SAMHSA’s Role: Integrating the Science & Technical Information into Regulated Testing

Federally Regulated Workplace Policy
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Division of Workplace Programs
Center for Substance Abuse Prevention
Substance Abuse and Mental Health Services Administration
The ASAM State of the Art Course
October 7, 2016
Disclosure Information

Ron R. Flegel, B.S., MT(ASCP), MS.
No disclosures
Behavioral Health is Essential To Health

Prevention Works

Treatment is Effective

People Recover
SAMHSA’s Role: Integrating the Science and Technical Information into Regulated Testing
Presentation Objectives

• Objectives / Goals:
  – **Past**: Program Oversight, Oversight of DFWP within the Executive Branch Agencies, National Laboratory Certification Program / Lab Inspections, and Emerging Issues
  – **Present**: Process for approving and implementing Oral Fluid as an alternative specimen in the Federal Workplace Drug Testing Programs and writing the Proposed Mandatory Guidelines for Hair
  – **Future**: Implementing the revised Urine Mandatory Guidelines and New Oral Fluid Mandatory Guidelines
  – **Goals**: Implementing synthetic opioid testing (oxycodone, hydrocodone, oxymorphone, hydromorphone).
Drug Free Workplace Programs

Federal Laws

Employer

“Drug Testing Policy”

Testing Issues

State Laws

congress.nsc.org

Contract / Legal Issues
Definitions

**Decriminalization**—Reduces penalties for possession and/or use of small amounts

**Medical Marijuana**—Permits defense against state criminal charges of marijuana possession if a medical need can be proven

**Legalization**—Makes possession and/or use of marijuana legal under state law
Division of Workplace Programs

- The Division of Workplace Programs (DWP)
  - Center for Substance Abuse Prevention (CSAP)
  - Substance Abuse and Mental Health Services Administration (SAMHSA)
  - U. S. Department of Health and Human Services (HHS)
- Under a delegation of authority from the Secretary of HHS, DWP assumes HHS’s role in managing the Federal Drug-Free Workplace Program
Program Oversight

Division of Workplace Programs
Governing Authorities*
- Executive Order 12564
- Public Law 100-71

Oversight Authority
- Interagency Coordinating Group – Executive Committee

Federal Partners
- DOT, NRC, DOI, DoD, NIDA, FDA, DOJ, DEA, DOE, DOL

Non-federal Partners/Stakeholders
- Regulated industries (FMCSA, FRA, FAA, FTA, PHMSA)
- State and Local Governments

Office of Personnel Management
- Department of Justice
- Department of Health and Human Services
- Office of National Drug Control Policy
Fitness for Duty / DUID?

- **Delta-9-tetrahydrocannabinol (THC)** is the primary psychoactive ingredient in marijuana.
- **Delta-9-tetrahydrocannabinol-9-carboxylic acid (THCA)** is the primary metabolite of THC formed in the body after cannabis use.
- THCA is currently tested in urine specimens. SAMHSA proposes that the UrMG continue to test for **THCA only**.
- The proposed Oral Fluid Mandatory Guidelines (OFMG) is still being reviewed for **THC vs. THCA or both**.
- Some points to consider
  - Limited technological capacity to implement testing for THCA in oral fluids on a national scale
  - Current laboratory capacity to test for THCA
  - Requiring all laboratories that are subject to the Mandatory Guidelines for Federal Workplace Drug Testing Programs to test for THC / THCA in oral fluid could impose implementation costs
  - A positive THC test is a scientifically valid method for detecting marijuana use in oral fluid. The failure to test oral fluid samples for THCA would not undermine the legal or scientific validity of a positive THC drug test.
In 2013, 32% of FT workers 18-64 years old indicated they lived in a state with laws allowing the use of medical marijuana.

Number of days marijuana was smoked in the past month

- 15 days: 32%
- 14 days: 68%

Prevalence of 30-day marijuana use by state law status

9.8% for 15 days
6.9% for 14 days
Approximately 21% of U.S. adults 18 and older entering substance treatment for the first time reported their employment status as full-time (FT) on the 2012 Treatment Episode Dataset (TEDS).

Percentage of FT workers who indicated their primary drug at admission was…

- Marijuana: 3 workers, 17.2%
- Prescription drugs: 2 workers, 12.2%
- Illicit drugs: 1 worker, 9.5%
Information Sharing
Validating Immunoassays for Urine Drug Testing

This is the first of a four-part Drug Testing Matters series on urine drug testing methods validation. This part covers validating immunoassay methods. The second part will cover validating specimen validity tests (SVTs); the third and fourth parts will cover validating mass spectrometry methods.

