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Vaping and Nicotine Replacement Therapy during the Perioperative Period

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Smoking is associated with severe morbidity and mortality and continues to be the primary cause of sudden and premature death in the US (1). In response to the growing use of tobacco products and rising concern for their deleterious effects, the Family Smoking Prevention and Tobacco Control Act was implemented to accord the US Food and Drug Administration the regulatory oversight over tobacco products (2). Consequently, the use of nicotine replacement therapy (NRT) and electronic (e)-cigarettes as substitutes for smoking to encourage smoking cessation is gaining traction (3). NRT items such as patches, lozenges, spray, and gums deliver nicotine to their users without heating or combustion, whereas e-cigarettes utilize a heating mechanism to deliver nicotine-containing vapor from a solution of tobacco extracts or flavors —a practice commonly referred to as vaping (4).

The rapid rise in vaping and use of NRT is attributable to the negative press that surrounds smoking and the string of smoking bans and restriction laws in many states and organizations. These restrictions continue to drive an increase in the production of NRT and vaping devices with the sales pitch of providing a safe and unrestricted smoking experience.

E-cigarettes, also known as e-vaporizers, are electronic nicotine delivery systems that have been in existence commercially in the US since 2007. E-cigarettes and NRT have become widely used in smoking cessation programs. Owing to their ubiquitous availability, the use of e-cigarettes and NRT has increased significantly; however, there are growing concerns about their safety and health implications (5, 6). Investigations into the safety of NRT and vaping have been controversial, and there is burgeoning evidence that NRT and vaping may have deleterious health effects. It is incontrovertible that smoking negatively affects health and surgical outcomes; however, data on the health effects of NRT and vaping are still scant. Thus, it is imperative to continue to investigate the potential adverse health effects of vaping and NRT exposure, and how they affect surgical outcomes. This article describes the health implications of vaping and NRT during the perioperative period and in surgical settings. Also, we review the available biomarkers of smoking, vaping, and NRT.

Health Implications of Vaping and NRT

Tobacco harm reduction involves initiatives to prevent smoking-attributable morbidity and mortality by substituting combustible tobacco products with supposedly less harmful smoking cessation products. This is premised on the assumption that the most abundant alkaloid in cigarettes, nicotine, is less harmful when administered through a noncombustible medium. Nicotine obtained through noncombustible products, although addictive, has been shown to pose little or no risk of lung cancer (7). However, with NRT and vaping, the risk of pathology and adverse events, although lower than smokers, is still higher than nonusers (8).

Nicotine from vaping is rapidly absorbed by the lungs and stimulates the release of epinephrine from the adrenal gland, which causes hypertension and tachypnea. Consistent with addictive substances, nicotine stimulates the reward center of the brain to release dopamine, which bolsters gratifying behavior. This pleasurable behavior incentivizes the users to continue or escalate its use, disregarding its

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potential deleterious effects. Switching from traditional smoking to vaping carries a relatively minimal increased or altered risk; however, because of the addictive nature of nicotine, vaping serves as a gateway to other addictive behaviors. Furthermore, the liquid used in e-cigarette, called e-liquid, contains other potentially toxic compounds that could irritate the lungs and drive pathology. Furthermore, nicotine is a vasoconstrictor and impedes blood flow—this particularly prevents optimal wound healing and results in scarred tissue after surgery. Also, many surgeons are concerned that nicotine exposure could cause poor postsurgical healing (9, 10). The associations between smoking and poor surgical outcomes have been well documented (11), and the current knowledge posits that the nicotine in cigarettes contributes significantly to poor postsurgical outcomes and adverse health effects. Thus, it is conceivable that, regardless of the source, excess exposure to nicotine will negatively affect health and significantly impair postsurgical wound healing.

The effect of smoking on surgical outcomes is unequivocal; as more people are switching from smoking to vaping and NRT, it is imperative to investigate whether the associations between smoking and poor surgical outcomes are recapitulated in individuals using e-cigarette and NRT.

