Cannabis / Marijuana:
Pharmacology to Treatment

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Supported by NIDA, CSAM, Arkansas Tobacco Settlement Funds
“Potential Conflicts”

• Funded by National Institute on Drug Abuse to do clinical and laboratory research related to cannabis abuse / dependence…

• Consultant / Participant: Office of National Drug Control Policy’s marijuana and kids media campaign…video trainings and expert panels…

• Scientific Review Board: Center for Medical Cannabis Research, State of California
The Plan

Epidemiology / Clinical Epidemiology
Pharmacology / Neurobiology / Genetics
Health/Social/Behavioral Consequences
Dependence / Diagnosis / Withdrawal
Clinical Approaches and Outcomes
- Adults and Adolescents
1936

Say, Larry! I know a reefer? How you feel? You're just nervous! What you need is a little pick-me-up! Go on -- try a reefer!

Sure, it's marijuana! A few drags on that stick and you'll forget you ever had any nerves.

I -- I hope so!

Shocking dope expose reefer madness seduction of the innocent
Cannabis is more similar than dissimilar to other substances of abuse.

Like other substances of abuse, a subset of persons who use cannabis develop problems...some not so serious, some serious.
Cannabis Epidemiology

Most commonly used illicit drug in U.S. and many other countries

National Household Survey (12yr and older)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percentage</th>
<th>Number</th>
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<tbody>
<tr>
<td>Lifetime</td>
<td>34%</td>
<td>76 million</td>
</tr>
<tr>
<td>Past year</td>
<td>8.3%</td>
<td>19 million</td>
</tr>
<tr>
<td>Past Month</td>
<td>4.8%</td>
<td>11 million</td>
</tr>
<tr>
<td>Weekly</td>
<td>2.6%</td>
<td>6 million</td>
</tr>
<tr>
<td>Daily</td>
<td>1.2%</td>
<td>2.5 million</td>
</tr>
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</table>

(www.samhsa.gov/oas/nhsda) monitoring the future study…websites
Marijuana Use and Perceived Risk of Harm

- Perceived great risk of harm from occasional marijuana use
- Used marijuana in past year

Year

# Cannabis Epidemiology

## By Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Past month</th>
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<tbody>
<tr>
<td>12-17 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>18-20 yrs</td>
<td>17%</td>
</tr>
<tr>
<td>21-25 yrs</td>
<td>11%</td>
</tr>
<tr>
<td>26-34 yrs</td>
<td>5.9%</td>
</tr>
<tr>
<td>35 + yrs</td>
<td>2.3%</td>
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## By Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Past month</th>
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<tbody>
<tr>
<td>8th</td>
<td>10%</td>
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<tr>
<td>10th</td>
<td>19%</td>
</tr>
<tr>
<td>12th</td>
<td>23%</td>
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</tbody>
</table>
## Cannabis Epidemiology
### Youth: 12-17yrs

<table>
<thead>
<tr>
<th>Sex</th>
<th>Past Month</th>
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<tbody>
<tr>
<td>Female</td>
<td>6.6%</td>
</tr>
<tr>
<td>Male</td>
<td>7.7%</td>
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</table>

### Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Past Month</th>
</tr>
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<tbody>
<tr>
<td>Cauc</td>
<td>7.8%</td>
</tr>
<tr>
<td>Afr-Am</td>
<td>5.4%</td>
</tr>
<tr>
<td>Hisp</td>
<td>6.6%</td>
</tr>
<tr>
<td>Native-Am</td>
<td>19.9%</td>
</tr>
<tr>
<td>Mixed</td>
<td>6.6%</td>
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</tbody>
</table>
## Cannabis Epidemiology
*(12yrs and older)*

