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Succinylcholine—Hollywood's Perfect Poison?

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The drug succinylcholine is renowned in modern medicine for its ability to provide short-term muscle paralysis to facilitate endotracheal intubation. Unfortunately, because of this unique property, it has also gained notoriety as a means to covertly commit homicide. Succinylcholine has gained a reputation by some as the perfect poison because of its ultrashort half-life and rapid metabolism into the endogenous biochemicals succinic acid and choline. This has led some to consider it to be forensically undetectable. In this review article, we discuss the drug's general history, pharmacology, metabolism, toxicity, laboratory testing, and several documented cases of its use as a poison, along with the resulting forensic science.

Background

Succinylcholine was initially synthesized in 1906, but its ability to produce a rapid neuromuscular blockade was not recognized until >40 years later. This special property was masked in the initial laboratory animal experiments conducted by Reid Hunt and Rene de M. Taveau who assessed >80 choline derivatives for their impact on circulation and blood pressure (1). Unfortunately, they tested these drugs in animals that were thoroughly anesthetized and also given the drug curare for neuromuscular blockade, thus hiding the paralytic effect of succinylcholine. Eventually in the late 1940s, Italian researchers discovered and published observations that succinylcholine induced effective short-term general paralysis. Physicians recognized the potential clinical utility of the drug and began to use it as a medicine in 1951. Succinylcholine rapidly facilitates intubation in emergency situations when immediate airway control is essential and only short neuromuscular blockage is required. Relative to other neuromuscular blocking agents, such as rocuronium, it has the fastest onset and the shortest duration of action. Succinylcholine is also used in veterinary medicine and laboratory animal science. Its global usefulness, spanning over a half century, has led to it being placed on the World Health Organization's List of Essential Medicines. Nonmedical uses of this drug have been far less benign. There have been multiple accidental postexposure fatalities as a consequence of the resulting respiratory paralysis, and its use has been documented in several murders.

Pharmacology

Succinylcholine, $C_{14}H_{30}Cl_2N_2O_4$, is a bisquaternary amine that consists of 2 acetylcholine (ACh) neurotransmitter molecules that are linked by their acetyl groups. This unusual chemical structure is illustrated in Fig. 1. The drug is highly water soluble, having an estimated V_D from 0.02 to 0.04 L/kg (2). It does not efficiently cross the blood–brain barrier, so it is relatively devoid of central nervous system effects.

The drug is usually sold as the dichloride salt in a 20-g/L solution for intravenous (IV) or intramuscular (IM) administration. Single adult doses normally range from 20 to 80 mg (2). Other names for succinylcholine include suxamethonium, succinyldicholine, Anectine, and Quelicin. An inexpensive generic form is also commercially available. Medical personnel often colloquially refer to succinylcholine as "SUX."

Relative to other muscle relaxants, it has a rapid onset of action and a very short duration of action. Induced paralysis occurs within 30 to 60 s if

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administered by IV or 2 to 3 min when administered by IM. It has a half-life of less than a minute, which usually results in the duration of action being <10 min when administered IV or up to 30 min if administered by IM.

Succinylcholine primarily acts as a nicotinic ACh receptor agonist at skeletal neuromuscular junctions. As with the neurotransmitter it is derived from, the quaternary ammonium moieties bind to the postsynaptic ACh receptor. This stimulates a conformational change that opens a channel that permits sodium and calcium to enter the motor cell and potassium to exit. This depolarizes the postsynaptic cell, resulting in a muscle contraction with delayed repolarization as long as succinylcholine remains within the synapse. Muscle fasciculations are often present before achieving flaccid paralysis.

In therapeutic doses, paralysis of the diaphragm typically coincides with paralysis in the muscles of the larynx. If the respiratory paralysis is not quickly compensated by mechanical ventilation, lethal apnea can occur. Once the level of succinylcholine falls in the synapse, normal neuromotor function is restored and the paralysis is resolved. It is worth noting that succinylcholine can also stimulate muscarinic ACh receptors in the heart, cause vagal nerve stimulation, and induce the release of histamines.

Metabolism

The biotransformation of succinylcholine involves a 2-step hydrolysis primarily catalyzed by butyrylcholinesterase (BChE, E.C. 3.1.1.8). Other common names for this enzyme include pseudocholinesterase and serum or plasma cholinesterase. Most individuals have high circulating levels of BChE of >3 μg/mL. The catalytic action of BChE first rapidly yields succinylmonocholine (SMC) and a choline molecule. SMC is 20 to 50 times less active than its parent and is ultimately converted into succinic acid and choline, which are both normal products of intermediary metabolism. The half-life of SMC is much longer than its parent, and it is estimated to circulate for 1 to 3 h (3). It is worth noting that acetylcholinesterase (E.C. 3.1.1.7) does not affectively metabolize succinylcholine (2).

