQ = headquarters; IND = investigational new drug; NIDA = National Institute on Drug Abuse; RAPC = Research Advisory Panel of California; SRB = scientific review board.

CMCR Clinical Studies Completed

Site	Disorder	Design	N	Dose (% THC)	Result
UCSD Mark Wallace	Healthy Volunteers (Experimentally-Induced Pain)	Crossover RCT	15	0%, 2%, 4%, 8%	+
UCSF Donald Abrams	HIV Neuropathy, Experimental Pain	Parallel Groups RCT	50	0%, 3.5%	+
UCSD Ronald Ellis	HIV Neuropathy	Crossover RCT	28	0%, 1-8%	+
UCD Barth Wilsey	Neuropathic Pain, Experimental Pain	Crossover RCT	33	0%, 3.5%, 7%	+
UCD Barth Wilsey	Neuropathic Pain	Crossover RCT	39	0%, 1.29%, 3.53% (Vaporized)	+
UCSD Jody Corey-Bloom	MS Spasticity	Crossover RCT	30	0%, 4%	+
UCSD Mark Wallace	Diabetic Neuropathy	Crossover RCT	16	0%, 2%, 4%, 7%	+

RCT = randomized, controlled trial; THC = tetrahydrocannabinol.

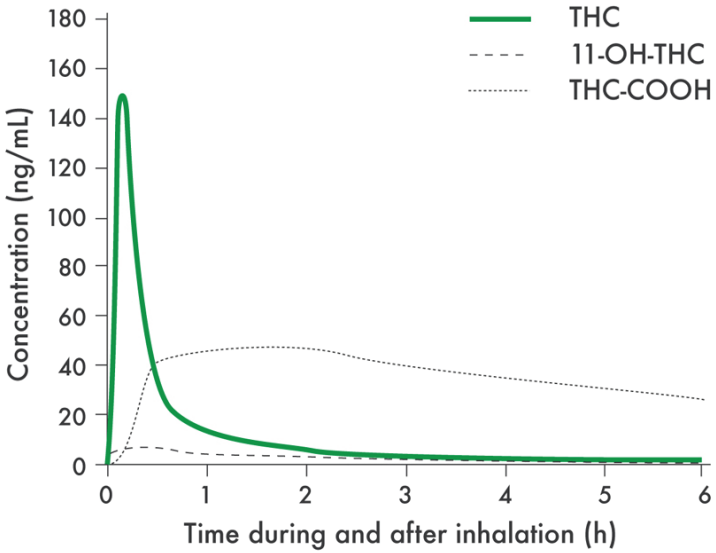
National Academies Report (2017) Evidence for Therapeutic Benefits of Cannabis

- Substantial/conclusive evidence of cannabinoid efficacy in:
  - Chronic pain
  - Spasticity of multiple sclerosis (MS)
  - Control of nausea
- Moderate evidence of cannabinoid efficacy in:
  - Improving sleep in those with chronic medical conditions (e.g., chronic pain, fibromyalgia)
- Limited evidence of cannabinoid efficacy in:
  - Treatment of certain anxiety disorders and posttraumatic stress disorder
  - Promoting appetite and weight gain
- No or insufficient evidence of cannabinoid efficacy in:
  - Treatment of cancers, irritable bowel syndrome, epilepsy, movement disorders due to Huntington disease or Parkinson's disease, schizophrenia

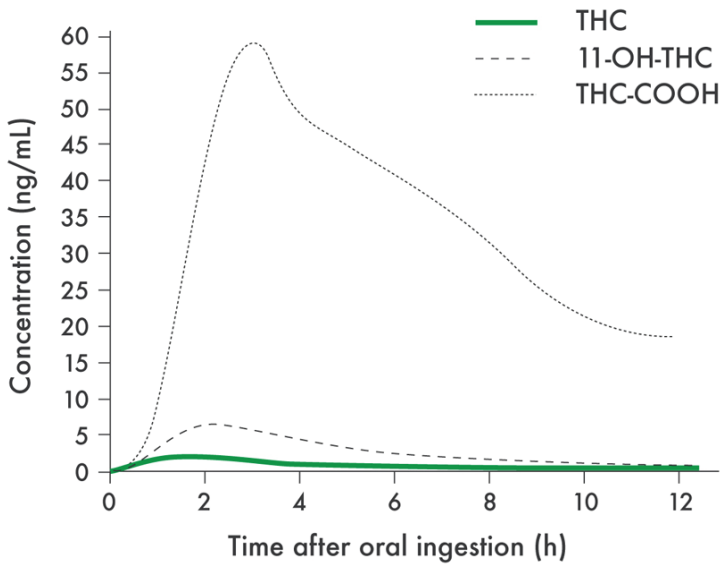
National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

