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Fiona Couper, Ph.D., Marilyn Huestis, Ph.D., Jennifer Fulford, Nicole Perkinson, Sheryl Miller, Ph.D., Paula Raymond, Alan Katz, Jennifer Symoun, DeReece Smither, Ph.D., and Amy Berning	

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16. Abstract

A continual concern in the United States and throughout the world is driving after the use of psychoactive substances. At issue are methods for identifying drug-impaired drivers on the road, assessment, and documentation of the impairment they display, availability of appropriate chemical tests, and interpretation of results. NHTSA's *Drugs and Human Performance Fact Sheets: 2024* are based on the latest scientific research and provide practical guidance for evaluating and understanding drug-impaired driving cases. The information is targeted at drug recognition experts and other law enforcement officers, attorneys, judges, and toxicologists. The fact sheets will also benefit those in research, public health, advocacy, and driver education fields. An expert panel provided invaluable insight to the development of this report.

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Glossary

addiction – Habitual, psychological, and physiological dependence on a substance beyond one's voluntary control.

additive effect – One mechanism of polydrug interaction. For a particular indicator of impairment, two drugs produce an additive effect if they both affect the indicator in the same way. For example, cocaine elevates pulse rate and PCP also elevates pulse rate. The combination of Cocaine and PCP produces an additive effect on pulse rate.

adverse reaction – Toxic physical or (less commonly) psychological reaction to a therapeutic agent. In the context of substance abuse, the term includes unpleasant psychological or physical reactions to taking a drug.

agonist – Substance that acts as a neural receptor to produce effects like those of the reference drug.

agoraphobia – Fear of places and situations that might cause panic, helplessness, or embarrassment.

akathisia – State of agitation, distress, and restlessness.

alcohol – In this report, the use of alcohol refers to ethanol.

analgesic – Drug that relieves or allays pain.

analog (of a drug) – Chemical that is very like the drug, both in terms of molecular structure and in terms of psychoactive effects. For example, the drug ketamine is an analog of PCP.

anemia – Lack of enough healthy red blood cells to carry oxygen throughout the body.

anesthetic – Drug that produces a general or local insensibility to pain and other sensation.

antagonistic effect (antagonist) – One mechanism of polydrug interaction. For a particular indicator of impairment, two drugs produce an antagonistic effect if they affect the indicator in opposite ways. For example, Heroin constricts pupils while cocaine dilates pupils. The combination of Heroin and Cocaine produces an antagonistic effect on pupil size. Depending on how much of each drug was taken, and on when they were taken, the suspect's pupils could be constricted, or dilated, or within the DRE Average range of pupil size.

anterograde amnesia – Loss of the ability to create new memories leading to the inability to recall the recent past.

antidepressant – One of a group of psychoactive agents prescribed for the treatment of depressive disorders; also used for certain other conditions such as panic disorder.

appetite suppressant – Agent used to reduce hunger and diminish food intake in the treatment of obesity.

asthenia – Physical weakness or lack of energy.

ataxia – Impaired balance or coordination.

barbiturate – CNS depressants that chemically are substituted derivatives of barbituric acid; examples are pentobarbital, phenobarbital, and secobarbital. They are used as antiepileptics, anesthetics, sedatives, and hypnotics.

bioavailability – Proportion of a drug which enters the circulation when introduced into the body and so can have an active effect.

biotransformation – Process by which the drug is chemically converted in the body to a metabolite. Biotransformation is usually an enzymatic process. A few drugs may also be changed chemically by a nonenzymatic process (e.g., ester hydrolysis). The enzymes involved in the biotransformation of drugs are located mainly in the liver. Other tissues such as kidney, lung, small intestine, and skin also contain biotransformation enzymes. Also called drug metabolism.

blood alcohol concentration (BAC) -- The amount of alcohol (ethyl alcohol or ethanol) in a person's blood stream. BAC is expressed in units of g/dL or mg/dL.

blood pressure – Force exerted by blood on the walls of the arteries. Blood pressure changes continuously, as the heart cycles between contraction and expansion.

body temperature – In humans this average temperature is estimated at around 98.6°F, although this can vary depending on time of day, and can fluctuate by person. The generally accepted range is 97° to 99°; anything over 100.4° is considered to indicate fever.

breath alcohol concentration (BrAC) – Amount of alcohol (ethyl alcohol or ethanol) measured in a person's breath. BrAC is expressed in units of g/210L.

cannabis – Drug category that includes marijuana. Marijuana comes primarily from the leaves of certain species of cannabis plants that grow readily all over the temperate zones of the earth. Hashish is another drug in this category and consists of the compressed leaves from female cannabis plants. The primary psychoactive ingredient in both marijuana and hashish is a chemical called delta-9 tetrahydrocannabinol, abbreviated THC.

carboxy THC – Metabolite of THC (tetrahydrocannabinol).

central nervous system (CNS) – System within the body consisting of the brain, the brain stem, and the spinal cord.

CNS depressants – One of the seven Drug Evaluation and Classification (DEC) program drug categories. CNS depressants include ethanol, barbiturates, anti-anxiety tranquilizers, and other drugs.

CNS stimulants – One of the seven DEC program drug categories. CNS stimulants include cocaine, the amphetamines, Ritalin, Desoxyn, and other drugs.

compulsion (compulsive) – Powerful urge – attributed to internal feeling rather than external influences – in this context to take a substance. These feelings are less characteristic of alcohol or drug dependence, than of the psychiatric syndrome of obsessive-compulsive disorder.

controlled substance – Drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of part B of the Controlled Substances Act and regulated by the Drug Enforcement Administration (DEA).

convergence – "Crossing" of the eyes that occurs when a person can focus on a stimulus as it is pushed slowly toward the bridge of their nose (see, also, "lack of convergence").

cross-tolerance – Development of tolerance to a substance, to which the individual has not previously been exposed, because of acute or chronic intake of another substance.

dependence – When the body adapts to a drug, requiring more of it to achieve a certain effect (tolerance) and eliciting drug-specific physical or mental symptoms if drug use is abruptly ceased (withdrawal). Physical dependence can happen with the chronic use of many drugs—including many prescription drugs, even if taken as instructed. Thus, physical dependence in and of itself does not constitute addiction, but it often accompanies addiction.

delusion – Belief held with absolute conviction, despite compelling evidence to the contrary.

depersonalization – Anomaly of self-awareness consisting of a feeling of watching oneself act without having control over a situation.

depressant – Any agent that suppresses, inhibits, or decreases some aspects of CNS activity.

designer drug – Novel chemical substance with psychoactive properties, synthesized specifically for the sale on the illicit market and to circumvent regulations on controlled substances.

diacetyl morphine – Chemical name for heroin.

dissociation – Mild to strong feelings of detachment from physical and emotional experience.

dissociative anesthetics – One of the seven DEC program drug categories. Dissociative anesthetics include drugs that inhibit pain by cutting off or disassociating the brain's perception of pain. PCP and its analogs are considered Dissociative Anesthetics.

divided attention – Concentrating on more than one thing at a time. The four psychophysical tests used by DRE s require the suspect to divide their attention.

downside effect – Effect that may occur when the body reacts to the presence of a drug by producing hormones or neurotransmitters to counteract the effects of the drug consumed.

driving – Operating a motor vehicle on a public road and does not include operating a motor vehicle when the vehicle has pulled over to the side of, or off, an active roadway and has stopped in a location where it can safely remain stationary.

drug – Any substance that, when taken into the human body, can impair the ability of the person to operate a vehicle safely.

drug recognition expert (DRE) – Person who successfully completed all phases of the DRE training requirements for certification established by the International Association of Chiefs of Police (IACP) and NHTSA. The words “evaluator,” “technician,” or similar words may be used as a substitute for “expert,” depending upon locale or jurisdiction.

dysphoria – Profound state of unease, malaise, or dissatisfaction.

elimination – Irreversible removal of drug from the body by all routes. The declining plasma drug concentration observed after systemic drug absorption shows that the drug is being eliminated from the body but does not indicate which elimination processes are involved. Drug elimination is usually divided into two major components: excretion and biotransformation.

ethanol – Often referred to as alcohol but is one type of alcohol. Produced by the natural fermentation of sugars. This is made for human consumption and is a colorless, volatile, flammable liquid with a characteristic odor and pungent taste.

excretion – Removal of the intact drug. Nonvolatile drugs are excreted mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately

into the urine. Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids. Volatile drugs such as gaseous anesthetics, alcohol, or drugs with high volatility, are excreted via the lungs into expired air.

GABA – Gamma-aminobutyric acid, sometimes spelled as gamma (γ)-aminobutyric acid or γ-aminobutyric acid in many of the journal reference citations. The principal inhibitory neurotransmitter in the CNS.ΔΔ

gait ataxia – Unsteady, staggering gait (walk) in which walking is uncoordinated and appears to be "not ordered."

Δ and γ – Greek capital and lowercase letters for "gamma," used in some chemical terms in this report.

general indicator – Behavior or observations of the subject that are observed and not tested for specifically tested (observational and behavioral indicators).

half-life – Time it takes for the concentration of the drug in the plasma or the total amount in the body to be reduced by 50 percent.

hallucinogens – One of the seven DEC program drug categories. Hallucinogens are drugs that induce alterations in perception, thinking, and feeling. Hallucinogens include LSD, MDMA, peyote, psilocybin, and other drugs.

hash oil – Sometimes referred to as "marijuana oil," it is a highly concentrated, syrup-like oil extracted from marijuana. It is normally produced by soaking marijuana in a container of solvent, such as acetone or ethanol for several hours and after the solvent has evaporated a thick syrup-like oil is produced with a high THC content.

hashish – Form of cannabis made from the dried and pressed resin of a marijuana plant. Usually smoked but sometimes added to food and eaten.

heroin – Powerful and widely abused narcotic analgesic that is chemically derived from morphine. The chemical name of heroin is "diacetyl morphine."

Homeostasis – Dynamic balance or steady state, involving levels of salts, water, sugars, and other material in body fluids.

horizontal gaze nystagmus (HGN) – Involuntary jerking of the eyes occurring as the eyes gaze to the side.

hydroxy THC – Metabolite of THC.

"Ice" – Crystalline form of methamphetamine that produces a very intense and long-lasting "high."

illicit – Substance for which the production, sale, or use is prohibited. Outside of legal channels.

impairment – One of several items describing degradation of mental and/or physical abilities necessary for safely operating a vehicle.

inhalants – One of the seven DEC program drug categories. Inhalants include volatile solvents (such as glue and gasoline), aerosols (such as hair spray and insecticides) and anesthetic gases (such as nitrous oxide).

insufflation – One method of ingesting certain drugs, also known as "snorting." Insufflation requires that the drug be in powdered form. The user rapidly draws the drug up into the nostril, usually via a paper or glass tube.

intoxication – Condition that follows the administration of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgement, affect, or behavior, or other psychophysiological functions and responses.

lack of convergence (LOC) – Inability of a person's eyes to converge, or "cross" as the person attempts to focus on a stimulus as it is pushed slowly toward the bridge of the nose.

lethargy – Lack of energy and enthusiasm; drowsiness and aversion to activity.

licit – Drug legally available by medical prescription in a jurisdiction, or sometimes, a drug legally available without prescription (over the counter, OTC).

major indicators – Physiological signs specifically assessed and are, for the most part, involuntary reflecting the status of the CNS homeostasis (physiological indicators).

marijuana – Common term for the *Cannabis sativa* plant. Usually refers to the dried leaves of the plant. This is the most common form of the cannabis category.

Marinol – Brand name of dronabinol, a drug containing a synthetic form of THC. Marinol belongs to the cannabis category of drugs, but Marinol is not produced from any species of cannabis plant.

medical impairment – Opinion made by a DRE based on evaluation that the state of a suspected impaired driver is more likely related to a medical impairment that has affected the subject's ability to operate a vehicle safely.

medical use – Food and Drug Administration (FDA)-approved use of a substance to treat, prevent, or cure a medical disease or illness.

metabolism – Combined chemical and physical processes that take place in the body involving the distribution of nutrients and resulting in growth, energy production, elimination of wastes, and other body functions. There are two basic phases of metabolism: anabolism, the constructive phase during which molecules resulting from the digestive process are built up into complex compounds that form the tissues and organs of the body; and catabolism, the "destructive" phase during which larger molecules are broken down into simpler substances with the release of energy.

metabolite – Chemical product formed by reaction of a drug with oxygen or other substances in the body.

narcotic analgesics – One of the seven DEC program drug categories. Narcotic analgesics include opium, natural alkaloids of opium (such as morphine, codeine and thebaine), derivatives of opium (such as heroin, Dilaudid, oxycodone and Percodan), and the synthetic narcotics.

neurotransmitter – Chemicals that pass from the axon of one nerve cell to the dendrite of the next cell, and that carry messages across the gap between the two nerve cells.

non-medical use – Use of a prescription drug, whether obtained by a prescription or otherwise, other than the manner or for the time period prescribed, or by a person for whom the drug was not prescribed.

null effect – One mechanism of polydrug interaction. For a particular indicator of impairment, two drugs produce a null effect if neither affects that indicator. For example, PCP does not affect pupil size, and ethanol does not affect pupil size. The combination of PCP and ethanol produces a null effect on pupil size.

nystagmus – Involuntary jerking of the eyes.

obtunded – Having diminished arousal and awareness; mentally clouded or dulled.

"on the nod" – Semi-conscious state of deep relaxation. Typically induced by impairment due to Heroin or other narcotic analgesics. The suspect's eyelids droop, and chin rests on the chest. Suspect may appear to be asleep but can be easily aroused and will respond to questions.

opiate – One of a group of alkaloids derived from the opium poppy with the ability to induce analgesia, euphoria, and in higher doses, stupor, coma, and respiratory depression. See also opioids.

opioid – General term applied to alkaloids from the opium poppy, their synthetic analogues, and compounds synthesized in the body, which interact with the same specific receptors in the brain, have the capability to relieve pain, and produce a sense of euphoria.

overdose – Use of any drug in an amount that acute adverse physical or mental effects are produced. Overdose may produce transient or lasting effects, or death; the lethal dose of a particular drug varies with the person and circumstances.

overlapping effect – One mechanism of polydrug interaction. For a particular indicator of impairment, two drugs produce an overlapping effect if one of them affects the indicator, but the other doesn't. For example, cocaine dilates pupils while ethanol doesn't affect pupil size. The combination of cocaine and ethanol produces an overlapping effect on pupil size: the combination will cause the pupils to dilate.

paradoxical – Effect of a chemical substance opposite to the effect which would normally be expected. An example of a paradoxical reaction is pain caused by a pain relief medication.

parasympathomimetic drugs – Drugs that mimic neurotransmitter associated with the parasympathetic nerves, artificially causing the transmission of messages that produce lower blood pressure, drowsiness, etc.

parenteral – Taken into the body or administered in a manner other than through the digestive tract, as by intravenous or intramuscular injection.

paresthesia – Burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body. “Pins and needles.”

peripheral – Situated away from the center, as opposed to centrally located.

peripheral (vision) – Type of vision that allows one to see objects that are not in the center of one's visual field.

pharmacodynamics – Branch of pharmacology concerned with the effects of drugs and the mechanism of their action.

pharmacokinetics – Branch of pharmacology concerned with the movement of drugs within the body.

pharmacology (pharmacological) – Branch of medicine concerned with the uses, effects, and modes of action of drugs.

phencyclidine – Contraction of phenyl cyclohexyl piperidine, or PCP. Formerly used as a surgical anesthetic, however, it has no current approved medical use in humans.

phenyl cyclohexyl piperidine (PCP) – Often called "phencyclidine" or "PCP," it is a specific drug belonging to the dissociative anesthetics category.

Physiology/physiological – Branch of biology that deals with functions and activities of life or living matter and physical and chemical phenomena involved. Physiological drug tolerance is when your body needs more of the drug to respond to the drug. This occurs due either to the body becoming less sensitive to the drug or because less of the drug reaches the designated target site.

pKa – Acid dissociation constant; quantitative measure of strength of an acid in solution.

pKb – Base dissociation constant; quantitative measure of strength of a base in solution.

polycategory use – Ingesting drugs from two or more drug categories.

polydrug use – Ingesting two or more different drugs.

potency – Measure of drug activity expressed in terms of the amount required to produce an effect of given intensity.

psychedelic – Psychoactive drug whose primary action is to alter cognition and perception.

psychoactive (drug) – Chemical substance that acts primarily upon the central nervous system where it alters brain function, resulting in temporary changes in perception, mood, consciousness, and behavior.

psychological – Affecting or arising in the mind; related to the mental and emotional state of a person. Psychological dependence is a state that involves emotional–motivational withdrawal symptoms, for example, anxiety and anhedonia, upon cessation of drug use or certain behaviors.

psychophysical tests – Methods of investigating the mental (psycho-) and physical characteristics of a person suspected of ethanol or drug impairment. Most psychophysical tests employ the concept of divided attention to assess a suspect's impairment.

ptosis – Droopy eyelids.

pulse – Rhythmic dilation and relaxation of an artery that results from the beating of the heart.

pulse rate – Number of expansions of an artery per minute.

pupil size – Diameter of the black circle in the center of the eye.

purity – Relative absence of extraneous matter in a drug that may or may not be harmful to the recipient or deleterious to the product.

pyrexia – Fever.

racemic/racemic mixture – Mixture of equal amounts of both enantiomers[1] of a chiral drug.

[1] Enantiomers are pairs of compounds with the same structure but opposite 3-dimensional shapes (i.e., mirror images, sometimes called “left-handedness” and “right-handedness” of molecules).

rebound dilation – Period of pupillary constriction followed by a period of pupillary dilation where the pupil steadily increases in size and does not return to its original constricted size.

recreational use – Use of a drug, usually illicit, in sociable or relaxing circumstances, but implication without dependence or other problems.

resting nystagmus – Jerking of the eyes as they look straight ahead.

sedative – Group of CNS depressants capable of relieving anxiety and inducing calmness and sleep.

sinsemilla – Unpollinated female *Cannabis* plant, with a relatively high concentration of THC. The word comes from the Spanish, "sin Semilla," without seeds.

snorting (see insufflation) – One method of ingesting certain drugs. Snorting requires the drug be in powdered form. The user rapidly draws the drug up into the nostril, usually via a paper or glass tube. Also known as insufflation.

"speedball" – Combination of a stimulant and an opioid.

standard deviation of lateral position (SDLP) test – Index of weaving while driving.

standardized field sobriety testing (SFST) – Standard test battery used by law enforcement during traffic stops to detect alcohol impairment. There are three SFSTs, horizontal gaze nystagmus (HGN), walk-and-turn (WAT), and one-leg stand (OLS). Based on a series of controlled laboratory studies, scientifically validated clues of impairment have been identified for each test. They are the only standardized field sobriety tests for which validated clues have been identified.

stimulant – Agent that activates, enhances, or increases neural CNS activity.

sympathomimetic drugs – Drugs that mimic the neurotransmitter associated with the sympathetic nerves, artificially causing transmission of messages that produce elevated blood pressure, dilated pupils, etc.

synapse (or synaptic gap) – Gap or space between two neurons (nerve cells).

synesthesia – Sensory perception disorder, in which an input via one sense is perceived by the brain as an input via another sense. An example of this would be a person "hearing" a phone ring and "seeing" the sound as a flash of light. Synesthesia sometimes occurs with people under the influence of hallucinogens.

tetrahydrocannabinol (THC) – Principal psychoactive ingredient in drugs belonging to the cannabis category.

tolerance – Adjustment of the drug user's body and brain to the repeated presence of a drug. As tolerance develops, the user experiences diminishing psychoactive effects from the same dose of the drug. As a result, the user typically will steadily increase the dose to achieve the same psychoactive effect.

vertical gaze nystagmus (VGN) – Involuntary jerking of the eyes (up-and-down) which occurs as the eyes are held at maximum elevation. The jerking should be distinct and sustained.

vertigo – Sensation of feeling off balance. If you have these dizzy spells, you might feel like you are spinning or that the world around you is spinning.

withdrawal – Occurs in someone who is physically addicted to a drug when the person is deprived of the drug. If the craving is sufficiently intense, the person may become extremely agitated, and even physically ill.

Acronyms and Abbreviations

ADH	alcohol dehydrogenases
ADHD	attention deficit hyperactivity disorder
C_{max}	maximum concentration
CBC	cannabichromene
CBD	cannabidiol
CBG	cannabigerol
CBN	cannabinol
CTI	clinical test for impairment
DEC(P)	Drug Evaluation and Classification (Program)
DFE	difluoroethane
DUI	driving under the influence
DUID	driving under the influence of drugs
EDDP	2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine
ELISA	enzyme-linked immunosorbent assay
EMDP	2-ethyl-5-methyl-3,3- diphenyl-1-pyrroline
FTN	finger to nose
GBL	gamma (γ)-butyrolactone
GDP	guanosine diphosphate
GHB	gamma (γ)-hydroxybutyrate
GTP	guanosine triphosphate
HCI	hydrochloride
HHA	3,4-dihydroxy derivatives
HHMA	3,4-dihydroxy methamphetamine
HMA	3- hydroxy-4-methoxyamphetamine
LC-MS/MS	liquid chromatography tandem mass spectrometry
LSD	lysergic acid diethylamide
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MAOIs	monoamine oxidase inhibitors
mCPP	meta-chlorophenylpiperazine
MDA	methylenedioxyamphetamine
MDMA	methylenedioxymethamphetamine
MRB	modified Romberg balance
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIOSH	National Institute for Occupational Safety and Health
NMDA	n-methyl-d-aspartate
NSO	novel synthetic opioids
OF	oral fluid
OLS	one-leg stand, a test that is part of the SFST
OSHA	Occupational Health and Safety Administration
PCC	piperidinocyclohexanecarbonitrile
PCE	phenylcyclohexamine (N-ethyl-1-phenyl-cyclohexanamine, an analog of PCP)
PCPP	phenylcyclopentylpiperidine
PHP	phenylcyclohexylpyrrolidine

PMA	paramethoxyamphetamine
RMS	root mean square
SDLP	standard deviation of lateral position
SDVS	standard deviation of vehicle speed
SFST	Standardized Field Sobriety Test
TCP	thienylcyclohexylpiperidine
THC-COOH	11-nor-9-carboxy-Δ^9-tetrahydrocannabinol
THCV	Δ^9-tetrahydrocannabivarin
T_{last}	In a research study, the time the drug was detected
T_{max}	time of maximum concentration

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Introduction

A continual concern to law enforcement officers, physicians, attorneys, forensic toxicologists, and traffic safety professionals in the United States and throughout the world is driving after the use of psychoactive drugs. At issue are methods for identifying impaired drivers on the road, assessment, and documentation of the impairment they display, availability of appropriate chemical tests, and interpretation of results. The National Highway Traffic Safety Administration's *Drugs and Human Performance Fact Sheets* are based on scientific research and provide practical guidance for evaluating and understanding drug-impaired-driving cases.

Target Audience

The fact sheets are intended primarily for use by drug recognition experts and other law enforcement officers, attorneys, judges, and toxicologists. However, the fact sheets may also be of interest to people in the research, public health, advocacy, and driver education fields. This Introduction provides information about the topics in the fact sheets with the goal of making them accessible to all readers.[1]

Background

NHTSA published the first edition of the *Drugs and Human Performance Fact Sheets* in 2004 (Couper & Logan, 2004). These fact sheets were based on the deliberations of the International Consultative Panel on Drugs and Driving Impairment, held in Seattle, Washington, in August 2000. NHTSA sponsored the meeting that included the National Safety Council, Committee on Alcohol and other Drugs, and the State of Washington Traffic Safety Commission. Delegates represented the fields of psychopharmacology, behavioral psychology, drug chemistry, forensic toxicology and medicine, and law enforcement experts trained in the recognition of drug effects on drivers in the field.

These updated fact sheets include scientific knowledge about the most frequently used drugs found in drug-impaired driving cases. An expert panel of forensic toxicologists, DRE s, and traffic safety resource prosecutors provided input to these updated fact sheets.

The expert panel helped identify which drugs to include (based on the drugs most commonly used in the United States and frequently found in impaired-driving toxicology results). It also provided suggestions on how to organize the fact sheets, so they were most useful to the target

[1] For more information on NHTSA's efforts related to alcohol-impaired driving, see the Advance Notice of Proposed Rulemaking (ANPRM). The Infrastructure Investment and Jobs Act (Bipartisan Infrastructure Law or BIL) directed NHTSA to issue a final rule establishing a Federal Motor Vehicle Safety Standard (FMVSS) requiring new passenger vehicles to have ''Advanced Impaired Driving Prevention Technology'' by 2024. The BIL also provided that an FMVSS should be issued only if it meets the requirements of the National Traffic and Motor Vehicle Safety Act (''Safety Act''). BIL defines the relevant technology as technology that can passively and accurately monitor driver performance to detect impairment or passively and accurately measure driver blood alcohol concentration (or both in combination) and prevent or limit vehicle operation if impairment is detected. In the ANPRM, NHTSA requested comments from the public on this topic. Comments were due March 5, 2024. Federal Register, January 5, 2024, Vol 80, No. 4. https://www.govinfo.gov/content/pkg/FR-2024-01-05/pdf/2023-27665.pdf

audience. These fact sheets include 33 drugs and four commonly found combinations of drugs, covering controlled and some non-controlled substances. While this revised publication includes some updated drug information to the original fact sheets, the focus was to include additional drugs and common drug combinations. There are also supplementary sections such as the interpretation of oral fluid test results. It is worth noting that the degree of information across the fact sheets varies, as the amount and strength of research across the drugs varies.

Summary of Research Study Designs

These updated fact sheets use behavioral research designs identifying drug effects on the body. These designs are systematic approaches studying human behavior and its underlying causes. It is important to note that each design has its own strengths and limitations, and the choice of design depends on the research question, resources, and ethical considerations involved. Therefore, it is difficult for one study on a topic to be the sole support for a theory, uphold a hypothesis, or make a causal claim. Quantitative studies tend to be more objectively and numerically focused on, for example, attempting to quantify how often some phenomenon happens, how much of a behavior is required for an effect to happen (or stop happening), how many people behave or think a certain way, etc. Qualitative research studies also play a role in behavioral research, but attempt to explore *why* the phenomena occurs, especially in the context in which it occurs. Qualitative studies tend to be more in-depth studies of fewer participants. The table below lists designs summaries along with limitations and examples of studies in this document. Following the table is a summary of several types of research studies commonly used in behavioral research.

Table 1. Research design summary

Design	**Description**	**Limitations**	**Example study (see p. #)**
Experimental Studies (Laboratory and Field Studies)	• Examines cause-effect relationships • High control over variables (independent variable [IV] and dependent variable [DV]) • Can be replicated • Can employ random selection and random assignment	• Generalizability can be limited • Can be costly • Time-consuming • Field studies have more external validity, but may not have the same degree of control	See the *Laboratory Studies* sections of the drug fact sheets Ex: Alprazolam: Scavone et al., 1992, p. 33
Drug Studies	• A specific type of experimental study to test legal and illegal drugs • Employ rigorous experimental methods, including randomized controlled trials • Essential for evaluating the safety and efficacy of drugs	• Random selection is not always likely or possible • Ethical considerations of drug dosing, including harm to participants, • Time-consuming • Resource intensive	Drug studies are cited throughout the drug fact sheets document.

Design	Description	Limitations	Example study (see p. #)
		• Very few studies address a drug's impact on driving performance	
Driving Simulator Studies	• Employ experimental designs • Precise control over variables, conditions • Safe environment for measurement (esp. for risky scenarios) • Replicability • Allows for the collection of a detailed, objective data	• Artificiality of the environments • Decreased generalizability • Learning effects • Technical limits	See the *Simulated Driving Studies* and *Over-the-Road Driving Studies* sections of the drug fact sheets Ex: Cannabinoids: Hartman et al., 2015b, p. 78 Fentanyl: Chung et al., 2005, p. 196
Quasi-Experimental Studies (e.g., case-control, natural experiments, epidemiological studies)	• Allows for manipulation of some naturally occurring characteristics; traits, phenomena, etc.	• Lacks control and precision of experimental designs • Determining causality may be difficult, limited • Lacks random assignment	See the *Epidemiological Studies* sections of the drug fact sheets Ex: Lysergic Acid Diethylamide (LSD): Tomaszewski et al., 1996, p. 160
Correlational Studies	• Examines the strength and direction of relationships between variables • Useful for initial investigations • Helps to understand naturally occurring phenomena or relationships	• Correlation does not equal causation • Other (observed or unobserved) variables may influence the relationship	See an example in the *Cannabis* chapter: Luo et al., 2019, p. 99

Survey Studies	• Collect data from many participants
	• Used to capture observed and unobserved attitudes and behaviors by various observational methods (mail, phone, in person)
		• Limited detail reduces nuance
		• Increased potential for
		  ○ response bias
		  ○ nonresponse bias
		  ○ sampling issues
			See an example in the *Ethanol (Alcohol)* chapter: Kelley-Baker et al., 2017, p. 79

Design	Description	Limitations	Example study (see p. #)
	• Rapid, detailed data collection is possible	• Question design can create problems	
Observational Studies	• Directly observe behavior/variables • Can be unobtrusive • Natural setting • Rich data • Rapid data collection is possible	• No control over variables • Greater potential for observer bias • Difficult to determine cause-effect relationship	See an example in the *Cocaine* chapter: Brookoff et al., 1994, p.136
Case Studies	• In-depth examination of a specific individual, group, event, etc. • Rich, detailed information • Real-life context • Starting point for hypotheses	• Very limited generalizability • Potential subjectivity and bias issues • Not easily replicated • Time and resource intensive • Lack of control	See the *Case Reports* sections of the drug fact sheets Ex: Amphetamine: Jones & Holgren, 2005, p. 21

Experimental Studies. Experimental behavioral research designs are used to investigate cause-and-effect relationships between variables by manipulating an independent variable (e.g., providing a treatment, drug, program) and observing its impact on a dependent variable (e.g., poor driving performance, agitation, better test scores). This type of study provides high control over variables, allows for the establishment of cause-and-effect relationships, and can be replicated. *True experiments* also employ random selection and random assignment of the participants to the experimental and control groups.

Depending on the type of experimental design, external validity may be an issue. *Field experiments* help offset issues with generalizability and context which are inherent to laboratory studies that take place in artificial settings. Experimental studies can also be time-consuming and costly because they require careful planning, randomization, and control over extraneous variables to ensure internal validity. Researchers must also consider ethical issues, sample size determinations, and statistical analysis techniques to draw accurate conclusions from their findings.

Many types of studies employ aspects of experimental designs. The study designs described below are frequently used in traffic safety research because they make it possible to study aspects of behavior, even when random assignment and a high degree of control are not feasible or ethical.

Drug Studies (studies of new, experimental drugs), also known as clinical trials, are essential for evaluating the safety and efficacy of medications. Drug studies follow a rigorous scientific methodology, including randomized controlled trials, and provide robust evidence for the safety and effectiveness of drugs. A significant limitation of drug studies relates the necessary ethical considerations of dosing participants on the drug concentrations under study. It is particularly

important to reduce harm and ensure participant safety throughout the study. Many drug studies involve testing new medications, which may have unknown side effects or risks that could harm participants during and after the study. These considerations contribute to the fact that drug studies often demand significant resources, including time, funding, and personnel. Like other areas of behavioral research, there is a tendency to publish positive results, which increases the likelihood of publication bias and skews the research findings for the drug under study.

Though there are significant limitations to performing drug research, the rationale for conducting these studies often offsets the potential limitations of this type of research, especially when drug studies are conducted in a scientifically rigorous and ethical manner. An important drawback for drug research pertinent to traffic safety is that very few studies purposefully investigate the impact of the drug being studied on driving performance. Until recently (see DHHS, 2017; Kay & Logan, 2011), there was no standard guidance, drug researchers were advised to use to investigate drug effects on the ability to drive a vehicle. A recent review of drug studies (Ghunney et al., n.d. [unpublished manuscript]) found that as of 2021, very few studies had begun to adopt the FDA guidance in their drug development studies.

Driving Simulator studies involve creating simulated environments or situations to study human behavior. Many employ forms of experimental design that give researchers precise control over variables and consistent, standardized conditions for all participants. Simulators have the potential to collect large quantities and varieties of precise measurements of behavior and performance that include the ability to test new or novel designs that do not exist or are too expensive or risky to implement in the real world (e.g., a new roadways design, crash-imminent situations, impaired drivers). An important limitation of the behavior observed in the simulator is the behavior observed may not accurately reflect how people would behave in real-world situations, in absolute performance. However, researchers can learn a great deal from patterns of responses or participant behaviors. Much like other experimental designs, researchers need to be aware of potential learning effects, if the design involves repeated exposure to the same stimuli. In evaluating the utility of simulator research designs for understanding a research question, considerations should be made of the tradeoffs between the degree of control used and the external validity of the results.

Quasi-Experimental Studies allow for the manipulation of an independent variable, like experimental design, but without random assignment. Participants are assigned to groups based on pre-existing characteristics, such as age, being involved in a crash, or being an unlicensed driver. These studies can provide valuable insights when it is not feasible or ethical to conduct a true experimental study. They can be conducted in real-world settings, making the findings more applicable to practical situations. Quasi-experimental designs lack the control and precision of true experimental design, making it difficult to establish causality. Lack of random assignment and limited control of extraneous variables can lead to alternate explanations and affect the reliability of the findings. Generalizability of findings also may be limited to the specific study populations and contexts.

Correlational Designs examine the direction, shape, and strength of the statistical relationship between variables. The direction of the correlation may be positively related, as one variable increase, so does the other. Or they may be negatively (or inversely) related, meaning as one variable increases, the other variable decreases. The variables evaluated can be categorical (e.g., age; previously convicted) or measured (e.g., test scores). The shape of a correlation may be linear (like a flat, straight line) or curvilinear (resembling a line having a curved shape). The

strength of the relationship between variables is determined by a statistical coefficient that goes from 0 (no relationship) to 1 (a perfect correlation). Correlational studies are *nonexperimental* meaning there is no manipulation of independent variables to determine an effect. Therefore, these studies cannot establish causality, as correlation does not imply causation. Correlational designs are especially useful when researchers cannot manipulate a variable because it is unethical or not feasible.

Though there may be a strong relationship between two variables, other variables may be influencing the observed relationship. Correlational studies can be a useful starting point for studying two or more naturally occurring phenomena and are useful for preliminary predictions and identifying experimental hypotheses.

Observational Studies let researchers directly observe behavior in natural (field) settings, providing rich and contextually valid data. These studies can be performed with and without the people under study knowing they are being observed.

Several limitations are associated with this type of design. Observational studies lack of control over variables which can lead to confounding explanations of the observed behavior and reduced internal validity. Like correlational studies, it is difficult to establish cause-and-effect relationships due to the possibility of alternate explanations. Observer bias and subjectivity may also unduly influence the quantity and quality of the data collected. The observed findings may have limited generalizability to other populations or contexts. These studies can be useful starting points for other studies, such as correlational or experimental studies.

Survey Research is a widely used method for collecting data and gathering insights from many people, providing a broader understanding of opinions, attitudes, and behaviors within a population. Surveys can be conducted using various methods, including online, phone, mail, or in-person. A drawback of survey research is the limited depth of information, as they typically rely on closed-ended questions with predefined response options, which may not capture the complexity or nuances of certain topics.

Several types of biases can negatively affect survey research, including respondents giving inaccurate or biased responses due to social desirability bias, recall bias, or low response rates, which can introduce nonresponse bias. All of these have the potential to affect the generalizability of the findings. Sampling is another important challenge to conducting survey research. Overrepresenting, underrepresenting, and exclusion of certain groups from participation also reduces the external validity and increases biases in the findings. Poorly designed survey questions can lead to confusion, misinterpretation, or response fatigue, resulting in inaccurate or incomplete data. Despite these limitations, survey research remains a valuable and widely used method for collecting data and gaining insights. Surveys that are rigorously and carefully designed to reduce potential biases are useful for gathering valuable information and making informed decisions for research and practical use.

Case Studies are detailed and in-depth examinations of a specific individual, group, event, or phenomenon. It is a research method used in various disciplines, such as psychology, sociology, business, and medicine, to gain comprehensive insights and understand complex issues. Because these studies tend to be focused on very few cases, it is possible to capture the rich, qualitative, and quantitative information in the context in which it occurs. Due to their specific focus on a particular case, it is often challenging to generalize the findings of case studies to a larger population or broader context. Researchers have limited control over external factors that can

influence the outcome, potentially affecting the replicability of the results. Case studies offer valuable insights and in-depth understanding of specific subjects or participants, but they also have limitations in terms of generalizability and potential biases. Case studies can be a useful starting point for other studies, such as correlational or experimental studies.

Behavioral research attempts to systematically understand complex human behavior and cognitive processes to aid in predicting future behaviors and outcomes, developing countermeasures, and evaluating implementation, among other things. Some designs study phenomena with a sizeable amount of control and manipulation, which may limit generalizability to real-world settings. Other studies provide valuable insights on natural behavior, without interference, but do not permit researchers to understand cause-effect relationships. As readers review the following Drugs and Human Performance Fact Sheets, it is important to consider the research designs of the studies discussed as they all have limitations. The summary above briefly describes several kinds of behavioral research study methods. There are many resources that can provide a more comprehensive explanation of the designs describe above (Shadish et al., 2002; Singleton, Jr. & Straits, 2017).

Drug Effects on Driving

Numerous drugs have the potential to impair a driver and cause harm on our nation's roadways. Potentially impairing drugs include all psychoactive substances. Psychoactive substances include alcohol, some over-the-counter drugs, some prescription drugs, and most illegal drugs. The mechanism by which these drugs affect the body and behavior, the extent to which they impair driving, and the time course for the impairment of driving can differ.

Ethanol (typically referred to as alcohol) is the most well understood of these drugs and serves as a reference point for what we know and do not know about other potentially impairing substances. Despite a recent uptick in fatalities from alcohol-impaired driving, significant progress had been made in reducing these fatalities (NCSA, 2023). This progress was especially evident in the 1980s and the 1990s with the adoption of policies such as establishment of a minimum legal drinking age and blood alcohol concentrations of .08 g/dL per se illegal limits. This was further enabled by improvements in alcohol testing, which allowed for countermeasures such as alcohol-based ignition interlock devices (Venkatraman et al., 2021).

Much of the progress in addressing the harm caused by alcohol-impaired driving derives from a scientific and public understanding of alcohol's pharmacokinetics and pharmacodynamics (Compton, 2017, see also Compton et al., 2009). Pharmacokinetics is the absorption, distribution, and elimination of a drug from the body. Pharmacodynamics is how a drug affects physiological processes and behaviors. The absorption and elimination rates of alcohol are understood and consistent. Alcohol readily passes through the blood brain barrier and the relationship between alcohol concentrations and impairment are clearly linked. As alcohol concentration increases, so does one's level of impairment and as alcohol concentration decreases, impairment decreases. This allows BACs or BrACs[1] to be used to infer the degree of impairment. Furthermore, alcohol concentrations are directly related to impairment across

[1] This report uses both BAC and BrAC, depending on the context of the sentence, and usage in the original research document. NHTSA's standard measurement uses g/dL for BACs, although 11 of the 50 States use slightly different nomenclature, such as millimeters or even "percentage," which is technically inaccurate (BACs are not "percentages" of anything). BrAC tests use the standard of a volume of 2,1000 mL of air, not blood, but are often "converted" to BAC terminology).

behavior (balance, coordination, reaction time), attention (divided attention, vigilance), cognition (decision making), risk taking, and judgment (Compton, 2017). Driver alcohol concentrations are also clearly linked to crash risk (Compton & Berning, 2015; Blomberg et al., 2005).

Drugs other than alcohol often have more complex absorption and elimination profiles. Also, measured concentrations of a drug may not directly correlate to impairment or crash risk. A given drug may affect different people in different ways and affect the same person differently across occasions. Despite these complexities, much is known, and the body of research is continuously growing. These updated fact sheets provide a valuable tool that can be used to reduce drug-impaired driving and improve traffic safety for all road users.

Specimens

Blood and Urine

Blood is the among the most tested biological specimens for identification of driver drug use.[1] Since a concentration of a drug in blood is closest to the drug concentration in the CNS, it may provide the best information concerning how a drug and its concentration are related to performance impairment. However, there is no well-established correlation between blood concentration and performance impairment for any drug other than ethanol (alcohol). Blood must be drawn by trained professionals, and there may be delays in collecting blood specimens, which may affect subsequent drug concentrations.

Urine is decreasingly collected in the United States for the identification of drug use in drivers. Urine should not be used to assess impairment as no direct relationship exists between a urine concentration of a drug and impairment. The identification of a drug in urine indicates the driver has consumed that drug; however, the substance may remain in the urine for several days after use. Urine also must be obtained under controlled conditions, such as direct observation and use of a bathroom, which limits the ease of use for assessments of impairment.

Oral Fluid

Technological advances over the past decades enabled expanded use of oral fluid for monitoring illicit drug use in drug treatment, workplace, and driving under the influence programs. OF collection can be more advantageous compared to more conventional biological matrices, such as blood and urine, because it is observable, rapid, non-invasive, less objectionable to donors, easier for those with poor venous access, less infectious than blood, more difficult to adulterate than urine, and eliminates the need for specialized collection facilities or same-sex collectors. For drugs taken by oral or inhaled (e.g., smoked, insufflation) routes of administration, the mouth may be coated with the drug, resulting in much higher drug OF concentrations than in blood for a period of several hours, after which the excess drug is cleared and OF concentrations parallel decreasing blood drug concentrations over time. Drugs that are ingested in capsules may not coat the mouth, with positive OF tests reflecting the absorption of drug into the systemic circulation and excretion into OF.

[1] For more information across this section on drug testing and specimens specifically related to traffic safety, see Compton, 2017.

Oral Fluid Physiology and Transfer of Drugs Into Oral Fluid

OF[1] is primarily water (> 97%), electrolytes, immunoglobins, enzymes, and proteins. The major salivary glands (parotid, submandibular, and sublingual), oral mucosa, and gingiva produce 500 to 1,500 mL/day OF and up to 10 mL/min when stimulated. The salivary flow rate and OF pH are influenced by circadian rhythms, physical activity, and health status of the person; the normal pH range for OF is 5.5 to 7.9. Stimulation of OF production increases flow rate and pH due to increased bicarbonate excretion, which can reduce the concentration of drugs in OF due to dilution. OF excretion decreases after stimulant, opioid, or cannabis intake, potentially increasing the time needed to collect an adequate OF specimen. Unlike creatinine-normalized urine drug concentrations,[2] there is no accepted biomarker to normalize OF drug concentrations.

The passage of drugs from the blood into OF is dependent on the lipophilicity[3] and pKa (acid dissociation constant) of the drug and the pH of the blood and the OF. Generally, the pH of OF is lower than blood, facilitating the accumulation of basic drugs into OF. Only non-charged lipophilic drug molecules cross plasma membranes easily, and an equilibrium is achieved for the non-charged species. However, non-charged basic drugs become charged when they reach the lower OF pH, moving the passage of additional drug into OF. This phenomenon is termed *ion trapping* because after the free drug crosses into OF, it ionizes and becomes "trapped" in the more acidic fluid. Acidic drugs are found in much lower concentrations in OF because pH differences between blood and OF favor accumulation of acidic drugs in the blood. Passive diffusion of nonpolar drugs, ultrafiltration of low molecular weight drugs such as ethanol, and/or active transport mechanisms for lithium are also involved in drug transfer into OF.

Oral Fluid Collection

To prevent contamination or incorrect results, for 10 minutes prior to OF collection, people should not have anything in their mouths, including gum or tobacco. People should be observed throughout the waiting period prior to sample collection.[4]

There are many OF collection devices on the market; however, selection of a device that is adequately and independently evaluated is important, as many devices have differing drug recoveries. Onsite devices collect OF and test for a limited range of drugs, generally via a form of lateral flow immunoassay. A sponge for OF collection is usually attached to a plastic handle, and manufacturer's instructions detail how long and whether to keep the device in the mouth, under the tongue or to gently scrub the cheeks to collect adequate OF volume. It is essential that the device has a volume adequacy indicator that notifies the user when adequate OF is collected. A smaller amount of OF is collected for onsite testing and, typically, a second specimen is collected for the confirmation test.

For confirmation, approximately 1 mL of OF is obtained by the collection device that is diluted with an elution/stabilizing buffer. The elution and stabilizing solvent pulls drugs off the sponge

[1] Oral fluid is a complex mixture as defined above; saliva is the fluid from a specific salivary gland and is free from other materials.
[2] In urine drug testing, the amount of drug is compared to the amount of creatinine, a substance that is excreted into the urine during normal physiologic processes. The comparison of a drug of interest to a reference molecule, such as creatinine, results in a "normalized" result.
[3] Lipophilicity is the ability of a chemical compound to dissolve in fats, oils, and non-polar solvents.
[4] For example, see SAMHSA's Collection Site Manual for the collection of oral fluid specimens for Federal agency workplace testing programs, (SAMSHA, 2022).

pad and into the buffer, improving drug recovery. The buffer reduces OF viscosity, improving measurement accuracy and increasing stability, but also dilutes analyte concentrations, requiring sensitive analytical procedures. The collection pad must remain in the buffer for the manufacturer-specified time (from 4 hours to overnight) to ensure adequate drug recovery. In addition, the buffer prevents degradation of labile drugs (e.g., cocaine, 6-acetylmorphine), improving the detection of the active parent drug. The mixture of the OF and elution buffer also provides a greater volume for analysis. The composition of elution/stabilizing buffers in OF collection devices is proprietary and different constituents can interfere with liquid chromatography tandem mass spectrometry analysis by suppressing or enhancing ionization. This requires that laboratories carefully evaluate each OF collection device in their method validation procedures. All onsite OF screening tests should be confirmed by gas chromatography or LC-MS/MS.

Interpretation of Oral Fluid Drug Test Results

OF drug tests may have high concentrations after drugs are eaten, smoked, snorted, or inhaled due to coating of the mouth. These high concentrations do not reflect simultaneous blood concentrations. As the coating dissipates in around 3 hours, the OF drug concentrations decline in tandem with blood concentrations. To date, no research supports attempting to predict blood drug concentrations from OF concentrations.

Detection times in OF are important for drug test interpretation to put into context when an individual used a drug, and to compare to an individual's statement of last drug use. Many factors influence drug detection times in OF including cutoffs, analytes, dose, route of administration, time since use, the amount of drug initially deposited in the mouth, OF collection method, and collection device.

OF testing does not replace documentation of impairment; if impairment is documented and an *on-site* OF drug test is negative, a confirmation sample should be collected and tested in the laboratory for other drugs. The limited number of drugs included in an onsite OF panel makes it clear that many other drugs could be the source of the observed impairment (for more on this issue, see Berning et al., 2022).[1]

Fact Sheet Organization

Case interpretation is complicated by factors such as the dose of the drug, route of administration, frequency and chronicity of use, acute and residual effects, development of tolerance, individual variability due to genetic and environmental factors and combined effects of drugs, including ethanol, to name but a few. It is recommended that all elements of each fact sheet be considered when evaluating a drug's effect on performance. Readers are also encouraged to use these fact sheets in connection with other impaired driving-related texts cited in each *References and Recommended Reading* section.

Individual fact sheets may contain the following subheadings and content.

[1] For information on the accuracy of selected on-site devices, see Buzby et al. (2021).

Fact Sheet Heading
Generic name of the drug, followed in parentheses by any abbreviations/acronyms and pharmacologically related drugs and/or metabolites that are discussed in the main text. A brief description of the drug or drugs in pure form.

Synonyms
Primarily trade names in the United States. Common street names may vary and change – readers are encouraged to refer to the DEA website for common street names (https://www.dea.gov/factsheets), where applicable.

Source
Current scheduling of the drug in the United States by the DEA, and its availability (natural occurrence, manufacturing, and/or commercial appearance.)

Drug Class
Common medical classification, based primarily on pharmacological effect.

Uses
Separated into clinical versus non-clinical uses (or industrial use, if applicable). Clinical uses include the foremost Food and Drug Administration-approved use in the United States and possible off-label uses. Non-clinical uses include common reasons for self-administration or use of the drug.

Potency, Purity, and Dose
Frequent potency and purity of street drugs. Commonly prescribed dosing schedules.

Route of Administration
Common ways users administer the drug, for both clinical and non-clinical purposes.

Pharmacodynamics
The principal biochemical, physiological, and/or molecular effects of the drug on the human body, where known. Includes primary receptor binding and/or chemical interactions.

Pharmacokinetics
Covers the fate of the drug in the human body following administration. Include oral bioavailability, percent plasma protein bound, volume of distribution, half-life, metabolism, and excretion, where known.

Blood to Plasma Concentration Ratio (or Breath, Urine, and Vitreous, where relevant)
Ratio of the concentration of drug in whole blood to the concentration of drug in plasma. Used to predict whole body pharmacokinetics of a drug and may aid in an approximate concentration conversion between specimens.

Interpretation of Blood Concentrations
Cited amounts of a drug in a volume of blood, following a known dose, typically listed as the number of nanograms of the drug per milliliter of blood (ng/mL) or the number of milligrams of the drug per liter of blood (mg/L). May include the maximum drug concentration measured (C_{max}) and the time of maximum concentration (T_{max}). Blood concentrations may be used clinically as an important determinant of clinical responses to the drug. Care must be taken not to definitively determine an exact dose and/or time and frequency of drug use from a single drug concentration without other supporting information. Most drug fact sheets contain information regarding blood concentrations following known therapeutic drug use or recreational use;

postmortem or overdose concentrations are typically not cited, nor are concentrations determined in traffic fatality cases, to avoid an inference of causation.

Interpretation of Urine Test Results
This section is only included in the ethanol and cannabis fact sheets, where limited interpretive information is covered. Urine is decreasingly collected in the United States to identify drug use in motor vehicle drivers, and it should not be used to assess impairment. The identification of a drug in urine only indicates that the suspect has been exposed to that drug.

OF(S) to Blood Concentration Ratio
Ratio of the concentration of drug in OF to the concentration of drug in whole blood.

Interpretation of OF Test Results
Cited amounts of a drug in a volume of OF, following a known dose, typically listed as the number of nanograms of the drug per milliliter of OF. May include the maximum drug concentration measured (C_{max}), time of maximum concentration (T_{max}), and the last time the drug was detected in a research study, given the research and testing methodology (T_{last}). Care must be taken not to definitively determine an exact dose and/or time and frequency of drug use from a single drug concentration without other supporting information.

General Effects
Lists commonly cited desired and adverse effects of a drug. Effects often depend on the dose of the drug, the route of administration, history of use, and tolerance. The focus is on effects following prescribed and/or recreational drug use and not on effects following an accidental drug overdose. The duration of effects following different routes of administration and tolerance, dependence, and withdrawal effects are also covered.

The table of general effects is broken down into *physiological*, *motor* (behavior), and *cognitive* effects. *Physiological effects* focus on those effects that are not controllable (internal action); *motor effects* focus on effects that are observable (external action); and *cognitive effects* focus on effects that occur automatically (internal mental action: e.g., perception, judgment, decision making) that may or may not be observable.

