Cannabinoids (CB): Outline

1

- PART #1: CB Primer
  - Epidemiology
  - Categorization:
    - Endogenous vs. exogenous
    - Natural vs. synthetic
  - Pharmacodynamics (PD)
  - Pharmacokinetics (PK)
  - CB receptor system
  - CNS regional effects
- PART #2: Potential Adverse Effects & Efficacy (*selected from much larger literature*)
  - Substance-related Disorders (*consistent with DSM-5 approach*)
    - CB Intoxication
    - CB Withdrawal
    - CB Use Disorder
- PART #3: National Academies Press (NAP) – *seminal report*

Part #1: Cannabinoid (CB) Primer

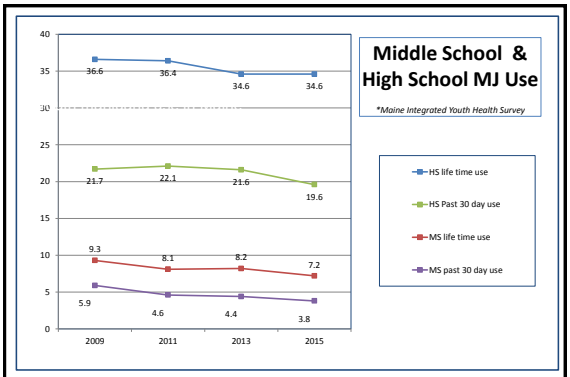
2

CB: Epidemiology

3

- Prevalence
  - Current (*i.e., past month*) MJ use among high school seniors: approximately **21.0%**
    - Daily use: **6%**
- Co-ingestion (*poly-substance use*)
  - MJ most common drug co-ingested with nonmedical use of Rx medications (*e.g., opioids*)
  - Recent change in drug use patterns
    - **MJ > Etoh** as most common **co-ingested drug**

McCabe et al. Drug Alcohol Depend (2012); Monitoring the Future (2015)



www.maine.gov/miyhs

CB: Categorization

5

- Natural CBs
  - Endogenous ligands
    - Primary example: Anandamide
  - Exogenous ligand (e.g., *CB sativa, CB indica*)
    - **Δ-9-tetrahydrocannabinol (THC)**
- Synthetic CBs
  - Prescription medications
    - Dronabinol (Marinol); nabilone (Cesamet)
    - Sativex (…not yet available in the U.S.)
  - Recreational use
    - "Spice/K2" (*potent CB agonist formulations*)

CB: Pharmacodynamics

6

- MJ is a complex plant
  - Numerous compounds
    - **60(+) CBs [note: not identical PD properties]**
  - Various strains
    - Differing CB concentrations
- Lack of correlation between **drug concentrations** and **physiologic effect**
- Highly variable drug administration
  - Concerns with self-titration and dosing

Borgelt et al. Pharmacotherapy (2013)

CB: Pharmacokinetics

7

- THC
  - Half-life = 30 hours (*wide variability*)
  - Smoked THC
    - Absorption: rapid (*within minutes*)
    - Bioavailability: wide range (**10-25%**)
  - Oral THC
    - Absorption: variable
    - Peak concentrations: **1-3 hours**
  - Other formulations: vaporized
- **Teter CJ: [Variability (PD) x Variability (PK)] = [Variability]**
  - (*i.e. lack PK/PD standardization*)

NOTE: Delay has contributed to AEs

Borgelt et al. Pharmacotherapy (2013)

Biological Underpinnings

ENDOGENOUS CB SYSTEM:

- ❑ Retrograde neurotransmission
  - ❑ See diagram
- ❑ Modulates neurotransmitter activity (e.g., glutamate)
- ❑ Multitude of CNS effects
  - ❑ Diverse CB receptor density throughout the brain