Laboratory studies indicate that, on average, 30 s after a conventional IV dose of 1 mg/kg succinylcholine, serum concentrations peak to around 52 μg/mL, then quickly decline to negligible levels (1). Peak SMC levels were attained by 2 min and averaged 16 μg/mL. Succinylcholine appeared in the urine immediately after IV administration, but at 30 min post-IV, it accounted for only approximately 2.2% of the dose and soon became undetectable. Peak SMC urine levels were reached 1 to 4 h post-IV and ranged from 9 to 186 μg/mL (3).

SMC has been used as a marker to detect previous exposure to succinylcholine. Recent antemortem studies have consistently shown that serum and urine are free of native SMC (4). There have been previous reports of SMC being endogenously produced in antemortem tissues, but this seems linked to a liquid chromatography–mass spectrometry method interference with the selected main ion transition (3). However, SMC does seem to be produced in some postmortem tissues after long-term storage or in significantly decomposed succinylcholine negative remains (3). It is generally assumed that the observed SMC was owing to microbial production. Forensic toxicologists should approach postmortem SMC positive results cautiously during their interpretations.

Toxicity

Exposure to succinylcholine can have many potentially undesirable side effects. The most serious include prolonged apnea, severe hyperkalemia, cardiac dysrhythmias, malignant hyperthermia, acute rhabdomyolysis, and fatal allergic reactions. Serum potassium levels will transiently increase approximately 0.5 mmol/L shortly after administration. Because the normal reference range of potassium is 3.5 to 5 mmol/L, this change is seldom dangerous in healthy patients.

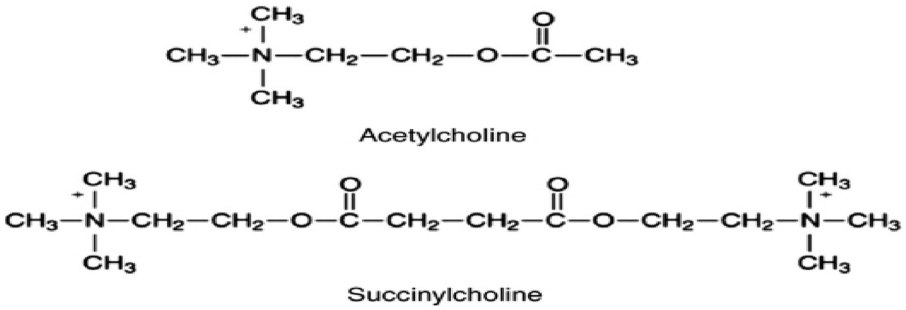

Figure 1. Chemical Structure of Acetylcholine on Top and Succinylcholine on the Bottom

A common misconception is that succinylcholine can produce unconsciousness or anesthesia. In fact, it is contraindicated in conscious patients because significant mental trauma can occur if given, as patients are then paralyzed yet feel pain and are unable to communicate. It is also contraindicated in people who are at risk of high blood potassium or who have a history of myopathy. Since 1995, a black box warning on the package insert has stated that it should be avoided in pediatric elective surgery, especially for patients younger than 8 years of age, because of the risk of previously undiagnosed skeletal myopathy (5).

Individuals with a preexisting BChE deficiency will have a slowed drug metabolism and a prolonged paralytic response to succinylcholine. Decreased BChE activity can be owing to a variety of disease states and previous exposure to certain chemicals. Acquired deficiencies are often because of underlying hepatic disease, malnutrition, or pregnancy. BChE inactivation can also occur owing to previous exposure to carbamates, organophosphorus compounds, and/or fluorides. Many people have low-activity BChE because of genetic variants; it is estimated that 5% of the population have a polymorphic form of BChE (6). At present, >65 autosomal recessive variants have been identified that can alter succinylcholine metabolism (6). Unfortunately, in the 1950s this led to some postexposure surgical patient fatalities that were ultimately attributed to the individuals expressing the atypical form of BChE. Previously, this condition was recognized in patients with a low dibucaine number, which indicated a BChE mutation that conferred significant resistance to dibucaine inhibition. Interestingly, this exemplified one of the earliest forms of pharmacogenomics, well before researchers identified the underlying genetic mutations. Blood testing for BChE function can be easily performed in the laboratory. It is worth noting that in patients with only 20% to 30% of normal BChE activity, the clinical duration of succinylcholine is less than doubled.

