

U.S. Military Forensic Drug Testing Program Succeeds in Reducing Illicit Drug Use Among Service Members

By Peter L. Platteborze, PhD, and Thomas M. Martin, PhD

The U.S. Department of Defense (DoD) has a robust and well-respected forensic urinalysis drug-testing program. This long-established program was designed primarily to deter and secondarily to detect drug abuse in American service members in the Army, Navy, Air Force, and Marine Corps (1–3). Deterring the use of illegal drugs is essential to maintaining safe, effective, and ready armed forces capable of deploying anywhere in the world on short notice. Those found abusing drugs can be punished, including receiving severe reprimands or being forced out of the service with an “other than honorable” or “bad conduct” discharge.

History

The DoD has conducted forensic drug testing for more than 40 years. The program was conceived near the end of the Vietnam War because of extensive drug abuse among deployed service members amid the widespread availability of cheap, high-quality heroin from the Golden Triangle. In May 1971, *The New York Times* reported that a staggering 10–25% of returning soldiers were heroin addicts. In response, President Richard Nixon demanded a remedy, fearing that addicted veterans would become a major societal problem and contribute to increasing the domestic crime rate.

The response was a quickly implemented program unofficially called “Operation Golden Flow” whereby the urine of service members was tested for drugs of abuse before they were shipped home. Those identified as positive were not allowed to return to the U.S. until they had passed another drug test, which typically occurred after about a week of detoxification. This program was highly successful. By September 1971, the positive rate for heroin was only 4.5%, and by February 1972, it was less than 2%. The lead-

ership declared that the heroin epidemic was over, but subsequent events would reveal that the lessons had not been learned.

In May 1981, another incident stimulated interest in military drug testing. A Marine jet crashed on the flight deck of the aircraft carrier USS Nimitz, killing three crew members and 11 bystanders. Another 48 sailors or Marines were injured. The total damage was estimated at \$150 million (about \$400 million in 2017 dollars) and included seven destroyed aircraft.

Autopsies revealed that THC was present in six of the deceased and that the pilot had been self-medicating with an antihistamine. In a sweep of the aircraft carrier’s crew, 47% tested positive for THC, clearly illustrating systemic marijuana drug abuse.

In response, President Ronald Reagan instituted a “zero tolerance” drug policy for military personnel that required mandatory urine testing of all service members. The DoD created a system of forensic toxicology drug-testing laboratories and authorized punitive actions against service members found abusing drugs. In addition to being discharged from the military, personnel faced actions such as the loss of pay, demotion in rank, forced drug rehabilitation, and even incarceration. The DoD drug-testing program continued to expand through the 1980s and beyond the Cold War to the present.

Current Laboratories

To support this critical mission, the DoD operates five high-throughput drug-testing laboratories. The Army and Navy each operate two of these labs, while the Air Force operates one.

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Military Drug Testing

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The Army labs are located at the Tripler Army Medical Center in Honolulu and Fort George Gordon Meade close to Baltimore. The Navy labs are at the Great Lakes Naval Training Center in Chicago and in Jacksonville, Fla. The Air Force laboratory is at the Lackland Air Force Base in San Antonio. The laboratories are governed by regulations and standard operating procedures that ensure equivalent testing procedures at all locations. Each lab tests at least 500,000 samples annually, with some exceeding 1 million. Each focuses primarily on its service-specific specimens with some notable exceptions.

The DoD program has assigned certain testing to specific laboratories. Because the Army is significantly larger than the other services, the workload was made equitable by assigning Army Reserve specimens to the Great Lakes Navy lab. This lab also conducts testing on nearly all military recruits. The Tripler Army laboratory conducts all U.S. Coast Guard testing through a contract between the Department of Homeland Security and the DoD.

The Fort Meade laboratory tests all DoD civilian (that is, nonmilitary) specimens (4). The lab can perform the civilian testing because it is accredited through the Substance Abuse and Mental Health Services Administration (SAMHSA) National Laboratory Certification Program. Several of the Fort Meade staff are certified by both the DoD and SAMHSA.