<table>
<thead>
<tr>
<th>Sex</th>
<th>Past Month</th>
<th>Past Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>6.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Male</td>
<td>10.4%</td>
<td>6.2%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Past Month</th>
<th>Past Year</th>
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<tr>
<td>Hisp</td>
<td>6.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Native-Am</td>
<td>15.3%</td>
<td>10.1%</td>
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<tr>
<td>Mixed</td>
<td>17.9%</td>
<td>12.5%</td>
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Clinical Epidemiology
NCS Study (Anthony et al. 1994)

<table>
<thead>
<tr>
<th>Lifetime Dependence</th>
<th>Conditional Dependence</th>
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</thead>
<tbody>
<tr>
<td>• Marijuana 4.2%</td>
<td>• Heroin 23.1%</td>
</tr>
<tr>
<td>• Cocaine 2.7%</td>
<td>• Cocaine 16.7%</td>
</tr>
<tr>
<td>• Stimulants 1.7%</td>
<td>• Stimulants 11.2%</td>
</tr>
<tr>
<td>• Heroin 0.4%</td>
<td>• Marijuana 9.1%</td>
</tr>
<tr>
<td>• Tobacco 24.1%</td>
<td>• Tobacco 31.9%</td>
</tr>
<tr>
<td>• Alcohol 14.1%</td>
<td>• Alcohol 15.4%</td>
</tr>
</tbody>
</table>
US Treatment Admissions by Primary Substance

Illustrates the general increase in treatment enrollment for cannabis over the last 15 years (SAMHSA, 2009)
U.S. Treatment Admissions by Primary Substance of Abuse

- Alcohol
- Cocaine
- Heroin/Opiates
- Marijuana

% of admissions

- All ages
- Ages 15-19
Treatment Admissions
(TEDS, 1998)

- UPDATE
- Marijuana abuse = 13% of all admissions
- 75% male
- 60% white
- 45% under 20 yrs (most common)
- 50% via criminal justice system
Adolescent/Young Adults Account for most of the Cannabis Treatment Cases

In US, approximately 45% of cannabis admissions are 20 yrs and younger.

In Australia, 26% are 10-19yrs, 41% are 20-29yrs.

50% of 10-19 yr old treatment cases were for cannabis.
Need for Prevention, Early Intervention, Treatment

- Majority of adults with cannabis disorder symptoms report they began smoking before age 18

- Treatment admissions for cannabis disorders have more than doubled in the past decade or so

- Large proportion of treatment admissions are adolescents and young adults
**Administration**

**Smoked**

smoked as a cigarette (joint), or in a pipe or bong, also in cigars known as “blunts”, also mixed with tobacco

**Oral administration**

oral ingestion has slower onset of effects, duration of effects is longer, but not usually as potent

**Vaporize** *(Volcano, VripTech Glass Heat Wand)*

reduces toxic, and carcinogenic by-products by heating; active compounds boil off into a vapor. No combustion.

**Oro-mucosal Mouth Spray** *(Sativex)*

- combination of delta9-THC and cannabidiol
Neurobiology

Endogenous cannabinoid system

Discovered in late 1980’s

Endogenous cannabinoid (at least 5):
- Anandamide, 2-arachidonoylglycerol (AG)
- 2-arachidonylglycerolether, O-arachinoyl-ethanolamine
- N-arachydonyl-dopamine (NADA)

Cannabinoid Receptors

- most widely expressed G protein-coupled receptors in brain?
- Two types named to date:
  - CB1: mediates psychoactive and reinforcing effects
  - CB2: more in periphery (immune system)
  - Likely non CB1-CB2 receptors in endothelial cells?
QuickTime™ and a decompressor are needed to see this picture.
Cannabinoid System
Receptor Location and Function

- Cerebellum - movement/coordination
- Hippocampus - learning, memory
- Cerebral Cortex - executive function
- Nucleus Accumbens - reward (dopamine system)
- Basal Ganglia - movement
- Hypothalamus - body regulation
- Amygdala - emotional responses
- Spinal Cord - sensation (pain)
- Brain Stem - sleep, arousal, motor
- Central Gray Matter - analgesia
- Nucleus solitary tract - visceral sensation, nausea/vomiting
Neurobiology of Self-administration, Dependence and Cessation

The CB1 receptor mediates the positive reinforcing effects of cannabis, cannabinoid dependence and expression of withdrawal; the has been verified across species.