Consequences of Vaping and NRT during the Perioperative Period

Smoking accentuates the risks of postoperative complications and prolongs postsurgical restoration of tissue function and healing (12). Perioperative smoking cessation is recommended for adequate blood perfusion and the tissue oxygen restoration necessary for wound healing. While smoking cessation is important for good surgical outcomes, the recommended duration of abstinence is equivocal (13). Different jurisdictions and hospitals/surgeons have different smoking cessation requirements, for example, the Oregon Health Authority Prioritized List of Health Services Ancillary Guideline A4 (dated January 1, 2017) requires a 30-day smoking cessation before elective surgery, and expects submission of evidence of abstinence in the patient's chart. However, surgical procedures such as reproductive, diagnostic, and cancer-related are exempt from this requirement. The American College of Surgeons recommends 4 to 6 weeks of smoking cessation before surgery and a 4-week smoke-free period postsurgery to prevent complications. As opined by the American Association of Orthopedic Surgeons, nicotine has a negative effect on bone-forming cells and consequently hampers wound healing in smokers. The American Association of Anesthesiologists has also associated smoking with an increased risk of breathing and lung problems. The specifics of the effects of smoking on obstetric and gynecologic surgery are limited. However, the overwhelming evidence of the adverse pregnancy and obstetrics outcomes associated with smoking warrants smoking cessation recommendations during pregnancy. Maternal smoking has been linked to fetal hypoxia; decreased uterine, placental, and fetal perfusion; and intrauterine growth restriction, among other associated adverse pregnancy and obstetrics complications. The American College of Obstetricians and Gynecologists wholly supports smoking cessation during pregnancy and follows the US Public Health Service's smoking cessation guidelines for pregnant women, which promote smoking cessation intervention during pregnancy.

For ardent smokers, perioperative smoking cessation poses a serious challenge that is mitigated by vaping or NRT. NRT has been shown to have >50% outcome when utilized with other smoking cessation modalities (14). Although there are potential benefits of NRT and vaping for smoking cessation, their effects on surgical outcomes remain controversial. Current knowledge suggests that NRT and vaping may provide similar level of risk for surgical outcomes compared to combustible products (15). Michaels et al. showed that NRT and vaping, as components of abstinence intervention before surgery, offered no benefits in alleviating surgical complications compared with smoking for surgery patients (10). This suggests that there are other components such as nicotine and toxic chemicals in e-liquid and NRT that are responsible for the poor surgical outcomes. Although e-cigarettes do not contain an appreciable amount of tobacco, e-liquid contains nicotine that is inhaled aerosolized.

The adverse outcomes during the postsurgical period associated with smoking are largely attributable to nicotine. Nicotine contributes to pre- and postsurgical complications and poor wound healing primarily by reducing blood flow to the surgical sites and increasing vasoconstriction. Nicotine affects the body's ability to heal after surgery and has the potential to interact with some drug formulations. This makes NRT and vaping equally unsafe as smoking for good cosmetic surgical outcomes.

It was previously documented that vaping delivered lower serum nicotine compared with NRT and cigarette smoking (16). However, emerging evidence now suggests that vaping delivers serum nicotine levels comparable with smoking (17), and greater than previously documented in NRT users (18). Interestingly, not all surgeons are in agreement

Table 1. Pharmacokinetic parameters of nicotine in cigarettes and e-cigarettes (43)

	C_{max},[a] ng/mL	t_{max}, min	AUC, ng·h/mL
Cigarette	6.2 (0.7–37.6)	6.0	4.0 (0.2–11.5)
New-generation e-cigarette	9.2 (0.0–40.2)	6.0	4.6 (0.0–15.6)
First-generation e-cigarette	5.1 (1.2–18.2)	9.0	2.9 (0.0–6.3)

Values are median (min–max). N = 18.
[a] C_{max}, maximum concentration observed; t_{max}, time of maximum concentration; AUC, area under the curve.

with NRT or vaping cessation in addition to smoking cessation before surgery because the perioperative period provides a window of opportunity for smoking cessation interventions (9, 15). Moreover, many patients find it challenging to abstain from smoking even during the day of surgery. Thus, it is a balancing act that surgeons need to consider the implication of smoking cessation vs the use of e-cigarette or NRT before surgery.

