Trends in Marijuana Use

Objectives

- Describe landscape and trends in marijuana use
- Identify pharmacology and physiologic effects of cannabinoids
- Discuss detection methods for marijuana use
- Discuss efforts designed to mitigate the risk of marijuana use

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Marijuana: A Complex Landscape

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Terminology

Cannabis: a.k.a. marijuana; a genus of flowering plant containing a number of different species (e.g. *Cannabis sativa*)

Cannabinoids: Chemical compounds secreted by cannabis flowers (e.g. THC and CBD)

Endocannabinoid: Compounds produced within the body that bind to cannabinoid receptors (e.g. CB-1 and CB-2)

*THC=Tetrahydrocannabinol CBD=Cannabidiol

Marijuana and Cannabinoids: A Neuroscience Research Summit. National Institutes of Health. Published March 2016. https://www.drugabuse.gov/sites/default/files/briefmjsummitmeetingsummary.pdf. Accessed August 15, 2017.

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Composition of Cannabis

Cannabis contains hundreds of chemical compounds. As well as the archetypal cannabinoids, there are flavonoids, terpenes, fatty acids and more, all with potential medical uses.

545 compounds

104 cannabinoids

441 non-cannabinoids

Δ^8- and Δ^9- THC are the main psychoactive ingredients. They bind to CB_1 receptors in the human body, particularly in the brain.

2 Δ^8-THC
3 Cannabicyclol (CBL)
8 Cannabichromene (CBC)
9 Cannabitriol (CBT)
17 Cannabigerol (CBG)
18 Δ^9-THC
22 Miscellaneous
2 Cannabinodiol (CBND)
5 Cannabielsoin (CBE)
8 Cannabidiol (CBD)
10 Cannabinol (CBN)

A nonpsychoactive component of cannabis that indirectly affects CB_1 and CB_2 receptors.

Cannabinol was the first cannabinoid to be isolated in 1899

Adapted from Gould J. The Cannabis Crop. *Nature*. Published September 24, 2015. http://www.nature.com/nature/journal/v525/n7570_supp/full/525S2a.html. Accessed August 15, 2017.

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Cannabis Products & Use

Three primary forms:

- Cannabis plant (e.g. leaves and flowering tops [buds])
- Resin ("hashish")
- Concentrated extract ("hash oil," "shatter," or "wax")

Methods of use:

- Smoking
  - "Joints" or "blunts," pipes, bowls, waterpipes ("bongs"), or vaporizers
- Ingesting alone or via food/drink

1. Why does cannabis potency matter? United Nations Office on Drugs and Crime Web site. http://www.unodc.org/unodc/en/frontpage/2009/June/why-does-cannabis-potency-matter.html. Accessed August 9, 2017.
2. Marijuana. . Center for Substance Abuse Research Web site. http://www.cesar.umd.edu/cesar/drugs/marijuana.asp. Accessed August 9, 2017.

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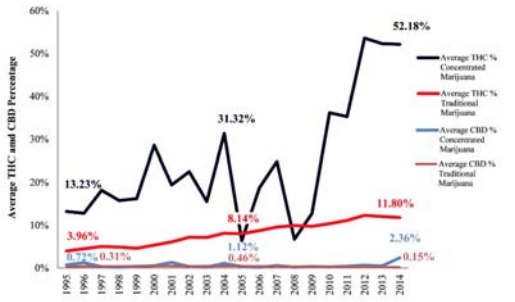
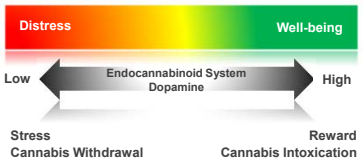
Average Cannabinoid Concentrations



2016 National Drug Threat Assessment Summary. U.S. Department of Justice Drug Enforcement Agency. Published November 2016. https://www.hsdl.org/?view&did=797265. Accessed August 9, 2017.
ElSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S., & Church, J. C. (2016). Changes in Cannabis Potency over the Last Two Decades (1995-2014) - Analysis of Current Data in the United States. *Biological Psychiatry*, *79*(7), 613–619. http://doi.org/10.1016/j.biopsych.2016.01.004

7

The Endocannabinoid System



- ECS modulates the interaction between stress and reward networks
- Two receptor types activated by endocannabinoids or consumed cannabinoids (e.g. THC, CBD): CB-1 (brain) and CB-2 (peripheral tissues and immune cells)
- Cannabinoids exhibit different effects based on which receptor they bind to; for example, CBD has a much lower affinity for CB-1 than THC

Volkow ND, Hampson AJ, Baler RD. Don't Worry, Be Happy: Endocannabinoids and Cannabis at the Intersection of Stress and Reward. *Annu Rev Pharmacol Toxicol*. 2017; 57: 285-308.

