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U.S. Military Forensic Drug Testing

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The U.S. Department of Defense Military Personnel Drug Abuse Testing Program lays out the guidelines for the military's sweeping, well-established forensic drug testing program (1, 2). This program applies to service members in all military departments, the Office of the Chairman of the Joint Chiefs of Staff and the Joint Staff, Combatant Commanders, the Office of the Inspector General of the Department of Defense (DoD), DoD field activities, and other organizations within the DoD (2). A separate instruction covers the Federal Drug Free Workplace Program for DoD civilians (3).

The purpose of the military drug testing program is to deter service members from abusing both illegal and prescription drugs.

This program, often referred to as a "Commander's program," directs Commanders to use it to assess the security, military fitness, readiness, good order and discipline of their Soldiers, Sailors, Marines, Airmen and Coast Guardsmen (2). Drug test results in this program are used for punitive and non-punitive actions to include discharge from military service.

History

Random urinalysis drug testing was established in 1974 because of significant and widespread drug abuse, primarily heroin and marijuana, in service members during the Vietnam era (4). It was not until 1981 that detection resulting from a urinalysis was permitted to be treated punitively, since the initial focus was to identify members for treatment. In 1983, the results of an investigative commission found that early procedures failed to meet forensic standards. Consequently, in 1984 the DoD formally defined forensic drug testing requirements and responsibilities for forensic testing in a formal directive.

Current Laboratories

Five drug-testing laboratories perform routine DoD drug testing of service members. Two laboratories are operated by the Army, 2 are operated by the Navy, and 1 is operated by the Air Force. The Army laboratories are located in Honolulu, Hawaii and Fort George Meade, Maryland. The Navy laboratories are located outside Chicago, Illinois and in Jacksonville, Florida. The Air Force laboratory is located south of San Antonio, Texas. In fiscal year (FY) 2019 these laboratories tested close to 4.5 million urine specimens, with each laboratory testing between 2,400 and 4,100 specimens per day (5).

Generally, each service tests their own service's specimens, but efficiencies based on regionalization and workload leveling mean that testing is increasingly 'purple,' a term used to describe the mixing of Army green, Marine Corps red, and the blue of Air Force, Navy and Coast Guard into a single mission. The ability of the laboratories to test any service member's specimen is a testament to the level of standardization in urine drug testing among the 5 laboratories and adherence to the DoD instructions. Standardization is further achieved through a joint central governance body called the Biochemical Testing Advisory Board, which has technical and policy representatives from each service. Because of standardization, laboratories can routinely shift workload during major building renovation or emergency operations, and all specimens are treated to the same standards and are capable of withstanding both legal and scientific scrutiny. In FY2019, each Navy laboratory tested over 1 million

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specimens, the Air Force laboratory tested 759K specimens, and the Army laboratories each tested approximately 670K specimens. Some of the laboratories also test unique populations. The Navy laboratory in Illinois tests all applicants to the military, which results in a slightly higher positive drug testing rate compared to the other drug testing laboratories. The Army laboratory in Maryland is certified to perform forensic drug testing for DoD civilians subject to the Federal Drug-Free Workplace Program. With accreditation by both DoD and the Substance Abuse and Mental Health Services Administration (SAMSHA) it is unique among the 5 laboratories. The Army laboratory in Hawaii performs testing of the US Coastguard on a contract basis with the Department of Homeland Security. The Navy laboratory in Florida and the Air Force laboratory often spearhead the development of new high-capacity analytical methods, as well as program-wide process improvement projects.

The Armed Forces Medical Examiner (AFMES) in Dover, Delaware supports the 5 routine drug testing laboratories through the Division of Forensic Toxicology's (DFT) Special Forensic Toxicology Drug Testing Laboratory (SFTDTL) and the DoD Quality Assurance (QA) program. The DFT's mission is to provide a full toxicological picture during death investigations. They utilize the latest technology to identify over 2,000 possible drugs, ranging from illicit drugs to commonly used medications, to ascertain drug-related causes of deaths, accidents, or other investigations. The SFTDTL plays three important roles: surveillance, special testing, and method development. This mission enables the DoD to identify emerging drug threats and allows the drug testing laboratories to adopt cutting-edge technology to further expand the drug detection and deterrence capability of the program. Further, the SFTDTL is formally certified to perform all confirmation testing for synthetic cannabinoids, fentanyl, and lysergic acid diethylamide (LSD). Using a method developed at the AFMES laboratories, the SFTDTL can differentiate strict use of medicinal synthetic Tetrahydrocannabinol, or THC (e.g., dronabinol) from the use of plant-based illegal THC (marijuana). The DoD QA laboratory monitors compliance to strict scientific and forensic standards required for the 5 laboratories to attain and maintain, certification. For example, the DoD QA laboratory sends out over 17,600 open and blind proficiency samples annually, not including special challenge sets, and oversees 3 annual inspections for each of the 5 laboratories. The DoD QA also specifies requirements for screening and confirmation method validation and internal laboratory quality assurance for the certified DoD laboratories. Finally, the AFMES conducts prevalence testing on drugs formerly on the testing panel to assess re-emergence of use.

Table 1. DoD initial screening test cutoff concentrations.