Biomarkers of Smoking, Vaping, and NRT

Self-reported smoking habits fail to represent the true smoking status of an individual owing to recall inaccuracies and deliberate omission. In addition, questionnaires on smoking habits often do not capture passive exposure. It is important to have an objective way to differentiate smokers from nonsmokers, users of e-cigarettes, and people on NRT. Robust modalities for the assessment of tobacco exposure and abuse pattern are important to characterize associated risks, smoking cessation, and surgery qualification. Biomarkers to assess smoking have not been rigorously validated to delineate conventional smoking from vaping and NRT. Tobacco use is associated with exposure to nicotine and other alkaloids; these have clinical utility as biomarkers of tobacco exposure. Conventional tobacco products, i.e., a cigarette, contain a large number of chemicals, many of which have been identified in e-cigarettes. Nicotine has been used historically to assess exposure to tobacco-containing products; however, the utility of nicotine in such settings has fallen out of favor owing to its fast clearance rate and relatively short half-life (2 h). This led to the validation of a more stable metabolite of nicotine, cotinine, as a suitable biomarker of nicotine exposure (19).

Nicotine represents 95% of the total alkaloid content of a combustible tobacco cigarette. The mean concentration of nicotine in a cigarette is 10 to 14 mg (20), and approximately 1.0 to 1.5 mg is absorbed during smoking (21). In addition to the major tobacco alkaloid nicotine, minor alkaloids such as anabasine, anatabine, and nornicotine are also found in measurable concentrations in cigarettes (22). Nicotine undergoes extensive hepatic metabolism and, to a lesser degree, renal and pulmonary metabolism to produce cotinine, which is hydroxylated to trans-3-hydroxycotinine.

Cotinine, a primary metabolite of nicotine, is a well-characterized clinical biomarker of nicotine exposure, with less variable concentration compared with nicotine owing to its long detection window and half-life (23, 24). High concentrations of cotinine are present in the urine, with a level 4 to 6 times higher than the concentration in blood and saliva, thus establishing urine as the matrix of choice to determine low levels of nicotine exposure (25). The longer half-life of cotinine also makes it a more stable biomarker. The blood levels of cotinine have been reported to range between 150 and 250 ng/mL after a stick of cigarette, and are comparable in users of combustible and noncombustible tobacco products (26). However, it has been challenging to characterize the levels of cotinine between smokers and users of e-cigarettes because a significant number of e-cigarette users also smoke (17, 27). Most e-cigarette liquids contain tobacco-nicotine extract and deliver nicotine at a comparable or higher concentration than combustible tobacco products (28). To delineate exposure to combustible and noncombustible/smokeless tobacco products, testing for markers such tobacco-specific nitrosamines (TSNAs), mainly 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and its metabolite, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and emission of carbon monoxide (CO) has been proposed; these are more specific to combustible tobacco product, as the heating temperature of e-cigarettes is not high enough to permit the emission of CO in quantifiable amounts (29-31). Of all biomarkers of nicotine exposure, cotinine provides the best marker of smoking status (32). Anabasine, a minor tobacco alkaloid, is also used to differentiate between smokers and nonsmokers, although it has low clinical sensitivity and is found in some supplements and e-cigarettes.

While it is desirable to identify a unique biomarker for e-cigarettes, biomarker efforts are compounded by the ubiquitous presence of e-cigarette components, such as flavorings, glycerol, and propylene glycol in foods, cosmetics, and household

products. Thus, it is prudent to acknowledge that at this time the best way to differentiate vaping and NRT from smoking is the presence of cotinine at a defined concentration and absence of combustion products of tobacco, such as TSNAs (NNAL), which are generally low in e-cigarettes (33, 34). The presence of anabasin and cotinine at a defined cutoff would exclude NRT.