Most individuals with a BChE deficiency typically have an extended apnea from 20 min to 4 h. Those with a homozygous deficiency may experience general paralysis lasting up to 12 h. It is recommended that patients who require >15 min to recover muscular function after a single intubating dose should be evaluated for BChE deficiency. Testing can be done by 1 of 3 methods. First, one can directly measure BChE activity present in the blood. The second is by phenotyping, which usually involves determining the dibucaine or fluoride inhibition number that indicates the percent of BChE inhibition. Patients with normal BChE activity should demonstrate 70% to 90% inhibition by dibucaine, whereas patients homozygous for the abnormal allele will demonstrate <30% inhibition. A decreased activity and a low dibucaine number (percent inhibition) suggest a high risk for prolonged paralysis following succinylcholine administration, although there are limitations to these tests and phenotyping may be inaccurate (7). Lastly, genetic tests can identify the specific presence of BChE variants. To avoid prolonged apnea in patients suspected of a BChE deficiency, a test dose of 0.1 mg/kg should be given before a full dose (8). If the patient is deficient, they will often develop flaccid paralysis or significant respiratory depression.

Overdose treatment involves keeping the patient sedated and providing supportive care with a focus on maintaining adequate ventilation until the neuromuscular blockade resolves. There are no currently accepted methods to enhance drug elimination.

Use as a Poison

The first well-documented criminal use of succinylcholine occurred in the mid-1960s and involved Dr. Carl Coppolino, a disabled anesthesiologist who had recently moved to Florida.

In August 1965, Carl's 32-year-old wife, Dr. Carmela Coppolino, died of an apparent heart attack in her sleep. Despite her having no previous medical history of cardiac issues, Carl convinced a physician friend that she had earlier complained of chest pain. This led to her death being attributed to a coronary thrombosis, and no autopsy was performed. Several weeks after Carmela's untimely death, Carl married a wealthy socialite, which aroused great public suspicion. A subsequent investigation revealed that he was a consummate philanderer with a lavish lifestyle and largely depleted finances. A few weeks before Carmela's death, he had increased her life insurance. In addition, a previous mistress from New Jersey testified to his role in the murder of her husband with succinylcholine that he had provided her. One month before his wife's death, Carl had obtained a lethal amount of succinylcholine from a physician friend to allegedly conduct animal experiments (9). Collectively, these facts led the criminal justice authorities to opine that he clearly had the means, motive, and opportunity to have committed a homicide using this drug. Based on this compelling circumstantial evidence, Carmela's remains were exhumed. The resulting criminal justice investigation ultimately culminated in a landmark case in the field of forensic toxicology.

Dr. Milton Helpern, New York City's Chief Medical Examiner, conducted the autopsy of Carmela's remains. Based on Carl's background, he suspected the use of succinylcholine and asked his Chief Toxicologist, Dr. Charles Umberger, to devise a new method to isolate the drug metabolites. Ultimately, they found significant amounts of succinic acid and choline in her brain and liver tissue

(9). Based on this and the previous evidence, the landmark trial *Coppolino vs the State of Florida* began in 1967 with renowned lawyer F. Lee Bailey representing Coppolino. The toxicological testimony presented at trial was based on the detection of these drug metabolites in abnormally high levels in Carmela's remains. He allegedly injected the drug into his wife's left buttock while she was asleep, which led to her death by asphyxiation. In addition, Dr. Bert LaDu observed a positive reaction for SMC around the needle track and in the surrounding fat of her left buttock (10). After only 4 h of jury deliberation, Coppolino was convicted of second-degree murder and received a life sentence. This verdict was unusual in that it implied an absence of premeditation. Carl appealed the conviction, arguing that the metabolite detection method was a novel test that had been developed solely for the case and did not meet the established Frye acceptance standards. The latter implies that scientific evidence presented in court must be generally accepted by the relevant scientific community.

This appeal was not supported by the Florida Supreme Court. They succinctly stated, *"the tests by which the medical examiner sought to determine whether the death was caused by succinyl-choline were novel and devised specifically for this case. This* ***does not render the evidence inadmissible****. Society need not tolerate homicide until there develops a body of medical knowledge about some particular lethal agent. The expert witnesses were examined, and cross examined at great length and the jury could either believe or doubt the prosecution's testimony as it chose."* Soon thereafter, it was determined that endogenous levels of succinic acid in postmortem brain and liver were so highly variable (>10×) as to have little meaning between normal individuals and those previously exposed to succinylcholine (2).