Drug class	Cutoff (ng/mL)
Amphetamines	500
Designer amphetamines	500
Benzodiazepines	200
Cannabinoids (marijuana)	50
Synthetic cannabinoids	10
Cocaine metabolites	150
Opioids (morphine/codeine)	2,000
Opioids (heroin metabolite 6-monoacetylmorphine)	10
Opioids (oxycodone/oxymorphone)	100
Opioids (hydrocodone/hydromorphone)	300
Opioids (fentanyl/norfentanyl)	1.0
Lysergic acid diethylamide	0.5

Testing Procedures

All certified laboratories follow the requirements in DoD Instruction 1010.16 and each has detailed procedures for service member urine specimens from receipt of the specimen to reporting of the final drug result (2). All laboratories use commercially available high-throughput immunoassay (IA) tests to screen for drugs of abuse and prescription medications. The purpose of screening is to identify and eliminate negative specimens from further testing. Specimens that have concentrations at or above the DoD screening cutoff advance to confirmation testing, while specimens below the cutoff are reported as negative (Table 1). A new aliquot of urine is always poured from the original specimen container for the confirmation testing.

Adjunct screening is performed in cases where the commercially available IA kits fail to provide sufficient specificity for a particular drug class. Initial positive screens for amphetamines and opioids are subject to a second IA test with different specificity for the drug class in question. For example, urine specimens are initially screened with an IA kit with high specificity for racemic amphetamines. The follow-on, more expensive IA kit is specific for d-amphetamine and d-methamphetamine which are both scheduled drugs. Adjunct testing significantly reduces confirmation workload by removing specimens that trigger the initial

screen but consistently fail to confirm for a given drug within a drug class. The same initial screening aliquot is used for subsequent adjunct testing which is performed by immunoassay or by RapidFire Mass Spectrometry, a high-throughput sampling and purification method that injects specimen directly into the mass spectrometer. Specimens that are negative on the adjunct test are reported negative for that drug. Specimens positive on adjunct screen are repoured from the original specimen container and a new aliquot is advanced to confirmation testing.

Confirmation testing is performed by chromatographic separation followed by mass-spectrometry to determine the specific drug present in the specimen and its concentration. This is a completely different testing methodology from IA. Either gas chromatography mass-spectrometry (GC-MS) or liquid chromatography tandem mass-spectrometry (LC-MS/MS) is used depending on the drug class. GC-MS and LC-MS/MS are recognized as accurate and reliable methods for drug identification and determination of drug concentration in urine. Isomeric separation of amphetamines is accomplished through chiral derivatization. Mass-spectral methods require a minimum of 3 mass ions for the analyte and 2 for the paired internal standard for MS, and at least 2 transitions for both analyte and internal standard for MS/MS. Confirmation data are collected using GC-MS in selected ion monitoring mode and in multiple reaction monitoring mode for LC-MS/MS. Characteristic ions, their relative abundances to one another, and retention times are used to make a positive drug identification. Specimens are deemed positive if they, and all batch controls (to include blinds), pass all chromatographic and quality control requirements and if the specimen concentration meets or exceeds the DoD confirmation cutoff levels (Table 2), as determined by an in situ calibrator.

Specimens for initial IA screening and confirmation testing are batched. Screening batches can vary in size but do not exceed 150 specimens. Confirmation batches, tested for the same drug class, rarely exceed 24 specimens. All batches contain both open and blind quality controls and must adhere to specific and stringent requirements. For confirmation batches, carryover is assessed by injection of a solvent blank between each specimen and control in a confirmation batch. Additionally, the movement and manipulation of all specimens and controls is annotated by a chain of custody (CoC) document that records the who, what, when, where, and why of all specimen manipulation and movement. All CoCs from the entire testing process are reviewed at each step and must be correctly annotated and must accurately account for the placement and manipulation of each specimen. Quality control failures or non-intact CoCs can result in the specimen being reported out as negative. All results are reviewed by a minimum of 2 independent certifying officials, prior to being reported. Positive specimens are retained in frozen storage for up to 1 year to support legal investigations and retests.

Current Test Panel

The current DoD drug testing panel consists of 28 drugs or drug metabolites (see Table 2). Due to cost constraints and low prevalence, the laboratories may only randomly screen a percentage of the specimens for some illicit drugs. Confirmation testing for low-prevalence drugs (e.g., synthetic cannabinoids, fentanyl, and LSD) is done at the SFTDTL at the AFMES.

Use of anabolic steroids as described in the Designer Anabolic Control Act of 2014 and performance-enhancing drugs listed in select classes of the World Anti-Doping Code Prohibited List are considered wrongful use for service members and subject to punitive measures. Sports Medicine Research and Testing Laboratory in Utah currently performs testing for steroids and performance-enhancing substances for the DoD for service member specimens.

Surveillance Program and Recent Test Menu Changes

The SFTDTL is critical to the DoD's Surveillance Program. The SFTDTL oversees 2 emerging drug surveillance programs—the DoD Emerging Designer Drugs Surveillance Program and the Center for Substance Abuse Research Program. The DoD Emerging Designer Drugs Surveillance Program provides senior Pentagon leadership with snapshots of new and emerging drug use and trends within service member populations. The SFTDTL significantly increased the number of new and emerging drugs that can be detected in urine from 140 to approximately 464 drugs, greatly widening the aperture for the number and types of drugs which can be detected by the DoD's Human Performance and Post-Mortem division, and potentially adopted by the 5 DoD drug testing laboratories.

