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A Toxicology Primer

The Psychomotor Impairments of Drugs of Abuse and Alcohol and How They Contribute to Motor Vehicle Accidents

By Christopher Spaeth, Ph.D.

A thorough understanding of a toxicologist's role in assessing driver impairment will enable defense attorneys to use this expert resource wisely.

Driving is complicated, and principally involves balancing a number of different tasks and goals at the same time, while constantly calculating and recalculating the risk of each action. Nearly 89 percent of United States residents aged sixteen and older reported that they drove a motor vehicle at least occasionally in 2016. AAA Foundation for Traffic Safety, 2018. This same study found that U.S. drivers made 186 billion trips in their vehicles, spent 70 billion hours driving, and, in total, drove 2.62 trillion miles. The World Health Organization (WHO) reports about 1.35 million deaths per year due to motor vehicle accidents, with an additional 50 million people a year experiencing vehicular-related injuries. WHO, 2018. In the United States, nearly 40,000 motor vehicle accident-related deaths, nearly 7 million police-reported motor vehicle accidents, and up to 10 million unreported crashes occur each year. NHTSA, 2017. The total cost of these accidents is over $245 billion, or just over 1 percent of the U.S. gross domestic product. NHTSA, 2015.

■ Christopher Spaeth is a senior consultant at Rimkus Consulting Group, Inc., Division of Toxicology and Food Safety, in Houston, Texas. His casework involves forensic investigation of neuronal deficits caused by drugs or toxins, drug toxicology, and alleged injuries caused by consumer products, especially cosmetics. Dr. Spaeth's previous training includes investigating the basic functions of neurons; drug, toxin, or genetically induced neuronal alterations; and the toxicological safety and regulatory compliance of consumer ingredients.

Compounding the risk of driving, drivers can be operating under the influence of one or more mind-altering drugs at the time of an accident. In 2018, 20.5 million drivers admitted to driving under the influence of alcohol and an additional 12.6 million people admitted driving under the influence of illicit drugs, with marijuana accounting for 8 million of those drivers. SAMHSA, 2019. Approximately 20 percent of drivers who tested positive for drugs during moving violations had opioids in their systems. NHTSA, 2017. Since some drugs, such as marijuana, are not completely eliminated from an individual's body for days or weeks after use, evaluating acute or chronic impairment based on the levels that are present is very difficult without additional testing or evidence. Many drivers may have more than one drug in their systems, thus complicating the extent for the attribution of impairment from the presence of a drug, or multiple drugs, at the time of an accident. The following article discusses the role of a toxicologist in drugged driving, driving impairments, and accident risk caused by alcohol, marijuana, opioids, and stimulants. Finally, this article discusses the increased impairments and risk due to using multiple drugs.

Forensic Toxicology for Drugged Driving

A major challenge is determining culpability in motor vehicle accidents. Often, the people involved in the accident are unreliable historians due to the many physical and psychological factors at the time of the incident. Thus, a non-biased investigation by experts is needed to gain an objective and scientifically based understanding of the accident. When drugs are involved, experts in toxicology can provide a scientifically based rationale for the causal or relative role that the drug(s) may have played in augmenting the events leading up to, at the time of, and the eventual outcome from an accident.

A forensic toxicology expert evaluates toxicological data. From the perspective of a motor vehicle accident involving one or more drivers with drugs present in their systems, the toxicologist can assess the evidence for the identification of the drug(s) associated with the accident. They can then determine whether the drug was at a sufficient concentration to cause impairment for a given individual. When multiple drugs are present, novel chemical combinations might be formed that are more potent than either individual drug alone, leading to additive or synergistic effects.

A significant part of the evaluation by the toxicologist involves understanding how the drug was administered to an individual; how it distributes once in the body and whether it is modified to more or less toxic chemicals; the current science behind the physiological effects of a drug(s) once it gets to its site of action; and, ultimately, how and at what rate these chemicals or metabolites are eliminated from a given individual. This can change depending on age, gender, length of use of a given drug, or the presence of other concurrent medical or even environmental conditions.

A toxicologist can then assess how the drug interacts in the body, if it has a specific target molecule(s) in the body, and the impairment that happens when the drug interacts with the target. Based on this target interaction, the toxicologist can then assess any cellular dysfunction and how the affected cells repair themselves or adapt to the changes caused by the drug. One example of adaptation is addiction, wherein an individual must take progressively increasing amounts of a drug to achieve the euphoric effect, due to physical and chemical changes in the brain caused by the drug. Another consideration is how an individual can modify his or her behavior to hide typical behaviors associated with impairment. This commonly occurs with addiction, such as highly functioning alcoholics. After taking the available chemical, physiological, genetic, and other data accumulated about the individual, before, during, and after the accident, the toxicologist can assess the systemic impairment caused by that drug and determine whether the impairments from the drug could potentially be the primary cause of, or contribute to, the accident. Thus, the role of a forensic toxicology expert in drugged driving is to evaluate whether an individual took a recreational or prescription drug that altered the normal driving ability to an extent that it contributed to the accident, based on the mechanism of action of each drug or combination of drugs present at the time of the accident.