Delta-9-THC and other CB1 agonists activate the mesolimbic dopamine system, the neurobiological substrate hypothesized to modulate the positive affective properties of stimuli (including drugs) that reinforce behavior in animals and humans.

Neurochemical responses in the limbic system to long-term cannabinoid exposure and subsequent withdrawal from cannabinoids closely resemble the response seen with other major drugs of abuse.
Neurochemical responses in the limbic system to long-term cannabinoid exposure and subsequent withdrawal from cannabinoids closely resemble the response seen with other major drugs of abuse.

THC appears to enhance dopamine (DA) neuronal firing and synaptic DA levels in the reward pathway of the brain, and enhances electrical brain-stimulation (EBS) reward.

Abrupt cessation of THC exposure increases corticotrophin-releasing factor, decreases DA, and inhibits EBS reward in the reward pathway (effects linked to withdrawal from alcohol, opiates, and cocaine, and thought to contribute significantly to relapse.)
Source Readings for Cannabinoid Function

International Review of Psychiatry (2009)
Special Issue on Cannabis and the Cannabinoids

**Editorial:**  
Budney & Lile

**Epidemiology:**  
Copeland & Swift

**Reinforcing Effects:**  
Cooper & Haney

**Neurobiology:**  
Breivogel & Sim-Selley

**Medicinal Chemistry (Structure):**  
Janero et al.

**Treating Addiction: inverse agonist /antagonist:**  
Beardsley et al.

**Pain: Cannabinoid -Opioid Interactions (pain):**  
Welch

**Psychosis:**  
Sewell et al.

**Eating Behavior:**  
Kirkham

**Neurodegenerative Diseases:**  
Ogado et al.
Genetic Influences

**Twin Studies:**
Genetic influences 50-75% of variance in susceptibility to cannabis use disorders

**Linkage studies:**
- regions on chromosomes 1, 3, 4, 9, 14, 17 and 18,
  candidates with biological relevance *MGLL, ELTD1*

**Gene association studies**
- genes posited to have specific influences on cannabis use disorders: *CNR1, CB2, FAAH, MGLL, TRPV1* and *GPR55*
- genes from neurotransmitter systems: non-specific influence *GABRA2, DRD2* and *OPRM1*
Health Consequences of Cannabis Use
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Acute Effects (under the influence) on Memory and Performance

- Short-term memory and attentional processes impaired
- Motor skills and reaction time impaired (complex tasks)
- Driving: association with alcohol use and slower driving make it difficult to know impact; definitely some impairment
- Decision-making and executive function (not robust)
- Higher doses: response perseveration, impairment in motor impulse control, divided attention, response adaptation, and working memory
- ** - Effects are dose-related
  - Covary with tolerance / cannabis use history
Chronic Cognitive Effects

- No evidence of severe impairment
- Subtle impairments of memory and attention detectable after 24 hrs of abstinence
- Impairment may be residual effect that dissipates with continued abstinence
- May be linked to duration of chronic use
Chronic Brain/Cognitive Effects

• Neuroimaging studies indicate that long-term cannabis users have altered brain function in the prefrontal cortex, cerebellum, and hippocampus.
• Chronic cannabis users exhibit a greater propensity for risky decision-making.
• Because most cognitive and performance tests are dependent on degree of attention and motivation, understanding how cannabis affects these processes is necessary for understanding of its influence on cognitive processing.
Psychotic Disorders

• Acute psychosis is rare and difficult to distinguish from exacerbation of chronic mental illnesses. Do appear to be cases of cannabis induced, transient psychosis.

• Growing evidence that cannabis use may increase risk for development of chronic mental disorders in otherwise mentally healthy individuals; % risk is very low.