The surveillance data from the SFTDTL at the AFMES is used to adjust the DoD drug testing panel (Table 2). Since 2017 fentanyl and LSD have been added to the panel.

Quality Assurance

As required by the DoD Instruction 1010.16, each laboratory has its own internal comprehensive QA program. This program is separate and independent from the external DoD QA program. Internal QA programs are robust and must monitor all processes associated with accessioning, handling, testing, reviewing, reporting, and

Table 2. DoD confirmation cutoff concentrations.

Initial presumptive positive test	Confirmation drug / metabolite	Cutoff (ng/mL)
Amphetamines	d-Amphetamine	100
	d-Methamphetamine	100
Designer amphetamines	3,4-Methylenedioxymethamphetamine	500
	3,4-Methylenedioxyamphetamine	500
Benzodiazepines	Lorazepam	100
	Nordiazepam	100
	Oxazepam	100
	Temazepam	100
	α-hydroxy-Alprazolam	100
Cannabinoids	11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid	15
Synthetic cannabinoids	AB-CHIMINACA	1.0
	AB-PINACA	1.0
	JWH-018-N-pentanoic acid	1.0
	JWH-073-N-butanic acid	1.0
	MAM-2201-N-pentanoic acid	1.0
	UR-144-N-pentanois acid	1.0
Cocaine metabolites	Benzoylecgonine	100
Opiates	Morphine	4,000
	Codeine	2,000
Heroin	6-monoacetylmorphine	10
Opioid	Oxycodone	100
	Oxymorphone	100
	Hydrocodone	100
	Hydromorphone	100
Fentanyl	Fentanyl	1.0
	Norfentanyl	1.0
Lysergic acid diethylamide	2-oxo-3-hydroxy LSD	0.2
	LSD	0.2

maintaining the forensic integrity of results. These internal programs are headed by an independent QA Officer (QAO) who reports directly to the laboratory Commander. In addition to process monitoring, QAOs also track run failures, non-conforming events, monthly audits, and provide monthly QA meetings and reports. Internal QAOs evaluate a laboratory's performance on monthly open and blind proficiency tests where each laboratory's performance is compared to collective peer results from the other 4 laboratories, the DoD QA laboratory, SFTDTL, and the AFMES Human Performance and Post-Mortem laboratory.

Failure to perform at an acceptable level on either monthly proficiency tests can lead to the loss of the laboratory's certification to test a given drug or drug class. Laboratories that lose certification to test a given drug can no longer report that drug until the issue is resolved and the DoD QA recommends re-certification of the laboratory to the Director of the Office of Drug Demand Reduction.

If a laboratory reports out a false-positive result, it immediately loses certification to test and the AFMES DoD QA will form an inspection team to investigate the problem. The laboratory cannot

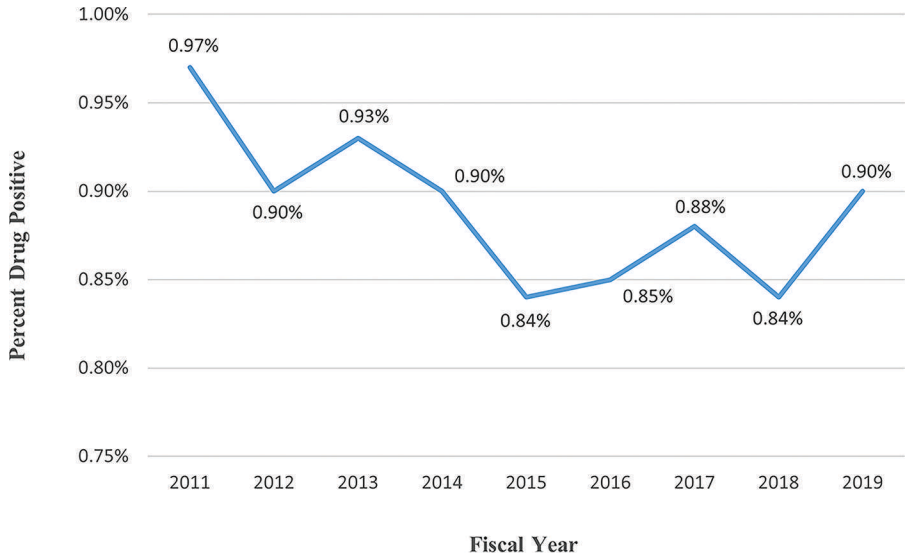

Figure 1. Overall DoD drug positive profile.

test or report drug testing results until certification is regained.

Each of the 5 routine drug testing laboratories is inspected 3 times a year, as is the SFTDTL. These inspections are coordinated by the AFMES, DoD QA, and can consist of external senior military, civilian DoD forensic toxicologists, and expert consultants from the civilian sector. In addition to extensive review of data and procedures, inspectors review each laboratory's ability to reach expected turnaround times of 4 working days for negative results and 6 working days for positive results. Poor turnaround times constitute an inspection finding.