Immunoassay Overview

Immunoassays utilized for laboratory testing date back to the 1950s with Berson and Yalow’s Nobel Prize-winning development of the first radio-immunoassay (RIA). All immunoassays are based upon an antigen-antibody reaction being coupled to an analytical chemistry application that measures the antigen-antibody binding. Depending upon the application, the antibody or the antigen may be the measured of interest.

For urine drug testing, drug(s) and/or drug metabolite(s) in the sample are both the antigens...
DWP Website Initiatives

• Audiences –DWP’s outreach.
• Possible audiences the information may reach – youth, young adults entering workplace, older adults, health care providers, states, federal agencies, etc…
• State have been asking for guidance on what to do about marijuana issues.
• Drug Testing and implications in the workplace for States and Workplaces.
Marijuana Toolkit

Decriminalization and Legalization of Marijuana: A Primer

Federal, state, and local (town and municipal) laws and policies around marijuana are changing rapidly and are complex, frequently inconsistent, or in conflict.

- **Changing Landscape in Marijuana Policy: How the U.S. Law and Interpretations Are Shifting**
  - It often is unclear what the law and actions are. How they are being used at the state and local levels, whether marijuana is regulated or decriminalized, how the laws and policies will be implemented, and what factors influence their trends. These issues can be confusing for the general public and people involved in the justice system.

- **Terminology and Complexity of Interpretations**
  - Legalization involves the process of formulating a particular action into being legal. In the case of marijuana, state and local policies varying in possession limits, age of sale, and other factors. Both the federal and state governments have jurisdiction over marijuana policies, and this complexity can lead to confusion.

- **How Safe Are Edibles?**
  - The safety of edible marijuana products is a public health issue. Many states have different rules regarding the use of edible marijuana, including the age limits, possession limits, and regulations for selling and labeling.

- **Marijuana's poor effects can be delayed by up to 4 hours after ingestion.**

- **Edible Marijuana: The Issues**
  - People who consume edibles may experience more intense and longer-lasting effects than those who smoke marijuana. Edibles are absorbed through the bloodstream, leading to higher blood levels of THC and a slower onset of effects. This can result in delayed reactions, as well as increased risk of impaired driving.

- **Marijuana tourism: Increased use and sales of marijuana in states where it is legal.**
Marijuana Toolkit

Employment Issues and Marijuana Use: Considerations for the Employee

Federal, state, and local (town and municipal) laws and policies around marijuana are changing rapidly and are complex, frequently inconsistent, or in conflict.

Many states are legalizing marijuana for recreational or medicinal use, meaning that they are implementing laws and policies that make possession, sale, or use of marijuana legal from the viewpoint of the government that passed the law and typically lower levels of government (because state law often creates local law). Other states are enacting laws that make possession, sale, or use of marijuana illegal, meaning that they are implementing laws and policies that make possession, sale, or use of marijuana illegal from the viewpoint of the government that passed the law and typically higher levels of government (because state law often creates local law). Other states are enacting laws that make possession, sale, or use of marijuana legal in some circumstances but illegal in others, meaning that they are implementing laws and policies that make possession, sale, or use of marijuana legal in some circumstances but illegal in others.

Employees may have questions about how the changing environment affects them. Many such decisions have upended an employer’s right to maintain a drug-free workplace because it must accommodate someone who has been linked to increased risk of injury and absenteeism from the workplace. Often times it is considered when seeking employment include:

- Knowing that marijuana use and contracts most closely with federal law, and
- Under the Americans with Disabilities Act, there is no obligation to accommodate medical marijuana use.

In 2019, 14 states with medical marijuana laws passed legislation allowing for the use of marijuana for medical reasons. These laws are often interpreted to cover the use of marijuana for medical reasons, although some of these laws require employees to be on-duty day users or prohibit workplace drug testing.

Drug Testing

To help maintain a drug-free workplace, many employers require drug testing of their employees and existing employees. Following is a description of the types of drug tests for various and employees may encounter at a subject of employment.

Pre-employment drug testing

In 2013, 40 percent of U.S. employees say that their employer conduct drug tests, including 43 percent of U.S. employees who work in professional, technical, or sales jobs. Some employers think that employees who use drugs are generally using marijuana and believe that marijuana users need to have the prospective employer’s policy.

Is marijuana a gateway drug leading to use of drugs such as heroin or cocaine?

The answer depends on the definition.

The answer to the question depends on how a gateway drug is defined. One interpretation could mean that marijuana is a gateway drug to the use of another drug, whereas another interpretation could mean that marijuana increases the risk of using another drug but does not necessarily lead to the use of another drug.

Pardoning the Data

In general, there are some dangers. It appears that marijuana users are at least twice as likely as non-users to progress to other illicit drug use. In 2011, 12.6% of marijuana users also reported using other illicit drugs, compared to 1.9% of non-users. Users of marijuana are at least eight times more likely to use an opioid prescription drug compared to non-users. The use of marijuana increases the risk of using another drug but does not necessarily lead to the use of another drug.