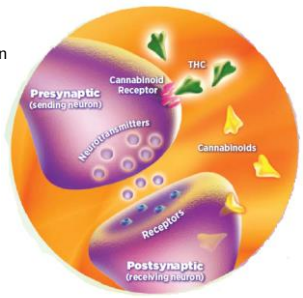


Image source: **NIDA-Scholastic**

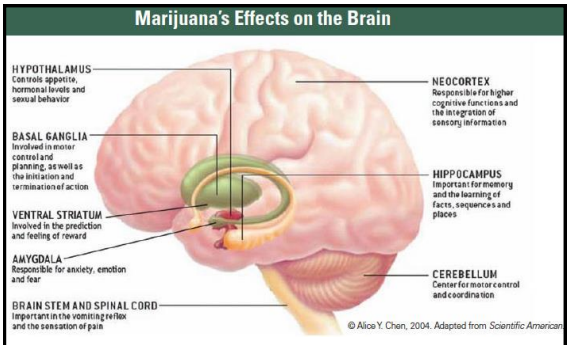
CB: Endocannabinoid System

9

- **CB1 Receptors**
  - CNS: Basal Ganglia, Cerebellum, Hippocampus, Hypothalamus, Limbic system, Neocortex
    - G-protein activity
      - Signal transduction pathways
      - Neuronal stabilization
      - CNS "dampening" effect
    - CB1 binding induces *dopamine activity*
- CB2 Receptors
  - Periphery: immune cells and tissue
  - CB2 binding effects in CNS not well-understood

EFFICACY PERHAPS??

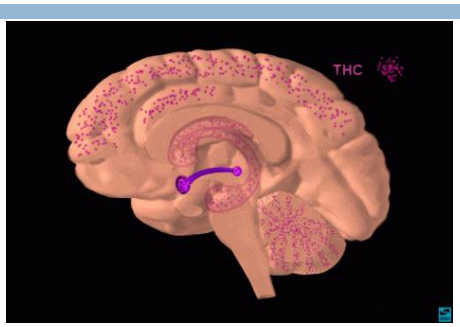
Bloomfield et al. Biol Psychiatry (2014); Borgelt et al. Pharmacotherapy (2013); Rodríguez de Fonseca et al. Alcohol Alcoholism (2004); www.cnsforum.com



Source (public domain): National Institute on Drug Abuse (NIDA)

CB: THC binding sites

11



Source (public domain): National Institute on Drug Abuse (NIDA)

12

Part #2: Selected Assessment of Adverse Events & Efficacy

(including Substance Use Disorders)

NIDA Research Report (2012)

[*public domain*]

13

Predictable (e.g., DSM-5 criteria)

Growing understanding

Consequences of Marijuana Abuse

Acute (present during intoxication)

- Impairs short-term memory
- Impairs attention, judgment, and other cognitive functions
- Impairs coordination and balance
- Increases heart rate (20-50 bpm)
- Psychotic episodes

Persistent (lasting longer than intoxication, but may not be permanent)

- Impairs memory and learning skills
- Sleep impairment

Long-term (cumulative effects of chronic abuse)

- Can lead to addiction
- Increases risk of chronic cough, bronchitis
- Increases risk of schizophrenia in vulnerable individuals
- May increase risk of anxiety, depression, and amotivational syndrome*

*These are often reported co-occurring symptoms/disorders with chronic marijuana use. However, research has not yet determined whether marijuana is causal or just associated with these mental problems.

CB: DSM-5 Criteria (*intoxication*)

14

- Recent CB use.
- Clinically significant problematic *behavioral or psychological changes* (developed during/shortly following CB use).
  - Includes: impaired motor coordination, *euphoria*, *anxiety*, sensation of slowed time, *impaired judgment*, and social withdrawal.
- Two (or more) following signs/symptoms develop within 2 hours of CB use:
  - Conjunctival injection
  - Increased appetite
  - Dry mouth
  - *Tachycardia*

- Must rule-out another medical condition, mental disorder, and other substance-related signs & symptoms.

DSM-5 (2013)

CB: DSM-5 Criteria (*withdrawal*)

15

A. Cessation of heavy/prolonged CB use.

B. Three (or more) of the following signs and symptoms develop within approximately one week after Criterion A:
   1. *Irritability*, anger, or aggression
   2. Nervousness or *anxiety*
   3. *Sleep difficulty* (e.g., insomnia, disturbing dreams)
   4. Decreased appetite or weight loss
   5. Restlessness
   6. Depressed mood
   7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache

C. Signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

DSM-5 (2013)

CB: DSM-5 Substance Use Disorder (*abuse/dependence*)