Medical Review Officer Evaluations

The DoD instruction requires each service to have a medical review process to review all positive drug test results that could be from lawful prescription drug use (2). The services approach this requirement slightly differently, although all services perform an initial and second medical review of each eligible drug positives results. The Navy (and Marine Corps) use laboratory certified expert witnesses to perform technical consultation. The Army allows physicians, physician assistants, nurse practitioners, and PhD toxicologists to perform medical reviews. The Air Force only allows physicians to perform the initial review of drug positive results, but laboratory certified expert witnesses may perform the second review. Incorrect medical reviews are returned for correction. For civilians subject to the Federal Drug-Free Workplace Programs, the medical review process is regulated by SAMSHA, and only physicians are allowed to perform the medical review.

Drug classes for which medical review is automatically triggered for service member specimens include amphetamines, benzodiazepines, hydrocodone, hydromorphone, oxycodone, and oxymorphone. Medical review can be performed by request for THC, cocaine, and fentanyl. The administration of fentanyl during procedures (e.g., dental, gastrointestinal) has posed a challenge to medical review, as medications given during a procedure may not be apparent in the pharmacy database and patients maybe unaware that they were given fentanyl during a procedure.

The electronic Prescription Review system (ePRs), in use since 2011, compares screening and confirms drug positive results against the pharmacy database for active-duty service members to look for a valid prescription to explain certain positive drug results within a given timeframe. The ePRs continues to significantly reduce the confirmation and medical review workload, especially for amphetamine and opiate drug classes.

The new DoDI 1010.16, released in June 2020, set limits on the validity of a prescription for schedule II-V drugs. Prescriptions for these drugs are considered expired 6 months after the most recent date of filling unless otherwise explicitly annotated. Services are in the process of developing regulations to comply with this requirement.

Recent DoD Results

According to the FY2019 Annual Report of Drug Use in the DoD, the 5 drug testing laboratories tested 4,456,458 specimens. On average, 1.6 urine specimens per service members were collected from those who were tested, but only 74% of

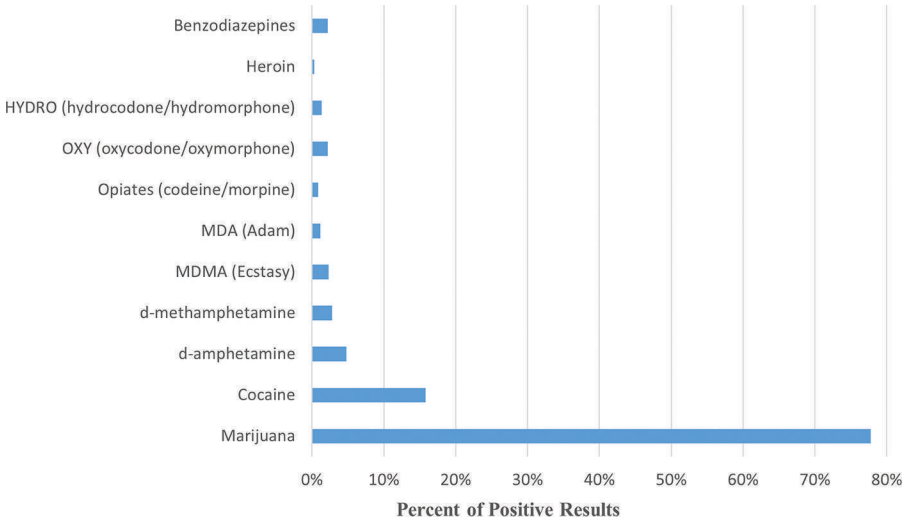

Figure 2. Breakdown of the DoD FY 2019 positive results by drug.

military personnel were subject to urinalysis. Over 15,000 service members had positive drug results, that is, 0.90% of the force tested positive for illicit or prescription drugs in 2019 (Figure 1). Positive results are after legal and medical review. Interestingly, the percentage of service members testing positive for drugs remained relatively steady from 2015 to 2018. In 2019 the percentage rose 7% (from 0.84% to 0.90%). This is generally attributed to an 11% increase in marijuana use from 2018 to 2019 (6).

Compared to US workforce data collected annually by Quest Diagnostics, DoD service members and the non-DoD workforce both saw a decrease in positivity for opioids (5, 6). In fact, the opioid-positive rate in the DoD has fallen consistently since 2014. Marijuana is the most-commonly detected substance in both the US workforce and DoD service members. Within the DoD, marijuana continued to be the primary illicit drug of abuse identified in 77.8% of the overall DoD drug-positive service member population (Figure 2). However, the overall positive rate for marijuana in the DoD was only 0.70%, which is much lower than for the general US workforce at 3.1% (4). Cocaine was the second most popular drug in the DoD, accounting for 15.8% of drug-positive service members, and a positive rate of 0.14%. For the US workforce, amphetamines at a positive rate of 1.3% was the second most commonly abused drug after marijuana.

Conclusion

The U.S. Department of Defense Military Personnel Drug Abuse Testing Program, led by its 5 drug testing laboratories continues to deter drug use by extensive, responsive, high quality forensic urine drug testing with punitive and administrative consequences. The overall drug positive rate for DoD service members remain under 1%. The adoption of new technologies and techniques allows the drug testing laboratories to not only test millions of specimens quickly, but to adapt to new and emerging drug threats. The program and the laboratories that support it consistently ensure that Commanders get a clear and accurate picture of force readiness.