Alcohol and Driving

The most commonly abused drug that affects driving is alcohol. SAMHSA, 2019. The alcohol molecule acts differently than many drugs as it does not have a specific binding site in cells. Instead, it binds to many different sites in the body to produce an effect. As a small molecule, alcohol easily distributes throughout the entire body and strongly and non-specifically affects neurons in the brain to alter behavior. Garriot, 2015. Alcohol affects the most abundant chemical-signaling molecule in the brain, gamma amino-butyric acid (GABA), via binding the very abundant GABA receptors. Engin et al., 2018. GABA accounts for a majority of brain signaling and primarily inhibits other neurons from acting. For a neuronal impulse to lead to an action or a decision or movement, chemical signaling from other sources must overcome this inhibition. By affecting GABA signaling in the brain, alcohol can produce widespread and deleterious impairments (discussed below). Engin et al., 2018. To a lesser extent, alcohol also decreases the activity of n-methyl-D-aspartate (NMDA) receptor channels. Alteration of NMDA receptors contributes to the impairments caused by alcohol, particularly the sedative effects. *Id*.

Blood-alcohol concentration (BAC) measures the amount of alcohol consumed. Olivera et al., 2010. It requires a blood draw that must take place in a hospital or medical facility, sometimes hours after the event. Since alcohol is processed, or metabolized, by the body at a highly variable rate, but within a known range, a toxicologist can use this metabolism range to calculate an estimated BAC at a given time, such as the time of the accident. As a person drinks, the alcohol is first absorbed, which increases the BAC, and then is eliminated, which lowers the BAC. If BAC is known, a calculation called retrograde analysis can be performed, using a standard range of absorption and elimination rates, so that the BAC of an individual can be estimated within a range of confidence at the time of an accident or at the time a person was last served. Retrograde BAC analysis assumes that the BAC is falling at the time of the blood draw. If additional information is available, such as a history of how many drinks were consumed, drinking experience, or food consumed prior to, during, or after alcohol consumption, this estimation can be further refined.

Alcohol causes a dose-dependent decrease in driving ability, as measured by the BAC. Studies have shown impairment after intoxication with alcohol for many psychomotor and behavioral categories. These include impairments in reaction time, attention tasks, information processing, and visual function. Not surprisingly, serious impairments are observed in actual driving skills on the road or simulator following alcohol consumption. Garriott, 2015. Of these, the skill that shows the greatest potential for driving impairment in laboratory studies was divided attention performance, followed by visual tracking performance. *Id*. Since driving requires an individual to focus on at least four different tasks simultaneously and follow moving objects, an inability to perform multiple tasks and follow moving objects impairs driving.

THC/Marijuana

Marijuana is the most abused illicit drug in the U.S., based on federal law, with an estimated 45.2 percent of people over the age of twelve using at least once in their lifetime in 2018. SAMHSA, 2019. Notably, many states have changed their laws on marijuana; however, this law change does not reflect the impairments caused by marijuana. The primary psychoactive chemical in marijuana is tetra-hydro-cannabinol (THC). Marijuana contains hundreds of other chemicals, including cannabidiol (CBD) and other cannabinoid-like chemicals. THC exhibits a chemical structure that mimics the brain neurotransmitter anandamide and competes with anandamide for binding to cannabinoid receptors. Neurons that contain cannabinoid receptors exist throughout the entire body, including the brain. Research on the biological role of cannabinoid receptors has suggested that they play a role in pain response, appetite, and perception; however, much needs to be explored surrounding the effects that marijuana has on the human brain and other organ systems.

A urine test for marijuana use assays for a breakdown product or metabolite of THC that is excreted in the urine, 11-nor-delta9-tetrahydrocannabinol-9-carboxycilic acid, or Δ9-THC-COOH. When administered through smoking or eating, Δ9-THC-COOH can typically be detected in the urine for between four to seven days; however, chronic users could test positive for Δ9-THC-COOH in their urine for up to thirty days. Moeller et al., 2017. Thus, even though an individual tested positive for Δ9-THC-COOH in his or her urine, he or she may not have been under the acute effects of THC at the time of a given accident. Urine screening is performed using an enzyme-linked immunosorbent assay (ELISA), which directly measures the amount of Δ9-THC-COOH that binds to a protein indicator. Laboratory confirmation using blood requires a technique known as gas chromatography/mass spectroscopy (GC/MS) or liquid chromatography/mass spectrophotometry (LC/MS). *Id*.