Since this landmark case, there have been many other documented cases of homicide involving succinylcholine. Some of the most renowned are summarized in Table 1. This includes cases in Japan (8) and China (3). Of most recent relevance is the bizarre case of Genene Jones, a licensed vocational nurse who resided in central Texas. In the early 1980s, a significant number of unexplained pediatric fatalities occurred in 2 separate medical facilities where she worked at different times. After directly linking this together, she was convicted of murdering a 15-month-old patient with succinylcholine in 1984 and sentenced to 99 years in prison. However, because of prison overcrowding and new policies that awarded credit for good behavior, her sentence was commuted to 33 years. Jones was scheduled to be released in 2018, but a grand jury indicted her with 5 new charges of homicide, so she will remain in custody until these are resolved. She is currently undergoing mental health evaluations to determine her competency to stand trial.

Laboratory Analyses

The determination of succinylcholine levels in biological fluids is not clinically useful but may be of value in suspected homicides or suicides. Succinylcholine and SMC can be identified and quantitated with gas or liquid mass spectrometry. There are multiple published extraction methods using solid phase and liquid-liquid approaches in a wide variety of matrices to include blood, urine, and an assortment of postmortem tissues (3, 11). Very few laboratories offer testing for these compounds, with the exceptions being NMS Laboratories and some law enforcement agencies.

An individual's serum BChE activity levels can be easily monitored with commercially available chromogenic Ellman reaction assays. In addition, multiple reference laboratories can conduct BChE phenotyping, including Quest Diagnostics, LabCorp, Mayo, the University of Washington, and ARUP Laboratories. A recent Internet search revealed that multiple companies advertise the capabilities to conduct BChE genotype testing. Although these tests are not commonly used clinically, they can be useful in select cases.

Succinylcholine is very labile; it undergoes rapid hydrolysis in aqueous alkaline solutions or in acidic solutions at increased temperatures (2). The drug can be eliminated from body fluids in 20 days unless precautions are taken. These include the addition of embalming fluid or a cholinesterase inhibitor to limit esterase activity. Adding paraoxon to 0.1 mg/L has been recommended to stabilize serum or urine specimens (12). Succinylcholine is also stable at 4 °C for 2 months when buffered to a pH of 3 in a

Table 1. Recent Homicidal Poisonings that Involved Succinylcholine

Name and Location	General Background
Efren Saldivar, CA	Respiratory therapist guilty of murdering 6 patients from 1989 to 1997
Unidentified, Osaka, Japan	From 1993 to 1994 guilty of murdering 5 business partners
Kimberly Hricko, MD	Surgical technician convicted of murdering spouse in 1998
Chaz Higgs, NV	Critical care nurse convicted of murdering spouse in 2006
Unidentified, China	In 2016 used poisoned darts to commit 3 homicides

tetramethylammonium hydroxide or at −70 °C for 4 months in plasma with 40 mg/L echothiophate (2).

Conclusion

Succinylcholine is a drug commonly used in emergency medicine for its remarkable ability to rapidly immobilize patients. Sadly, the drug has also been used in multiple documented murders since the 1960s case *Coppolino vs the State of Florida*. For many decades, succinylcholine has been regarded as an undetectable and, thus, a perfect poison because of its short half-life and quick degradation to endogenous compounds. Although these technical challenges exist, it is not impossible to detect the drug or SMC via mass spectrometry. Forensic toxicologists need to be attuned to possible malicious use of the drug in cases when there is a sudden, unexpected, and unexplained death involving a medical professional as a potential suspect.

Learning Objectives

After reading this article, the reader will be able to summarize the medical uses of succinylcholine and the impact of butyrylcholinesterase deficiency on succinylcholine action. The reader will be to identify the role and limitations of targeting the succinylcholine metabolite succinylmonocholine in forensic investigations of deaths owing to succinylcholine. The reader will appreciate the historic role of the Dr. Coppolino trial in forensic investigations of succinylcholine-induced homicides.