Learning Objectives

After reading this article, the reader will be able to identify the instructions that govern the DoD drug testing program and describe testing procedures, the current testing panel, and the external and internal quality assurance programs for the DoD drug testing laboratories. The reader will be familiar with the medical review process among the services, and the DoD drug positive rates.

References

1. U.S. Department of Defense. Instruction 1010.01: Military Personnel Drug Abuse Testing Program (MPDATP). DoD Issuances, Washington, D.C., 2018. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/101001p.pdf?ver=2019-04-08-104416-893 (accessed February 2021).
2. U.S. Department of Defense. Instruction 1010.16: Technical Procedures for the Military Personnel Drug Abuse Testing Program. DoD Issuances, Washington, D.C., 2020. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/101016p.pdf (accessed February 2021).
3. U.S. Department of Defense. Instruction 1010.09: DoD Civilian Employee Drug-Free Workplace Program. DoD Issuances, Washington, D.C., 2018. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/101009p.pdf?ver=2018-06-28-074214-763 (accessed February 2021).

4. The Vietnam Drug User Returns, Final Report, September 1973, Lee N. Robbins, Ph.D. U.S. Government Printing Office, Washington DC.
5. Status of Drug Abuse in the Department of Defense, Fiscal Year 2019 Drug Testing Statistical Report and Analysis.
6. Quest Diagnostics. Workforce Drug Testing Positivity Climbed to Highest Rate in 16 Years, New Quest Diagnostics Drug Testing Index™ Analysis Finds. http://questdiagnostics.com/home/physicians/health-trends/drug-testing.html. (accessed February 2021).

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CBD Use in the US Pain Management Population

By Richard A. Lundberg, PhD

Chronic pain is defined as pain that persists or recurs for more than 3 months after healing is expected to have taken place, or which exists in the absence of tissue damage (1). It can result in disability, suffering, emotional disturbance, and social withdrawal and negatively impact the sufferer's ability to work, participate in daily activities, and enjoy a good quality of life. The impact of chronic pain is wide with some studies estimating more than 20% of the global population suffering from its effects (2).

Treatment of chronic pain is complex. It often involves pharmacological and/or non-pharmacological (psychotherapy, cognitive behavioral therapy, and exercise) treatments to aid the patient in managing their pain to an acceptable level (3). Pharmacological therapies that are often employed to treat various types of chronic pain include non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, serotonin-reuptake inhibitors (SSRIs), muscle relaxants, hypnotics, anxiolytics, and opioids (2, 4). Opioid therapy rose to popularity in the mid-1990s with the promise of low addiction potential, until peaking in 2012 in the US with over 255 million prescriptions, which was enough for every adult in the country to have a bottle of pills (5). Unfortunately, the rise of opioid use in the US was accompanied by a dramatic increase in opioid overdose deaths with almost 450,000 deaths attributed to opioid overdoses between 1999 and 2018 (6). The opioid epidemic in the US and around the world has exposed the risk of opioid therapy and driven the search for alternate pharmacological treatment options.

One alternate chronic pain treatment option that has gained interest in recent years is cannabinoids. The use of cannabinoids, the active components of the cannabis plant, for help in treating pain has been a long-standing controversy, but recent changing political and societal viewpoints surrounding cannabis use in the US and around the world has brought increased interest to using cannabis for medical purposes, including treatment of pain (7-9). The *Cannabis sativa* plant contains at least 144 cannabinoids, but most medicinal interest is focused on the most common cannabinoids: Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (10). THC is the main psychoactive compound associated with the high attributed to cannabis use and has been linked to many pharmacological actions including analgesic, anti-inflammatory, anti-oxidant, antipruritic, bronchodilatory, anti-spasmodic, and muscle-relaxing activities. However, THC has also been associated with many side effects, including anxiety, impaired memory, and immunosuppression (7). CBD is non-psychoactive and is thought to have analgesic, anti-inflammatory, anti-convulsant, and anxiolytic activities (7, 8, 11). The pharmacological activity profile of CBD combined with its safety profile and lack of psychoactive properties has made CBD an attractive candidate for pain management (8).

The only pharmaceutical containing CBD approved for use in the United States is Epidiolex® (GW Pharmaceuticals, Cambridge, US). It was approved by the US Food and Drug Administration in June 2018 to treat seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) (8, 9, 11). Epidiolex is the only plant-derived *Cannabis* compound approved by the FDA and contains 99% pure oral CBD extract prepared as a liquid solution at a concentration of 100 mg/mL (13, 14). In July 2020, Epidiolex was approved by the FDA as a treatment of seizures associated with tuberous sclerosis complex (TSC) (14). GW Pharmaceuticals makes a second cannabinoid-containing pharmaceutical named Sativex®. Sativex is an oromucosal spray that is a formulated cannabis extract (called nabiximols) containing a 1:1 ratio of THC:CBD.

Sativex has not been approved for use in the US but has been approved in >30 countries for treatment of spasticity due to multiple sclerosis (MS) (11). It has also been approved in the UK and Canada to treat central neuropathic pain associated with MS and as an adjunctive analgesic treatment of cancer pain unresponsive to opioid therapy (8).