16

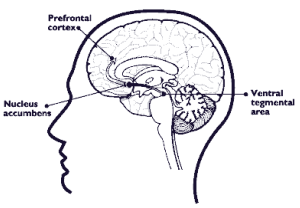
A. Problematic pattern of CB use leading to clinically significant impairment or distress; includes at least two of the following (within 12-month period):
   1. CB often taken in larger amounts or over longer period than intended.
   2. Persistent desire or unsuccessful efforts to cut down or control CB use.
   3. Great deal of time spent in activities necessary to obtain/use/recover from CB use.
   4. Craving, or a strong desire or urge to use CB.
   5. Recurrent CB use resulting in failure to fulfill major role obligations at work, school, or home.
   6. Continued CB use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of CB.
   7. Important social, occupational, or recreational activities given up/reduced due to CB use.
   8. Recurrent CB use in situations in which it is physically hazardous.
   9. CB use continued despite knowledge of having persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by CB.
   10. **Tolerance** (defined by either of the following):
       - Need for markedly increased amounts of CB to achieve intoxication or desired effect.
       - Markedly diminished effect with continued use of the same amount of CB.
   11. **Withdrawal** (manifested by either of the following):
       - Withdrawal syndrome for CB (refer to Criteria A and B for CB withdrawal).
       - CB (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

DSM-5 (2013)

CB: Addiction (*risk*)

17

- Research has demonstrated:
  - Approximately **9%** of those who use marijuana may become addicted.
    - Rate increases to **17%**, for those who start in their teens.
    - Up to **25–50%** among daily users.



Lopez-Quintero et al (2011); Volkow et al. NEJM (2014)
Image source: NIDA (public domain)

CBs: Neurocognitive Effects

18

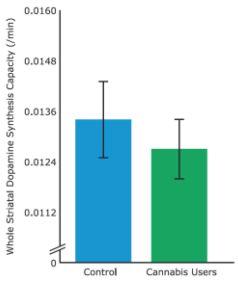
- **Alterations** among [**adolescent/young adult**] CB users:
  - Hippocampal volume changes
  - Cortical thickness
  - White/gray matter
  - Executive functioning
  - Processing speed
  - Intelligence quotient (IQ) – [conflicting data]
  - Complex attention
  - Verbal memory
  - Impulsivity
  - Blood oxygen dependent signal (BOLD)

Jacobus & Tapert (2014); Lisdahl et al. Curr Addict Rep (2014)

CBs: Neurocognitive Effects

19

- CB users experience:
  - Decreased:
    - Lifetime achievement
    - Success in school
    - Life satisfaction
  - Lack of motivation:
    - THEORY:
      - Direct CB effects
      - **Dopamine depletion**



Bloomfield et al (2014); NIDA Teens (2013); Volkow et al (2014)

CBs: Neurocognitive Effects

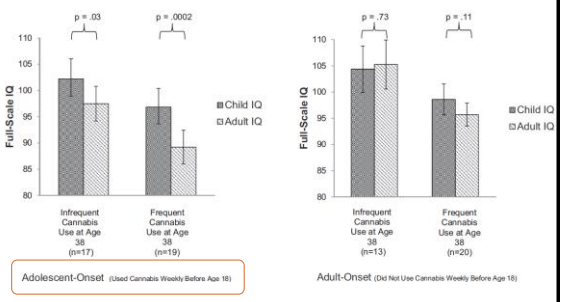
20

- Impact of persistent CB use on IQ
  - Methods:
    - Study design: prospective, longitudinal (*birth to 38 years*)
    - Sample size: **1000(+)** individuals
    - Study setting: New Zealand
    - Assessments:
      - CB use (*over time*)
      - Neuropsychological testing
  - Results:
    - Neuropsychological decline
    - Early CB onset associated with greatest decline

Meier et al. PNAS (2012)

CBs: Neurocognitive Effects

21



Meier et al. PNAS (2012)

CB (*acute*): Synthetic Formulations

22

- Incense/potpourri products
  - "K2", "spice", etc.
- Botanical ingredients
  - Sprayed with **full CB agonists** (e.g., JWH-018)
- CB intoxication
  - (-) routine urine toxicology analysis
  - Sudden onset *anxiety* or *psychosis*
- Schedule I

Castellanos & Thornton (2012); Cohen et al (2012); Schubart et al (2011); Seely et al (2012)

CB (*acute*): Synthetic Formulations

23

- Proposed MOA for AEs:
  - Potent CB agonists
    - Intensified PD effects
  - Lack cannabidiol (**?**)
    - Example: higher cannabidiol concentrations may lessen psychotic experiences
- Management:
  - No specific antidote
  - Aggressive benzodiazepine use

Castellanos & Thornton (2012); Cohen et al (2012); Schubart et al (2011); Seely et al (2012)