Marijuana users from other users or assess the likelihood that marijuana users will progress to other Schedule I drugs. Often statements indicate that users who use both marijuana and other Schedule I drugs typically use marijuana once before other Schedule I drugs. Other studies have suggested that marijuana use is associated with risk for substance use disorders, such as heroin and cocaine use. There is evidence that marijuana use is associated with increased risk for substance use disorders, such as heroin and cocaine use. There is evidence that marijuana use is associated with increased risk for substance use disorders, such as heroin and cocaine use.
Marijuana Toolkit

How Strong is Marijuana Today?

The average marijuana extract now contains more than 50 percent THC, and certain samples may have THC concentrations of more than 80 percent.

Why the Change in Potency?

Several factors account for marijuana's increasing strength:

1. "Weed" has become more potent due to increases in THC levels.
2. "Weed" is now more potent due to decreases in CBD levels.
3. "Weed" is now more potent due to changes in growing and breeding practices.

Advantages for Users

Although marijuana may not yet lead to the effects of increased THC exposure (such as the body), there are several advantages to using marijuana:

1. A recent study found that marijuana use is associated with higher levels of endocannabinoids in the brain.
2. Marijuana is a natural remedy for a variety of conditions, including cancer, epilepsy, and chronic pain.
3. Marijuana is a natural source of vitamin A, which is essential for good health.

Public Health Implications

The current spread of marijuana use is a public health concern, especially for young people. marijuana users are at risk for increased risk of suicide, depression, and addiction.

This fact sheet includes the definitions of common terms related to marijuana.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBD</td>
<td>Cannabidiol, the main component of marijuana that is not psychoactive.</td>
</tr>
<tr>
<td>THC</td>
<td>Tetrahydrocannabinol, the psychoactive ingredient in marijuana that causes the &quot;high.&quot;</td>
</tr>
<tr>
<td>CSHD</td>
<td>A musical term used for &quot;chords&quot; in music.</td>
</tr>
<tr>
<td>RVO</td>
<td>A medical term used to describe &quot;residual volume&quot; in the lungs.</td>
</tr>
<tr>
<td>CVG</td>
<td>A medical term used to describe &quot;constant volume&quot; in ventilation.</td>
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</tbody>
</table>

Marijuana: Definitions and Terms

Marijuana, also known as "pot," "marihuana," "mary jane," or "reefer," is a CNS depressant that is a plant product of the Cannabis sativa plant. It contains over 300 compounds, including THC and CBD.

Cannabinoids are the psychoactive compounds in marijuana. THC is the primary psychoactive compound in marijuana, and is responsible for the "high" associated with marijuana use.

Marijuana is a Schedule I controlled substance under federal law, which means it is illegal to grow, sell, or use.

Marijuana is a Schedule I controlled substance under federal law, which means it is illegal to grow, sell, or use.
Medical Review Officer (MRO) Certifying Entities & Prescription Drug Initiatives
MRO Overview

• Medical Review Officer (MRO)
  – Licensed physician who has either a Doctor of Medicine (M.D.) or Doctor of Osteopathy (D.O.) degree,
  – Has knowledge regarding the pharmacology and toxicology of licit and illicit drugs,
  – Has completed the training necessary to serve as an MRO, and
  – Has satisfactorily passed an examination administered by a nationally recognized entity that certifies MROs or subspecialty board for physicians performing a review of Federal employee drug tests results, which has been approved by the Secretary

• Mandatory Guidelines for Federal Workplace Drug Testing Programs
  – Subpart M – Medical Review Officer (MRO), Section 13.1
MRO Manual Update

• Major Issues
  – Addressing the addition of Rx opioid drugs to drug testing panel:
    • Oxycodone, oxymorphone, hydrocodone, hydromorphone.
  – Hydrocodone combination drugs have been rescheduled to Schedule II
  – “What is considered a valid prescription under the Drug-Free Workplace Programs and how will it be interpreted by the Medical Review Officer?”
DTAB Membership

- Unique among SAMHSA’s councils in that Drug Testing Advisory Board is a scientific advisory panel
  - Designated Federal Official – nonvoting members
  - Chair – nonvoting member
  - 10 members – voting members
  - 3 Ex-officio members – nonvoting members
- Ex-Officio’s from 5 Agencies (FDA not pictured)
Proposed Mandatory Guidelines for Oral Fluid
Organization of Proposed Guidelines

Proposed Mandatory Guidelines for Federal Workplace Drug Testing Programs using Oral Fluid

• The preamble
  – Describes the differences between the Mandatory Guidelines using Urine specimens (UrMG) and the proposed Mandatory Guidelines using Oral Fluid (OFMG)
  – Presents a number of remaining issues