A specific individual may not display all or even most of the listed effects – the effects listed are those most commonly described in the cited references, following consumption of the drugs.

Driving-Related Studies
Describes published studies about the effects of the drug on driving. The studies are categorized as laboratory studies, simulated driving studies, on-the-road driving studies, case reports, and epidemiological studies.

Laboratory Studies
These take place in laboratory settings and usually measure performance of subjects on a variety of psychomotor tests following controlled drug administration and other controlled conditions.

Care must be taken interpreting results of laboratory studies. Although there may be statistically significant changes in subject performance on measures such as choice reaction time, critical tracking, recall tests, vigilance, etc., these differences may not be large enough to affect real-world driving performance.

Simulated Driving Studies
A subset of laboratory studies, these measure performance using driving simulator settings. The simulator measures performance of subjects on driving skills (e.g., reaction time, errors, and selection of speed, position, and distance) following controlled drug administration and other controlled conditions.

Although there may be statistically significant changes in subject performance on measures such as standard deviation of lateral position, these differences may not be large enough to affect real-world driving performance.

On-the-Road Driving Studies
These studies occur in real-world driving settings and measure performance of subjects on driving skills (e.g., reaction time, errors, and selection of speed, position, and distance) following controlled drug administration and other controlled conditions. The driving courses may be open or closed to other road users and may include any combination of public or private roads. Instrumented vehicles may be used to collect data.

Case Reports
These summarize real-world incidents of drug use or exposure in individuals while driving, drug concentrations detected, and observed signs of potential impairment and driver behavior. Drug administration and other conditions are not controlled.

Epidemiological Studies
These investigate real-world driving events and can include descriptions of the distributions (who, when, where), frequency, patterns, and determinants of traffic events (e.g., crashes, roadside surveys) in a defined population. These may include culpability studies that compare the rate at which crash-involved, drug-positive drivers and drug-negative drivers are deemed to be at fault for their crashes; or case-control studies which compare drug use by crash-involved drivers to drug use by non-crash-involved drivers.

Interactions With Ethanol
Commonly cited effects and interactions of the drug in combination with ethanol, with preference to known dosing studies.

Interactions With Other Drugs
Commonly cited effects and interactions of the drug in combination with other drugs, with preference to known dosing studies. The focus was to include information on other impairing substances; it does not include non-impairing prescription medications or drugs not typically tested for and/or present in driving cases.

Drug Evaluation and Classification Program Category
The formal categorization of the drug class, as designated by the Drug Evaluation and Classification program. The DEC program uses seven drug categories or a combination of categories: CNS depressant, CNS stimulant, cannabis, narcotic analgesic, dissociative anesthetic, hallucinogen, and inhalant. More information about the seven drug categories is at the IACP web page and portal (n.d.)

Drug Evaluation and Classification Program Profile
Observed indicators most consistent with the stated DEC category.

Analytical Considerations
Pertinent analytical information that may affect the detection of a drug.

References and Recommended Reading
List of cited references used throughout the main text, in addition to similar recommended articles. Review articles are designated as such and are useful sources for general drug information. Cited research articles focus on the effects of drugs in humans; research articles based on animal models were generally not included. The references listed immediately below tend to apply to most of fact sheets, but not necessarily to everyone. In that sense, they tend to be generic, or apply to a group or class of drugs or sometimes of drug interactions. References specific to each fact sheet are included at the bottom of that fact sheet.

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Ethanol (Alcohol)

Ethanol is a volatile, colorless liquid with a slight odor. Often referred to as alcohol but is only one type of alcohol. Produced by the natural fermentation of sugars. This is made for human consumption and is a colorless volatile flammable liquid with a characteristic odor and pungent taste.

Synonyms

Drinking alcohol, ethyl alcohol, grain alcohol.

Source

Commercially available as alcoholic beverages (e.g., beer, wine, spirits). Alcohol is also available as a compound in many elixirs, mouthwashes, hand sanitizers, and medicinal liquids, and available in the manufacturing industry as a solvent. Ethanol is naturally produced by the fermentation of sugars by yeast.

Drug Class

CNS depressant

Uses

Clinical

Ethanol is rarely used therapeutically, although it may be administered to patients poisoned by methanol or ethylene glycol ("antifreeze") to prevent their conversion to toxic metabolites.

Non-Clinical

Ethanol is primarily consumed for enjoyment and relaxation, to enhance sociability, to decrease anxiety or stress, or to become intoxicated. However, alcohol use disorder (characterized by medical, legal, and social consequences of excessive alcohol intake), commonly called alcoholism, affected more than 14.5 million Americans in 2019 (National Institute on Alcohol Abuse and Alcoholism, 2022). Alcohol is also commercially used as an antiseptic and disinfectant.

Potency, Purity, and Dose

Ethanol is typically present at 3 to 13 percent by volume in naturally fermented beer, 10 to 12 percent in wines, and 20 to 60 percent in distilled liquors. Information on a "standard drink" is available at the NIAAA website www.niaaa.nih.gov/what-standard-drink.

Route of Administration

Primary routes include oral (recreational) and intravenous (clinical) administration. Inhalational exposure may occur, for example, in an industrial setting but would likely not result in significant blood alcohol levels or intoxication.

Pharmacodynamics

Ethanol primarily increases the effects of the major neurotransmitter γ-aminobutyric acid (GABA) in the brain, which leads to suppression of excitation in the CNS.

Pharmacokinetics

Ethanol has high oral bioavailability of 80 percent or more, and low plasma protein binding. It distributes readily and evenly throughout the body fluids and is in higher concentrations in areas that have a high-water content, such as blood. The volume of distribution is approximately 0.58 to 0.83 L/kg for males and 0.43 to 0.73 L/kg for females. Following oral consumption, ethanol is primarily absorbed in the small intestine and, to a lesser degree, in the stomach. Food ingestion tends to slow the absorption of ethanol and decrease the peak blood alcohol concentration but does not significantly prolong the time to peak alcohol concentration. Peak BACs are usually reached 30 to 90 minutes post-ingestion (average 45 to 60 minutes; 30 minutes if fasted). Ethanol is not appreciably absorbed by inhalation through the lungs or diffusion through the skin.

Ethanol is extensively metabolized in the liver (90%), mediated primarily by the ADH enzyme system, to acetaldehyde, then to acetic acid, and carbon dioxide and water. Following oral consumption, elimination rates may range from approximately .01 to .03 g/dL (average of .015 g/dL in males and .018 g/dL in females) (Academy Standards Board, 2024). The rate of ethanol elimination can be increased by chronic use of ethanol (e.g., .025 g/dL) and by food intake. Approximately 5 to 10 percent of consumed ethanol is eliminated unchanged in urine, breath, and sweat.

Plasma to BAC Ratio

Reported values range from 1.10 to 1.35 (average 1.18).

Interpretation of Blood Concentrations

Although ethanol is naturally present in the human body, endogenous BACs are typically well below .001 g/dL in living subjects.

Retrograde extrapolation may be used to estimate the ethanol concentration range at the time of an incident by projecting backwards from the time a specimen is collected (Academy Standards Board, 2024). As ethanol is evenly distributed in body water, resulting BACs can be reasonably estimated based on a person's sex, body weight, and degree of adiposity; however, this estimate is based upon ranges and assumptions. Extrapolation should not be attempted unless there is at least a 2-hour difference between the last drink and the time of specimen collection, as the subject could still be in an absorptive state.

Forward extrapolation may be used to estimate the amount of ethanol consumed from a BAC. Forward extrapolation can be attempted if the amount of ethanol consumed is known, along with such variables as the weight and sex of the subject, and period and rate of consumption. Although subject to the same limitations as retrograde extrapolation (i.e., estimation based upon averages and assumptions), this can be relevant in estimating the BAC from the time of a driving event and/or corroborating or contradicting the results of a chemical test or claims of a drinking scenario (Academy Standards Board, 2024).

In clinical settings (e.g., emergency departments), serum ethanol tests are commonly used, as opposed to whole blood commonly used in law enforcement settings. Serum ethanol testing is distinct from BACs in that the serum ethanol concentrations are approximately 9 to 18 percent higher than those found in whole blood. Accurate interpretation of ethanol concentrations requires knowing which matrix was analyzed.

Blood to BrAC Ratio

Reported values average approximately 2,100:1.

Interpretation of BrAC Test Results

When people provide an adequate breath sample for the purposes of ethanol testing, the deep lung air (alveolar or end-expiratory breath) sample provided is most representative of the ethanol concentration in arterial blood. Several studies indicate the BrAC measured will be approximately 10 percent less than the BAC measured at the same time point. Evidential test results provide the most accurate and reliable BrAC results for interpretation compared to non-evidential test results.

OF(S) to Blood Concentration Ratio

1.08 (range 0.84 to 1.36)

Interpretation of OF(S) Test Results

OF contains more ethanol than blood due to its higher water content. The OF to BAC ratio is not affected by the phases of ethanol absorption, distribution, and elimination.

Urine to BAC Ratio

1.3 to 1.5 for the elimination phase

Interpretation of Urine Test Results

If the urine ethanol concentration is less than the corresponding BAC, then the subject is in the absorption phase and the BAC is increasing. If the urine ethanol concentration is greater than the corresponding BAC, then the subject is in the post-absorptive phase, and the BAC is plateaued or decreasing. They should not be used to estimate blood alcohol levels or impairment.

General Effects

The main effects of ethanol are those of a CNS depressant and the intensity of CNS effects is proportional to the BAC. Cognitive functions such as vigilance, divided attention, and vocabulary tests may be impaired even at low concentrations (e.g., .02 g/dL). Effects may be exacerbated by sleepiness. Hangover effects may include drowsiness, headache, dry mouth, concentration problems, fatigue, sweating, nausea, gastrointestinal problems, and anxiety.

Table 2 provides a range of effects, including side effects that subjects may experience following ethanol consumption.

Table 2. Physiological, motor, and cognitive side effects of ethanol consumption

Physiological	Motor (behavioral)	Cognitive
• Reduced visual acuity • Reduced peripheral vision • Delay in glare recovery • Horizontal gaze nystagmus • Double vision • Decreased body temperature • Increased pain threshold • Respiratory depression • Vomiting • Incontinence	• Sociability • Talkativeness • Increased confidence • Reduced inhibitions • Drowsiness • Disorientation • Lethargy • Slurred speech • Delayed reaction time • Sensory-motor incoordination • Lack of balance • Body sway • Staggering gait • Inability to stand or walk • Reduced consciousness	• Mild euphoria • Diminished attention • Slowed information processing • Loss of critical judgement • Reduced perception and memory • Diminished comprehension

(Fillmore et al, 2008; Garriot, 1996; Landauer & Howat, 1983; Weafer & Fillmore, 2012; Wigmore, 2011).

Duration of Effects

Acute effects may last 2 to 3 hours following 1 to 2 drinks, and up to 24 hours following 8 to 10 drinks. Hangover effects may last up to 24 hours.

Tolerance, Dependence, and Withdrawal Effects

The CNS effects of ethanol are more pronounced when the BAC is increasing than when decreasing, which is believed to result from acute (functional) tolerance to ethanol, achieved during drinking. Subsequently, the physical effects of ethanol intoxication are often more obvious shortly after drinking ceases (e.g., 15 to 20 minutes) compared to several hours later. It may be difficult to detect obvious physical signs of intoxication in subjects with high tolerance (i.e., chronic ethanol users). Importantly, while tolerance may develop to the subjective self-perception of intoxication, tolerance does not develop to impairment of executive functions. For example, someone with elevated BAC with high ethanol tolerance may have the ability to control for slurred speech and have a lucid conversation with the examiner, but they will not be able to suppress the induced horizontal gaze nystagmus associated with such elevated BACs (Fillmore et al., 2008; Garriot, 1996; Holland & Ferner, 2017; Jones, 2011; Landauer & Howat, 1983; Weafer & Fillmore, 2012; Wigmore, 2011).

Driving-Related Studies

A concentration-dependent relationship between BAC and driving-related impairment and crash risk has been established through diverse and numerous studies. Specifically, ethanol use can produce diminished cognitive, perceptual, and motor ability. Driving-related functions including depth perception, judgment, divided attention, reaction time, awareness of inebriation and risk tolerance can be affected by ethanol use.

Simulated Driving Studies

In general, driving simulator studies show increasing impairment of driving-related abilities with increasing BACs. Ethanol increases stopping distance and affects control of lane position and the ability to negotiate turns. Chronic drinkers may subjectively feel less impaired than social drinkers; however, they still perform poorly in driving simulator studies.

In one study, 26 subjects received varying doses of ethanol or placebo, consumed within 10 minutes. Males (n=18) received 0, 0.2, 0.4 and 0.6 g ethanol per kg of body weight, and females (n=8) received 0, 0.16, 0.32 and 0.48 g/kg. Average BACs for all subjects were 0, .021, .050, and .073 g/dL, respectively. A direct relationship was demonstrated between increasing BACs and increased driving errors such as decreased ability to anticipate signals, incorrect steering, and over/under steering. Further, subjects with BACs averaging .050-.073 g/dL self-reported considerably more drowsiness for up to 3 hours after ethanol consumption (Landauer & Howat, 1983).

In another study, 14 subjects received a single dose of 0.6 g/kg ethanol or placebo, consumed within 2 minutes. The average peak breath ethanol concentration attained was .089 g/dL. Compared to placebo, there was a greater deviation of lane position, increased line crossings, more failures to stop at red lights, more abrupt steering, greater acceleration, and faster overall speed in the subjects that consumed ethanol (Fillmore et al., 2008). Additionally, a single dose of 0.65 g/kg ethanol or placebo, consumed within 7 minutes by 24 binge drinkers and 16 non-binge drinkers, resulted in an average peak BrAC of .090 g/dL. Subjects drove a 19-mile course and were to maintain a constant speed. Compared to placebo, all subjects who consumed ethanol had difficulty maintaining lane position and the target speed, and made increased driving errors (Marczinski et al., 2008).

On-the-Road Driving Studies

Many years ago, a review article of laboratory, simulator, and instrumented car studies focused on ethanol's influence on reaction time and braking performance. The author concluded that ethanol increases reaction time (both simple and choice) appreciably more in driving situations than in laboratory experiments. The author also found braking performance of driving subjects at high BACs was abrupt, unsmooth, and less controlled compared to either sober drivers or the same subjects driving with no ethanol. Additionally, high BACs both increased the time necessary to begin braking, as well as reduced the degree of control in actual braking during stopping. The author reported these two factors in combination probably accounts for a large part of ethanol's contribution to highway crashes (Perrine, 1976).

Epidemiological Studies

Another older study of BACs in over 12,000 drivers who were either controls or involved in motor vehicle crashes was conducted in Grand Rapids, Michigan. The results demonstrated increasing risk of causing crashes with increasing BACs. All BACs over .04 g/dL were associated with increased crash rates. At a BAC of .06 g/dL the relative risk of causing a crash was two times higher compared to sober drivers; at .08 g/dL the relative risk was four times higher; at .10 g/dL the relative risk was seven times higher; and at .15 g/dL the relative risk was 25 times higher. When crashes occurred, drivers with a BAC over .08 were more likely to have single vehicle crashes that were more severe in terms of injury and damage (Borkenstein et al., 1974).

In a similar study in Germany, BACs were determined in 9,087 drivers who voluntarily stopped at roadside surveys and 1,968 drivers involved in traffic crashes. There was no apparent increase in risk at BAC less than .05 g/dL. At BACs from .05 to .08 g/dL, the risk was 2.8 times higher; at .08 to .11 g/dL, 15.6 times higher; at .11 to .159 g/dL, 15.1 times higher; and at concentrations greater than .16 g/dL, the crash risk was 37 times higher (Kruger & Vollrath, 2004).

In a NHTSA case-control study of 2,871 crash-involved drivers in Long Beach, California, and Fort Lauderdale, Florida, the effect of age and BAC on crash risk was evaluated. At all BACs (.01 to .15 g/dL), a greater relative risk of a crash was observed for drivers under 21 years old compared to drivers 21 to 55^{+} years old, and this risk increased exponentially as BACs increased (Blomberg et al., 2009). In another NHTSA case-control study, researchers collected biological specimens from 3,000 drivers involved in crashes in Virginia Beach, Virginia. Drug test results from these drivers were compared to those from 6,000 drivers not involved in crashes (control group). This study demonstrated that drivers with BrACs > .05 g/210L had twice the crash risk when adjusted for age and gender. Drivers with BrACs > .08 g/210L had close to four times the crash risk when adjusted for age and gender (Lacey et al., 2016).

Given the large body of research assessing psychomotor impairment and risk of crash with incremental increases of BAC, ethanol has a detrimental effect on driving performance. It is important to recognize that this impairment in driving is present even at lower BACs, and risk of crash is directly linked to increasing BAC.

Interactions With Other Drugs

Acute ethanol exposure may attenuate the effects of neurostimulatory drugs (e.g., cocaine, methamphetamine) and augment the effects of neuroinhibitory drugs (e.g., opioids, GHB) (Singh, 2019). Cannabis appears to have an additive effect on psychomotor impairment (Ramaekers et al., 2011; Singh, 2019). Amphetamines and other CNS stimulant drugs may antagonize the depressant effect of ethanol to some degree, but do not effectively counteract the cognitive and motor dysfunctions induced by ethanol (Garriot, 1996).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 3 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and interactions with other drugs.

Table 3. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include the odor of ethanol and behavior such as unsteady walk, lack of balance and coordination, slurred speech, disorientation, and poor performance on field sobriety tests. Note that ethanol may also elevate pulse rate.

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Amphetamine

Amphetamine hydrochloride is a white crystalline powder. Amphetamine base is a liquid. Amphetamine exists in the dextroamphetamine (*d)*- or levoamphetamine (*l)*-isomeric form.

Synonyms

Amphetamine: Dexedrine, Adderall, Benzedrine, DextroStat, Biphetamine, Gradumet.

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Amphetamine is a Schedule II controlled substance and is usually supplied as the sulfate salt of the *d*-isomer (Dexedrine), or a mixture of the *d*- and *l*-isomers (Adderall). Dexedrine is available in 5, 10, and 15 mg strength capsules, or 5 mg tablets. Adderall is available in 5, 7.5, 10, 12.5, 20, and 30 mg strength tablets. An extended-release formulation is also available.

Drug Class

CNS stimulant; sympathomimetic; appetite suppressant

Uses

Clinical

Amphetamine is FDA-approved to treat narcolepsy and attention deficit hyperactivity disorder.

Non-Clinical

Amphetamine is misused to increase alertness, relieve fatigue, control weight, treat mild depression, and for its intense euphoric effects.

Potency, Purity, and Dose

To treat ADHD, doses of 2.5 to 10 mg/day are administered, depending on age. To treat narcolepsy, 5 to 60 mg/day are ingested in divided doses.

Route of Administration

Amphetamine is ingested orally for therapeutic purposes, but can be snorted, smoked, and intravenously administered for non-clinical purposes.

Pharmacodynamics

Amphetamine increases synaptic levels of the norepinephrine, dopamine, and serotonin (5-HT), and has α and β adrenergic agonist effects. Norepinephrine is responsible for amphetamine's alerting, anorectic, locomotor, and sympathomimetic effects; dopamine stimulates locomotor effects, psychosis, and perception disturbances; and 5-HT is responsible for delusions and psychosis. Racemic (*dl*-) amphetamine and *d*-amphetamine have similar chemical properties and actions to methamphetamine but are less potent.

Pharmacokinetics

Amphetamine has an oral bioavailability of 75 to 100% and is 10 to 20% plasma protein bound. The volume of distribution is 3.2 to 6.5 L/kg. The elimination half-life ranges from 7 to 34 hours and is urine pH dependent, with acidification reducing the half-life. Amphetamine is metabolized to phenylacetone and benzoic acid, both inactive. A small amount of amphetamine is converted to the active metabolite norephedrine. Approximately 30 percent of an administered dose is eliminated in the 24-hour urine as unchanged drug; this can increase to over 70 percent in acidified urine and decrease to less than 5 percent in alkaline urine.

Blood to Plasma Concentration Ratio

Amphetamine: 0.6 to 1.0

Interpretation of Blood Concentrations

Twelve subjects were given single oral doses of 12.5 and 25 mg *d*-amphetamine, resulting in average plasma concentrations of amphetamine of 21.0 ± 2.5 ng/mL at 120 minutes following the 12.5 mg dose, and 42.8 ± 4.2 ng/mL for the 25 mg dose. At 145 minutes post-dose, amphetamine concentrations were 23.8 ± 1.6 and 46.6 ± 3.4 ng/mL, respectively. Maximal amphetamine plasma concentrations were then obtained at 240 minutes post-dose and were 24.2 and 47.5 ng/mL, respectively. At 12 hours post-dose, concentrations declined to 15 to 33 ng/mL (Heishman et al., 1998). Eight subjects were given single oral doses of 30 mg, resulting in average peak plasma concentrations of 110 ng/mL at 2.5 hours, declining to 84 ng/mL at 4.5 hours (Baselt, 2020).

Plasma concentrations as high as 590 ng/mL occurred in chronic users 1 hour following intravenous administration of 160 mg amphetamine. A tolerant amphetamine user who orally consumed an average of 1,000 mg/day maintained steady state blood concentrations of 2,000 to 3,000 ng/mL (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Amphetamine: 7.2 (*n*=15) (Gjerde et al., 2010)

Amphetamine: 29 (*n*=40; median 22; range 5.6 to 86) (Langel et al., 2014)

Interpretation of OF(S) Test Results

Amphetamine pKa 10.1

Amphetamine is a lipid-soluble, weakly basic drug with a high pKa and low plasma protein binding. Oral coating is possible after recent drug use if it was orally ingested, snorted, or smoked. Amphetamine additionally ion traps in oral fluid, leading to higher oral fluid concentrations compared with blood.

Amphetamine concentrations were detected in 190 oral fluid specimens from patients treated for chronic pain, with an average concentration of 798.5 ng/mL (median 179.8; range 5.9 to 21,093 ng/mL) (Heltsley et al., 2011). The median last detection time for amphetamine has been reported as 2 days, with a range of last detection time of 0 to 8 days (Arnold et al., 2019).

General Effects

The pharmacological effects of amphetamine depend on the dose, route of administration, experience of the user, and tolerance. Amphetamine effects are less intense after oral ingestion than following smoked or intravenous use.

Table 4 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when consuming higher than therapeutic doses.

Table 4. Physiological, motor, and cognitive side effects of amphetamine consumption

Physiological	Motor (behavioral)	Cognitive
• Increased heart rate • Palpitations • Irregular heartbeat • Increased respiration rate • Increased blood pressure • Elevated temperature • Dilated pupils • Twitching • Dry mouth • Abdominal cramps • Suppressed appetite • Insomnia • Reduced fatigue	• Rapid speech • Excitation • Wakefulness • Poor impulse control • Motor restlessness • Hyperactivity • Improved reaction time	• Euphoria • Sense of well-being • Increased alertness • Improved motivation • Improved concentration • Improved working memory • Improved recall of information • Rapid flight of ideas

Other adverse effects may include light sensitivity, irritability, nervousness, tremors, anxiety, blurred vision, grinding of teeth, sweating, nasal congestion, mood swings, and aggression. Chronic use may lead to weight loss, hallucinations, paranoia, psychosis, hyperthermia, and convulsions (Baselt, 2001; Baselt, 2020; Forney, 1977; Hurst, 1987; Logan, 2001; PDR, 2021).

Duration of Effects

Onset of effects is rapid following intravenous use and smoking, while effects evolve more slowly following oral use. Onset of effects is 30 to 60 minutes with immediate release oral formulations and 1.5 to 2 hours with extended-release formulations. Overall effects typically last 2 to 3 hours.

Tolerance, Dependence, and Withdrawal Effects

Tolerance is rapidly achieved following repeated doses of intravenous amphetamine. Withdrawal symptoms frequently appear within 24 hours of abrupt discontinuation of chronic, high-dose use and can last up to 3 to 4 weeks. Withdrawal symptoms may include anxiety, agitation,

irritability, drug craving, depression, fatigue, sleepiness, increased appetite, problems with concentration and attention, and lack of motivation (Wagener [Ed.], 2021; PDR, 2021).

Driving-Related Studies

Laboratory Studies

Orally administered therapeutic doses (5 to 15 mg) of amphetamine improve reaction time, relieve fatigue, improve cognitive function testing, increase subjective feelings of alertness, increase time estimation, and increase euphoria. However, subjects were willing to make more high-risk choices. Such improvements in mental and motor performance are typically observed in people who are fatigued or sleep-deprived; in general, amphetamine does not enhance the performance of people who are alert and attentive (Baselt, 2001).

Laboratory-based studies have been limited to much lower doses than those typically used by people with amphetamine use disorders. Further, these studies have not investigated the effects of snorting or intravenous use of amphetamine or repeated/chronic dosing. Performance effects following much higher than therapeutic doses may include agitation, irritability, inability to focus attention on divided attention tasks, inattention, restlessness, motor excitation, time distortion, depressed reflexes, poor balance and coordination, and inability to follow directions (Logan, 2001).

Case Reports

In a Swedish study of 46 drivers arrested for impaired driving, selected for their unusually high levels of amphetamine (> 5,000 ng/mL), the average blood concentration detected was 6,700 ng/mL (range 5,000 to 17,000 ng/mL). This is in comparison to a median blood amphetamine concentration of 700 ng/mL in 6,613 impaired driving offenders in Sweden. The most frequent signs of drug use in the 46 high-dose drivers, reported by arresting police officers, included bloodshot and watery eyes, restlessness, talkativeness, exaggerated reflexes, and slurred speech. Unsteady gait and dilated pupils were observed in some but not all drivers. Benzodiazepines and cannabis were also detected in some drivers. Anecdotal information reported those with the very highest amphetamine concentrations had swallowed the drug to prevent being apprehended for drug possession (Jones & Holgren, 2005).

Interactions With Ethanol

Ethanol was shown to increase the absorption and C_{max} of amphetamine without altering its elimination (Singh, 2019). In general, high doses of amphetamines are likely to increase the impairing effects of ethanol.

Interactions With Other Drugs

Monoamine oxide inhibitors slow metabolism and clearance of norepinephrine and other biogenic amines from adrenergic nerve endings, thereby creating a synergistic effect with coadministration of amphetamine. In addition, the MAOI selegiline is metabolized to methamphetamine and amphetamine and so should never be co-administered with amphetamine. Drugs that increase serotonin neurotransmission such as antidepressants and certain synthetic opioids (particularly fentanyl) can lead to severe serotonin toxicity known as the serotonin syndrome. Antipsychotics such as haloperidol block dopamine receptors, which reduces the

effects of higher dopamine levels caused by amphetamine. Thus, use of antipsychotic medications may inhibit the CNS stimulant effects of amphetamines such as psychosis and excited delirium (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS stimulant

Drug Evaluation and Classification Program Profile

The indictors in Table 5 are the most consistent with the category; however, variation may be observed due to individual reaction, dose taken, and interactions with other drugs.

Table 5. DEC program profile of a CNS stimulant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	dilated	slow	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include restlessness, body tremors, talkativeness, rapid flight of ideas, paranoia, auditory and visual hallucinations, spontaneous and irregular body movements (choreoathestosis), exaggerated reflexes, anxiety, and hallmarks of illicit drug use such as track marks or recent injection sites.

Analytical Considerations

The *l*- and *d-isomer* forms of amphetamine may be separated using chiral columns or equivalent separation techniques. This is necessary to differentiate between certain pharmaceuticals that contain one or both stereoisomers such as Adderall and Benzodrine.

References and Recommended Reading

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Benzodiazepines

This introductory section contains general comments regarding this class of drug. Refer to the individual benzodiazepine fact sheets for specific information on:

- alprazolam,
- clonazepam,
- diazepam (and nordiazepam, oxazepam, temazepam),
- lorazepam, and
- designer benzodiazepines.

Benzodiazepines are a class of substances that bind to gamma-aminobutyric $acid_A$ receptors in the brain to produce sedative, anxiolytic, and anticonvulsant effects. They can be classified based on their elimination half-lives (*short-intermediate:* alprazolam [Xanax, etc.], oxazepam [Serax]*; intermediate:* lorazepam [Ativan, Loreev, etc.], temazepam [Restoril, etc.]*; long:* clonazepam [Klonopin, Rivotril], diazepam [Valium, Diastat, etc.], nordiazepam) or potency (*low:* oxazepam, temazepam*; medium:* diazepam*; high*: alprazolam, clonazepam, lorazepam).

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Prescription benzodiazepines are Schedule IV controlled substances and are available in tablet, gel, and injectable forms. Illicit designer benzodiazepines are available as street drugs in powder, tablet, or capsule form, and are sold primarily online.

Drug Class

Tranquilizer; sedative; anxiolytic; anticonvulsant; CNS depressant

Uses

Clinical

Benzodiazepines are used in the management of anxiety disorders, as an adjunct for the relief of skeletal muscle spasm, in convulsive disorders/status epilepticus, and as sedatives. Benzodiazepines also suppress or dampen acute ethanol withdrawal and anxiety-related gastrointestinal disorders such as stress ulcers.

Non-Clinical

Benzodiazepines are misused as sedatives, relaxants, and anxiety reducers, to enhance the positive subjective effects of ethanol or opioids (e.g., feelings of euphoria), and lessen the impact of withdrawal symptoms of other drugs.

Route of Administration

Administration of benzodiazepines is typically via the oral route; however, intravenous injection is possible after preparing a solution from crushed tablets. Commercially available solutions can be injected. Gel formulations can be rectally administered, typically to treat seizures.

Pharmacodynamics

Benzodiazepines enhance the effects of GABA at its receptor. GABA is the major inhibitory neurotransmitter in the CNS. There are two types of GABA receptors, $GABA_A$ and $GABA_B$. Benzodiazepines bind with high affinity to the $GABA_A$ receptor complex at the $\alpha 1$, $\alpha 2$, $\alpha 3$ and $\alpha 5$ subunits, in combination with the β and γ subunits. The $\alpha 1$-subunit is associated with the sedative and amnestic effects of benzodiazepines, whereas the $\alpha 2$-subunit is associated with their anxiolytic effects. The γ-subunit is also essential for modulation of chloride transport by benzodiazepines.

The GABA receptor controls tonic or baseline inhibition and reduces neuronal excitability. Benzodiazepines increase chloride transport through ion-channels, resulting in hyperpolarized postsynaptic membranes. This enhances the CNS depression response to endogenous GABA and ultimately decreases the excitability of neurons and reduces the arousal of the cortical and limbic systems in the CNS.

Pharmacokinetics

Benzodiazepines are well absorbed with oral availability typically ≥ 90 percent, and plasma protein binding generally ≥ 80 percent. Benzodiazepines differ in their elimination half-lives and potency – refer to individual fact sheets.

Interpretation of Blood Concentrations

Simple interpretation of blood concentrations without any knowledge of drug-taking history is not advisable. Given changing responses with repeated use due to tolerance and variability in response, blood concentrations do not always provide a clear indication of behavioral effects. Blood concentrations may be several-fold higher after chronic use compared to single use, and increased blood concentrations in older adults may occur due to changing pharmacokinetics with age.

Interpretation of OF(s) Test Results

Benzodiazepines are weakly basic, highly protein-bound, and moderately lipid-soluble molecules with a low pKa. Subsequently, benzodiazepines are found in relatively low concentrations in oral fluid (i.e., 0.1 to 50 ng/mL) and have shorter detection times in oral fluid compared to blood. Parent drugs are present in higher concentrations than their metabolites. The analysis of benzodiazepine concentration in oral fluid cannot accurately estimate benzodiazepine concentration in blood.

General Effects

At low doses, most benzodiazepines are moderate tranquilizers causing sedation, drowsiness, confusion, reduced alertness, and some loss of anterograde memory. Benzodiazepines can produce a state of intoxication like that of ethanol, including slurred speech, disorientation, and severe sedation. In high doses or overdose, paradoxical reactions of anxiety, insomnia, stimulation, aggression, hallucination, and acute hyperexcited states may occur. Shallow breathing, clammy skin, dilated pupils, weak and rapid pulse, respiratory depression, and coma are possible. Older adults are more likely to develop significant adverse CNS effects.

Table 6 shows a range of effects including side effects that subjects may experience.

Table 6. Physiological, motor, and cognitive side effects of benzodiazepine consumption

Physiological	Motor (behavioral)	Cognitive
• Headache • Dry mouth • Blurred or double vision • Excessive perspiration • Nausea and vomiting • Tremor • Sedation • Vertigo • Hypotension • Respiratory depression • Urinary retention	• Slurred speech • Drowsiness • Confusion • Excitement • Reduced inhibitions • Diminished reflexes • Ataxia	• Reduced alertness • Loss of anterograde memory • Amnesia • Depression

Tolerance, Dependence, and Withdrawal Effects

Regular, long-term use produces tolerance to many of the sedative, memory, and adverse effects, but tolerance may not occur for the anxiolytic benefits. Tolerance may take several weeks or months to develop depending on dose and frequency of administration. Benzodiazepines can produce mild physical and psychological dependence and are regarded as having a moderate to significant abuse potential.

When treatment with benzodiazepines is stopped, subjects may experience recurrent or rebound symptoms. Recurrent symptoms are a gradual return of the patient's original symptoms and rebound symptoms are a rapid return of worsening original symptoms. Anxiety and insomnia are common rebound symptoms. Abrupt discontinuation, particularly following higher doses and/or long-term use, may produce withdrawal symptoms such as excitement, restlessness, dysphoria, anxiety, apprehension, fearfulness, dizziness, headache, muscle stiffness, tremors, insomnia, and sensitivity to light and sound. These symptoms are typically transient and last less than a week. More severe symptoms may include intense rebound nausea, vomiting, abdominal cramps, delirium, hallucinations, hyperthermia, sweating, panic attacks, confusional or paranoid psychoses, increased heart rate and blood pressure, and occasionally seizures or convulsions.

Driving-Related Studies

A meta-analysis by Barker et al. (2004), reviewed 13 research studies examining cognitive functioning following long-term benzodiazepine use. The average duration of clinical benzodiazepine use in subjects across all research studies ranged from 1 to 34 years (average 9.9 years), with an average dose equivalent to 17.2 mg of diazepam/day. Cognitive categories examined included sensory processing, nonverbal memory, speed of processing, attention/concentration, general intelligence, working memory, psychomotor speed, visuospatial

cognition, problem solving, verbal memory, motor control/performance, and verbal reasoning. Long-term benzodiazepine users were consistently and significantly more impaired than controls across all cognitive categories examined.

In a meta-analysis by van der Sluiszen et al. (2017), the influence of long-term benzodiazepine use on neurocognitive skills was evaluated across 13 research studies (of which 5 were also included in Barker et al., 2004). The average duration of use of benzodiazepines was 5 to 15 years (range 3 months to 27 years). The presence of neurocognitive impairments in long-term benzodiazepine users increased with increasing benzodiazepine exposure. Additionally, sensitivity to acute benzodiazepine impairment decreased in long-term users, suggesting development of some tolerance to the impairing properties of benzodiazepine treatment. The authors cautioned that the sensitivity of some neurocognitive tasks to drug effects, and their validity to predict fitness to drive, was not generally known.

The same authors conducted a study of 22 people who were regular users of benzodiazepines and Z-drugs (a category of benzodiazepine-like drugs: e.g., zolpidem, zopiclone) for at least six months, in comparison to 65 controls. Groups were compared in both neurocognitive testing and standardized on-the-road driving tests. Long-term benzodiazepine users showed decreased reaction time and vigilance, and an increase in standard deviation of lateral position (SDLP)[1] in road testing. Interestingly, in people who had been users for more than 3 years, the effect size was diminished (van der Sluiszen et al., 2019).

In a review article of 24 on-the-road driving studies, the relationship between blood concentrations of benzodiazepines and performance on the on-the-road driving test were evaluated by the SDLP test. In 11 of the 24 driving studies, actual blood drug concentrations were measured following the administration of the benzodiazepine being studied. The authors demonstrated that higher doses (i.e., higher average blood concentrations) were associated with a greater change in SDLP than lower doses. However, the measured blood drug concentrations of benzodiazepines were not reliably predictive of changes in SDLP (Verster & Roth, 2013).

Smink et al. (2008) conducted a retrospective study of 171 driving cases in which drivers suspected of being under the influence tested positive for benzodiazepines but had BACs under the illegal limit. The cases included both suspected impaired drivers and drivers involved in crashes. The authors divided peoples' benzodiazepine concentrations into sub-therapeutic, therapeutic, or elevated concentration groups, based on a comparison to reference concentrations cited in the literature. The authors noted a significant relationship between benzodiazepine concentrations (between groups) and behavior, walking on a line, walking on a line after turning, and the Romberg test. No relationship was observed between benzodiazepine concentration and pupil size, nystagmus, or orientation (to time, place, person).

Interactions With Ethanol

Ethanol enhances drowsiness, sedation, and decreased motor skills, and can also exacerbate the memory-impairing effects of benzodiazepines. Acute and chronic ethanol consumption decreased benzodiazepine elimination occurring by demethylation or hydroxylation (e.g., diazepam), and reduced lorazepam clearance (Jann et al., 2014). The combined effects of ethanol

[1] While there may be statistically significant changes in performance with measures such as SDLP, there may not be practical differences when related to real-world driving performance and safety.

and benzodiazepines potentiate each other's CNS depressant actions, including respiratory depression. Ethanol's most prominent pharmacological activity occurs at the ion-gated channels at $GABA_A$ receptors, which accounts for the enhanced pharmacodynamic effects when ethanol and benzodiazepines are co-ingested.

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 7 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 7. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	Slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include behavior like ethanol intoxication without the odor of ethanol, to include unsteady walk, lack of balance and coordination, slurred speech, and disorientation.

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Alprazolam

Alprazolam is a white crystalline powder.

Synonyms

Xanax, Xanax XR, Niravam

Source

Alprazolam is a Schedule IV controlled substance and is available as the free base in 0.25 to 2 mg regular tablets, 0.25 to 2 mg disintegrating tablets, 0.5 to 3 mg extended-release tablets, and 1 mg/mL solution for oral administration.

Drug Class

Anxiolytic: CNS depressant

Uses

Clinical

Alprazolam is a short-acting antidepressant and anxiolytic agent used in the short-term treatment of generalized anxiety disorders, moderate to severe anxiety during ethanol withdrawal in alcoholics, panic attacks with or without agoraphobia, panic disorders, and depression. Off-label uses include the treatment of insomnia and depression.

Non-Clinical

Alprazolam is misused for its relaxing qualities, to reduce day-to-day anxiety, to relieve drug-induced agitation and insomnia caused by stimulant drug use, and to enhance relaxation and euphoric effects of other depressant drugs and marijuana.

Potency, Purity, and Dose

Alprazolam is a high-potency benzodiazepine. Daily doses to treat anxiety range from 0.75 to 4 mg and for phobic and panic disorders daily doses of 6 to 9 mg are administered. Doses can be taken as 0.25 to 2 mg three times a day of the immediate-release formulation, or 1 to 6 mg once daily of the extended-release formulation.

Pharmacokinetics

Alprazolam has high oral bioavailability (80 to 90%) and is 80 percent plasma protein bound. The volume of distribution is 0.8 to 1.3 L/kg. Following oral administration, the elimination half-life ranges from 6 to 27 hours (commonly reported as 10 to 18 hours). Alprazolam is extensively metabolized in the liver by oxidation, mediated by the cytochrome P450 gene CYP3A4, and conjugation. Its two main metabolites, α-hydroxyalprazolam and 4-hydroxyalprazolam, are present at low plasma concentrations and have less benzodiazepine receptor affinity than alprazolam. Approximately 80 percent of an administered dose is eliminated in the urine, with approximately 20 percent of a dose excreted as unchanged alprazolam.

Blood to Plasma Concentration Ratio

Reported values range from 0.6 to 0.8.

Interpretation of Blood Concentrations

Steady state alprazolam concentrations are typically reached after 2 to 3 days, independent of the dosage schedule, and are higher than concentrations obtained following single doses. Extended-release formulations result in peak plasma concentrations that are approximately half of those observed with immediate-release formulations. Peak plasma concentrations are often higher in older adults; alprazolam clearance is reduced, and its elimination half-life may be prolonged in both older adults and people with cirrhosis.

The following findings are from several different studies.

- Single oral doses of 1 and 2 mg alprazolam were given to 12 subjects, resulting in average plasma alprazolam concentrations of 12.9 ± 1.7 ng/mL at 60 minutes following the 1 mg dose and 25.8 ± 2.9 ng/mL for the 2 mg dose. At 105 minutes post-dose, alprazolam concentrations were 15.5 ± 1.5 and 31.3 ± 2.0 ng/mL, respectively. Plasma concentrations of both doses plateaued from 105 to 180 minutes, then declined gradually to 9 to 18 ng/mL at 11 hours post-dose. Plasma concentrations of α-hydroxyalprazolam were not detected for either dose in most subjects (Heishman et al., 1998).
- A single oral dose of 1 mg oral or sublingual alprazolam given to 12 healthy subjects resulted in a plasma C_{max} of 12.0 ng/mL at 1.8 hours, and 11.3 ng/mL at 2.8 hours, for the oral and sublingual doses, respectively (Scavone et al., 1992).
- A single 2 mg oral dose of alprazolam was given to 12 subjects resulting in a plasma C_{max} of 33 ± 10 ng/mL at 1.9 ± 1.4 hours (Ji et al., 2019).
- In six adult patients receiving either 3, 6, or 9 mg/day alprazolam, resulting average steady state plasma alprazolam concentrations were 29 ng/mL, 61 ng/mL, and 102 ng/mL, respectively. Similarly, daily oral doses of 1.5 to 6 mg alprazolam given to six patients resulted in steady state serum alprazolam concentrations of 25 to 55 ng/mL (Baselt, 2020).
- A single oral dose of 3 or 6 mg extended-release alprazolam given to 12 to 14 healthy subjects resulted in average peak plasma alprazolam concentrations of 25 ng/mL at 6.7 hours, and 50 ng/mL at 9.3 hours, respectively. The same doses administered for 3 days resulted in higher average peak plasma alprazolam concentrations of 38 ng/mL at 6.8 hours, and 86 ng/mL at 4.4 hours (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Average 0.41 (*n*=74; median 0.33; range 0.029 to 2.2) (Langel et al., 2014)

Median 0.43 (*n*=75; 25th and 75th percentiles corresponded to 0.28 to 0.66) (Gjerde et al., 2010)

Interpretation of OF(S) Test Results

Alprazolam pKa 2.4

A single oral dose of 0.5 mg alprazolam was given to 11 healthy subjects and oral fluid samples were collected for up to 5 days. The median C_{max} for alprazolam in oral fluid was 0.98 ng/mL (range 0.12 to 23 ng/mL) at 2 hours (range 2 to 13 hours). The median last detection time was 26 hours (range 4 to 37 hours; Temte et al., 2019).

In six subjects admitted to a closed detoxification ward, alprazolam concentrations in oral fluid samples ranged from 1 to 22 ng/mL. The last detection times for alprazolam in oral fluid ranged up to 60 hours (Nordal et al., 2015). Similar concentrations in seven detoxification subjects (2 to 25 ng/mL) and chronic pain patients (0.7 to 46 ng/mL) were noted in a review article by Desrosiers & Huestis, (2019). In oral fluid samples collected from 582 pain patients, average alprazolam concentrations were 118.5 ng/mL (median 11.1; range 0.5 to 13,880 ng/mL; Heltsley et al., 2011).

General Effects

The pharmacological effects of alprazolam depend on the dose, route of administration, experience of the user, and tolerance. Table 8 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 8. Physiological, motor, and cognitive side effects of alprazolam consumption

Physiological	Motor (behavioral)	Cognitive
• Headache • Nausea • Dry Mouth • Hypotension • Sedation	• Slurred Speech • Unsteadiness • Ataxia • Reduced inhibitions • Drowsiness	• Euphoria • Reduced alertness • Anterograde amnesia • Reduced concentration

Some people may experience an opposite or "paradoxical" reaction to alprazolam, characterized by agitation, irritability, and hostility or aggression (Barker et al., 2004; Baselt, 2020; Bond et al., 1992; Chouinard, 2004; Ellinwood et al., 1983; Linnoila et al., 1990; PDR, 2021; Reissig et al., 2015; Verster & Volkerts, 2004).

Duration of Effects

Onset of sedation and main effects is within 10 to 20 minutes following an intravenous dose and within 40 minutes after oral dosing. Main effects are observed for up to 6 to 8 hours.

Tolerance, Dependence, and Withdrawal Effects

There has been little tolerance to alprazolam's therapeutic effects reported; however, sedation and tiredness can improve within several days of continuous use, and some cognitive function effects may improve with continuous, long-term use. Long-term use can cause adaptive changes in benzodiazepine receptors, making them less sensitive to stimulation. Tolerance lasts only as long as alprazolam therapy is continued daily. There is an increased chance of withdrawal and rebound symptoms if alprazolam is administered in high daily doses, longer treatment duration, and/or with abrupt discontinuation. Symptoms of withdrawal may include tachycardia,

palpitations, muscle tremors, restlessness, insomnia, fatigue, increased dysphoria and depression, decrease in intellectual efficacy and energy, and panic attacks. Less common but more severe withdrawal effects include seizures, manic symptoms, and suicidal ideation (Walker, 2021; Chouinard, 2004; PDR, 2021; Reissig et al., 2015; Verster & Volkerts, 2004).

Driving-Related Studies

It may be important to take comorbidity into account when evaluating alprazolam impairment in people with panic disorder, anxiety, or depression. Anxiety and depression have been shown themselves to impair cognitive and psychomotor performance (Verster & Volkerts, 2004).

Laboratory Studies

A single oral dose of 1 mg oral or sublingual alprazolam was given to 12 healthy subjects. The resulting plasma C_{max} values were 12.0 and 11.3 ng/mL, at 1.8 and 2.8 hours, for oral and sublingual alprazolam, respectively. Both alprazolam formulations produced sedation, fatigue, impaired digit symbol substitution, slowed reaction time, and impairment of acquisition and recall of information. These performance effects were observed from 0.5 to 8.0 hours (Scavone et al., 1992).

A single oral alprazolam dose of 1, 2 or 4 mg, or a single inhaled alprazolam dose of 0.5, 1 or 4 mg, or placebo, were administered to 14 healthy people. Objective and subjective effects were determined on several occasions in the following 9 hours, using digit symbol substitution and Circular Lights tasks. Both the oral and inhaled routes produced orderly, dose and time-related effects, with higher doses producing greater and longer lasting effects. For the 2 mg dose for either route, average time to onset was 11.3 ± 2.3 minutes (inhaled) and 6.8 ± 3.9 minutes (oral). Five subjects felt inhaled effects starting at 2 minutes. For the 2 mg dosages, average time to peak effects was 51.7 ± 14.3 minutes (inhaled) versus 120.1 ± 5.9 minutes (oral). For the 2 mg dosages, average time to offset participant-rated drug effects was 216 ± 19.2 minutes (inhaled) versus 262 ± 19.0 minutes (oral). Both inhaled and oral alprazolam produced dose-related decreases in performance on the Circular Lights and digit symbol substitution tasks. Dose-related slurred speech, confusion/disorientation, relaxation, and sedation were also observed (Reissig et al., 2015).

In a review of 39 double-blind, placebo-controlled studies, data from psychomotor performance measured after acute administration of 0.25 to 2.0 mg oral alprazolam was compared and evaluated. Psychomotor tests included reaction time, tapping, cancelation, tracking, digit symbol substitution, symbol copying, critical flicker fusion, card sorting, vigilance, Stroop, and balance tests. Performance-impairing effects were significantly different from placebo at doses of 0.5 mg and higher. While 13 percent of overall tests showed impairment following doses of 0.25 mg, this increased to 75 to 92.9 percent of tests showing impairment following doses of 1.0 to 2.0 mg alprazolam (Verster & Volkerts, 2004). The authors additionally reviewed 22 studies evaluating the effect of 0.25 to 2.0 mg oral alprazolam on memory functioning. Memory tests included immediate and delayed recall, recognition, digit span, arithmetic, Sternberg memory scanning, and story recall. While 11.8 percent of overall tests showed impairment following doses of 0.25 mg, this increased to 100 percent of tests showing impairment following a dose of 2.0 mg alprazolam. Immediate and delayed recall and recognition were impaired at doses of 0.5 mg and higher. Overall, acquisition and retrieval of newly learned information is impaired with alprazolam, whereas previous learned information remains intact.

Simulated Driving Studies

A single oral dose of 1 mg alprazolam or placebo was given to 8 healthy subjects. At 3 hours post-dose, subjects participated in a driving simulator test, at the National Advanced Driving Simulator, capturing various scenarios (e.g., urban, rural, straight, curvy, different speed limits, day-time and night-time). Clear detrimental effects of alprazolam were observed on driving measures of lateral control and longitudinal control. There was marked degradation in several parameters in the driving simulation – significant detrimental effects were observed on steering, deviation from lane position, and lane departures across almost all driving scenarios, and driving appeared to be more aberrant at higher speeds and in rural scenarios. Significant increases in self-reported drowsiness were also noted in all subjects (Brown et al., 2018).

On-the-Road Driving Studies

A single oral dose of 1 mg alprazolam given to 20 healthy subjects was evaluated for its effect on driving ability. In addition to laboratory tests, subjects performed an on-the-road driving test during normal traffic at 1-hour post-dose to assess overall vehicle control. Subjects were instructed to drive with a steady lateral position (standard deviation of lateral position test, SDLP[1]) at a constant speed of 60 mph (speed variability test) over a 100 km highway circuit. Observations included a significant increase in the side-to-side weaving of the car, repeated excursions out-of-lane into both the adjacent traffic lane and the road shoulder, and a significant increase in speed variability. The authors found that SDLP increment after 1 mg alprazolam was equal to that observed with blood ethanol concentrations of .15 g/dL. Notably, 6 out of the 20 subjects had to stop their driving test prior to completion because they fell asleep behind the steering wheel within the first half of their driving test. The laboratory test results further confirmed the detrimental performance effects of alprazolam (Verster et al., 2002).

A single oral dose of 1 mg immediate-release or 1 mg extended-release alprazolam was given to 18 healthy subjects. At 4 hours post-dose, subjects participated in a standardized driving test on a highway in normal traffic. Additional cognitive and psychomotor tests were administered at 1, 2.5, and 5.5 hours post-dose. Both formulations of alprazolam significantly impaired performance at 4 to 5 hours. The impairment measured following dosing with the extended-release was approximately half that measured following the immediate-release alprazolam (Leufkens et al., 2007).