Postexposure Concentration and Biological Cutoff Levels for Nicotine Exposure

The establishment of biomarker cutoffs is clinically useful in providing information about exposure to tobacco products from smokers and nonsmokers. The cutoff points are matrix dependent. The levels of cotinine in the urine are 6 times higher than serum concentrations (35). Genetic differences may also affect the selection of a suitable cutoff, e.g., non-Hispanic blacks have been shown to have higher cotinine levels compared with non-Hispanic whites and Mexicans (36). Nicotine in venous circulation following the smoking of one cigarette is between 5 and 30 ng/mL, with a mean of 10.9 ng/mL (37). In contrast, arterial concentration of nicotine could be extremely high after smoking a cigarette, in the range 20 to 60 ng/mL and can be upward of 100 ng/mL (38, 39). Users of combustible tobacco products, chewing tobacco, and snuff have comparable peak venous concentration of nicotine; however, nicotine levels peak quicker in cigarette users (40, 41).

The maximal plasma level of nicotine in a first-generation e-cigarette after 1-h ad libitum postexposure has been quantified at 15.75 ng/mL contingent upon the nicotine composition of the e-liquid (42). The second-generation e-cigarettes deliver more nicotine compared with first-generation e-cigarettes after the same time postexposure at 23.47 ng/mL. Moreover, an advanced e-cigarette delivers equal or higher nicotine compared with a combustible cigarette (42). Table 1 shows the pharmacokinetic parameters of nicotine in cigarettes and e-cigarettes (43).

Various organizations and institutions have published different cotinine cutoff concentrations to differentiate smokers from nonsmokers, based on their unique population. Plasma/saliva and urine cotinine cutoff concentrations of 15 ng/mL and 50 ng/mL, respectively, have been established to distinguish smokers from nonsmokers (44). An additional challenge is that some individuals are nonsmokers but are exposed to second-hand smoke and may have low levels of nicotine and tobacco biomarkers. Reports from the National Health and Nutrition Examination Surveys from 1999 to 2004 show that the optimum cutoff point for cotinine to differentiate smokers from nonsmokers is 3.08 ng/mL and 2.99 ng/mL for adults and adolescents, respectively (45). The serum cotinine concentration used to distinguish smokers from nonsmokers by some clinical laboratories is 10 ng/mL, and for urine, it is 100 ng/mL; however, it is not uncommon for active smokers to have concentrations $>$1000 ng/mL depending on the chronicity and duration of exposure.

Conclusion

The use of e-cigarettes and NRT for smoking cessation has become pervasive, and there are concerns about their potential health implications, particularly during the perioperative period. Although vaping and NRT hold great promise for smoking cessation and their benefits in this regard are undeniable, the available data on the postsurgical effects of nicotine, a major component of e-cigarette and NRT, cannot be discounted. Vaping and NRT have been controversially linked to poor surgical outcomes owing to the presence of nicotine. Currently, it is impossible to distinguish smoking from vaping and NRT using nicotine/cotinine because e-cigarettes and NRT could contain comparable concentrations of nicotine, which makes the establishment of clinically useful cotinine cutoffs challenging. Although some surgeons are equivocal about NRT and vaping cessation during the perioperative period, it is acknowledged that the poor postsurgical wound healing associated with smoking is attributable to nicotine; e-cigarettes and NRT contain nicotine and, thus, are potentially harmful during the perioperative period. Furthermore, a cotinine cutoff of 10 ng/mL is frequently used for surgery qualification purposes, which is also the serum cotinine concentration used to distinguish smokers from nonsmokers. This cutoff seems reasonable as an acceptable cutoff for surgery qualification in e-cigarette and NRT users.

The perioperative period undoubtedly provides an opportunity to administer smoking-cessation intervention using NRT and e-cigarettes. As the search for more robust biomarkers that would disentangle smoking from vaping and NRT use continues, the onus is on the surgeons to weigh the benefits of NRT and e-cigarettes against their risks during the perioperative period.

Learning Objectives

After reading this article, the readers will be able to describe the health implications of vaping and nicotine replacement therapy (NRT), discuss the consequences of vaping and NRT during the perioperative period, and list the biomarkers of smoking, vaping, and NRT.