The DoD also recently implemented a degree of test regionalization in which laboratories support other nearby service installations to reduce turnaround times and save resources. For example, Army specimens collected at Fort Sam Houston in San Antonio are tested at the nearby Air Force Lackland lab. Samples are driven daily 20 miles to the nearby Lackland lab to avoid expensive overnight shipping fees and reduce the turnaround time by at least one day. Typically, the laboratory that performs the testing also provides expert witness testimony in any associated court proceedings.

Testing Procedures

All urine specimens are collected and delivered to the laboratories under strict chain-of-custody procedures. DoD standard operating procedures mandate that the specimen collection be observed and that forensic documentation accompany each sample.

All specimens undergo the same well-defined testing procedures at each laboratory. They are screened for the presence of various drug classes using commercially available immunoassays on high-throughput automated analyzers. For samples to screen presumptively positive, they must have concentrations at or above the DoD established screening cutoffs (Table 1) and meet strict quality control (QC) standards.

Table 1. Screening Test Cutoff Concentrations

Drug class	Cutoff concentration (ng/mL)
Amphetamines	500
Benzodiazepines	200
Cannabinoids (marijuana)	50
Synthetic cannabinoids	10
Cocaine metabolites	150
Designer amphetamines	500
Opiates (morphine/codeine)	2,000
Opioid (6-monoacetylmorphine)	10
Opioid (oxycodone/oxymorphone)	100
Opioid (hydrocodone/hydromorphone)	300

In the case of a positive screening result, a new urine aliquot is poured for confirmation analysis via gas chromatography-mass spectrometry (GC-MS). In all confirmation tests, a negative saline blank is placed between samples to identify sample carryover issues. This analysis unequivocally identifies the specific drug or drug metabolite of interest and accurately quantifies the amount present. Table 2 lists the DoD confirmation cutoffs.

Specimen preparation for GC/MS typically involves a solid-phase extraction with a deuterated internal standard followed by chemical derivatization. A chiral derivatizing agent is used during the amphetamine/methamphetamine extraction, which allows accurate quantification of the d- and l-isomers of each drug. The volatile extracts produced from the extractions are then analyzed by GC/MS using the selected ion monitoring mode with one quantitative ion and two qualifier ions. Chromatography, peak symmetry, and mass-to-ion ratios need to meet well-defined acceptance requirements or the data is rejected and re-analyzed or new specimens are poured and re-extracted.

The Navy and Air Force laboratories recently adopted liquid chromatography-tandem mass spectrometry (LC-MS/MS) to support the more complex benzodiazepine confirmation testing.

For any sample to be reported as positive to its originating unit, it must test positive in an immunoassay and through mass spectrometry. After the testing is complete, the results are relayed electronically to the submitting installation via a secure DoD web portal. Positive specimens are retained in a secure freezer for at least one year and upon official request are made available for retesting. All the associated forensic documents for these samples are retained for a minimum of three years.

In both screening and confirmation assays, specimens are batched together and each batch must meet stringent internal QC criteria. The laboratory must correctly analyze both open and blind QC specimens (with both positive and negative samples) for each