References

1. Dorkins HR. Suxamethonium—the development of a modern drug from 1906 to the present day. Med His 1982;26:145–68.
2. Baselt R. Disposition of toxic drugs and chemicals in man. 11th Ed. Seal Beach (CA): Biomedical Publications; 2017. p. 1982–4.
3. Kuepper U, Musshoff F, Madea B. Applicability of succinylmonocholine as a marker for succinylcholine administration—comparative analysis of samples from a fatal succinylcholine intoxication versus postmortem control specimens. Forensic Sci Int 2011;207:84–90.
4. Xing J, Li W, Tong F, Liang Y, He G, Zhou Y. Three homicides with darts tainted with succinylcholine: autopsy and toxicology. Int J Legal Med 2016;130:1541–5.
5. Quelicin package insert. http://labeling.pfizer.com/ShowLabeling.aspx?id=4621 (Accessed May 2019).
6. Platteborze PL. Acetylcholinesterase and butyrylcholinesterase. In: Kazmierczak SC, Azzazy HME, editors. Diagnostic enzymology. 2nd Ed. Boston (MA): De Gruyter; 2014. p. 19–40.
7. Parnas ML, Procter M, Schwarz MA, Mao R, Grenache DG. Concordance of butyrylcholinesterase phenotype with genotype: implications for biochemical reporting. Am J Clin Pathol 2011;135:271–6.
8. Cass NM, Doolan LS, Gutteridge GA. Repeated administration of suxamethonium in a patient with atypical plasma cholinesterase. Anesth Intensive Care 1982;10:25–8.
9. 1967 May 5. Trials: tracing the untraceable. Time magazine.
10. Murderpedia. https://murderpedia.org/ (Accessed May 2019).
11. Maeda H, Fujita MQ, Zhu BL, Ishidam S, Oritani S, Tsuchihashi H, et al. A case of serial homicide by injection of succinylcholine. Med Sci Law 2000;40:169–74.
12. Ballard KD, Vickery WE, Nguyen LT, Diamond FX. An analytical strategy for quaternary ammonium neuromuscular blocking agents in a forensic setting using LC-MS/MS on a tandem quadrupole/TOF instrument. J Am Soc Mass Spectrom 2006;17:1457–68.

Samantha Parma and Carla Leal-Willett wrote a part of this review article for the new forensic toxicology course offered at St. Mary's University in San Antonio, TX. Samantha recently graduated and plans to pursue an advanced degree in forensics. Peter Platteborze, PhD, DABCC, FAACC, is an assistant professor at St. Mary's University and the program director of the forensic science criminology program. He also serves as a part-time lab director. E-mail: peter.platteborze@gmail.com.

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Impact of the Addition of Oxycodone, Oxymorphone, Hydrocodone, and Hydromorphone to the HHS Mandatory Guidelines for Federal Workplace Drug Testing Programs

By Marquita Brogdon, MBA, and Lois Holliday, MS

Four additional opioids (oxycodone, oxymorphone, hydrocodone, and hydromorphone) were added to the Department of Health and Human Services (HHS) Mandatory Guidelines for Federal Workplace Drug Testing Programs published on January 23, 2017, with an effective date of October 1, 2017. Because some federal agencies were not prepared to add the additional analytes to their testing programs by the October 1, 2017, effective date, the Substance Abuse and Mental Health Services Administration (SAMHSA) instructed agencies to notify their service providers of the date they planned to begin testing their workplace specimens for the added opioids. The Department of Transportation implemented testing for the added opioids on January 1, 2018. The addition of these prescription opioids has caused a significant increase in the overall positivity rate of federally regulated specimens.

In preparation for the added opioids, HHS-certified laboratories were required to validate initial and confirmatory drug test methods. The National Laboratory Certification Program (NLCP) prepared a practice performance test (PT) set containing the

added opioid analytes at concentrations focused on the initial and confirmatory test cutoffs. This PT set was sent to each laboratory for internal use in evaluating their initial and confirmatory procedures. The laboratories were not required to report their results to the NLCP. To assess laboratory readiness, the NLCP subsequently sent 3 qualifying PT sets to the laboratories in May, June, and July 2017. The NLCP graded the PT results from the qualifying sets and remediated identified deficiencies with the laboratories. To enable a thorough review of opioid assay validation records and the qualifying PT data, the NLCP reduced the number of nonnegative specimens reviewed at NLCP maintenance inspections or audits from September 2017 to February 2018.

The NLCP revised the sample scheme for the certification maintenance PT sets sent to HHS-certified laboratories each quarter (October, January, April, and July). The new scheme included the same number of samples with more analytes, while maintaining enough challenges per analyte to enable evaluation over 2 consecutive PT occasions. This was accomplished by reducing the number of specimen validity test challenges and increasing the number of analytes in each PT sample.