Mode of Cannabinoid Administration May Influence Efficacy, Duration of Action, Side Effect Profile

Inhaled Cannabis ~34 mg THC



15 mg Oral THC (dronabinol)



Mean plasma concentrations of Δ9-THC, 11-OH-THC, and 11-nor-9-carboxy-THC (THC-COOH) following administration smoked cannabis versus oral dronabinol.
THC bioavailability from oral averages 6%, versus up to 50% inhaled.

Grotenhermen F, et al. *Clin Pharmacokinet*. 2003;42(4):327-360.

Current or Potential Cannabinoid Modulators that May Be Administered Orally

- Agonists
  - Cannabis itself
  - Synthetic THC
    - Dronabinol and analogs
    - Nabilone
    - Selective CB1 or CB2 agonists
- Antagonists, partial agonists
  - Rimonabant, Taranabant, etc.
- Modifiers of endocannabinoid metabolism
  - FAAH inhibitors
  - Possibly monoglyceride lipase (MGL) inhibitors

Cannabidiol (CBD)

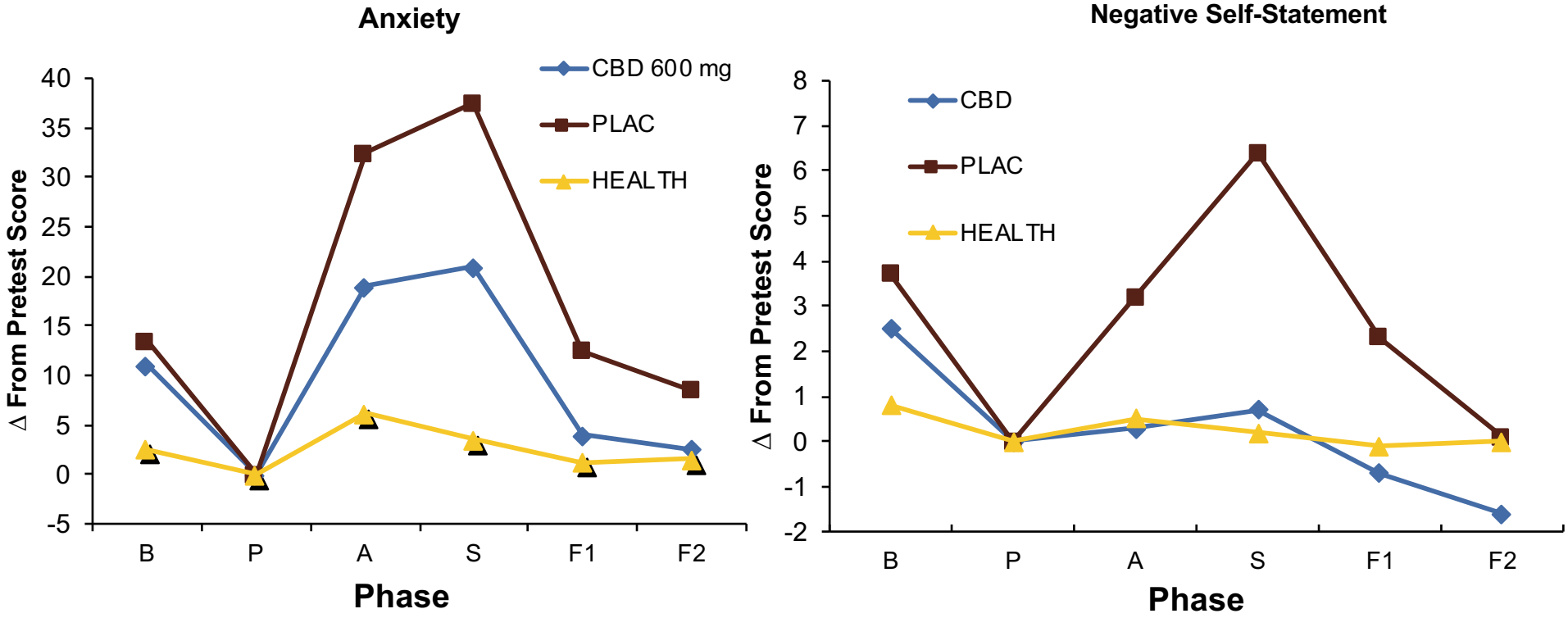
- Natural component of the Cannabis plant
- Constitutes up to 40% of marijuana extracts
- Devoid of typical psychological effects of THC
- Suggested applications as:
  - Anti-inflammatory
  - Analgesic
  - Anti-emetic
  - Hypnotic and sedative
  - Antipsychotic
  - Anticonvulsive
  - Neuro-protective
  - Anxiolytic
  - Others
- Attenuation of psychoactive effects of THC when both contents are administered concomitantly?