Part #3:

Available at: https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state

NASEM: Weight of Evidence

- Conclusive
- Substantial
- Moderate
- Limited
- No/Insufficient

Focus of this lecture

NASEM: Box 11-1, page 11-7

Developmental Implications Among Adolescents

While adolescents were clustered into many of these systematic reviews (e.g., Broyd et al., 2016), it is important to note that they were the minority, often less than 20 percent of the full sample, and rarely examined independently (e.g., Batalla et al., 2013) to uncover potential developmental differences in cognitive function and/or its interference between the age groups. Much work needs to be done specifically examining the impact of cannabis on these cognitive contexts in adolescents and emerging adults specifically (e.g., ages 14–25). This is highly important for three reasons. First, data in the cited systematic reviews and elsewhere (e.g., Batalla et al., 2013, and Filbey et al., 2015) continue to indicate that an early age of initiation tends to be connected to bigger differences in brain function during adulthood. Second, the brain does not complete development until approximately age 25 (e.g., Giedd, 2015), and data from the field of alcohol use reflect that substance use exposure during this period when the brain undergoes rapid transformation could have a more lasting impact on cognitive performance (e.g., Lisdahl et al., 2013). This interference in cognitive function during the adolescent and emerging adult years, which overlap with the critical period in which many youth and young adults' primary responsibility is to be receiving their education, could very well interfere with these individuals' ability to optimally perform in school and other educational settings.

While the evidence for an association between cannabis use and effects on cognitive development during adolescence is limited at this time, the committee recognizes the important initiative recently begun by the National Institutes of Health (NIH) for the landmark study on brain development and child health, Adolescent Brain Cognitive Development Study (ABCD) (Adolescent Brain Cognitive Development Study, 2016). The ABCD Study is the largest long-term study on cognitive development, tracking the biological and behavioral development of at least 10,000 children beginning at ages 9–10 for 10 years through adolescence into adulthood using neuropsychological evaluations and advanced brain imaging to observe brain growth with precision. This study, which began in 2015, will examine how biology and environment interact and relate to developmental outcomes such as physical health, mental health, and life achievements.

Conclusive/Substantial Evidence

- Efficacy findings:
  - Cannabis: chronic pain in adults
    - Localization in pain 'centers' (e.g., CNS and spinal cord)
    - MOA: topic of ongoing investigation
      - Example: vanilloid receptor activity
  - Oral cannabinoids: nausea & vomiting (chemotherapy)
  - Oral cannabinoids: patient reported spasticity symptoms (multiple sclerosis)

Conclusive/Substantial Evidence

- Adverse health effects:
  - Smoking cannabis: bronchitis episodes
  - Maternal cannabis: lower birth weight in offspring
  - Cannabinoids: ***motor vehicle accidents***
    - How are we going to monitor this situation??
    - Teter CJ. Drugged Driving. Journal Tribune 2016/2017
      - Pharmacokinetic/Pharmacodynamic issues

QUESTION FOR THE AUDIENCE: what concrete information does a given blood concentration of THC provide?

Marijuana vs. Alcohol (*monitoring example*)

BLOOD ALCOHOL CONTENT (BAC)
Table for Male (M) / Female (F)

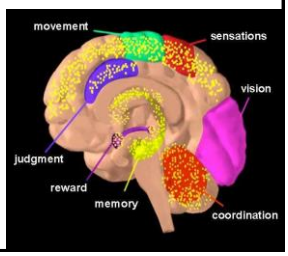
Number of Drinks		Body Weight in Pounds								Driving Condition
		100	120	140	160	180	200	220	240	
0	M	.00	.00	.00	.00	.00	.00	.00	.00	Only Safe Driving Limit
	F	.00	.00	.00	.00	.00	.00	.00	.00	
1	M	.06	.05	.04	.04	.03	.03	.03	.02	Driving Skills Impaired
	F	.07	.06	.05	.04	.04	.03	.03	.03	
2	M	.12	.10	.09	.07	.07	.06	.05	.05	
	F	.13	.11	.09	.08	.07	.07	.06	.06	
3	M	.18	.15	.13	.11	.10	.09	.08	.07	
	F	.20	.17	.14	.12	.11	.10	.09	.08	
4	M	.24	.20	.17	.15	.13	.12	.11	.10	Legally Intoxicated
	F	.26	.22	.19	.17	.15	.13	.12	.11	
5	M	.30	.25	.21	.19	.17	.15	.14	.12	
	F	.33	.28	.24	.21	.18	.17	.15	.14	

Subtract .01% for each 40 minutes of drinking.
1 drink = 1.5 oz. 80 proof liquor, 12 oz. 5% beer, or 5 oz. 12% wine.
Fewer than 5 persons out of 100 will exceed these values.