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Confounding CBD in Urine Drug Testing

By Gregory C. Janis

Detecting marijuana use is a component of tens of millions of urine drug screens performed annually for legal, employment, and medical reasons. Urine drug screens target a single carboxylated metabolite of the primary psychoactive component in marijuana, Δ^9-tetrahydrocannabinol (THC). THC is the best known and most studied cannabinoid, but it is just one of more than 100 structurally related cannabinoids found in marijuana and cannabis. Over the last few years the nonintoxicating cannabinoid —cannabidiol (CBD)—has gained popular interest and acceptance as a natural remedy for a seemingly endless variety of medical conditions. A resulting meteoric rise in the demand for CBD has been met by an exponential proliferation of commercially available CBD products. This is in addition to the medication Epidiolex®, which was recently approved by the Food and Drug Administration (FDA) for the treatment of certain rare epileptic conditions.

Legally, CBD exists in a precarious spot. Before the approval of Epidiolex, the Drug Enforcement Administration (DEA) classified CBD with all other cannabinoids (other than pharmaceutical Marinol®) as a Schedule I material with no legitimate use, akin to LSD and heroin. With the FDA approval of Epidiolex, the DEA classified Epidiolex and any future generic version of Epidiolex containing <0.1% THC as a Schedule V drug, along with other pharmaceuticals with limited abuse potential, such as cough syrups containing codeine. However, the reclassification of Epidiolex did not affect any other formulation or product containing CBD. From the perspective of the DEA, all nonpharmaceutical CBD preparations remain classified as Schedule I drugs with no legitimate medical use and a high potential for abuse.

With the approval of Epidiolex, the FDA can also claim regulatory oversight of CBD products because the FDA has clear governance over all drug products. As with any other substance, any health claims attributed to CBD must be substantiated by controlled clinical trials, and that data must be submitted and approved by the FDA. However, only data pertaining to Epidiolex have been submitted to the FDA. Unsubstantiated claims of the medical benefits of CBD products abound, and the FDA has exercised their enforcement rights against companies making these claims by issuing warning letters. Additionally, as an approved pharmaceutical agent, CBD may not legally be present in any food or supplements without specific approval from the FDA. The FDA also regulates all new food additives. From this perspective, the FDA finds insufficient scientific evidence to conclude that CBD is generally recognized as safe and, thus, cannot legally be considered a food additive. In response, a few municipalities throughout the US have pulled from store shelves any food or drinks containing CBD.

The FDA remains concerned about markers of liver injury associated with high CBD doses that were observed during clinical trials of Epidiolex. Additionally, drug–drug interactions involving CBD, as well as potential toxicity from chronic use,

remain uninvestigated areas of concern. Despite these concerns, the FDA has been exploring potential pathways for CBD products to be marketed lawfully.

The 2018 Farm Bill provided the mechanism for the recent unprecedented proliferation of CBD products. The Farm Bill legalized and legitimized the production of hemp and differentiated marijuana from hemp based upon the content of THC (or the prodrug 2-carboxy-THC). Cannabis with no more than 0.3% THC by dry weight is legally defined as hemp and, therefore, is legal to produce under the supervision of state-run hemp programs. Legally produced hemp is grown for a multitude of purposes, but it is also the starting material for the production of commercial CBD. The Farm Bill does not address questions of acceptable levels of THC in any hemp product or extracts other than the dried plant. However, whether it is appropriate, an acceptance limit of 0.3% THC has been popularly transferred and applied to all CBD products.

Unlike Epidiolex or medical/recreational marijuana products in state-administered programs, the majority of commercially available CBD products are sold without regulations on quality, purity, or contaminants. Consequentially, many CBD products contain some degree of THC contamination. It is commonly assumed that CBD products contain <0.3% THC, but measured THC levels may significantly exceed that limit. An analytical survey of commercial CBD products will find common contaminating THC levels anywhere from essentially zero to a few percent. Based upon our survey of CBD products, it appears generally that smokable hemp flowers contain higher levels of contaminating THC compared with more commercially refined products, such as vape oils, edible products, and packaged supplements.

Except in the most extreme cases, contaminating THC levels are typically still too low for a CBD user to experience any of the psychoactive effects of THC. Thus, the CBD user likely has no knowledge that they may be or are being exposed to THC. Long-term or high-dose use of CBD products contaminated with THC could potentially result in significant exposures to THC, which would be predicted to bioaccumulate owing to the highly lipophilic nature and long half-life of THC in the body. Additionally, as the half-life of THC appears dramatically longer than that of CBD, THC levels may continue to climb long after steady-state CBD levels have been achieved following repeated dosing.