Acute intoxication from marijuana has many impairing effects on the neurocogni-

tive system. Functions that are impaired by acute marijuana usage that would be used in operating a vehicle include visual tracking and divided attention, similar to alcohol. Other impairments related to driving include increased anxiety, euphoria, sensation of time slowing, decreased pain, paranoia, irritability, worsened short-term memory, poor attention, altered awareness of the passage of time, impaired judgment, decreased coordination and balance, and distorted spatial perception. Bosker et al., 2013. These impairments were still observed even after three weeks of abstinence from the drug, which also corresponds to the average time it takes for marijuana chemicals to leave the body in habitual smokers. *Id*. A long-term study evaluating cannabis use in a group of individuals starting at age eighteen found impairments in several functions that may be related to the operation of a motor vehicle, including visual information processing. These impairments often lasted even when the user quit using the drug, although not as severe as for an acute high. Meir et al., 2012. Taken together, these data support the growing body of scientific knowledge that indicates that chronic marijuana smokers have a baseline level of impairment that may impair their ability to operate a vehicle properly even when not acutely high. Bosker et al., 2013. Consistent with these described deficits, impaired drivers with THC in their blood were roughly twice as likely to be involved in a fatal motor vehicle accident than sober drivers. SAMHSA 2019; Capler et al., 2017.

Not all individuals with measurable THC or its metabolites in their system are impaired. Capler et al., 2017. Chronic users of THC exhibit tolerance, in that they might be less impaired by a dose of THC compared to someone who does not use THC as often. The effects of THC tolerance are difficult to measure and are highly variable, as exhibited in driving tests. *Id*.

Opiates

Opiates include both prescription pain relievers and illicit drugs that are all similar to morphine. Nestler, 1992. Opioid use is highly prevalent in the United States, as 191 million prescriptions for opioids were filled in 2017, which is a rate of 58.5 prescriptions filled per 100 people. CDC, 2018. Although decreasing, the Center for Disease Control (CDC) estimates that one in three people have an opioid prescription, suggesting that as many as one-third of drivers in the U.S. may be using opioids. CDC, 2018. Consistent with this massive flood of opioids, over 11 million people were estimated to misuse prescription opioid pain relievers, 886,000 reported use of illicit opioids, and 2.1 million Americans were estimated to have an opioid-use disorder. SAMHSA, 2019. Given the widespread use of prescription or illicit opioids, it is not surprising to find that many drivers are under the influence of opioids, with 19.7 percent of drugged drivers testing positive for opioids. CDC, 2017.

The opioid class of drugs acts to increase the release of the neurotransmitter dopamine and decrease the release of the neurotransmitter GABA. In the brain stem, extra dopamine release and decreased GABA release lead to pain-suppressing, or analgesic, effects. Listos et al., 2019; Nestler, 1992. These drugs also affect dopamine and GABA in other brain areas that regulate how we perceive the world around us and how we form memories. Nestler et al., 2004; 1992. Changing the chemistry of how we perceive the world around us leads to euphoria, and the impairments associated with these drugs often lead to long-term changes. By changing the chemistry of how we form memories, these drugs directly change the structure of the brain to create a physical addiction to the drug. *Id*. Although both prescription and recreational opioids exhibit the same mechanism in the brain, prescription drugs are designed to be carefully monitored to decrease the chances of serious impairments and addiction (although this does not always happen). Examples of prescription opioids include oxycontin, hydrocodone, tramadol, and vicodin. In contrast, recreational drugs, such as heroin, are self-administered or administered by untrained individuals and taken for the express purpose of creating euphoria, almost guaranteeing an addiction, especially over repeated uses. *Id*. Opioids can be detected in the urine for up to four days after use. Moeller et al., 2017. Pharmaceutical use of opioids will often not be detected in a urine drug screen by design, especially at lower prescriptions. Dowell et al., 2016. Impairments experienced by opioid users can exist even if opioids cannot be detected in a urine screen. Urine screens for opioids are termed "presumed positive," and additional testing evidence and/or laboratory testing is needed for confirmation, such as GC/MS or LC/MS of blood samples.