Case Reports

There have been several case reports in the literature involving alprazolam in suspected impaired driving cases, including:

- 102 driving cases with blood alprazolam concentrations ranging from 8 to 642 ng/mL, with 30 percent of concentrations exceeding 100 ng/mL (Baselt, 2001);
- 430 driving cases with an average blood alprazolam concentration of 90 ng/mL, ranging up to 3,900 ng/mL (Jones, 2007);
- 714 driving cases with a median blood alprazolam concentration of 74 ng/mL, ranging from 1 to 530 ng/mL, 78 percent of which had other drugs detected (Harper, 2013); and

[1] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful amount of differences when related to real-world driving.

- 16 alprazolam-only driving cases with blood concentrations ranging from 10 to 437 ng/mL (Walls et al., 2013).

Interactions With Ethanol

A single oral dose of 1 mg alprazolam, with and without 0.5 g/kg ethanol, was given to 48 healthy subjects. A variety of psychological tests were conducted at 90 to 210 minutes post-dose and included measures of central and peripheral activity such as electroencephalogram (EEG), auditory evoked response and tremor, and self-ratings of intoxication. Alprazolam alone caused significant decreased auditory evoked potential, showed characteristic changes in EEG, and led to self-reported intoxication and increased sway. The impairment after ethanol alone was less pronounced than that observed for alprazolam. The performance effects of both drugs in combination were not greater than predicted from the sum of the single dose effects, suggesting an additive effect and not a synergistic effect. However, the effects were not always additive, and effects due to alprazolam were dominant (Bond et al., 1992).

A single oral dose of 0.5 or 2 mg alprazolam or placebo were given to 10 subjects, followed by 0.8 g/kg ethanol or placebo 3 hours later. Performance tests were conducted over the following 4 hours and included tracking, choice reaction time, word list recall, and sedation self-rating. Plasma alprazolam concentrations averaged 5 ng/mL during the study period for the 0.5 mg dose, and 20 to 30 ng/mL for the 2 mg dose. Plasma ethanol concentration peaked at 0.07 percent and declined to 0.02 percent, and alprazolam did not appear to affect clearance of ethanol. The low alprazolam dose plus ethanol produced moderate declines in performance on some tests, compared to alprazolam alone. The higher alprazolam dose plus ethanol produced significant and relatively long-lasting impairments on tracking, information processing and memory, and caused decreased blood pressure and drowsiness. Coadministration of ethanol with alprazolam produced additive decrements in performance, as opposed to synergistic effects (Linnoila et al., 1990).

Interactions With Other Drugs

Coadministration of alprazolam and opioids significantly increases the risk of respiratory depression, profound sedation, low blood pressure, and death. Coadministration of alprazolam with other CNS depressants can potentiate CNS effects, such as increased sedation or respiratory depression. The coadministration of barbiturates can increase the clearance of orally administered alprazolam and shorten its elimination half-life. Concurrent use of fluoxetine and alprazolam has been shown to increase the plasma C_{max} of alprazolam by 46 percent and increase its elimination half-life by 17 percent (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant.

Drug Evaluation and Classification Program Profile

The indicators in Table 9 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 9. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence present.
* present in high doses.

Other characteristic indicators may include behavior like ethanol, intoxication without the odor of ethanol, staggering and stumbling, lack of balance and coordination, slurred speech, and disorientation.

References and Recommended Reading

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Clonazepam

Clonazepam is an off-white to light yellow crystalline powder.

Synonyms

Klonopin, Rivotril, Klonopin

Source

Clonazepam is a Schedule IV controlled substance and is available as 0.5 to 2 mg regular tablets, 0.25 to 2 mg disintegrating tablets/wafers for oral administration, and 1 mg/mL solution for intravenous, intramuscular, and subcutaneous injections. It is also available in an extended-release formulation for use as a subcutaneous injection to deliver clonazepam over a period of 7 days.

Drug Class

Anticonvulsant; anxiolytic; CNS depressant

Uses

Clinical

Clonazepam is an anticonvulsant used to prevent and treat seizures, panic disorders with or without agoraphobia, and akathisia. Clonazepam is meant for the short-term (up to 4 weeks) management of epilepsy, as tolerance to its anticonvulsant effects can develop.

Non-Clinical

People self-administer clonazepam for its pleasurable effects such as mild euphoria, relaxation, reduced anxiety, drowsiness, and reduced inhibitions.

Potency, Purity, and Dose

Clonazepam is a high-potency benzodiazepine. Daily doses are typically 0.5 to 2 mg administered 2 to 4 times daily for panic disorders, while the maximum recommended daily dose for seizure disorders is 20 mg (in divided doses).

Pharmacokinetics

Clonazepam has high oral bioavailability (90 to 98%) and is 82 to 86 percent plasma protein bound. The volume of distribution is 1.4 to 4.4 L/kg. Following oral administration, the elimination half-life ranges from 19 to 60 hours (commonly reported as 30 to 40 hours). Clonazepam is extensively metabolized, primarily to its active metabolite 7-aminoclonazepam. Approximately 50 to 70 percent of an administered dose is eliminated in the urine, with less than 1 percent excreted as unchanged clonazepam.

Blood to Plasma Concentration Ratio

Reported values range from 0.5 to 0.65.

Interpretation of Blood Concentrations

A single 2.7 mg subcutaneous injection of clonazepam administered to each of nine healthy subjects was compared to an oral clonazepam dose of 0.5 mg three times a day for 7 days in the same subjects. The single subcutaneous dose reached an average plasma C_{max} of 3.0 ng/mL at 72 hours post-dose and remained above 1 ng/mL for 12 days. Average plasma concentrations during the first 24 hours following the oral dose of 0.5 mg three times a day were ~2 ng/mL following the first dose, ~4 ng/mL after the second dose, and ~6 ng/mL after the third dose. On the seventh day of the oral treatment, average steady state plasma concentrations were ~15 ng/mL at 2 hours after the last dose. The extent of accumulation at steady state relative to the first day of treatment averaged 3.3-fold (Greenblatt et al., 2005).

In a single-dose study of a 2 mg dose of clonazepam given to 12 healthy volunteers, oral administration resulted in a peak plasma concentration of 15 ng/mL after 1.7 hours, intramuscular administration resulted in a peak plasma concentration of 11 ng/mL at 3.1 hours, and intravenous administration resulted in a peak plasma concentration of 27 ng/mL at 5 minutes (Baselt, 2020).

Chronic treatment of 6 mg/day of oral clonazepam given to 25 patients resulted in average plasma concentrations of 29 to 75 ng/mL for clonazepam, and 23 to 137 ng/mL for 7-aminoclonazepam (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Clonazepam: Median 0.14 (*n*=47; 25th and 75th percentiles corresponded to 0.06-0.27) (Gjerde et al., 2014)

Clonazepam: Average 0.19 (*n*=35; median 0.15; range 0.029-0.74) (Langel et al., 2014)

7-aminoclonazepam: Average 0.43 (*n*=8; median 0.28; range 0.10 to 1.5 (Langel et al., 2014)

Interpretation of OF(S) Test Results

Clonazepam pKa 1.5

In 16 subjects admitted to a closed detoxification ward, concentrations in oral fluid samples ranged from 1 to 35 ng/mL for clonazepam (*n*=10) and 1.3 to 10 ng/mL for 7-aminoclonazepam (*n*=7). Detection times ranged up to 6 days for clonazepam and up to 5 days for 7-aminoclonazepam (Nordal et al., 2015). Concentrations of clonazepam were determined in oral fluid specimens from 35 patients in chronic pain clinics, with an average clonazepam concentration of 135.5 ng/mL (median 5.2; range 1.1 to 3,821 ng/mL; Heltsley et al., 2011).

General Effects

The pharmacological effects of clonazepam depend on the dose, route of administration, experience of the user, and tolerance. Table 10 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 10. Physiological, motor, and cognitive side effects of clonazepam consumption

Physiological	Motor (behavioral)	Cognitive
• Dry mouth • Hypotension • Weakness • Sedation	• Relaxation • Mild euphoria • Reduced inhibitions • Slurred speech • Unsteadiness • Ataxia • Drowsiness • Dizziness • Lightheadedness	• Mild euphoria • Reduced anxiety • Anterograde amnesia • Loss of concentration

Other adverse effects may include diplopia, lethargy, confusion, fatigue, blurred vision, balance problems, short-term memory loss, depression, and incontinence. As with other benzodiazepines, people may have a paradoxical reaction to clonazepam, resulting in agitation, dysphoria, aggression, and irritability (Baselt, 2020; Chouinard, 2004; dos Santos et al., 2009; Ellingwood et al., 1993; PDR, 2020).

Duration of Effects

Onset of effects begins within 1 hour following an oral dose and may last 6 to 12 hours, depending on dose and frequency.

Tolerance, Dependence, and Withdrawal Effects

Tolerance to clonazepam's anticonvulsant effects can occur, and dependence has been reported in up to one-third of users if clonazepam is taken for longer than 4 weeks. Rebound symptoms can occur on discontinuation and can include insomnia, rebound anxiety symptoms, worsening of depression, and seizures. Withdrawal symptoms are more likely if high doses are taken and/or with extended use, and can include anxiety, irritability, dysphoria, confusion, insomnia, tremor, headache, stomach pain, nausea, sweating, depression, suicidal ideation, seizures, and possibly catatonia and psychosis (Guarnotta, 2021; PDR, 2021).

Driving-Related Studies

Laboratory Studies

Single oral doses of 0.5 and 1.0 mg clonazepam or placebo were given to 10 healthy subjects. Performance testing occurred on nine occasions over the following 24 hours and included choice reaction time (visual), critical flicker fusion, digit symbol substitution, body sway, and sedation self-rating. Peak plasma concentrations at approximately 2 hours post-dose averaged 4 ng/mL for the low dose and 7 ng/mL for the higher dose. The low dose impaired performance on the digit symbol substitution, body sway, and subjective alertness evaluation, while the higher dose significantly impaired performance on all tests (Baselt, 2001).

A single oral dose of 2 mg clonazepam or placebo was given to 10 healthy subjects. Performance tests were conducted at 1.5 hours post-dose and included critical flicker fusion, choice reaction

time (visual), smooth pursuit, and sedation self-rating. Clonazepam significantly impaired performance on all tests (Baselt, 2001).

A single oral 4 mg dose of clonazepam was given to 23 male subjects and digit symbol substitution was monitored for 72 hours. A 72 percent decrease in performance was observed on the digit symbol substitution test from 1.5 to 4 hours post-dose (25th to 75th percentile). The development of tolerance even after a single dose was also noted (dos Santos et al., 2009).

A single oral dose of 4 mg clonazepam or placebo was given to eight healthy subjects, followed by performance on behavioral tasks for the following 7 hours. Clonazepam impaired performance on subcritical tracking (neuromotor task) and digit symbol substitution, compared to placebo. Clonazepam impaired performance for up to 4 hours longer than when compared to a 2 mg oral dose of alprazolam. Development of acute tolerance occurred for the single dose of clonazepam on both tasks (Ellinwood et al., 1993).

Case Reports

Blood clonazepam concentrations averaging 50 ng/mL were detected in 164 subjects arrested for suspected impaired driving (Baselt, 2020).

Interactions With Ethanol

Coadministration of clonazepam and ethanol can significantly increase the risk of respiratory depression, profound sedation, and low blood pressure (PDR, 2021).

Interactions With Other Drugs

Coadministration of clonazepam and opioids significantly increases the risk of respiratory depression, profound sedation, and low blood pressure. Coadministration of clonazepam with other CNS depressants can potentiate CNS effects, such as increased sedation or respiratory depression. When clonazepam is co-administered with strong cytochrome P450 gene CYP3A4 inducers, such as barbiturates, a decrease in clonazepam C_{max} can occur (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 11 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 11. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence
* present in high doses.

Other characteristic indicators following high doses may include behavior like ethanol, intoxication without the odor of ethanol, staggering and stumbling, lack of balance and coordination, slurred speech, and disorientation.

Analytical Considerations

Specimens containing clonazepam and 7-aminoclonazepam should be preserved, refrigerated or frozen, and analyzed quickly to avoid losses due to thermal and/or bacterial degradation. Specimens exposed to sunlight for 1 hour showed 99 percent reductions of the drug. Reported reductions in blood clonazepam concentrations include 51 percent loss after 1 week of storage at room temperature, 25 percent loss after 1 week at 6 °C, 50 to 80 percent loss at 4 °C for 6 months, and up to 20 percent at -20 °C (Baselt, 2020).

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Diazepam, Nordiazepam, Oxazepam, and Temazepam

Diazepam is a colorless, crystalline compound. Diazepam's three main metabolites, nordiazepam, oxazepam, and temazepam, have also been developed and marketed as medications. While the focus on this fact sheet is on diazepam, information is also provided for these metabolites due to the similarity of their effects and as metabolites of diazepam that can also be taken as parent drugs.

Synonyms

Diazepam; Valium, Diastat, Dizac
Nordiazepam: Nordaz
Oxazepam: Serax
Temazepam: Normison, Restoril

Source

Diazepam is a Schedule IV controlled substance and is available by prescription in tablet (2 to 10 mg), gel (5 mg/mL), oral solution (1 mg/mL), and injectable (5 mg/mL) forms.

Drug Class

Anxiolytic; anticonvulsant; sedative; CNS depressant

Uses

Clinical

Diazepam is a long-acting benzodiazepine used clinically in the management of anxiety disorders, as an adjunct for the relief of skeletal muscle spasm, for convulsive disorders/status epilepticus, and as a minor tranquilizer or sedative. Diazepam is also used to suppress or dampen acute ethanol withdrawal and anxiety-related gastrointestinal disorders such as stress ulcers. Off-label uses for diazepam include the treatment of insomnia, restless leg syndrome, and pre/post-operative sedation. Nordiazepam is primarily used for the treatment for anxiety disorders; oxazepam is preferable in the treatment of older adults, or hepatically impaired patients; and temazepam is used for the treatment of insomnia.

Non-Clinical

Diazepam is misused as a sedative and to enhance the relaxation and euphoric effects of ethanol or opioids. Cocaine users take diazepam to increase seizure threshold, and both cocaine and heroin user take it to reduce the impact of withdrawal symptoms between doses.

Potency, Purity, and Dose

Commonly prescribed diazepam doses are 5 to 40 mg daily. For anxiety, doses range from 2 to 10 mg taken two to four times daily. Dosing for ethanol withdrawal varies. Hospital protocol dosing can range from 5 to 20 mg orally or intravenously; 10 mg autoinjectors for home administration dose three to four times per day are also available. For the injectable form, 2 to 20 mg is administered intramuscularly or intravenously. Illicit doses may consist of several tablets administered at once.

Pharmacokinetics

Diazepam has high oral bioavailability (93 to 100%) and is 95 to 99 percent plasma protein bound. The volume of distribution is 0.7 to 2.6 L/kg. Following oral administration, the elimination half-life of diazepam is 43 ± 13 hours but ranges from 40 to 100 hours if the contribution from active metabolites is included. The half-life can increase in older adults and can be significantly prolonged in obese subjects. Diazepam is primarily metabolized to nordiazepam, with oxazepam and temazepam as minor metabolites. Nordiazepam is at least as active as diazepam; oxazepam and temazepam are also active but do not accumulate to an appreciable level in blood as metabolites. Diazepam is excreted in urine mainly as oxazepam conjugate (~33%) and temazepam conjugate, with only traces of diazepam and nordiazepam present.

Nordiazepam is 97 percent plasma protein bound, has a volume of distribution of 0.5 to 2.5 L/kg, and an elimination half-life of 31 to 97 hours. Oxazepam is 87 to 95 percent plasma protein bound, has a volume of distribution of 0.6 to 2.0 L/kg, and an elimination half-life of 5 to 16 hours. Temazepam is 97 percent plasma protein bound, has a volume of distribution of 0.8 to 1.0 L/kg, and an elimination half-life of 8 to 24 hours.

Blood to Plasma Concentration Ratio

Reported values range from 0.55 to 0.70 for diazepam; 0.58-0.60 for nordiazepam; 0.64 to 1.1 for oxazepam; and 0.5 for temazepam.

Interpretation of Blood Concentrations

Therapeutic blood concentrations following single or chronic dosing typically range from 100 to 1,000 ng/mL. Plasma concentrations of 300 to 400 ng/mL are recommended for anxiolytic effects, and > 600 ng/mL for control of seizures. Unless otherwise noted, the following studies are summarized in Baselt (2020).

Single oral dose

- A single oral dose of 10 mg diazepam given to 48 healthy adults resulted in average plasma diazepam concentrations of 406 ng/mL (median 403; range 253 to 586 ng/mL) (Jones & Holmgren, 2012).
- A single oral dose of 10 mg diazepam given to four healthy subjects resulted in average peak blood diazepam concentrations of 148 ng/mL at 1 hour, declining to 37 ng/mL by 24 hours. Average concentrations of nordiazepam peaked at 29 ng/mL at 24 hours.

Chronic daily doses

- Chronic daily doses of 20 mg diazepam (range 2 to 55 mg) in 110 outpatients with an average duration of diazepam treatment of 5.1 years (range 1 to 14 years), resulted in average steady state concentrations of diazepam and nordiazepam in plasma at 329 ng/mL (median 183 ng/mL) and 389 ng/mL (median 216 ng/mL), respectively (Jones & Holmgren, 2012).
- Chronic daily oral doses of 30 mg diazepam given to four subjects resulted in average steady state plasma concentrations of 1,030 ng/mL (range 700 to 1,500 ng/mL) for diazepam and 430 ng/mL (range 350 to 520) for nordiazepam.

Single intramuscular or intravenous dose

- A single 5 mg intramuscular dose of diazepam given to five healthy subjects resulted in average peak plasma diazepam concentrations of 130 ng/mL at 0.6 hours.
- A single 20 mg intramuscular dose of diazepam given to six healthy subjects resulted in average peak plasma concentrations of 290 ng/mL at 1.0 hour.
- A single 20 mg intravenous injection of diazepam given to six healthy subjects resulted in average peak serum concentrations of 1,600 ng/mL at 15 minutes, declining to 440 ng/mL by 2 hours.

Nordiazepam

- Single oral doses of 5 or 10 mg nordiazepam given to eight healthy subjects resulted in average peak plasma nordiazepam concentrations of 118 and 228 ng/mL, respectively, at 2 hours.
- Oral doses of 5 mg nordiazepam, given three times a day for 7 days to six healthy subjects, resulted in average steady state plasma concentrations of 380 ng/mL (range 187 to 570 ng/mL).

Oxazepam

- A single oral dose of 15 mg oxazepam given to seven subjects resulted in average peak serum concentrations of 310 ng/mL at 1.5 hours.
- A single oral dose of 45 mg oxazepam given to eight subjects resulted in average peak serum concentrations of 1,060 ng/mL at 2 hours, declining to 370 ng/mL by 8 hours.

Temazepam

- A single oral dose of 10 mg temazepam given to 10 older adults resulted in average peak plasma concentrations of 305 ng/mL within 15 to 90 minutes.
- A single oral dose of 20 mg temazepam given to six subjects resulted in average peak plasma concentrations of 668 ng/mL within 15 to 75 minutes.
- A single oral dose of 30 mg temazepam given to 24 healthy subjects resulted in average peak plasma concentrations of 870 ng/mL at 1.4 hours.

OF(S) to Blood Concentration Ratio

Diazepam: Average 0.056 (*n*=42; median 0.035; range 0.020 to 0.34) (Langel et al., 2014)

Diazepam: Median 0.037 (*n*=68; 25th and 75th percentiles corresponding to 0.027 to 0.100) (Gjerde et al., 2014)

Nordiazepam: Average 0.053 (*n*=78; median 0.045; range 0.015 to 0.12) (Langel et al., 2014)

Nordiazepam: Median 0.045 (*n*=98; 25th and 75th percentiles corresponding to 0.033 to 0.076) (Gjerde et al., 2014).

Oxazepam: Average 0.15 (*n*=26; median 0.0.098; range 0.017 to 0.51) (Langel et al., 2014)

Interpretation of OF(S) Test Results

Diazepam pKa 3.4; nordiazepam pKa 3.5; oxazepam pKa 1.7; temazepam pKa 1.3

A single oral dose of 10 mg diazepam was given to 11 healthy subjects and oral fluid samples were collected for up to 7 days. The median C_{max} for diazepam in oral fluid was 2.43 ng/mL (8.54 nmol/L) (range 1.44 to 6.49 ng/mL) at 2 hours (range 2 to 11 hours). The median last detection time in oral fluid for diazepam was 109 hours (range 50 to 133 hours). For nordiazepam, the median C_{max} in oral fluid was 1.41 ng/mL (range 0.68 to 2.92 ng/mL) at 60 hours (range 35 to 84 hours). The median last detection time in oral fluid for nordiazepam was 132 hours (range 109 to 136 hours). The metabolites oxazepam and temazepam were not detected in any of the oral fluid samples (Temte et al., 2019).

In five subjects admitted to a closed detoxification ward, diazepam concentrations in oral fluid samples ranged from 1.3 to 25 ng/mL for diazepam and 1.3 to 45 ng/mL for nordiazepam. Detection times ranged up to 7 days for diazepam and up to 9 days for nordiazepam (Nordal et al., 2015). Patients with a history of high, long-term drug use were admitted to a closed detoxification setting. Last detection times in oral fluid were 168 hours for diazepam and 216 hours for nordiazepam (Lee, 2018).

In a study of oral fluid drug concentrations in a series of pain patients, concentrations of diazepam were determined in oral fluid specimens from 396 patients with an average concentration of 184.2 ng/mL (median 5.5; range 1.0 to 67,030 ng/mL). Nordiazepam concentrations were detected in 307 oral fluid specimens with an average concentration of 17.3 ng/mL (median 11.69; range 2.0 to 171.3 ng/mL). Temazepam concentrations were detected in 168 oral fluid specimens with an average concentration of 4.7 ng/mL (median 1.6; range 0.5 to 61.5 ng/mL). Oxazepam concentrations were detected in 166 oral fluid specimens with an average concentration of 2.3 ng/mL (median 1.2; range 0.5 to 56.0 ng/mL; Heltsley et al., 2011).

In eight subjects receiving oral doses of 15 or 30 mg oxazepam, the median oral fluid oxazepam C_{max} was 11 ng/mL (range 8 to 24 ng/mL) and 19 ng/mL (range 15 to 45 ng/mL), respectively. Oxazepam was detected in oral fluid for at least 8.5 hours (Desrosiers & Huestis, 2019).

General Effects

At low doses, diazepam is a moderate tranquilizer, causing sedation, sleepiness, drowsiness, confusion, and some loss of anterograde memory. At high doses, excitement, reduced inhibitions, severe sedation, and effects on respiration may occur, particularly if respiration is impaired by other drugs or by disease. Diazepam can produce a state of intoxication like ethanol, including slurred speech, disorientation, and sedation.

Table 12 provides a range of effects, including side effects, which subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 12. Physiological, motor, and cognitive side effects of diazepam consumption

Physiological	Motor (behavioral)	Cognitive
• Dry mouth • Blurred or double vision • Headache • Tremor • Vertigo • Sedation • Hypotension • Respiratory depression	• Slurred speech • Drowsiness • Confusion • Excitement • Reduced inhibitions • Ataxia • Dizziness	• Euphoria • Loss of anterograde memory • Reduced alertness • Reduced concentration • Reduced anxiety

Other adverse effects may include excessive perspiration, nausea and vomiting, depression, and diminished reflexes. Older adults are more likely to develop significant adverse CNS effects from the use of diazepam. In overdose, paradoxical reactions of anxiety, insomnia, stimulation, hallucination, and acute hyperexcited state may occur. Shallow breathing, clammy skin, dilated pupils, worsening of seizures, weak and rapid pulse, and coma have also been described (Baselt, 2020; Calcaterra & Barrow, 2014; Chouinard, 2004; Drummer, 2002; Kozena et al., 1995; PDR, 2021).

Duration of Effects

Dose-dependent; however, onset of effects following therapeutic doses occurs within 30 minutes and significant effects can last for 12 to 24 hours.

Tolerance, Dependence, and Withdrawal Effects

Regular use will produce tolerance to most of the sedative and adverse effects, but tolerance may not occur for the anxiolytic benefits of diazepam. Tolerance may take several weeks or months to develop depending on dose and frequency of administration. Diazepam can cause mild physical and psychological dependence and is regarded as having a significant abuse potential. Abstinence or abrupt withdrawal, particularly following higher doses and/or long-term use, may produce excitement, restlessness, dysphoria, anxiety, apprehension, fearfulness, dizziness, headache, muscle stiffness, tremors, insomnia, and sensitivity to light and sound. More severe symptoms may include intense rebound nausea, vomiting, abdominal cramps, delirium, hallucinations, hyperthermia, sweating, panic attacks, confusional, psychosis, tachycardia, increased blood pressure, and occasionally seizures or convulsions (Guarnotta, 2021; Calcaterra & Barrow, 2014; Chouinard, 2004; Drummer, 2002; PDR, 2021).

Driving-Related Studies

Laboratory studies have shown that single doses of diazepam (5 to 20 mg) can cause significant performance decrements, with maximal effect occurring at approximately 2 hours post dose and lasting up to at least 3 to 4 hours (Baselt, 2001). Decreased ability to perform divided attention tasks, such as lane movement, slowed reaction time (auditory and visual), increased braking time, decreased eye-hand coordination, and impairment of tracking, vigilance, information

retrieval, psychomotor and cognitive skills have been recorded. Lengthened reaction times have been observed up to 9.5 hours post dose. Lethargy and fatigue are common, and diazepam increases subjective perceptions of sedation. Such performance effects are likely to be exacerbated in older adults.

Laboratory Studies

A single oral dose of 10 mg diazepam was given to 10 healthy subjects, resulting in average peak serum concentrations of 299 ± 64 ng/mL at 1 hour. Performance tasks, administered for up to 7 hours, included choice-reaction, tracking/coordination, flicker fusion, visual parameters (adaption to darkness, sensitivity to brightness, bright counter-light), perceptual speed, and subjective assessments of feelings and driving ability. Diazepam impaired perceptual speed, reactive and coordinative skills, flicker fusion discrimination, and visual parameters, for up to 5 hours post-dose (Seppala et al., 1976).

On-the-Road Driving Studies

Driving studies have shown that diazepam produces significant driving impairment over several doses. Single doses of diazepam can increase lateral deviation of lane control, reduce reaction times, reduce ability to perform several tasks, decrease attention, adversely affect memory and cognition, and increase the effects of fatigue. Significant impairment is further increased when diazepam is combined with low concentrations of ethanol (0.05 g/dL). The following studies are summarized in Baselt (2001).

- Single oral doses of 5 or 10 mg diazepam or placebo were given to nine healthy subjects. At 1 hour post-dose, a 1-hour highway driving test was performed that monitored for speed and lateral position control. The 10 mg diazepam dose significantly impaired lateral position control.
- Chronic doses of 5 mg diazepam given three times a day for 4 weeks were given to 12 anxious patients. At 1.5 hours post-dose on the evening of the 7th day of each week, subjects performed a 100 km highway driving test where constant speed and lateral position control were monitored. Diazepam impaired speed control during the first week and impaired lateral position control for the first 3 weeks.
- Nightly oral doses of 50 mg oxazepam or placebo were given for two nights to 18 healthy subjects. Approximately 10 hours later, on each morning following the doses, subjects drove a 100 km highway circuit at constant speed and steady lateral position. Oxazepam significantly impaired driving performance on both measures on both days.
- A single oral dose of 20 mg temazepam or placebo was given to 12 healthy subjects before bedtime. Subjects participated in a closed course driving test in the morning, at 12 hours post-dose. The driving test involved a slalom and gap acceptance task. Temazepam treatment was associated with significantly more errors (described as carelessness) on the gap acceptance test.
- Nightly oral doses of 20 mg temazepam or placebo were given to 11 insomniacs for eight nights. Subjects were tested 10 and 16 hours later after the 2nd, 4th and 7th nightly doses by driving a 100 km highway course at constant speed and steady lateral position.

Temazepam had no significant residual effects on driving the morning after a nightly dose.

- Nightly oral doses of 20 mg temazepam were given to 16 insomniacs for 7 nights. Driving tests were performed on the morning after the 1st and 7th nightly dose and consisted of a 25 km course under realistic traffic conditions for 1 hour. Subjects were monitored for speed, acceleration, and steering control. Temazepam treatment was associated with a decrease in errors compared to baseline on both days and improved steering control after the 7th dose.

Case Reports

Blood samples collected from 1,000 apprehended drivers were positive for both diazepam and nordiazepam. Average concentrations detected were 370 ng/mL for diazepam (median 200; range 50 to 6,100 ng/mL), and 690 ng/mL for nordiazepam (median 200; range 50 to 5,600 ng/mL; Jones & Holmgren, 2012).

Epidemiology Studies

A number of epidemiological studies have been conducted to evaluate the risk of crashes associated with the use of diazepam and other benzodiazepines. These show a range of relative risk, but most demonstrate increases in risk compared to drug-free drivers. These increases have been twice to several fold. Older adults may have an increased risk of a motor vehicle crash (Drummer, 2002).

Interactions With Ethanol

Ethanol has been shown to impair the clearance of diazepam from blood (by 24%), resulting in higher blood concentrations and a longer half-life (Garriot, 1996).

Ethanol enhances such effects as drowsiness, sedation, and decreased motor skills, and can also exacerbate the memory impairing effects of diazepam. Laboratory studies testing the effect of ethanol on subjects already using benzodiazepines demonstrate further increases in impairment of psychomotor and other driving skills, compared to either drug alone. In a summary of laboratory studies, doses of 10 mg diazepam and moderate doses of ethanol resulted in enhanced impairment of coordination, tracking skills, oculomotor coordination, reaction, intoxication indices, subjective alertness, and enhanced nystagmus. Overall, ethanol was found to enhance the impairing effects of diazepam in an additive manner (Baselt, 2001).

Daily oral doses of 15 mg diazepam (5 mg in morning, 10 mg at night) or placebo were given to 16 healthy subjects for 9 days, followed by administration of 0.8 g/kg ethanol, consumed over 30 minutes, immediately following the morning diazepam dose on the last day. On days 1, 8, and 9, subject performance was evaluated 1, 3, and 5 hours post-dose using a driving simulator and a divided attention task. Diazepam alone impaired performance on both tasks at all test times. The degree of impairment increased over the 9 days. Coadministration of ethanol on the last day further enhanced the impairing effects of diazepam (Baselt, 2001).

A single dose of 10 mg diazepam was given to 10 subjects, followed by 0.5 g/kg ethanol. A simulated driving test was performed 30 to 70 minutes post-dose. The combination of diazepam and ethanol enhanced the number of collisions and driving off the road instances (Linnoila et al., 1990).

Interactions With Other Drugs

Other benzodiazepines, phenothiazines, narcotic analgesics, barbiturates, monoamine oxide inhibitors (MAOIs), and other CNS depressants may potentiate the CNS depressant actions of diazepam. Coadministration of diazepam and opioids significantly increases the risk of respiratory depression, profound sedation, low blood pressure, and death. Cimetidine delays clearance of diazepam and barbiturates may increase the metabolism of diazepam. Fluoxetine may increase the half-life of diazepam. Theophylline has an antagonistic action to some of the deleterious effects of diazepam (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 13 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 13. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include behavior like ethanol, intoxication without the odor of ethanol, staggering and stumbling, lack of balance and coordination, slurred speech, and disorientation.

References and Recommended Reading

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Lorazepam

Lorazepam is a nearly white powder.

Synonyms

Ativan

Source

Lorazepam is a Schedule IV controlled substance and is available as the free base in 0.5 to 2 mg tablets and a 2 mg/mL solution for oral administration, and as a 1 to 4 mg/mL solution for intravenous or intramuscular injection.

Drug Class

Anticonvulsant; anxiolytic; CNS depressant

Uses

Clinical

Lorazepam is an intermediate-acting anticonvulsant, anxiolytic, and sedative-hypnotic agent used in the treatment of status epilepticus and the relief of anxiety and insomnia. Lorazepam is recommended for short-term (2 to 4 weeks) treatment. Off-label uses include the treatment of alcohol withdrawal symptoms and/or delirium, management of agitated patients, muscle spasm, panic disorders, nausea and vomiting, seizures, and procedural sedation.

Non-Clinical

People self-administer lorazepam for its mild euphoric effects, as well as its relaxing, anxiolytic, sedating, and inhibition-reducing properties.

Potency, Purity, and Dose

Lorazepam is a high-potency benzodiazepine. Daily doses of 0.5 to 1 mg are administered orally every 4 to 6 hours or 1 to 4 mg for intravenous/intramuscular doses. For insomnia, a single 2 to 4 mg bedtime dose is recommended.

Pharmacokinetics

Lorazepam has high oral bioavailability (85 to 90%) and is 80 to 90 percent plasma protein bound. The volume of distribution is 0.9 to 1.3 L/kg, and as high as 1.48 L/kg in children. Following oral administration, the elimination half-life ranges from 8 to 25 hours (commonly reported as 10 to 20 hours). Lorazepam is metabolized to an inactive metabolite, lorazepam glucuronide, which has a slightly longer half-life, accumulates in blood, and achieves concentrations equal to or greater than the parent compound. Approximately 88 to 90 percent of an administered dose is eliminated in the urine, with less than 1 percent of a dose excreted as unchanged lorazepam. Lorazepam itself is a metabolite of diclazepam (also known as chlorodiazepam), which is not currently approved for use as a medication.

Blood to Plasma Concentration Ratio

Data not available.

Interpretation of Blood Concentrations

The following studies are summarized in Baselt (2001).

- A single oral dose of 2 mg lorazepam given to eight healthy subjects resulted in average plasma lorazepam concentrations of 18 ng/mL at 2 hours, declining to 9 ng/mL by 12 hours.
- Chronic daily oral administration of 10 mg lorazepam, given in two divided doses to nine healthy subjects, resulted in average steady-state plasma concentrations of 181 ng/mL (range 120 to 240).
- A single intramuscular injection of 4 mg lorazepam given to six healthy subjects resulted in average peak plasma lorazepam concentrations of 57 ng/mL at 1.5 hours.
- A single intravenous injection of 5 mg lorazepam given to four healthy subjects resulted in average peak plasma concentrations of approximately 140 ng/mL within the first few minutes.

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Lorazepam pKa 1.3.

In a study of oral fluid drug concentrations in chronic pain patients, concentrations of lorazepam were determined in oral fluid specimens from 19 patients. Average lorazepam concentrations were 984.6 ng/mL (median 64.8; range 1.4 to 16,684 ng/mL; Heltsley et al., 2011).

General Effects

The pharmacological effects of lorazepam depend on the dose, route of administration, experience of the user, and tolerance. Table 14 provides a range of effects, including side effects, which subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 14. Physiological, motor, and cognitive side effects of lorazepam consumption

Physiological	Motor (behavioral)	Cognitive
• Hypotension • Sedation • Stupor	• Drowsiness • Lethargy • Reduced inhibitions • Confusion • Dizziness • Unsteadiness • Ataxia	• Euphoria • Anterograde amnesia/memory impairment • Reduced anxiety • Reduced concentration

Lorazepam has a profound effect on memory compared to other benzodiazepines, and long-term impairment of cognitive functioning can occur. Other adverse effects may include respiratory depression, hostility, aggression, agitation, depression, and seizures (Baselt, 2020; Chouinard, 2004; PDR, 2021; Seppala et al., 1976).

Duration of Effects

Onset of effects is within 1 to 5 minutes following an intravenous dose, 15 to 30 min following an oral or intramuscular dose. Regardless of route of administration, effects may last as long as 12 to 24 hours.

Tolerance, Dependence, and Withdrawal Effects

Tolerance to some of lorazepam's effects, particularly its strong amnesic effect, can develop with long-term use. Withdrawal or rebound symptoms are more common if recommended doses and/or treatment length are exceeded. Abrupt discontinuation can produce withdrawal symptoms, such as headaches, anxiety, tension, depression, insomnia, restlessness, disorientation, irritability, sweating, dysphoria, nausea, vomiting, stomach spasm, agitation, panic attacks, hallucinations, autonomic instability, and seizure (AAC, 2021; Chouinard, 2004; PDR, 2021).

Driving-Related Studies

Laboratory Studies

The following studies are summarized in Baselt (2001).

- Single oral doses of 0.5, 1, or 2 mg lorazepam or placebo were given to 20 healthy subjects. Subject performance was tested at 3 hours post-dose and included smooth pursuit, paired words, word list recall, semantic recognition, digit span, short story, digit symbol substitution, and sedation self-rating. Lorazepam caused subjective sedation and dose-related impaired performance on all tasks except digit span.
- Single oral doses of 1 or 3 mg lorazepam or placebo were given to 15 healthy subjects. Subject performance was tested at 1-, 3-, and 7-hours post-dose and included the Buschke task (a memory test), digit span, critical flicker fusion, reaction time (visual), tapping rate, arithmetic, and sedation self-rating. The 1 mg lorazepam dose impaired performance on the arithmetic and Buschke tasks. Except for critical flicker fusion, the 3 mg dose impaired performance on all tasks for up to 7 hours. Subjective drowsiness was noted throughout the study.
- A single oral dose of 2 mg lorazepam or placebo was given to 12 healthy subjects. Subject performance was tested during the following 0.25 to 3 hour period and included critical flicker fusion, critical tracking choice reaction time (visual), letter recognition, vigilance (visual), and sedation self-rating. Lorazepam impaired performance on all tasks for up to 2 hours.
- A single oral dose of 2 mg lorazepam or placebo was given to 14 healthy subjects, resulting in average peak plasma lorazepam concentrations of 16 ng/mL at 2.1 hours. Subject performance was tested over the following 24 hours and included digit symbol substitution, word list recall, and sedation self-rating. Lorazepam impaired performance on both tasks for up to 6 hours and caused subjective sedation.

- A single oral dose of 2 mg lorazepam or placebo was given to nine healthy subjects. Subject performance was tested at 2 and 4 hours post-dose and included digit symbol substitution, divided attention tasks, and sedation self-rating. Lorazepam impaired performance on all tasks at both 2 and 4 hours post dose and caused subjective sedation.
- A single oral dose of 2 mg lorazepam or placebo was given to 20 healthy subjects. Subject performance was tested during the following 0.25 to 1.25 hour period and included choice reaction time (auditory), semantic recognition, logical reasoning, word recall list, spatial memory, critical tracking, critical flicker fusion, and sedation self-rating. Lorazepam impaired performance on all tasks and caused subjective sedation.
- A single oral dose of 2 mg lorazepam or placebo was given to nine healthy subjects. Subject performance was tested over the following 4 hours and included word list recall, critical flicker fusion, discriminant reaction time, the Buschke task, and sedation self-rating. Lorazepam caused significant sedation and impairment of vision, reaction time, acquisition memory and retrieval memory.
- A single oral dose of 2 mg lorazepam or placebo was given to 10 healthy subjects. Subject performance was tested at 3.5 hours post-dose and included the Buschke task, digit span, digit symbol substitution, pattern recognition, clerical, critical flicker fusion, number recall, reaction time (visual), choice reaction time (visual), arithmetic, tapping rate, and hand steadiness. Lorazepam significantly impaired performance on all tasks except critical flicker fusion and choice reaction time.
- A single oral dose of 2.5 mg lorazepam or placebo was given to 18 healthy subjects. Subject performance was tested at 4 hours post-dose and included critical flicker fusion, digit symbol substitution, word list recall, symbol copying, digit cancellation, and sedation self-rating. Lorazepam impaired performance on all tasks except critical flicker fusion and caused subjective drowsiness and confusion.
- A single oral dose of 4 mg lorazepam or placebo was given to eight healthy subjects, resulting in average peak serum lorazepam concentrations of 61 ng/L at 0.7 hours. Subject performance was tested over the following 12 hours and included tracking and digit symbol substitution. Lorazepam significantly impaired performance on both tests for 8 to 10 hours.
- Chronic oral doses of 2 mg lorazepam were given to 12 healthy subjects three times a day for 7 days. Subject performance was tested 1 hour after dosing on days 1 and 7 and included critical flicker fusion, choice reaction time, tracking, and sedation self-rating. Lorazepam significantly impaired choice reaction time and tracking on both days and caused sedation through the 7 days. Lorazepam impaired critical flicker fusion on day 1 but this performance returned to baseline on day 7.
- Nightly oral doses of 2 mg lorazepam or placebo were given to eight insomniacs for 3 weeks. Subject performance testing was conducted in the mornings throughout the week and included digit span, digit symbol substitution, and reaction time. Lorazepam did not impair performance on tasks in the morning following treatment.

In another study (Seppala et al., 1976), a single oral dose of 2.5 mg lorazepam or placebo was given to 10 healthy subjects, resulting in an average peak serum lorazepam concentration of 34 ± 15.7 ng/mL at 3 hours, and only declining to an average of 27 ± 9.3 ng/mL at 7 hours. Performance tasks, administered for 7 hours, included choice-reaction, tracking/coordination, flicker fusion, visual parameters (adaption to darkness, sensitivity to brightness, bright counter-light), perceptual speed, and subjective assessments of feelings and driving ability. Lorazepam significantly impaired almost all the measured skills compared to placebo and produced greater and more prolonged performance effects compared to a 10 mg oral dose of diazepam. In an additional seven healthy subjects in the same study, reactive skills and flicker fusion discrimination remained affected for up to7 to 12 hours.

Driving Studies

Oral doses of 1 mg lorazepam or placebo were given to nine healthy subjects three times a day for 3 days. At 30 minutes after the morning dose of 1 mg lorazepam or placebo on the 4th day, subjects started a closed-course driving test that measured parking, braking, turning, slalom, and gap estimation abilities. Lorazepam treatment impaired performance on all driving tests except gap estimation (Baselt, 2001).

Twice daily oral doses of 2 mg lorazepam or placebo were given for 8 days to 18 subjects with anxiety conditions. At 3 hours after the morning dose on days 1 and 8, subjects began a 100 km highway driving circuit to be driven at constant speeds and steady lateral position. Lorazepam impaired standard deviation of lateral position (SDLP[1]) control on day 1 and impairment on this task was present to a lesser degree on day 8 (Baselt, 2001).

Case Reports

Lorazepam was the only drug detected in 23 suspected impaired driving cases, where lorazepam concentrations averaged 51 ng/mL (range < 10 to 380 ng/mL, median 30 ng/mL). Common observations in these drivers were erratic driving, slow and slurred speech, horizontal gaze nystagmus, poor coordination, sedation, dizziness, weakness, and unsteadiness (Clarkson et al., 2004). Blood lorazepam concentrations averaging 30 ng/mL (range 3 to 332 ng/mL) were detected in another 22 subjects arrested for suspected impaired driving (Baselt, 2001).

Interactions With Ethanol

Ethanol has been shown to impair the clearance of lorazepam by 18 percent from blood, resulting in higher blood concentrations and a longer half-life (Garriot, 1996). The following studies are summarized in Baselt (2001).

- A single oral dose of 1 mg lorazepam or placebo was given to nine healthy subjects, followed by a 0.34 g/kg ethanol dose or placebo 1.5 hours after the lorazepam dose. The ethanol was consumed over 10 minutes. Subjects were tested at 0.5 to 1.5 hours after the ethanol dose (2 to 3 hours after the lorazepam dose). Tests included digit symbol substitution, symbol copying, digit cancellation reaction time (auditory), number recall, work list recall and sedation self-rating. Lorazepam alone impaired performance on digit symbol substitution, number recall, word list recall, and caused subjective sedation.

[1] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful differences when related to real-world driving.

Ethanol alone impaired reaction time and caused subjective sedation. In combination, lorazepam and ethanol impaired symbol copying and digit cancellation performance and further increased subjective sedation.

- A single oral dose of 2.5 mg lorazepam or placebo, together with a single oral dose of 1 g/kg ethanol or placebo, was given to 12 healthy subjects. Blood ethanol concentrations averaged 0.08 percent at 1.75 hours post-dose. Subject performance was tested at 1.5- and 3 hours post-dose and included body sway, tracking, choice reaction time (auditory/visual), critical flicker fusion, hand steadiness, tapping rate, horizontal gaze nystagmus, Maddox wing, and sedation self-rating. Lorazepam alone impaired performance on all tasks except hand steadiness and tapping rate. Ethanol alone impaired performance on all tasks except critical flicker fusion. The combination of lorazepam and ethanol impaired performance in an additive manner on all tasks, except for body sway and tracking tasks, which were impaired in a synergistic manner.
- A single oral dose of 2.5 mg lorazepam or placebo was given to nine healthy subjects, followed by 1 g/kg ethanol 1.25 hours later, consumed over 30 minutes. Performance testing occurred at 0.75 and 2.25 hours after the ethanol consumption and included critical flicker fusion, choice reaction time (auditory/visual), tracking, Maddox wing (an instrument to measure alignment of the eyes), body sway, and sedation self-rating. Lorazepam alone impaired performance on all tasks and ethanol increased lorazepam's impairing effects on all tasks except Maddox wing.
- Twice daily oral doses of 1 mg lorazepam or placebo were given to nine healthy subjects for 4 days. On the fourth day, subjects additionally consumed ethanol over 30 minutes with their morning lorazepam dose. Blood ethanol concentrations averaged 0.05 percent 1.5 hours after the lorazepam dose. Subject performance was tested at 1.5-, 3.5-, 5.5-, and 11.5-hours post lorazepam dose on days 3 and 4. Performance tests included critical flicker fusion and reaction time. Lorazepam alone impaired performance on both tasks, as did ethanol. The combination of lorazepam and ethanol enhanced performance impairment on reaction time for up to 5.5 hours.

Interactions With Other Drugs

Coadministration of lorazepam and opioids significantly increases the risk of respiratory depression, profound sedation, and low blood pressure (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 15 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 15. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	Normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include behavior like ethanol, intoxication without the odor of ethanol, staggering and stumbling, lack of balance and coordination, slurred speech, and disorientation.

References and Recommended Reading

Baselt, 2001; Baselt, 2020; Garriot, 2008; Heltsley et al., 2011, 529-540; PDR, 2021.

American Addiction Centers. (2021). *Ativan (lorazepam) withdrawal and treatment.* [Web page]. https://withdrawal.net/benzodiazepine/lorazepam/

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Clarkson. J. E., Gordon, A. M. & Logan, B. (2004, August 28-September 3). *Lorazepam and death investigation*. 2004 FBI Laboratory Symposium on Forensic Toxicology and Joint Meeting of the Society of Forensic Toxicologists & the International Association of Forensic Toxicologists, Washington, DC.

Seppala, K., Korttila, K., Hakkinen, S., & Linnoila, M. (1976). Residual effects and skills related to driving after a single oral administration of diazepam, medazepam or lorazepam. *British Journal of Clinical Pharmacology,* (5):831-41.

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Designer Benzodiazepines

Designer benzodiazepines are a rapidly growing recreational drug class used for their sedating and intoxicating effects or for their ability to enhance/reduce the effects of other abused drugs. Examples of designer benzodiazepines include phenazepam, etizolam, flubromazolam, flualprazolam, clonazolam, diclazepam, and pyrazolam. Designer benzodiazepines are not currently approved for clinical use in the United States but are readily available through online markets. They are benzodiazepine derivatives and share many similar effects to traditional benzodiazepines such as sedative, anxiolytic, hypnotic, anticonvulsant, and amnesic effects. Like traditional benzodiazepines, designer benzodiazepines are positive allosteric modulators of the GABA receptor, enhancing inhibitory signaling in the CNS. They are of high potency, with low doses producing strong sedation and amnesia (Logan et al., 2017). Many have longer durations of action than pharmaceutical benzodiazepines; there have been reports of drug-induced confusional states lasting several days.

In a summary of 77 cases (suspected impaired drivers and other criminal offenders), the following designer benzodiazepines and corresponding blood concentrations were detected: median flubromazolam concentration 12 ng/mL (n=25; range 0.48 to 100 ng/mL); median flubromazepam concentration 55 ng/mL (n=24; range 4.7 to 1,200 ng/mL); median diclazepam concentration 13 ng/mL (n=15; 2.1 to 57 ng/mL); median etizolam concentration 50 ng/mL (n=14; range 19 to 170); median clonazolam concentration 5.3 ng/mL (n=7; range 1.9 to 11 ng/mL); and a single pyrazolam concentration of 74 ng/mL (Hoiseth et al., 2016). The designer benzodiazepine was the sole drug detected in blood in only six of the 77 cases.

Phenazepam

Phenazepam is commercially available in Russia for the treatment of epilepsy, anxiety, and sleeping disorders. It is estimated to be 5 to 10 times more potent than diazepam. Its onset of action occurs within 2 to 3 hours. Following clinical doses of 0.5 to 5 mg, peak phenazepam concentrations are 20 to 60 ng/mL, approximately 4 hours after dosing. Phenazepam has an elimination half-life of up to 60 hours. Reported effects following the use of phenazepam include loss of coordination, drowsiness, dizziness, blurred vision, slurred speech, amnesia, and ataxia (Logan et al., 2017).

Phenazepam was detected in 11 suspected impaired driving cases, with phenazepam the only drug detected in five cases. The average blood phenazepam concentration was 500 ng/mL (median 170 ng/mL; range 40 to 3,200 ng/mL). In the phenazepam-only cases, the average blood phenazepam concentration was 690 ng/mL (median 680 ng/mL; range 40 to 3,200 ng/mL). In these five cases, commonly cited observations were like those of a CNS depressant and included slow and slurred speech, slow reactions, lack of balance, drowsiness, and disorientation. Other noted observations included signs of lethargy and intoxication, clues of impairment during standardized field sobriety tests, and sometimes horizontal gaze nystagmus. The subject with the highest phenazepam concentration (3,200 ng/mL) exhibited memory loss, disorientation, dilated pupils, and slurred speech, and had driven off the road into a tree (Stephenson et al., 2013). In another study, a 24-year-old male driver was involved in a two-vehicle collision when he failed to stop at an intersection. Phenazepam, at a blood concentration of 76 ng/mL, was the only substance detected. Slurred speech, disorientation, unsteadiness and staggering, and profound psychomotor impairment were noted (Kerrigan et al., 2013).

Etizolam

Etizolam is commercially available in Japan, Korea, and Italy for the treatment of anxiety and for its muscle relaxant properties. It is estimated to be 6 to 10 times more potent than diazepam. Peak plasma concentration occurred at 0.5 to 2 hours, with a half-life of 3.4 hours. A single oral dose of 2 mg etizolam resulted in an average plasma C_{max} of 25 ng/mL. Reported effects following the use of etizolam include drowsiness, sedation, muscle weakness, muscle incoordination, fainting, headache, confusion, depression, slurred speech, visual disturbances, and tremors. In 11 cases involving urinalysis (subjects and circumstances unknown), urine phenazepam concentrations were 5.8 to 270 ng/mL (Logan et al., 2017). Etizolam has no approved therapeutic use in the US but is available via the Internet.

Flubromazolam

Flubromazolam is highly potent, producing strong sedation and amnesia at oral doses as little as 0.5 mg. Observed symptoms included hypotension, tachycardia, hypoventilation, and deep coma. Flubromazolam was detected in serum at 59 ng/mL and in urine at 105 ng/mL. In 96 cases involving urinalysis (subjects and circumstances unknown), urine flubromazolam concentrations ranged from 5.4 to 1,500 ng/mL (Logan et al., 2017).