The situation precipitates the question if real-life use of commercial CBD products could result in a positive drug test for marijuana either as a result of CBD itself or as a result of contaminating levels of THC in CBD products. Luckily, most of the evidence indicates that the presence of CBD in a urine sample will not appear positive in either properly executed screening assays or confirmation assays for 11-carboxy-THC if they are well designed and performed properly. Most manufacturers of immunoassays targeting 11-carboxy-THC have tested their kits for cross-reactivity against CBD. However, unmetabolized CBD would not be expected to be present in a urine sample. CBD appears to have a more variable metabolism than THC with glucuronide conjugates of CBD and conjugated carboxy and hydroxyl metabolites found in high concentrations in urine. Owing to a lack of available reference materials, cross-reactivity has historically not been investigated against these phase I or phase II metabolites of CBD. Despite the risk of inadvertently and unknowingly detecting CBD metabolites in a screen for 11-carboxy-THC, reactivity of most immunoassays to CBD metabolites appears small based on recent experiments with CBD metabolites and on studies with real samples from persons exposed only to CBD. Despite this, some risk remains. Antibody cross-reactivity to metabolites of cannabinoids other than CBD and THC, which are found in full-spectrum CBD products, still needs to be investigated, and at this point must be considered to potentially cross-react with antibodies against 11-carboxy-THC.

The risk to confirmatory tests targeting 11-carboxy-THC in the presence of CBD and metabolites is highly dependent on the methodology of the confirmation method. 7-Carboxy-CBD is the analogous metabolite to 11-carboxy-THC, and they are structural isomers of each other. The 2 isomers also have very similar fragmentation patterns. Thus, differentiating the 2 metabolites by mass spectrometric parameters without the aid of a preionization separation technique is risky even with MS/MS or high-resolution techniques. Chromatographic separation of 7-carboxy-CBD from 11-carboxy-THC is easily achieved with a well-designed method but should be checked to ensure clean chromatographic resolution. Analytical techniques using a derivatization can cleanly distinguish 7-carboxy-CBD from 11-carboxy-THC as a result of the one additional derivatization site located on the open ring of 7-carboxy-CBD. However, derivatization techniques add another significant risk. Highly acidic derivatization techniques such as ones using trifluoroacetic anhydride have been shown to cyclize the open ring in CBD to form THC (1). This reaction will result in the production of parent THC and 11-carboxy-THC from any 7-carboxy-CBD that could be present in the sample. Luckily, most laboratories have moved away from such harsh derivatization methods, thereby avoiding the potential for a highly problematic conversion that could result in a false-positive 11-carboxy-THC result.

The use of CBD products contaminated with THC poses a far more troubling challenge for drug testing. Typical THC contamination levels in CBD products are <1%. From a single dose of CBD, this

THC exposure is negligible. However, real-world patterns of CBD use do not reflect an acute use of 10 or 20 mg of CBD. Long-term use of hundreds of milligrams of CBD is common. As such, chronic CBD users may be exposing themselves to a daily dose of THC nearing a milligram. This amount is far too low for the user to perceive any of the psychotropic effects of THC, but with the long half-life of THC, steady-state levels of THC may take weeks to achieve. Once steady state is reached, the CBD user may unknowingly be excreting 11-carboxy-THC at concentrations sufficient to trigger a positive drug test. In our laboratory, we have measured urinary 11-carboxy-THC levels from donors personally known to be using commercial CBD products but abstaining from any known exposure to THC. The products consumed, dose, and length of use all varied between donors, but some donors reported taking CBD doses of hundreds of milligrams for approximately 6 months. More than 75% of these urine samples contained measurable levels of 11-carboxy-THC, ranging from 3.2 to 57.2 ng/mL. Thus, some samples exceeded the 11-carboxy-THC reporting limit for regulated testing (15 ng/mL), and most exceeded the lower reporting limits of 3 or 5 ng/mL used in more stringent tests. These samples illustrate the problem caused by THC within CBD products. A positive THC test in a CBD user inadvertently exposed to trace THC is not a false-positive result because the sample does contain marijuana biomarkers. However, the result is also misleadingly identifying the donor as a marijuana user when they are, in fact, not.