8

Adverse Effects

Short-Term	Long-Term
Impaired short-term memory	Addiction
Impaired motor coordination	Altered brain development
Altered judgment	Poor grades/educational outcome
Increased heart rate, dry mouth, bloodshot eyes	Diminished life satisfaction and achievement
Increased appetite	Cognitive impairment
Paranoia and psychosis (at high doses)	Increased risk of chronic psychosis disorders (e.g. schizophrenia) in those predisposed
	Symptoms of chronic bronchitis

Negative effects are more likely with chronic use, high-potency THC products, and use during adolescence

Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014; 370(23): 2219-2227.

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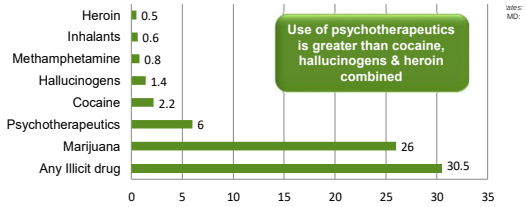
Illicit Drug Use (2017)

Past Month Users, Age 12 or older (Millions)



3.2 million nonmedical users of prescription pain relievers, second only to marijuana among specific abused substances

Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

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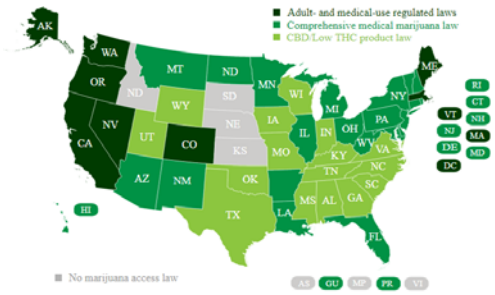
Marijuana Laws by State



Deep Dive: Marijuana. National Conference of State Legislatures Web site. http://www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx. Published 2018. Accessed June 27, 2018.

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State Marijuana Policies Timeline

Deep Dive: Marijuana. National Conference of State Legislatures Web site. http://www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx. Published 2018. Accessed June 27, 2018.

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Proposed Medical Uses

"Medical marijuana" is the use of cannabis and cannabinoids to treat disease or improve symptoms

- Glaucoma
- Nausea
- AIDS-associated anorexia and wasting syndrome
- Chronic pain
- Inflammation
- Multiple sclerosis
- Epilepsy

Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med.* 2014; 370(23): 2219-2227.

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Related Medical Products

- Cannabis plant material
- Dronabinol (Marinol®, Syndros®): synthetic THC indicated for appetite stimulation in the treatment of AIDS-related anorexia and chemotherapy-induced nausea and vomiting
- Nabilone (Cesamet®): synthetic cannabinoid approved for nausea and vomiting associated with chemotherapy; does not contain THC
- Nabiximols (Sativex®): THC & CBD extract indicated for the treatment of neuropathic pain and spasticity due to multiple sclerosis, or cancer-related pain [not approved in U.S.]

1. Marinol® [package insert]. AbbVie Inc. North Chicago, IL; June 2016. https://www.drugs.com/pro/marinol.html. Accessed August 9, 2017.
2. Syndros® [package insert]. Insys. Chandler, AZ; July 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205525s000lbl.pdf. Accessed August 9, 2017.
3. Cesamet® [package insert]. Meda Pharmaceuticals Inc. Somerset, NJ; May 2015. https://www.drugs.com/pro/cesamet.html. Accessed August 9, 2017.
4. Sativex® [package insert]. GW Pharma Ltd. Cambridge, UK; March 2015. https://www.old.health.gov.il/units/pharmacy/trufot/alonim/Sativex_oromucosal_spray_03-2015_Patient_ENGLISH_1437885407833.pdf. Accessed August 9, 2017.