References and Recommended Reading

Logan et al., 2016, 35-38.

Høiseth, G., Tu, S. S., & Karinen, R. (2016). Blood concentrations of new designer benzodiazepines in forensic cases. *Forensic Science International*, *268*:35-38.

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Cannabinoids (e.g., Δ9-tetrahydrocannabinol, dronabinol)

Cannabis is a plant that can be divided into three species—*Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.

Δ^9-tetrahydrocannabinol (Δ^9-THC[1]) is a psychoactive component in cannabis. There are a variety of products people may ingest for therapeutic or euphoric effects, including marijuana,[2] hashish, sinsemilla, "dabs", wax, and edibles.

In addition to Δ^9-THC, cannabis contains more than 110 other cannabinoids, including minor cannabinoids cannabidiol, cannabinol, cannabigerol, cannabichromene (CBC), Δ^8-THC, Δ^9-tetrahydrocannabivarin, and cannabinoid precursors including tetrahydrocannabinolic acid, cannabidiolic acid. There are also more than 400 other chemicals including polyaromatic hydrocarbons, terpenes, and flavonoids.

Synonyms

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Marijuana refers to the dried shredded leaves and flowering tops of the cannabis plant; the buds are often preferred because of their higher Δ^9-THC content. Hashish consists of the Δ^9-THC-rich resinous secretions of the plant, which are collected, dried, compressed and smoked. Hashish oil or "dabs" are produced by extracting cannabinoids from plant material with an organic solvent (e.g., butane).

Marijuana is a Schedule I controlled substance under the Federal Controlled Substances Act (CSA; 21 U.S.C. §801 et seq.) In 2018 the CSA was revised, removing hemp (cannabis containing no more than a 0.3 percent concentration of the psychoactive compound delta-9-tetrahydrocannabinol [delta-9-THC]) from the definition.[3]

Marinol (dronabinol) is a Schedule III FDA-approved synthetic Δ^9-THC available in strengths of 2.5, 5, or 10 mg in round, soft gelatin capsules. Syndros (dronabinol) is available as a 1- and 5-mg/mL strength oral solution. Epidiolex is the first FDA-approved CBD medication available as a 100 mg/mL strength oral solution; it is currently unscheduled in the United States due to its lack of abuse liability. Sativex (nabiximols) is available as a sublingual spray in Canada, the United Kingdom, and several European Union countries, but not in the United States; each 100 µL spray contains 2.7 mg Δ^9-THC and 2.5 mg CBD.

Drug Class

Cannabis: Cannabis' spectrum of behavioral effects is unique, preventing classification of the drug as solely a stimulant, sedative, tranquilizer, or hallucinogen, although it has effects in common with all these drug classes.

Dronabinol: Appetite stimulant; antiemetic

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[1] Pronounced "delta 9 THC."

[2] "Cannabis" and "marijuana" are often used interchangeably although they do not entirely mean the same thing.

[3] For more on the Controlled Substance Act see, Congressional Record Service (May 2, 2024). The *Federal Status of Marijuana and the Policy Gap with States,* https://crsreports.congress.gov/product/pdf/IF/IF12270

Uses

Clinical

In the United States, all but four States legalized some form of therapeutic-use cannabinoids. Marinol is FDA-approved for treatment of HIV/AIDS wasting disease and chemotherapy-associated nausea and vomiting. Epidiolex is FDA-approved for two rare but severe childhood seizure disorders: Dravet and Lennox-Gastaut Syndrome. Sativex is under investigation in the United States for the treatment of spasticity in multiple sclerosis and analgesia of neuropathic pain; it is currently approved in several European countries but does not yet have FDA approval in the United States.

Non-Clinical

Cannabis is self-administered for its mood-altering effects, euphoria, and relaxation. Cannabis is the most common recreational drug worldwide behind ethanol (alcohol). It is also the drug with the highest prevalence in cases involving driving under the influence of drugs, other than ethanol, and the source of more positive results in workplace drug tests than any other drug of abuse.

Potency and Dose

Potency of cannabis products is dependent upon Δ^9-THC concentration and is expressed as %Δ^9-THC per dry weight of plant material. ElSohly et al. (2016), monitored cannabis potency in 38,681 samples seized by the DEA over two decades and found the potency of illicit cannabis consistently rose from approximately 4 percent Δ^9-THC in 1995 to approximately 12 percent in 2014. The CBD content fell on average from approximately 0.28 percent in 2001 to < 0.15 percent in 2014. Dabs and oils are even more potent cannabis products (up to 90% Δ^9-THC) that can be vaped in e-cigarettes.

People can titrate their Δ^9-THC dose based on the way they inhale smoked or vaporized cannabis. People immediately feel the subjective effects and physiological heart rate increase with their first puff and can adjust the amount and rate of Δ^9-THC intake, based on their smoking or inhalation typography. Inexperienced cannabis users may not have the ability to titrate an inhaled dose. It is not possible to titrate an oral dose because of the substantial delay in Δ^9-THC absorption and effects.

The initial starting dose of Marinol is 2.5 mg, twice daily, increasing to up to 20 mg a day. A starting dose of Sativex is four sprays (approximately 10.8 mg Δ^9-THC) with a variable maximum of 16 or more sprays. Epidiolex has a starting dose of 5 mg/kg daily increasing to a maximum of 20 mg/kg daily. These high doses are necessary to suppress previously uncontrollable seizures. An increase to 30 mg/kg can be considered as necessary based on the presence of adverse effects.

Route of Administration

Inhalation (smoking, vaporization) is the most common route of administration, although oral ingestion of edible products including sodas, beer, bakery products, and candies is becoming more common. “Dabbing” is slang for inhalation of a high-potency (generally higher than 75%) Δ^9-THC cannabis extract.

Pharmacodynamics

The endogenous cannabinoid neurotransmitter system is critical for maintaining homeostasis or stability in important physiological functions such as the control of locomotion, emotional behavior, cognitive function, cardiovascular responses, pain, feeding behavior, and addiction. The entire cannabinoid system consists of central and peripheral CB_1 cannabinoid receptors, primarily peripheral CB_2 cannabinoid receptors, several endogenous cannabinoids termed *eicosanoids* (anandamide, arachidonyl ethanolamine, and others) that bind to the receptors, enzymes for inactivating anandamide (fatty acid amide hydrolase, or FAAH) and arachidonyl ethanolamine (monoacylglycerol lipase), and transporters of endocannabinoids across cell membranes. Cannabinoid receptors, which belong to the G protein class of receptors, are found in high density in the cerebral cortex, hippocampus, amygdala, striatum, and cerebellum, which are functional areas associated with the most prominent behavioral and motor effects of cannabinoids.

Δ^9-THC, a partial agonist at both the CB_1 and CB_2 receptors, binds to and interferes with normal cannabinoid physiological, psychomotor, and cognitive function. CB_1 cannabinoid receptors regulate functions such as sleep, appetite, perception of time, short-term memory, and coordination. CB_2 cannabinoid receptors modulate the immune system, pain, inflammation, and tissue damage. Low concentrations of CB_2 cannabinoid receptors are found in the brain but are increased during inflammation in this organ. Binding via other mechanisms, such as to serotonin, β-adrenergic, and μ-opioid receptors, may explain additional cannabinoid effects.

Cannabinoids have varying affinity on CB_1 and/or CB_2 receptors –some of these can act as partial agonists (e.g., Δ^8-THC, CBN), while others can act as antagonists (e.g., THCV). Endogenous and exogenous cannabinoids may bind to additional G-protein coupled receptors termed orphan receptors including GPR 18, 55, 119, PPAR nuclear receptors, and a wide variety of ion channel receptors including transient receptor potential (TRP) receptors found throughout the body.

Pharmacokinetics

Δ^9-THC is absorbed rapidly during smoking or vaporization with peak blood concentrations occurring within 5 to 10 minutes. Intense and strongly reinforcing effects may be produced, owing to the almost immediate exposure of the CNS to the drug. Absorption is slower following the oral route of administration with lower, more delayed peak Δ^9-THC concentrations over several hours. Bioavailability is reduced following oral ingestion due to degradation in the stomach and extensive first pass metabolism in the liver. Δ^9-THC is 94 to 99 percent protein bound in the blood. Δ^9-THC is highly lipid soluble and is rapidly distributed through the body to organs with high blood flow such as the brain, heart, liver and kidney, and later distribution into the fat.

Δ^9-THC is primarily metabolized in the liver to 11-hydroxy-tetrahydrocannabinol (11-OH-THC), which is equipotent to Δ^9-THC. The 11-OH-THC is further metabolized to 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH), which is not psychoactive. Most Δ^9-THC is excreted via the feces (~ 65%) with approximately 30 percent of the Δ^9-THC being eliminated in the urine, both as glucuronic acid conjugates of primarily THC-COOH, 11-OH-THC and small amounts Δ^9-THC -glucuronide. Less than 0.05 percent is excreted in the urine as unchanged Δ^9-THC. Blood Δ^9-THC and urinary THC-COOH elimination half-lives are best estimated at 3 to 4 days,

where the rate-limiting step is the slow redistribution of Δ^9-THC sequestered in the tissues back into blood. Shorter half-lives are reported due to limited collection intervals and less sensitive analytical methods.

The pharmacokinetics of chronic frequent cannabis use are different than occasional cannabis use because of the buildup of stored Δ^9-THC in body fat with daily intake, and the slow release of Δ^9-THC into the blood, even during sustained abstinence. It is the active Δ^9-THC that is stored, not the inactive THC-COOH metabolite. Bergamaschi et al. (2013), found low Δ^9-THC concentrations up to 30 days after last cannabis use in two of 27 chronic frequent cannabis users' blood at a 0.3 ng/mL limit of quantification, only 1 of 11 participants was negative at 26 days, and 5 percent of participants had Δ^9-THC ≥ 1.0 ng/mL for 12 days. The chronic frequent users resided on a closed research unit with no access to drug for up to 30 days; almost half of the users' blood had no detectable Δ^9-THC 19 hours after entrance onto the research unit. Median 11-OH-THC concentrations were 1.1 ng/mL on admission, with no results ≥ 1.0 ng/mL 24 hours later. THC-COOH detection rates were 96.7 percent on admission, decreasing slowly to 95.7 percent and 85.7 percent on days 8 and 22, respectively; 4 of 5 participants remained THC-COOH positive (0.6 to 2.7 ng/mL) after 30 days.

The brain is a highly lipophilic organ due to the myelin sheaths on the nerves; Δ^9-THC can still be measured in the brain when it is no longer detectable in blood (Mura et al., 2005). The extended detection of cannabinoids in blood of frequent cannabis smokers is consistent with the time course of psychomotor impairment in frequent cannabis users described by Bosker et al. (2013), and the decreased density of CB_1 cannabinoid receptors in the brains of frequent cannabis users described by Hirvonen et al. (2012).

Blood to Plasma Concentration Ratio

Reported average and median ratios vary both inter- and intra-individually.

Δ^9-THC: 0.68 (0.31 to 1.1) (Desrosiers et al, 2014b); 0.67 (0.53 to 0.71) (Giroud et al., 2001)

11-OH-THC: 0.63 (0.38 to 1.1) (Desrosiers et al., 2014b); 0.59 (0.45 to 0.53) (Giroud et al., 2001)

THC-COOH: 0.59 (0.41 to 1.2) (Desrosiers et al., 2014b); 0.625 (0.56 to 0.67) (Giroud et al., 2001)

THC-COOH-glucuronide: 0.47 (0.24 to 1.1) (Desrosiers et al., 2014b)

CBN: 0.84 (0.47 to 1.3) (Desrosiers et al., 2014b)

Interpretation of Blood Concentrations

The number, duration, and spacing of puffs, the hold time in the lungs, and the inhalation volume greatly influence the degree of Δ^9-THC exposure. These factors contribute to the high variability (18 to 50%) in Δ^9-THC delivery by the smoked route; the actual dose is much lower than the amount of Δ^9-THC and Δ^9-THC precursor present in cannabis.

The absorption, distribution, metabolism, and initial elimination of Δ^9-THC and metabolites were characterized in occasional cannabis users, where blood was collected continuously from the start of cannabis smoking through the first hour, followed by individual blood collections over 7 days. The following was a computer-paced controlled cannabis administration study, rather than

an *ad libitum* administration. It provided data on Δ^9-THC absorption during actual smoking; following the first puff of a 1.75 percent (15.8 mg) or 3.55 percent (33.8 mg) Δ^9-THC cigarette, plasma Δ^9-THC concentrations averaged 7.0 ng/mL (range 0 to 20.0 ng/mL) and 18.1 ng/mL (range 1.8 to 37.0 ng/mL), respectively. Peak plasma concentrations averaged 84.3 ng/mL (range 50 to 129 ng/mL) and 162.2 ng/mL (range 76 to 267 ng/mL), respectively. Average Δ^9-THC concentrations 15 and 30 minutes after smoking were approximately 60 percent and 20 percent of peak concentrations, respectively, demonstrating the rapid decrease in Δ^9-THC concentrations after the end of smoking. Within 2 hours, plasma Δ^9-THC concentrations were ≤ 5 ng/mL. Using a GC-MS with a limit of quantitation (LOQ) of 0.5 ng/mL, Δ^9-THC's window of detection was 3 to 12 hours after the low (1.75%) Δ^9-THC dose and 6 to 27 hours after the high (3.55%) Δ^9-THC dose cigarette. Although the amount of Δ^9-THC in the doses was lower than is present in many cannabis cigarettes in 2020, the peak concentrations are like those reported today because cannabis users titrate their dose to obtain their desired level of high in tandem with their tolerable heart rate increases (Huestis et al., 1992b).

In the same study, peak plasma concentrations of 11-OH-THC were approximately 6 to 10 percent of concurrent peak Δ^9-THC concentrations; C_{max} occurred on average at 13.5 minutes (range 9.0 to 22.8 minutes) after smoking initiation. 11-OH-THC concentrations decreased gradually, with average detection times of 4.5 hours and 11.2 hours after the two doses, respectively, using a 0.5 ng/mL cutoff. THC-COOH concentrations in the plasma increased slowly and plateaued for up to 4 hours. This inactive metabolite was detected in the plasma of all participants within 8 minutes after the start of cannabis smoking. Peak concentrations were consistently lower than peak Δ^9-THC concentrations; average peak plasma THC-COOH concentrations were 24.5 ng/mL (range 15 to 54 ng/mL) and 54.0 ng/mL (range 22 to 101 ng/mL) after the low- and high-dose cannabis cigarettes, respectively. THC-COOH detection times averaged 84 hours (range 48-≥ 168 hours) and 152 hours (range 72-≥ 168 hours), respectively, using a 0.5 ng/mL LOQ.

In a search for a marker of recent cannabis intake, nine frequent cannabis smokers smoked one 6.8 percent Δ^9-THC cigarette, *ad libitum*. Median C_{max} blood concentrations of 50 ng/mL for Δ^9-THC, 6.4 ng/mL for 11-OH-THC, 41 ng/mL for THC-COOH, 1.3 ng/mL for CBD, 2.4 ng/mL for CBN, and 89 for THC-COOH-glucuronide were reported 15 minutes after smoking initiation. At 30 minutes, the median blood C_{max} was 0.7 ng/mL for Δ^9-THC-glucuronide. At these C_{max} levels, detection rates in blood were 60 percent CBD, 80 percent for CBN, and 50 percent for THC-glucuronide. CBD and CBN were not detectable after 1 hour. Blood Δ^9-THC and THC-COOH concentrations decreased to 10 and 27 ng/mL, respectively, at 1-hour post-dose, and further decreased to 1.4 and 16 ng/mL at 6 hours (Schwope et al., 2011).

Blood concentrations of free and glucuronidated cannabinoids were measured in 11 frequent and nine occasional cannabis users after the *ad libitum* smoking, inhalation and eating of approximately 50.6 mg Δ^9-THC (one 6.9 percent Δ^9-THC) cigarette. Median (range) C_{max} blood concentrations in frequent cannabis users after smoked, vaporized and oral administration were 117 ng/mL (52.8 to 471 ng/mL), 88 ng/mL (24.7 to 170 ng/mL), 15.6 ng/mL (4.7 to 34.8 ng/mL) for THC; 7.2 ng/mL (1.9 to 30.9 ng/mL), 6.2 ng/mL (1.6 to 10.7 ng/mL), 7.5 ng/mL (2.2 to 14.3 ng/mL) for 11-OH-THC; 50.7 ng/mL (15.6 to 137 ng/mL), 41.4 ng/mL (13.5 to 98.0 ng/mL), 71.8 ng/mL (33.5 to 119 ng/mL) for THC-COOH; and 106 ng/mL (49.9 to 248 ng/mL), 66.8 ng/mL (18.1 to 225 ng/mL), 113 ng/mL (84.9 to 304 ng/mL) for THC-COOH-glucuronide, respectively. Median (range) C_{max} blood concentrations in occasional cannabis users after

smoked, vaporized and oral administration were 44.4 ng/mL (1.3 to 174 ng/mL), 34.8 ng/mL (5.2 to 137 ng/mL), 10.1 ng/mL (3.6 to 22.5 ng/mL) for THC; 1.9 ng/mL (0.5 to 8.7 ng/mL), 1.6 ng/mL (0.7 to 3.5 ng/mL), 5.1 ng/mL (2.4 to 11.0 ng/mL) for 11-OH-THC; 7.4 ng/mL (0.7 to 17.5 ng/mL), 5.3 ng/mL (1.4 to 15.9 ng/mL), 37.8 ng/mL (12.5 to 70.4 ng/mL) for THC-COOH; and 21.4 ng/mL (11.8 to 25.0 ng/mL), 16.1 ng/mL (5.3 to 23.7 ng/mL), 124 ng/mL (70.9 to 178 ng/mL) for THC-COOH-glucuronide, respectively. Δ^9-THC C_{max} was significantly lower after oral compared to inhaled doses in frequent and occasional cannabis users. 11-OH-THC C_{max} and T_{last} (time of last detection) after oral dosing was significantly greater and later in occasional smokers only. Frequent smokers' Δ^9-THC and THC-COOH C_{max} levels were significantly higher after smoking than vaporization (Newmeyer et al., 2016).

It was further determined that at the frequent smokers' final collection time (72 hours post dose), 100 percent, 90.9 percent and 100 percent of specimens were Δ^9-THC positive after smoked, vaporized, and oral cannabis; concentrations were 0.5 to 4.3, 0.7 to 3.7, and 0.8 to 2.5 ng/mL, respectively. In contrast, 100 percent, 100 percent, and 88.9 percent of occasional smokers' specimens were negative at the final collection (54 hours post dose) after smoked, vaporized, and oral cannabis, respectively. For 11-OH-THC, 90.9 percent, 81.8 percent and 90.9 percent of frequent smokers were negative 72 hours after smoked, vaporized and oral doses, respectively; T_{last} varied among those participants (5.0 to 56, 2.5 to 38, and 5.0 to 50 hours, respectively). Occasional smokers' 11-OH-THC T_{last} (average [range]) after smoking (1.7 [0.25 to 3.5] hours) and vaporization (1.5 (0.25 to 3.5) hours] were significantly shorter than after oral dosing (14 [5.0 to 32]) hours. Frequent smokers' observed 11-OH-THC C_{max} levels were significantly greater and T_{last} significantly later than occasional smokers', regardless of route. If present, CBD, CBN, CBG, and THCV were present only after smoked and vaporized cannabis, concentrations were too low following the oral route. CBG and CBN were frequently identified in blood after smoking with short detection windows, but their absence does not exclude recent cannabis use. Overall, the presence of minor cannabinoids (CBG, CBN, THCV) and Δ^9-THC -glucuronide in blood may be good markers of recent cannabis intake; however, CBD cannot be used as a marker of recent cannabis use because there are many high-concentration CBD-only products on the market.

Concentrations vary depending on the potency of cannabis, the dose, route of administration, and the frequency of cannabis intake. Peak concentrations occur during smoking or vaporization within 5 to 10 minutes, while peak concentrations generally occur 2 to 4 hours after oral ingestion. Concentrations in frequent cannabis users are generally higher than in occasional cannabis users because they can titrate their inhaled dose and may develop partial tolerance to the cardiovascular and physiological effects of cannabis. Tolerance may be different for each cannabis effect and is never complete. The 11-OH-THC concentrations occur within about 30 minutes after the start of smoking. Concentrations of both analytes decline rapidly. In occasional smokers, blood Δ^9-THC was detected for only a median of 4 hours (range 1 to 6 hours) after smoking a single 54 mg Δ^9-THC cigarette (Hartman et al., 2016a). In driving-under-the-influence cases, blood is typically collected approximately 1 to 4 hours after an incident or crash, with an unknown last cannabis intake time. This complicates interpretation of blood Δ^9-THC concentrations because Δ^9-THC concentrations decrease rapidly after the last inhalation. In a study of the effects of low dose ethanol and cannabis on driving impairment conducted at the National Advanced Driving Simulator at the University of Iowa, Hartman et al. (2016a) observed about a 74 percent decrease in blood Δ^9-THC concentration 30 minutes after the Δ^9-THC C_{max} and 90 percent decrease after 1.4 hours.

It is difficult to establish a relationship between a person's Δ^9-THC blood or plasma concentration and performance impairing effects. A positive blood THC-COOH concentration documents prior cannabis exposure but does not necessarily indicate impairment. It is possible for a person to be affected by marijuana use with concentrations of Δ^9-THC in their blood below the LOQ. Substantial inter- and intra-individual variability in cannabis intake and metabolism, dose, cannabis use history, and lack of zero-order pharmacokinetics (a constant predictable decline, as in ethanol metabolism) preclude retrograde-extrapolation of a Δ^9-THC result (Hartman et al., 2016a).

A prior frequent cannabis intake history produces the additional complication of residual Δ^9-THC in the blood. Due to the large Δ^9-THC body burden, residual Δ^9-THC may be detected in some chronic, frequent smoker's blood for up to 30 days after the start of sustained abstinence (LOQ 0.25 ng/mL; Bergamaschi et al., 2013). Odell et al. (2015) monitored Δ^9-THC in the blood of Australian frequent cannabis users from the start of cannabis abstinence. In 11 people providing one blood sample each day for 7 days, nine were Δ^9-THC -positive (≥ 1 ng/mL) for all 7 days. One frequent smoker had a blood Δ^9-THC concentration ≥ 5 ng/mL for as long as 5 days of sustained abstinence.

The lack of a direct correlation between blood Δ^9-THC concentrations and performance impairing effects necessitates introduction of other evidence to prove effects on driving. DRE evaluations documenting impairment consistent with cannabis use is often the evidence needed to prove that a driver was impaired, with the toxicology blood Δ^9-THC result confirming which drug produced or contributed to the observed impairment.

OF(S) to Blood Concentration Ratios

Δ^9-*THC*: median 9.4 (*n*=413; range 0.3 to 887) (Hartman et al., 2015c)

Δ^9-*THC*: median 14 (*n*=46; average 31; range 1.0 to 190) (Langel et al., 2013)

Δ^9-*THC*: median 4.7, (*n*=11; average 8.2) (Gjerde et al., 2010)

THC-COOH: median 3.7 (*n*=339; range 0.6 to 20.9) (Hartman et al., 2015c)

The ratio of OF Δ^9-THC to blood Δ^9-THC varies with the time after drug intake (Desrosiers & Huestis, 2019). Immediately after cannabis inhalation or oral ingestion, the concentration of Δ^9-THC in the OF is high (1,000's of ng/mL) due to the exposure of the oral mucosa to Δ^9-THC -laden smoke or food. In two to three hours, Δ^9-THC dissipates and concentrations in OF parallel Δ^9-THC concentrations in blood. Thus, the ratios change substantially over time. In every case studied, this variability precludes predicting cannabinoid blood concentrations from cannabinoid OF concentrations.

Oral Fluid to Plasma Concentration Ratios

Δ^9-*THC*: median 7.3 (*n*=455; range 0.2 to 585) (Hartman et al, 2015c)

THC-COOH: median 2.4 (*n*=341; range 0.4 to 13.3) (Hartman et al, 2015c)

Interpretation of OF(S) Test Results

Δ^9-THC pKa 10.6

A major challenge in detecting recent cannabis use is that blood Δ^9-THC concentrations rapidly decline after smoking or vaping cannabis, often becoming undetectable after 3 hours. OF testing represents a possible solution because it can be performed by police officers at the roadside and its detection window extends beyond 3 hours to confirm recent cannabis use.

Cannabinoid detection windows in OF are influenced by administration route, dose, and drug use history. Δ^9-THC OF concentrations can be > 1,000 ng/mL shortly after smoking, whereas minor cannabinoids are detected at 10-fold and metabolites at 1,000-fold lower concentrations (Hartman et al, 2015b). Δ^9-THC concentrations in OF primarily reflect the coating of the oral mucosa with drug during smoking, vaporization, or ingestion of Δ^9-THC, followed by gradual removal through salivary flow. 11-OH-THC and THC-COOH concentrations in OF are in the pg/mL concentration range and are not present in cannabis products. When these Δ^9-THC metabolites are found in OF, it suggests cannabis intake; Δ^9-THC entered the systemic circulation and was metabolized. Identification of the minor cannabinoids THCV and CBG (≥ 0.3 ng/mL) resulted in detection windows indicative of recent cannabis intake.

While the OF matrix has an improved window of detection for cannabinoids, quantitation of cannabinoids is highly variable among users. In one study OF was collected from 10 cannabis users following *ad libitum* smoking of one 6.8 percent Δ^9-THC cigarette, at time intervals from 15 minutes to 22 hours. In the first sample at 15 minutes, the median maximum (C_{max}) Δ^9-THC concentration was 644 ng/mL, with a range of 68.0 to 10,284 ng/mL. Concentrations dropped to 212 ng/mL (40.0 to 6,362 ng/mL), 287 ng/mL (18.9 to 2,440 ng/mL), and 94.1 ng/mL (16.0 to 519 ng/mL) at 0.5, 1 and 2 hours, respectively. All samples were Δ^9-THC positive at 6 hours (range 2.1 to 44.4 ng/mL), and four were still positive at 22 hours. The median C_{max} for THC-COOH was 115 pg/mL, with all samples positive at 6 hours (range 14.8 to 263 pg/mL) and five still positive at 22 hours (Lee et al., 2012).

Chronic frequent cannabis smokers may have higher initial OF concentrations than occasional smokers due to more efficient smoking topography and/or tolerance development. Toennes et al. (2010) reported that chronic cannabis smokers had significantly higher Δ^9-THC C_{max} (average 12,457 ng/g) than occasional smokers (1,715 ng/g) despite body weight normalized doses (500 µg/kg Δ^9-THC cigarettes). When comparing OF cannabinoid concentrations collected from 19 hours before to 30 hours after smoking a 6.8 percent Δ^9-THC cigarette, in chronic frequent and occasional cannabis smokers, all OF specimens were Δ^9-THC-positive for up to 13.5 hours after smoking, without significant differences between frequent and occasional smokers over 30 hours (Anizan et al., 2013). Out of 292 OF samples, THC-COOH was detected in only 25 occasional smokers compared to 212 frequent smokers. THC-COOH in OF has a much greater prevalence in frequent than occasional users.

In addition to higher initial OF concentrations after cannabis use, chronic frequent cannabis smokers may have a longer detection window for OF cannabinoid measurement. Frequent and occasional cannabis smokers received one active (6.9 percent Δ^9-THC, approximately 50.6 mg) cannabis cigarette that was vaporized or smoked and OF collected for up to 54 (occasional) or 72 (frequent) hours after dosing. OF cannabinoid C_{max} occurred during or immediately after cannabis consumption. Significantly greater Δ^9-THC C_{max} were observed after smoked and vaporized cannabis compared to oral cannabis in frequent smokers only. Following the smoked and vaporized doses, the last detection times for Δ^9-THC were 24.7 and 18.6 hours in occasional users, respectively, and 61.0 and 55.4 hours in frequent smokers, respectively. This highlights

the need for adequate pairing of laboratory results with actual roadside assessment of impairment (Swortwood et al., 2017).

OF Δ^9-THC concentrations peak after 10 minutes of smoking or vaporizing cannabis, but the dose of Δ^9-THC used does not adequately correlate With OF Δ^9-THC concentration. Spindle et al. (2020), measured OF Δ^9-THC in 17 occasional cannabis users following smoked or vaporized cannabis containing 10 and 25 mg Δ^9-THC, at baseline and for 8 hours after administration. Δ^9-THC was detected longer in OF compared to blood. Following the 10 and 25 mg smoked Δ^9-THC dose, the average C_{max} was 167 ng/mL (range 0 to 1,063 ng/mL) and 496 ng/mL (58 to 2,368 ng/mL), respectively. After the same doses vaporized, the average C_{max} was 91 ng/mL (range 7 to 383 ng/mL) and 506 ng/mL (60 to 1,646 ng/mL), respectively. Last detection times after 10 and 25 mg smoked Δ^9-THC were 5.9 hours (range, 2.0 to 8.0 hours) and 5.8 hours (1.0 to 8.0 hours), respectively. After the same vaporized doses, the last detection times were 5.2 hours (1.0 to 8.0 hours) and 4.2 hours (0.5 to 8.0 hours). In another study, OF samples were collected for 30 hours following 10 minutes of *ad libitum* smoking of a 6.8 percent (approximately 50 mg) Δ^9-THC cigarette; Δ^9-THC last detection times were 2 to ≥ 30 hours (Arnold et al., 2019). Variability in last detection times may be problematic when attempting to confirm exposure to cannabis within a defined period.

The OF matrix relies on exposure of the oral mucosa to bioavailable Δ^9-THC. Certain pharmaceutical formulations of Δ^9-THC may prevent the oral mucosa from coming in contact with Δ^9-THC. For example, following oral administration of 37 doses of 20 mg dronabinol/synthetic Δ^9-THC (Marinol) to 10 frequent cannabis users around-the-clock for 9 days, Δ^9-THC, 11-OH-THC, CBD, and CBN and THC-COOH were quantified in OF samples. THC-COOH was the most prevalent analyte in 432 samples (98.2%), with concentrations up to 1,118 pg/mL. 11-OH-THC was not detected and Δ^9-THC was present in only 20.7 percent of samples, with highest concentrations occurring near their admission to the study (median 4.2, range 0.6 to 482 ng/mL) from previously self-administered smoked cannabis (Milman et al., 2010). Dronabinol is encapsulated and does not deposit Δ^9-THC in the oral mucosa during administration. People who are only taking prescription Marinol may not have a Δ^9-THC positive OF sample despite the potential for driving impairment.

Several studies have demonstrated OF Δ^9-THC detection after cannabis edible consumption. Vandrey et al. (2017), measured OF Δ^9-THC after consumption of brownies containing approximately 10, 25 or 50 mg Δ^9-THC by six subjects, resulting in an average OF Δ^9-THC C_{max} of 192 ng/mL (range 47.0 to 412 ng/mL), 478 ng/mL (70.0 to 1,128 ng/mL), and 598 ng/mL (350 to 1,010 ng/mL), respectively. THC-COOH C_{max} was 50.8 pg/mL (range 0.0 to 231 pg/mL), 140 pg/mL (23.0 to 251 pg/mL), and 314 pg/mL (0.0 to 822 pg/mL), respectively. The average OF Δ^9-THC T_{max} occurred immediately following the oral brownie administration and OF samples remained positive for an average of 1.9 hours (up to 3 hours), 3.0 hours (2 to 6 hours) and 9.5 hours (3 to 22 hours), respectively. THC-COOH generally peaked later and was detected for a much longer period (up to 78 hours) in some people and not detected at all in others.

Newmeyer et al. (2017), compared OF Δ^9-THC concentrations between frequent and occasional cannabis smokers after ingesting cannabis edibles. Participants consumed approximately 50.6 mg Δ^9-THC in a brownie within 10 minutes, and OF samples were collected for 48 hours; Δ^9-THC and THC-COOH analyzed by LC-MS/MS with a 0.5 ng/mL and 5 ng/mL LOQ, respectively. Peak OF Δ^9-THC concentrations were observed at the first collection (0.33 hours) with no significant difference in average C_{max} between frequent (573 ng/mL, range 39.3 to 2,111 ng/mL)

and occasional (362 ng/mL, range 115 to 696 ng/mL) smokers. OF Δ^9-THC was detected in frequent smokers for significantly longer (39 hours, 20-> 48 hours) than occasional smokers (23 hours, 20 to 26 hours). At discharge (48 hours), 44.4 percent of frequent smokers were Δ^9-THC -positive (0.3 to 2.6 ng/mL), while no occasional smoker was Δ^9-THC positive beyond 26 hours. With 2 ng/mL cutoffs, 100 percent of frequent smokers were Δ^9-THC -positive at 0.33 hours post dose, decreasing to 22.2 percent at 20 hours, and 11.1 percent at 48 hours, respectively; no occasional smoker was still positive at 26 hours. With a 5 ng/mL cutoff, no frequent or occasional smoker was positive by 20 or 5 hours, respectively. Differences between groups in THC-COOH pharmacokinetics were not observed. Five frequent (55.6 percent, 24.9 to 159 pg/mL) and 1 occasional (16.7%, 18.5 pg/mL) smokers were OF THC-COOH-positive at baseline. Concentrations remained ≥ 15 pg/mL throughout 48 hours, with all frequent (23.5 to 643 pg/mL) and 42.9 percent of occasional (16.4 to 77.9 pg/mL) smokers positive at 48 hours. THC-COOH T_{max} was highly variable across groups (frequent, average 12 hours, range 3.5 to 48 hours; occasional, average 10 hours, range 0.33 to 20 hours).

Measurements in the hundreds ng/mL range of Δ^9-THC in OF clearly indicates recent use and reflects the coating of the oral mucosa with Δ^9-THC -laden smoke, vapor, or food. After 2 to 3 hours from ingestion, OF Δ^9-THC concentrations are much lower and parallel blood Δ^9-THC concentrations.

Interpretation of Urine Test Results

Detection of total Δ^9-THC metabolites in urine, primarily THC-COOH-glucuronide, only indicates prior exposure and cannot be correlated to drug impairment. THC-COOH-glucuronide urine detection times are longer than windows of intoxication and impairment, even in occasional cannabis users (Huestis et al., 1995). However, this evidence can be important in establishing use and determining the reliability of other evidence in DUID cases.

Cannabinoids and metabolites may be present in urine for an extended period after last use. In 33 chronic frequent cannabis users during sustained abstinence on a closed research unit for up to 33 days, identification of total THC-COOH in urine was documented for more than 24 days (Lowe et al., 2009). Brenneisen et al. (2010), suggested that identifying Δ^9-THC and 11-OH-THC in urine after beta-glucuronidase and alkaline hydrolysis reported recent cannabis use. Extended excretion of Δ^9-THC for up to 24 days and 11-OH-THC for more than 24 days was documented in seven of 33 chronic cannabis users' urine during sustained abstinence, negating their effectiveness as biomarkers of recent cannabis exposure, and substantiating long terminal elimination times for urinary cannabinoids following chronic cannabis smoking (Lowe et al., 2009).

Cannabinoids must be metabolized and actively eliminated before becoming detectable in urine. Desrosiers at al. (2014a), measured THC-COOH, THC-glucuronide, and THC-COOH-glucuronide in all of 14 frequent smokers' urine, collected for 30 hours after smoking one 6.8 percent Δ^9-THC cigarette. This was in comparison to THC-COOH, THC-glucuronide, and THC-COOH-glucuronide measurable in 60 percent, 100 percent, and 100 percent of 10 occasional smokers' urine samples, respectively. Urinary cannabinoid excretion variability resulted in initial negative urine samples at 50 ng/mL cut-off, interspersed with positive samples later in elimination.

Not all cannabinoids found in cannabis will end up in urine. A randomized, placebo-controlled within-subject dosing designed study collected and analyzed all urine specimens from 11 frequent and nine occasional cannabis users for 11 cannabinoids, for up to 85 hours following controlled smoked, vaporized, or oral 50.6 mg Δ^9-THC. No CBD, CBN, CBG, THCV, Δ^9-THC, 11-OH-THC, Δ^9-tetrahydrocannabinolic acid were detected in urine. Median THC-COOH-glucuronide C_{max} following smoked, vaporized, and oral routes were 68.0, 26.7 and 360 ng/mL for occasional and 378, 248 and 485 ng/mL for frequent users, respectively. T_{max} was 5.1 to 7.9 hours for all routes and all users, although C_{max} in some frequent cannabis users does not occur for up to 40 hours after last use (Huestis et al., 2020a).

Urine drug screen analysis should not be used to assess acute cannabis exposure. Seventeen occasional cannabis users smoked and vaporized 10 and 25 mg Δ^9-THC and total urine THC-COOH was measured for the following 8 hours. THC-COOH concentrations peaked 4 to 6 hours after cannabis administration. At the Federal workplace drug-testing criteria (immunoassay screening cutoff of 50 ng/mL and GC/MS concentration ≥ 15 ng/mL), urine specimens were positive in 47 percent of vaporized sessions and 21 percent of smoked sessions. Infrequent cannabis users may excrete relatively low THC-COOH concentrations following acute inhalation of smoked or vaporized cannabis (Spindle et al., 2020).

Intake of CBD products containing less than 0.3 percent Δ^9-THC is legal. These CBD products, and others that are inappropriately labeled and contain higher Δ^9-THC percentages, may produce positive THC-COOH urine tests depending upon the amount and frequency of use.

Interpretation of Cannabinoid Breath Test Results

There is a major ongoing effort to develop a breathalyzer for cannabis, with a spectrum of devices based on colorimetric measurement to miniaturized mass spectrometers. Breath from frequent and occasional cannabis smokers before and after smoking a 6.8 percent Δ^9-THC cigarette showed that Δ^9-THC was the major cannabinoid in breath, with no measurable THC-COOH and only one sample with CBN. For frequent smokers (n=13), all breath samples were positive for Δ^9-THC at 0.89 hours, 76.9 percent at 1.38 hours, 53.8 percent at 2.38 hours, and only one sample was positive at 4.2 hours after smoking (using a 50 pg/pad limit of quantitation for Δ^9-THC.) For occasional smokers (n=11), 90.9 percent of breath samples were positive for Δ^9-THC at 0.95 hours, and 63.6 percent at 1.49 hours (Himes et al., 2013). Breath may offer an alternative matrix for testing for recent driving under the influence of cannabis but is limited to a short detection window (0.5 to 2 hours).

One promising approach for the confirmation of Δ^9-THC in breath was published by Luo et al. (2019). They describe a novel derivatization method based on an azo coupling reaction that significantly increases the ionization efficiency of cannabinoids for LC-MS/MS analysis and does not require further sample clean-up after derivatization. LOQs are sub-pg/mL to pg/mL for five cannabinoids in breath samples, i.e., only 5~50 femtograms of an analyte was required for quantification. Cannabinoids were quantified in breath samples collected within 3 hours of smoking cannabis (n=180). A linear correlation between Δ^9-THC and CBN in human breath was observed.

General Effects

The pharmacological effects of cannabis vary with the dose, route of administration, experience of user, vulnerability to psychoactive effects, and setting of use.

Table 16 provides a range of effects, including side effects that subjects may experience:

Table 16. Physiological, motor, and cognitive side effects of cannabinoid consumption

Physiological	Motor (behavioral)	Cognitive
• Increased heart rate • Red, bloodshot eyes • Dry mouth • Dry throat • Increased appetite • Vasodilation • Sedation	• Relaxation • Relaxed inhibitions • Disorientation • Drowsiness • Panic reactions	• Euphoria • Sense of well-being • Altered time and space perception • Lack of concentration • Reduced learning & memory • Alteration in thought formation and expression • More vivid sense of taste, sight, smell and hearing • Anxiety • Paranoia

Thirty percent of cannabis users experience hypotension approximately 20 minutes after the start of inhalation. Stronger doses intensify reactions and may cause fluctuating emotions, flights of fragmentary thoughts with disturbed associations, a dulling of attention despite an illusion of heightened insight, image distortion, and psychosis.

Other adverse effects may include fatigue, memory problems, depersonalization, mood alterations, urinary retention, constipation, decreased motor coordination, lethargy, slurred speech, and dizziness. Impaired health including respiratory damage, behavioral changes, and reproductive, cardiovascular, and immunological effects are associated with frequent cannabis use. Chronic frequent cannabis smokers may develop many of the same respiratory problems as tobacco smokers (daily cough and phlegm, symptoms of acute and chronic bronchitis), but unlike tobacco smoking, there has been no conclusive link between cannabis smoking and asthma, chronic obstructive pulmonary disease, or lung cancer. Cannabinoid hyperemesis syndrome may develop in a select group of chronic cannabis users. There has been an association with cannabis use and schizophrenia, although whether there is a causal association is unclear. Cannabis use has been shown to have detrimental effects on the developing brain. Lastly, cannabis use during pregnancy can lead to intrauterine growth retardation (Baselt, 2020; Bramness et al., 2010; Colizzi et al., 2019; Hartman & Huestis, 2013; Hartman et al., 2016a; Hirvonen et al., 2012; Huestis et al., 1992a, 2020b; Klumpers & Thacker, 2019; PDR, 2021; Ramaekers et al., 2011, 2020).

Duration of Effects

Due to rapid absorption through the respiratory tract and subsequent rapid distribution to the central nervous system, effects from smoking cannabis products are felt almost immediately and reach their peak in 10 to 30 minutes. Typical cannabis smokers experience a high that lasts approximately 3 hours. Most behavioral and physiological effects return to baseline levels within 3 to 4 hours after drug use, although some investigators demonstrated residual effects in specific behaviors up to 24 hours, such as complex divided attention tasks. Psychomotor impairment can persist after the perceived high dissipates. In chronic frequent users, even after periods of abstinence, selective attention (ability to filter out irrelevant information) was shown to be adversely affected with increasing duration of use, and speed of information processing was shown to be impaired with increasing frequency of use. Unlike smoking cannabis, oral formulations of Δ^9-THC, such as edibles and dronabinol, have an onset of action from 30 to 60 minutes, with peak effects occurring at 2 to 4 hours and appetite stimulation for up to 24 hours (the desired therapeutic effect of dronabinol).

Tolerance, Dependence, and Withdrawal Effects

Although evidence suggests partial tolerance to some acute cannabis psychomotor impairment effects with chronic frequent intake, not all effects show tolerance. Frequent cannabis users developed tolerance to neurocognitive tasks, such as critical tracking task, stop-signal task, and the Tower of London test. Tolerance was not always shown for divided attention and reaction time tasks. Tolerance development requires frequent cannabis use over time due to a downregulation of CB_1 receptors in the brain, but it disappears rapidly with short periods of abstinence. The actual frequency and/or amount of cannabis intake required to develop partial or full tolerance to an acute Δ^9-THC challenge is unknown. Frequent cannabis users do not appear to develop cross-tolerance to the impairing effects of ethanol, but when present in combination with ethanol, cannabis selectively potentiates ethanol's effects on divided attention.

Recently in a systematic review of 36 human studies, tolerance to the acute effects of cannabis in frequent users was noted most consistently in cognitive and psychomotor domains, and to a lesser degree for psychotomimetic and physiological symptoms (Colizza & Bhattacheryya, 2018). Chronic frequent cannabis users may invest more effort during cannabis intoxication to compensate for the impairing effects on neurocognitive function. However, the volitional control that users must overcome their functional impairment during cannabis intoxication appears limited. Awareness of intoxication and compensatory strategies during driving under the influence of cannabis did not eliminate driver impairment.

Cannabis is addicting as it causes compulsive drug craving, seeking, and use, even in the face of negative health and social consequences. A withdrawal syndrome is commonly seen in chronic cannabis users following abrupt discontinuation. Withdrawal symptoms may occur in 1 to 2 days and last 2 to 6 days, with some symptoms lasting up to 3 weeks or more in heavy cannabis users. Symptoms include restlessness, anxiety, irritability, mild agitation, hyperactivity, insomnia, nausea, cramping, decreased appetite, chills, sweating, and disturbed sleep and increased dreaming (Connor et al., 2021; PDR, 2021; Ramaekers et al., 2011, 2020).

Driving-Related Studies

The short-term effects of cannabis use include problems with memory and learning, distorted perception, difficulty in thinking and problem-solving, and loss of coordination. Frequent users

may have increased difficulty sustaining attention, shifting attention to meet the demands of changes in the environment, and in registering, processing, and using information. In general, laboratory performance studies indicate that sensory functions are not highly impaired, but perceptual functions are significantly affected. The ability to concentrate and maintain attention are decreased during cannabis use, and impairment of hand-eye coordination is dose-related over a wide range of dosages. Impairment in retention time and tracking, subjective sleepiness, distortion of time and distance, vigilance, and loss of coordination in divided attention tasks have been reported. Significant performance impairments are usually observed for at least 1 to 2 hours following cannabis use, and residual effects are reported for up to 24 hours. Difference in study designs frequently account for inconsistency in results between studies.

Laboratory Studies

Lamers & Ramaekers (2001), studied the effects of visual search at intersections in combination with general driving proficiency after participants drank ethanol to approximately 0.05 g/dL, followed by smoking 100 µg/kg cannabis 1 hour later. The City Driving Test commenced 15 minutes after smoking and lasted 45 minutes. An eye movement recording system was mounted on each subject's head for providing relative frequency measures of appropriate visual search at intersections. After placebo treatment, subjects searched for traffic approaching from side streets on the right in 84 percent of all cases. Visual search frequency in these subjects did not change when treated with ethanol or cannabis alone. However, following the combination of ethanol and cannabis, the frequency of visual search dropped by 3 percent. Performance as rated on the Driving Proficiency Scale did not differ between treatments. It was concluded that the effects of low doses of Δ^9-THC (100 µg/kg) and ethanol (BAC < .05 g/dL) on higher-level driving skills as measured in the present study are minimal. It should be noted that the cannabis dose was only 7 mg, a dose which evokes few effects.

A single 300 µg/kg Δ^9-THC dose was administered to 122 subjects over 15 minutes, via a vaporizer. Subjects were tested at 1 hour post-dose using psychomotor assessments such as the Tower of London, stop signal task, critical tracking task, divided attention task, and subjective evaluation of intoxication. Executive function, impulse control, attention, psychomotor function, and subjective intoxication were all significantly impaired after cannabis administration (Ramaekers et al., 2016).

Twenty-five and 50 mg oral Δ^9-THC produced strong subjective effects and markedly impaired cognitive and psychomotor functioning compared with placebo. Pharmacodynamic effects appeared 30 to 60 minutes after ingestion, and peak effects occurred 1.5 to 3 hours post-administration. Blood Δ^9-THC concentrations were substantially lower than for cannabis inhalation (Schlienz et al., 2020).

Simulated Driving Studies

Cannabis impairs performance on driving simulator tasks and on open and closed driving courses for three or more hours. Decreased car handling performance, increased reaction times, impaired time and distance estimation, inability to maintain headway, lateral travel, subjective sleepiness, motor incoordination, and impaired sustained vigilance were all reported (Hartman et al, 2013). Some drivers may be able to improve performance for brief periods by overcompensating for self-perceived impairment. However, the greater the demands placed on the driver (increasing task complexity), the more critical the likely impairment. Cannabis may particularly impair

monotonous and prolonged driving. Decision times to evaluate situations and determine appropriate responses increase. Despite purported tolerance in frequent smokers, complex tasks still show impairment. Mixing ethanol and cannabis may dramatically produce effects greater than either drug on its own.

In a placebo-controlled double-blind crossover study of 18 participants at the National Advanced Driving Simulator, the effects of cannabis with and without low dose (.05 g/dL) alcohol intake were evaluated for correlation between impaired driving and blood THC concentrations (Hartman et al., 2015b). Each participant inhaled two THC doses (2.9 and 6.7 percent THC cigarettes) *ad libitum* on separate days but, owing to variable titration, the delivered doses were not significantly different, and active doses were analyzed together. Maximum THC blood concentrations (10 minutes after the start of inhalation) were significantly higher when administered with ethanol than alone (median 38.2 versus 47.9 ng/mL), most likely because ethanol increases THC absorption by dilating blood vessels (Hartman et al., 2016c). Another key finding was that the ethanol T_{max} occurred significantly later when THC and ethanol were co-administered, as opposed to ethanol alone. This delay in ethanol absorption may be due to THC slowing gastric emptying, which would directly slow absorption of ethanol in the small intestine, although this was not directly tested (Hartman et al., 2015b). Many toxicologists back-extrapolate the ethanol concentration to the time of a crash or police stop, but this may not be accurate when cannabis is co-ingested with ethanol.

Subjects drove a simulator course especially constructed to be sensitive to the effects of cannabis for 45 minutes, 0.5 to 1.3 hours post-inhalation, with a focus on standard deviations of lateral position (SDLP, lane weave), steering angle, lane departures/minute, and maximum lateral acceleration. Cannabis and ethanol were both shown to increase SDLP.[1] Blood THC concentrations of 8.2 and 13.1 ng/mL during driving increased SDLP like .05 and .08 g/210L BrAC, respectively (Hartman et al., 2015b). Note that these THC concentrations were present at the time of driving, 0.5 to 1.3 hours post-inhalation, and were not the expected THC concentrations at times typically collected 1.4 to 4 hours after a crash or traffic stop (Huestis & Smith 2018). Overall, the cannabis and ethanol SDLP effects were additive rather than synergistic. THC concentrations decreased rapidly, with a 74 percent decrease in 30 min and 90 percent decrease in 1.4 hours, clearly highlighting the importance of rapid blood collection to document THC intake (Hartman et al., 2016b). The International Association of Chiefs of Police now recommends that blood collection is moved to the first step in the DRE evaluation of drugged driving, where previously it constituted the last step.

Cannabis effects on driving longitudinal control with and without ethanol, relative to THC blood concentrations, were also evaluated. Occasional cannabis smokers drank placebo or low-dose ethanol, and inhaled 500 mg placebo, 2.9 percent, or 6.7 percent THC vaporized cannabis over 10 minutes *ad libitum* in separate sessions. After cannabis smoking, participants performed simulated drives at the National Advanced Driving Simulator 0.5 to 1.3 hours post-inhalation. Average speed relative to the road limit, standard deviation of speed, percent time spent > 10 percent above/below the speed limit, longitudinal acceleration, and ability to maintain headway relative to a lead vehicle were studied with blood THC and BrAC. Among 18 completing drivers, THC was associated with decreased average speed, increased percent low speed, and increased average following distance during headway maintenance. BrAC was associated with

[1] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful differences when related to real-world driving.

increased SD speed and increased percent speed high, whereas THC was not. A less-than-additive THC*BrAC interaction was detected in percent speed high, suggesting cannabis mitigated drivers' tendency to drive faster with ethanol. Cannabis was associated with slower driving and greater headway, suggesting a possible awareness of impairment and attempt to compensate (Hartman et al., 2016c). People who consume concurrent cannabis and ethanol may experience more elevated or rising ethanol concentrations longer than with ethanol alone, thereby increasing the driving risk.

