ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics

Agenda

Webex link to join from PC, Mac, iOS or Android:

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For attendance, purposes please text the following code: BEGROX to 608-260-7097

Session Date: Friday, March 19, 2021

Didactic Topic and Presenter:
Cannabinoid Pharmacology, Therapeutics, and Risks

Natalie S. Schmitz, MPA, PharmD, PhD
Assistant Professor
Pharmacy Practice Division
School of Pharmacy, University of Wisconsin, Madison, WI

Content Experts:
Ritu Bhatnagar, MD; Lindsey Peterson, MS, CRC; Sheila M. Weix, MSN, RN, CARN

- 12:15 PM: Attendance text-in – Introductions
- 12:25 PM: Case Presentation
  - Presenter: Glenn R. Kauppila, DO, FACOFP - *Addiction Medicine Fellow, University of Wisconsin – Madison, School of Medicine and Public Health, Dept. of Family Medicine and Community Health*
- 1 PM: Didactic Presentation
  - Presenter: Natalie S. Schmitz, MPA, PharmD, PhD
- 1:15 PM: End of Session

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Interprofessional Continuing Education Partnership
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School of Medicine and Public Health
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Project ECHO
University of Wisconsin

ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics
2020-2022

Cannabinoid Pharmacology, Therapeutics, and Risks
Natalie S. Schmitz, MPA, PharmD, PhD-Didactic Presenter
Glenn Kauppila, DO, FACOFP–Case Presenter

Provided by the University of Wisconsin–Madison Interprofessional Continuing Education Partnership (ICEP)

Intended Audience:
Nurses, Nurse Practitioners, Pharmacists, Physicians, Physician Assistants, Pharmacy Technicians, Psychologists, Social Workers, Patient/Caregivers, Students

Objectives:
As a result of this educational regularly scheduled series, learners as members of the healthcare team will be able to:

1. Implement appropriate opioid prescribing and monitoring practices.
2. Effectively participate in office-based, collaborative management of substance use disorders.
3. Consistently provide in overdose prevention education to appropriate patients.
4. Identify the role of medication assisted therapies, such as methadone, naltrexone, and buprenorphine, and contributions of different members of the healthcare team to the management of substance use disorders.

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Name/Role	Financial Relationship Disclosures	Discussion of Unlabeled/Unapproved uses of drugs/devices in presentation?	COI completion date
Randall Brown, RSS Chair	No relevant financial relationships to disclose	Yes	3/11/21
Kathleen Maher, RSS Coordinator	No relevant financial relationships to disclose	No	3/15/21
Nada Rashid, RSS Coordinator	No relevant financial relationships to disclose	No	3/11/21
Ritu Bhatnagar, Planner	No relevant financial relationships to disclose	Yes	3/12/21
Paul Hutson, Planner	No relevant financial relationships to disclose	No	3/15/21
Susan Mindock, Planner	No relevant financial relationships to disclose	No	3/11/21
Lindsey Peterson, Planner	No relevant financial relationships to disclose	No	3/11/21
Sheila Weix, Planner	No relevant financial relationships to disclose	No	3/15/21
Natalie S. Schmitz, Speaker/Author	CytoCBD (Grant) UWCCC Pancreas Cancer Research Task Force (Grant)	Yes	2/25/21
Glenn Kauppila, Speaker/Author	No relevant financial relationships to disclose	Yes	3/4/21

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Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics

Patient Case Presentation Form

***Please do not attach any patient-specific files or include any Protected Health Information.**

1. Date: 3/19/2021
2. Presenter Name: Glenn Kauppila, DO
3. Presenter Organization: UW – Madison - School of Medicine and Public Health- Dept. of Family Medicine and Community Health
4. ECHO ID: 7125
5. Have you presented this patient during this teleECHO clinic before? No
6. Please state your main question for this case:

Management of transition from poppy seed tea (PST) to buprenorphine-naloxone. He would like to be medication prescribed by a physician as he knows he needs shoulder surgery and they may not operate on him if he's using PST. He also cites some emotional distress and concern about having less control over use regarding tea.

