NIDA CANNABIS SCIENCE RESEARCH AREAS

- **EPIDEMIOLOGY**: National and Local Surveys, including co-occurring MI and SUD
- **PREVENTION**: ABCD; SBI; Implementation of evidence based programs; Effective messaging and programs for “legal cannabis”
- **NEUROSCIENCE**:
  - Endocannabinoid System
  - Impact of exposure/use/addiction on brain structure and function; cognition; motivation; affect; fetal development
- **TREATMENT** of Cannabis Use Disorder:
  - Medications, Devices (e.g., TMS), psychosocial (behavioral)
  - Relapse prevention and withdrawal treatment
- **POLICY**: *Developing a research agenda now*
  - Identify greatest needs: e.g., better measures, including impairment; social consequences; regulatory models
CANNABIS: MOST COMMONLY USED “ILLICIT” DRUG IN THE U.S.

• Over 22 million Americans 12 and older were past month marijuana users.
• Approximately 4.0 million Americans met criteria for cannabis use disorders in 2015.
• An estimated 2.6 million Americans used it for the first time; 1.2 million were between the ages of 12 and 17.

Source: 2016 National Survey on Drug Use and Health, SAMHSA

Past Month Use of Cigarettes, Marijuana, and Alcohol in 12th Graders

And...nearly 6% report daily use of marijuana

Source: University of Michigan, 2016 Monitoring the Future Study
**Marijuana Potency** (% Δ-9 THC) Tripled in Past 20 Years

Science = Solutions
Variation in Legal Status of Marijuana

Increasing Regular Use of Marijuana, by Adults

SAMHSA, National Survey on Drug Use and Health, 2015.
Declining Marijuana Use in 12-17 year olds Despite Declining Risk Perception: **Associated with Tobacco Use Declines?**

Han, Compton, et al. *Journal of Clinical Psychiatry*, 2017

![Graph showing declining marijuana use and risk perception over time](chart.png)
What We Know:

- Use among youth (12-17) has not increased in recent years despite decreased perception of risk
- Use has increased in older teens and adults
- Current users use more often (daily, nearly daily) than in 2002
- Potency is increasing; plant components are changing
- Cannabis is being administered through different routes

What We Need to Know:

- Need improved measures of frequency, dosage, patterns of use
- Persuasive Messaging (especially for youth) to counter the trend of decreasing harm perception
- Greater knowledge of the impact of changing potency, constituents, and alternative routes of administration
- Regional differences based on changing laws, policies, and social norms
- Use of other substances: complementarity vs. substitution
CANNABIS’ ACUTE EFFECTS
(INTOXICATION PHASE)

• Euphoria
• Calmness
• Appetite stimulation
• Altered perception of time
• Heightened sensation
• Impairs coordination and balance
• Increased heart rate: 20 - 100%
• Orthostatic (postural) hypotension
• Increased risk of accidents (~2 fold), higher when combined with alcohol

• Impaired short-term memory
  • Difficulty with complex tasks
  • Difficulty learning
• Executive Function
  • Impaired decision-making
  • Increased risky behavior – STDs, HIV?
• Mood (especially after high doses or Edibles)
  • Anxiety – panic attacks
  • Psychosis – paranoia
More Teenage Use of Cannabis Associated with Worse Longer Term Outcomes in 20’s (3 large Australia/New Zealand Studies)

O.R. = Odds Ratio

Silins, et al., Lancet Psychiatry 2014;1:286-293
Recovery of Cognition and CBF with Abstinence

Brain blood flow after 28 days monitored abstinence

Mean CBF (ml/100g/min)

- Marijuana Users
- Controls

* p < .01
~ Age 18
N = 46

Verbal Memory
Working Memory
Attention

- 19 users
- 21 non-users

Mean CBF (ml/100g/min)

- Marijuana Users
- Controls

* p < .01
~ Age 18
N = 46

Tapert, 2016

Left Insula
Medial Frontal Gyrus

Tapert, 2016
When MJ Sales Were Restricted in The Netherlands, University Grades Improved
Cannabinoid Receptors Are Located Throughout the Brain

Regulation of:
- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immunological Function
- Appetite
- Motivational Systems & Reward
Cannabinoid Receptors Are Also Located Throughout the Body

Whole Body Distribution of CB1 Receptors (2, 25, and 100 min after injection of 11C-MePPEP)

PET images of [11C]-NE40 (CB2R radioligand)

Terry et al., Eur J Nucl Med Mol Imaging. 2010
Ahmad et al., Mol Imaging Biol. 2013 A
Cannabis Use During Pregnancy is increasing


Source: Brown et al., 2017
Cannabinoid (CB₁) Receptors are Expressed in Human Fetal Brain

Wang et al., Neuroscience, 2003

A Powerful Cannabinoid Agonist (CP-55,940) Causes Brain Malformations in Fetal Mice

Marcoita et al., Neurotox Teratology, 2015.