Table 2. Confirmation Cutoff Concentrations

Initial presumptive positive test	Confirmation drug/metabolite	Cutoff (ng/mL)
Amphetamines	d-Amphetamine	100
	d-Methamphetamine	100
Designer amphetamines	Methylenedioxymethamphetamine (MDMA)	500
	Methylenedioxyamphetamine (MDA)	500
Benzodiazepines	Lorazepam	100
	Nordiazepam	100
	Oxazepam	100
	Temazepam	100
	α-Hydroxy-alprazolam	100
Cannabinoids	Tetrahydrocannabinol-carboxylic acid	15
Synthetic cannabinoids	Synthetic cannabinoid compounds resulting in excretion of:	
	JWH-018-N-pentanoic acid	1.0
	JWH-073-N-butanoic acid	1.0
	UR-144-N-pentanoic acid	1.0
	5-Fluoro-PB22-3-carboxyindole	1.0
	MAM-2201-N-pentanoic acid	1.0
	AB-Chminaca metabolite	1.0
	AB-Fubinaca metabolite	1.0
	AB-Pinaca metabolite	1.0
Cocaine metabolites	Benzoyllecgonine	100
Opiates	Morphine	4,000
	Codeine	2,000
Heroin	6-Monacetylmorphine	10
Opioid	Oxycodone	100
	Oxymorphone	100
	Hydrocodone	100
	Hydromorphone	100

drug being assayed. If the lab fails any QC challenge, the results associated with that drug are rejected, and those samples must be re-analyzed.

Current Test Menu

The current DoD drug-testing panel consists of 26 drugs or drug metabolites. All forensically acceptable specimens are screened for the presence of everything in the test menu except for synthetic cannabinoids. Due to cost constraints and low prevalence, approximately 40% of the specimens are randomly screened for synthetic cannabinoids. Confirmation testing for the synthetic cannabinoids is done using LC-MS/MS and is performed only at the Lackland laboratory and the DoD Armed Forces Medical Examiners System (AFMES) forensic laboratory at Dover Air Force Base in Delaware.

Recent Test Menu Changes

The DoD drug-testing program is dynamic; the managers monitor prevalence rates and drop drugs with consistently low positive rates from the testing

menu and add new emerging drugs. The prevalence studies by the AFMES usually involve assessing from 20,000 to 30,000 specimens. In 2005, the program removed the barbiturate class of drugs (such as, pentobarbital, secobarbital, butalbital, and phenobarbital) from the menu. LSD was removed in 2007 and PCP in 2012. Reflecting the general rise of opioid pain medication abuse in the U.S., oxycodone and oxymorphone were added in 2006, followed by hydrocodone and hydromorphone in 2012. One year later, benzodiazepines were added, followed by synthetic cannabinoids in 2014.

At present, the program tests for five different benzodiazepines and eight synthetic cannabinoids. The DoD currently has a contract with the Sports Medicine Research and Testing Laboratory in Salt Lake City to conduct steroid testing of specimens from service members suspected of abusing these drugs. The AFMES Division of Forensic Toxicology Testing performs tests for the discontinued drugs and other non-routine drugs, such as rohypnol, ketamine, gamma-hydroxybutyrate, methadone, fentanyl, mescaline, ethanol, and bath salts.

Quality Assurance

Each DoD laboratory must participate in an extramural quality assurance (QA) program directed by AFMES as well as having their own robust internal QA program. Every month AFMES sends to each laboratory open and blind proficiency samples.

Each laboratory is graded on its test results versus the collective peer results from the other four labs and AFMES. Failures can result in the loss of the lab's certification to report certain drugs in the DoD test panel until AFMES has deemed that the issue has been resolved. During the interim, affected samples are sent to the other laboratories for analysis. Although extremely rare, any false-positive results similarly lead to the loss of certification to test and an inspection team is formed immediately to investigate the problem.

AFMES also requires a rigorous inspection of each laboratory three times a year. Inspection teams consist of external senior military and civilian DoD forensic toxicologists as well as non-DoD expert consultants. Turnaround times are closely monitored with the expectation that on average negative results are released within four working days and positive results within six working days from arrival at the lab.

Medical Review Officer Evaluations

The DoD mandates that all positive tests in the oxycodone, hydrocodone, opiate, steroid, benzodiaze-

pine, and amphetamine drug classes be assessed by a medical review officer (MRO) prior to being released to the unit (2). If requested, MRO assessments are also completed for THC and cocaine positive results because these drugs are occasionally prescribed. The MRO reviews the service member's medical record to determine whether a prescription could have caused the positive test. If so, the MRO documents an authorized "legitimate" use on a DoD secure online portal, and the positive result is not released to the unit.