Patient Demographic Information:

7. Age: 65
8. Sex: Male
9. Education/Literacy: Some education beyond high school. Literate.
10. Income source: Retired.
11. Social Factors/History:

He is married and lives with his wife who is supportive of his recovery efforts. He does not have children.

12. **Substance Use History:**

He identifies as a recovering "alcoholic" who has been abstinent for 17 years. He did attend a rehab facility for 30 days to achieve abstinence from alcohol. He continues to attend AA once per week. He states that he has been dependent on opioids many years ago and has misused other substances over the years including cannabis, heroin, crack cocaine, and cocaine. Last use of any unprescribed substances (other than poppy seed tea and cannabis) was > 10 years ago. He continues to use cannabis on a daily basis.

He was previously on morphine 30 mg TID prescribed by PCP for chronic pain but was eventually tapered off due to a drug screen positive for THC in 2020. He researched PST and started it for control of pain with good effect.

He purchases bulk poppy seeds online and makes his own tea. He cites significant cost associated with purchase.

13. **Consequences of Substance Use:**

- Social/occupational/educational:
  He feels more socially withdrawn and depressed from using PST.
- Physical (including evidence of tolerance/withdrawal):
  He does not endorse tolerance or withdrawal though has been consistent taking tea daily without missed doses. Exact quantity of tea unknown but typically drank once per day (about 1 cup).

14. **Interventions that have been tried:**

He has been working with pain psychologist regarding his chronic pain and history of SUDs, who suggested he consider MOUD for his use of PST. Pain psychologist referred him to addiction medicine consultant for full evaluation.

Since seeing ADM – initiated on buprenorphine-naloxone

15.

Current Addiction and Mental Health-related Medications:	Medical/Behavioral Health Diagnosis:
• Duloxetine 60mg daily • Gabapentin 600 mg TID	• Depression • PTSD • AUD, in sustained remission • h/o polysubstance use (opioids and cocaine)

16.

Patient Strengths/protective factors:	Risk factors:
• Active recovery program (for AUD) • Motivated to change • Supportive partner • Goal to return to prior level of physical activity (long distance cycling)	• Ongoing use of cannabis • depression

17. **Labs (as indicated), include summary of urine testing or last urine drug screen results:**

Urine drug testing was positive for; morphine, codeine, hydromorphone, hydrocodone, norhydrocodone, gabapentin, and marijuana metabolites.

18. **Patient Goals/Motivations for Treatment:**

Be on a physician-prescribed medication that would manage pain and allow him to not use PST. His other motivation is that he anticipates surgery in the future and he may not have been eligible while dependent on PST. He is also motivated for better pain control. PST helps pain but he remains significantly limited with regard to physical activity. He is a long distance cycler and would like to be able to resume more regular/longer riding.

19. **Proposed Diagnoses:**

Opioid use disorder, moderate (poppy seed tea)
Alcohol use disorder, prolonged sustained remission
Cannabis use

Chronic pain syndrome

20. **Proposed Treatment Plan:**

Home induction to Suboxone.

Pt took last dose of poppyseed tea on a Sunday.

Provider called pt Monday AM and not yet having withdrawal. Late Monday starting to feel mild withdrawal sx.

Provider called pt Tuesday AM. He woke up at 3 am (usual wake up time) and was very nauseated and vomited. Took 4-1 mg film and cut into "5 slivers." Between 4 am and 8 am took a full 4-1 mg film. Felt better by 8 am and then slept for about an hour. Awoke around 9:15 feeling very nauseated again. Was actively vomiting when provider spoke to him on the phone. Instructed to take another 2 mg, then repeat 2 mg if needed. By end of Tuesday had taken total 8 mg.

Provider called pt on Wednesday AM. He had taken only 4 mg in early hours of Wed AM. Felt some GI sx. Encourage to take the additional 4 mg. Instructed he could take 1-2 mg more as needed. In PM was feeling tearful which he attributed to withdrawal so took another 1 mg for total of 9 mg.

Pt had video apt on Thursday. At that point had taken 8 mg and was feeling very well. Reported he had been able to do yard work on Wednesday and pain was "better than in years." No withdrawal sx.