To resolve this conundrum, techniques are needed capable of discriminating marijuana and THC use from the use of CBD products containing trace amounts of THC. In the end, there will be more than one way to achieve this goal, but our laboratory is using a technique in which metabolites of both THC and CBD are measured and compared (2). In addition to measuring 11-carboxy-THC and THC, the assay also measures levels of 2 primary CBD metabolites: CBD from the glucuronide and 7-carboxy-CBD also from the glucuronide conjugate. In samples from users of CBD without other exposures to THC, measured CBD levels ranged from 5.7 to 113.4 ng/mL and levels of 7-carboxy CBD ranged from 1.8 to 116.8 ng/mL. In all samples from CBD users trusted to not be using marijuana, the sum of the 2 measured CBD metabolites exceeded measured 11-carboxy-THC levels by at least 10-fold. Conceptually, a technique of comparing metabolite levels is similar to one seen by Pacifici et al., in which blood levels of CBD were compared with circulating THC levels for users of "light" marijuana containing low levels of THC (3). In that study, users of light marijuana had circulating THC levels exceeding CBD levels by less than a factor of 2, yet the ratio exceeded a factor of 10 in users of illicit marijuana.

In summary, the combination of recent trends in CBD use, along with the proliferation of unregulated CBD products containing unknown, trace quantities of THC, presents a very difficult challenge for laboratory drug testing. The popular acceptance of CBD as a home remedy and not a drug of abuse forces laboratories to find mechanisms to ensure a positive result for 11-carboxy-THC on a urine drug test represents marijuana use. No laboratory solution to this problem is likely to be perfect because the detected 11-carboxy-THC is the direct result of THC exposure, even if the exposure is small and unintentional. The problem can only be truly solved by regulating CBD products to contain no detectible THC.

Learning Objectives

After reading this article, the reader will be able to explain why the use of CBD does not in itself affect urine drug testing results. The reader also will be able to explain why the use of impure CBD products containing trace amounts of THC can result in a positive urine drug test.

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Testing Urine for Drugs of Abuse during a Pandemic

By Tiffany N. Heady, PhD, Charla Gaddy, PhD, and Claudia Henemyre, PhD

Urine drug testing is widely applied for a variety of settings, including law enforcement, hiring, random testing in high-risk professions, healthcare,

Table 1. Transmission-based precautions (21)

Standard precautions (least stringent)	Contact precautions
Hand hygiene	Ensure appropriate patient[a] placement
Glove	Use PPE[b] appropriately
Facial protection	Limit transport and movement of patient[a]
Gown	Use disposable or dedicated patient[a] equipment
Respiratory hygiene and cough etiquette	Prioritize cleaning and disinfection of the rooms
Environmental cleaning	
Waste disposal	
Droplet precautions	**Airborne precautions (most stringent)**
Source control: put a mask on the patient	Source control: put a mask on the patient
Ensure appropriate patient[a] placement	Ensure appropriate patient[a] placement in an airborne infection isolation room
Use PPE appropriately	Restrict susceptible healthcare personnel from entering the room
Limit transport and movement of patient[a]	Use PPE appropriately
	Limit transport and movement of patients[a]

[a]For the purposes of this article, the patient can be likened to urine specimen.
[b]PPE, personal protective equipment.

the US military, professional sports, and addiction medicine and rehabilitation. Large laboratories may test thousands of urine specimens a day, but how safe is testing during the COVID-19 pandemic?

Coronaviruses are single-strand RNA viruses with crown-shaped spikes on their surface (1). There are 7 coronaviruses that can infect humans, one of which is SARS-CoV-2, the virus that causes COVID-19 (1). SARS-CoV-2 is most commonly spread by person-to-person interaction when respiratory droplets from an infected person come in contact with the mouth or nose of a nearby person or are inhaled into the lungs (2).