The added opioids did not affect the format of NLCP maintenance inspections; however, the NLCP did adjust the ratio of specimens by nonnegative category selected for audits to accommodate the expected increase in the number of opioid-positive results.

The NLCP Manual for Urine Laboratories was also revised to include program requirements and guidance for the new initial and confirmatory tests (e.g., assay validation) and for reporting results. Many laboratories elected to validate opioid confirmatory assays using liquid chromatography–tandem mass spectrometry (LC-MS/MS), which was not a widely used methodology for regulated workplace drug testing at the time. Thus, the addition of the new analytes has now made LC-MS/MS testing more common among HHS-certified laboratories.

The September 2017 NLCP Inspector/Laboratory Director Workshop included presentations on the Qualifying PT Results, the NLCP Manual Changes, LC-MS/MS Data Review, Lessons Learned in Automated Sample Prep for LC-MS/MS, and Testing for Semi-Synthetic Opioids in Urine.

Before implementation, SAMHSA evaluated the costs and benefits of testing for the added opioids and determined that overall costs would be minimal, as most HHS-certified laboratories were already testing for these analytes in their nonregulated programs. Additionally, the NLCP provided the practice and qualifying PT sets to the laboratories at no cost. The benefits of adding these analytes in the HHS Mandatory Guidelines for Federal Workplace Drug Testing Programs include deterrence, providing a healthier and more alert workforce, a decreased risk of accidents for those in safety-sensitive positions, and a reduction in dependence or addiction (1).

Based on information the NLCP has received from HHS-certified laboratories, the addition of oxycodone, oxymorphone, hydrocodone, and hydromorphone has increased the amount of nonnegative specimen results dramatically. The number of drug-positive results from January 2014 until December 2017 remained relatively constant with a range of 8000 to 12 000 total drug-positive results each month, averaging approximately 10 200 per month. From January 2018 until April 2019, the number of drug-positive results ranged from 13 000 to 18 000 per month, averaging approximately 15 500 each month (Fig. 1). This

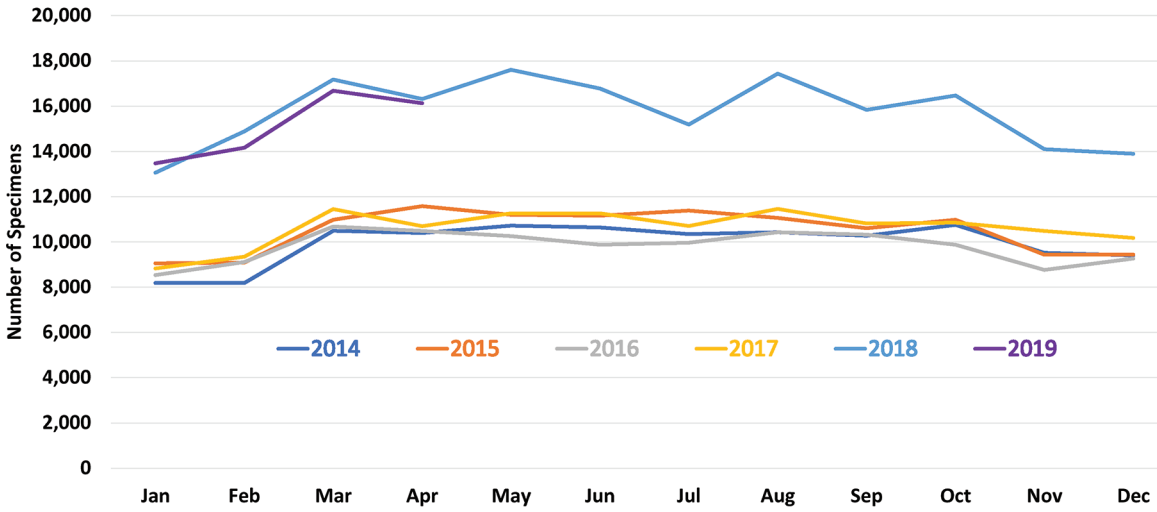

Figure 1. Non-Negative Results (January 2014 –April 2019). Data obtained by the NLCP.