Reviewed that it may take more time to achieve steady state and final dose. Ok to continue 8 mg qday or may increase to 10 mg as needed. May consider split dosing as this may help with analgesia which is secondary desired effect (with chronic pain).

By initialing here _gk_____ you have acknowledged that Project ECHO case consultations do not create or otherwise establish a provider-patient relationship between any ECHO clinician and any patient whose case is being presented in a teleECHO clinic.

DSM 5 Criteria for Substance Use Disorder

A use disorder is characterized by maladaptive use resulting in repetitive consequences over the previous 12 months. A minimum of 2-3 criteria is required for a mild substance use disorder diagnosis, while 4-5 is moderate, and 6-7 is severe (American Psychiatric Association 2013)

1. Taking the substance in larger amounts and for longer than intended
2. Wanting to cut down or quit but not being able to do it
3. Spending a lot of time obtaining the substance
4. Craving or a strong desire to use
5. Repeatedly unable to carry out major obligations at work, school, or home due to use
6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by use
7. Stopping or reducing important social, occupational, or recreational activities due to opioid use
8. Recurrent use in physically hazardous situations
9. Consistent use despite acknowledgment of persistent or recurrent physical or psychological difficulties from using
10. *Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (Does not apply for diminished effect when used appropriately under medical supervision)
11. *Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (Does not apply when used appropriately under medical supervision)

Cannabinoid Pharmacology, Therapeutics, and Risks

March 19, 2021

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Disclosures

- Grant support and product donation from CytoCBD
- Grant support from UWCCC Pancreas Cancer Research Task Force

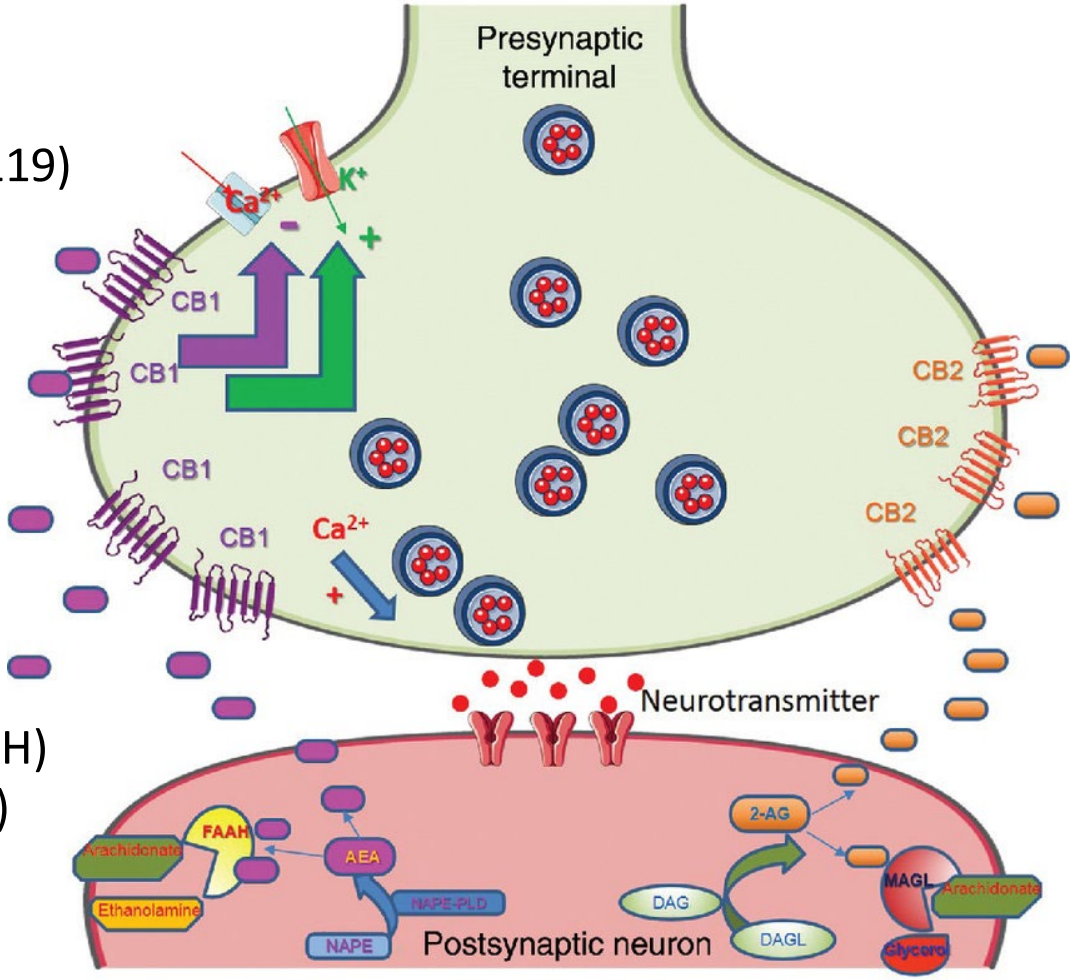
- This presentation includes off-label and unapproved uses of drugs