MRO evaluations play a critical role in the drug-testing process to ensure that personnel taking prescribed medications are not stigmatized as drug abusers. MROs are trained and certified by the senior toxicologists in their services. In the Army and Navy, MROs may be licensed physicians, physician assistants, certified registered nurse anesthetists, and PhD toxicologists, while the Air Force permits only physicians. All electronically submitted reviews are examined by their service's most senior toxicologists to guarantee accuracy prior to being released to the unit. Questionable evaluations are returned to the MRO with additional guidance to be assessed prior to resubmission.

Recent DoD Results

Based on the most recent comprehensive data from fiscal year (FY) 2015, the DoD laboratories tested a total 4,276,093 samples. This equates to approximately 81% of the force being tested, and on average the collection of 2.41 urine specimens per service member annually. There were 14,693 service members with positive results, which represents 0.84% of the military force tested. This is a 26% reduction since FY 2010, when the rate was 1.13% (Figure 1).

These DoD prevalence rates and trends are in striking contrast to what has been observed with the non-DoD American work force. Quest Diagnostics annually tests close to 10 million specimens and its Drug Testing Index showed a steady increase in drug positive prevalence from 2012 to 2015 (5). In fact,

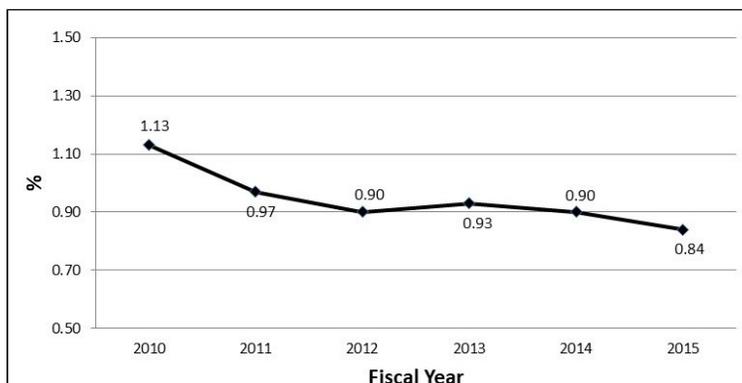


Figure 1. Overall Drug Positive Rate

2015 represented a ten-year peak, with approximately 4% of the total U.S. work force abusing drugs.

Figure 2 gives a breakdown of the 2015 DoD prevalence rates by drug. These results include MRO evaluations, so are considered to indicate illicit use by the service member. Marijuana was the most abused drug by far, accounting for nearly 70% of the positive results. Marijuana has consistently been the most abused drug since DoD testing began, which reflects American general society (6,7). Marijuana

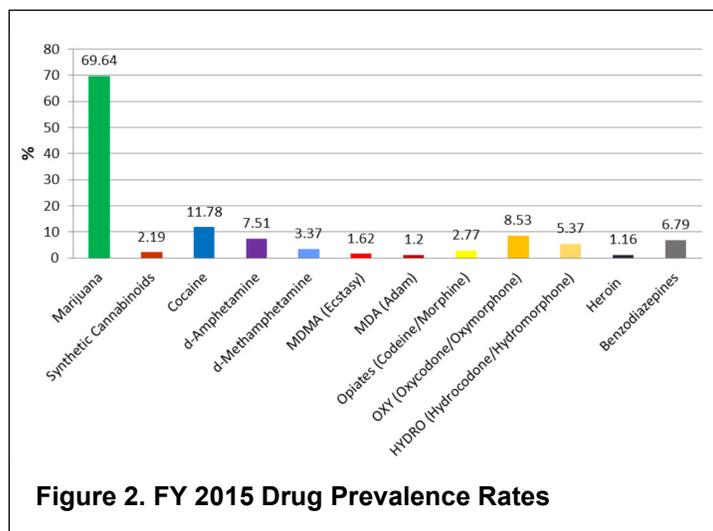


Figure 2. FY 2015 Drug Prevalence Rates

accounted for nearly half of the drug-positive individuals in the U.S. general work force in 2015 (5).