• The Mandatory Guidelines for both Urine and Oral Fluid are arranged and organized by the same
  – Sections / Questions / Content and Context.
Major Points

Proposed Mandatory Guidelines for Federal Workplace Drug Testing Programs using Oral Fluid

- Adding Oral Fluid as an alternative specimen
- The testing of Delta-9-tetrahydrocannabinol (THC) to detect cannabis use or testing of Delta-9-tetrahydrocannabinol-9-carboxylic acid (THCA) within the federal drug testing process.
- Allowing federal executive branch agencies to test four additional Schedule II narcotic prescription medications (i.e., oxycodone, oxymorphone, hydrocodone, and hydromorphone)
Synthetic Marijuana / Emerging Issues
Synthetic Marijuana

- The main chemical used to produce synthetic marijuana is JWH-018, similar to THC.
- No psychopharmacological differences exist between JWH-18 and marijuana.
- Both chemicals are considered cannabinoids, which attach themselves to the cannabinoid, or CB, receptors in the brain.
- However, the synthetic compounds and THC differ in levels of potency.
  - Potential problem with synthetic marijuana is rapid and cost-effective ability to identify the substances (analytical screening test).
  - Recognize the immediate effects (pharmacological) they may have on an individual.
Herbal Incense (e.g. Spice)

- K₂
- K₉
- Spice Gold
- Silver or Diamond
- Budda Blend,
- Yucatan Fire
Synthetic Marijuana

Synthetic Cannabinoids (THC)

- Dronabinol (Marinol)
- Nabilone (Cesamet)
- THC + CBD (Sativex)
- Cannabinol Extract (Cannador)
- CBD (Epidiolex) in IND-Phase III trials
Mandatory Guidelines Update – Urine, Oral Fluids, and Hair
### Mandatory Guidelines Update

<table>
<thead>
<tr>
<th></th>
<th>Urine</th>
<th>Oral Fluids</th>
<th>Hair</th>
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<tbody>
<tr>
<td></td>
<td>The most current version of the Urine Mandatory Guidelines will include testing for 4 prescription opioids – hydrocodone, hydromorphone, oxycodone, and oxymorphone</td>
<td>The Oral Fluids Mandatory Guidelines are in the approval process and are expected to have an implementation date within the next year.</td>
<td>The Hair Mandatory Guidelines are being drafted by the Division of Workplace Programs and will include the scientific and technical information about hair as a alternative specimen for drug testing.</td>
</tr>
</tbody>
</table>
Areas for Further Research

• The topic areas in which further research is required
  – Biomarkers / Metabolites / Cutoffs
  – Specimen Validity Testing / Valid Specimen
  – Biomarkers for Synthetic Urine
  – Collection Processes
  – Collection Devices
  – Initial and Confirmatory Testing using Alternative Technology
  – Other significant scientific, legal, and public policy concerns related to the oral fluid specimen collection and testing
Ongoing and Future Studies

- Oral Cannabis Ingestion Study
- Vaporizer / Inhalation Study
- DUID or Roadside Testing / Established Cutoffs
- POCT Device Evaluation
- MRO Interpretation / Synthetic Opiates
- Collection Devices Stability / Recovery
- Marijuana: Legalization Issues
- Federal Program Evaluations (NTSB,NHTSA,DOT,NRC)
- Other scientific, legal, and public policy concerns for safety sensitive positions (Emerging Issues)
Thank You
Are There Any Questions?

Team Acknowledgment
Ed Cone (Johns Hopkins School of Medicine)
Ryan G. Vandrey & George E. Bigelow (JHU, School of Medicine)
John M. Mitchell (RTI International)
Charles LoDico (SAMHSA, DWP)
THE NEW WEED CHANGES THE PARADIGM AND CAN GET YOU INTO TROUBLE

EDWARD J. CONE, PH.D.
JOHNS HOPKINS SCHOOL OF MEDICINE
The ASAM State of the Art Course
6 October 7, 2016

Disclosure Information

Edward J. Cone, Ph.D.
RTI International Consultant
Expenses and time paid by RTI for ASAM presentation
Outline

- The changing landscape of cannabis
- Recent research findings
  - Passive exposure to cannabis smoke
  - Smoked cannabis
  - Oral cannabis
- Implications in the workplace
- Performance and impairment issues
Cannabis Potency Over the Years

**Marijuana Users, Treatment Admissions, and Average Potency: 1986-2010**

- Millions of current marijuana users
- 10,000s of primary marijuana treatment admissions
- Average seizure potency