• Cannabis use can be considered a risk factor for schizophrenia and a predictor of poor outcome in schizophrenic patients, but its role as an etiological factor remains uncertain.
**Immunological Systems**

Mixed findings; no clear effects in humans, but many reasons for concern.

A better understanding of the functional significance of cannabis' effects on the immune system is imperative as attempts are made to develop safe and effective models for the medical use of cannabis and cannabinoids.

**Cardiovascular System**

Acute effects: increased heart rate and blood pressure.

Functional significance???

- may challenge at-risk individuals.
Reproductive System

Affects some female and male hormones, but functional significance is unclear. Male fertility may be affected but results variable / reversible. Lower birth weight, some data, but not consistent. No gross birth defects. Subtle cognitive effects in children exposed in utero; functional significance not clear.

Respiratory System

Impaired lung function; associated with chronic bronchitis and related symptoms. Data related to lung cancer is equivocal.
Special Concerns with Adolescent Cannabis Use

Adolescent cannabis use is associated with less stability in adult social roles (e.g., college, employment, relationships)

Earlier cannabis (substance) use is related to greater involvement in drugs in adulthood (26 yrs +)

Acute effects on memory and learning warn against chronic use during adolescence

Cannabis use is associated with poorer academic achievement

Cannabis use escalates to problematic use (dependence) more quickly than with older initiators
Special Concerns with Adolescent Cannabis Use

Heavy use and/or Early Initiation in adolescence related to:
- impaired attention, learning, processing speed
- subtle abnormalities in brain structure
- increased activation of cortical areas (working harder)
- impaired sleep quality
- persist for up to a month of abstinence; likely resolves

Raises concern regarding adolescent cannabis use and its impact on brain development, however, more research is needed to better understand the long-term significance.

More vulnerable to these effects than adults?
The traditional “gateway” hypothesis: marijuana is a “stepping stone” to the use of “harder” drugs (cocaine, heroin/opiates, methamphetamine drugs)
- Increases probability of exposure
- Represents crossing of “moral” line (doing illegal drugs)
- Changes in brain; increase susceptibility to reinforcement from other substances
- Are data to “support” these hypotheses
- Statistically true: it does precede other illicit drug use
Cannabis Dependence / Addiction

Does Cannabis Dependence exist?

If so, how severe is it?
Answer: YES

Behavioral Evidence
• Individuals meet DSM criteria for dependence
• Individuals seek help for cannabis use problems
• Nonhuman/human studies demonstrate withdrawal

Biological Evidence
• Discovery of the cannabinoid system in the brain and elsewhere in the body
• Effects of administration and cessation on the brain is similar to that with other drugs of abuse
How Does Cannabis Dependence Compare to Other Types of Dependence? (Budney et al., 2006)

Treatment seekers meet 4.7-5.9 of the 7 DSM-IV criteria…reflects a lower severity syndrome

Associated types of problems are comparable to other substance dependent populations

The “structure” of cannabis dependence is more similar than different than others

- unidimensional factor structure
- full range of criterion items are endorsed
- generally less severe
Cannabis Withdrawal

- Withdrawal is considered by many scientists and clinicians as an important marker of dependence or addiction.

- Cannabis (Marijuana) withdrawal is not currently in the DSM-IV... however,
Cannabis Withdrawal

• Cannabis (cannabinoid) withdrawal has been demonstrated in:
  – Non-human studies (primate, rodent, dog)
  – Clinical survey studies
  – Human inpatient/outpatient laboratory studies
“True” Withdrawal Syndrome exists for Cannabis

• Reliability and validity established
• Clear and transient timecourse
• Pharmacological Specificity
• Syndrome is not rare
• Has clinical importance…
DSM IV stated that there appeared to be a withdrawal syndrome, but its clinical importance was not clear...research since has demonstrated:

- Similar in magnitude and severity to Tobacco Withdrawal
- Cannabis users report using cannabis (and other substances) to relieve Withdrawal
- Those attempting to quit complain of Withdrawal and indicate it makes quitting difficult
- Significant Others observe significant withdrawal symptoms suggesting it disrupts daily functioning.
Symptom List (proposed for DSM-V)

3 (or more) of the following within several days of cessation

1) irritability, anger, or increased aggression
2) nervousness or anxiety
3) sleep difficulty (insomnia)
4) decreased appetite or weight loss
5) restlessness
6) depressed mood
7) at least 1 physical symptom causing significant discomfort (stomach pain, shakiness/tremors, sweating, fever, chills, headache)

** Text: disturbing/strange dreams, fatigue, yawning, difficulty concentrating, and increased appetite following decreased appetite during the early stages of withdrawal
Timecourse
Withdrawal Discomfort Score
(Budney et al. 2003)
Timecourse

- Mean onset of symptoms between 1-4 days
- Distress up to 15-20 days
- Sleep / dream reports may last longer
Comments

Don’t typically observe significant medical or psychiatric symptoms, but...

**does not mean the syndrome is insignificant**

Psychological symptoms are indicative of the major CNS effects of withdrawal, and may be as, if not more, important in precipitating dependence or relapse than physical symptoms.
Treatment Outcome Literature

Types of Treatment (Adults)

• Social Support Group (1 study)
• Cognitive Behavior Therapy (CBT) (8 studies)
  – Group
  – Individual
• Motivational Enhancement Therapy (MET) (8 studies)
• MET / CBT combination (5 studies)
• Contingency Management (CM) (4 studies)
### Published Randomized Treatment Trials (Adults)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments</th>
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<tr>
<td>Stephens, et al. (1994)</td>
<td>SS, CBT</td>
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<tr>
<td>Stephens, et al. (2000)</td>
<td>MET, CBT</td>
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<tr>
<td>Budney et al. (2000)</td>
<td>MET, MET/CBT, <strong>MET/CBT/CM</strong></td>
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<tr>
<td>Copeland et al. (2001)</td>
<td>MET, CBT</td>
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<tr>
<td>Sinha et al., (2003)</td>
<td>MET, MET/CM</td>
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<tr>
<td>MTPG (2004)</td>
<td>MET, MET/CBT</td>
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<td>Budney et al. (2006)</td>
<td>MET/CBT, CM, <strong>MET/CBT/CM</strong></td>
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<td>Carroll et al. (2006)</td>
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<td>Kadden et al. (2007)</td>
<td>MET/CBT, CM, <strong>MET/CBT/CM</strong></td>
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## Response Rates at Participant Level

<table>
<thead>
<tr>
<th></th>
<th>End Tx</th>
<th>6 m FU</th>
<th>12m FU</th>
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<tbody>
<tr>
<td><strong>MET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent:</td>
<td>9%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Improved:</td>
<td>17%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td><strong>MET/CBT</strong></td>
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<td></td>
</tr>
<tr>
<td>Abstinent:</td>
<td>23%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>Improved:</td>
<td>30%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td><strong>CM only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent:</td>
<td>40%</td>
<td>13-23%</td>
<td>14-17%</td>
</tr>
<tr>
<td><strong>MET/CBT/CM</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Abstinent:</td>
<td>24-43%</td>
<td>25-46%</td>
<td>28-37%</td>
</tr>
</tbody>
</table>
Computerized vs. Therapist-delivered MET/CBT/CM

Cannabis Abstinence

Wks of Abstinence

% UA n

Consecutive Weeks

% Negative

p = .47

p = .48
Adult Cannabis Tx Conclusions

- Cannabis Use Disorders not “easy” to treat

- We have well-specified efficacious treatments for decreasing use and engendering abstinence

- Innovations in behavioral approaches continued to provide incremental increases in outcomes

- We need to keep working along this path, as there remains much room for improvement in the rate of “success”

- Dissemination/use of most efficacious interventions is poor

- Technology offers many innovative strategies for enhancing the effectiveness of behavioral interventions
Adolescents