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil.

Possible Mechanisms of Action of CBD

- Does not activate CB1 or CB2
- Desensitizes transient receptor potential channels (e.g., TRPV1): antinociceptive to inflammatory pain?
- Blocks GPR55, which may also play a role in neuropathic and inflammatory pain
- Enhances glycine receptor activity: anticonvulsant?
- Inhibits FAAH: increasing availability of anandamide?
- Enhances 5HT1A receptor: anxiolytic effect?
- Modulates cytochrome P450 2C metabolism of THC to more psychoactive 11-hydroxy-THC (11-OH-THC)?

CBD Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

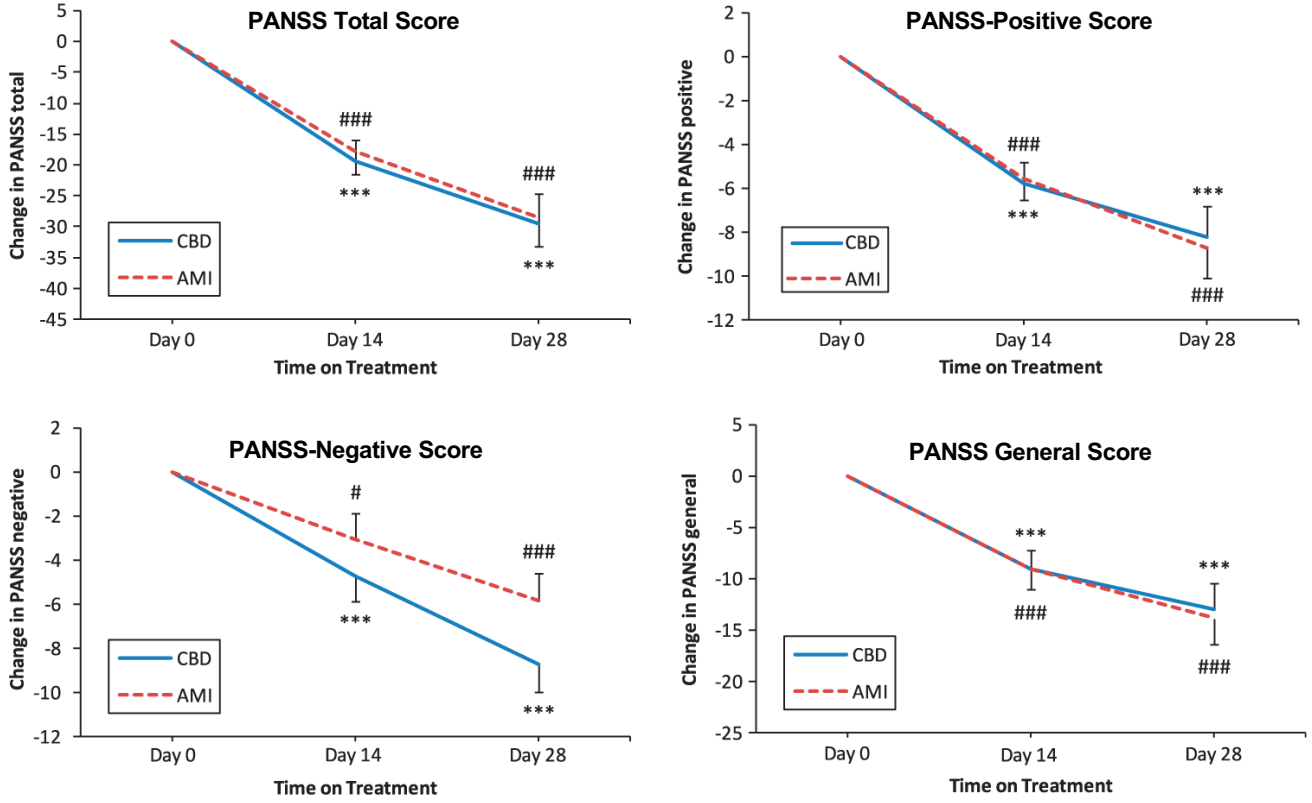


Bergamaschi MM, et al. *Neuropsychopharmacology*. 2001;36(6)1219-1226.