Overview

- Describe the endocannabinoid system
- Review cannabis botany and US policy
- Discuss therapeutic applications and risks of THC and CBD use
- Identify important considerations for cannabis product selection

Endocannabinoid System

- 3 key components:
  - Cannabinoid Receptors
    - CB1 and CB2
    - Orphan receptors (GPR 19, 55, 119)
  - Cannabinoids
    - Endogenous
      - Anandamide (AEA)
      - 2-arachidonoylglycerol (2-AG)
    - Exogenous
      - Synthetic
      - Phytocannabinoids
  - Enzymes that synthesize and degrade cannabinoids
    - Fatty acid amide hydrolase (FAAH)
    - Monoacylglycerol lipase (MAGL)



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Endogenous vs Exogenous Cannabinoids

Endocannabinoids

- Anandamide (AEA) and 2-arachidonoylglycerol (2-AG)
- Synthesized at or near the site of action
- Rapidly broken down at the site of action
- Signals are quick and localized

Synthetic or Phytocannabinoids

- THC and CBD
- Marinol, Nabilone, Sativex, Epidiolex
- Large volume of distribution
- Metabolized by the liver
- Sustained and global effect

Targets and Mechanisms of Action

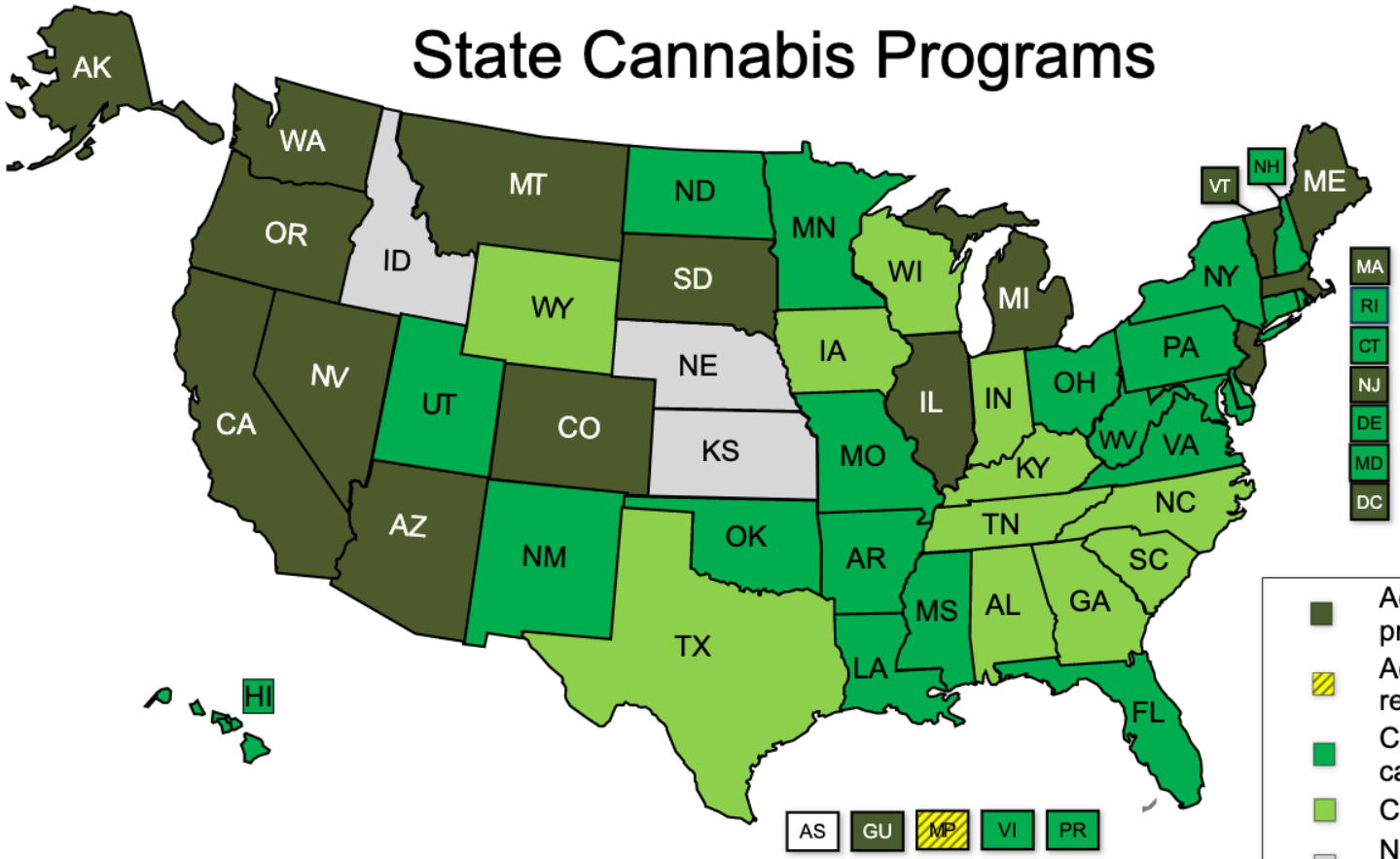
CBD

- Inverse agonist CB1 and CB2
- TRPV1 and TRPV2,3 agonist
- $5HT_{1a}$ agonist
- GPR55 and GPR18 antagonist
- Inhibits adenosine uptake
- Inhibits FAAH
- Inhibits release of proinflammatory cytokines

THC

- Partial agonist at CB1 and CB2
- Active metabolite (11-OH-THC)

State Cannabis Programs



Limited adult possession and growing allowed, no regulated production or sales: DC

- Adult & medical use regulated program
- Adult use only no medical regulated program
- Comprehensive medical cannabis program
- CBD/Low THC program
- No public cannabis access program

November 2020