Young adults have a higher risk of automobile crashes, which may increase if they use cannabis. The effects of inhaled cannabis on driving performance (in useful-field-of-view and driving-simulation tests) and self-reported perceptions (driving ability and safety, cannabis effects) in 45 young adults was assessed 1, 3 and 5 hours after inhalation of 100 mg cannabis. Significant cannabis effects were noted on complex useful-field-of-view tasks at 3 hours and the complex selective-attention task at 5 hours after cannabis use when the tasks were novel. Participants were significantly more likely to be classified as having a high crash risk after cannabis use and self-reported significantly lower perceived driving ability at 1, 3 and 5 hours after cannabis inhalation (Ogourtsova et al., 2018).

Multiple investigators report that acute cannabis intoxication impairs driving ability. Dahlgren et al. (2020), assessed the potential impact of cannabis use on driving performance in a simulator in non-intoxicated, frequent, recreational cannabis users and healthy controls without a history of cannabis use. Cannabis users demonstrated impaired driving relative to controls with increased crashes, speed, and lateral movement, and reduced rule-following. However, when participants were divided based on age of onset of regular cannabis use, driving impairment was localized to those with onset before age 16. Impulsivity had a significant impact on performance differences.

Chronic frequent cannabis use was associated with worse driving performance in non-intoxicated drivers, and earlier onset of use was associated with greater impairment. These results may be related to other factors associated with early exposure such as increased impulsivity.

Epidemiological Studies

NHTSA's National Roadside Survey uses biological data from drivers at 60 sites across the country on weekends about every ten years, to estimate the prevalence of alcohol- and drug-positive drivers. The drug with the largest increase in weekend nighttime across a decade was THC. In the 2007 study 8.6 percent of weekend nighttime drivers were positive for THC (based on either the combined oral fluid or blood tests), and 12.6 percent of similar drivers were positive for THC in the 2013/2014 survey (Berning et al., 2015).

Experimental studies show that THC impairs cognition, psychomotor function and driving performance in a dose related manner. A THC dose of 300 µg/kg produced equivalent impairment to a blood ethanol concentration (BAC) ≥ .05 g/dL the illegal limit for driving under the influence in most European countries. Highly automated behaviors, such as road tracking control, were more affected by THC as compared to more complex driving tasks requiring conscious control (Ramaekers et al., 2004). Epidemiology studies showed that when THC was positive in blood, particularly at higher concentrations, drivers were about two to seven times more likely to be responsible for their crash as drivers that did not use drugs or ethanol (Drummer et al., 2004).

In NHTSA's Crash Risk study conducted in Virginia Beach, Virginia, biological samples were obtained from drivers who were involved in a crash, and a comparison group of drivers, who were at the same location – same day of the week, same time of day, a week later. Of the drugs tested for, THC was the most frequently used by drivers, detected in 7.6 percent of the crash-involved drivers and 6.1 percent of the comparison drivers. In contrast, 5 percent of drivers in crashes were positive for alcohol, and 2.7 percent were positive in the comparison drivers (Compton, R. & Berning, A., 2015).

A 2022 NHTSA study (Thomas et al., 2022) examined alcohol and drug prevalence among seriously or fatally injured road users who were involved in motor vehicle crashes and taken to traumas. The most prevalent drug category among the 4,243 drivers taken to trauma centers was cannabinoids, with 25 percent positive. Cannabinoids were the second most prominent drug among the 555 drivers in medical examiner cases, with 31.7 percent positive (alcohol was the most prominent at 38.9%).

In Sweden there is a zero-tolerance law for DUID. From 1995 to 2004, 18 to 30 percent of all DUID suspects had measurable THC in their blood (> 0.3 ng/mL) alone or with other drugs (Jones et al, 2008). The frequency distribution of THC concentrations (n= 8,794) was skewed to the right with average, median and highest concentrations of 2.1, 1.0, and 67 ng/mL, respectively. THC concentration was < 1.0 ng/mL in 43 percent of cases and below 2.0 ng/mL in 61 percent of cases. The concentration of THC in blood at the time of driving is higher than at the time of sampling (30 to 90 minutes later). In December 2013, Uruguay legalized cannabis for recreational purposes. The association between implementation of legalization and changes in traffic fatality rates was assessed in Montevideo and four rural provinces from January 1, 2012, to December 31, 2017 (Nazif-Munoz et al., 2020). Cannabis legalization was associated with a 52.4 percent immediate increase in light motor vehicle drivers' but not motorcyclists' fatality rate.

In an Australian study of 5,000 drivers injured in vehicular collisions, THC was detected in 11.1 percent of drivers. When THC was present in the absence of any other potentially impairing substance, the odds of culpability was 1.9-fold higher than controls, however, the increase in odds was most apparent at higher blood THC concentrations. At 5 ng/mL and above the odds ratio was 3.2, and at THC concentrations of 10 ng/mL and above the OR was 10 indicating that the odds of culpability increase with rising concentration. Only 1 percent of the 5,000 drivers had THC ≥ 10 ng/mL. When THC was the only drug present, the odds of culpability was 2.8 (95 percent confidence interval (CI) 1.7 to 4.5) times greater than the controls, and when THC and ethanol were combined the increased odds of culpability was 21 (95 percent CI 6.4 to 68; Drummer et al., 2020). Meta-analyses of crash risk associated with cannabis and driving determined an OR of 1.6 for culpability studies and higher depending on the type of study (Asbridge et al., 2012). Another review found the OR (1.1) was not significantly elevated (Elvik et al., 2013). A recent Bayesian analysis of 13 published studies estimated the pooled increased risk of a culpable crash as 1.46 with a 95 percent credibility interval of 1.11 to 1.75 (Rogeberg, 2019). Despite the variations that naturally exist between studies and models chosen, findings from these studies appear to suggest lower odds of culpability than that seen with ethanol and methamphetamine.

Driving simulator studies on cannabis users generally found a decrease in the ability to control a motor vehicle, both through lane control as measured by SDLP and ability to respond to unexpected situations (Downey et al., 2013; Lenne et al., 2010; Micallef et al., 2018; Tank et al.,

2019). Similarly, studies using volunteers and instrumented cars have generally also shown deficits in performance shortly after smoking cannabis (Ramaekers et al., 2000; Hartman et al., 2015b; Arkell et al., 2019). However, it may not always be possible to differentiate the direct effects of cannabis use on driving performance since users of this drug tend to be inherently riskier drivers (Bergeron & Paquette, 2014). Behavioral changes and the effects seen in various psychomotor performance and cognitive testing following cannabis use are well known and documented (Ramaekers et al., 2004).

Interactions With Ethanol

Low doses of THC and ethanol that may not affect psychomotor function when given alone may still impair performance when given in combination (Lamers & Ramaekers, 2001) and the combined use of ethanol and THC in occasional cannabis users increased the magnitude of cognitive and motor impairments in an additive manner (Toennes et al., 2011). Cannabis is commonly consumed with ethanol, and many assume that cannabis users develop cross-tolerance to ethanol effects. Nineteen frequent cannabis users were administered ethanol to achieve a steady BACs of approximately 0, .05 and .07 g/dL over a 5-hour period, then smoked about 28 mg THC 3 hours post-onset of ethanol dosing. The apparent elimination half-life of THC was slightly prolonged (1.59 versus 1.93 hours, $p < 0.05$) and the THC concentration 1 hour after smoking was slightly lower (24 versus 17 ng/mL, $p < 0.05$) with the higher ethanol dose. The prolonged THC elimination might be explained by a small ethanol-mediated change in distribution to and from deep compartments. Concentrations and pharmacokinetics of 11-OH-THC and THC-COOH were not significantly influenced by ethanol (Toennes et al., 2011).

Ethanol and cannabis share many behavioral effects such as euphoria, analgesia, sedation, and cognitive and motor dysfunction. Therefore, a combination of the two in occasional cannabis users may additively alter the magnitude of cognitive and motor impairment.

Ethanol may appear to influence THC concentrations when the two drugs are consumed concurrently (Hartman et al., 2015b). A single inhaled dose of 2.9 percent THC (low), 6.7 percent THC (high), or placebo was given to 18 occasional cannabis users via a vaporizer, over 10 minutes *ad libitum*, either with or without a low-dose of ethanol. The median maximum blood concentration at 0.17 hours was 38.2 ng/mL (range 11.4 to 137) for the 2.9 or 6.7 percent THC dose in the absence of ethanol, and 47.9 ng/mL (range 13.0 to 210) in the presence of ethanol. Subsequent declines in THC concentrations were observed between the ethanol and non-ethanol participants similarly.

Interactions With Other Drugs

Combined cocaine or amphetamine use with THC/cannabis may lead to increased hypertension, tachycardia, and possible cardiotoxicity. Combined use with benzodiazepines, barbiturates, opioids, antihistamines, muscle relaxants and other CNS depressants may increase drowsiness and CNS depression.

Drug Evaluation and Classification Program Category

Cannabis

Drug Evaluation and Classification Program Profile

The indicators in Table 17 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 17. DEC program profile of cannabis

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	present	dilated	normal	elevated	elevated	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include odor of cannabis in car or on subject's breath, cannabis debris in mouth, green coating of tongue, bloodshot eyes, body and eyelid tremors, relaxed inhibitions, and incomplete thought process. Note that pupil size may also be normal.

The ability of the DEC program parameters to identify cannabis-driving impairment in 302 toxicologically confirmed (blood THC ≥ 1 ng/mL) and examiner identification of cannabis-only cases was compared to the data from 302 non-impaired people. Physiological measures, pupil size/light reaction, and performance on psychophysical tests (one-leg stand, walk-and-turn, finger to nose, modified Romberg balance) were evaluated. Cases significantly differed from controls ($p < 0.05$) in pulse (increased), systolic blood pressure (elevated), and pupil size (dilated). Blood collection time after arrest significantly decreased THC concentrations; no significant differences were detected between cases with blood THC < 5 ng/mL versus ≥ 5 ng/mL. The FTN best predicted cannabis impairment (sensitivity, specificity, positive/negative predictive value, and efficiency ≥ 87.1%) using ≥ 3 misses as the deciding criterion; MRB eyelid tremors produced ≥ 86.1 percent for all diagnostic characteristics. Other strong indicators included OLS sway, ≥ 2 WAT clues, and pupil rebound dilation. Requiring ≥ 2/4 of ≥ 3 FTN misses, MRB eyelid tremors, ≥ 2 OLS clues, and/or ≥ 2 WAT clues produced the best results (all characteristics ≥ 96.7%). This study examined how the DEC program can sensitively identify cannabis, as well as ethanol, impairment. The 5 ng/mL blood THC *per se* cutoff showed limited relevance in discriminating impaired from non-impaired drivers (Hartman et al., 2016b).

Analytical Considerations

Blood specimens should be collected in gray top tubes (containing potassium oxalate as an anticoagulant and sodium fluoride as a preservative), stored refrigerated or frozen, and analyzed within 3 months of collection. The National Safety Council Alcohol, Drugs and Impairment Division recommends cutoffs for toxicological investigations of suspected ethanol and drug-impaired driving cases and motor vehicle fatalities (D'Orazio et al., 2021). In blood, a 10 ng/mL enzyme-linked immunosorbent assay screening cutoff targeting THC-COOH and, for confirmation, and a 5 ng/mL cutoff is recommended; and for the cutoff for THC and 11-OH-THC confirmations 1 ng/mL is recommended. A 4 ng/mL screening cutoff for THC in oral fluid and a 2 ng/mL THC confirmation cutoff is recommended for all DUID testing.

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Synthetic Cannabinoids

Synthetic cannabinoids are the largest class of novel psychoactive substances. They were initially developed to study the activity of the endogenous cannabinoid receptor, CB-1, and typically stimulate this receptor far greater than classic phytocannabinoids such as THC. Over 400 synthetic cannabinoids have been identified, and in the United States they are classified as Schedule I controlled substances. Synthetic cannabinoids were first introduced in the United State as an illicit recreational drug as part of an herbal blend labelled "not for human consumption" (e.g., K2, Spice, Potpourri), and commonly sold at gas stations and truck stops around the country. The synthetic cannabinoid compound is sprayed onto an inert herbal mixture that is then smoked. The compounds can now be purchased in powder, pill, and capsule form via novel online marketplaces found on the "dark web," potentially introducing the drugs at higher concentrations to novice drug users at younger ages. Some synthetic cannabinoids are also available in liquid form for use in electronic cigarettes and vaporizers and may be present in products legally sold for use in vaporizers.

Synthetic cannabinoids first became popular recreationally in approximately 2008. Early compounds were those in the JWH-, HU- and then AM- series (e.g., JWH-018, JWH-081, JWH-210; HU-210, HU-331; AM-2201, AM-694). Since then, a multitude of synthetic cannabinoids have been available, often cycling out after several months of popularity only to be replaced by others. Commonly detected compounds have included UR-144, XLR-11, AB-PINACA, AB-CHMINACA, AB-FUBINACA, ADB-PINACA, 5F-ADB, and 5F-PB-22.

The spectrum of behavioral effects for individual synthetic cannabinoids is unique, preventing a universal classification as solely stimulants, sedatives, tranquilizers, or hallucinogens, although they often have effects in common with each of these drug classes.

Synthetic cannabinoids are structurally unlike phytocannabinoids like THC, and act as full agonists at the cannabinoid type 1 (CB1) and/or type 2 (CB2) receptors. CB1 receptors are associated with euphoric and relaxation effects, sleep, appetite, perception of time, short-term memory, and coordination effects. CB2 receptors are associated with immune functions. In most cases, synthetic cannabinoids show stronger agonist activity on CB1, compared to THC. Their strength and effects are far less predictable as they are often added onto compounds/materials and are of unknown purity and potency. As such, negative side effects are far more likely with synthetic cannabinoids than with cannabis use. Side effects that are like cannabis use include eye redness, mild sedation, tachycardia, agitation, anxiety, hypertension, memory deficits, an impaired sense of time, and hallucinations. Side effects that are unlike cannabis use include seizures, hypokalemia, hypertension, nausea and vomiting, agitation, violent behavior, hypothermia, cardiac arrest, and coma. Subjects admitted to emergency departments following synthetic cannabinoid use have been reported to experience confusion, sedation, cognitive impairment, slurred speech, excessive sweating, hypertension tachycardia, renal failure, pulmonary damage, myocardial infarction, self-harm, seizures, stroke, and coma.

Single recreational doses of synthetic cannabinoids are believed to range from 3 to 20 mg and the desired effects of euphoria, relaxation, altered perception, and feeling 'stoned' may last from 2 to 6 hours. Depending on the drug, elimination half-lives can range from 8 hours to 41 days in chronic users. Most synthetic cannabinoids appear to undergo extensive biotransformation, often with over a dozen metabolites identified in urine samples.

Interpretation of Blood Concentrations

An “herbal blend” smoked by a recreational user resulted in peak blood concentrations of 4.8 ng/mL JWH-018 and 4.2 ng/mL JWH-073 at 19 minutes (Kacinko et al., 2011).

A powder containing 3.5 mg/70 kg dose of JWH-018 was smoked by two subjects, resulting in average peak serum JWH-018 concentrations of 9.1 ng/mL at 5 minutes, 1.8 ng/mL at 1 hours, and 0.2 ng/mL at 6 hours (Baselt, 2020).

After smoking “K2,” one subject had a blood JWH-018 concentration of 0.5 ng/mL at 4.5 hours; side effects included nausea, emesis, tremor, blurred vision, and ataxia (Baselt, 2020).

In one subject, oral ingestion of 5 mg AM-2201 resulted in a peak serum AM-2201 concentration of 0.56 ng/mL at 1.6 hours, declining to < 0.02 ng/mL by 21 hours (Baselt, 2020).

Driving-Related Studies

Case Reports

Overall, synthetic cannabinoids demonstrate a higher risk of adverse effects and driving impairment than cannabis.

Blood AB-CHMINACA concentrations of 0.6->10 ng/mL were detected in 33 drivers arrested for impaired driving performance, while blood AB-PINACA concentrations of 0.6 to 41 ng/mL were detected in another 25 drivers (Peterson, BL & Couper F., 2015). Commonly observed driver performance included erratic driving, slumped over or unconscious at the wheel, inappropriate stopping in roadway, and collisions with stationary objects. Horizontal gaze nystagmus was seen in 50 to 60 percent of subjects for both compounds, and vertical gaze nystagmus was observed in several drivers.

XLR-11 and/or UR-144 were detected in the blood of 18 suspected impaired driving cases, 11 of which had DRE evaluations performed. Of the studied cases, six were positive for only UR-144, whereas eight contained only XLR-11. Four cases were found to have both. All cases were negative for other commonly detected drugs that affect the central nervous system, although one case was additionally positive for other synthetic cannabinoids. Most of the drivers demonstrated poor driving prior to the traffic stop. Slurred speech, bloodshot eyes, lack of convergence, dilated pupils, horizontal gaze nystagmus, poor coordination, and body and eyelid tremors were commonly documented characteristics. However, performance on the standardized field sobriety tests yielded inconsistent diagnostic information. Pulse and blood pressure of the subjects were within the expected range but elevated (Louis et al., 2014).

Concentrations of other synthetic cannabinoids in suspected impaired driving cases include: blood 5F-ADB concentrations of 0.2 to 1.2 ng/mL in 32 impaired drivers (Capron, 2016); blood AM-2201 concentrations ranging from 0.1 to 8.7 ng/mL in 30 drivers (Baselt, 2020; Yeakel & Logan, 2013); blood 5F-APINACA concentrations of 0.9 to 6.5 ng/mL in 4 impaired drivers, and blood APINACA concentrations of 0.24 to 24.5 ng/mL in 3 impaired drivers (Karinen et al., 2015); and blood JWH-018 concentrations of 0.2 to 9.9 ng/mL in 3 drivers (Yeakel & Logan, 2013).

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Carisoprodol and Meprobamate

Carisoprodol is a white, crystalline powder. Meprobamate is a white powder. Both are available in tablet form.

Synonyms

Carisoprodol: Soma, Sodol, Soprodol, Soridol

Meprobamate: Miltown, Equanil, Equagesic, Meprospan

Source

Carisoprodol and meprobamate are available by prescription only and are Schedule IV drugs. Soma is available as a 350 mg strength round, white tablet; Soma Compound is a 250 mg strength two-layered, white, and light orange round tablet (also contains aspirin); and Soma Compound with Codeine is a 250 mg strength two-layered, white, and yellow oval tablet (also contains aspirin and codeine phosphate) and is a Schedule III-controlled substance. Miltown is available as 200 and 400 mg strength white tablets; Equanil is available as 200 and 400 mg strength tablets; and Equagesic is a 200 mg strength two-layered, pink, and yellow round tablet (also contains aspirin).

Drug Class

Carisoprodol: muscle relaxant; CNS depressant

Meprobamate: anxiolytic; CNS depressant

Uses

Clinical

Carisoprodol is a centrally acting skeletal muscle relaxant prescribed for the treatment of acute, musculoskeletal pain. Meprobamate is a major metabolite of carisoprodol, and is a CNS depressant in its own right, reported for the management of anxiety disorders or for short-term treatment of anxiety symptoms. While carisoprodol remains commonly used, meprobamate is rarely used in current clinical practice.

Non-Clinical

Use of these drugs frequently begins with prescription for muscular pain or anxiety, and abuse may develop for their sedative-hypnotic effects, resulting in increased dosage without medical advice, or continued use after pain or anxiety has subsided.

Potency, Purity, and Dose

Carisoprodol is present as a racemic mixture. During treatment, the recommended dose of carisoprodol is one 350 mg tablet taken three times daily and at bedtime (1,400 mg/day). The usual dose for meprobamate is one 400 mg tablet taken four times daily, or daily divided doses of up to 2,400 mg. When used to treat chronic pain, carisoprodol is often taken concurrently with other drugs, particularly opioids, benzodiazepines, barbiturates, and other muscle relaxants.

Route of Administration

Oral

Pharmacodynamics

The pharmacological effects of carisoprodol appear to be due to the combination of the effects of carisoprodol and its active metabolite, meprobamate. Meprobamate is equipotent to carisoprodol. There is evidence suggesting carisoprodol is a $GABA_A$ receptor indirect agonist With CNS chloride ion-channel conductance effects. In animals, carisoprodol produces muscle relaxation by blocking intraneuronal activity and depressing transmission of polysynaptic neurons in the descending reticular formation and spinal cord. It is unknown if this mechanism of action is also present in humans. In addition to the desired skeletal muscle relaxing effects, carisoprodol and meprobamate produce weak anticholinergic, antipyretic, and analgesic properties.

Pharmacokinetics

Carisoprodol is rapidly absorbed from the gastrointestinal tract and rapidly distributed throughout the CNS. Protein binding is 41 to 67 percent for carisoprodol and 14 to 24 percent for meprobamate. Carisoprodol is predominantly dealkylated to meprobamate in the liver, and to a lesser extent hydroxylated to hydroxycarisoprodol and hydroxymeprobamate, followed by conjugation and excretion. The volume of distribution of carisoprodol is 0.93 to 1.3 L/kg and its half-life is 99 minutes. Some people exhibit impaired metabolism of carisoprodol, resulting in a half-life of two to three times that of normal subjects. The volume of distribution of meprobamate is approximately 1.5 L/kg, and its half-life is many times longer than that of carisoprodol, from 6 to 17 hours. As a result of the significantly longer half-life of meprobamate relative to carisoprodol, accumulation of meprobamate during chronic therapy may occur.

Blood to Plasma Concentration Ratio

Carisoprodol: Data not available.

Meprobamate: 3.3 to 5.0

Interpretation of Blood Concentrations

Following therapeutic doses of carisoprodol, blood concentrations are typically from 1 and 5 mg/L for carisoprodol, and from 2 and 6 mg/L for meprobamate. A single oral dose of 350 mg carisoprodol produced average peak plasma concentrations in 18 people of 2.1 mg/L carisoprodol at 1 hour, declining to 0.24 mg/L at 6 hours. Following a single oral dose of 700 mg, the average peak plasma concentrations of carisoprodol in nine people was 3.5 mg/L at 45 minutes, and meprobamate concentrations of 4.0 mg/L were obtained in 220 minutes (Baselt, 2020). A single oral dose of 700 mg carisoprodol has also produced peak plasma concentrations of 4.8 mg/L carisoprodol.

Following administration of meprobamate in the treatment of anxiety, concentrations are typically around 10 mg/L, but can range from 3 and 26 mg/L. A single oral dose of 1,200 mg meprobamate produced concentrations of 15.6 mg/L at 4 hours. Plasma meprobamate concentrations of greater than 100 mg/L have been associated with deep coma; light coma from 60 and 120 mg/L; and patients with levels below 50 mg/L are invariably conscious (Robertson & Marinetti, 2003).

OF(S) to Blood Concentration Ratio

Carisoprodol: ~0.07 (*n*=1) (Gjerde et al., 2010)

Meprobamate: 0.2 (*n*=1) (Gjerde et al., 2010)

Interpretation of OF(S) Test Results

Carisoprodol pKa 4.2

An individual prescribed 350 mg carisoprodol once daily for 2 weeks had an oral fluid sample collected 12 hours after the last dose; no carisoprodol was detected (limit of quantification 0.01 mg/L) while meprobamate was detected at a concentration of 1.015 mg/L (Coulter et al., 2012). Concentrations of carisoprodol were determined in oral fluid specimens from 496 chronic pain patients, with an average concentration of 0.346 mg/L (median 0.179; range 0.010 to 4.503 mg/L). Meprobamate was detected in 439 oral fluid specimens with an average concentration of 1.890 mg/L (median 1.543; range 0.019 to 20.572 mg/L; Heltsley et al., 2011).

General Effects

The pharmacological effects of carisoprodol and meprobamate depend on the dose, route of administration, experience of the user, and tolerance. Table 18 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 18. Physiological, motor, and cognitive side effects of carisoprodol and meprobamate consumption

Physiological	Motor (behavioral)	Cognitive
• Nystagmus (more evident as concentration increases) • Bloodshot eyes • Tremor • Sleep disturbances • Sedation	• Slurred speech • Dizziness • Drowsiness • Confusion • Disorientation • Sluggish movements • Ataxia	• Slowed information processing • Lack of comprehension

Other adverse effects may include agitation, tremor, paresthesia, irritability, depression, facial flushing, headache, vertigo, postural hypotension, fainting, impairment of visual accommodation, tachycardia, nausea, vomiting, and stomach upset. In abuse or overdose, subjects are consistently sedated and obtunded, frequently becoming comatose. Overdose symptoms may include shallow breathing, clammy skin, dilated pupils, weak and rapid pulse, paradoxical excitement and insomnia, and convulsions. Meprobamate overdose can produce drowsiness, ataxia, severe respiratory depression, severe hypotension, shock, and heart failure (Baselt, 2020; Maddock & Bloomer, 1967; PDR, 2021; Reeves et al., 1997; Robertson & Marinetti, 2003).

Duration of Effects

The effects of carisoprodol begin within 30 minutes of oral administration, and last for up to 4 to 6 hours. In overdose, coma may last from several hours to a day or more. Meprobamate has a much longer duration of effect than carisoprodol due to a much longer half-life.

Tolerance, Dependence, and Withdrawal Effects

Development of abuse and moderate physical and psychological dependence can occur with chronic use of both carisoprodol and meprobamate. Abrupt discontinuation of long-term use can be followed by withdrawal symptoms such as anxiety, abdominal cramps, insomnia, headache, nausea, vomiting, ataxia, tremors, muscle twitching, confusion, and occasionally chills, convulsions, delusions, and hallucinations. Onset of withdrawal from meprobamate occurs within 12 to 48 hours following cessation of use and can last a further 12 to 48 hours. Carisoprodol has been shown to produce cross-tolerance to barbiturates (PDR, 2021; Reeves et al., 2012; Robertson & Marinetti, 2003; Rust et al., 1993).

Driving-Related Studies

Laboratory Studies

Limited studies are available for carisoprodol; however, a single oral dose of 700 mg carisoprodol given to 10 healthy subjects was not shown to significantly affect limited psychomotor and cognitive tests within 3 hours of dosing. In contrast, single oral doses of meprobamate can cause significant performance impairment, with effects peaking at approximately 3 to 4 hours and persisting up to 12 hours with higher doses. Performance effects include impaired divided attention, impaired coordination, and balance, slowed reflexes, and increased reaction time (Baselt, 2001). With chronic dosing of either drug, it is likely that decrements in psychomotor performance would be even more pronounced.

Case Reports

Reported signs of psychomotor and cognitive impairment in subjects found to be driving under the influence of carisoprodol/meprobamate include poor perception, impaired reaction time, slow driving, confusion, disorientation, inattentiveness, slurred or thick speech, slow responses, somnolence, lack of balance and coordination, unsteadiness, and difficulty standing, walking, or exiting vehicles (Marinetti-Scheff & Ludwig, 1997; Robertson & Marintetti, 2003).

Logan et al. (2000) describes 21 driving under the influence cases where carisoprodol and/or meprobamate were the only drugs detected. The average carisoprodol and meprobamate concentrations were 4.6 mg/L (range 0 to 15 mg/L) and 14.5 mg/L (range 1 to 36 mg/L), respectively. While signs of impairment, documented by law enforcement officers, were noted at blood concentrations as low as 1 mg/L of meprobamate, the most severe observed impairment and the most overt symptoms of intoxication occurred in drivers whose combined carisoprodol and meprobamate blood concentrations were greater than 10 mg/L. Signs consistent With CNS depression were typically observed by law enforcement officers, including poor balance and coordination, horizontal gaze nystagmus, slurred speech, dazed or groggy appearance, depressed reflexes, slow movements, disorientation to place and time, and a tendency to doze off or fall asleep. Other commonly observed driving behaviors included extreme lane travel and weaving, striking other vehicles and fixed objects, and slow speed.

Forty-five drivers arrested for driving under the influence had an average blood carisoprodol concentration of 9.6 mg/L (range 1.3 to 24 mg/L) and average meprobamate concentration of 21 mg/L (range 2.8 to 45 mg/L). The clinical effects of carisoprodol, as measured by a clinical test for impairment, resembled those of benzodiazepines. Other common effects cited were a reduced level of consciousness, horizontal gaze nystagmus, hand tremor, involuntary movements, and tachycardia (Bramness et al., 2004).

Interactions With Ethanol

Ethanol enhances the impairment of physical abilities produced by carisoprodol, and increased sedation, extreme weakness, dizziness, agitation, euphoria, and confusion may be observed. Ethanol inhibits the metabolism of meprobamate, as both compounds compete for the same enzyme binding site and produces an additive depressant effect on the CNS that includes sleepiness, disorientation, incoherence, and confusion. However, the half-life of meprobamate may be decreased by half after 4 weeks of ethanol consumption (Mozayani & Raymon, 2012; Weatherman & Crabb, 1999).

Interactions With Other Drugs

The concurrent administration of other centrally acting drugs such as opioids, benzodiazepines, barbiturates, and other muscle relaxants can contribute to impairment. Meprobamate may enhance the analgesic effects of other drugs (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 19 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 19. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* may be present in high doses.

Other characteristic indicators may include slurred speech, drowsiness, and disorientation. Note that pupil size may also be dilated.

References and Recommended Reading

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Cocaine

Cocaine base is white to beige in color, waxy/soapy to flaky solid chunks. Cocaine hydrochloride is a white to light brown crystalline powder, shiny rather than dull.

Synonyms

Cocaine base, *cocaine hydrochloride*

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Naturally derived CNS stimulant extracted and refined from the leaves of the coca plant (*Erythroxylon coca*), grown primarily in the Andean region of South America and to a lesser extent in India, Africa, and Indonesia. The picked coca leaves are dried in the open air and then "stomped" as part of the process to extract the alkaloid, resulting in coca paste and eventually cocaine hydrochloride. It is illegal to possess and sell cocaine in the United States and cocaine is a Schedule II controlled substance. "Crack" is the street name given to cocaine that has been processed from cocaine hydrochloride. It is prepared by adding baking soda to aqueous cocaine hydrochloride and heating it until the free-base cocaine precipitates into small pellets. The mixture is cooled and filtered and then the "rocks" are smoked in a crack pipe.

Drug Class

CNS stimulant; local anesthetic

Uses

Clinical

Minor use as a topical local anesthetic for ear, nose, and throat (ENT) surgery, and for control of recalcitrant nosebleed.

Non-Clinical

Traditionally, coca leaves are chewed or brewed into a tea for refreshment and to relieve fatigue. Cocaine is also misused to increase alertness, relieve fatigue, feel stronger and more decisive, and for its intense euphoric effects.

Potency, Purity, and Dose

In ENT surgery, cocaine is commercially supplied as the hydrochloride salt in a 40 or 100 mg/mL solution. Depending on the region, purity of illicit cocaine hydrochloride can range from 20 to 95 percent, while that of crack cocaine is 20 to 80 percent. The hydrochloride powder is often diluted with a variety of substances such as sugars for bulk (lactose, sucrose, inositol, mannitol), other CNS stimulants (caffeine, ephedrine, phenylpropanolamine), or other local anesthetics (lidocaine, procaine, benzocaine). Commonly abused doses are 10 to 120 mg. Repeated doses are frequently taken to avoid the dysphoric crash that often follows the initial intense euphoric effects. Cocaine is frequently used in combination with other drugs: injected with heroin ("speedball"), taken with ethanol to reduce irritability, smoked with phencyclidine, or smoked in marijuana blunts.

Route of Administration

Topically applied for use as a local anesthetic. Coca leaves can be chewed; however, some cocaine users smoke "crack" in a glass pipe or inject the hydrochloride salt intravenously. Cocaine hydrochloride can be smoked to some effect, but this is very inefficient as the powder tends to burn rather than vaporize. Snorting (insufflation/intranasal) is also popular. Subcutaneous injection (skin-popping) is rarely used.

Pharmacodynamics

Cocaine is a potent CNS stimulant that interferes with the reabsorption of catecholamines, particularly dopamine, a chemical messenger associated with pleasure and movement. Cocaine prevents the reuptake of dopamine by blocking the dopamine transporter, leading to increased extracellular dopamine and persistent stimulation of postsynaptic dopamine receptors. This results in the euphoric "rush." When dopamine levels subsequently fall, users experience a dysphoric "crash." Similarly, cocaine interferes with the uptake of norepinephrine and serotonin (5-HT), leading to accumulation of these neurotransmitters at postsynaptic receptors. As a local anesthetic, cocaine reversibly blocks the initiation and conduction of nerve impulses. Cocaine additionally produces vasoconstriction and dilated pupils.

Pharmacokinetics

Cocaine is rapidly absorbed following smoking, snorting, and intravenous administration. Bioavailability is 57 percent following snorting and ~70 percent following smoking. Cocaine is 91 percent protein-bound in plasma. Cocaine is extensively metabolized to a variety of compounds: benzoylecgonine, ecgonine, and ecgonine methyl ester are the major metabolites and are centrally inactive. Benzoylecgonine is produced upon loss of the methyl group and is the major urinary metabolite. Norcocaine is a very minor metabolite but is active and neurotoxic. Cocaethylene, formed following concurrent ingestion of cocaine and ethanol, is also active and is equipotent to cocaine in blocking dopamine reuptake. The apparent half-life for cocaine is short, approximately 0.8 ± 0.2 hours, while the half-life of benzoylecgonine is 6 hours.

Blood to Plasma Concentration Ratio

Reported value is 1.0.

Interpretation of Blood Concentrations

The presence of cocaine at a given blood concentration usually cannot be associated with a degree of impairment or a specific effect for a given individual without additional information. This is due to many factors, including individual levels of tolerance to the drug and artificial changes in cocaine concentrations on storage. There is a large overlap between therapeutic, toxic, and lethal cocaine concentrations and adverse reactions have been reported after prolonged use even with no measurable parent drug in the blood. Typical concentrations in abuse range from 0 to 1,000 ng/mL; however, concentrations up to 5,000 ng/mL and higher are survivable in tolerant people.

Following nasal insufflation of 106 mg, peak plasma concentrations of cocaine averaged 220 ng/mL at 30 minutes, while benzoylecgonine concentrations averaged 611 ng/mL at 3 hours. Oral administration of 140 mg/70 kg cocaine resulted in peak plasma concentrations averaging

210 ng/mL of cocaine at 1 hour. Single 32 mg intravenous doses of cocaine produced an average peak plasma concentration of 308 ng/mL of cocaine within 5 minutes. Smoking 50 mg of cocaine base resulted in peak plasma cocaine concentrations averaging 203 ng/mL at 48 minutes and 151 ng/mL of benzoylecgonine at 1.5 hours (Baselt, 2020).

Two chronic users of cocaine were given daily oral doses of 2 g cocaine, in divided doses, for 16 days. The average peak plasma concentrations of cocaine was 1,260 ng/mL at 1 to 2 hours after the last dose, and the corresponding average peak plasma concentration of benzoylecgonine was 4,910 ng/mL at 2 to 3 hours (Jufer et al., 2000).

OF(S) to Blood Concentration Ratio

Cocaine: Average 20 (*n*=23; median 17; range 1.2 to 63) (Langel et al., 2014)

Benzoylecgonine: Average 3.3 (*n*=40; median 1.7, range 0.18 to 31) (Langel et al., 2014)

Interpretation of OF(S) Test Results

Cocaine pKa 8.6; benzoylecgonine pKa 3.15

Cocaine and benzoylecgonine are readily detected in oral fluid, with highest concentrations typically observed following smoked cocaine. Artificially elevated concentrations may be found, in part, due to ion trapping and coating of the oral mucosa during smoking or insufflation. Contamination from coating typically dissipates within 0.5 to 1 hour. Cocaine is readily detected for 0.5 to 0.6 hours following a single smoked administration, and 6 to ≥ 12 hours after a single intranasal dose. Detection windows are extended following repeated dosing.

A single intravenous dose of 25 mg cocaine was given to 10 subjects and oral fluid samples were collected from subjects using two different devices. Both cocaine and benzoylecgonine were detected in oral fluid at 0.17 hours using both devices. For one device, the median cocaine C_{max} in oral fluid was 932 ng/mL (range 394 to 1,574 ng/mL) and cocaine was detected up to 12.5 hours post-dose; the median benzoylecgonine C_{max} was 248 ng/mL (range 96.9 to 953 ng/mL) and benzoylecgonine was detected up to 30.5 hours. For the other device, the median cocaine C_{max} was 732 ng/mL (range 83.3 to 1,892 ng/mL) and cocaine was detected up to 6.5 hours post-dose; the median benzoylecgonine C_{max} was 360 ng/mL (range 77.2 to 836 ng/mL) and benzoylecgonine was detected up to 28 hours (Ellefsen et al., 2016).

A single subcutaneous dose of 75 mg/70 kg cocaine was given to 19 subjects and a further 14 subjects received a single subcutaneous dose of 150 mg/70 kg. All subjects resided in a closed research unit for up to 10 weeks under constant medical supervision. Cocaine first appeared in oral fluid at 0.08 to -0.32 hours after dosing and demonstrated a rapid elimination half-life of 1.1 to 3.8 hours. Benzoylecgonine first appeared in oral fluid at 0.08 to 1.0 hours after dosing, with a longer elimination half-life of 3.4 to 13.8 hours. Oral fluid and corresponding plasma concentrations were significantly correlated for both cocaine and benzoylecgonine (Scheidweiler et al., 2010).

Six subjects were administered either 25 mg intravenous or 32 mg intranasal or 42 mg smoked cocaine. Cocaine C_{max} in oral fluid ranged from 25 to 1,303 ng/mL, 75 to 1,255,380 ng/mL, and 94 to 12,582 ng/mL, respectively (Desrosiers & Huestis, 2019).

A single smoked dose of 40 mg cocaine base or an intravenous dose of 44.8 mg was given to seven subjects. Peak cocaine concentrations following intravenous administration ranged from

428 to 1,927 ng/mL, whereas peak concentrations following smoking cocaine ranged from 15,852 to 504,880 ng/mL (Jenkins et al., 1995).

Concentrations of cocaine were determined in oral fluid specimens collected from 313 pain patients and averaged 262.8 ng/mL (median 17.6; range 2.0 to 26,504 ng/mL). Benzoylecgonine concentrations were detected in 270 oral fluid specimens and averaged 159.9 ng/mL (median 24.7; range 2.0 to 6,129 ng/mL; Heltsley et al., 2011).

In a review article summarizing the last detection times of cocaine and benzoylecgonine, the following time ranges were reported: 2 to ≥ 69 hours for cocaine and 3 to ≥ 69 hours for benzoylecgonine after a 25 mg intravenous dose; 4 to 28.5 hours for cocaine and 4 to ≥ 72 hours for benzoylecgonine after a 75 mg/70 kg body weight subcutaneous dose (Arnold et al., 2019).

General Effects

The pharmacological effects of cocaine depend on the dose, route of administration, experience of the user, and tolerance. Table 20 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed. Higher doses may also exhibit a pattern of psychosis with confused and disoriented behavior, delusions, hallucinations, irritability, fear, paranoia, antisocial behavior, and aggressiveness.

Table 20. Physiological, motor, and cognitive side effects of cocaine consumption

Physiological	**Motor (behavioral)**	**Cognitive**
Early phase • Increased heart rate • Increased blood pressure • Dilated pupils • Increased light sensitivity • Constriction of peripheral blood vessels • Dyskinesia • Nausea • Vomiting • Loss of appetite Late phase • General CNS depression • Normal heart rate • Normal sized pupils • Drug craving • Insomnia • Fatigue	Early phase • Excitation • Self-centered • Rapid speech • Increased talkativeness • Dizziness • Motor restlessness Late phase • Itching, picking, scratching • Agitation • Nervousness • Restlessness	Early phase • Mental clarity • Euphoria • Feeling of well-being • Increased focus and alertness Late phase • Dysphoria • Depression

Other adverse effects may include tremors, anxiety, and irritability. Chronic use may lead to personality changes, hyperactivity, psychosis, paranoia, and fear. Cocaine overdose can be characterized by agitation, enhanced reflexes, hostility, headache, tachycardia, irregular respiration, chills, nausea, vomiting, abdominal pain, increase in body temperature, hallucinations, convulsions, delirium, unconsciousness, seizures, stroke, cerebral hemorrhage, heart failure, and death from respiratory failure.

Excited delirium is a syndrome often caused by excessive cocaine use, and is associated with a dissociative state, violence to people and property, exaggerated strength, hyperthermia, cardiorespiratory arrest, and sudden death. Burnt lips and fingers from crack pipes are frequently seen, as are rashes and skin reddening from scratching. Smokers may suffer from acute respiratory problems including cough, shortness of breath, and severe chest pains with lung trauma and bleeding. Prolonged cocaine snorting can result in ulceration of the mucous membranes of the nose and perforations of the nasal septum (Baselt, 2001, 2020; Ellinwood & Nikaido, 1987; Gawin & Kleber, 1986; Isenschmid, 2002; Javaid et al., 1978; Oliveira et al, 2019; PDR, 2021; van Dyke et al., 1978; Weddington et al., 1990).

Duration of Effects

Faster absorption produces a more intense and rapid high, but a shorter duration of action. Injecting or smoking cocaine produces an intense effect almost immediately and will typically produce a high lasting up to 15 to 20 minutes. Snorting cocaine produces effects within 3 to 5 minutes and the resulting high may last 20 to 30 minutes or longer. Onset of action is slower after oral ingestion, approximately 30 to 60 minutes, with a reduced high lasting up to 90 minutes. General effects may persist for 1 to 2 hours, depending on the dose. Late phase effects following binge use may last several days.

Tolerance, Dependence, and Withdrawal Effects

Cocaine is a powerfully addictive drug of abuse and an appreciable initial tolerance to the euphoric high may develop. Cocaine is psychologically addicting, particularly with heavy or frequent use, and possibly physically addicting as well. The short duration of effects is one reason leading to the high probability of cocaine use disorder. As effects wear off, people often administer more drug, and a pattern of repeated use develops. Following binge use of cocaine, the “crash” can last from 9 hours to 4 days and may consist of agitation, depressed moods, insomnia to hypersomnolence, and drug craving. Withdrawal symptoms can typically last from 1 to 3 weeks and may consist of alternating low and high drug craving, low to high anxiety, paranoia, dysphoria, depression, apathy, irritability, disorientation, hunger, fatigue, bradycardia, and long periods of sleep (Patterson, 2021; Gawin & Kleber, 1986; Heninger & Kleber, 1991; Isenschmid, 2002; PDR, 2021; Oliveira et al., 2019; Weddington et al., 1990).

Driving-Related Studies

Laboratory Studies

Single oral or intranasal doses of cocaine (48 to 210 mg) have been shown to enhance attentional abilities and increase subjective feelings of alertness, but no enhancement effects on learning, memory, and other cognitive processes. Faster reaction times and diminished effects of fatigue have been observed. Such improvements are typically observed in people who are fatigued or

sleep-deprived; in general, cocaine does not necessarily enhance the performance of people who are alert and attentive (Baselt, 2001).

Laboratory-based studies have not investigated the effects following repeated or chronic use of cocaine. Performance effects following repeated and/or higher doses may include agitation, anxiety, distress, inability to focus on divided attention tasks, inability to follow directions, confusion, hostility, time distortion, and poor balance and coordination, increased risk-taking behaviors (rapid braking or steering) and deleterious effects on vision related to mydriasis. Self-reported increases in sensitivity to light, seeing halos around bright objects, flashes, or movement of light in the peripheral visual field, difficulty focusing, blurred vision, and glare recovery problems have been reported (Ellinwood, 1987; Isenschmid, 2002; Siegel, 1987).

Case Reports

Observed signs of impairment in driving performance have included subjects losing control of their vehicle, causing collisions, turning in front of other vehicles, high-risk behavior, inattentive driving, and poor impulse control. Speeding is also commonly observed. As the effects of cocaine wear off subjects may suffer from fatigue, depression, sleepiness, and inattention (Brookoff et al., 1994; Isenschmid, 2002; Siegel, 1987).

An examination of 253 fatally injured drivers in Wayne County, Michigan, from 1996 to 1998 found that 10 percent of cases were positive for cocaine and/or metabolites in the blood (Isenschmid, 2002). On review of crash and witness reports, the most common finding was aggressive driving (high speed and loss of vehicle control). Ethanol was detected in 56 percent of these cases, and all of these drivers lost control of their vehicles. In Memphis, Tennessee, in 1993, 13 percent of 150 drivers stopped for reckless driving were determined to be driving under the influence of cocaine based on observations of behavior and appearance, and positive urine cocaine tests. While the cocaine-positive drivers were considered clinically intoxicated, most performed normally on SFSTs (Brookoff et al., 1994).

Baselt (2001) summarized two cases of suspected impaired driving involving cocaine. A 25-year-old male driver, who made an improper turn against oncoming traffic, had a cocaine blood concentration of 40 ng/mL and 60 ng/mL of benzoylecgonine, 2 hours after the collision. A 30-year-old female caused a crash after failing to stop at a traffic light; the driver admitted to ingesting a large amount of cocaine ~2.5 hours prior to the collision, and 320 ng/mL cocaine was detected in her blood 1 hour post-crash.

Focusing on cocaine concentrations alone, 61 arrested impaired drivers had average blood concentrations of 100 ng/mL for cocaine and 1,000 ng/mL for benzoylecgonine (Baselt, 2020). In 734 suspected impaired drivers, average plasma concentrations were 840 ng/mL (range 10 to 2,000 ng/mL) for cocaine and 670 ng/mL (<10 to 2,000 ng/mL) for benzoylecgonine (Musshoff & Madea, 2010).

Interactions With Ethanol

Users will often perceive greater reward effects when ethanol and cocaine are co-administered compared to either drug administered alone. The combined use of cocaine and ethanol forms cocaethylene in the body, a substance which enhances cocaine's euphoric effects. Cocaine has been shown to partially reverse or antagonize the learning deficits, self-reported sedation, and

psychomotor performance deficits such as reaction time, induced by ethanol (Baselt, 2001; Mozayani & Raymon, 2012; Pennings et al., 2002).

Ethanol has been shown to increase plasma cocaine concentrations and decrease cocaine metabolism leading to accumulation of cocaine in the body (Singh, 2019). The combination of ethanol and cocaine tends to have greater-than-additive effects on heart rate, concomitant with up to 30 percent increased blood cocaine levels (Pennings et al., 2002).

Interactions With Other Drugs

The concomitant use of cocaine with other sympathomimetics can cause excessive cardiovascular or CNS stimulation (Mozayani & Raymon, 2012). The combined long-term use of cocaine and cannabis can cause prolonged negative cognitive effects on speed processing, inhibitory control, and sustained attention (Oliveira et al. 2019).

Drug Evaluation and Classification Program Category

CNS stimulant

Drug Evaluation and Classification Program Profile

The indicators in Table 21 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 21. DEC program profile of a CNS stimulant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	dilated	slow	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include excessive activity, increased alertness, talkativeness, irritability, argumentativeness, nervousness, body tremors, anxiety, redness to nasal area and runny nose.

References and Recommended Reading

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Cyclobenzaprine

Cyclobenzaprine is a white to off-white crystalline powder.

Synonyms

Flexeril, Amrix and EnovaRX (extended-release), Fexmid

Source

Cyclobenzaprine is currently not a controlled substance in the United States under the Controlled Substance Act. It is available by prescription as the hydrochloride salt in 10 mg tablets normal release and 15 to 30 mg extended-release capsules.

Drug Class

Muscle relaxant

Uses

Clinical

Cyclobenzaprine is a centrally acting skeletal muscle relaxant recommended for use in the treatment of acute skeletal muscle spasms. Off-label uses include reducing pain and/or sleep disturbances in patients with fibromyalgia.

Non-Clinical

The 20 to 50 mg doses of cyclobenzaprine are misused to induce a long-lasting feeling of relaxation/calmness or to enhance the effects of ethanol and other drugs. People may also self-medicate with cyclobenzaprine to ease pain and/or induce sleep.

Potency, Purity, and Dose

Recommended daily doses are 5 to 10 mg three times a day for the normal release tablets or 15 to 30 mg once daily for the extended-release capsules. Recommended treatment is for no longer than 2 to 3 weeks.

Route of Administration

Oral

Pharmacodynamics

Cyclobenzaprine acts on the CNS at the brain stem, rather than targeting the peripheral nervous system or skeletal musculature. This action is thought to diminish the activity of efferent gamma and alpha motor neurons, decreasing tonic somatic motor activity, and producing skeletal muscle relaxation. Cyclobenzaprine is an antagonist at the serotonin $5HT_2$ receptor – more recently it has been proposed that depression of the monosynaptic reflex potential in the spinal cord via inhibition of descending sertonergic systems is responsible for the muscle relaxant effect. Cyclobenzaprine is structurally like tricyclic antidepressants and may have similar actions, including antagonist effects on histamine and muscarinic receptors, increase in heart rate, and a sedative effect.

Pharmacokinetics

Cyclobenzaprine has a moderate oral bioavailability (55%) and is 93 to 97 percent plasma protein bound. The volume of distribution is approximately 2.1 L/kg. Following oral administration, the elimination half-life is 18 to 37 hours. Cyclobenzaprine is metabolized by oxidative and conjugative pathways and the main metabolites are norcyclobenzaprine, 3-OH-cyclobenzaprine, and cyclobenzaprine N-oxide. Approximately 51 percent of a dose is excreted in urine over 5 days, with less than 1 percent as unchanged parent drug.

Blood to Plasma Concentration Ratio

Data not available.

Interpretation of Blood Concentrations

Steady state reached within 3 to 4 days, where plasma concentrations are typically 4-fold higher than observed after single doses.

Eighteen healthy young subjects (21 to 43 years old) received a 10 mg oral dose of cyclobenzaprine three times a day. After the first dose, the average peak plasma concentration was 13.0 ± 4.6 ng/mL at a median time of 4 hours (range 2.5 to 6 hours); after the second dose, the overall plasma C_{max} averaged 18.1 ± 5.4 ng/mL at a median time of 12 hours (range 12 to 24 hours) post-initial dose. Seventeen of the same subjects received a single oral dose of 30 mg of extended-release cyclobenzaprine, resulting in an average plasma C_{max} of 19.2 ± 5.6 ng/mL at a median time of 6 hours (range 4 to 12 hours; Darwish et al., 2008). The same two dosing scenarios were given to 18 older adults (65 to 73 years old). After the first dose of 10 mg cyclobenzaprine, the average plasma C_{max} was 12.2 ± 2.6 ng/mL at a median time of 5 hours (range 3 to 8 hours); after the third dose, the overall plasma C_{max} averaged 18.5 ± 3.3 ng/mL at a median time of 22 hours (range 12 to 24 hours) post-initial dose. The single oral dose of 30 mg extended-release cyclobenzaprine resulted in an average plasma C_{max} of 19.2 ± 5.1 ng/mL at a median time of 8 hours (range 6 to 14 hours; Darwish & Xie., 2009). When steady state pharmacokinetics were evaluated over 7 days using the once daily 30 mg cyclobenzaprine extended-release formulation, steady state plasma C_{max} and C_{min} were 41.1 ± 13.3 and 21.4 ± 8.7 ng/mL, respectively (Darwish & Hellriegel, 2011).