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil.

CBD Improves Positive and Negative Symptoms of Schizophrenia

42 Cases Randomized to Receive 800 mg/d CBD or Amisulpride



PANSS = Positive and Negative Syndrome Scale.

Leweke FM. *Transl Psychiatry*. 2012;2:e94.

Data show predicted means and side effects. Statistical significance is calculated between groups and versus baseline, that is, 0 (*CBD, #AMI; #$P < 0.001$; ***/###$P < 0.05$).

Summary: Current Status of Medicinal Cannabis/ Cannabinoid Modulators in Neuropsychiatry

- The endocannabinoid system exerts homeostatic influence in many systems: nervous, immune, cardiovascular, and others. Agents that modulate endocannabinoid signaling, whether natural (from plants) or synthetic, represent new therapeutic potential.
- Despite regulatory challenges, clinical studies on medicinal cannabis have shown positive results.
- Smoked/vaporized cannabis and extracts containing a THC/CBD mix are probably efficacious in neuropathic pain, MS spasticity, and nausea.
- CBD shows initial promise in the treatment of anxiety, schizophrenia, and psychosis. Its mode of action is unclear but likely not primarily via CB1 and CB2 receptors.
- The potential utility of other synthetic CB1 agonists is not yet established.
- The anti-inflammatory actions of cannabinoids deserve further exploration.

Medical Marijuana in Neurology

Paul R. Carney, MD
Professor of Neurology
University of North Carolina at Chapel Hill
Chapel Hill, NC

Where Are We At Now?

- Most of the evidence for beneficial effects of cannabis in neurology is from observation and open-label studies
- Adverse effects reported in the literature are most often benign, though there are deleterious effects that depend highly on the route and frequency of administration
- Some reports overemphasize the potential for drug dependence, even suggesting that cannabis is a “gateway” drug to “hard” drugs of abuse
- It is possible that combinations of cannabinoids are necessary to produce clinical benefits

Real Life Experience of Medical Cannabis in Autism: Assessment of Daily Activities

	Sleep			Eating with Appetite			Concentration on daily tasks			Bowel Activity		
	Before	During	p value	Before	During	p value	Before	During	p value	Before	During	p value
Severe difficulty	44 (47.3)	2 (2.2)		2 (2.2)	1 (1.1)		75 (80.6)	21 (22.6)		3 (3.2)	2 (2.2)	
Moderate difficulty	18 (19.4)	27 (29.0)		6 (6.5)	13 (14.0)		11 (11.8)	41 (44.1)		13 (14.0)	17 (18.3)	
No difficulty	28 (30.1)	39 (41.9)	<0.001	59 (63.4)	47 (50.5)	0.751	2 (2.2)	11 (11.8)	<0.001	71 (76.3)	54 (58.1)	0.242
Good	2 (2.2)	15 (16.1)		10 (10.8)	16 (17.2)		0	10 (10.8)		5 (5.4)	13 (14.0)	
Very Good	1 (1.1)	8 (8.6)		16 (17.2)	14 (15.1)		0	3 (3.2)		1 (1.1)	4 (4.3)	

Ability to perform activities of daily living was assessed prior to and six months after initiation of cannabis treatment. Numbers in parenthesis represent the % of patients.

Schleider LB, et al. Published January 17, 2019. www.nature.com/scientificreports

Sleep Disorders

- Limited data exist on the utility of cannabis/cannabinoids in the treatment of sleep disorders
- One study showed improvement in obstructive sleep apnea
- No studies available on the effects of cannabinoids in patients with narcolepsy, and restless legs syndrome
- Most studies show improved sleep architecture and reduced sleep disturbance
- Some evidence that CBD improved post-traumatic stress disorders and that cannabis is used for coping with sleeping problems

Prasad B, et al. *Front Psychiatry*. 2013;4:1. Bitencourt RM, Takahashi RN. *Front Neurosci*. 2018;12:502.
Metrik J. *Psychology of Addictive Behaviors.* 2016;30(7):743-754.

Multiple Sclerosis

- UK clinical placebo-controlled study: 630 subjects, cannabis did not improve spasticity but did improve mobility[1]
- Nabiximols, an oral mucosal delivery system for cannabinoids, has been studied for MS in 11 countries and has received regulatory approval in another 13 countries
- Phase A, single-blind, 4-week treatment period showed 20% reduction in spasticity; follow-up phase B, 12-week, double-blind, randomized, placebo-controlled showed improvement in spasticity[2,3]

1. Bruni N, et al. *Molecules*. 2018;23(10):2478. 2. Zajicek J, et al. *Lancet*. 2003;362(9395):1517-1526.
3. Novotna A, et al. *Eur J Neurol*. 2011;18(9):1122-1131.