The impairments from opioids can be observed by physical changes in the brain. Tolomeo et al., 2017; 2016. Their principal mode of action is the impairment of executive function. Executive function is defined as all the activities required for goal-oriented behavior. These activities include working memory, impulse inhibition, logical reasoning, and flexible thinking. Listos et al., 2018; Ersche and Sahkian, 2007. Related to these effects, opioids decrease visuospatial memory, a specific aspect of remembering the location of recently observed objects. Tolomeo et al., 2019; Ersche and Sakharian, 2007; Ersche et al., 2006. Opioids also cause miosis, defined as "pinpoint pupils." Rollins et al., 2014. Normally functioning pupils adjust their size to account for the light in the environment, such that pupils become larger in dark situations to take in more light and smaller in bright conditions to block out extra light. Active opioid use prevents pupils from enlarging in dark situations, thereby, decreasing the ability to see objects properly. Opioid-dependent miosis is not affected by tolerance to opioids and would be present regardless of the duration of opioid dosing. Rollins et al., 2014. Miosis would also prevent someone from observing an object in a dark environment that pulled out of a bright environment. *Id*.

Given the nature and prevalence of deficits from opioid use, it is not surprising to observe an increased risk of motor vehicle accidents for opioid users, consistent with impairments in goal-oriented behavior, reflex response, and visual acuity. Deficits for drivers with opioids in their bloodstream can exist for nearly all levels of opioids investigated. Chihuri et al, 2019. From 1993 until 2016, the odds of a two-vehicle crash for drivers who tested positive for opioids were more than twice the odds for those who tested negative for opioids. *Id*. Based on the large number of accidents investigated by Chihuri and colleagues, the risk of an accident for drivers using prescription opioids was independent of demographical characteristics, driving history, and alcohol use. *Id*. Driving errors for drivers testing positive for opioids included: failure to keep in the proper lane, failure to yield the right of way, driving too fast for conditions, failure to obey traffic signs or other traffic control devices, and reckless operation of the vehicle. *Id*. Some individuals can safely drive with opioids in their system, and a positive screen or measurable opioids in a blood test do not strictly correlate to levels of impairment, particularly in the context of prescription opioids. Gilson et al., 2013.

Stimulants — Cocaine, Methamphetamine, Amphetamines

Drugs that act as stimulants to the brain include both the illicit drugs cocaine and methamphetamines, as well as amphetamines that are prescribed for medical conditions such as ADD/ADHD. In the brain, these drugs act to increase levels of the neurotransmitters dopamine, norepinephrine, and serotonin. Nestler et al., 2004. These neurotransmitters are associated with increased pleasure, satiety, and decreased anxiety. *Id*. Although use of cocaine has decreased in the U.S. since the 1980s, cocaine use still accounts for a significant fraction of illicit drug use, with an estimated 14.9 percent of people aged twelve and over reporting cocaine use in their lifetime, with an additional 3.5 percent using crack (smoked cocaine). SAMHSA, 2019.

Cocaine activates the release of the neurotransmitter dopamine, leading to euphoria. The half-life of cocaine in the body is typically between one to two hours, and thus, the duration of acute effects is typically short lived. Based on multiple research reports, however, long-term or chronic use of cocaine may also create impairments in individuals who are not acutely high. Screening for cocaine uses an ELISA assay similar to that described for THC, wherein specific metabolites of cocaine that are excreted in urine, such as benzoylecgonine or ecgonine, are measured at a cutoff level for positive or negative. Unmetabolized cocaine can also be detected within six hours of use. Huestis et al., 2007. Further and more specific quantification for cocaine or metabolites can occur via GC/MS or LC/MS of blood samples. Benzoylecgonine may be present in urine post-use for up to five days after use. Moeller et al., 2017.

Users of cocaine can exhibit several, pronounced psychomotor impairments important for driving, such as increased impulsive behavior, loss of emotional control, inconsistency in delayed gratification tasks, lack of interest in others' needs, and a preference for magical or irrational explanations to solve problems. Czermainski et al., 2019. High impulsiveness as a hallmark of cocaine use can be understood through the context of decreased inhibitory control. Czermainski et al., 2019; Hobkirk et al., 2019. Cocaine users exhibit impairments in inhibitory control, such as less flexible decision making and an inability to adapt their decision making as circumstances change. Czermainski et al., 2019. Cocaine users also consistently fail at the input aspect of inhibitory control, such as attentional selection, visual scanning, and dealing with irrelevant information. *Id*. Finally, cocaine users also fail in response inhibition or controlling themselves from acting (the output measure of inhibitory control). These failures in cocaine users may be maintained when the individual is not under the acute effects of the drug and have been correlated to specific structural changes in the user's brain. Hirsiger et al., 2019.