Eighteen healthy young subjects received single oral doses of 2.5, 5, and 10 mg normal release cyclobenzaprine, resulting in plasma C_{max} of 2.1, 4.3 and 8.5 ng/mL at 3.8 to 3.9 hours. When the same doses were given 3 times a day for 7 days, the resulting plasma C_{max} levels were 7.1, 14.9 and 25.9 ng/mL at 3.8 to 4.0 hours (Winchell et al., 2002). The authors also found that steady-state plasma concentrations of cyclobenzaprine were approximately twice as high in older adults and hepatically-impaired subjects compared to younger healthy subjects.

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Cyclobenzaprine pKa 8.47

Information not available.

General Effects

The pharmacological effects of cyclobenzaprine depend on the dose, route of administration, experience of the user, and tolerance. Table 22 provides a range of effects, including adverse effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 22. Physiological, motor, and cognitive side effects of cyclobenzaprine consumption

Physiological	Motor (behavioral)	Cognitive
• Muscle weakness • Mild analgesia • Headache • Dry mouth • Hypotension • Tachycardia	• Relaxation • Calmness • Drowsiness • Dizziness	• Mild euphoria • General cognitive impairment, more likely in older adults

Other adverse effects may include blurred vision, nausea, paresthesia, muscle twitching, lethargy, insomnia, irregular heartbeat, depressed mood, and anxiety. Agitation and psychosis are reported with long-term therapeutic treatment, and agitation, confusion, delirium, and cognitive impairment are more likely to occur in older adults (Baselt, 2020; Darwish & Hellriegel, 2011; Katz & Dube, 1988; Keegan et al., 2006; O'Neil et al., 2000; PDR, 2021; Spiller et al., 1995).

Duration of Effects

Onset of effects is within 20 to 30 minutes and main effects last 4 to 6 hours. Cyclobenzaprine decreases pain within the first 2 weeks of treatment; however, there is no proven benefit after 2 to 3 weeks.

Tolerance, Dependence, and Withdrawal Effects

Mild withdrawal symptoms can occur consisting of nausea, headache, and malaise.

Driving-Related Studies

Simulated Driving Studies

In a three-way, randomized, blinded, crossover study performed on a driving simulator, driving safety and cognitive effects of cyclobenzaprine (10 mg) were compared to tolperisone (150 mg) and placebo. Thirty-one healthy volunteers completed the full study; participants received 10 mg cyclobenzaprine three times a day, and were tested on days 1, 2 and 3 of dosing. Testing consisted of a simulated driving test (monotonous 100 km highway route) where participants were instructed to maintain speed and lane position. Other testing measures included lane exceedance, speed deviation, excessive speed in corners, divided attention, collisions, and cognitive function tests. Compared to placebo, cyclobenzaprine demonstrated significant performance impairment on most measures, on all 3 days. Additionally, cyclobenzaprine dosed participants reported increased sleepiness (day 1) and decreased motivation (days 1 and 2) more often than placebo (Caron et al., 2020).

Case Report

In 34 suspected impaired driving cases, blood concentrations of cyclobenzaprine ranged from < 25 to 240 ng/mL (Gordon, 2002).

Interactions With Ethanol

The combination of ethanol and cyclobenzaprine may produce extreme weakness, dizziness, agitation, euphoria, confusion, enhanced impairment of physical abilities, and increased sedation (Weatherman & Crabb, 1999).

Interactions With Other Drugs

The administration of cyclobenzaprine with other serotonin-enhancing drugs has been associated with serotonin syndrome, with symptoms of autonomic instability and severe agitation (Keegan et al., 2006).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

Typical signs shown may differ from the classical CNS depressant profile, which is shown in Table 23. Variations may also be observed due to individual reaction, dose taken, and drug interactions.

Table 23. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* may be present in high doses.

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Dextromethorphan

Dextromethorphan is a white powder.

Synonyms

Anaplex-DM, Diabe-Tuss DM, Benylin, Pertussin, Delsym, Sucrets, Bromfed-DM, Robitussin, Vicks Formula 44, etc.

Source

Dextromethorphan is a synthetic analog of codeine and the *d*-isomer of 3-methoxy-N-methymorphinan. It is not a controlled substance in the United States under the Controlled Substance Act. It is available as over-the-counter cough and cold remedies in the form of lozenges, capsules, tablets, and cough syrups, and in a variety of prescription medications. Products contain dextromethorphan alone or in combination with guaifenesin, brompheniramine, pseudoephedrine, phenylephrine, promethazine, codeine, acetaminophen, and/or chlorpheniramine. For example, Diabe-Tuss DM syrup contains 15 mg dextromethorphan; Benylin Adult and Pediatric formulas contain 15 mg and 7.5 mg dextromethorphan, respectively; and Anaplex-DM contains 30 mg dextromethorphan, 4 mg brompheniramine and 60 mg pseudoephedrine.

Drug Class

Non-opioid antitussive; cough suppressant; CNS depressant (in high doses

Uses

Clinical

Dextromethorphan is used as an antitussive for the temporary relief of coughs caused by minor throat and bronchial irritation.

Non-Clinical

Dextromethorphan is misused for effects ranging from mild stimulation and intoxication to dissociation.

Potency, Purity, and Dose

As an antitussive, the recommended dosage for adults and children 12 and older is 60 to 120 mg daily in divided doses; for children 6 to 12 years old, 30 to 60 mg daily in divided doses; and for children 2 to 6 years old, 15 to 30 mg daily in divided doses. Each brand contains different quantities of dextromethorphan, generally 20 to 30 mg per dose, and many are co-formulated with other drugs as previously mentioned. People who misuse dextromethorphan typically self-administer 100 to 1,400 mg at a time.

Route of Administration

Oral

Pharmacodynamics

Dextromethorphan acts centrally to elevate the threshold for coughing and has no significant analgesic or sedative properties at antitussive doses. It is proposed that dextromethorphan is an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist. It may also increase serotonin $5HT_{1A}$ activity, possibly via NMDA antagonism.

Pharmacokinetics

Dextromethorphan has a low oral bioavailability and is 60 to 70 percent plasma protein bound. The volume of distribution is 0.8 to 1.3 L/kg. Dextromethorphan is metabolized by CYP2D6 in the liver, and genetic polymorphisms of this gene affect pharmacokinetics. Dextromethorphan is demethylated to dextrorphan, an active metabolite, and to 3-methoxymorphinan and 3-hydroxymorphinan. Following oral administration, the elimination half-life ranges from 2 to 4 hours in extensive metabolizers and approximately 24 hours in poor metabolizers. Up to 30 percent of a dose is excreted in the 24-hour urine as conjugated dextrorphan, 15 percent as conjugated 3-hydroxymorphinan, less than 2.5 percent as unchanged dextromethorphan, and less than 1 percent as 3-methoxymorphinan.

Blood to Plasma Concentration Ratio

1.7 to 1.8

Interpretation of Blood Concentrations

A single 20 mg oral dose of dextromethorphan given to 12 subjects produced peak concentrations of 1.8 ng/mL in serum after 2.5 hours. Chronic oral dosing of 120 mg daily for 7 days, given to 16 healthy adults in divided doses, resulted in peak plasma dextromethorphan concentrations of 0.5 to 5.9 ng/mL (average 2.4 ng/mL) in extensive metabolizers, and 182 to 231 ng/mL (average 207 ng/mL) in poor metabolizers (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Dextromethorphan pKa 8.3

In 30 oral fluid samples collected from child and welfare agencies, concentrations ranged from 5.9 to 2,713.4 ng/mL for dextromethorphan; 28 cases were also positive for dextrorphan with concentrations ranging from 2.1 to 308.4 ng/mL (Amaratunga et al., 2016). Three volunteers received a single dose of 30 mg dextromethorphan. At 3 hours post-dose, concentrations in oral fluid samples ranged from 5.5 to 76.6 ng/mL for dextromethorphan and 4.9 to 10.9 ng/mL for dextrorphan. At 48 hours post-dose, two subjects were still positive for dextromethorphan and dextrorphan, at concentrations of 0.9 and 1.4 ng/mL each, respectively (Rodrigues et al., 2008).

General Effects

At recommended antitussive doses, dextromethorphan produces little or no CNS depression. At recreational doses, desired effects may include acute euphoria, elevated mood, dissociation of mind from body, creative dream-like experiences, and increased perceptual awareness. Other

effects include disorientation, confusion, pupillary dilation, altered time perception, visual and auditory hallucinations, and decreased sexual functioning. Recreational doses of approximately 100 to 200 mg have a mild, stimulant effect; doses of 200 to 500 mg produce a more intoxicating effect; 500 to 1,000 mg may result in mild hallucinations and a mild dissociate effect and an overall disturbance in thinking, senses, and memory, while doses over 1,000 mg may produce a fully dissociative effect. Recreational doses are capable of impairing judgment, memory, language, and other cognitive tasks.

Table 24 provides a range of effects, including side effects that subjects may experience.

Table 24. Physiological, motor, and cognitive side effects of dextromethorphan consumption

Physiological	Motor (behavioral)	Cognitive
• Dilated pupils • Nausea • Gastrointestinal disturbances • Blurred vision • Nystagmus	• Elevated mood • Drowsiness • Disorientation • Confusion	• Euphoria • Heightened perceptual awareness • Altered time perception • Impairment of judgment • Impairment of memory • Dissociation • Visual and auditory hallucinations

Other adverse effects following recommended antitussive doses are rare; however, nausea, other gastrointestinal disturbances, slight drowsiness, and dizziness can occur. Following acute doses of from 250 to 1,500 mg, the following clinical and overdose symptoms have been reported: excitation, nausea, vomiting, drowsiness, dizziness, blurred vision, nystagmus, dilated pupils, body itching, rash, ataxia, sweating, hot/cold flashes, fever, hypertension, shallow respiration, urinary retention, diarrhea, opisthotonos (spasm where head and heels are bent back, and torso is bent forward), toxic psychosis (hyperactivity, marked visual and auditory hallucinations), coma, and an increase in heart rate, blood pressure and body temperature (Baselt, 2020; Cranston & Yoast, 1999; PDR, 2020; Pender & Parks, 1991; Zawertailo et al., 1995).

Duration of Effects

Dextromethorphan exerts its antitussive effects within 15 to 30 minutes of oral administration. The duration of action is approximately 3 to 6 hours following clinical dosages.

Tolerance, Dependence, and Withdrawal Effects

At recommended antitussive doses, addiction is very unlikely to occur. Mild psychological dependence and depression may occur with regular use of increased doses. Abrupt discontinuation of higher doses may produce insomnia, dysphoria, and depression. Poor metabolizers of dextromethorphan have been shown to tolerate lower doses of the drug compared to extensive metabolizers, and report greater sedation, dysphoria, and psychomotor

impairment. Preliminary evidence also suggests that extensive metabolizers may report a greater dextromethorphan abuse potential due to the increased rate of metabolism to the active metabolite dextrorphan (PDR, 2021; Zawertailo et al., 1995, 1998).

Driving-Related Studies

Minimal performance effects are observed following therapeutic dosing; however, with high doses, cognitive and psychomotor impairment may occur.

Simulated Driving Studies

Forty healthy subjects received a single maximum daily dose of 120 mg dextromethorphan or a 400 mg dose of guaifenesin as a control. Subjects' ability to drive was assessed via a driving simulator and an SFST. The 120 mg dextromethorphan dose did not demonstrate decrements in performance in driving simulator tasks or increased SFST failures compared to guaifenesin 400 mg (Perry et al., 2015).

Case Reports

In 108 suspected impaired driving cases positive for dextromethorphan, blood concentrations ranged from > 5 to 1,800 ng/mL (average 207 ng/mL), compared to an expected therapeutic concentration range of 0.5 to 5.9 ng/mL. Ninety-six percent of the specimens included in this study were also found to be positive for drugs other than dextromethorphan. A review of police and DRE reports from several of these cases showed that dextromethorphan-impaired drivers exhibited overall signs of CNS depression (Cochems et al., 2007).

In four suspected impaired driving cases positive for dextromethorphan, blood concentrations ranged from 190 to 1,000 ng/mL (average 570; median 545 ng/mL). The drivers generally displayed symptoms of CNS depressant intoxication and there was gross evidence of impairment in their driving, including weaving, leaving the lane of travel, failing to obey traffic signals, and involvement in collisions. DREs opined that the subjects were under the influence of a drug in the CNS depressant category (Logan, 2009).

Interactions With Ethanol

Information not available.

Interactions With Other Drugs

High doses of dextromethorphan combined with monoamine oxide inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs) may induce serotonin syndrome (hyperthermia, hypertension, arrhythmias). Dextromethorphan metabolism may increase when taken with amphetamines (Mozayani & Raymon, 2012).

Drug Evaluation and Classification Program Category

CNS depressant. Dissociative anesthetic in higher doses.

Drug Evaluation and Classification Program Profile

Data not available; however, Table 25 shows the profile for a dissociative anesthetic. Such effects are more likely seen following higher recreational doses of dextromethorphan. Variation may also be due to individual reaction, dose taken, and drug interactions.

Table 25. DEC program profile for a dissociative anesthetic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present	present	normal	normal	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
Note that pupil size may also be dilated.

Analytical Considerations

The *l* and *d* forms of dextromethorphan may be separated using chiral columns or equivalent separation techniques.

References and Recommended Reading

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Diphenhydramine

Diphenhydramine is a white, crystalline powder.

Synonyms

Benadryl, Unisom Sleepgels, Sominex, Dytuss, Dramamine

Source

Diphenhydramine is not a controlled substance in the United States under the Controlled Substance Act. It is available in capsules, tablets, chewable tablets, syrups, elixirs, topical, and injectable forms in a variety of prescription and over-the-counter medications. Products contain diphenhydramine alone or in combination with other drugs such as pseudoephedrine and acetaminophen. Diphenhydramine is also an ingredient in several Tylenol (i.e., acetaminophen) preparations. Dimenhydrinate (Dramamine) is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.

Drug Class

Antihistamine; antiemetic; sleep aid; sedative; CNS depressant

Uses

Clinical

Diphenhydramine products are used as antihistamines for the temporary relief of seasonal and perennial allergy symptoms. Diphenhydramine is also used as a sleep aid and a cough suppressant and has been used as a centrally acting antitussive although the mechanism for this action is unclear. Dramamine is used as a prophylaxis against and for the treatment of motion sickness.

Non-Clinical

Diphenhydramine may be misused for its mild euphoric, sedating, and intoxicating effects. In higher doses it can be hallucinatory.

Potency, Purity, and Dose

As an antihistamine, recommended doses for adults are 25 to 50 mg diphenhydramine every 6 to 8 hours, not to exceed 50 to 100 mg every 4 to 6 hours. For children, 12.5 to 25 mg three or four times daily is recommended. As a sleep aid the dose is 50 mg at bedtime. Adults can be given 10 to 50 mg intravenously or intramuscularly, up to a maximum daily dose of 400 mg.

Route of Administration

Oral, injected, and topical applications.

Pharmacodynamics

Diphenhydramine is a first-generation antihistamine and is a H_1 receptor antagonist. Antagonism is achieved through blocking the effect of histamine more than blocking its production or release. Diphenhydramine inhibits most responses of smooth muscle to histamine and the vasoconstrictor

effects of histamine. The antagonism may also produce anticholinergic effects, antiemetic effects, and significant sedative side effects.

Pharmacokinetics

Diphenhydramine has an oral bioavailability of 40 to 60 percent and is 80 to 85 percent plasma protein bound. The volume of distribution is approximately 4.5 L/kg. Following oral administration, the elimination half-life ranges from 2 to 9 hours; shorter and longer half-lives have been reported for children and older adults, respectively. Diphenhydramine is metabolized to nordiphenhydramine (active metabolite), dinordiphenhydramine, and diphenylmethoxyacetic acid. Approximately 96 percent of a dose is eliminated in the urine, with less than 4 percent excreted as unchanged diphenhydramine.

Blood to Plasma Concentration Ratio

Reported values range from 0.77 to 0.83.

Interpretation of Blood Concentrations

Following a single oral dose of 50 mg diphenhydramine, average peak plasma concentrations of 66 ng/mL were detected at 2.3 hours. Similarly, a single oral dose of 50 mg resulted in an average peak plasma concentration of 83 ng/mL diphenhydramine detected at 3 hours, declining to 9 ng/mL by 24 hours. A single oral 100 mg dose resulted in average peak plasma concentrations of 112 ng/mL at 2 hours post dose (Baselt, 2020).

OF(S) to Blood Concentration Ratio

0.33 (Sharp et al., 1983)

Interpretation of OF(S) Test Results

Diphenhydramine pKa 8.9

In three volunteers who received a single 50 mg oral dose of diphenhydramine hydrochloride, oral fluid diphenhydramine concentrations averaged 15.3 ng/mL at 1 hour, 40.0 ng/mL at 2 hours, and 34.3 ng/mL at 3 hours (Sharp et al., 1983).

General Effects

First generation H_1 antagonists can both stimulate and depress the CNS. Stimulation results in restlessness, nervousness, and inability to sleep, while depressive effects include diminished alertness, slowed reaction time and somnolence. Diphenhydramine is particularly prone to cause marked sedation. Drowsiness, reduced wakefulness, altered mood, and impaired cognitive and psychomotor performance may also be observed.

Table 26 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 26. Physiological, motor, and cognitive side effects of diphenhydramine consumption

Physiological	Motor (behavioral)	Cognitive
• Dry mouth • Sedation	• Restlessness • Nervousness • Reduced alertness • Slowed reaction time • Drowsiness • Agitation • Confusion	• Mild euphoria • Reduced alertness • Reduced concentration • Diminished attention • Reduced working memory

Other adverse effects may include agitation, anticholinergic side effects such as dry mouth, fatigue, disturbed coordination, irritability, paresthesia, blurred vision, and depression. In overdose, symptoms may include excitement, ataxia, tremor, sinus tachycardia, fever, hallucination, athetosis, convulsions or seizures, hypotension, deep coma, cardiorespiratory collapse, and death. Fixed and dilated pupils may also be observed. Gastrointestinal symptoms are less with diphenhydramine than with other H_1 antagonists (Baselt, 2020; Gengo et al., 1989; PDR, 2020; Ramaekers, 1998; Simons, 1994).

Duration of Effects

Dose-dependent; however, following oral administration of therapeutic doses, peak plasma concentrations are reached in 2 to 3 hours and effects usually last 4 to 6 hours.

Tolerance, Dependence, and Withdrawal Effects

Some tolerance may develop to the sedative effects of diphenhydramine with repeated oral dosing. No reported dependence or withdrawal effects with recommended doses (Baselt, 2001; PDR, 2021; Simons, 1994).

Driving-Related Studies

Laboratory Studies

Laboratory studies have shown therapeutic dosing of diphenhydramine to decrease alertness, decrease reaction time, induce somnolence, impair concentration, impair time estimation, impair tracking, decrease learning ability, and impair attention and memory within the first 2 to 4 hours post dose. Significant adverse effects on vigilance, divided attention, working memory, and psychomotor performance have been demonstrated (Baselt, 2001). Deficits in balance, visual tracking and reaction time have also been observed with doses as low as 25 mg. It is important to note that impairment has been shown to occur even in the absence of self-reported sedation (Cohen, 1984). Further, young children and adults suffering from seasonal allergic rhinitis have performed significantly worse on tests of learning and using knowledge after acute treatment with 50 mg diphenhydramine, compared to placebo and untreated subjects suffering from allergies (Vuurman et al., 1996).

Simulated Driving Studies

In a double-blind, placebo-controlled study, using the National Advanced Driving Simulator at the University of Iowa, Weiler et al. (2000) compared the effects of a single oral dose of 50 mg diphenhydramine to the effects corresponding to a blood ethanol concentration of 0.1 g/dL. Diphenhydramine caused significantly less ability to maintain a constant distance (coherence) and decreased steering instability and crossing center line (lane keeping) compared to ethanol. Overall driving performance was the poorest after taking diphenhydramine versus ethanol, and participants were drowsier after taking diphenhydramine (before and after testing) than ethanol. The authors concluded that diphenhydramine consistently impaired driving performance and may have an even greater impact than does ethanol on operating a motor vehicle.

On-the-Road Driving Studies

In a review of 16 double-blind, placebo-controlled studies using the on-the-road driving test during normal traffic, Verster and Volkerts (2004) concluded that all first-generation antihistamines, including diphenhydramine, significantly impaired driving performance after both one-time and repeated (daily) administration. Diphenhydramine has been shown to severely impair tracking and reaction time performance in actual on-the-road driving tests. For example, single doses of 50 mg diphenhydramine have been shown to cause significant impairment during a 90 km highway test, measuring vehicle following, constant speed, and lateral position) (Ramaekers & O'Hanlon, 1994).

In contrast, single 25 to 100 mg doses of diphenhydramine caused no significant driving effects during a short 15-minute driving test. At 2, 4, and 6 hours following diphenhydramine dosing, the subjects participated in a standardized driving school road test involving low speed vehicle maneuvering and estimation of distances. Performance on the driving test was not affected by diphenhydramine at any dose at the 2, 4, and 6 h marks, though participants rated themselves as physically and mentally sedated at the 100mg dose. However, all doses of diphenhydramine affected performance in the laboratory testing, with significant effects on adaptive tracking, body sway, and reaction times observed on the 2 and 4 h tests. Participants rated themselves as mentally and physically sedated at the 25, 50, and 100mg diphenhydramine doses during psychopharmacology laboratory testing (Cohen et al., 1984).

Interactions With Ethanol

Twelve healthy adults received a single dose of 50 mg diphenhydramine or placebo, followed by 32 mL ethanol or placebo 30 minutes later. Breath ethanol concentrations averaged .043 g/dL 30 minutes after ethanol dosing. Subject performance was tested from 1 to 7.5 hours post-dose and included reaction time (visual), tracking, smooth pursuit, body sway, and sedation self-rating. Diphenhydramine alone impaired performance on all tasks except reaction time. Ethanol alone caused impairment for reaction time, smooth pursuit, and subjective self-rating. In combination, diphenhydramine and ethanol caused performance impairment on all tasks in an additive manner (Baselt, 2001).

Twelve healthy adults received a single dose of 0.58 g/kg ethanol or placebo, consumed over 30 minutes, followed 10 minutes later by a single oral dose of 52 mg/70 kg diphenhydramine or placebo. Breath ethanol concentrations averaged 0.070 percent 30 minutes after ethanol dosing. Blood diphenhydramine concentrations averaged 66 ng/mL at 2 hours post-dose. Subject performance was tested from 0.5 to 1.5 hours post-drinking and included divided attention

(tracking/visual search), tracking, visual backward masking, and critical tracking. Ethanol alone and diphenhydramine alone both impaired performance on all tasks, with greater impairment observed following ethanol only dosing. In combination, ethanol and diphenhydramine resulted in further performance impairment in an additive manner (Burns & Moskowitz, 1980).

Interactions With Other Drugs

Twenty healthy young adults received a single oral dose of 10 mg diazepam or placebo, followed immediately by a single dose of 100 diphenhydramine. Subject performance was tested at 2- and 4-hours post-dose and included critical flicker fusion, continuous performance, manual dexterity, letter recognition and letter cancellation, visual and auditory reaction time, and sedation self-rating. Diazepam alone significantly impaired critical flicker fusion and reaction time. The combination of diazepam and diphenhydramine caused significant decrements in performance for all tests except letter recognition for up to 2 to 4 hours (Baselt, 2001).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

Data not available; however, Table 27 shows the profile for a CNS depressant. Variations may be observed due to individual reaction, dose taken, and drug interactions.

Table 27. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal*	slow	down*	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present at high doses.

References and Recommended Reading

Baselt, 2001; Baselt, 2020; Gengo & Manning, 1990, 1034-9; O'Hanlon et al., 1995, 81- 8; PDR, 2021; Ramaekers, 1998, 189-208; Sharp et al., 1983, 11-14; Verster. & Volkerts, 2004, 294-304.

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Gabapentin

Gabapentin is a white to off-white crystalline solid.

Synonyms

Neurontin, Gabarone, Horizant, Gralise

Source

Gabapentin is not controlled under the United States Controlled Substance Act; however, several states have listed gabapentin as a Schedule V Controlled Substance independently.[1] It is available in immediate-release formulations as 100 to 400 mg capsules; 600 to 800 mg tablets; and a 250 mg/5 mL oral solution. Gabapentin enacarbil (Horizant), a prodrug to gabapentin, and gastroretentive gabapentin (Gralise) both produce extended release of gabapentin.

Drug Class

Anticonvulsant

Uses

Clinical

Medicinally, gabapentin is reported in the treatment of partial seizures in adults with epilepsy and for chronic pain relief in patients with postherpetic neuralgia. It is widely used off-label for a variety of conditions such as chronic pain, bipolar disorder, diabetic neuropathy, fibromyalgia, migraines, and managing mild ethanol withdrawal syndrome and dependence. Subjects may also self-medicate with gabapentin for uncontrolled pain, anxiety, or to treat withdrawal from other drugs such as cocaine or opioids. Gabapentin enacarbil is reported for the treatment of restless leg syndrome and postherpetic neuralgia.

Non-Clinical

People may self-administer higher than recommended doses to achieve euphoric highs and intoxication. Gabapentin is also misused to enhance the desired effects of opioids or to avoid cocaine withdrawal symptoms. It is frequently abused by people who have a history of opioid or other drug abuse and is commonly detected in people alongside opioids, benzodiazepines, and antidepressants.

Potency, Purity, and Dose

Daily doses of gabapentin are typically 900 to 1,800 mg in divided doses. Maximum recommended daily doses are up to 1,800 mg for postherpetic neuralgia and up to 3,600 mg for epilepsy. Abused doses are generally taken as single supra-therapeutic doses – median daily doses have been reported as 3,600 mg (range 1,500 to 12,000 mg).

[1] For information on state-imposed restrictions, see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9585149/

Route of Administration

Gabapentin is typically administered orally. Other routes include injecting, smoking, or snorting/insufflating crushed tablets. Parachuting or bombing refers to emptying crushed tablets or the contents of capsules into a pouch and swallowing, to absorb larger quantities at one time and to avoid the unpleasant, bitter taste of the drug.

Pharmacodynamics

Gabapentin is an analog of the inhibitory neurotransmitter GABA. It is thought to exert GABA-mimetic properties but does not have activity in GABAergic neuronal systems. Gabapentin has high affinity binding to the $\alpha_2\delta$ protein, an auxiliary subunit of voltage-gated calcium channels in CNS neuronal tissues. It inhibits calcium influx, subsequently reducing the release of excitatory neurotransmitters such as glutamate, noradrenaline, and substance P, which are thought to be the basis of its anticonvulsant, anxiolytic, and antinociceptive effects, respectively. Gabapentin may also influence the dopaminergic system which could contribute to its abuse liability and explain why gabapentin has been anecdotally reported to produce dissociative properties.

Pharmacokinetics

Gabapentin displays saturable absorption following oral administration; absolute bioavailability drops from 60 percent to 33 percent as the gabapentin dosage increases from 900 to 3,600 mg/day. Gabapentin enacarbil was designed to increase the oral bioavailability of gabapentin and is approximately 75 percent orally absorbed. Gabapentin does not bind to plasma proteins, has a volume of distribution of 0.65 to 1.04 L/kg, and a half-life of 5 to 7 hours. Steady state concentrations are rapidly achieved. Gabapentin undergoes negligible metabolism and is eliminated primarily as unchanged drug in urine (76 to 81%) over a 4-day period. Elimination half-life increases in people with renal impairment.

Blood to Plasma Concentration Ratio

Reported value of 1.0.

Interpretation of Blood Concentrations

Gabapentin is absorbed slowly after oral administration. The time to reach peak concentrations is a function of the dose administered, with low doses (100 mg) having a T_{max} of ~1.7 hours and higher doses taking 3 to 4 hours to reach T_{max}. Orally administered gabapentin also exhibits saturable absorption; subsequently, plasma concentrations of gabapentin do not increase proportionally with increasing dose (Bockbrader et al., 2010). Concentrations are less proportional to dose when greater than 1,800 mg per day are given, and concentrations tend to plateau with doses greater than 3,600 mg per day (McLean, 1994). A standard meal or a high-fat meal results in a 10 percent increase in the maximum concentration reached. Further, the concentration to dose ratio increases with age, with patients older than 65 years having double the concentration to dose ratio than younger adults (19 to 65 years). Consequently, older patients may need only half the dose per body weight to achieve a similar plasma concentration (Armijo et al., 2004).

A summary of blood concentrations include:

- A single oral dose of 300 mg gabapentin given to 24 healthy adults resulted in an average peak plasma concentration of 1.7 mg/L at 2.5 hours (Baselt, 2020).
- A single 300 mg gabapentin capsule given to 66 subjects (children and adults) resulted in average peak plasma concentrations of 2.7 mg/L at 2 to 3 hours (Armijo et al, 2004).
- A single oral dose of 400 mg gabapentin given to 60 healthy adults resulted in an average peak plasma concentration of 3.4 mg/L (range 2.2 to 6.1 mg/L) at 4 hours. The same dose administered to subjects with moderate renal disease averaged 4.8 mg/L (range 2.3 to 6.1 mg/L) at 5.1 hours and averaged 4.8 mg/L (range 2.3 to 8.9 mg/L) at 8 hours in people with severe renal impairment (Baselt, 2020).
- Random serum levels in 23 adult patients treated for epilepsy, receiving chronic daily doses of 1,800 mg, averaged 4.8 mg/L (Baselt, 2020).
- An average daily gabapentin dose of 1,741 mg (range 600 to 3,600 mg) resulted in an average serum concentration of 5.4 mg/L (range 1.8 to 15.9 mg/L) (Armijo et al, 2004).

Steady state plasma concentrations are approximately proportional to dose, with a C_{max} of 4.0, 5.5 and 8.5 mg/L reached following doses of 300, 400, and 600 mg three times a day, respectively. At these dosages, trough plasma gabapentin concentrations are generally 1 to 10 mg/L (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Gabapentin pKa 3.7

Information not available.

General Effects

The pharmacological effects of drugs depend on the dose, route of administration, experience of the user, and tolerance.

Table 28 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 28. Physiological, motor, and cognitive side effects of gabapentin

Physiological	Motor (behavioral)	Cognitive
• Facial edema • Peripheral edema • Diplopia • Blurred vision • Nystagmus • Dry mouth	• Relaxation • Enhanced sociability • Drowsiness • Dizziness • Slowed reactions • Ataxia	• Euphoria • Sense of calm • Reduced anxiety • Lack of concentration • Memory loss

Physiological	Motor (behavioral)	Cognitive
• Slurred speech • Nausea • Paresthesia • Vasodilation • Hypertension • Tremor • Fatigue • Sedation	• Lethargy	

Other adverse effects may include hypotension, tachycardia, altered mental status, irritability, and motor incoordination. Less common adverse effects may include seizures, dissociation, and audio and visual hallucinations and are more likely with supra-therapeutic doses (Baselt, 2020; Bockbrader et al., 2010; Evoy et al., 2017; Leung et al., 2015; PDR, 2021; Peckham et al., 2017; Schmidt & Rao, 2018; Smith et al., 2016).

Duration of Effects

Onset of effects may occur within 30 minutes after ingestion and typically resolve within 10 hours.

Tolerance, Dependence, and Withdrawal Effects

Abrupt discontinuation of gabapentin has been shown to produce withdrawal symptoms suggestive of physical dependence. Onset of withdrawal symptoms can begin from 12 hours and 7 days after cessation of use, with most cases occurring from 24 to 48 hours. Effects tend to mimic ethanol and benzodiazepine withdrawal symptoms, possibly because on GABA shared by these drugs. Common symptoms include agitation, irritability, confusion, disorientation, sweating, gastrointestinal symptoms such as pain and cramps, tremor, itchiness, tachycardia, hypertension, insomnia, anxiety, and cravings. Less common symptoms can include the development of delirium tremors, depression, and seizures (Evoy et al., 2017; Mersfelder & Nichols, 2016; PDR, 2021).

Driving-Related Studies

Laboratory Studies

Chronic daily dosing of gabapentin in healthy adults has been shown capable of causing some degree of impairment of psychomotor abilities under laboratory conditions, although epileptic patients were not adversely affected (Baselt, 2001).

Twenty-seven patients (children and adults) with epilepsy received doses of 400, 600, or 800 mg gabapentin or placebo 3 times a day for 4 weeks. Patients were tested prior to and at the end of the study; tests included choice reaction time (visual), visual search, Stroop, paired associates, digit span, and subjective measures of cognition, worry, temper, dysphoria, and drowsiness. For the three ascending doses, average peak steady state plasma concentrations were 4.7, 6.8, and 8.6 mg/L, respectively. Overall, gabapentin had no effect on composite psychomotor or cognitive scores, but sedation was produced at the highest dose (2,400 mg per day; Leach et al., 1997).

Six healthy adults received daily oral doses of 1,200 mg gabapentin for 1 week, followed by increasing doses of 400 mg per week for 3 weeks (maximum of 2,400 mg during the fourth week). Patients were tested 3 hours after first dose and within 5 hours of the previous dose during weeks 2 and 4. Tests included choice reaction time (visual), arithmetic, digit symbol substitution, Buschke task, free recall, and sedation self-rating. Serum gabapentin concentrations averaged 9.6 mg/L during the fourth week. No significant adverse effects were noted relative to baseline (Baselt, 2001).

In a 5-week study, 35 healthy adults initially received daily oral doses of 300 mg gabapentin, increasing gradually to 2400 mg per day, in divided doses, at the end of 5 weeks. Subjects were tested before treatment and 3 hours after the morning dose at the end of the 5-week period. Tests included continuous performance, digit cancellation, arithmetic, divided attention (critical tracking/letter recognition), choice reaction time, evoked potential, tapping rate, grooved pegboard, spatial recognition, Buschke task, short story, digit symbol substitution, Stroop, and sedation self-rating. Serum gabapentin concentrations averaged 7.7 mg/L at the end of the study. Gabapentin was found to impair performance for the digit cancellation and evoked potential tasks relative to baseline, but improved scores on the choice reaction time (Baselt, 2001).

Simulated Driving Studies

Fifty-nine healthy subjects received a single nighttime dose of 250 mg gabapentin or placebo. They were tested the following morning using a simulated driving performance test. During the 100 km driving scenario, there were no deviations in standard deviation of lateral position (SDLP[1]) or speed in the treated subjects, although lane excursions increased. Overall, a low dose of gabapentin had no appreciable next-day effects on simulated driving performance or cognitive functioning (Kay et al., 2016).

Thirty-two healthy subjects received daily doses of 600 mg gabapentin three times a day or 1,800 mg gastroretentive gabapentin or placebo for 3 days. Subjects took a simulated driving performance test (driving attentiveness on rural highway setting for 1 hour) at 2 hours after the final dose of each treatment and subjected to cognitive and sedation tests at approximately 4 hours. After day 1 of treatment, the C_{max} for gabapentin was 4.4 mg/L (average 0.96 mg/L) at 6 hours. Subjects treated with gastroretentive gabapentin showed less change in variation in lateral lane position, less tremor, and fewer visual disturbances compared with gabapentin-treated subjects. Although gabapentin showed the greatest variation in SDLP and standard deviation of vehicle speed compared to placebo, the difference was not significant (Schmidt & Rao, 2018).

Case reports: In 137 suspected impaired drivers positive for gabapentin, the average blood concentration measured was 8.4 mg/L (range < 2.0 to 24.7 mg/L; median 7.0 mg/L). Almost all cases were positive for other drugs, with the most common co-administered drugs being benzodiazepines, opioids, and antidepressants. A total of 4 drivers had only gabapentin detected and were subjected to a full Drug Recognition Evaluation (DRE) exam. The blood gabapentin concentrations in these 4 drivers ranged from < 2 to 15 mg/L. Consistently observed signs of impairment were lane travel, lethargy, sleepiness, and slow movements/reactions. DRE indicators consistent with a CNS depressant included horizontal gaze nystagmus, and poor performance on the walk-and-turn and one-leg-stand tests. DRE indicators not consistent with a

[1] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful differences when related to real-world driving.

CNS depressant included normal to elevated pulse, normal to elevated blood pressure, lower body temperature, and normal to dilated pupils (Peterson, 2009).

Interactions With Ethanol

Seventeen healthy, non-ethanol dependent subjects received a single oral dose of 1,000 and 2,000 mg gabapentin or placebo. Four hours later, an ethanol dose of 0.75 g/kg was consumed, given in four divided doses every 20 minutes. Gabapentin impaired the ability of subjects to balance but was not shown to significantly alter the subjective and performance effects of ethanol. Gabapentin also enhanced ethanol-induced tachycardia (Bisaga & Evans, 2006).

Interactions With Other Drugs

The bioavailability of gabapentin can increase by 50 percent when a 600 mg dose is co-administered with oral morphine (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

Data not available; however, Table 29 shows the profile for a CNS depressant. Variations observed may be due to individual reaction, dose taken, and drug interactions.

Table 29. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present at high doses.

Other characteristic indicators may include somnolence, and poor performance on standardized field sobriety tests.

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Gamma-Hydroxybutyrate (GHB, GBL, and 1,4-BD)

GHB is a clear liquid or a white powder with a dry soap-like texture. Precursor drugs such as gamma-butyrolactone (GBL) and 1,4 butanediol (1,4-BD) are clear liquids.

Synonyms

GHB: Sodium oxybate, Xyrem oral solution, Somatomax

GBL: 2(3)-furanone dihydro; Blue Nitro, G3, Invigorate, Jolt, ReActive, REMForce, RenewTrient, Rest-eze, Revivarant, Verve, V35

1,4-BD: tetramethylene glycol; Amino Flex, Enliven, FX, GHRE, Inner G, NRG3, Pine Needle Extract, Revitalize, Serenity, SomatoPro, Thunder Nectar, Zen

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

GHB was first synthesized in 1960 as an experimental GABA analog and was classified as a food and dietary supplement and sold in health food stores in 1980s. It was available in tablet, capsule, and liquid forms. In late 1990 the FDA banned over-the-counter sales of GHB in the United States. In 1999 the FDA issued warnings on the dangers of its precursor drugs GBL and 1,4-BD, which are metabolized to GHB. In early 2000 GHB was Federally reclassified as a Schedule I controlled substance, with an exemption for FDA-approved formulations that would be placed in Schedule III. GBL and 1,4-BD were not scheduled, but GBL was classified as a List 1 chemical, and GBL and 1,4-BD are controlled substance analogs. Sodium oxybate (Xyrem), a pharmaceutical preparation of GHB, available as an oral solution, was approved by the FDA in 2002 and is classified as a Schedule III controlled substance.

GHB can be clandestinely made using ingredients available in kit form over the internet. GHB is made from GBL and a base (e.g., lye/sodium hydroxide [NaOH]), the mixture is heated, and vinegar is added to reduce the pH. Acetone can then be added and the mixture dried, resulting in GHB powder. GBL and 1,4-BD are commercially available as industrial solvents and are used as ingredients in cleaners, solvents, paint removers, and engine degreasers. They are also sold as "natural supplements" over the Internet and in some health food stores and gymnasiums, and are marketed as natural, non-toxic dietary supplements.

Drug Class

CNS depressant, sedative, anesthetic

Uses

Clinical

In Europe GHB is used as an anesthetic adjunct and hypnotic agent, used to treat narcolepsy and to suppress symptoms of ethanol-dependence and opiate withdrawal syndrome. In the United States medically formulated sodium oxybate (Xyrem) has been approved as a Schedule III controlled substance for the treatment of cataplexy (sudden loss of muscle tone) and excessive daytime sleepiness in patients with narcolepsy.

Non-Clinical

GHB is misused for its intoxicating effects (euphoria, reduced inhibitions, sedation) and by bodybuilders as an alternative to anabolic steroids. GBL and 1,4-BD rapidly convert to GHB following oral administration and are taken as GHB substitutes. They are marketed as anti-aging drugs, for weight loss, to treat insomnia, anxiety, and depression, and as mood enhancers and energizers.

Potency, Purity, and Dose

Clinical doses for ethanol withdrawal syndrome are 25 to 50 mg/kg every 12 hours (1.7 to 3.5 g/70 kg); sleep induction 20 to 30 mg/kg (1.5 to 2.25 g/70 kg); prolonged deep sleep 75 to 100 mg/kg (5 to 7 g/70 kg); and anesthetic induction greater than 100 mg/kg (> 7 g/70 kg). Illicit manufacture often introduces impurities and wide variations in potency. Recreational use of GHB often involves doses well more than one teaspoon (~2.5 g, or 35 mg/kg in a 70 kg adult) of the powder dissolved in water/ethanol, or one capful of liquid GHB, GBL, or 1,4-BD; such doses far exceed therapeutic doses. Chronic use can consist of dosing every few hours, around the clock, for months to years. GHB and its precursor drugs are often used in combination with ethanol, ecstasy (MDMA), marijuana, methamphetamine, and cocaine.

Route of Administration

Oral, intravenous

Pharmacodynamics

GHB is a naturally occurring compound present in both mammalian CNS and peripheral tissue. It is also a minor metabolite and precursor of the major inhibitory neurotransmitter GABA. GHB is also the pharmacologically active form of both GBL and 1,4-BD. GHB has weak agonist activity at $GABA_B$ receptors and there appears to be a distinct GHB receptor in the brain. GHB dose-dependently alters dopaminergic activity; at sub-anesthetic doses there is an initial excitation of dopamine neurons producing elevated levels of synaptic dopamine; at anesthetic doses GHB blocks impulse flow from dopamine neurons resulting in a build-up of dopamine in the nerve terminals. GHB mimics natural physiological sleep, enhances rapid eye movement (REM) sleep, and increases stage 3 and 4 of slow-wave sleep. GHB decreases ethanol consumption and intensity of withdrawals. Beyond the CNS effects, GHB has significant cardiovascular effects, causing bradycardia and dysregulation of blood pressure (hyper- and hypotension). Interestingly, GHB causes a detectable increase in growth hormone and prolactin concentrations with doses as small as 3 g, and this is the basis for its use in body building despite there being no evidence of an actual increase in body mass.

Pharmacokinetics

Oral doses are rapidly absorbed from the gastrointestinal tract and undergo first-pass metabolism. Absorption is capacity limited (an increase in dose results in increased time to peak concentration). There is an increased rate of absorption of GHB on an empty stomach, leading to a decreased time to peak concentration and an increased concentration. Accumulation is not known to occur following repeated doses. GHB readily crosses the blood-brain barrier and placental barrier, and is distributed in the brain, cerebrospinal fluid, vitreous, liver, and kidney. The dose-response curve is steep, and a large between and within subject variability is noted.

GHB is rapidly eliminated and has a half-life of 27 minutes (range 20 to 53 minutes), which appears to increase with higher doses, suggesting zero order or saturation kinetics. GHB is metabolized to succinic semialdehyde (SSA) via GHB-dehydrogenase, then to succinic acid via SSA-dehydrogenase. GBL is metabolized to GHB via lactonase; while 1,4-BD is first metabolized to γ-hydroxybutyraldehyde via ethanol dehydrogenase, then to GHB via aldehyde dehydrogenase. GHB appears to exhibit non-linear kinetics; higher doses cause an increase in absorption, elimination half-life, and in time to peak plasma concentration after oral administration.

Blood to Plasma Concentration Ratio

Reported value of 1.2.

Interpretation of Blood Concentrations

Peak plasma concentrations are observed at 20 to 45 minutes. Due to rapid elimination, GHB is undetectable in plasma or blood after 6 to 8 hours. A single oral dose of 50 mg/kg of GHB given to five subjects resulted in average plasma C_{max} for GHB of 83.1 mg/L at 30 minutes (Abanades et al., 2007).

Following single oral doses of 25 mg/kg GHB in 10 ethanol dependent patients, the average peak plasma GHB concentrations was 54 mg/L (24 to 88 mg/L). Single oral doses of 12.5, 25, and 50 mg/kg in eight healthy subjects produced average peak plasma GHB concentrations of 23, 46 and 80 mg/L, respectively. Single oral doses of 26 to 52 mg/kg in six narcoleptic patients resulted in an average peak plasma GHB concentration of 63 mg/L (30 to 102 mg/L). The same doses were administered to the same subjects 4 hours later, and the average peak GHB concentration obtained was 91 mg/L (47 to 125 mg/L). An intravenous dose of 50 mg/kg in an adult produced a peak blood GHB concentration of approximately 170 mg/L within 15 minutes (Baselt, 2001).

Patients presenting to an emergency department with GHB overdose/intoxication, had blood GHB concentrations ranging from 29 to 432 mg/L (average 118 mg/L; n=54) (Couper et al., 2004).

Although GHB is naturally present in the human body, endogenous blood GHB concentrations are typically well below 1 mg/L in living subjects. In contrast, endogenous postmortem production of GHB can occur; GHB concentrations of up to 193 mg/L have been reported in fluoride-preserved, refrigerated postmortem blood in non-GHB using subjects, and up to 433 mg/L in non-fluoride-preserved, non-refrigerated blood. In postmortem analysis, the analysis of specimens such as vitreous and urine is recommended, with urine appearing to be less affected by post-mortem GHB production (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Reported as being <1.0 (Abanades et al., 2007).

Interpretation of OF(S) Test Results

Endogenous GHB is detectable in oral fluid samples. In 120 people (75 females and 45 males), average, median, and range of endogenous GHB concentrations were 1.29 mg/L, 1.13 mg/L, and 0.15 to 3.33 mg/L, respectively (Busardo et al., 2018). Five subjects received a single oral dose

of 50 mg/kg of GHB, followed by the collection of plasma and oral fluid samples. GHB concentrations in oral fluid peaked at 30 minutes post-dose and ranged from 11.6 to 49.0 mg/L, decreasing to less than 0.5 mg/L by 6 hours (Abanades et al., 2007).

General Effects

Table 30 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 30. Physiological, motor, and cognitive side effects of GHB consumption

Physiological	Motor (behavioral)	Cognitive
• Nausea • Vomiting • Profuse sweating • Visual disturbances/loss of peripheral vision • Nystagmus • Uncontrollable shaking/seizures • Bradycardia • Hypothermia • Suppression of gag reflex • Respiratory depression • Sedation	• Relaxation • Reduced inhibitions • Confusion • Dizziness • Drowsiness • Inebriation • Agitation • Combativeness • Transient or unarousable unconsciousness	• Euphoria • Reduced anxiety • Short-term amnesia • Hallucinations

Other adverse effects may include incontinence, apnea, severe ataxia, sinus bradycardia, twitching, seizure-like activity, and hypothermia. In overdose, symptoms may include severe respiratory depression, acute respiratory acidosis, sinus bradycardia or sinus tachycardia, suppression of gag reflex, acute delirium, combativeness, unarousable unconsciousness, and coma. The CNS and respiratory depression resulting from GHB intoxication is so profound that people are often intubated and placed on ventilator support, only to abruptly recover normal mental and respiratory functions hours later (Baselt, 2020; Chin et al., 1998; Couper & Marinetti, 2002; Couper et al., 2004; Dyer, 1991; Kamal et al., 2016; Liakoni et al., 2018; PDR, 2021).

Duration of Effects

Onset of effects occurs within 10 to 20 minutes, peak plasma concentrations are achieved within 20 to 45 minutes, and effects generally last 2 to 5 hours. Complete recovery from GHB overdose can occur within 3 to 6 hours. Sleep induction time is shortest with GBL and longest with 1,4-BD, as GBL is more lipophilic and is absorbed faster. There is a longer duration of effect following 1,4-BD ingestion as it metabolizes more slowly to GHB than does GBL.

Tolerance, Dependence, and Withdrawal Effects

Tolerance can develop to GHB with chronic abuse and even following chronic treatment. Subjects do not become tolerant to all the effects (e.g., tolerance does not develop to the enhanced sleep that GHB produces). Cross-tolerance exists between GHB and ethanol. Severe physical and psychological addiction occurs with chronic abuse. Clinical presentation of withdrawal can start as early as 1 to 2 hours after the last dose in addicted people and may persist for several days. Withdrawal symptoms may include tremors, miosis, sweating, tachycardia, palpitations, dyspnea, nausea, vomiting, diarrhea, abdominal pain, and prevailing anxiety-related behavior. More severe symptoms include hypertension, insomnia, agitation, paranoia, disorientation, confusion, aggression, and auditory and visual hallucinations. In severe cases, delirium and/or psychosis have been reported (Couper & Marinetti, 2002; Dyer et al., 2001; Kamal et al., 2016; PDR, 2021).

Driving-Related Studies

Oral GHB doses of 1 to 2 g have been shown to not deteriorate reactive, attentive, and coordination skills related to driving, nor increase the effects of low dose ethanol. It is important to note, however, that these represent therapeutic doses and do not correlate with the amounts found in case studies.

Laboratory Studies

Twelve subjects received single oral doses of 12.5 or 25 mg/kg GHB or placebo. Testing over the following 3 hours demonstrated that both single doses of GHB had no significant effect on attention, vigilance, alertness, short-term memory, or psychomotor coordination; although dizziness or dullness were experienced in 50 to 66 percent of subjects for up to 60 minutes (Ferrara et al., 1999).

Ten subjects received a single intravenous dose of 10 mg/kg GHB or placebo. Subject performance was tested from 5 to 90 minutes post-dose and included the critical flicker fusion only. GHB caused significant performance impairment on this task for up to 15 minutes (Baselt, 2001).

Simulated Driving Studies

Sixteen subjects received a single oral dose of 50 mg/kg GHB or placebo. Blood samples were collected at 1, 3, and 6 hour post-dose and subjects participated in driving simulator sessions immediately following the blood draws. Median plasma GHB concentrations of 83.1 mg/L (range 54 to 110 mg/L) and 24.4 mg/L (range 7.2 to 49.7) were reached at 1 and 3 hours, respectively. GHB was not detected in plasma at 6 hours post-dose. Regarding performance, GHB dosing caused significant differences for life-threatening outcome collisions and off-road crashes at 1 hour, compared to placebo. GHB also caused significantly more weaving and erratic driving. No significant impairment was found at 3- and 6-hours post-dose (Liakoni et al., 2018).

Case Reports

Several driving case reports have reported signs of behavioral effects and impaired performance. In 13 driving under the influence cases where GHB was detected, the reported symptoms were generally those of a CNS depressant. The subjects were typically stopped because of erratic

driving, such as weaving, ignoring road signs, and near-collisions. Common signs of impairment across cases included confusion and disorientation, incoherent speech, short-term memory loss, dilated pupils, lack of balance and unsteady gait, poor coordination, copious vomiting, unresponsiveness, somnolence, and loss of consciousness. GHB concentrations in blood specimens collected from 1 to 3.5 hours of the arrest ranged from 26 to 155 mg/L (median 95 mg/L; Couper & Logan, 2001). In another 11 cases of driving under the influence of GHB, concentrations of GHB in blood and urine specimens ranged from 81 to 360 mg/L and 780 to 2,380 mg/L, respectively. Observed driving behavior, and signs of impairment were like the previous study (Couper & Marinetti, 2002). A 38-year-old male was arrested seven times for driving-under-the-influence, and had a blood specimen drawn from 1.5 to 2.5 hours after each arrest, with GHC concentrations ranging from 44 to 184 mg/L. In six of these arrests, GHB was the only drug detected (thiopental and diazepam were detected in the remaining arrest). Observed signs of impairment and other symptoms included erratic driving (severe lane travel, collisions, near collisions), slurred speech, disorientation, slow to react, shaking, agitation, unable to focus, poor coordination and balance, poor performance of field sobriety tests, somnolence, and unconsciousness (Couper & Logan, 2004).