CP 55,940-treated fetal mice showing abnormalities of the brain, eyes, palate, and mandible. CP 55,940 is 45-times more potent than THC.
Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Zalesky et al., Brain 2012
Use of Rewarding Substances During Adolescence Primes the Reward System, Increasing Risk for Drug Abuse

THC Exposure Alters Nicotine Self-Administration (SA)

Adolescent Δ9-THC Exposure Alters WIN55,212-2* SA in Adult Rats

Mean WIN Intake Over the last 7 Training Sessions

Panlilio LV et al., Neuropsychopharmacology 2013; 38:1198-1208.

Scherma M et al., Neuropsychopharmacology 2016; 41:1416-1426.
Heavy Cannabis Use Increases Risk for Schizophrenia in People with a Genetic Predisposition

**Study of Swedish Conscripts (n=45570)**

![Bar chart showing the number of cannabis cases per thousand based on the number of times cannabis was taken.](chart1.png)


**Prospective Dunedin study (n=1037)**

![Bar chart showing the risk of schizophrenia-like psychosis at age 26 years.](chart2.png)

Arseneault et al. BMJ 2002

**Risk Conferred by AKT1 Gene**

![Bar chart showing the effect of AKT1 gene on schizophrenia-like psychosis.](chart3.png)

Di Forti et al., Biological Psychiatry, 2012.

**Effect of Potency on Risk of Psychosis**

![Bar chart showing the adjusted odds ratio for different cannabis types and consumption frequencies.](chart4.png)

Di Forti M et al., The Lancet, 2015.
Other Marijuana-related Health Concerns

• Addiction potential (increased with heavy use and adolescent onset)
  ➢ *Need for better treatments of Cannabis Use Disorder*

• Second hand exposure
Adolescent Brain and Cognitive Development (ABCD) Study
NIDA, NIAAA, NCI, NICHD, NIMH, NIMHD, OBSSR, NINDS

Ten year longitudinal study 10,000 children from 10 to 20 years to assess effects of drugs (including nicotine, and, marijuana and alcohol) on individual brain development trajectories and functional outcomes
Exploiting the Cannabinoid System for Therapeutic Purposes

- Exogenous compounds
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Dronabinol
- Endogenous manipulation
  - FAAH inhibitors
  - MAGL inhibitors
  - Allosteric modulators
- Receptor targets
  - CB₁, CB₂, TRPV₁, PPAR, 5-HT, peripheral, others...
Marijuana contains ~100 cannabinoids plus other chemicals in varying concentrations.
Enzyme Inhibitors (e.g., AEA degradation)

Indirect enhancers of CB activity—more selective, less side effects

What have we learned?

- Very mild side effect profile in animals and humans
- Reduce nicotine addiction
- Reduce anxiety-like behaviors
- Reduce depression-like behaviors
- Enhance social behavior in ASD models
- May be effective for cannabis use disorder

Piomelli, 2016
Cannabidiol in Treatment Resistant Dravet Syndrome (Epilepsy)

Recent meta-analyses support the use of cannabinoids for chronic neuropathic non-cancer pain, but…

- Studies generally short, small, with modest effect sizes.

“Currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.”
- M.E. Lynch & M.A. Ware; J Neuroimmune Pharmacology 2015

“There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics.”
- A. Deshpande et al; CFP 2015

“There is evidence for the use of low-dose medical marijuana for chronic noncancer pain.”
- A. Deshpande et al; CFP 2015

There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.
- P.F. Whiting et al; JAMA 2015
Marijuana is the most commonly used illicit drug in U.S.

Marijuana use generally begins in adolescence.

Use of marijuana can have a wide range of effects on an individual’s brain, body and behavior including short and long term effects on such functions as:

- Brain development
- Memory and cognition
- Motivational systems and reward
- Addiction
- Lung health

Research on the impact of marijuana on the developing adolescent brain is important.

Medical uses of marijuana are most likely from plant cannabinoid constituents.
Drugs + Your Body: It Isn't Pretty

Web interactive

Includes graphics, videos, quizzes and much more on the wide-ranging harmful effects of drugs on the brain and body.