Image source: BACtrack

Conclusive/Substantial Evidence

- Adverse mental health effects:
  - Cannabinoids: psychoses/schizophrenia
    - ***Frequency*** of CB use
    - Longitudinal outcomes:
      - ***Conversion*** to psychosis
  - Causality??
    - Dose-response
    - Temporal relationships
    - Biological plausibility



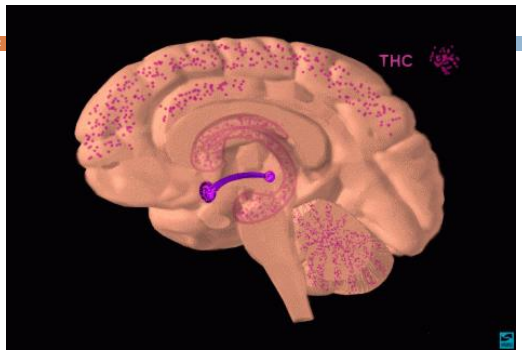
Conclusive/Substantial Evidence

- Substance use behaviors:
  - Problem cannabinoid use
    - Risk factors:
      - Male and smoking cigarettes
      - ***Frequency*** of CB use
      - ***Early age of initiation***
    - Non-risk factors:
      - ADHD treatment with stimulant medication

Is cigarette smoking the true "gateway" drug??

CB: THC binding sites

32



Source: National Institute on Drug Abuse (NIDA)

Frequency: Theory of Problem Use

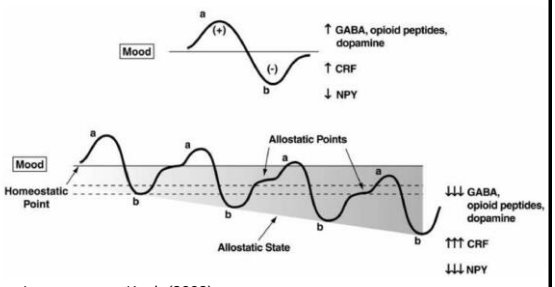
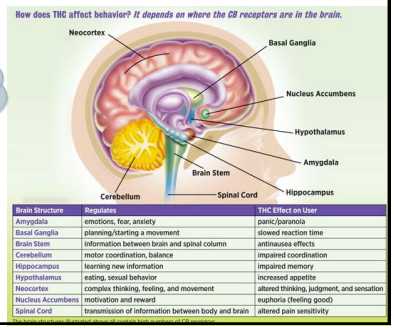


Image source: Koob (2008)

Closing Remarks

34

- CB evidence-base is continually growing
  - PNAS 2016 Study
  - Decreased IQ not necessarily associated with CB specifically
- Much remains to be learned in regards to CB use among all age groups
- Figure Source (public domain): NIDA



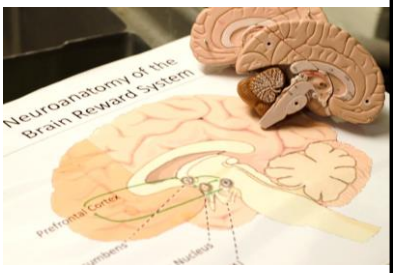
Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	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

35

Next Steps/Future Directions

UNE K-12 Educational Outreach

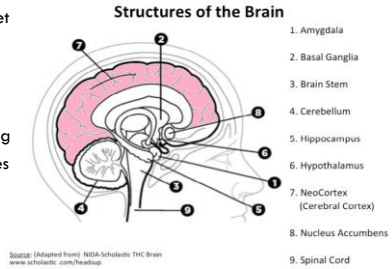
- Provide facts and information
- Not an intervention
- Interactive activities (e.g., 2-D poster + 3-D brain model
- Collecting data on whether these educational outreach activities produce any positive outcomes



UNE K-12 Educational Outreach

37

- Example worksheet provided to K-12 students
- Aim is to keep students engaged with active learning
- CB-centric activities



Source: (Adapted from) NIDA-Scholastic THC Brain www.scholastic.com/headsup

38

Question & Answer Session