https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Proposed Pharmacologic Effects of Cannabinoids

- Analgesic
- Antispasmodic
- Anti-anorectic
- Antiemetic
- Neuroprotectant
- Anti-cancer
  - Antiproliferative
  - Anti-metastatic
  - Anti-angiogenesis
- Antioxidant
- Antibacterial
- Antifungal
- Antiparasitic
- Anti-inflammatory
- Immunosuppressive
- Anti-host vs graft
- Dermatologic
  - Anti-psoriatic
  - Anti-eczema
  - Anti-keratotic
  - Anti-pruritic
  - UV light reducing
- Bronchodilatory
- Anti-glaucoma
- Anti-diabetic
- Bone-stimulant
- Anxiolytic
- Antipsychotic
- Antidepressant
- Vasorelaxant
- Anti-ischemic
- Anticonvulsant
- ↓ GI motility
- ↓ GI secretions
- ↓ Stomach acid
- ↓ Acid reflux
- ↓ Sleep induction

Potential Therapeutic Applications

- Pain (acute pain, chronic inflammatory, neuropathic)
- Psychiatric disorders
- Cancer supportive care
- Gastrointestinal disorders
  - Chron's
  - Ulcerative colitis
- Sleep (insomnia, sleep apnea)
- Migraine headaches
- Harm reduction, alternative to opioids
- Spastic disorders
- Autoimmune disorders
- Neurodegenerative disorders
  - Alzheimer's disease
  - Parkinson's disease
  - ALS
- Glaucoma
- Skin diseases
- Epilepsy
- Autism
- Tourette's
- HIV/AIDS

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Bridgeman et al. P&T 2007; Hergenrather 2016

Evidence of Cannabinoid Efficacy

Target symptom	Tetrahydro-cannabinol	Cannabidiol
Neuropathic pain	+++	+
Chemotherapy-induced		
Peripheral neuropathy	++	?
Nausea or vomiting	+++	Preclinical animal models
Anticipatory nausea	+	Preclinical animal models
Appetite stimulation	++	?
Spasticity or spasms	+++	+
Inflammation	+	++
Seizures	+	+++
Anxiety	+ or –	Simulated situations
Depression	+ (adjuvant)	Preclinical animal models
Malignancy		
Preclinical	++	++
Clinical	+	?