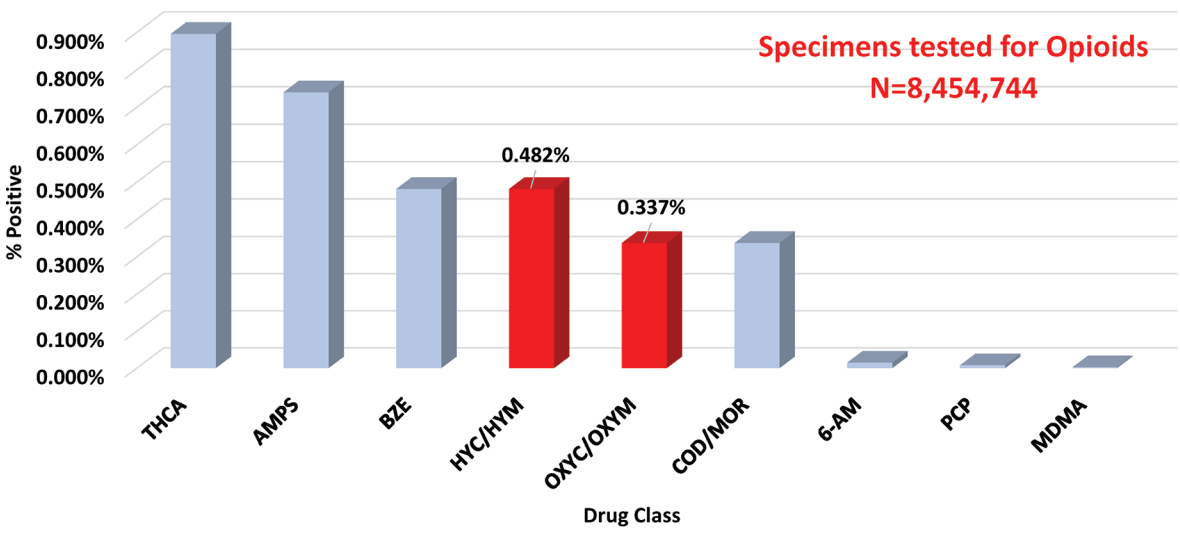

Figure 2. Positivity Rate by Drug Class (January 2018 –April 2019). Data obtained by the NLCP.

equates to an overall increase of approximately 46% more drug-positive results each month for HHS-certified laboratories. The overall drug positivity rate from 2014 through 2017 was approximately 2.0%, which increased to 2.9% in 2018. For >8 million specimens tested between January 2018 and April 2019, the positivity rate by drug class was 0.482% for hydrocodone/hydromorphone and 0.337% for oxycodone/oxymorphone (Fig. 2). The number of drug-positive specimens and the positivity rate of oxycodone, oxymorphone, hydrocodone, and hydromorphone further justify the inclusion of these analytes in the HHS Mandatory Guidelines for Federal Workplace Drug Testing Programs.

Learning Objectives

After reading this article, the reader will be able to describe the impact that additional opioid drugs have had on the National Laboratory Certification Program since the implementation of the added opioids on October 1, 2017. The reader will also be able to describe the overall opioid-positivity rates.

Reference

1. Department of Health and Human Services (HHS). Mandatory guidelines for federal workplace drug testing programs using urine, regulatory impact and notices; January 23, 2017; 82 FR 7920. https://www.samhsa.gov/sites/default/files/workplace/frn_vol_82_7920_.pdf (Accessed September 2019).

The information utilized in this article comes from the Drug Free Workplace Program managed and funded by the Substance Abuse and Mental Health Services Administration (SAMHSA).

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CBD and the FDA

By Andrea Terrell, PhD, DABCC

Cannabis sativa is believed to be 1 of the oldest cultivated crops in the world. The 2 primary subspecies are hemp and marijuana. Hemp was bred to produce fiber, oils, seeds, and other food products, and is grown to maximize the fiber content. Marijuana was bred for its medicinal or psychoactive effects and is grown to maximize flowering parts. D-9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the 2 best known cannabinoids, but >80 have been identified. To be considered hemp, any part of the *C. sativa* plant, including seeds, extracts, and cannabinoids, must have a THC content of ≤0.3% on a dry weight, as defined in the 2018 Farm Bill. Hemp and marijuana can cross-pollinate, although the offspring are not desirable. Plants grown from the resulting seed have intermediate levels of both THC and CBD.