While CBD is available in limited pharmaceutical products, it has been added to many non-pharmaceutical products, often as dietary supplements, and can be ordered online and over the counter around the world. Consumers can purchase CBD in the form of oils, tinctures, capsules, beverages, gummies, cosmetics and even toilet paper. The fact that the FDA does not recognize CBD as a dietary supplement and has issued warning letters for selling these products and that the DEA classifies all CBD products as Schedule I drugs has not greatly restricted the availability of these products in the US (15). US CBD product sales have doubled from 2017 ($367 million) to 2019 ($845 million) and are projected to double again by 2022 (16).

The effectiveness of CBD alone as a treatment for pain has not been extensively evaluated in human studies (4, 8, 9). Recent clinical studies have shown some promise in the treatment of chronic, neuropathic, and inflammatory pain, but the studies have been small and have not demonstrated statistically significant improvements compared to placebo in primary endpoints. Benefits observed in secondary endpoints or reported quality of life improvements have provided optimism in conducting larger studies to investigate further the use of CBD in treatment of chronic pain (4).

Despite the lack of clinical studies demonstrating the efficacy of CBD as an analgesic, many consumers are using it as a specific therapy to treat their chronic pain (11). In an online survey of over 2,400 CBD users, 62% of the respondents reported using CBD to treat a specific medical condition. Chronic pain was identified as the most frequently targeted condition followed by arthritis and anxiety. Almost 36% of these users reported that CBD treated their medical condition "very well by itself" (11). Adding to the confusion of consumers, CBD products have been actively marketed for a number of unsubstantiated uses, including treatment of chronic pain (17). Thus, whether there is clinical data or not to support CBD as a treatment for chronic pain, consumer's perception is that CBD works to reduce their pain and they are turning to it as a therapy option.

How prevalent is CBD use in patients being treated for chronic pain in the US? To evaluate the potential prevalence of CBD in the chronic pain population, the database of specimens submitted to our laboratory for a pain management drug compliance test were reviewed for CBD listed as a declared medication. Physicians have the option to provide a list of medications the patient is taking that is submitted along with the patient specimen. The medication lists are a combination of physician ordered prescriptions and donor-reported use. The first time that CBD was listed as a declared medication was May 6, 2017. From May to December 2017, only 0.01% of medication lists indicated CBD as a declared medication. Declared use of CBD has steadily increased year over year and reached 0.51% in the first two months of 2021 (Table 1). Of particular note, declaration of CBD more than quadrupled from 2018 to 2019, increasing from 0.07% to 0.34%. As discussed earlier, Epidiolex was approved in the US in 2018 for treatment of seizures of two rare forms of epilepsy. There are no CBD-containing FDA approved products in the US for treating pain. It is possible that the FDA approval of Epidiolex allowed patients to become more comfortable disclosing CBD use to their physicians and/or implied a sense of safety of all CBD products that emboldened them to try CBD to treat their chronic pain.

Table 1. CBD listed as a declared medication

Year	Total specimens	CBD declared	% CBD declared
2017[a]	401,395	25	0.01%
2018	677,894	503	0.07%
2019	647,709	2,228	0.34%
2020	479,907	2,241	0.47%
2021[b]	83,506	422	0.51%

[a]May–December.
[b]January–February.

Only a portion of CBD use may be captured on medication lists. Many donors may be shy to disclose CBD use as it would likely be self-prescribed and not come from the ordering physician. In addition, some physicians are selective in the drugs that they report on the medication list and only report medications that they deem relevant to the pain management compliance test, such as opioids. The previously mentioned pain management compliance test does not report CBD, but the presence of CBD metabolite 7-carboxy-CBD is monitored for informational purposes. To evaluate actual CBD use in patients being treated for chronic pain, 7-carboxy-CBD was evaluated in almost 2,700 random patient specimens from January 2020 to March 2021. CBD use was detected in 3.6% (98 out of 2,696) of the evaluated specimens in this time frame (Table 2). Thus, the actual use of CBD in the chronic pain patient population is approximately 7 times higher than declared use from the same time period. This

Table 2. CBD detected in patient specimen

Period	Total specimens evaluated	CBD positive	% CBD positive
Q1 2020	387	10	2.6%
Q2 2020	626	17	2.7%
Q3 2020	566	29	5.1%
Q4 2020	579	23	4.0%
Q1 2021	538	19	3.5%
Total	2,696	98	3.6%

suggests that CBD use is under-reported in this population.