Sources: NSDUH, TEDS, National Seizure System
Passive Cannabis Smoke Exposure

- Studies in the 80’s conducted with 1-3% THC
- Need for re-evaluation with high potency (>10% THC) cannabis
- Cannot study all conditions, so designed “extreme” exposure study to represent “worst-case” scenario
Passive Study Design

- Six active smokers, six non-smokers per session
- Enclosed room with air flow control, Plexiglas walls for observation
- Smokers smoked as much as they wanted to without limitation in a “social-like” setting
- Three exposure sessions:
  - Session 1: smokers each smoke ad lib MJ cigarettes (5.3% THC) for one hour, no active air flow
  - Session 2: smokers each smoke ad lib MJ cigarettes (11.3% THC) for one hour, no active air flow
  - Session 3: smokers each smoke MJ ad lib MJ cigarettes (11.3% THC) for one hour, with active air flow simulating room air conditioning
JHU Exposure Chamber

- Constructed of plexiglass and aluminum
- Dimensions: 10’ x 13’ x 7’ (W x L x H), 910 cu ft (25.73 m³)
- Sealed door closure
- Optional no ventilation/ventilation comparable to A/C in home
Start of Session 1: 5.3% MJ, no Ventilation
Midway of Session 1: 5.3% MJ, no Ventilation
Midway of Session 2: 11.3% MJ, no Ventilation
End of Session 2: 11.3% MJ, no Ventilation
Midway of Session 3: 11.3% MJ, With Ventilation
Passive Exposure Results

- Urine: multiple positives confirmed at 20 ng/mL cutoff, but none at 50 ng/mL
- Oral fluid: confirmed positives up to ~3 hours
- Blood: up to ~2 ng/mL
- Behavioral & performance effects
Passive Study: Bottom Line

- Extreme passive study is a form of drug administration
  - Estimated that non-smokers inhaled 5-15% of the amount of THC that smokers did
  - Could test positive at lower cutoffs (e.g., 20 ng/mL)
  - SAMHSA urine cutoff (50 ng/mL) differentiated “passive” from “active”
Cannabis Edibles

- Increasing popularity of oral “Edible” cannabis products
  - 16-26% of medical cannabis users
  - No combustion
  - Longer time course of effects
- Most controlled human cannabis research uses smoked/inhaled route of administration
- Federal organizations that regulate medicine & food cannot regulate cannabis
Cannabis Edibles
Edibles Study Goals

- Evaluate pharmacodynamic time course of THC and metabolites in blood, oral fluid and urine following oral cannabis administration in healthy adults
- Examine dose effects on subjective, cardiovascular, and performance measures
Cannabis Brownie Preparation

- Cannabis ground into powder
- Heated for 30 min at 250°F (121°C)
- Individual doses stirred into brownie batter and baked for 30 min at 325°F (163°C)
- Individual doses of 10, 25, & 50 mg of THC

(Courtesy of Ryan Vandrey, JHU)
Edible Results: Urine

- THC-COOH Cmax (ng/mL):
  - 10 mg THC = 106 (34 – 278)
  - 25 mg THC = 335 (75 – 729)
  - 50 mg THC = 713 (216 – 1025)
- Window of detection was 74 – 216 hrs

(Courtesy of Ryan Vandrey, JHU)
Edible Results: Oral Fluid

THC Cmax (ng/mL):

- 10 mg THC = 192 (47 – 412)
- 25 mg THC = 478 (70 – 1128)
- 50 mg THC = 598 (350 – 1010)

Window of detection for THC and THCCOOH was 1.5-22, 0-126 hours respectively

(Courtesy of Ryan Vandrey, JHU)
Edible **Results: Blood**

- Highest concentrations of THC was < 5 ng/mL for THC; only 2 participants @ 50 mg THC achieved 5 ng/mL
- No THC detected for 2 participants (10 mg)
- Cmax THCCOOH (ng/mL)
  - 10 mg THC = 7 (5 – 14)
  - 25 mg THC = 21 (12 – 39)
  - 50 mg THC = 29 (16 – 44)
Edible Results: “Drug Effect”

(Courtesy of Ryan Vandrey, JHU)
Cannabis Edibles: Bottom Line

- Cannabis edibles produced severe behavioral effects
- Urine and oral fluid tests were positive
- **Blood levels of THC were extremely low and most participants who were highly impaired would not have tested positive during periods of impairment or later**
- Behavioral effects lasted considerably longer than smoked route
Reflections

- Cannabis potency has increased significantly over last decade
- Risks of extreme passive exposure are real and begin to look like active use
- Cannabis edibles produce significant impairment, but could go undetected by blood tests
  - No opportunity for “titration”
  - Once ingested, effects are dependent upon dose and individual response
  - Anxiety, paranoia is common at higher dose
- Problem for DUID
Team Acknowledgement