Methamphetamine use accounts for another significant fraction of illicit drug use in the U.S., with an estimated 5.4 percent of people aged twelve and over reporting using methamphetamine in their lifetime as of 2018. SAMHSA, 2019. Although methamphetamine also increases dopamine, just like cocaine, the increase in dopamine due to methamphetamine is much higher than observed for cocaine. The half-life of methamphetamine is twelve hours, and thus, the duration of acute effects is much longer than that of cocaine. Methamphetamine can be detected in urine for up to four days for most users and, potentially, longer for chronic users. Moeller et al., 2017. Urine testing for methamphetamine is the least specific testing for the drugs mentioned here. Although urine testing has improved, false positives for methamphetamine include commonly used over-the-counter drugs, such as pseudoephedrine (Sudafed), metformin, labetalol, phentermine, and buproprion (Wellbutrin). *Id*. In methamphetamine cases, it is especially important to understand whether the individual has a noted history of methamphetamine use, or a more definitive assay such as a GC/MS or LC/MS of blood must be used to confirm the drug is present.

The most pronounced impairments for methamphetamine users occurred in executive function tasks, such as object recognition, decision making, and adjusting to external circumstances as they change. Ballard et al., 2015. Users of methamphetamine could also show severe impairments in visuospatial and working memory. Luo et al., 2019; Farhadian et al., 2017; Ballard et al., 2015. Even for individuals not currently exhibiting acute euphoric effects of methamphetamine, they could still demonstrate impairments in executive function and object recognition. Berheim et al., 2015. Not all doses of methamphetamine impair driving, and similar to THC, urine screening or blood tests of methamphetamine do not correlate linearly to expected impairment, potentially due to the effects of tolerance. Ballard et al., 2015.

Multiple Drugs

Recent survey data estimates that a majority of drivers (63.2 percent) who test positive for drugs are under the influence of multiple drugs at the time of a motor vehicle accident. SAMHSA, 2019. Using multiple drugs creates novel euphoric experiences for users that are more powerful than single drugs alone. Nestler, 2004. Since each specific drug or drug family produces its own impairments, the impairments from multiple drugs would be worse than for a single drug. Sometimes, these effects can be additive or synergistic, such that the combined impairment is greater than what would occur if only one or the other was present alone.

One example is the combined use of alcohol and marijuana. The combination of these two drugs produces stronger euphoria and stronger impairment than either drug alone. Garriott, 2015; Downey et al., 2012. For example, mean reaction time during driving increased by 36 percent when drivers were under the influence of alcohol and marijuana as compared to alcohol alone. Harris et al., 2000. This same study found that low doses of alcohol (0.05

g alcohol/dL blood), when combined with marijuana, increased the effective BAC impairment to an equivalent of 0.14 g alcohol/dL blood. A separate study found significant impairments in "straddling the solid line," "straddling the barrier line," and "insufficient stopping clear space," when THC was consumed with alcohol. Downey et al., 2013. Interestingly, people who consumed both alcohol and marijuana had higher concentrations of THC in the blood, suggesting people increase THC consumption while drinking alcohol and an additive pleasurable effect of the two drugs in combination. *Id.*

Another example is cocaine and alcohol. Data from a ten-year study indicates that almost three-fourths of drivers who tested positive for cocaine were also under the influence of alcohol. Wilson et al., 2014. The combined use of cocaine and alcohol results in several physiological effects that would increase impairment in a driver. Garriott, 2015; Althobaiti and Sari, 2016. One effect is that the combination of these two drugs can result in the production of a unique metabolite, cocaethylene, that acts similarly to cocaine in its pharmacological properties, but stays in the system for much longer than cocaine. Althobaiti and Sari, 2016. Second, concurrent alcohol reduces the metabolic rate of cocaine clearance and increases the concentration of cocaine in the plasma by as much as 15 percent, resulting in a higher concentration of the drug available to cause impairing effects on an individual. *Id.* There is also a reported heightened sense of pleasure and euphoria when users combine these substances as compared to individual use of these substances, thus, increasing the chances of additional use of both drugs together. *Id.*

Summary

Driving is a complicated skill that requires experience and full cognitive abilities for the consistent successful completion of at least four different tasks at the same time. Other activities while driving include proper goal-oriented behavior, understanding and remembering multiple moving visual cues, and deciding which information is important and which information is not. By taking drugs, an individual increases the chance of failure of any or all of the steps necessary to operate a motor vehicle safely and properly. Toxicology experts can provide the expertise for evaluation of cases involving motor vehicle accidents and drugs. Each type of drug consumed has different properties, and an understanding of the various changes in an individual's ability to function is critical to understanding culpability for motor vehicle accidents.

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