In FY 2015, the second most abused drug was cocaine, followed by oxycodone, d-amphetamine, the benzodiazepines, and hydrocodone. The FY 2014 pharmacy records indicate that the five most prescribed drugs in the DoD were ibuprofen, hydrocodone, naproxen, oxycodone, and acetaminophen; the 45th most prescribed drug was d-amphetamine. The high prescription rates of hydrocodone and oxycodone combined with their high prevalence of positive tests lend credence to the belief that many of these prescriptions are being diverted for illicit use. However, it should be noted that within two years of the implementation of testing for these opioids, the DoD positive rates dropped by over 50%.

The other drugs on the panel had relatively low positive prevalence, suggesting that their abuse is more limited. We were surprised that the heroin rate has dropped about 12% since peaking in FY 2013 because the opposite is occurring in the American general populace. Quest Diagnostics data indicate the heroin positive rate increased 146% from 2011 to a peak in 2015 (5).

Recent Army Results

The authors have published two papers on the U.S. Army drug prevalence rates before and after

MRO evaluations (6,7). From 2009–2012, about 78% of the Army MRO evaluations deemed the positive result to be an authorized “legitimate” use (6). In the absence of MRO evaluations, the most used drugs in FY 2011 were oxycodone, followed distantly by marijuana and d-amphetamine (7). This prevalence changed after MRO evaluations were taken into consideration; the most abused drugs marijuana, followed distantly by cocaine and d-amphetamine.

We also assessed the drug abuse prevalence rates in the U.S. Army from FY 2001–11 (7). Over these 11 years we observed a substantial decrease in the prevalence rates for THC and cocaine and increased rates for oxycodone and d-amphetamine. We presumed the lower THC rates were related to the emergence of commercially available synthetic cannabinoids that DoD was not testing for at that time.

In this paper, we also assessed drug abuse in the three Army components: Active Duty, Reserve, and National Guard. The National Guard had the highest abuse rates at 1.94%, followed by the Reserve at 1.53%, and the Active Duty force at 0.84%. These results are not surprising when one considers that the National Guard and Reserve members serve in a part-time capacity, so are more like the civilian population. A similar analysis of Army drug-testing data from FY 2012–16 is ongoing and should shed new insights into more recent drug use trends.

Conclusion

The DoD’s forensic urine drug-testing program continues to succeed in reducing drug abuse. Our findings reported here expand the body of knowledge about military drug use and illustrate progress in meeting the program’s objective to drive inappropriate drug use to a very low level. This program not only serves as a deterrent to prevent service members from abusing drugs, but also identifies drug abusers so their command can take corrective action. The DoD’s mission readiness continues to benefit significantly from having its military personnel fit for duty and free from drug abuse.

Learning Objectives

After reading this article, the reader will be able to describe the U.S. Department of Defense’s forensic drug-testing program, including its policies, procedures, history, current status, and emerging drugs. The reader will also be familiar with the program’s drug panel, prevalence rates, and medical review officer evaluation process.

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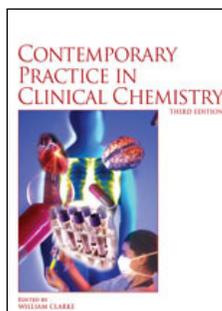
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New Resource from AACC Press “Contemporary Practice in Clinical Chemistry” Covers TDM and Toxicology



The third edition of *Contemporary Practice in Clinical Chemistry* provides a clear and concise overview of important subjects in the field. Several chapters focus on topics related to toxicology or therapeutic drug monitoring, including: “Pharmacokinetics for the Practicing Clinical Chemist,” “Therapeutic Drug Monitoring,” “Toxicology and the Clinical Laboratory,” and

“Pharmacogenetics.” It also includes new sections on NMR, laboratory automation, standardization-harmonization of clinical tests, body fluid analysis, and pediatric clinical chemistry.