CBD has been listed by the United States Drug Enforcement Administration (DEA) as a Schedule 1 drug since 1970. When the 2018 Farm Bill was signed into law in December 2018, the new law effectively removed hemp as a controlled substance under federal law, provided the THC content requirements are met. Any cannabis plant that contains >0.3% THC would be considered nonhemp

cannabis, aka marijuana. The Farm Bill does preserve the Food and Drug Administration (FDA)'s authority to regulate products containing cannabis or cannabis-derived compounds. Because the FDA had previously approved 4 cannabis-derived or cannabis-related drug products containing natural or synthetic CBD or THC, any subsequently produced product containing those substances technically must be approved. CBD oil, for example, cannot be marketed as a nutritional supplement or added to a food product, and would also be prohibited to be delivered via interstate commerce because it is already an active ingredient in an FDA-approved pharmaceutical product. Retailers marketing CBD products with any health benefit claims or as dietary supplements have in fact been the recipients of FDA warning letters giving the company 15 days to resolve the violation(s). Warning letters can be viewed at https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products. This isn't the case for all cannabis-derived products. Hemp seeds, hemp seed protein powder, and hemp seed oil all have a "generally recognized as safe" designation and can be legally added to food.

It is clear the public wants more access to CBD products. Consumer Reports did a telephone survey of 4355 adults and found an estimated 64 million Americans have taken CBD, and 63% found it effective. Half of respondents were very confident that regulations were in place to ensure safety and efficacy. Internet searches are rife with articles and testimonials about how CBD has helped people manage epilepsy, pain, anxiety, insomnia, arthritis, mood disorders, and other ailments.

The FDA is listening, and on May 31, 2019, the agency held its first ever public hearing on CBD, entitled "Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds." The hearing can be viewed at https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/scientific-data-and-information-about-products-containing-cannabis-or-cannabis-derived-compounds. The hearing was intended to be an information-gathering session from stakeholders across many industries. Speakers were heard, and sometimes questioned, by a panel with representatives from the FDA, including from both the CBD and marijuana working groups. The acting FDA commissioner, Dr. Ned Sharpless, began by explaining the FDA's role in regulation of cannabis and cannabis-derived compounds, covered in the previous section.

The industries represented included manufacturers, cannabis researchers, testing laboratories, agriculture, animal feed, veterinarians, retailers, and pharmaceutical companies. After 10 h of testimony from >100 stakeholders, it is clear that the public wants CBD products, but that too many of the available products are questionably safe. A researcher from Arkansas tested the CBD content of 2 dozen CBD products and found labeling inaccuracies in nearly every one. Products contained anywhere from 0 to 2× the amount labeled. A forensic toxicologist found dextromethorphan and synthetic cannabinoids in CBD products after patients started having hallucinations when using these products.

Testimony was heard from representatives of the epilepsy community, who expressed concerns about the quality of the product and lack of production standards but are more afraid of an FDA-approval process that could take products off the market.

One manufacturer urged the FDA to require manufacturers to be certified by a third party and urged the agency to adopt terminology standards for the different forms of CBD.

- Isolate = pure CBD without any other component
- Full spectrum = CBD plus a host of other cannabinoids and terpenes, including residual THC
- Broad spectrum = full spectrum minus the residual THC

From the laboratory industry, we heard from a representative from A2LA, a certification body for clinical and other types of labs, who discussed the lack of standardization in cannabis product testing. Cannabis testing laboratories individually develop and validate their own methods, and there are no commercially available proficiency testing programs to provide independent assurance of a method's validity. She discussed the need for a recognized standard of quality and assurance of competence for cannabis testing laboratories and requested that the FDA require that any outcome of the agency's request for information include language that a laboratory performing cannabis testing be accredited to ISO 17025 by a signatory accreditation body.

In summary, the FDA's first duty is to safeguard public health. Officials with the agency repeatedly asked speakers follow-up questions about adverse reactions, negative side effects, and drug interactions with CBD. Although state laws have changed as a result of the power of personal stories extolling the benefits of CBD and marijuana, the FDA doesn't work like that. Policy must be established based on scientific evidence. The FDA has the authority to regulate; the public is desperate for product, but the FDA is equally desperate for high quality data to help them set the most appropriate regulatory path.

Rarely has America seen such a reversal in public opinion as it has with cannabis legalization. Many states have taken it upon themselves to respond to the public's desire by legalizing or decriminalizing cannabis. The 2018 Farm Bill sets the stage for discussion at the federal level, and we can expect hearty debate as the FDA decides on a path forward. This path is complicated like maybe no other in its history, as the product they are charged with regulating has already become part of mainstream society.

Learning Objectives

After reading this article, the reader will be able to summarize how the FDA and DEA have categorized hemp and hemp related products, and how the 2018 Farm Bill has changed with respect to hemp. The reader will be able to describe why there are restrictions on labeling CBD containing products as dietary supplements and/or claiming these products carry health benefits.

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The author has nothing to disclose.

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

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