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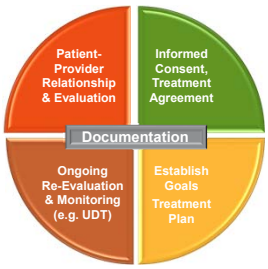
Risk Mitigation: Medical Marijuana



1. FSMB 2016 Model Guidelines for the recommendation of marijuana in patient care
Available at https://www.fsmb.org/Media/Default/PDF/BRD_RPT_16-2_Marijuana_Model_Guidelines.pdf
2. Savage SR, Romero-Sandoval A, Schatman M, et al. Cannabis in pain treatment: Clinical and research considerations. *J Pain.* 2016; 17(6): 654-68.

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Further Considerations: Savage et al. 2016

Review of medical marijuana and prescription opioids research:

- Patients prescribed opioids for pain that test positive for illicit marijuana are more likely to test positive for other illicit drugs
- However, among medical marijuana users, concurrent use of prescribed opioids appears not to increase the risk of illicit drug use
- Some data suggests that medical marijuana may improve analgesia in patients using opioids and thus possibly be opioid-sparing

Savage SR, Romero-Sandoval A, Schatman M, et al. Cannabis in pain treatment: Clinical and research considerations. *J Pain*. 2016; 17(6): 654-68.

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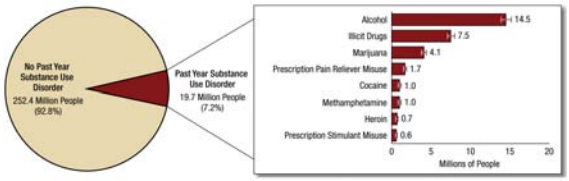
Illicit Drug and Alcohol Use Disorder Treatment

- In 2017, 20.7 million persons needed treatment for an illicit drug or alcohol use problem (7.6% of the population aged 12 or older)[1]
- Of these, only 2.5 million received treatment at a specialty facility (12.2%)

Numbers of People Aged 12 or Older with a Past Year Substance Use Disorder: 2017



1. Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

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DSM-V Cannabis Use Disorder Criteria

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, within a 12-month period:

- Increasing amounts of use over time
- Inability to control consumption
- Craving
- Recurrent use despite negative impact on social, professional, and educational life
- Tolerance
- Withdrawal

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5.Washington, D.C: American Psychiatric Association; 2013.
2. Copeland J, Pokorski I. Progress toward pharmacotherapies for cannabis-use disorder: an evidence-based review. *Subst Abuse Rehabil*. 2016; 7: 41–53.

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Cannabis Use Disorder Treatment

- Demand for treatment increasing
- Adults seeking treatment have typically used >10 years
- Psychosocial treatments (e.g. cognitive behavioral and motivational)
- Mindfulness-based meditation
- Counseling
- Currently no approved medications, though certain medications may be used to assist with withdrawal and cravings

1. Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L. Psychosocial interventions for cannabis use disorder. *Cochrane Database Syst Rev*. 2016; (5): CD005336.
2. Copeland J, Pokorski I. Progress toward pharmacotherapies for cannabis-use disorder: an evidence-based review. *Subst Abuse Rehabil*. 2016; 7: 41–53.

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Urine Drug Testing (UDT) Rationale

UDT provides objective information to support improved clinical decision making.

UDT helps clinicians to:

- Monitor and support decisions about medication therapy, particularly controlled substances
- Identify recent use of prescription medications, non-prescribed medications, and illicit substances
- Detect medications that may result in drug-drug interactions
- Advocate for and communicate with patients about individual treatment plans
- Identify possible illicit drug or medication abuse, misuse, or diversion

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Types of UDT

Presumptive Immunoassay Screen	Definitive Mass Spectrometry
In-office Point-of-Care (POC), or Laboratory Qualitative	Laboratory Quantitative (GC-MS or LC-MS/MS)
Minutes (POC) or days (Lab)	Hours to days
Drug classes and some select meds/substances	Specific medications, substances, and metabolites
Guidance for preliminary treatment decisions	Definitive quantitative results
Higher cutoff levels and cross-reactivity common; more false positives and false negatives	Lower cutoff levels. False positive and false negative results are rare

The clinician must choose testing method based on the needs dictated by the patient's history, presentation, community factors and treatment plan goals. The clinician's rationale for test and the analytes ordered must be documented in the patient's medical record.