The 851-page book costs \$99 (\$79 for AACC members). It can be ordered online (www.aacc.org) and click on the “Store” link) or by calling (800) 892-1400 or (202) 857-0717.

Many AACC Meeting Sessions Cover Toxicology and TDM Topics

By Kamisha Johnson-Davis

The 69th AACC Annual Scientific Meeting and Clinical Lab Expo will be held July 30 to August 3 in San Diego. It features a great lineup of speakers related to therapeutic drug monitoring and toxicology, including symposia on presenting expert testimony and MALDI-TOF mass spectrometry.

The TDM and Toxicology Division membership meeting and luncheon is on Monday, July 31.

Here are some of the highlights of sessions related to TDM, toxicology, and pharmacogenetics:

Monday, July 31st

42109/52209 *How People Try to Beat Drug Testing and Defend Positive Results*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

42114/52214 *The Role of Pharmacogenomics in Therapeutic Drug Monitoring of Immunosuppressants*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

42117/52217 *Troubleshooting and Method Development for the Extraction and Quantification of Cannabinoids from Oral Fluid*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

42129/52229 *Doping with Testosterone: Testing Strategies and Factors Influencing Detection*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

32105 *Novel Psychoactive Substances in Emergency Toxicology*. Morning symposium. 10:30 am–12:00 pm.

32220 *Presenting Expert Testimony in the Courtroom*. Afternoon symposium. 2:30–4:00 pm.

Tuesday, August 1

43119/53219 *Biomarkers to Detect Alcohol Exposure*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

43124/53224 *Strategies for Streamlining Analytical and Post-Analytical Processes in Clinical Urine Multi-Target Drug Testing Using LC-MS/MS Technology*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

43125/53225 *A Case-Based Discussion: Therapeutic Drug Monitoring for Reduction of Adverse Drug Reactions*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

43126/53226 *Use of Frequency Distribution Curves to Determine Drug Cutoffs*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

33103 *Integrating TDM in the Health Care Environment: Team-Based Care with Pharmacists*. Morning symposium. 10:30 am–12:00 pm.

33104 *Precision Medicine and Therapeutics*. Invited oral abstracts. 10:30 am–12:00 pm.

33215 *Cannabis Impaired Driving: Biological Markers and Behavioral Indicators of Recent Cannabis Intake*. Afternoon symposium. 2:30–5:00 pm.

33212 *MALDI-TOF Mass Spectrometry: Not Just for Clinical Microbiology Labs Anymore*. Afternoon symposium. 2:30–5:00 pm.

Wednesday, August 2nd

44106/54206 *Overview of Marijuana Metabolites, Pharmacokinetics, and the Utility of Potential Biomarkers*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

44118/54218 *Drug Screens: Basic Principles, Principle Problems, and Future Approaches*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

44129/54229 *Case Studies in Clinical Toxicology: How to Make Sense of Urine Drug Screen Results?* Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

44108/54208 *Evaluation of MALDI-TOF Mass Spectrometry for Pharmacogenetic Testing in Clinical Laboratories*. Brown bag. 7:30–8:30 am and repeated at 12:30–1:30 pm.

34216 *Precision Medicine Guided Pharmacotherapy in Cancer*. Afternoon symposium. 2:30–5:00 pm.

34219 *Beyond the Traditional Environments: Defining the Role of Laboratory Medicine in Pharmacy and Direct to Consumer Testing*. Afternoon symposium. 2:30–5:00 pm.

Thursday, August 3rd

15001 *Modern, Effective Care for Substance Use Disorders: Findings from the 2016 Surgeon General's Facing Addiction Report*. Plenary. 8:45–10:15 am.