Support for family-based and group / individual behavioral treatments (Waldron 2008: review)

Waldron et al. -- FFT, CBT, combo
Liddle et al. -- MDFT
Henggeler et al. -- MST
Dennis et al. - CYT: MET/CBT, ACRA
Santisteban et al. - BSFT

Stanger, Budney et al. (2009) -
Treatments for Adolescents

Behaviorally-based, Family, Group, Individual

Family Behavior Therapy **FBT**
Functional Family Therapy **FFT**
Cognitive Behavior Therapy **CBT**
Multidimensional Family Therapy **MDFT**
Multisystemic Therapy **MST**
MET/CBT (5 or 12 sessions)
Community Reinforcement Approach **CRA**
MET/CBT+Family Support Network **FSN**
Contingency Management **CM/MET/CBT**
Cannabis Youth Treatment Study
Abstinence at Discharge

(Dennis et al., 2004)
CM added to MET/CBT
Stanger, Budney et al., (2009)

During Treatment Abstinence

% Adolescents Abstinent

MET/CBT+CM  MET/CBT+PE

>=6 wks
>= 8 wks
>=10 wks
Co-Morbidity
Disruptive Behaviour Disorders (DBD) and Substance Use

- Extensive research documenting links between childhood conduct/behavioral problems and substance use/abuse
- Substance use → Conduct Disorder → Substance Abuse
- Relationship described as “reciprocal” – each exacerbating the other
- Can be viewed as different expressions of the same construct
- Within youth with SUD, DBD is the most common comorbid disorder
- Within youth with CD, there is an increased risk for SUD: OR = 5.9
DBD and SUD

- DBD-SUD link holds across gender and cultures (Heath et al., 1997; Marmorstein & Locono, 2001; Chong et al., 1999)
- Research suggests a common genetic diathesis
- Genetic factor described as “disinhibitory psychopathology,” failure to refrain from risky behaviors $h^2 = 0.8$, “highly heritable” (Young et al., 2000; Krueger et al, 2002)
- Similarities in parenting practices:
  - low monitoring
  - high parent-child conflict
  - low positive involvement/interest
Continuous Abstinence During Treatment

% With > 10 Weeks Abstinence

No DBD

DBD
Continuous Abstinence During Treatment

% With > 10 Weeks Abstinence

- PDE: 5 (DBD) | 38 (No DBD)
- CM: 48 (DBD) | 53 (No DBD)
Adolescent Cannabis Tx Conclusions

- Cannabis Use Disorders not “easy” to treat
- We have well-specified efficacious treatments for decreasing use and engendering abstinence
- We need to keep working along this path, as there remains much room for improvement in the rate of “success”
- Dissemination/use of most efficacious interventions is poor
Pharmacotherapy

- No clear demonstrations of effective medications

- Clinical and Laboratory Targets have included:
  - Withdrawal symptoms: mood, sleep, anxiety, irritability, restlessness
  - Agonist substitution with oral formulations of THC
  - Antagonist, inverse agonist (block the effects of THC)
    - rimonabant (Acompli)
  - Medicinal chemists seek to develop agonist, antagonist, and enzymatic targets (FAAH)
Is Cannabis Abuse/Dependence a Public Health Issue?

Yes

- Relatively large numbers seek treatment
- Impacts a significant proportion of youth and adults
- Multiple consequences associated with abuse
If You Answer Yes

Does not mean:
- you can’t investigate potential benefits of cannabis
- you can’t explore harm reduction strategies
- you believe it is worse than alcohol or tobacco
- you believe it is the same as cocaine and heroin
- you believe it should or should not be legalized or decriminalized
Why is all this important?

• Demonstrates that the biological risk factors for developing cannabis use disorders appear more similar to other well-recognized “addictive“ drugs than previously believed

• Argues against notions that cannabis dependence is trivial in comparison to other drugs dependencies