AEs with CBD Treatment: Florida Department of Health–Sponsored CBD Study

Safety analysis (N = 29)		AEs		ADRs	
		Patients (%)	Events	Patients (%)	Events
Adverse events/drug reactions		23 (79.3)	45	12 (41.4)	15
Severity	Mild	20 (69.0)	41	11	13
	Moderate	3 (10.3)	4	1	2
	Severe	0 (0.0)	0	0 (0.0)	0
Common Adverse Events	Drowsiness	17 (58.6)	17	8 (27.5)	12
	Diarrhea	10 (34.4)	9	0 (0.0)	0
	Somnolence	8 (27.5)	6	2 (6.9)	1
	Agitation	4 (13.8)	3	1 (3.4)	1
	Irratability	2 (6.9)	6	0 (0.0)	0
	Loss of appetite	2 (6.9)	1	1 (3.4)	1
	Weight loss	1 (3.4)	1	0 (0.0)	0
	Sleep disruption	1 (3.4)	1	0 (0.0)	0
	Altered mood	1 (3.4)	1	0 (0.0)	0
Events resulting in discontinuation		0 (0.0)	0	0 (0.0)	0
Death		0 (0.0)	0	0 (0.0)	0

ADRs = adverse drug reactions.

Carney P, et al. Presented at the American Epilepsy Society Annual Meeting, Washington DC, 2017. Abstract 1.048.

Marijuana Legalization and Advocacy

Joel J. Silverman, MD
Chairman, Department of Psychiatry
James Asa Shield, Jr., MD, Professor of Psychiatry
Medical College of Virginia
Virginia Commonwealth University
Richmond, VA

Pro-Marijuana Lobby

- Strong pro-marijuana lobby
  - Users – legal and available
  - Sellers – $
  - States – $
  - Providers

Marijuana Use by Age

"Medical" marijuana is legal in 33 states, plus the District of Columbia.
Recreational marijuana is legal in 10 states, plus the District of Columbia.

Marijuana Use by Age	
12-17	6.5%
18-25	20.8%
>26	7.2%

Ahrnsbrak R, et al. SAMSHA. 2017.

Social Obligation

- Do you have an obligation to…
  - Counsel patients and families
  - Work with schools
  - Work with media
  - Work with legislators

What Will You Say?

When is it Dangerous?

- Large amounts
- Frequent use
- Developing brains
- Genetic vulnerability to mental illness
- Driving, etc.
- When using unregulated products
  - In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content[2]

1. Gladwell M. Is Marijuana as Safe as We Think?. *The New Yorker.* Published January 14, 2019.; 2. Humphreys K, Saitz R. *JAMA.* Published online February 01, 2019. doi:10.1001/jama.2019.0077.

Be Aware of Unintended Consequences

- Use by women of child-bearing age
- 2nd and 3rd hand exposure to smoke in the home environment
- Access to edibles from children—poisonings

VCU Psychiatry Mini Mental Health University

Advocation

- When advocating:
  - Know articulate facts
  - Clear communications
  - Give examples
  - Use of relationships
  - Partners
  - Expect resistance
  - Be tenacious
- Advocate for:
  - Better education at all levels
  - Money for addictions treatment
  - Money for research

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Stay up-to-date on the emerging cannabinoid therapies for neuropsychiatric and neurological disorders.
- Utilize cannabidiol in appropriate patients with Dravet's syndrome and Lennox-Gastaut syndrome
- When and in whom it is appropriate, counsel patients and their families on the applicable use of marijuana

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.

References

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Ellis RJ, et al. *Neuropsychopharmacology*. 2009;34(3):672-680.

Wilsey B, et al. *J Pain*. 2016. pii: S1526-S5900(16):30072-30074.

Wilsey B, et al. *J Pain*. 2013;14(2):136-148.

Wilsey B, et al. *J Pain*. 2008;9(6):506-521.

Corey-Bloom J, et al. *CMAJ*. 2012;184(10):1143-1150.

Corey-Bloom J, et al. Poster presented at the 60th Annual Meeting of the American Academy of Neurology (Chicago, IL). 2008.

Wallace MS, et al. *J Pain*. 2015;16(7):616-627.