Interactions With Ethanol

Ethanol enhances the sedative effect of GHB in a synergistic fashion. In rats, ethanol has significant synergistic effects on the sedative, behavioral, and toxic effects of GHB, GBL, and 1,4-BD. Ethanol also delays the conversion of 1,4- BD to GHB, because both 1,4-BD and ethanol use alcohol-dehydrogenase in their metabolic pathways (Singh, 2019).

Interactions With Other Drugs

Potential additive effects between GHB and other sedating CNS depressants, including antidepressants, antipsychotics, antihistamines, and muscle relaxants. Several drugs have been shown to inhibit GHB-dehydrogenase and it is not known clinically what effects these drugs would have if administered concurrently. These drugs include valproate, ethosuximide, salicylate, amobarbital, phenytoin, disulfiram, and cyanide.

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 31 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 31. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	Down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators include vomiting, sweating, slurred speech, somnolence or transient unconsciousness, and poor balance and coordination. Note that pupil size may be dilated, and while pulse rate and blood pressure may decrease after GHB ingestion, both parameters may be elevated during drug withdrawal.

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Inhalants

The term inhalants, as used throughout these fact sheets, refers to those substances that are misused primarily via inhalation for the purposes of producing psychoactive or mind-altering effects. They encompass a broad range of chemicals found in hundreds of different products and have varying pharmacological effects. They are often inexpensive and easily available, and consequently are commonly abused by children and teenagers. Examples of inhalants include:

- Volatile solvents: liquids that vaporize at room temperature (e.g., markers, glues, toluene, paint thinners/removers, dry-cleaning fluids, gasoline, lighter fluid, correction fluids, electronic contact cleaners);
- Aerosols: sprays that contain propellants and solvents (e.g., spray paints, deodorant and hair sprays, aerosol computer cleaners, vegetable oil sprays, fabric protector sprays.);
- Gases: medical anesthetics that make patients lose sensation during surgical procedures, or gases found in household/commercial products (e.g., ether, chloroform, nitrous oxide/whipped cream dispensers, halothane, butane lighters, propane tanks, refrigerants); and
- Nitrites: prescription medications used as vasodilators to alleviate chest or heart pain, or liquids found in household products (e.g., isoamyl [amyl] nitrite and isobutyl [butyl] nitrite, cyclohexyl nitrite, video head cleaner, room odorizers, leather cleaner).

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Inhalant fumes can be sniffed/snorted directly from containers; sniffed/inhaled fumes from substances sprayed or deposited inside a bag (i.e., bagging); inhaled from an inhalant-soaked rag stuffed in the mouth (i.e., huffing); inhaling from balloons filled with nitrous oxide; and aerosols can be sprayed directly into the nose or mouth. Observable signs and symptoms of inhalant use may include chemical odors on breath or clothing, paint or other stains on face, hands, or clothing; containers of sprays/solvents or chemical soaked rags.

Inhaled substances are rapidly absorbed in the bloodstream through the lungs and then rapidly distributed to the brain and other organs. Solvents, aerosols, and gases directly affect the CNS and slow down brain activity, while nitrites act to dilate blood vessels and relax the muscles. Recreationally, nitrites are used primarily as sexual enhancers rather than to alter mood.

Within seconds, the user experiences intoxication and euphoria along with other CNS depressant effects such as drowsiness, dizziness, reduced inhibitions, slurred speech, inability to control movements. The high often lasts just a few minutes and users may try to make it last by repeat inhalations.

Users may also experience lightheadedness, confusion, nausea and vomiting, lingering headache, inattentiveness, lack of coordination, lethargy, depressed reflexes, and general muscle weakness. Agitation, hallucinations, delusions, and loss of consciousness may also occur. Repeated inhalant use can lead to addiction, hearing loss, liver and kidney damage, limb spasms from nerve damage, and delayed behavioral development. Mild withdrawal syndrome may occur with long-term inhalant abuse and include nausea, loss of appetite, sweating, problems sleeping, and mood changes.

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Difluoroethane (DFE)

Difluoroethane is a colorless, odorless gas.

Synonyms

1,1-difluoroethane, DFE, fluorocarbon, Freon 152; FC-152a, Dust-Off, Endust

Source

Difluoroethane is not a controlled substance in the United States under the Controlled Substance Act and is available as a liquefied gas.

Drug Class

Inhalant; CNS depressant

Uses

Industrial

Difluoroethane is a halogenated hydrocarbon used as a refrigerant and as a propellant in products designed for dusting electronic equipment and air brush painting.

Non-Clinical

Difluoroethane is misused to induce feelings of euphoria, reduced stress and anxiety, peacefulness, and intoxication.

Route of Administration

Sniffing (direct passage from canister to nose), bagging (spraying the chemical in a bag and inhaling from bag), and huffing (soaking a rag with the chemical and inhaling from the rag).

Pharmacodynamics

Difluoroethane crosses the blood-brain barrier and stimulates GABA receptors, causing inhibition in the central nervous system like the effects of other CNS depressants.

Pharmacokinetics

Inhalation uptake during passive exposure is low (< 6%), most of which is exhaled post-exposure. Higher amounts would be absorbed with recreational abuse. Only minor amounts are excreted unchanged in urine (Ernstgård et al., 2014).

Blood to Plasma Concentration Ratio

Data not available.

Interpretation of Blood Concentrations

Upon inhalation there is a rapid initial increase in blood difluoroethane concentration, and an apparent steady state is reached within a few minutes.

Ten healthy volunteers were exposed to 0, 200, or 1,000 ppm DFE for 2 hours at light exercise in an exposure chamber (Ernstgård et al., 2012). Capillary blood, urine, and exhaled air were sampled up to 22 hours post-exposure and analyzed for DFE. Within a few minutes of exposure, DFE increased rapidly in blood and reached average end-of-exposure peak blood concentrations of 7.4 and 34.3 μM (equivalent to 0.5 and 2.3 ng/mL), respectively. The post-exposure decreases in blood were fast and parallel to those in exhaled air.

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Information not available.

General Effects

Table 32 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 32. Physiological, motor, and cognitive side effects of difluoroethane

Physiological	Motor (behavioral)	Cognitive
• Tremors • Increased heart rate • Pulmonary irritation • Muscle weakness • Headache • Decreased pain sensation	• Slurred speech • Drowsiness • Sedation • Ataxia • Dizziness • Disorientation • Confusion • Lightheadedness • Lethargy	• Euphoria • Reduced anxiety

Other adverse effects may include unconsciousness, suffocation, loss of muscular coordination, arrhythmias, frostbite at mucosal surfaces, auditory and/or visual hallucinations, delusions, and inarticulate speech. Long term adverse effects of excessive inhalation can include paresthesia, tinnitus, stupor, persistent low moods, concentration problems, loss of hearing, and cardiac arrhythmias (Baselt, 2020; Novotny et al., 2019, Tiscione & Rohrig, 2021; Vance et al., 2012).

Duration of Effects

Very rapid in onset. Intoxicating effects can be felt almost immediately, which in turn dissipate within minutes.

Tolerance, Dependence, and Withdrawal Effects

Withdrawal symptoms can start within a few hours or days after discontinuation of frequent use, and include sweating, shakiness, loss of sleep, nervousness, hallucinations, headache, muscle pain, and psychotic symptoms.

Driving-Related Studies

Case Reports

Difluoroethane blood concentrations from 14 suspected impaired driving subjects averaged 9.0 mg/L (range 0.6 to 54 mg/L) in blood taken on average 1.4 hours after initial police contact (Pieters et al., 2010). Median blood difluoroethane concentrations in 53 people arrested for suspected impaired driving was 8.0 mg/L (range 0.2 to 290 mg/L) (Chan-Hosokawa, 2014).

A 24-year-old female driver was observed inhaling "Dust-Off" cleaner prior to losing control of her vehicle, resulting in her death. The difluoroethane concentration in postmortem femoral blood was 29.8 mg/L, vitreous 21.2 mg/L, and urine 71.0 mg/L (Hahn et al., 2006). A blood difluoroethane concentration detected in a separate traffic fatality driver was 78 mg/L, in addition to being positive for blood alcohol (0.13%; Broussard et al., 1997).

Tiscione and Rohrig (2021) detailed five impaired driving subjects in which difluoroethane was the only impairing substance identified. Two of the five subjects were involved in more than one collision/traffic stop. Commonly observed driving behaviors included swerving out of the travel lane, veering into oncoming traffic, veering off the roadway, and colliding into objects. Blood samples were collected from approximately 30 minutes to 2 hours following the traffic stop and/or collisions; qualitative testing was performed. The authors noted that since the effects of difluoroethane last only minutes, it was not unexpected for police officers to observe little to no residual signs of impairment upon their arrival.

Interactions With Ethanol

Information not available.

Interactions With Other Drugs

Information not available.

Drug Evaluation and Classification Program Category

Inhalant

Drug Evaluation and Classification Program Profile

The profile for difluoroethane differs from that of the general class of "inhalants." The indicators in Table 33 are the most consistent for difluoroethane; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 33. DEC program profile of difluoroethane

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	present	normal to dilated	normal to slow	Elevated	elevated	normal to elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include burns around the lips.

Analytical Considerations

Fluorocarbon losses can occur if precautions are not taken. Biological samples need to be collected as soon as practicable, placed in air-tight containers, and stored at the lowest possible temperature to avoid heat. It is also recommended to test for volatiles before other toxicology testing to mitigate any potential impact from loss due to repeated specimen sampling.

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Toluene

Toluene is a colorless, flammable liquid with a sweet pungent odor.

Synonyms

Toluol, methylbenzene, methyl benzol, and phenylmethane

Source

Toluene is an aromatic hydrocarbon, occurring naturally in crude oil and in the tolu tree. It is produced during the process of making gasoline and other fuels from crude oil, in making coke from coal, and as a by-product in the manufacture of styrene. Toluene has numerous commercial and industrial applications and is a solvent in paints, lacquers, thinners, glues, correction fluid and nail polish remover, and is used in the printing and leather tanning processes. Due to its easy accessibility, low cost, and ease of concealment, some states within the United States have placed restrictions on the sale of these products to minors. Toluene is not scheduled under the United States Controlled Substance Act.

Drug Class

Volatile solvent; CNS depressant

Uses

Industrial

Toluene is used as a solvent in paints, lacquers, thinners, glues, correction fluid and nail polish remover and is used in printing and leather tanning processes.

Non-Clinical

Toluene is misused for its intoxicating effects. Recreational use is most common among younger adolescents primarily because it is readily available, inexpensive, and legal.

Potency, Purity, and Dose

Solvents in many commercial and industrial products are often mixed and the solvent "sniffer" is often exposed to other solvents in addition to toluene. Acute and chronic accidental exposure to toluene can also occur, particularly in work environments.

Regulatory Limits: The Occupational Safety and Health Administration recommends a maximum of 200 ppm toluene in workplace air for an 8-hour workday, 40-hour work week; the National Institute for Occupational Safety and Health recommends an exposure limit of 100 ppm toluene in workplace air; and the American Conference of Governmental Industrial Hygienists recommends an exposure limit of 50 ppm in workplace air.

Route of Administration

Inhalation of vapor. May be sniffed directly from on open container, or "huffed" from a rag soaked in the substance and held to the face. Alternatively, the open container or soaked rag can

be placed in a bag where the vapors can concentrate before being inhaled. Exposure can also occur by ingesting the liquid or via skin contact.

Pharmacodynamics

Solvents have three proposed mechanisms of action: they may alter the structure of membrane phospholipid bi-layers, impairing various ion channels; they may alternatively alter membrane bound enzymes or receptor-site specificity for endogenous substrates; or they may produce toxic metabolites modifying the hepatic microsomal system and possibly adducting ribonucleic acid and deoxyribonucleic acid molecules. Toluene depresses neuronal activity and reversibly enhances $GABA_A$ receptor-mediated synaptic currents and α1-glycine receptor-activated ion channel function. Toluene also inhibits glutamatergic neurotransmission via NMDA receptors and alters dopaminergic transmission.

Pharmacokinetics

Toluene is well-absorbed following oral ingestion and rapidly absorbed following inhalation. It has a plasma protein binding of 95 percent. Toluene is detectable in the arterial blood within 10 seconds of inhalation exposure. It is highly lipid soluble and accumulates in adipose tissue, tissues with high fat content, and highly vascularized tissues. Highest concentrations are found in the liver, kidney, brain, and blood. The initial half-life in whole blood averages 4.5 hours (range of 3 to 6 hours, then toluene undergoes a second phase elimination from adipose tissue ranging 34 to 38 hours. Approximately 80 percent of a dose is metabolized in the liver. Side-chain hydroxylation to benzyl ethanol is followed by oxidation to benzaldehyde by alcohol dehydrogenase, oxidation to benzoic acid by aldehyde dehydrogenase, and conjugation with glycine to hippuric acid or reaction with glucuronic acid to form benzoyl glucuronide. Ring hydroxylation to o- and p-cresol is a minor (~1%) metabolic pathway. Overall, 4 to 20 percent is excreted unchanged by the lungs, < 0.1 percent is excreted unchanged in the urine, 60 to 70 percent is excreted in urine as hippuric acid (glycine conjugate), and 10 to 20 percent as benzoic acid glucuronide conjugate.

Blood to Breath Concentration Ratio

Reported values range from 7 to 15.

Blood to Plasma Concentration Ratio

Reported value of 1.7.

Interpretation of Blood Concentrations

In 37 non-exposed people, average toluene concentrations have been measured at 0.47 µg/L (i.e., 0.00047 mg/L) in non-smokers and 1.14 µg/L (0.00114 mg/L) in smokers (Brugnone et al., 1989). In 292 unexposed adults, blood toluene concentrations averaged 0.44 µg/L (range 0.02 to 4.88 µg/L; or 0.00002 to 0.00488 mg/L; Jia et al, 2012).

Occupational exposure of 100 workers to 34 ppm for 8 hours resulted in average end-of-shift blood toluene concentrations of 0.457 mg/L, decreasing to 0.038 mg/L after 16 hours (Brugnone et al., 1995). Exposure to 100 ppm for 30 minutes produced 0.4 mg/L of blood toluene in resting people and 1.2 mg/L after exercise (Astrand et al., 1972). In a summary of 136 toluene abusers hospitalized or arrested while intoxicated, blood toluene concentrations ranged from 0.3 to 30

mg/L (Baselt, 2020). Three fatalities from acute toluene inhalation had blood concentrations of 50, 60, and 79 mg/L (Nomiyama et al., 1978). In a summary of eight fatal cases of accidental or intentional acute exposure of toluene, blood concentrations ranged from 10 to 48 mg/L (average 22 mg/L) (Baselt, 2020).

In 53 toluene abusers, blood concentrations of less than 1.0 mg/L corresponded to an odor of "chemical" on the subject's breath; some signs of impairment were observed at concentrations of 1.0 to 2.5 mg/L; 50 percent of subjects with concentrations of 2.5 to 10 mg/L were hospitalized with marked intoxication including hallucinations; and unconsciousness or death were reported at concentrations of 10 mg/L or greater (Baselt, 2020). In six subjects with blood toluene concentrations ranging from 9.8 to 31 mg/L, slurred speech, slow movements, and an inability to concentrate were observed within minutes of cessation of use (Garriott et al., 1981). In 99 blood samples from glue sniffers, toluene ranged from 0.1 to 74.7 mg/L (Park et al., 1998).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Information not available.

General Effects

Mild exposure (100 to 1500 ppm) dose-dependently results in euphoria, dizziness, reduced inhibitions, feelings of inebriation like ethanol intoxication, headache, nausea, lethargy, slow thought and speech, impairment of coordination, loss of memory, slowed reaction time, fatigue, sedation, confusion, impaired cognition function, impaired visual perception, staggering gait, muscular fatigue, and insomnia. More severe intoxication (10,000 to 30,000 ppm) will lead to tremors, arrhythmias, paralysis, unconsciousness, coma, and death. Chronic exposure may result in paranoid psychosis, temporal lobe epilepsy, mental retardation, and visual impairment.

Table 34 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 34. Physiological, motor, and cognitive side effects of toluene consumption

Physiological	Motor (behavioral)	Cognitive
• Nose irritation • Throat irritation • Eye irritation • Headache • Nystagmus • Impaired color vision • Nausea & vomiting • Weakness • Respiratory depression • Convulsions • Seizures	• Slurred speech • Drowsiness • Dizziness • Confusion • Slowed reaction time • Staggering • Ataxia • Coma	• Euphoria • Grandiosity • Floating sensation • Reduced concentration • Distorted perception of time and distance • Loss of memory or memory impairment • Attention deficits • Delusions • Hallucinations

Physiological	Motor (behavioral)	Cognitive
• Fatigue		

Other adverse effects may include hearing loss, and brain, liver, and kidney damage. Death can result from heart failure, asphyxiation, or aspiration. Toluene also owes its pharmacology to a mucosal irritant effect from an exothermic reaction with water. This results in vomiting, lacrimation and ocular burning, cough, chest pain, wheezing and possible interstitial edema, and kidney toxicity with tubular acidosis (Baelum, 1991; Baselt 2020; Byrne et al., 1991; Evans & Balster, 1991; Gjerde et al., 1990; Rahill et al., 1996; U.S. EPA, 2005).

Duration of Effects

Once inhaled, the extensive capillary surface of the lungs allows rapid absorption of toluene and blood levels peak rapidly. Entry into the brain is extremely fast and the onset of effects is almost immediate. Toluene effects generally last several hours.

Tolerance, Dependence, and Withdrawal Effects

Tolerance to the effects of toluene has been shown in rats. Toluene has the potential to produce physical and psychological dependence, and its abuse liability is significant. Signs of physical dependence are observed on withdrawal. Withdrawal symptoms may include headache, anxiety, insomnia, restlessness, irritability, nausea and vomiting, tremor, depressed mood, and aggressive behavior, lasting up to 2 days. Severe withdrawal may include severe tremor, hypertonia, hallucinations, and disturbances of orientation, memory, and concentration (Kouzoupis et al., 2010; Perron et al., 2009).

Driving-Related Studies

Laboratory Studies

Most analyses on performance have been on subjects exposed to 50 to 200 ppm over a 6 to 8-hour work period. Compared to control groups, significant impairment in neurological and neuropsychological test performance has been observed in toluene exposed workers, including short-term memory, sustained attention and concentration, visual scanning, perceptual-motor speed, and finger dexterity (Boey et al., 1997; Foo et al., 1990).

Case Reports

Blood toluene concentrations were above ~1.0 mg/L in 114 drivers arrested on suspicion of driving while intoxicated in Norway from 1983 to 1987. In 29 of these cases toluene was the only detected drug, with average blood concentrations of 10 mg/L (range 1 to 29.3 mg/L). The authors stated there was no simple relation between blood toluene concentrations and degree of impairment; however, almost all drivers with blood toluene concentrations greater than 9.2 mg/L were considered by the police officer as being impaired or highly probably impaired. No driving observations were documented (Gjerde et al., 1990).

Blood toluene concentrations in six subjects arrested for driving under the influence ranged from 12 to 45 mg/L (median 23 mg/L). These subjects displayed signs and symptoms such as balance problems and/or loss of coordination, confusion and disorientation, inability to follow

instruction, horizontal gaze nystagmus, increased pulse and blood pressure, and decreased body temperature (Capron & Logan, 2009).

Interactions With Ethanol

The metabolism of toluene is inhibited by ethanol. When ethanol was administered to people during exposure to toluene (80 ppm), blood toluene concentrations were 42.5 percent greater on average compared to the same exposed people with no ethanol, most likely due to competition for alcohol dehydrogenase which is required for the breakdown of both substances (Waldron et al., 1983).

Interactions With Other Drugs

There is a likely synergy or potentiation of effects with other solvents and CNS depressants.

Drug Evaluation and Classification Program Category

Inhalant

Drug Evaluation and Classification Program Profile

The indicators in Table 35 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 35. DEC program profile of an inhalant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	Elevated	elevated	down to normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include strong odor of solvent or chemical on breath or clothes, residue of substance around nose, mouth or hands, slurred speech, and general intoxication.

Analytical Considerations

Toluene concentrations fall rapidly in blood samples stored at 4 °C and 23 °C. Recommend storing blood frozen (Gjerde et al., 1990).

References and Recommended Reading

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Ketamine

Ketamine is a white, crystalline powder or clear liquid.

Synonyms

Ketalar, Ketaject, Ketaset, Vetalar

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Available by prescription only and is commercially available as a veterinary anesthetic. It is difficult to synthesize clandestinely and is obtained illegally from veterinarian offices or diverted from legitimate pharmaceutical sources in liquid form. Ketamine is currently a Schedule III controlled substance in the United States. Methoxetamine, a compound structurally like ketamine and with similar effects, is available for sale online.

Drug Class

Dissociative anesthetic; hallucinogen; psychotomimetic

Uses

Clinical

Primarily used in veterinary applications as a tranquilizer. Also used as an anesthetic induction agent for diagnostic and surgical procedures in humans, prior to the administration of general anesthetics. Frequently used in the management of agitated people by emergency medical service (EMS) and emergency personnel. Ketamine is used as a short-acting general anesthetic for children and older adults, as an analgesic agent in hospital settings, and as an adjunct for the treatment of major depressive disorder (Strayer, R., 2024).

Non-Clinical

Ketamine is misused as a psychedelic and for its dissociative effects.

Potency, Purity, and Dose

Ketamine is available as a racemic mixture with the S- (+)- isomer being more potent than the R- (-)- isomer. Commercially supplied as the hydrochloride salt in 10 mg/mL, 50 mg/mL and 100 mg/mL solutions. For induction of 5 to 10-minute surgical anesthesia, a dose of 1.0 to 4.5 mg/kg is intravenously administered; 6.5 to 13 mg/kg is given intramuscularly for 12 to 25 minutes of surgical anesthesia. The liquid from injectable solutions can be gently heated to evaporate the water, leaving a white powder (ketamine hydrochloride) that can be snorted or orally ingested. Recreational doses are highly variable. Common doses are 25 to 50 mg intramuscularly, 30 to 75 mg snorting, and 75 to 300 mg oral. Snorting a small line (“bump,” 30 to 50 mg) usually results in a dreamy effect. A profound dissociative state, often referred to as the “K-hole,” can be obtained following a dose of 60 to 125 mg intramuscularly or by snorting 100 to 250 mg. Impurities are rarely seen, although ketamine hydrochloride itself can be used as a heroin adulterant.

Route of Administration

Injected, snorted, orally ingested, and rectally administered. Like phencyclidine (PCP), ketamine can be added to tobacco or marijuana cigarettes and smoked.

Pharmacodynamics

Involves analgesia, anesthetic, and sympathomimetic effects that are mediated by different sites of action. Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonism is associated with the analgesic effects; opioid receptors may contribute to analgesia and dysphoric reactions; and sympathomimetic properties may result from enhanced central and peripheral monoaminergic transmission. Ketamine blocks dopamine uptake and therefore elevates synaptic dopamine levels. Inhibition of central and peripheral cholinergic transmission could contribute to induction of the anesthetic state and hallucinations. Ketamine is structurally like PCP, but 10 to 50 times less potent in blocking NMDA effects.

Pharmacokinetics

Bioavailability following an intramuscular dose is 93 percent, intranasal dose 25 to 50 percent, and oral dose ≤ 20 percent. Ketamine is rapidly distributed into the brain and other highly perfused tissues and is 12 percent bound in plasma. The elimination half-life is 2 to 4 hours. Oral administration produces lower peak concentrations of ketamine, but increased amounts of the metabolites norketamine and dehydronorketamine. Ketamine and its metabolites undergo hydroxylation and conjugation. Norketamine produces effects like those of ketamine. There are no significant differences between the pharmacokinetic properties of the S-(+) and R-(-)-isomers.

Blood to Plasma Concentration Ratio

Reported values of 0.82 to 1.7.

Interpretation of Blood Concentrations

There is no direct correlation between ketamine concentrations and behavior. Drowsiness, perceptual distortions, and intoxication may be dose related in a concentration range of 50 to 200 ng/mL, and analgesia begins at plasma concentrations of about 100 ng/mL. During anesthesia, blood ketamine concentrations of 2,000 to 3,000 ng/mL are used, and patients may begin to awake from a surgical procedure when concentrations have been naturally reduced to 500 to 1,000 ng/mL.

Five patients received a single intravenous dose of 2.5 mg/kg ketamine, resulting in average serum ketamine concentrations of 1,000 ng/mL at 12 minutes, declining to 500 ng/mL by 30 minutes. Three subjects received a single intravenous dose of 4 mg/kg ketamine, resulting in plasma concentration as high as 5,800 to 6,300 ng/mL at 5 minutes post-injection (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Ketamine pKa 7.5

In the oral fluid of 21 volunteers at a rehabilitation center, who were addicted to drugs of abuse, ketamine was detected at concentrations of 27 to 11,546 ng/mL. Norketamine was detected in 19 of these subjects at 11 to 1,434 ng/mL, and dehydronorketamine was detected in 16 of the subjects at 8 to 118 ng/mL (Tsui et al., 2012).

General Effects

Users have likened the physical effects of ketamine to those of PCP and the visual effects to lysergic acid diethylamide (LSD). The pharmacological effects of ketamine depend on the dose, route of administration, experience of the user, and tolerance. Table 36 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 36. Physiological, motor, and cognitive side effects of ketamine consumption.

Physiological	Motor (behavioral)	Cognitive
• Anesthesia • Cataplexy • Immobility • Tachycardia • Increase blood pressure • Nystagmus • Hypersalivation • Increased urinary output • Profound insensitivity to pain • Sedation • Vivid dreams	• Disorientation • Slurred speech • Uncommunicative • Ataxia	• Decreased awareness of general environment • Impaired thought processes • Impaired perception to body, time, sounds and surroundings • Amnesia • Out of body experiences • Dream-like state • Feelings of invulnerability • Delirium • Hallucinations

There is a high incidence of other adverse effects which include anxiety, chest pain, palpitations, severe agitation, rhabdomyolysis, flashbacks, delirium, dystonia, psychosis, schizophrenic-like symptoms, vomiting, seizures, and paranoia (Adler et al., 1998; Baselt, 2020; Bowdle et al., 1998; Curran & Morgan, 1998; Ghoneim et al., 1985; Mozayani, 2002; Newcomer et al., 1999; PDR, 2021; Umbricht et al., 2000; Weiner et al., 2000).

Duration of Effects

Onset of effects is within seconds if smoked, 1 to 5 minutes if injected, 5 to 10 minutes if snorted, and 15 to 20 minutes if orally administered. Effects generally last 30 to 45 minutes if injected, 45 to 60 minutes if snorted, and 1 to 2 hours following oral ingestion. Ketamine is often re-administered due to its relatively short duration of action. Some subjects may experience dreams 24 hours later. Marked dissociative effects, schizotypal symptoms, and impaired semantic memory are found in some recreational users days after drug use.

Tolerance, Dependence, and Withdrawal Effects

In long-term exposure, high tolerance, drug craving, and flashbacks are described. There is little evidence of a physiological withdrawal syndrome unless abrupt discontinuation in chronic users (Janse & Darracot-Cankovic, 2001).

Driving-Related Studies

Laboratory Studies

Studies have demonstrated a broad spectrum of cognitive impairments and marked dissociative effects. Overall, single sub-anesthetic intravenous and intramuscular doses of ketamine have been shown to impair laboratory-based performance for up to 2 hours post dose. Commonly reported adverse effects include subjective sedation, dizziness, perceptual distortions, hallucinations, intoxication, and blurred vision (Baselt, 2001).

Nineteen healthy adults received a 40-minute intravenous infusion of 0.1 or 0.5 mg/kg ketamine. Subject performance was tested during the last 20 minutes of infusion. Ketamine impaired performance on card sorting, free recall, and visual vigilance in a dose-related manner (Krystal et al., 1994).

Ten healthy subjects received continuous ketamine infusions for 30 minutes, with the aim of reaching and maintaining plasma concentrations of 0, 50, 100, 150 and 200 ng/mL. Subject performance was tested at 20 minutes into the infusion, including a visual analog rating of 13 symptoms scale. One hour after the infusions, a psychological inventory and hallucination rating scale was performed. Dose-related subjective feelings of drowsiness, perception disorders (colors, sound, surrounding, thoughts, time, voices), and intoxication ("high") were observed up to 2 hours (Bowdle et al., 1998).

Simulated Driving Studies

A randomized, placebo-controlled, crossover study evaluated simulated driving performance of 107 healthy subjects following single doses of ketamine, rapastinel (a novel antidepressant), alprazolam, and placebo. Approximately 45 minutes after a 0.5 mg/kg intravenous infusion of ketamine, subjects participated in a 60-minute, 100 km simulated driving scenario designed to measure standard deviation of lateral position (SDLP[19]), lane exceedances and duration, and total number of collisions. Cognitive (CogScreenSDC test) and self-reported measures (sleepiness, motivation, self-appraisal of driving performance) were also documented. Ketamine impaired driving, cognitive, and self-reported measures for up to 105 minutes following dosing (Su et al., 2022).

Interactions With Ethanol

Information not available.

[19] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful amount of differences when related to real-world driving.

Interactions With Other Drugs

Midazolam attenuates altered perception and thought processes. Lorazepam may decrease ketamine-associated emotional distress but does not decrease cognitive or behavioral effects of ketamine. Acute administration of diazepam increases the half-life of ketamine. Lamotrigine significantly decreases ketamine-induced perceptual abnormalities but increases the mood elevating effects. Haloperidol may decrease impairment by ketamine in executive control functions, but does not affect psychosis, perceptual changes, negative schizophrenic-like symptoms, or euphoria. Alfentanil is additive to ketamine in decreasing pain and increasing cognitive impairment. Physostigmine and 4-aminopyridine can antagonize some pharmacodynamic effects of ketamine (PDR, 2021).

Drug Evaluation and Classification Program Category

Dissociative anesthetic

Drug Evaluation and Classification Program Profile

The indicators in Table 37 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 37. DEC program profile of a dissociative anesthetic.

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present	present	normal	normal	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Nystagmus is very prominent in ketamine exposure. Other characteristic indicators may include rigid muscles, cyclic behavior, and lack of response to painful stimuli.

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Lysergic Acid Diethylamide (LSD)

LSD is a white powder or a clear, colorless liquid.

Synonyms

d-lysergic acid diethylamide; acid

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

LSD is a lysergamide hallucinogenic, manufactured from lysergic acid which occurs naturally in the ergot fungus that grows on wheat and rye. It is a Schedule I controlled substance, available in liquid, powder, tablet (microdots), and capsule form. The liquid is often applied to blotter paper squares (frequently with colorful designs), stickers, sugar cubes, candy, or soda crackers. LSD is also available in dropper bottles or in the form of gelatin sheets/shapes.

Drug Class

Hallucinogen; psychedelic; psychotomimetic

Uses

Clinical

No approved clinical use.

Non-Clinical

Used as a hallucinogen and for its ability to alter human perception and mood.

Potency, Purity, and Dose

The strength of illicit LSD nowadays ranges from 20 to 80 µg per dose, which is considerably less than doses reported during the 1960s and early 1970s of 100 to 200 µg or higher per unit. Experienced users typically administer 100 to 200 µg for a "good high." The minimum effective dose is 25 µg. The potency of liquid LSD in dropper bottles may vary because the liquid is water-based.

Route of Administration

Primarily oral administration, but can be inhaled, injected, and transdermally applied.

Pharmacodynamics

LSD is primarily a non-selective serotonin (5-HT) agonist. LSD may exert its hallucinogenic effect by interacting with 5-HT_{2A} receptors as a partial agonist and modulating the N-methyl-D-aspartate (NMDA) receptor-mediated sensory, perceptual, affective, and cognitive processes. LSD acts at 5-HT_{1A} receptors, producing a marked slowing of the firing rate of serotonergic neurons, and stimulates both D_1 and D_2 dopamine receptors.

Pharmacokinetics

LSD has a plasma half-life of 2.5 to 4 hours. Metabolites of LSD include N-desmethyl-LSD, hydroxy-LSD, 2-oxo-LSD, and 2-oxo-3-hydroxy-LSD. These metabolites are all inactive.

Blood to Plasma Concentration Ratio

Data not available.

Interpretation of Blood Concentrations

Threshold toxic dose in humans has been reported with 100 to 200 µg with associated blood concentrations of 2 to 30 ng/mL. Intravenous doses of 1 to 2 µg /kg have been associated with blood concentrations of 1 to 5 ng/mL LSD. Single oral doses of 160 µg resulted in peak plasma concentrations of up to 9 ng/mL LSD (Upshall & Wailling, 1972).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

LSD pKa 7.8

General Effects

Effects are unpredictable and depend on the ingested dose; the user's personality, mood, and expectations; and the user's surroundings. Table 38 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 38. Physiological, motor, and cognitive side effects of LSD consumption

Physiological	Motor (behavioral)	Cognitive
• Tachycardia • Hypertension • Dilated pupils • Sweating • Dry mouth • Loss of appetite • Tremors • Piloerection	• Speech production difficulties • Sleeplessness	• Increased color perception • Synesthesia-like symptoms • Perceptual changes in body image • Impaired depth, time and space perception • Hallucinations (visual and auditory • Temporary psychosis • Delusions

Users may feel several emotions at once or swing rapidly from one emotion to another. "Bad trips" may consist of severe terrifying thoughts and feelings, fear of losing control, and despair. Other adverse effects may include rhabdomyolysis, renal failure, prolonged mania, panic, impairment in color discrimination, and residual visual effects. LSD users may manifest

relatively long-lasting psychoses, such as schizophrenia or severe depression. Long-term visual disturbances and flashbacks have been reported for up to 5 years post last ingestion (Abraham, 1992; Baselt, 2020; Kawasak & Purvin, 1996; Kulig, 1990; Smith & Seymour, 1985; Vardy & Kay, 1983).

Duration of Effects

Onset of effects is rapid following intravenous administration (10 minutes). Following oral ingestion, onset of the first effects is experienced in 20 to 30 minutes, peaking at 2 to 4 hours, and gradually diminishing over 6 to 8 hours. Residual effects may last longer.

Tolerance, Dependence, and Withdrawal Effects

Frequent, repeated dosing of LSD is atypical and therefore tolerance is not commonly seen. Tolerance does develop to the behavioral effects after daily dosing for as little as 2 to 4 days, but this tolerance dissipates rapidly after the drug is held for two days, and no withdrawal syndrome has been described. LSD is not considered an addictive drug as it generally does not produce compulsive drug-seeking behavior.

Driving-Related Studies

In studies examining the effect of LSD on driving-related tasks, LSD produces significant psychedelic effects with doses as low as 25 to 125 μg. LSD impairs reaction time (auditory and visual), choice reaction time, and visual acuity for up to 4 hours (Baselt, 2001). Impaired divided attention, ataxia, and grossly distorted perception have also been reported following LSD use.

Epidemiology studies suggest the incidence of LSD in driving under the influence cases is extremely rare. For example, in one study in Denver, Colorado from January 1988 to June 1990, 242 drivers detained for driving while impaired were evaluated by drug recognition examiners. Urine testing was performed in all cases and only one subject was positive for LSD (Tomaszewski et al., 1996).

Interactions With Ethanol

In a retrospective study involving 22 LSD users, ~87 percent reported a complete reduction of subjective ethanol effects, while the remaining users reported a diminished response. It was proposed that LSD's effect on ethanol intoxication involved interactions with various serotonergic and/or dopaminergic receptor systems (Barrett et al., 2000).

Interactions With Other Drugs

Cross-tolerance with mescaline and psilocybin has been demonstrated in animal models. Possible seizures noted when concurrently taken with lithium or fluoxetine. Given the serotenergic mechanism, serotonin toxicity could occur when LSD is used in conjunction with other serotonergic xenobiotics.

Drug Evaluation and Classification Program Category

Hallucinogen

Drug Evaluation and Classification Program Profile

The indicators in Table 39 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 39. DEC program profile of a hallucinogen

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	dilated	normal	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include extreme changes in behavior and mood, trance-like state, sweating, body tremors, rigid muscle tone, piloerection, hallucinations, paranoia, and changes in sense of light, hearing, touch, and smell.

Analytical Considerations

LSD degrades readily in biological specimens unless protected from light and elevated temperatures. False positive immunoassay testing for LSD has been reported after exposure to several medications, including haloperidol, verapamil, sertraline, and fentanyl (Ritter et al., 1997; Gagajewski et al., 2002).

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Methamphetamine

Methamphetamine hydrochloride is a white to light brown crystalline powder, or clear chunky crystals resembling ice. Methamphetamine base is a liquid.

Synonyms

Desoxyn

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

The majority of street methamphetamine is produced in clandestine laboratories (e.g., reduction of *l*-ephedrine or *d*-pseudoephedrine over red phosphorus with hydroiodic acid, or reduction with sodium or lithium in condensed liquid ammonia). Methamphetamine use is on the rise in many parts of the United States. *d*-Methamphetamine is a Schedule II controlled substance (Desoxyn) available in 5 mg white, 10 mg pink, and 15 mg yellow strength tablets.

Drug Class

CNS stimulant; sympathomimetic; appetite suppressant

Uses

Clinical

Methamphetamine is used in the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD). Methamphetamine is infrequently used in the treatment of obesity, overeating disorders, and weight loss, due to its abuse potential.

Non-Clinical

Methamphetamine is misused to increase alertness, relieve fatigue, control weight, treat mild depression, and for its intense euphoric effects.

Potency, Purity, and Dose

Purity of methamphetamine is currently very high, at 60 to 90 percent, and is predominantly *d*-methamphetamine which has greater CNS potency than the *l*-isomer or the racemic mixture. Common abused doses are 100 to 1,000 mg/day and up to 5,000 mg/day in chronic binge use. Therapeutic doses of Desoxyn are 2.5 to 10 mg daily, with dosing not to exceed 60 mg/day. Typically, clinical use of greater than six weeks is not recommended.

Route of Administration

Methamphetamine users often begin with intranasal or oral use and progress to intravenous use and occasionally smoking. In contrast to cocaine, the hydrochloride salt of methamphetamine can itself be smoked. Methamphetamine is used sometimes with ethanol or marijuana, particularly during the withdrawal phase.

Pharmacodynamics

Methamphetamine increases synaptic levels of the neurotransmitters dopamine, serotonin (5-HT) and norepinephrine, and has α- and β-adrenergic agonist effects. Norepinephrine is responsible for methamphetamine's alerting, anorectic, locomotor, and sympathomimetic effects; dopamine stimulates locomotor effects, psychosis, and perception disturbances; and 5-HT is responsible for delusions and psychosis. Methamphetamine's effects are like cocaine, but the onset is slower, and the duration is longer.

Pharmacokinetics

Following oral administration, peak methamphetamine concentrations are seen in 2.6 to 3.6 hours and the average elimination half-life is 10.1 hours (range 6.4 to 15 hours). The amphetamine metabolite peaks at 12 hours. The plasma protein binding for methamphetamine and amphetamine are 15 to 40 percent and 10 to 20 percent, respectively. Following intravenous injection, the average elimination half-life is slightly longer (12.2 hours). Methamphetamine is metabolized to amphetamine (active), p-OH-amphetamine and norephedrine (both inactive). Several other drugs are metabolized to amphetamine and methamphetamine, including benzphetamine, selegeline, and famprofazone.

Blood to Plasma Concentration Ratio

Methamphetamine: 0.65 (Langel et al., 2014)

Interpretation of Blood Concentrations

Blood concentrations can generally be used to distinguish therapeutic use from abuse. Concentrations of 20 to 50 ng/mL are typical for therapeutic use, with levels up to 200 ng/mL having been documented. Concentrations greater than this are considered supratherapeutic. Concentrations do not predict phase of use (see General Effect section). Typical concentrations in recreational use may range from 10 to 2,500 ng/mL (median 600 ng/mL). Concentrations above this range will likely be associated with severe, possibly life threatening, toxicity. There is no evidence for improved performance in any task or test following use of doses greater than 40 mg (or concentrations greater than 200 ng/mL). Peak blood methamphetamine concentrations occur immediately after injection, a few minutes after smoking, and around 3 hours after oral dosing.

Six subjects received a single oral dose of 0.125 mg/kg (8.75 mg/70 kg) methamphetamine, resulting in average peak plasma concentrations of 20 ng/mL at 3.6 hours. Ten subjects received a single oral dose of 30 mg methamphetamine, resulting in average peak serum concentrations of 94 ng/mL (range 62 to 291 ng/mL) within 3 to 5 hours (Baselt, 2001). Single oral doses of 12.5 mg methamphetamine were given to 10 adults, resulting in average peak blood concentrations of 20 ng/mL at 2.5 hours, declining to 16 ng/mL by 6 hours and 10 ng/mL by 24 hours (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Methamphetamine: 4.5 (n=11) (Gjerde et al., 2010)

Methamphetamine: 23 (n=52; median 19; range 3.3 to 78) (Langel et al., 2014)

Interpretation of OF(S) Test Results

Methamphetamine pKa 10.1 (Langel et al., 2014)

Methamphetamine is a lipid-soluble, weakly basic drug with a high pKa and low plasma protein binding. Oral coating is possible after recent drug use if it was taken orally, snorted, or smoked. Amphetamines also ion trap in oral fluid, leading to higher oral fluid concentrations compared with blood.

Eight subjects received four oral doses of 10 mg methamphetamine sustained-release tablets over 1 week. Methamphetamine was detected in oral fluid as early as 0.08 to 2 hours after dosing and the average C_{max} reached was 106 ng/mL (range 24.7 to 312 ng/mL). Following the administration of four oral doses of 20 mg methamphetamine sustained-release tablets the average C_{max} was 192 ng/mL (range 75.3 to 322 ng/mL). Amphetamine was also detected in these subjects but at lower concentrations; the average C_{max} was 8.6 ng/mL (range 3.8 to 21.3 ng/mL) and 14.2 ng/mL (range 2.8 to 20.2 ng/mL) for the low and high dose methamphetamine, respectively. Maximal oral fluid concentrations were reached in 2 to 12 hours (Schepers et al., 2003).

Concentrations of methamphetamine were determined in oral fluid specimens from 44 pain patients, with an average concentration of 600.9 ng/mL (median 105.3; range 8.1 to 9,139.5 ng/mL). Amphetamine concentrations were detected in 190 oral fluid specimens with an average concentration of 798.5 ng/mL (median 179.8; range 5.9 to 21,093 ng/mL; Heltsley et al., 2011).

In 25 patients admitted to a closed detoxification ward, oral fluid was collected twice daily for up to 10 days. Subjects self-reported doses of methamphetamine as 0.5 to 2 g. The median last detection time for amphetamine and methamphetamine in oral fluid were 2 and 3 days, respectively, while the range of last detection times were 0 to 8 days for both substances (Arnold et al., 2019).

General Effects

The pharmacological effects of methamphetamine depend on the dose, route of administration, experience of the user, and tolerance. Methamphetamine effects are less intense after oral ingestion than following smoked or intravenous use.

Table 40 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 40. Physiological, motor, and cognitive side effects of methamphetamine consumption

Physiological	Motor (behavioral)	Cognitive
Early phase • Increased heart rate • Increased respiration rate • Increased blood pressure	Early phase • Excitation • Exhilaration • Rapid speech • Impulsive actions • Motor restlessness • Reduced drowsiness • Increased reaction time	Early phase • Euphoria • Increased alertness • Sense of well-being • Rapid flight of ideas • Hallucinations • Delusions • Psychosis

Physiological	Motor (behavioral)	Cognitive
• Elevated temperature • Palpitations • Irregular heart beat • Dry mouth • Abdominal cramps • Suppressed appetite • Twitching • Pallor • Dilated pupils • Reduced fatigue • Insomnia Late phase • Normal heart rate • Normal to small pupils • Pupils reactive to light • Lack of coordination • Drug craving • Fatigue	Late phase • Itching/picking/scratching • Sleepiness with sudden starts • Restlessness • Nervousness • Agitation • Violence/aggression	• Poor impulse control • Feelings of increased physical strength Late phase • Dysphoria • Pseudo-hallucinations • Delusions • Psychosis • Paranoia

Binge use of methamphetamine can be broken down into the following phases:

- Rush – (~5 minutes) intense euphoria, rapid flight of ideas, sexual stimulation, high energy, obsessive/compulsive activity, thought blending, dilated pupils;
- Shoulder – (~1 hour) less intense euphoria, hyperactivity, rapid flight of ideas, obsessive/compulsive activity, thought blending, dilated pupils;
- Binge use – (~1 to 5 days) the drug is frequently re-administered to regain or maintain euphoria;
- Tweaking – (~4 to 24 hours) dysphoria, scattered and disorganized thought, intense craving, paranoia, anxiety and irritability, hypervigilance, auditory and tactile hallucinations, delusions, and normal pupils;
- Crash – (~1 to 3 days) intense fatigue, uncontrollable sleepiness and catnapping, continuing stimulation, drug craving;

- Normal – (~2 to 7 days) apparent return to "normalcy" although drug craving may appear;
- Withdrawal – anergia, anhedonia, waves of intense craving, depression, hypersomnolence, exhaustion, extreme fatigue.

Other adverse effects may include light sensitivity, irritability, insomnia, nervousness, headache, tremors, anxiety, suspiciousness, paranoia, aggressiveness, delusions, hallucinations, irrational behavior, and violence. Severe adverse effects include hyperthermia, tachycardia, severe hypertension, convulsions, chest pains, stroke, cardiovascular collapse, and possible death. Other coexisting medical conditions associated with methamphetamine use disorder include septicemia, abscesses, collapsed blood vessels, and malnutrition. Chronic abuse generally produces a psychosis that resembles schizophrenia and is characterized by paranoia, picking at the skin, preoccupation with one's own thoughts, and auditory and visual hallucinations. Violent and erratic behavior is frequently seen among chronic users. Over time, methamphetamine appears to cause reduced levels of dopamine, which can result in symptoms like those of Parkinson's disease (Baselt, 2020; Forney, 1977; Hurst, 1987; Logan, 2001; Logan, 2002; PDR, 2021; Perez-Reyes et al., 1991; Smith & Fischer, 1970).

Duration of Effects

Onset of effects is rapid following intravenous use and smoking, while effects evolve more slowly following oral use. Effects peak at 2 to 3 hours and typically last 4 to 8 hours; residual effects can last up to 12 hours.

Tolerance, Dependence, and Withdrawal Effects

Methamphetamine has a high potential for abuse and dependence. Tolerance may develop, and people may quickly become addicted and use it with increasing frequency and in increasing doses. Abrupt discontinuation of use can produce extreme fatigue, long periods of sleep (disturbed, fitful sleep), mental depression, apathy, mood changes, anxiety, severe agitation, irritability, and disorientation (AAC, 2021; Logan, 2002; PDR, 2021).

Driving-Related Studies

Laboratory Studies

Laboratory studies have been limited to much lower doses than those often used by people who misuse methamphetamine. Oral and intravenous doses of 10 to 30 mg methamphetamine have been shown to improve reaction time, relieve fatigue, improve cognitive function testing, increase time estimation, and increase subjective feelings of alertness and euphoria (Baselt, 2001).

Epidemiological Studies

In epidemiological studies, drive-off the-road type crashes, high speed, failing to stop, diminished divided attention, inattentive driving, impatience, and high-risk driving have been reported. In a review of 101 driving under the influence cases, where methamphetamine was the only drug detected, blood concentrations ranged from < 50 to 2,360 ng/mL (average 350 ng/mL, median 230 ng/mL). Driving and driver behaviors were reported as speeding, lane travel

changes, erratic driving, crashes, nervousness, rapid and non-stop speech, unintelligible speech, disorientation, agitation, staggering and awkward movements, irrational or violent behavior, and unconsciousness. Impairment was attributed to distraction, disorientation, motor excitation, hyperactive reflexes, general cognitive impairment, or withdrawal, fatigue, and hypersomnolence (Logan, 2002). Similar behaviors and symptoms were documented in 28 drivers arrested for impaired driving or killed in resulting traffic collisions. Blood methamphetamine concentrations ranged from 50 to 2,600 ng/mL. Typical driving behaviors included drifting out of the lane of travel or off the road, weaving and erratic driving, speeding, and high-speed collisions. Observed symptoms included rapid and/or confused speech, dilated pupils, increased pulse rate, agitation, paranoia, and aggressiveness. In approximately one-third of these cases, the drivers had co-consumed cannabis (Logan, 1996).

Interactions With Ethanol

It has been shown that ethanol increased the absorption and C_{max} of methamphetamine without altering its elimination (Singh, 2019). Ethanol may inhibit methamphetamine metabolism, resulting in higher blood methamphetamine concentrations, with an increase in its stimulating effects on brain and heart, resulting in significant negative effects on mood, performance, and physiological behaviors. Ethanol also increased heart rate and systolic blood pressure.

Interactions With Other Drugs

Phenobarbital, propoxyphene, phenytoin, and monoamine oxide inhibitors (MAOIs) slow the metabolism of amphetamines and increase their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings. Amphetamines may counteract sedative effects of antihistamines. Methamphetamine may restore ethanol-induced impairment in simple repetitive tasks of short duration; however, there is no restoration of ethanol-induced deficits of balance and steadiness. In general, high doses of amphetamines are likely to increase the impairing effects of ethanol. Chlorpromazine and haloperidol block dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS stimulant

Drug Evaluation and Classification Program Profile

The indicators in Table 41 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 41. DEC program profile of a CNS stimulant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	dilated	slow	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include restlessness, body tremors, talkativeness, exaggerated reflexes, anxiety, deterioration of skin and dental hygiene (dental caries, periodontal lesions, tooth wear), and track marks or recent injection sites.

Analytical Considerations

l and *d* forms of methamphetamine may be separated using chiral columns or equivalent separation techniques.

References and Recommended Reading

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Methylenedioxymethamphetamine (MDMA, Ecstasy)

MDMA is a white, tan, or brown powder.

Synonyms

3,4-methylenedioxymethamphetamine; ecstasy

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

MDMA is the methylenedioxy derivative of methamphetamine. Starting materials in its illicit manufacture include isosafrole (Leuckart reaction) and safrole (Merck patent). MDMA is most commonly found in tablet form in various colors, carrying distinctive markings on one side such as a dove, E, yin/yang symbol, etc. MDMA is a Schedule I controlled substance.