35106 *At the Juncture of Pain Management and Addiction*. Morning symposium. 10:30 am–noon.

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Medical Cannabis Acceptance and Use of Medical Marijuana Continue to Grow

By Kamisha L. Johnson-Davis, PhD

The first documented medical use of cannabis was in the year 2737 B.C., from the time of the Emperor Shen Neng of China (1). In China, cannabis was used to treat constipation and rheumatic pain and as anesthesia for surgery (2). Medical and psychoactive use of cannabis gradually spread through the Middle East, Europe, and Africa (1).

Cannabis seeds were transported from Africa to Brazil via the slave trade. The plant eventually spread to North America, where in the late 19th century William O'Shaughnessy used it experimentally in medicine as a sedative hypnotic, as an analgesic, and to enhance appetite and digestion. As cannabis research progressed, U.S. and European drug companies began to market cannabis extracts in the 19th and 20th centuries (3).

Medical Cannabis in the U.S.

In 1970, marijuana use was restricted by the federal Controlled Substances Act, which classified it as a Schedule I drug because of its high potential for abuse. In the mid-1980s and early 1990s, synthetic forms of the active ingredient in marijuana, delta-9-tetrahydrocannabinol (Δ^9 -THC or THC), were marketed as Cesamet (nabilone) and Marinol (dronabinol) and were listed as Schedule II and III, respectively. These drugs are prescribed to relieve nausea and vomiting from cancer chemotherapy and as appetite stimulants for patients with AIDS wasting syndrome.

Public support and legislative efforts in recent decades led to the legalization of cannabis for medical use in 23 states as of the end of 2016.

Cannabis Plant

The components of the cannabis plant are the stem, leaves, nodes, buds (cola), flowers (calyx), hairs (pistil), resin (trichomes), and seeds. Cannabis seeds comprise essential fatty acids and proteins; they are low in THC. There are male, female, and hermaphrodite cannabis plants. The hermaphroditic plant is self-pollinating. The female plants produce the most THC and are harvested for medical and recreational use.

There are three known species of the cannabis plant: *Cannabis sativa*, *C. indica*, and *C. ruderalis* (4). *C. sativa* is indigenous to Europe and grows to eight to 12 feet tall. It has long, narrow leaves and is typically cultivated outdoors. *C. indica* is native to India and grows to three to six feet. The plant has many branches, wide leaves, and is typically grown indoors. *C. ruderalis* is native to Europe and Asia. It

grows to about two and a half feet and produces less THC than *C. indica* (5).

Cannabis contains more than 400 compounds, including over 60 cannabinoid compounds. The most abundant cannabinoids include the psychoactive THC, cannabidiol (CBD) (which has 10% of the activity of THC), and cannabidiol (CBD) as well as the nonpsychoactive cannabichromene and Δ^9 -tetrahydrocannabivarin (6,7).

Pharmacology of THC and CBD

In 1964, Gaoni and Mechoulam identified the chemical structure of THC. THC activates two G-protein-coupled cannabinoid (CB) receptors to mediate its pharmacological effects. The endocannabinoid system modulates pain sensation and analgesia, food intake, inflammation, epilepsy, cancer, mental disorders, movement disorders, and more (8).

CB type 1 receptors are located in the brain, spinal cord, and peripheral tissues, such as the lungs, liver, and kidneys. CB type 2 receptors are in the immune system and hematopoietic cells, where they modulate immune function via the release of cytokines (8).

Pharmacological effects of THC and CBD vary by dose, route of administration (inhalation, oral, transdermal, sublingual, ocular, or rectal), and frequency of use. The psychoactive effects of THC include relaxation, sedation, euphoria, paranoia/altered perception/psychosis, and impaired cognitive function (6). The physical effects include increased heart rate, appetite stimulation, analgesia, and decreased intraocular pressure. THC is used to treat glaucoma. Chronic use can lead to tolerance, dependence, and withdrawal.