CBD use poses potential challenges to interpretation of drug test results. Since there is no CBD pharmaceutical product approved for treatment of chronic pain, the majority of CBD use is self-prescribed use of consumer products. Consumer CBD products may contain trace levels of THC which result in unexpected positive THC drug tests. The 2018 Federal Farm Bill defined legal hemp, the starting material for most consumer CBD, as containing no more than 0.3% THC as measured by dry weight, but the production of commercial CBD products is not well regulated (18). The levels of THC in consumer CBD products have been found to be variable and, in some cases, unexpectedly high (17, 19). In addition, the labelling indicating the CBD and THC content of CBD products has often been found to be unreliable (19, 20). Over 50% of urine drug tests from trusted donors who claimed exclusive CBD use had positive 11-nor-carboxy-Δ^9-THC (11-COOH-THC, the primary metabolite of THC) results ranging from 3 to 57 ng/mL (18). Furthermore, in evaluation of 425 specimens from pain management patients claiming CBD use, 25% of the urine drug tests from the pool of specimens that clustered as likely exclusive CBD users based on CBD/THC ratios had positive 11-COOH-THC results, averaging 17.3 ng/mL and ranging from 2.8 to 109.0 ng/mL (18). Thus, care must be taken in interpreting positive THC drug tests in the context of possible CBD use.

In summary, the complex nature of treatment for chronic pain in combination with the worldwide opioid epidemic has driven a search for alternate treatment options. The pharmacological activity of CBD in non-human models combined with its safety record has garnered interest and support for exploring CBD as a potential option in treating chronic pain. Despite the lack of clinical studies demonstrating the efficacy of CBD in treating pain, users' perception is that it does help relieve their medical condition. The prevalence of CBD use in the chronic pain population appears to be relatively small with less than 4% of urine drug tests from pain management population specimens showing signs of CBD use. However, only a fraction of CBD use is disclosed to the ordering physician which has the potential to complicate the physician's ability to best treat their patient. Undisclosed CBD use also can confound interpretation of drug test results as unexpected THC positives results could be observed.

Learning Objectives

After reading the article, the reader will be able to:

- Outline how the opioid epidemic has driven the search for alternate pharmacological treatment options for chronic pain.
- Summarize why cannabidiol has become an attractive non-opioid chronic pain treatment candidate in recent years.
- Describe how undisclosed patient use of cannabidiol can pose challenges to interpretation of drug test results.

References

1. Treede RD, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). Pain 2019;160(1): 19–27.
2. Uberall MA. A Review of scientific evidence for THC: CBD oromucosal spray (Nabiximols) in the management of chronic pain. J. Pain Research 2020;13:399–410.
3. Clauw D, et al. Reframing chronic pain as a disease, not a symptom: rational and implications for pain management. Postgrad Med 2019;131:185–198.
4. Urits I, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. Best Pract Res Clin Anaesthesiol 2020;34:463–477.
5. Center for Disease Control and Prevention. U.S. Opioid Dispensing Rate Maps. https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html. (Accessed March 22, 2021).
6. Wilson N, et al. Drug and opioid-involved overdose deaths-United States, 2017-2018. Morb Mortal Wkly Rep 2020;69:290–297.
7. Vuckovic S, et al. Cannabinoids and pain: new insights from old molecules. Front Pharmacol 2018;9:3–19.
8. Boyaji S, et al. The role of cannabidiol (CBD) in chronic pain management: an assessment of current evidence. Curr Pain Headache Rep 2020;24:4.
9. Urits I, et al. An update of current cannabis-based pharmaceuticals in pain medicine. Pain Ther 2019;8:41–51.
10. Freeman T, et al. Medicinal use of cannabis based products and cannabinoids. BMJ 2019;365:l1141.
11. Coroon J, Phillips JA. A cross-sectional study of cannabidiol users. Cannabis Cannabinoid Res 2018;3.1: 152–161.
12. World Health Organization Expert Committee on Drug Dependence 39th Meeting. Cannabidiol (CBD) pre-review report agenda item 5.2. November 2017.
13. Sekar K, Pack A. Epidiolex as adjunct therapy for treatment of refractory epilepsy: a comprehensive review with focus on adverse effects. F1000Research 2019;8:234.

14. FDA approves new indication for drug containing an active ingredient derived from cannabis to treat seizures in rare genetic disease. https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-drug-containing-active-ingredient-derived-cannabis-treat-seizures-rare. (Accessed March 24, 2021).
15. FDA regulations of cannabis and cannabis-derived products, including cannabidiol (CBD). https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd. (Accessed March 24, 2021).
16. Total U.S. cannabidiol (CBD) product sales from 2014 to 2022. https://www.statista.com/statistics/760498/total-us-cbd-sales/. (Accessed March 24, 2021).
17. Hazekamp A. The trouble with CBD oil. Med Cannabis Cannabinoids 2018;1:65–72.
18. Goggin M, Janis G. Using measured cannabidiol and tetrahydrocannabinol metabolites in urine to differentiate marijuana use from consumption of commercial cannabidiol products. Clin Toxicol 2020; published online Oct 29. https://doi.org/10.1080/15563650.2020.1827148.
19. ElSohly MA, et. al. Analysis of cannabidiol, Δ^9-tetrahydrocannabinol, and their acids in CBD oil/hemp oil products. Med Cannabis Cannabinoids 2020;3:1–13.
20. Mead A. Legal and regulatory issues governing cannabis and cannabis-derived products in the United States. Front Plant Sci 2019;10:697.