The Health Effects of Cannabis and Cannabinoids. 2017

Adverse Effects and Potential Risks

CBD

- Dry mouth
- Diarrhea
- Elevated liver enzymes

THC

- Acute negative effects on attention, short term memory, balance, and reaction time
- Acute increases in heart rate and blood pressure
- Increase risk of angina
- Bronchitis
- Possible link to testicular cancer
- Cannabis hyperemesis syndrome
- Bi-phasic effect on mood and anxiety
- Dose dependent association with acute psychosis, suicidality
- Early use and heavy use is associated with schizophrenia
- Tolerance and dependence

Drug Interactions

- THC and CBD inhibit CYPs 1A1, 2C9, 2C19, 2D6 and 3A
- Warfarin
  - THC and CBD increase warfarin levels
  - Frequent cannabis use associated with increased INR
- Theophylline
  - THC decreases theophylline levels
- Clobazam
  - CBD increases clobazam levels
- Additive CNS depressant effects
  - Alcohol
  - Barbiturates
  - Benzodiazepines

Cannabis (THC dominant) Drug Safety

Contraindications

- Acute psychosis or unstable psychiatric condition
- Severe and unstable cardio-pulmonary disease
- Pregnant or breastfeeding
- History of alcohol or substance abuse

Precautions

- Severe cardiovascular, immunological, liver, or kidney disease
- History of arrhythmias
- Personal history of psychiatric disorder
- Family history of schizophrenia
- Association with hyperemesis syndrome
- Pediatric and elderly patients
- Drug interactions

Cannabis Onset and Duration of Action

Route of administration	Action		Amenable to self-titration
	Onset (min)	Duration (h)	
Smoked	5	2–4	++++
Vaporized	5	2–4	++++
Oral			
Botanical			
Cooked	30–60	8–12	+
Oil	30–60	8–12	+
Tea	30–60	8–12	+
Nabilone	60–90	8–12	+
Dronabinol	30–60	4–6	+
Oromucosal (nabiximols)	15–40	2–4	++

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Cannabinoid Therapies in Oncology – Current Oncology 23: 398 – 406

Product Selection

- Pure cannabis vs crude cannabis
  - Side effects/health risk
  - Cost – crude cannabis may be cheaper
  - Lack of control
    - Cannabis content
    - Contaminants
    - Dosing
  - Fewer available routes of administration
    - Crude – smoking or ingested
    - Pure – inhaled, oral, topical, sublingual, rectal
  - Illegal in some states
- Potential Contamination
  - Fungal and bacterial pathogens
  - Pesticides
  - Heavy metals
- Labeling Accuracy

Conclusions

- The endocannabinoid system plays a major role in homeostatic regulation
- Although there are over 120 cannabinoids in the cannabis plant, CBD and THC are the most heavily researched cannabinoids
- There are many potential therapeutic applications for CBD and THC, but it is important to weigh the possible risks
- Health risks, route of administration, appropriate product selection, and dosing are all important considerations when pursuing cannabinoid therapies

Thank you!

Natalie.Schmitz@wisc.edu

DSM-5 Substance Use Disorder ("Addiction")

- Tolerance
- Withdrawal

} Physical Dependence ≠ Use Disorder

- Larger amts/longer periods than intended
- Persistent desire/failed attempts to quit/control use
- Much time obtaining/using/recovering
- Important activities sacrificed
- Continued use despite known adverse effects
- Failure to fulfill major obligations
- Recurrent hazardous use
- Craving
- Ongoing use despite interpersonal problems

2-3 = mild
4-5 = moderate
≥ 6 = severe