CBD has analgesic, anticonvulsant, anxiolytic, antipsychotic, and anti-inflammatory effects (9). CBD does not act on either CB receptor; therefore, it does not produce the psychoactive effects that THC does.

THC and CBD are lipid-soluble, are highly bound to plasma protein, and have an extensive volume of distribution, accumulating in fat tissues. The cannabinoids are metabolized in the liver by CYP2C9, 2C19, 2D6, and 3A4 to several metabolites. The predominant active metabolite of THC is 11-hydroxy-THC; the primary inactive metabolite is 11-nor-9-carboxy-THC. The primary metabolite of CBD is 7-hydroxy-CBD (10,11). These cannabinoids have half-lives of several days and are excreted primarily in the urine and feces.

Medical Cannabis

Each cannabis species has unique genetics that determines the THC and CBD concentrations. The hemp plant, derived from *C. sativa*, lacks the gene to produce the enzyme tetrahydrocannabinolic acid (THCA) synthase to make THCA, which is the precursor to THC (4). Instead, the hemp plant has the

enzyme cannabidiolic acid synthase, which produces CBD. Hemp contains more CBD and low concentrations of THC (<1%), while *C. indica* contains more THC than CBD. *C. indica* contains the gene that codes for the enzyme THCA synthase, so it produces high levels of THC (~20%). This enzyme converts cannabigerolic acid into THCA, which becomes THC when heated to remove carbon dioxide.

Cannabis Strains

Medical cannabis plants are bred to produce more CBD than THC, a hybrid combination, and more THC (these are often used for recreation). THC content in cannabis plants grew from 1% in the 1970s to about 20% in the 1990s (6).

C. sativa strains are consumed to alleviate pain and mental conditions such as anxiety, depression, and stress. The *C. sativa* strains sold in dispensaries may have THC content of 14–18%. High CBD strains can also reach concentrations of 14–20%.

Hybrid strains that cross *C. sativa* and *C. indica* are used for their effects on both the mind and body to treat insomnia, pain, depression, stress, and anxiety. A hybrid strain may contain 15–25% THC with variable CBD concentrations. *C. indica* strains tend to be medically suitable for people with chronic pain, muscle spasms, anxiety, nausea, appetite stimulation, and insomnia. Some *C. indica* strains contain THC concentrations up to 20–27%, with CBD concentrations that can vary down to <1%.

Medical cannabis can also be delivered in the forms of edibles, oils, lotions, and creams. The dose of CBD and THC in common edibles can range from <1 to 20 mg, and the ratio of the two cannabinoids can span from 1:1 to 20:<1. The concentrations of THC and CBD in oils and concentrates for transdermal administration or inhalation vary, and can exceed 70%.

Summary

Cannabis use has grown worldwide. An estimated 20 million people use marijuana in the U.S. (12), and global cannabis use is estimated to be 182.5 million (3.8% of the world's population between the ages of 15 and 64) (13). Despite the many medical benefits and state legalization for medical use across the country, cannabis is still classified as an illegal substance by the federal government, with limitations for pharmaceutical development and medical research.

Learning Objectives

After reading this article, the reader will be able to describe the components of the various species of cannabis plants and summarize the pharmacological effects of cannabidiol and Δ -9-tetrahydrocannabinol for medical use.

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Learning Objectives

Learning objectives vary by article, but in general, after completing *Clinical & Forensic Toxicology News*, the reader will be able to:

- Describe emerging and changing trends in drug abuse, including new designer drugs, usage patterns, and contaminants/adulterants.
- Identify potential analytes (drugs, metabolites, biomarkers) of clinical and/or forensic significance.
- Evaluate methodologies for their utility and limitations relative to the needs of toxicology labs.
- Discuss relevant regulations, such as analytical performance requirements, or the legality of new drugs of abuse.
- Explain the analytical and regulatory issues unique to specific applications, including postmortem toxicology, workplace drug testing, and drug screening.
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