Urine drug testing requires 30 to 60 mL of urine for initial and confirmatory testing. Healthy kidneys excrete approximately 500 mL/day of urine as a clear, yellow liquid, pH 5 to 6, with a specific gravity between 1.005 and 1.030 (3). Urine is not sterile but contains bacteria and both eukaryotic and bacteriophage viruses (4-6). RT-PCR is typically used to identify viral RNA; however, it is unclear if viable SARS-CoV-2 virus is found in the urine of infected patients (7-19). A PubMed search for "SARS-CoV-2 virus in urine" returned 12 results for human study participants (7-18). One article reported detecting SARS-CoV-2 virus in the urine of 1 critically ill patient of 96 COVID-19-positive patients tested daily, while another reported that 1 of 9 COVID-19-positive patients had virus detected in the urine (12,18). Ten papers reported no detection of viral RNA in urine from COVID-19-positive patients (13-17). The largest study had no SARS-CoV-2 virus detected in 72 urine specimens from a cohort of 205 COVID-19-positive patients (16). Current reports suggest that the risk of contracting COVID-19 from urine is extremely low. Even though urine is not sterile, there is no evidence that the level of virus in urine is viable, or sufficient to result in transmission, particularly if appropriate precautions are in place.

Forensic urine specimens for drug testing are significantly different from clinical specimens because they are usually collected from visibly healthy individuals. Owing to the highly infectious nature of COVID-19, collectors should not collect from visibly sick individuals. The CDC general guidance for testing of clinical specimens that *may* contain potentially infectious material is adoption of standard precautions (20). Standard precautions include use of gloves, gown, mask, and eye protection (21). The CDC changed the term from universal to standard precautions in 1996 to include contact with all body fluids, not just blood (22). Given the population donating urine for forensic drug testing is usually not overtly sick and the low likelihood of contagious virus in urine, standard precautions are appropriate for forensic drug testing laboratories.

Whether laboratory procedures for processing urine during drug testing increase the risk of COVID-19 infection is a concern. The following laboratory

procedures were associated with the generation of infectious aerosols and droplets: centrifugation; pipetting; vortexing; mixing; shaking; sonicating; removing caps; decanting liquids; aliquoting and loading specimens; loading syringes; manipulating needles, syringes, or sharps; aspirating and transferring body fluids; spilling specimens; and cleaning up spills (23). Large urine drug testing laboratories aliquot thousands of specimens daily, perform initial screens on large automated immunoassay platforms, and physically and chemically manipulate urine specimens for confirmation by GC and LC-MS (24). What precautions lessen the risk associated with these laboratory procedures involving urine that *may* contain the SARS-CoV-2 virus?

Most importantly, laboratories should conduct a detailed risk assessment of their entire drug testing process to include shipping urine specimens and waste disposal (25-27). Standard precautions are assumed; therefore, residual risks not mitigated by standard precautions may be mitigated by using the appropriate precaution detailed in Table 1 (21). Risk assessments should be flexible and modified as new SARS-CoV-2 information is available. When new infectious agents emerge and little is initially known about them, laboratory leaders can consult the CDC Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings to decide what precautions may be appropriate for forensic and reference laboratories (28).

Drug testing is an essential workplace management tool in a variety of career fields. Laboratorians must stay abreast of evolving threats that could jeopardize the safety of forensic drug testing. At present, there is no evidence that the SARS-CoV-2 virus can be transmitted through urine, and the risk of contracting COVID-19 during urine drug testing appears low. Person-to-person transmission of COVID-19 may be the greatest risk to laboratory staff in drug testing laboratories. Practicing social distancing measures in the workplace, such as keeping employees 6 feet apart and adjusting schedules to minimize the number of employees on a given shift, may reduce the risk of person-to-person transmission and prove as important as adoption of appropriate precautionary measures (29).

Learning Objectives

After reading this article, the reader will be able to describe the routine laboratory risks of performing urine drug testing during a pandemic and how to mitigate these risks. The reader will also be able to identify the 4 levels of transmission-based precautions and identify relevant resources for the next pandemic.

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- Identify potential analytes (drugs, metabolites, biomarkers) of clinical and/or forensic significance.
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