- Ryan G. Vandrey & George E. Bigelow (JHU, School of Medicine)
- John M. Mitchell (RTI International)
- Charles LoDico & Ron Flegel (SAMHSA, DWP)
THE CHANGING LANDSCAPE OF CANNABIS PRODUCTS AND HOW THIS IMPACTS DRUG TESTING PROGRAMS
The ASAM State of the Art Course
October 7, 2016
Disclosure Information

John M. Mitchell, PhD
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SAMHSA Contract (HHSS 27720130000c)
RTI International
Outline

- The Marijuana Plant
- Marijuana Use in Times Past
- Cannabinoids from the Marijuana Plant
- The March Toward Legalization
  - Scheduling
  - Business Perspective
  - Medical Perspective
  - Impact of Legalization
  - Modes of Dosing and Current Products
- Review
The Marijuana Plant

- Two Marijuana Plant Species
  - *Cannabis sativa* - tall bushy plant grown in North and South America that can reach the size of a small tree
  - *Cannabis indica* – shorter, hardier variety with rounded blue-green leaves, grown in Middle East for hashish
- The bud of the female plant, called semsemilla, is the part most smoked as marijuana
- The resin found on flower clusters and top leaves of the female plant is the most potent drug source and is used to prepare hashish, a potent grade of cannabis.
Marijuana Use in Times Past

- Marijuana use spread from China to India to North Africa, then reached Europe at least as early as A.D. 500
- Marijuana (hemp), a major crop in colonial North America, was grown as a source of fiber for making ropes
- It was listed in the United States Pharmacopeia from 1850 until 1942, and was prescribed for various conditions including labor pains, nausea, and rheumatism
- Its cultivation in the US is either prohibited or highly regulated
Trends in the US: 40’s through 70’s

- Marijuana was the number 2 drug of choice with alcohol being number 1
- It was of low potency, known as ditch weed, but sufficiently potent to provide the means to get high
- In the 1960’s, its use was a sign of rebellion against societal mores and a hallmark of the hippie generation
Trends in the US: 80’s and 90’s

- Introduction of hemp products
  - Edibles
    - Ex: Seedy Sweeties
  - Beverages
    - Ex: Hempen Ale
- Health products
- Hemp oil
Trends in the US: 2000’s

- Improved cultivation practices
  - In vitro regenerated plants, tissue culture, genetic monitoring
  - Increased consistency in plant quality and cannabinoid content
- Indoor propagation allowed growers to control plant life cycle and health through
  - Light
  - Humidity
  - Irrigation
  - CO2 levels
  - Nutrition
  - Reduced use of pesticides, fungicides and herbicides
Cannabinoids from the Marijuana Plant

- 545 compounds have been isolated from the marijuana plant
  - 104 are phytocannabinoids
  - 3 types of cannabinoids are of major interest
    - **THC** - Tetrahydrocannabinol - Principal psychoactive cannabinoid
      - Dronabinol (Marinol®)
    - **CBD** - Cannabidiol – Little psychoactivity
      - Potential application in treating Dravet Syndrome
    - **CBN** - Cannabinol - Formed as degradation product of THC
      - Possible anti-inflammatory
  - All 3 exist as an acid in the plant material and are formed when the acid is decarboxylated in the presence of heat or over time
Plant Cannabinoids

Tetrahydrocannabinolic Acid (THC Acid) → Tetrahydrocannabinol (THC)

Tetrahydrocannabivalaric Acid → Cannabivarin (THCV)

Thomas, BJ and Elsohly, MA "The Analytical Chemistry of Cannabis", 2016 Publisher Elsevier
Phytocannabinoid vs. Metabolite

Tetrahydrocannabolic Acid (THC Acid)

11-nor 9-carboxy-delta 9 Tetrahydrocannabinol ("THCA", "9-carboxyTHC", "THCCOOH")
Other Plant Cannabinoids of Interest

- Cannabidiolic Acid (CBDA)
- Cannabidiol (CBD)
- Cannabinolic Acid (CBNA)
- Cannabinol (CBN)
- Cannabidivarinic Acid (CBDVA)
- Cannabidivarin (CBDV)
Oxidative and Metabolic Products of THC

- Tetrahydrocannabinol (THC)
- Cannabinol (CBN)
- 11-nor 9-carboxy-delta 9 Tetrahydrocannabinol ("THCA", "9-carboxyTHC", "THCCOOH")
Trends In Marijuana Potency: DEA Seizures

Trends in Marijuana Potency

Percent Seizures containing THC >12%

ElSohly et al (2016) Biological Psychiatry, DOI: http://dx.doi.org/10.1016/j.biopsych.2016.01.004
The March Toward Legalization

- July 19, 2016: the DEA announced that “...marijuana continues to meet the criteria for Schedule I control under the CSA”

  However:

- Medical cannabis use is allowed in 23 states
  - 11 of the 23 allow use of cannabidiol (CBD) only
- 4 states (Alaska, Colorado, Oregon, Washington) and Washington, DC have allowed recreational use of marijuana
- An additional 11 states are considering legalizing recreational use
The March Toward Legalization: Business Perspective

- **Cannabis is big business!** The *Independent UK* reports:
  - “Cannabis continues to be the world’s favourite illicit drug with around 147 million people using it annually”

- The ArcViewGroup has estimated that legal sales of marijuana in the US reached 2.7 billion in 2015: a 232 percent increase over the previous year. This is thought to be a conservative estimate since Colorado reports that marijuana sales exceeded $900 million in 2015

- The GreenWaveAdvisors estimate that by 2020, sales are expected to surpass $22 billion, the group said in a recent report, with California making up $6.4 billion of that market”
The March Toward Legalization: Medical Perspective

- Does THC have valid medical use?
  - There are 3 FDA-approved drugs based on THC for treating nausea and vomiting induced by cancer chemotherapy and anorexia in HIV patients
    - Marinol (dronabinol) - Schedule III drug available as a pill
    - Cesamet (Nabilone) - Schedule II synthetic cannabinoid available as a capsule
    - Syndros (dronabinol) - Schedule III drug available as an oral solution
  - Treatment of other medical conditions – the jury is still out
The March Toward Legalization: Impact of Legalization

- Potential areas of impact
  - Workplace
    - Issues concerning on-the-job use
    - Impact of recreational use outside business hours
    - Fitness for Duty or WUI (working under the influence)
  - Driving
    - Criteria for DUI
  - Youth
    - Increased use?
The March Toward Legalization: Modes of Dosing and Current Products

- Smoking continues to be preferred by long-time users
  - Joints, bongs, pipes
  - Allows control of dose
  - Preferred for social settings
The March Toward Legalization: Modes of Dosing and Current Products

- **Vaping**
  - Pens allow controlled dosing in public
  - Use marijuana extracts and waxes
  - Volcanos provide dosing from plant material without burning and allow use of waxes, oils and other extracts of marijuana plant material
The March Toward Legalization: Mode of Dosing and Current Products

- Edibles
  - Candies, cookies, teas and other beverages
  - Restaurant dining
The March Toward Legalization: Mode of Dosing and Current Products

- **Suppositories**
  - THC in natural oils for anal and vaginal routes of administration
  - Questionable efficacy
    - Previous work has shown THC is not absorbed in free form
    - Hemisuccinate ester of THC is absorbed
Marijuana is here to stay.

While it has some medical applications, its full potential will not be known until it is no longer a Schedule I drug and research is encouraged.

The full extent of its effects upon individuals is not fully known or documented. This is particularly true for the developing brain.

The effect of the modes of delivery and the safety of the products compatible with each mode is unknown and uncontrolled.
Review

- As with any substance with abuse potential, the effect on society prior to legalization is mostly unknown.
  - However, if the abuse/addiction effects are no more than tobacco or alcohol, we are looking at another burden to individuals as well as society as a whole.
- Questions yet to be answered:
  - Will there truly be benefits from the legalization of marijuana?
  - Will marijuana become the “Soma” of our “Brave New World”?
LINKING BIOMARKERS WITH BEHAVIOR:
THE COMPLEXITIES OF CANNABIS

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The ASAM State of the Art Course
October 7, 2016
Disclosure Information

Ryan Vandrey, Ph.D.
SAMSHA/RTI International - Funding – Various Studies
Zynerba Pharmaceuticals – Consulting Fee – Consultant
Battle Memorial Institute – Consulting Fee – Consultant
CW Botanicals- Consulting Fee- Consultant
Insys Therapeutics – **????** - Honorarium
9 Major Health Benefits of Medical Marijuana

1. Treats Migraines
   Cannabis has been shown to be effective in the treatment of migraine headaches. Marijuana extract has been used in various forms and are often prescribed by doctors.

2. Prevents Seizures
   Studies have shown that cannabis helps to slow down the frequency and intensity of seizures. This is especially true for individuals with epilepsy who are unable to control their seizures with traditional medicines.

3. Slows Down Tumor Growth
   Cancer patients who are unable to control their symptoms due to cancer may find relief in cannabis. Studies have shown that cannabis can slow down the growth of tumors and potentially reduce the size of tumors.

4. For ADD and ADHD
   Many people with ADD and ADHD report that cannabis helps them to focus better and improve their concentration.

5. Relieves Symptoms of Chronic Diseases
   Cannabis is one of the best natural pain relievers that can help relieve chronic pain without the side effects of other pain medications.