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Sources of False Positive Results
Presumptive/Immunoassay Testing

Test Strip	Drug or Drug Class	Drugs Targeted by an Immunoassay	Substances Known to Cause a False Positive Test Result
AMP	Amphetamine	Amphetamine (i.e. Adderall® and Vyvanse®) Note: Amphetamine is a metabolic product of Benzphetamine, Desoxyn®, and Selegiline.	Bromphenioramine, Bupropion, Chlorpromazine, Dimethylumylamine (DMMA), Ephedrine, Labetalol, Ofloxacin, Phentermine, Phenylpropanolamine, Promethazine, Pseudoephedrine, Ranitidine, Trazodone Positives for Amphetamine are also caused by Vicks® Nasal Inhaler (l-isomer).
BAR	Barbiturates	Amobarbital, Butalbital, Phenobarbital, Secobarbital, and other Barbiturates	Fenoprofen, Ibuprofen, Naproxen
BUP	Buprenorphine	Belbuca®, Buprenex®, Buprenex®, Butrans®, Subovone®, Subutex®, Zubsolv®	Chloroquine, Codeine, Dihydrocodeine, Hydroxychloroquine, Methadone, Morphine, Pluquenil®, Tramadol
BZO	Benzodiazepines	Alprazolam, Nordiazepam, Oxazepam, Temazepam, and other Benzodiazepines to varying degrees	Efavirenz; Oxaprozin, Sertraline
COC	Cocaine	Cocaine	Unknown/Infrequent
MTD	Methadone	Methadone	Chlorpromazine, Clomipramine, Diphenhydramine, Doxylamine Succinate/Pyridoxine HCL, Quetiapine, Tapentadol, Thioridazine, Verapamil
MET	Methamphetamine	Methamphetamine Note: Methamphetamine is a metabolic product of Benzphetamine, Desoxyn®, and Selegiline.	Adderall®, Bromphenioramine, Bupropion, Chlorpromazine, Ephedrine, Phentermine, Phenylpropanolamine, Promethazine, Pseudoephedrine, Ranitidine, Trazodone. Positives for Methamphetamine are also caused by Vicks® Nasal Inhaler (l-isomer).
MDMA	Methylenedioxy-methamphetamine	Methylenedioxymethamphetamine	Ephedrine, Phentermine, Phenylpropanolamine, Pseudoephedrine, Ranitidine, Trazodone
OPI/MOP	Opiates	6-MAM (Heroin metabolite), Codeine, Hydrocodone, Hydromorphone, Morphine	Dextromethorphan, Doxylamine Succinate/Pyridoxine HCL, Naltrexone, Oxycodone (at high concentrations), certain Quinolones, Rifampin Positives for Opiates are also caused by poppy seeds which contain morphine.
OXY	Oxycodone	Oxycodone, Oxymorphone	Codeine, Morphine, Hydrocodone, Hydromorphone
PCP	Phencyclidine	Phencyclidine	Dextromethorphan, Diphenhydramine, Doxylamine Succinate/Pyridoxine HCL, Ibuprofen, Imipramine, Ketamine, Lamotrigine, MDPV, Meperidine, Thioridazine, Tramadol, Venlafaxine
THC	THC (Marijuana)	Marijuana, Marinol®	Efavirenz; NSAIDs, Prilosec®, Protonix®
TCA	Tricyclic Antidepressants	Amitriptyline, Nortriptyline, Imipramine, Desipramine, Doxepin, and other Tricyclics to varying degrees	Carbamazepine, Cyclobenzaprine, Cyproheptadine, Diphenhydramine, Hydroxyzine, Quetiapine

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Comparison of Two Common UDT Methods