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A Short Review of Naloxone

By Pradip Datta, PhD, DABCC

Naloxone is an important tool as an antidote during the epidemic of opioid overdose. The US Food and Drug Administration (FDA) requires that naloxone be included in all labeling of opioid pain medicine and medicine to treat opioid use disorders. Additionally, the FDA recommends all healthcare professionals discuss the availability of naloxone with patients and caregivers, both when beginning and renewing treatment (1). During the last decade, the use of synthetic opioids like heroin, fentanyl, fentanyl analogues, hydrocodone, oxycodone, and methadone have greatly increased; some of these being promoted by pharmaceutical companies as pain medications. The illicit use of cheap synthetic opioids like fentanyl also increased drug overdoses resulting in death. Opioid-involved overdose deaths rose from 21,088 in 2010 to 49,860 in 2019 (2). Naloxone (C19H21NO4), an opioid receptor antagonist, has almost no analgesic property, but can specifically reverse respiratory depression from opioid overdose. Naloxone has a very similar structure as the opioid, oxymorphone (Fig. 1); however, they

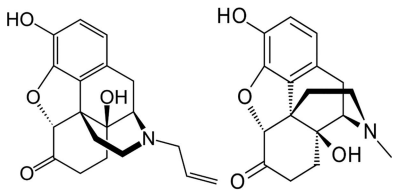

Fig. 1. Chemical structures of naloxone (1), and oxymorphone (2).

differ in that the methyl group on the nitrogen atom in oxymorphone is replaced by an allyl group in naloxone. In fact, naloxone may be synthesized from oxymorphone.

Naloxone was first approved by the FDA in 1971 for treating opioid overdoses by intravenous (IV) or intramuscular (IM) injection. The antidote acts fast, and after administration, the overdosed person quickly begins breathing and regains consciousness. In 2015, the FDA approved a nasal spray version of naloxone, the trade name, Narcan. This product required no formal training and could be used by the general public. Narcan can be used without a prescription in 43 states (3).

Naloxone is a pure mu-opioid antagonist that binds to opioid receptors in the central nervous system. Its binding affinity to the opioid receptor is much higher than that of opioids, but lacks mu receptor efficacy. So, naloxone displaces the opioids from receptor sites to reduce their effects. Naloxone affinity to kappa and sigma opioid receptors is less than that to mu receptor (4).

Oral administration of naloxone is generally ineffective (bioavailability only 2%), because there is a significant first-pass effect—meaning after it is given orally, the liver will metabolize a large portion of the drug before it can work systemically. If it is administered by IV, a majority (60%–65%) of naloxone is eliminated through the kidneys, but it also undergoes significant metabolism in the liver. The half-life of naloxone ranges between 30 and 90 min after IV or IM administration. With a pKa of 7.9, it binds weakly to plasma proteins, effectively penetrates the blood brain barrier, and quickly reaches the central nervous system (4).

The standard adult dose of naloxone is 0.4 mg by IV or 4 mg by intranasal (IN) administration (e.g., Narcan). The IV bioavailability is 100%, IN is 4%, and IM is 35% (4). The drug rapidly takes effect in different time durations, dependent upon the routes of administration. When given by IV an effect usually occurs in less than 2 min, by IM from 2 to 5 min, and by IN in about 5 min. Because naloxone's duration of effect may be shorter (30–60 min) than many opioids', repeat doses may be required. If a response is not observed within 2–3

min, dosing should be repeated until a maximum dose of 10 mg is given. In severe cases a continuous infusion may be necessary (4).

Naloxone, alone, exerts little to no pharmacologic effect (3). At the standard doses of up to 1 mg/kg by IV, it had no effect in patients naïve to opioids or not dependent on opioids. The only toxicity concern of naloxone is the severe withdrawal symptoms that may occur when given to those who are opioid-dependent or acutely intoxicated with opioids. Common symptoms like agitation, emesis, hypertension, and tachycardia are observed.

Naloxone may be tested in random urine using liquid chromatography tandem mass spectrometry (LC-MS/MS) using a cut off concentration of 2 ng/mL. There is no naloxone immunoassay available, but naloxone may cross-react to produce positive results in some opiate and oxycodone immunoassays (5).

Easy to use and fast acting, naloxone has become a vital tool against the opioid epidemic. Although naloxone is a prescription drug, most states allow it to be dispensed without a prescription, and it is routinely administered by emergency personnel when opioid overdose is suspected.

Learning Objectives

After reading this article, the reader will be able to explain the mechanism of action of naloxone, the antidote for opioid overdose.

References

1. FDA NEWS RELEASE. https://www.fda.gov/news-events/press-announcements/fda-requiring-labeling-changes-opioid-pain-medicines-opioid-use-disorder-medicines-regarding. Accessed April 2021.
2. National Institute on Drug Abuse. Overdose Death Rates. Accessed March 2021. Overdose Death Rates | National Institute on Drug Abuse (NIDA).
3. Jordan MR, Morrisonponce D. Naloxone. In: Stat Pearls. Treasure Island, FL: Stat Pearls Publishing: Accessed March 2021. Naloxone - StatPearls - NCBI Bookshelf (nih.gov), 2020.
4. Rzasa Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. Ther Adv Drug Saf 2018;9:63–88.
5. Straseski JA, Stolbach A, Clarke W. Opiate-positive immunoassay screen in a pediatric patient. Clin Chem 2010;56:1220–3.

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

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- 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.
- Describe the medical implications of drug abuse, toxicity associated with therapeutic agents, and exposure to other toxicants.

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