6. Relieve PMS
   Millions of women have used cannabis to relieve symptoms of PMS, such as cramping and mood swings.

7. Prevents Alzheimer’s
   Cannabis helps to reduce the occurrence of depression in Alzheimer’s patients, which is often difficult to control in these individuals.

8. Calm those with Tourette’s and OCD
   Some studies have shown that cannabis can help to calm the symptoms of Tourette’s and OCD.

9. Treats Glaucoma
   Some studies have shown that cannabis can help to lower intraocular pressure, which is often associated with glaucoma.

Marijuana
Proud Sponsors Of...

Umm... We Forget!

STATE OF THE ART
Course in Addiction Medicine
Pharmacodynamic Effects of Cannabis

- Euphoria, increased appetite, rapid heart rate, dry mouth, red and irritated eyes, paranoia, anxiety, vomiting, somnolence
- Cognitive impairment (memory, attention, time estimation, complex cognition, driving ability)
Linking Toxicology and Behavior

- Many controlled studies
- Few include both PK and PD
- Often limited in scope
- Difficult to compare across studies
  - Different doses, measures, populations
- Most smoked cannabis only
Great Early Science!

**Fig. 4.** Time course of “high” and relation to plasma concentration of THC following smoking of cannabis.

**Fig. 6.** Time course of “high” (lower curve) and relation to plasma concentration of THC (upper curve) following oral administration of THC.

**Fig. 2.** Time course of “high” and relation to plasma concentration of THC following intravenous administration of THC.
Limitations of Prior Studies

- Progress in drug testing technology
- New matrices of interest
- Limited cognitive performance testing
- Many used single dose; doses tend to vary across routes of administration
- Typically enrolled frequent users
Important Study Characteristics

- Dose
- Route of Administration
- Ensuring consistent/complete dose delivery
- Participant Characteristics (age, tolerance, sex)
- Breadth and timing of outcome measures
SAMHSA’s Study Platform

- Phase I laboratory protocols
- Controlled drug administration
- Healthy adults, non-tolerant to cannabis effects
- Blood, oral fluid, urine, hair
- Subjective + cognitive drug effects
Dosing

- Cannabis obtained from NIDA
- Passive, vaporized, ingested, smoked
- PL, 10mg, 25mg, and 50mg doses
Methods of Assessment

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Do you feel a drug effect?

not at all

Extremely

2
Progress to Date

- Passive inhalation and oral ingestion of cannabis studies completed
- Inhalation of smoked and vaporized cannabis is ongoing
Can I Get a Contact High?

Modest effect on psychomotor performance noted.
Is That Reflected in Drug Tests?

- Modest subjective and performance effects for 1-2 hrs
- Urine: $C_{\text{max}}$, 2-11 hrs; >15 ng/mL, 2-30 hrs
- OF: $C_{\text{max}} = 0.25$ hr; > 4 ng/mL, 0.25-2 hrs
- Blood: $C_{\text{max}} = 0.25$-2 hrs; Two > 5 ng/mL
Oral Administration

Blood Cannabinoids After 50mg Dose

Hours

VAS (mm)

0 1 2 3 4 5 6 7 8

0 10 20 30

THC
-11-OH-THC
THCCOOH

Placebo
10mg
25mg
50mg
What About Brownies?

- THC = Passive
- THC = Smokers at baseline
- Drug Effect much greater
PASAT # Correct
# PK/PD Correlations

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<tr>
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<th>Whole Blood THC</th>
<th>Whole Blood 11-OH-THC</th>
<th>Whole Blood THCCOOH</th>
<th>Oral Fluid THC</th>
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*Correlation is significant at the 0.01 level (2-tailed).*
Smoked and Vaporized Cannabis

Drug Effect: Smoked

Drug Effect: Vaporized
Smoked and Vaporized Cannabis

**PASAT: Smoked**

**PASAT: Vaporized**

- Smoke PL
- Smoke 10mg
- Smoke 25mg

- Vape PL
- Vape 10mg
- Vape 25mg
“Drug Effect” by Route of Admin

![Route Comparison: 10mg THC](chart1)

![Route Comparison: 25mg THC](chart2)
Other Points of Interest

- Females had stronger drug effects
- Other outcomes followed similar pattern
- Adverse events included nausea/vomiting, dizziness, anxiety/paranoia, and dry mouth
Summary

- Route of administration impacts the time course of drug effects and biomarkers
- Oral dosing:
  - Blood cannabinoids significantly correlated with subjective drug effects, not performance
  - Low correlations with OF cannabinoids and PD
- Smoked/Vaped study results are preliminary and PK results are pending
Thanks!!

- Ed Cone, John Mitchell, Ron Flegel, Charles LoDico, Evan Herrmann, George Bigelow, Eugene Hayes
- JHU, RTI, and SAMHSA staff

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