POSITIVE DRUG RESULTS IMMUNOASSAY (IA) vs DIRECT DEFINITIVE TESTING AND CLINICAL FALSE NEGATIVE RATES			
DRUG	ABOVE DEFINITIVE CUTOFF	ABOVE IA CUTOFF	DIFFERENCE
Opiates	77318	58007	-25.0%
Oxycodone	55061	49335	-10.4%
Benzodiazepines	65808	43477	-33.9%
Methadone	13532	10909	-19.4%
Zolpidem	13882	13289	-4.3%
THC	22686	13407	-40.9%
Tramadol	13984	13326	-4.7%

- 218,927 specimens; 23 analytes
- Laboratory IA screen with reflex of positives to quantitation (only IA positives are sent for more definitive testing)
- Direct definitive testing/quantitative approach

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UDT Considerations with Marijuana

- Marijuana and its metabolites are lipophilic (“fat-loving”)
- THC is metabolized to cTHC
- Chronic users can take weeks to months to eliminate low levels of cTHC
- Creatinine-normalized results should be used to help determine if re-use has occurred
- UDT cannot distinguish between medical and recreational use of THC-containing products
- CBD alone is unlikely to cause a positive for THC, but products may contain both

cTHC=delta-9-tetrahydrocannabinol carboxylic acid

Savage SR, Romero-Sandoval A, Schatman M, et al. Cannabis in pain treatment: Clinical and research considerations. *J Pain*. 2016; 17(6): 654-68.

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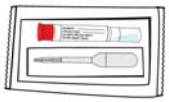
Oral Fluid Testing (OFT) Considerations

- Easily observed; collection almost anywhere
- Reduced risk for adulteration or substitution
- OFT detects the parent compound (THC) with a window of detection of up to 12 hours for single use and up to 48 hours for chronic use
- Prescription dronabinol is not anticipated to cause positive results for THC via OFT



Heltsley R, Depriest A, Black DL, et al. Oral fluid drug testing of chronic pain patients. II. Comparison of paired oral fluid and urine specimens. *J Anal Toxicol.* 2012 Mar;36(2):75-80.

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Synthetic Cannabinoids

- Large family of compounds functionally similar to THC
- Chemicals created in a laboratory, typically sprayed on plant material
- Product typically smoked
- Most imported from Asia
- Available via internet and head shops
  - Sold as “herbal incense”
  - Labeled “Not for human consumption”

Department of Justice: Statement of Joseph Rannazzisi, Deputy Administrator, Office of Diversion Control, Drug Enforcement Administration: For a hearing entitled "Dangerous Synthetic Drugs" presented on September 25, 2013
Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. *Psychopharmacology.* 2013;228(4):525-40.

Photograph used with authors' permission

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Synthetic Cannabinoids: Urine Drug Testing Implications

- Numerous compounds: Use of specific compounds and frequency of use is constantly evolving
- Immunoassay may not reliably identify the numerous synthetic cannabinoids
  - Will not test positive for THC on immunoassay
- Laboratory quantitative testing available
- Laboratories must continually reassess compounds being used and detected

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Medical Necessity

Criteria to establish medical necessity must be based on patient-specific elements identified during the clinical assessment and documented in the patient's medical record by the provider.

Documenting Medical Necessity

- Orders must be individualized
- Tests ordered and reasons for testing must be documented in the patient's medical record
- Risk assessment and stage of treatment should match testing frequency

Documenting How the Test Results Were Used

- Review of results and use in the treatment plan

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Other Important Themes

- Decriminalization
- Regulations and Taxation
- Impairment While Driving
- Public Safety
- Education and Prevention

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Education

- National Institute on Drug Abuse – www.drugabuse.gov
- Centers for Disease Control and Prevention – www.cdc.gov
- Drug Enforcement Administration – www.justthinktwice.com
- Partnership for Drug Free Kids – www.drugfree.org

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Summary

- Marijuana is the most widely available and commonly used illicit drug in the United States
- Marijuana remains federally illegal, while many states have passed laws allowing for medical and/or recreational adult use
- THC concentrations in marijuana products have risen, contributing to negative effects
- Evidence supporting medical marijuana may be limited in some cases and use should be appropriately managed
- Understanding the benefits and limitations of UDT and OFT are critical for providers to appropriately monitor and apply results

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