Drug Class

Mild CNS stimulant; empathogen; entactogen; mild hallucinogen and psychedelic; appetite suppressant

Uses

Clinical

Originally patented as an appetite suppressant and used as a possible adjunct to psychotherapy, there is currently no approved medical use in the United States.

Non-Clinical

MDMA is misused as a party, rave, or dance drug for its stimulant, mild hallucinogenic, and empathogenic properties.

Potency, Purity, and Dose

MDMA exists as a racemic mixture, with the S-(+)- enantiomer having greater CNS potency compared to the R-(-)-enantiomer. Potency of street samples is highly variable, and tablets sold as “ecstasy” may in fact contain little or no MDMA, but may instead contain caffeine, ephedrine, phenylpropanolamine, paramethoxyamphetamine (PMA), methylenedioxyamphetamine (MDA), dextromethorphan, amphetamine, methamphetamine, and/or ketamine. Some tablets have been reported to contain LSD or heroin. Typical doses in a series of pills can range from 10 to 150 mg of MDMA, and commonly ingested doses can range from 50 to 700 mg in a session. The most common pattern of use is binge consumption at all night raves or dance parties. MDMA is frequently taken with other drugs such as ethanol, marijuana, cocaine, methamphetamine, nitrous oxide, and GHB.

Route of Administration

Primarily oral administration, although MDMA could conceivably be dissolved and injected, or crushed and insufflated.

Pharmacodynamics

MDMA is a phenylethylamine that has stimulant as well as psychedelic effects. MDMA is related in structure and effects to methamphetamine; however, it has significantly less CNS stimulant properties than methamphetamine. MDMA has a high affinity for serotonin $(5\text{-HT})_2$ receptors. Both S- and R- enantiomers of MDMA cause acute depletion of presynaptic 5-HT, depression of 5-HT synthesis by tryptophan hydroxylase, and retrograde destruction of 5-HT neurons following high doses. MDMA also increases levels of norepinephrine and dopamine. The MDMA metabolite, S-(+)-MDA, elicits more stereotypic behavior and is an even more potent neurotoxin than the parent drug. MDA destroys serotonin-producing neurons that play a direct role in regulating aggression, mood, sexual activity, sleep, and sensitivity to pain.

Pharmacokinetics

MDMA is rapidly absorbed. The elimination half-life of MDMA is approximately 7 hours, although non-linear pharmacokinetics have been observed due to stereoselective pharmacokinetics of the enantiomers. MDMA is metabolized to MDA which is the only metabolite reported in blood and plasma. The elimination half-life of MDA is approximately 13 hours. S-(+)- MDA accumulates in blood due to stereoselective metabolism of S-(+)-MDMA. MDA is further metabolized to its 3-hydroxy-4-methoxy and 3,4-dihydroxy derivatives (HMA and HHA). Additional MDMA metabolites include 3-hydroxy-4-methoxymethamphetamine (HMMA) and 3,4-dihydroxymethamphetamine (HHMA). These polar hydroxylated metabolites are conjugated prior to their excretion in urine.

Blood to Plasma Concentration Ratio

Data not available.

Interpretation of Blood Concentrations

No clear correlation exists between MDMA blood concentrations and effects. MDMA and MDA are the analytes detected in blood, with MDA concentrations typically only 5 to 10 percent of the corresponding MDMA concentrations. Higher MDA:MDMA ratios may indicate coadministration of MDA.

Single oral doses of 50, 100, 125 and 150 mg MDMA have produced average peak plasma concentrations of 106, 180, 220, and 465 ng/mL, respectively, from 1.5 to 2.4 hours. In the same studies, the average peak plasma concentrations of MDA were 28, 11, 11, and 33 ng/mL, respectively, from 4 to 10 hours post-dose (Baselt, 2020).

OF(S) to Blood Concentration Ratio

MDMA 5.1 (n=4) (Gjerde et al., 2010)

Interpretation of OF(S) Test Results

MDMA pKa 9.9

MDMA is readily detected in oral fluid. MDMA can typically be detected in oral fluid for 12 to 48 hours after a single dose. Initial MDMA-positive oral fluid samples occur as early as 0.25 hours but are more commonly 0.5 to 0.75 hours after dosing.

Single oral doses of 1.0 and 1.6 mg/kg MDMA, given to eight healthy adults, resulted in median C_{max} of 1,643 ng/mL (range 1,160 to 3,382) and 4,760 ng/mL (range 2,881 to 11,985), respectively (Desrosiers & Huestis, 2019). OF from 6,441 patients being treated for chronic pain were screened for illicit drug use – two patients had measurable concentrations of MDMA, with an average concentration of 946.7 ng/mL (range 73.5 to 1,819.8 ng/mL) (Heltsley et al., 2011). Following a 100 mg dose of MDMA, the first detection time in oral fluid was at 1.5 hours and the last detection time was 24 hours for MDMA (Lee, 2018).

General Effects

The pharmacological effects of MDMA depend on the dose, route of administration, experience of the user, and tolerance. Table 42 provides a range of effects, including side effects that people may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 42. Physiological, motor, and cognitive side effects of MDMA consumption.

Physiological	**Motor (behavioral)**	**Cognitive**
Low to moderate dose (50 to 200 mg) • Mild visual disturbances (blurred or double vision, light sensitivity) • Dilated pupils • Heightened sensitivity and responsiveness to touch • Dry mouth • Sweating • Muscle tension • Involuntary jaw clenching	Low to moderate dose (50 to 200 mg) • Mild intoxication • Relaxation • Increased physical and emotional energy • Increased sociability & closeness • Ataxia Higher doses • Agitation • Panic attacks	Low to moderate dose (50 to 200 mg) • Empathy • Euphoria • Feelings of well-being • Changes in perception Higher doses • Impairment of cognitive, perception and mental associations • Illusory or hallucinatory experiences

Subjects may also experience fatigue, uncoordinated gait, decreased fine motor skills, attentional dysfunction (difficulty to maintain attention during complex tasks), preoccupation, hyperthermia, tachycardia, hyponatremia, convulsions, and catatonic stupor. Prolonged cognitive and behavioral effects may occur including poor memory recall, flashbacks, panic attacks, psychosis, and depersonalization due to serotonergic neuron damage and decreased serotonin production resulting from long-term use (Guarnotta, 2021; Baggott et al., 2019; Baselt, 2020; Brookhuis et al., 2004; Climko et al., 1986-1987; Downing, 1986; Logan & Couper, 2003; Morgan, 1998; Parrott et al., 1998).

Duration of Effects

Following oral administration, effects onset in 20 to 30 minutes and desired effects may last only an hour or more, depending on dose. Other general effects last for approximately 2 to 3 hours.

LSD is sometimes used in combination with MDMA to increase its duration of effects. Residual and unwanted effects are generally gone within 24 hours although confusion, depression, and anxiety may last several weeks.

Tolerance, Dependence, and Withdrawal Effects

Drug stacking refers to the ingestion of single doses consecutively as effects begin to wane, like cocaine or methamphetamine binges. Such extensive or binge use often occurs over weekends, and can result in exhaustion, apathy, depression, irritability, insomnia, anxiety, paranoia, muscle tension and drug craving early the next week (referred to as "terrible Tuesdays"). Tolerance may develop quickly and users who consistently abuse MDMA may develop a problem with compulsive use and eventually show symptoms of a substance use disorder. Withdrawal symptoms may include fatigue, insomnia, depression, appetite loss, and problems with thinking, memory, and concentration, which may last several days to weeks. Persistent neurological deficits may occur, including serotonergic neuron damage which leads to less production of serotonin (Guarnotta, 2021; McGuire, 2000)

Driving-Related Studies

MDMA can enhance impulsivity and make it difficult for a person to maintain attention during complex tasks, especially in attention tasks such as those testing selective attention and divided and sustained attention.

Laboratory Studies

Single oral doses of MDMA (1 tablet, or 105 to 119 mg/70 kg) have been shown to cause subjective excitability, anxiety, perceptual changes, poor memory recall, derealization, thought disorders, and heightened sensory awareness 1 to 3 hours post dose (Baselt, 2001). Higher-dose effects of MDMA on performance have not been assessed in experimental, placebo-controlled studies due to medical and ethical constraints.

Simulated and On-the-Road Driving Studies

In a review article of the effects of stimulatory drugs on driving performance, the authors summarized that the effects of single doses of MDMA on measures of simulated and actual driving were neutral for most of the driving measures or even positive for specific measures (i.e., road tracking). While subjective data reported that MDMA increased arousal and decreased sleepiness, it has also been shown to reduce some driving tasks such as accuracy of speed adaption during car-following performance and impair cognitive functions such as working memory and movement perception (Ramaekers et al., 2012). In the same review article, the effects of sleep deprivation with or without MDMA, sleep loss has been shown to produce severe impairment in actual and simulated driving performance, typically expressed by a significant rise in standard deviation of lateral position (SDLP) in road tracking scenarios. Overall, MDMA has not been shown to compensate for the impairing effect of sleep loss on simulated and actual driving performance.

Case Reports

In 18 subjects arrested for driving under the influence, blood MDMA concentrations ranged from < 50 to 1,900 ng/mL; in six of these subjects, MDMA was the only drug detected at blood

concentrations ranging from < 50 to 580 ng/mL. These six subjects typically experienced muscle twitching, body tremors, perspiration, dilated pupils, and slow pupillary reaction to light (Logan & Couper, 2001).

In 493 driving under the influence subjects, average blood MDMA concentrations were 230 ng/mL (median 100 ng/mL, highest 3,500 ng/mL; Jones et al., 2008). In two other case studies of impaired drivers, average blood MDMA concentrations of 340 ng/mL (range 140 to 670 ng/mL) were detected in 17 subjects, and an average of 260 ng/mL (range 140 to 460 ng/mL) were detected in eight subjects (Baselt, 2020).

Interactions With Ethanol

A single oral dose of 0, 75, or 100 mg MDMA or placebo was given to 18 healthy adults, followed by an ethanol dose calculated to yield a blood alcohol concentration of 0.06 g/dL, or placebo. Subjects were tested on their psychomotor performance, subjective effects, and pharmacokinetics. Plasma concentrations of MDMA were slightly higher after the use of ethanol at 1.5 hours (137.4 versus 147 ng/mL at 75mg MDMA dose, 191.8 versus 208.5 ng/mL at 100 mg MDMA dose), whereas plasma concentrations of ethanol showed slight (9 to 15%) decreases (640 mg/mL alone versus 590 mg/mL, and 590 mg/mL, when combined with MDMA at 75 mg and 100 mg doses, respectively). The MDMA-ethanol combination did result in some increases in reaction time (Ramaekers & Kuypers, 2006). In a review article of combined MDMA and alcohol studies, the authors reported that stimulatory effects of MDMA are overall not sufficient to fully overcome alcohol-induced impairments of driving performance, psychomotor function, and cognition (Ramaekers et al., 2012).

Interactions With Other Drugs

The dopamine D_2 receptor antagonist, haloperidol, attenuates psychological effects of MDMA but has no impact on physiological effects. Selective serotonin reuptake inhibitors (SSRIs) decrease the effect of MDMA as they compete for binding sites in the brain – this can lead to serotonin syndrome due to a buildup of serotonin in the CNS.

Drug Evaluation and Classification Program Category

Hallucinogen (with many characteristics like a CNS stimulant)

Drug Evaluation and Classification Program Profile

The indicators in Table 43 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 43. DEC program profile of a hallucinogen

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	None	dilated	slow	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include profuse sweating, muscle twitching, body tremors, and poor performance in field sobriety tests. Subjects are usually described as very cooperative

and “laid-back.” Note that elevated blood pressure and body temperature are not always observed.

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Opioids

Opioids are a class of substances that bind to opioid receptors (mu [μ], kappa [κ], delta [δ], and nociception receptors) to produce morphine-like effects, such as analgesia. They include natural, semi-synthetic and synthetic alkaloidal substances. The following opioids section contains general comments regarding this class of drugs – refer to individual opioid fact sheets for specific information regarding buprenorphine, fentanyl, hydrocodone, and hydromorphone, mitragynine, morphine and codeine, oxycodone and oxymorphone, and tramadol. A summary of fentanyl analogs and novel synthetic opioids is also provided.

Source

Most opioids are either Schedule II or III controlled substances and are obtained via prescription or through illegal sources. Naturally occurring opioids are those extracted from the opium poppy, *Papaver somniferum*. The milky resin that seeps from incisions made in the unripe seedpod is dried and powdered to make opium, which contains several alkaloids including morphine, codeine, and thebaine. Semi-synthetic opioids derived from morphine include heroin and hydromorphone. Opioids derived from codeine include dihydrocodeine and hydrocodone, while buprenorphine, oxycodone and oxymorphone are synthesized from thebaine. Synthetic opioids have chemical structures unlike morphine and include fentanyl, meperidine, methadone, propoxyphene, and tramadol.

Drug Class

Narcotic analgesic

Uses

Clinical

Opioids are used primarily for the relief of moderate to severe pain in both acute and chronic pain management. Other indications include sedation of patients pre-operatively, to facilitate the induction of anesthesia, as antitussives, antidiarrheal agents, and maintenance therapy for people with opioid use disorder.

Non-Clinical

Opioids are misused to achieve euphoric highs and contentedness, for sedation or relaxation, self-medication for pain relief, or to relieve or prevent withdrawal symptoms.

Potency, Purity, and Dose

Clinically, the dosage of opioids depends on the agent and is typically patient-dependent (the dose increases as tolerance is achieved). For non-clinical purposes, doses vary greatly, and potency and purity can depend on the demographic region where the opioid is available. Illicit opioids are often deliberately or surreptitiously combined with a variety of different cutting agents and/or other illicit substances.

Route of Administration

Clinically, opioids are administered via oral, intramuscular, intravenous, rectal, epidural, and intrathecal routes. In misuse, opioids can be ingested orally, smoked, and snorted. Solutions, or tablets that have been crushed can be injected intravenously ("mainlining") or subcutaneously ("skin popping"). Crushed tablets can also be placed into a pouch and swallowed ("parachuting/bombing").

Pharmacodynamics

The pharmacological effects of opioids are due to their interaction with different opioid receptors in the brain, spinal cord, peripheral sensory neurons, and gastrointestinal tract. Opioid receptors are coupled to G-proteins, and activation of opioid receptors causes guanosine triphosphate (GTP) to be exchanged for guanosine diphosphate (GDP) on the G-proteins which in turn down regulates adenylate cyclase, reducing concentrations of cyclic adenosine monophosphate (cAMP), and decreasing cAMP-dependent influx of calcium ions into the cell. This results in hyperpolarization of the cell and reduced neuronal excitability. Opioids inhibit the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine, and noradrenaline.

Individual opioids bind to the distinct opioid receptors with differing affinities, resulting in the varying responses observed with each opioid.

Mu-($\mu_{1,2,3}$) receptors are located in the brain, spinal cord, peripheral sensory neurons, and intestinal tract. Interactions at μ_1-receptors result in CNS depression, analgesia, pain modulation, respiratory depression, miosis, euphoria, and decreased gastrointestinal motility. Interactions at μ_2-receptors produce respiratory depression, drowsiness, nausea, and mental clouding. μ-receptors are also involved in changes in body temperature, tolerance, and increased addiction potential.

Kappa-($\kappa_{1,2,3}$) receptors are located in the brain, spinal cord, and peripheral sensory neurons; interactions with κ-receptors produce analgesia (spinal), diuresis, sedation, dysphoria, miosis, and mild respiratory depression.

Delta-($\delta_{1,2}$) receptors are located in the brain and peripheral sensory neurons; δ-receptors are involved in analgesia, dysphoria, delusions, and hallucinations.

Nociceptin receptors are located in the brain and spinal cord, and produce changes in anxiety, depression, and appetite.

Pharmacokinetics

Refer to individual fact sheets.

General Effects

The pharmacological effects of opioids depend heavily on the dose, route of administration, experience of the user, and tolerance. Table 44 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 44. Physiological, motor, and cognitive side effects of opioid consumption

Physiological	Motor (behavioral)	Cognitive
• Analgesia • Decreased heart rate • Respiratory depression • CNS depression • Sedation • Nausea & vomiting • Weakness • Reduced gastrointestinal motility • Constipation • Flushing of face & neck • Cramping • Sweating • Constricted pupils	• Relaxation • Drowsiness • Lethargy • Disconnectedness • Diminished reflexes • Depressed consciousness	• Euphoria • Feeling of well-being • Mental clouding ('mental fog') • Inability to concentrate

Other adverse effects may include drowsiness, apathy, lessened physical activity, tremors, itching, bradycardia, severe respiratory depression, and pulmonary complications such as pneumonia. Medical complications among people who use illicit opioids arise primarily from adulterants found in street drugs and in non-sterile injecting practices, and may include skin, lung, spinal, and brain abscesses, joint infections, collapsed veins, and endocarditis. Signs of overdose can include slow, shallow breathing, clammy skin, convulsions, extreme somnolence, severe respiratory depression, apnea, circulatory collapse, cardiac arrest, coma, and death.

Illicit opioids are frequently used in combination with stimulants like cocaine and methamphetamine. When used together, the stimulant can produce atypical symptoms for opioid use, including tachycardia and agitation.

Duration of Effects

Onset and duration depend largely on the dose, formulation, and route of administration. The onset of effects following oral administration can be within 15 to 60 minutes and effects may last 4 to 6 hours; however, agents like continuous-release oxycodone, methadone, and fentanyl patches can exert their effects for over 12 hours. Onset of effects following intravenous administration can be instantaneous with overall effects wearing off in 30 to 60 minutes (fentanyl) or 3 to 5 hours (morphine and hydromorphone).

Tolerance, Dependence, and Withdrawal Effects

Many opioids confer a high risk of physical and psychological dependence, and abuse. With regular use, tolerance may develop early due to the duration and intensity of euphoria and analgesia. Withdrawal symptoms may occur if use is abruptly stopped or reduced. Withdrawal

can begin within 24 hours after the last dose, peak within 48 to 72 hours, and may last up to 10 days (for long-acting opioids or in heavy use). Withdrawal symptoms can include watery eyes, runny nose, restlessness, irritability, dysphoria, loss of appetite, tremors, diarrhea, nausea and vomiting, drug craving, elevated heart rate and blood pressure, chills alternating with flushing and excessive sweating, goose-flesh, abdominal cramps, body aches, muscle and bone pain, muscle spasms, insomnia, and severe depression.

Driving-Related Studies

In one literature review, the effects of opioids on driving were attributed to cognitive effects and sedation. The authors of this review identified illicit opioid use, initiation of therapy, and opioid use in combination with other psychoactive medications as contexts most clearly associated with impairment of driving-related functions and/or operation of a motor vehicle (Cameron-Burr et al., 2021.)

See individual fact sheets for additional information.

Interactions With Ethanol

Acute ethanol exposure has been shown to potentiate the opioid-induced increase in analgesia and CNS depression, leading to serious side effects including profound sedation, respiratory depression, coma, and death (Singh, 2019).

Interactions With Other Drugs

In general, there is a higher risk of respiratory depression, hypotension, profound sedation, or coma with concurrent treatment with or use of other CNS depressant drugs such as barbiturates, benzodiazepines, hypnotics, tricyclic antidepressants, general anesthetics, monoamine oxidase inhibitors (MAOIs), and antihistamines. Partial agonists such as buprenorphine, nalbuphine, butorphanol, and pentazocine will attenuate the effects of opioids and may precipitate opioid withdrawal.

Opioids that are metabolized by the cytochrome P450 CYP3A4 system (oxycodone, hydrocodone, methadone, fentanyl, tramadol) can have significant interaction potential with other commonly prescribed drugs that are CYP3A4 substrate inhibitors or inducers (Jann et al., 2014). Coadministration of CYP3A4 substrates or inhibitors, such as alprazolam, can potentially increase opioid serum concentrations or result in more of the opioid being metabolized to its active metabolite.

Naltrexone reverses the effects of opioid analgesics by binding to the various opioid receptors in the central nervous system, including the μ-, κ- and δ-opioid receptors. This leads to an inhibition of the typical actions of opioid analgesics, including analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence (Stoops et al., 2012).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 45 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 45. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include presence of fresh injection marks, track marks, flaccid muscle tone, droopy eyelids, drowsiness or being "on-the-nod," and low raspy slow speech.

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Buprenorphine

Buprenorphine and its hydrochloride (HCl) salt are both white or almost white crystalline powders.

Synonyms

Belbuca, Butrans, Buprenex, Sublocade, Suboxone (with naloxone), Subutex

Source

Buprenorphine is a synthetic thebaine derivative. Its hydrochloride salt is available in 0.3 mg/mL ampules for parenteral administration; 75 to 900 μg buccal films for transmucosal administration; 0.2 and 0.4 mg tablets for sublingual administration; higher dose 4 to 24 mg tablets for sublingual administration (Suboxone); 5 to 20 mg patches for transdermal application; and 0.324 mg/mL for intravenous or intramuscular injection. Buprenorphine is a Schedule III controlled substance.

Drug Class

Narcotic analgesic

Uses

Clinical

Buprenorphine is used in the treatment and management of moderate to severe pain and in maintenance therapy for opioid dependence. When used in the treatment of opioid use disorder, buprenorphine significantly reduces mortality due to overdose. Suboxone is buprenorphine coformulated with the opioid antagonist naloxone (tradename Narcan), to discourage misuse by injection. Due to poor oral bioavailability, naloxone has virtually no effect when Suboxone is used as directed (via buccal or sublingual routes.)

Non-Clinical

Buprenorphine can be misused to produce euphoria and relaxation. However, diverted buprenorphine is often used to avoid opioid withdrawal and among people trying to stop other drug use.

Potency, Purity, and Dose

Usual adult doses are in the range of 75 to 900 μg buccally, every 12 hours; 0.2-0.4 mg sublingually, 3 to 4 times per day (for pain); 2 to 24 mg sublingually per day (for opioid dependence); and 0.3-0.6 mg intravenously/intramuscularly. Transdermal patches deliver 5 to 20 μg/hour buprenorphine over 7 days and subdermal implants supply 320 mg buprenorphine over a 6-month period. When administered orally, buprenorphine is thought to have 25 to 40 times the analgesic potency of morphine. For the treatment of opioid dependence, induction therapy with sublingual tablets starts at 2 to 4 mg/day and builds up to a maintenance dose of 4 to 24 mg/day. Induction therapy for pain using buccal films starts with 75 μg, 1 to 2 times per day and builds up to a maintenance dose of 450 μg every 12 hours, if needed.

Route of Administration

Buccal, sublingual, oral, transdermal, intranasal, intravenous, intramuscular, subcutaneous injection, and implants.

Pharmacodynamics

Buprenorphine is a partial agonist at the mu (μ)-opioid receptor and an antagonist at the kappa (κ)- and delta (δ)-opioid receptors. It is also a weak partial agonist at nociceptin receptors. Buprenorphine can displace or block morphine binding to μ-opioid receptors, therefore contributing to reduced opioid dependence. Its antagonist actions at the κ-opioid receptors could contribute to reduced tolerance and an antidepressant-like activity. Norbuprenorphine, the active metabolite of buprenorphine, is a full agonist at the δ-opioid receptor and a partial agonist at μ- and κ-opioid receptors.

Pharmacokinetics

Buprenorphine has low oral bioavailability (46 to 51%) and is 96 percent protein bound. The volume of distribution is 1.4 to 6.2 L/kg. It has a half-life of 2 to 4 hours following parenteral administration and 20 to 73 hours (average 37 hours) following sublingual or transdermal applications. Buprenorphine is metabolized primarily by N-dealkylation to its active metabolite norbuprenorphine (which is subsequently conjugated) and by conjugation of buprenorphine. Approximately 30 percent is eliminated in the urine, with parent drug accounting for only 1 percent of the total dose.

Blood to Plasma Concentration Ratio

Reported values range from 1.0 to 1.4.

Interpretation of Blood Concentrations

Following single doses of from 75 to 1,200 μg buprenorphine given transmucosally to 25 subjects, peak plasma buprenorphine concentrations occurred at 2.5 to 3 hours. The average C_{max} ranged from 0.17 ng/mL for the low 75 μg dose and 1.43 ng/mL for the high 1,200 μg dose. The C_{max} of norbuprenorphine was approximately one-tenth that of buprenorphine (Bai et al., 2016).

A single sublingual 2 mg dose of buprenorphine given to six healthy adults resulted in average peak plasma concentration of 1.6 ng/mL at 1.3 hours (Baselt, 2020). A single sublingual dose of 4 mg given to six healthy adults resulted in average peak plasma concentrations of 3.3 ng/mL at 0.8 hours for buprenorphine and 0.31 ng/mL at 4.0 hours for norbuprenorphine (Kuhlman et al., 1996). Single sublingual doses of 8, 16, or 32 mg given to 12 opioid-experienced adults resulted in average peak plasma concentrations of 5.8, 8.4, and 14 ng/mL for buprenorphine at 1.0 to 1.2 hours, and 1.5, 3.5, and 2.5 ng/mL for norbuprenorphine at 1.0 to 1.4 hours (Baselt, 2020).

A 10 μg/hour transdermal patch was given to 36 healthy adults to wear for 1 week, with replacement patches provided each week for an additional 2 weeks. Average peak plasma concentration for buprenorphine, tested at 72 hours, was 0.2 ng/mL (Baselt, 2020). A single transdermal patch was given to 12 people with opioid use disorder, supplying 80 μg/hour over 1 week. Average peak plasma concentrations ranged from 0.7 ng/mL at 60 hours for buprenorphine and 0.1 ng/mL at 120 hours for norbuprenorphine (Baselt, 2020).

The administration of 0.3 mg intramuscularly to 11 adult surgical patients resulted in average peak plasma concentrations of 3.6 ng/mL buprenorphine at 5 minutes. Administration of 0.3 mg intravenously to another group of 10 adult patients resulted in average peak plasma concentrations of 15 ng/mL buprenorphine at 2 minutes (Baselt, 2020). An intravenous dose of 1.2 mg administered to six healthy males resulted in average peak plasma buprenorphine concentrations of 38 ng/mL at 2.5 minutes and average peak buprenorphine concentrations of 0.5 ng/mL at 8 to 10 minutes (Kuhlman et al., 1996). Single doses of 2, 4, 8, 12, or 16 mg buprenorphine were given intravenously to five opioid-experienced males. Corresponding peak plasma concentrations were 19.3, 44.5, 85.2, 124.6, and 137.7 ng/mL, respectively, at 10 minutes post-dose. Following the 16 mg dose, an average peak plasma norbuprenorphine concentration of 3.7 ng/mL was reached at 10 to 15 minutes post-dose (Huestis et al., 2013).

Intranasal insufflation of crushed 8 mg sublingual tablets by 10 healthy adult opioid users resulted in average peak plasma buprenorphine concentrations of 11 ng/mL at 6 hours and 0.9 ng/mL of norbuprenorphine at 3.1 hours (Middleton et al., 2011).

OF(S) to Blood Concentration Ratio

Reported value of 1.

Interpretation of OF(S) Test Results

Buprenorphine pKa 8.5

In three pregnant women receiving 14 to 20 mg/day of sublingual buprenorphine HCl, the range of oral fluid C_{max} was 672 to 12,300 ng/mL for buprenorphine and 8.9 to 122 ng/mL for norbuprenorphine (Concheiro, 2011). High concentrations occurred most likely due to sublingual buprenorphine coating. Concentrations of buprenorphine were determined in oral fluid specimens from 122 pain patients, with an average concentration of 140.1 ng/mL (median 16.0; range 0.6 to 3,886.9 ng/mL). Norbuprenorphine concentrations were detected in 80 oral fluid specimens with an average concentration of 19.6 ng/mL (median 7.9; range 2.0 to 196 ng/mL) (Heltsley et al., 2011).

General Effects

The pharmacological effects of buprenorphine depend on the dose, route of administration, experience of the user, and tolerance.

Table 46 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 46. Physiological, motor, and cognitive side effects of buprenorphine consumption

Physiological	Motor (behavioral)	Cognitive
• Analgesia • Nausea & vomiting • Headache • Lightheadedness • Warm/sweaty	• Relaxation • Dizziness • Drowsiness • Reduced alertness • Confusion	• Euphoria • Lack of concentration • Reduced attention • Memory loss

Physiological	Motor (behavioral)	Cognitive
• Clammy • Dry mouth • Lowered blood pressure • Constricted pupils • Coughing • Sedation • Postural hypotension	• Slurred speech • Itching	

Chronic high doses of buprenorphine may result in blurred vision, hallucinations, hypotension, labored and/or rapid shallow breathing, renal failure, seizures, coma, and opioid addiction (Baselt, 2020; MacDonald et al., 1989; PDR, 2021; Soyka, 2014; Strand et al., 2019a).

Duration of Effects

Onset of effects is quickest following intravenous administration and slower following oral or transdermal[1] applications. Clinical and psychological effects of buprenorphine last at least 3 to 4 hours after an intravenous dose, 6 to 8 hours after an intramuscular dose, and up to 8 hours after a single dose given by oral routes. Steady state is reached within 3 days of twice a day buccal dosing.

Tolerance, Dependence, and Withdrawal Effects

Onset of tolerance to the analgesic effects of buprenorphine is slower than the onset of tolerance to morphine and is of less magnitude. Cross-tolerance to the behavioral effects of other μ-opioid receptor agonists may occur. There are moderate withdrawal symptoms upon abrupt discontinuation, and they are milder than those seen with full agonists. Onset of withdrawal is within 48 hours after the last dose, peaks at approximately the third day, and may last up to 10 days. Withdrawal symptoms may include yawning, lacrimation, nausea, vomiting, diarrhea, headaches, body aches, restlessness, sweating, chills, anxiety, mood lability, blurred vision, dizziness, lightheadedness, insomnia, and sleepiness (PDR, 2021; Tripathi et al., 1995).

Driving-Related Studies

Single doses of buprenorphine have been shown to induce some impairment in healthy volunteers, but less than that found in chronic users (Soyka, 2014).

Laboratory Studies

Single doses of 0.2 and 0.4 mg sublingual buprenorphine were administered to 22 healthy subjects. On-road driving tests, neurocognitive tests, and subjective questionnaires were administered. Low to moderate, yet significant, correlations were observed between blood

[1] Transdermal is typically slower to onset of effect than other routes. However, it may not be meaningful to comment on the "duration" of effect of transdermal, as they are designed to have ongoing drug delivery while applied (i.e., if the patch still contains active drug).

buprenorphine concentrations and standard deviation of lateral position (SDLP[1]), and psychomotor function (reaction time, divided attention, balance), alertness, contentedness, and sleepiness (Strand, 2019b).

A single dose of 0.4 mg sublingual buprenorphine or placebo was administered to 12 healthy adults. At 2- and 4-hours post-dose, tests performed included digit symbol substitution, critical flicker fusion, pupillary response, Maddox wing, HGN, driving simulator, and sedation self-rating. Impaired performance was observed on digit symbol substitution, critical flicker fusion, Maddox wing, and HGN tests. Subjective perception of sedation was also noted at 4 hours (Baselt, 2001).

An average dose of 7.7 mg/day of sublingual buprenorphine was given to 30 subjects. Tests included performance under stress, visual orientation, concentration, attention, vigilance, and reaction time. Patients receiving stable doses of sublingual buprenorphine showed some impairment, albeit not significant, of complex psychomotor or cognitive performance (Shmygalev, 2013).

A single dose of 0.3 mg buprenorphine or placebo was administered intramuscularly to 12 healthy males. Psychomotor tests were conducted pre- and 1.5-, 4,- and 8-hours post-dose. Buprenorphine caused significant psychomotor impairment in the following: choice reaction time (recognition), choice reaction time (cancellation), critical flicker fusion (central integrative capacity), driving (steering accuracy and brake reaction time), digital symbol substitution (short term memory), attention, posterior and lateral sway, and mental and physical sedation. These effects peaked consistently at 4 hours post-dose and often lasted at least 8 hours post-dose (MacDonald et al., 1989). Single intravenous doses of 0.075, 0.15, or 0.3 mg buprenorphine or placebo were given to 16 healthy adults. Testing occurred on five occasions over 6 hours post-dose and included sedation self-rating, Maddox wing, tracking, digit symbol substitution, reaction time (auditory), semantic recognition, and word list recall. Significant dose-related impairment was observed on all tests for up to 6 hours, except word list recall (Baselt, 2001).

On-the-Road Driving Studies

Single doses of 0.2 and 0.4 mg sublingual buprenorphine were administered to 22 healthy, non-user subjects. Performance was assessed 4 hours after drug administration using an on-road driving test in normal traffic. Subjects were tested for standard deviation of lateral position (SDLP) (weaving), a measure of road tracking control. At 2 and 6 hours after dosing, subjects also participated in lab tests used to measure cognitive functions such as reaction time, sustained and divided attention, critical tracking, digit symbol substitution, and postural balance. The 0.4 mg sublingual buprenorphine significantly increased SDLP, but driving impairment was described as mild, although three subjects stopped their driving test due to sleepiness. It also produced impairments of the cognitive functions, and increased sleepiness, particularly at the higher dose. Overall, analgesic doses of buprenorphine produced mild impairing effects on driving and related cognitive skills. Blood concentration for the 0.2 mg buprenorphine dose averaged 0.16 ng/mL at 1 hour, 0.21 ng/mL at 2 hours, then declined to 0.05 ng/mL by 6.5 hours post-dose. Blood concentration for the 0.4 mg buprenorphine dose averaged 0.30 ng/mL at 1

[1] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful differences when related to real-world driving.

hour, 0.38 ng/mL at 2 hours, then declined to 0.09 ng/mL by 6.5 hours post-dose (Strand et al., 2019a).

Case Reports

Out of a total of 204 suspected impaired drivers testing positive for buprenorphine and/or norbuprenorphine, only four had no other drugs detected. Blood concentrations of buprenorphine and norbuprenorphine in all drivers averaged 2.0 ng/mL (range 0.6 to 14 ng/mL) for buprenorphine and 2.1 ng/mL (range 0.5 to 20 ng/mL) for norbuprenorphine. For the four buprenorphine-only cases, three were involved in a crash or exhibited poor/reckless driving. Buprenorphine blood concentrations in three of the four drivers ranged from 1.2 to 4.1 ng/mL (average 2.6 ng/mL) and norbuprenorphine concentrations ranged from 1.3 to 9.2 ng/mL (average 5.4 ng/mL) in all drivers. For clinical indicators, only one of the four drivers had HGN, none had vertical gaze nystagmus (VGN), and many clues were observed on the Walk and Turn and One Leg Stand tests. Lack of balance and coordination were also noted during SFSTs. Two drivers had full DRE evaluations performed and additional observations were: lack of convergence not present, reaction to light slow to normal, normal to depressed blood pressure, normal to high heart rate, and normal temperature. In these two cases the DRE officer opined to the use of a CNS stimulant in one case and the use of a CNS stimulant and narcotic analgesic in the other case (Edwards, 2019). Blood buprenorphine concentrations in 16 adults suspected of impaired driving averaged 2.2 ng/mL (Jones et al., 2007).

Interactions With Ethanol

Information not available.

Interactions With Other Drugs

Prolonged somnolence and bradypnoea have been observed with the combination of buprenorphine and lorazepam (Mozayani & Raymon, 2012).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 47 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 47. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	Little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

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Fentanyl

The citrate salt is a white granule or a white glistening crystalline powder.

Synonyms

Fentanyl Citrate, Duragesic, Sublimaze, Abstral, Fentora, Onsolis, Lazanda, Actiq

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Fentanyl is a Schedule II controlled substance in the United States. Fentanyl base is available as a sublingual solution in strengths of 100 to 1,600 μg and as transdermal patches in strengths of 12.5 to 100 μg/hour. It is also available as the citrate salt in buccal lozenges in strengths of 200 to 1,600 μg (of fentanyl), buccal tablets 100 to 800 μg, nasal solution 100 to 400 μg/spray, parenteral injection 50 μg/mL, and sublingual tablets 100 to 800 μg. As a street drug, fentanyl is found in counterfeit pills and in powders, either alone or in combination with other drugs such as opioids, cocaine, and/or fentanyl analogs. The contamination and replacement of heroin with illicit fentanyl have fueled the striking increase in opioid-associated deaths seen since the mid-2010s.

Drug Class

Narcotic analgesic

Uses

Clinical

Fentanyl is a synthetic opioid used for the relief of moderate to severe pain and as an adjunct to surgical anesthesia. Fentanyl nasal sprays are used in the management of breakthrough pain in opioid-tolerant cancer patients, while fentanyl patches are frequently used in patients with chronic pain or undergoing palliative care who require around-the-clock pain management.

Non-Clinical

Fentanyl is misused to produce analgesia and euphoria, and to prevent opioid withdrawal.

Potency, Purity, and Dose

Fentanyl has up to 100 times the potency of morphine. For management of chronic pain, transdermal fentanyl patch doses of 25 to 100 μg/hour are given for 72 hours, nasal spray solution doses of 100 to 800 μg up to four times daily, sublingual spray doses of 100 to 1,600 μg taken twice within 30 minutes and every 4 hours thereafter, and single intravenous or intramuscular doses of 25 to 100 μg. Drugs such as heroin and cocaine have been known to be laced with fentanyl, and fentanyl has been detected in numerous counterfeit pills and powders, either alone or in combination with other opioids such as oxycodone and fentanyl analogs.

Route of Administration

Buccal, sublingual, nasal, oral, epidural, intramuscular, intrathecal, intravenous, and transdermal. Patches can also be chewed or used more than recommended doses, or the gel inside the patch can be extracted and injected.

Pharmacodynamics

Fentanyl is a potent mu (μ)-agonist. Its effect on μ-receptors leads to a reduction in the release of neurotransmitters such as substance P, gamma-aminobutyric acid (GABA), dopamine, acetylcholine, and noradrenaline, subsequently reducing neuronal excitability.

Pharmacokinetics

The approximate oral bioavailability of different fentanyl formulations are as follows: transmucosal lozenges 50 percent, sublingual tablets 54 percent, nasal spray 64 percent, buccal tablets 65 percent, and sublingual spray 76 percent. Fentanyl is 79 to 87 percent protein bound and has an intravenous volume of distribution of 3 to 8 L/kg. Maximum plasma concentrations are reached at 20 to 40 minutes following administration of fentanyl as transmucosal lozenges, 40 to 80 minutes following sublingual spray, and at 3 to 4 hours when transdermal systems are used. The elimination half-life ranges from 3 to 16 hours, depending on the formulation. The main metabolites of fentanyl include norfentanyl, hydroxyfentanyl, hydroxynorfentanyl, and despropionylfentanyl. Approximately 75 percent of an intravenous dose is excreted in the urine within 72 hours, with 26 to 55 percent excreted as norfentanyl and < 7 percent as unchanged drug. Drug metabolism and elimination are slower in older adults and/or in subjects with decreased liver function.

Blood to Plasma Concentration Ratio

Fentanyl 0.8 to 1.0

Norfentanyl 1.0 to 1.3

Interpretation of Blood Concentrations

A single 200 μg or 1,600 μg dose of fentanyl transmucosal lozenges given to 12 healthy males resulted in average maximum blood concentrations of 0.4 ± 0.1 ng/mL and 2.5 ± 0.6 ng/mL, respectively, at 20 to 40 minutes (Streisand, 1998). A single 100 μg or 800 μg dose of fentanyl sublingual spray given to 53 subjects resulted in average maximum plasma concentrations of 0.20 ± 0.06 ng/mL and 1.61 ± 0.60 ng/mL, respectively, at 41 to 85 minutes (Parikh, 2013). A single transdermal patch delivering a 25 μg/hour dose of fentanyl was given to 10 subjects for 30 hours, resulting in an average maximum serum concentration of 0.24 ± 0.20 ng/mL at 3.6 ± 1.3 hours. When heat was applied to the patches in the first 4 hours, average maximum serum concentrations increased to 0.63 ng/mL (Ashburn, 2003). A single 200 μg/100 μL dose of fentanyl nasal spray was given to 24 subjects resulting in an average maximum plasma concentration of 0.815 ± 0.301 ng/mL (Nave, 2013).

Following administration of single 100, 200, 400, and 800 μg doses of fentanyl as sublingual tablets in healthy people, peak plasma concentrations were attained at a median of 30 to 60 minutes (range 19 minutes to 4 hours) and averaged 0.19, 0.30, 0.77, and 1.4 ng/mL, respectively (McEvoy, 2017). Following the application of single 25, 50, 75, and 100 μg/hour fentanyl

transdermal patches, serum concentration ranges of 0.3 to 1.2 ng/mL, 0.6 to 1.8, 1.1 to 2.6, and 1.9 to 3.8 ng/mL were reached within 24 hours, respectively (PDR, 2021). A single 140 µg/70 kg intravenous fentanyl dose was given to four subjects resulting in an average maximum serum concentration of 11 ng/mL, declining to approximately 1 ng/mL at 1 hour (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Fentanyl: average 3.0 (n=54) (Heiskanen et al., 2015)

Interpretation of OF(S) Test Results

Fentanyl pKa 8.4

Concentrations of fentanyl were determined in oral fluid specimens from 424 pain patients, with an average concentration of 49.8 ng/mL (median 6.6 ng/mL; range 0.2 to 5,341.3 ng/mL). Norfentanyl concentrations were detected in 148 oral fluid specimens with an average concentration of 4.7 ng/mL (median 1.6 ng/mL; range 0.5 to 125 ng/mL; Heltsley et al., 2011).

General Effects

The pharmacological effects of fentanyl depend on the dose, route of administration, experience of the user, and tolerance. Table 48 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 48. Physiological, motor, and cognitive side effects of fentanyl consumption

Physiological	Motor (behavioral)	Cognitive
• Analgesia • Nausea and vomiting • Constipation • Lowered blood pressure • Lowered heart rate • Sedation • Tremor • Constricted pupils • Loss of appetite • Muscle flaccidity • Weakness • Cold and clammy skin	• Drowsiness • Dizziness • Lethargy • Ataxia • Confusion	• Euphoria • Reduced attention • Anxiety • Depression

Other adverse effects may include hallucinations, addiction, respiratory depression, stupor, coma, pulmonary edema, and apnea (Baselt, 2020; Kuczynska et al., 2018; PDR, 2021; Schneider et al., 1999).

Duration of Effects

In general, the onset of effects following intravenous and intramuscular administration is rapid; peak analgesia can occur within several minutes. Analgesia fades within 1 to 2 hours, with other effects lasting longer, approximately 2 to 3 hours. The time course following intramuscular administration is like intravenous administration.

Tolerance, Dependence, and Withdrawal Effects

With continued use, tolerance to the pharmacological and adverse effects of fentanyl can develop; however, the rate of tolerance development varies between people. Withdrawal symptoms include yawning, lacrimation, sweating, fever, vomiting, abdominal pain or cramping, insomnia, body aches, headache, fever, chills, runny nose, diarrhea, anxiety, and restlessness. Symptoms typically peak during the first three days and decrease within a week. Drug cravings, anxiety, and depression can last much longer (Wagener [Ed.], 2021; PDR, 2021).

Driving-Related Studies

Laboratory Studies

The following studies are summarized in Baselt (2001).

- A 1 hour continuous intravenous infusion of fentanyl or placebo was given to nine healthy adults, at doses calculated to produce plasma concentrations of 1.0, 1.5 or 2.5 ng/mL. Plasma concentrations achieved were 0.5 to 1.3, 1.5 to 2.3, and 2.5 to 3.5 ng/mL. Performance testing occurred on five occasions throughout the infusion period. The lowest fentanyl dose had no significant adverse effect on performance; the middle dose impaired critical flicker fusion; and the high dose impaired verbal learning, delayed word recognition, spontaneous recall, and caused subjective mental and physical sedation.
- A single intravenous dose of 50 μg /70 kg fentanyl or placebo was given to six healthy men, followed by performance testing on four occasions over the next 3 hours. Fentanyl impaired performance on the Maddox wing task and caused subjective sedation during the first 3 hours post-dose but did not impair digit symbol substitution or tracking.
- A single intravenous dose of 25, 50, or 100 μg /70 kg fentanyl or placebo was given to 13 healthy adults, followed by performance testing on four occasions over the next 3 hours. All doses caused subjective sedation, peaking at 15 to 60 minutes, returning to near baseline levels at 3 hours. The two higher doses impaired tracking ability at 15 minutes, which resolved by 60 minutes post-dose.
- A single intravenous dose of 100 or 200 μg fentanyl or placebo was given to 10 healthy men, followed by performance testing at 2, 6, and 8-hours post-dose. At 2 hours, the 200 μg fentanyl dose significantly impaired performance on the digit span and tapping rate tasks and caused subjective sedation.
- A single intravenous dose of 175 μg /70 kg fentanyl or placebo was given to seven healthy adults, followed by performance testing on nine occasions over the next 3 hours. Fentanyl caused maximal performance decrements on critical flicker fusion and the Maddox wing tasks at 5 min, with a gradual return to near baseline values by 3 hours. Subjective sedation peaked at 45 minutes and subsided by 2 hours post-dose.

A single intravenous fentanyl dose of 0.2 mg/kg body weight or placebo was given to 12 healthy males, followed by performance testing over the next 2-hour period. Fentanyl serum concentrations averaged 1.9 and 0.7 ng/mL at 15 and 30 minutes post-dose, respectively. Fentanyl produced significant cognitive impairment on auditory reaction time, signal detection, sustained attention, and recognition (Schneider et al., 1999).

Simulated Driving Studies

Intravenous doses of fentanyl were given to 22 patients undergoing left knee orthoscopic surgery. Performance of patients was tested pre-operatively and 2 hours and 24 hours post-operatively using a driving simulator. Significant impairment of driving skills was observed at 2 hours post-operatively compared to pre-operatively, including longer reaction times, higher occurrence of attention lapses, microsleep intrusions, and impaired alertness. No significant differences were observed 24 hours post-operatively (Chung et al., 2005).

Case Reports

In 26 suspected impaired driving cases, fentanyl was detected in nine cases, with concentrations ranging from 1.0 to 9.8 ng/mL (average 5.1; median 4.9 ng/mL). Norfentanyl was detected in 12 of the cases, with concentrations ranging from 0.11 to 3.5 ng/mL (average and median of 1.2 ng/mL) (Sofalvi et al., 2017).

In a study including data from three toxicology laboratories in the Northeast, Southeast, and Midwest regions of the United States, blood fentanyl concentrations ranged from 0.1 to 157 ng/mL in living drivers, with a 466 percent to 524 percent increase in fentanyl-positive driving under the influence of drugs cases from 2014 to 2019, depending on the region. While many fentanyl cases involved poly-drug use, 21 case histories were presented where fentanyl was the only drug identified. In these cases, fentanyl concentrations ranged from 2.0 to 16 ng/mL; the average fentanyl concentration was 5.2 ± 3.8 ng/mL with a median of 3.7 ng/mL. In these cases, common presentations included the driver being found unresponsive behind the wheel, the vehicle left the travel lane or roadway, and the driver was involved in a crash. The authors noted that some opioid users may display limited physical signs of impairment either due to tolerance or naloxone administration (Rohrig et al., 2021).

Interactions With Ethanol

Information not available.

Interactions With Other Drugs

The combination of midazolam or diazepam with fentanyl has been consistently found to result in potentiation of the sedative and, in some cases, respiratory depressant effects of fentanyl (Mozayani & Raymon, 2012). It is suggested that the drugs interacted in a synergistic manner.

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 49 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 49. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	Little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

References and Recommended Reading

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Hydrocodone and Hydromorphone

Hydrocodone tartrate and hydromorphone hydrochloride are both fine, white, crystalline powders.

Synonyms

Hydrocodone: dihydrocodeinone, Vicodin, Lortab, Norco, Lorcet

Hydromorphone: dihydromophinone, Dilaudid

Source

Hydrocodone and hydromorphone are Schedule II controlled substances in the United States.

Hydrocodone is a semisynthetic opioid prepared from codeine. It is available as an antitussive in cough syrups and tablets (2.5-5 mg) and as an analgesic in tablets and capsules (5 to 10 mg). It is also available in combination with acetaminophen, ibuprofen, chlorpheniramine, and guaifenesin Extended-release formulations are available in a 10 mg/5 mL suspension, 10 to 50 mg capsules, and 20 to 120 mg tablets.

Hydromorphone is a semisynthetic opioid prepared from morphine. It is supplied in 2, 4, and 8 mg tablets, and a 1 and 5 mg/5 mL syrup for oral administration. It is also available in 1, 2, and 4 mg/mL injectable solutions for intramuscular, intravenous, or subcutaneous use.

Drug Class

Narcotic analgesic

Uses

Clinical

Hydrocodone is used for the relief of moderate to severe pain, and for the symptomatic relief of nonproductive cough, alone or in combination with other antitussives or expectorants.

Hydromorphone is used for the relief of acute and chronic severe pain. Long-term use of hydromorphone is only recommended for severe pain in cancer patients.

Non-Clinical

Both hydrocodone and hydromorphone are misused for self-medication of pain, and heightened euphoria, relaxation, and contentedness.

Potency, Purity, and Dose

Hydrocodone has approximately six times the analgesic potency of codeine and one tenth that of morphine. Oral doses of hydrocodone may be taken every 4 to 6 hours with a maximum daily limit of 45 mg. Hydrocodone extended-release formulations are to be taken once every 12 to 24 hours, providing a total daily dose of 20 to 120 mg.

Hydromorphone has 7 to 10 times the potency of morphine. Typical oral doses range from 1 to 4 mg, every 4 to 6 hours.

Pharmacodynamics

Hydrocodone is a weak μ-receptor agonist, with minimal affinity for κ- or δ-opioid receptors.

Hydromorphone is a strong μ agonist, with minimal affinity for κ- or δ-opioid receptors .

Pharmacokinetics

Hydrocodone has an oral bioavailability of approximately 60 percent and is 20 to 50 percent plasma protein bound. The volume of distribution is 3.3 to 4.7 L/kg, and the elimination half-life is 3.3 to 8.8 hours. Biotransformation occurs via *O*- and *N*-demethylation to hydromorphone and norhydrocodone, reduction of the 6-keto group to 6-α-hydrocodol and 6-α-hydromorphol, followed by conjugation. Approximately 26 percent of a dose is excreted in the urine within 72 h, with about 12 percent as the unchanged drug, 5 percent as norhydrocodone, and 4 percent as conjugated hydromorphone.

Hydromorphone has an oral bioavailability of approximately 50 percent and is approximately 20 percent plasma protein bound. The volume of distribution is 2 to 4 L/kg and the elimination half-life is 3 to 9 hours for intravenous or immediate-release and 10 to 22 hours for extended-release formulations. Hydromorphone is metabolized to the 6α- and 6β -hydroxy metabolites (6-hydromorphol), followed by conjugation. Within 24 hours, approximately 6 percent of a dose is excreted in urine as free hydromorphone and 30 percent as conjugated hydromorphone.

Blood to Plasma Concentration Ratio

Hydromorphone 1.0 to 1.1

Data not available for hydrocodone.

Interpretation of Blood Concentrations

Hydrocodone

A single oral dose of 5 mg hydrocodone given to one subject resulted in a peak serum concentration of 11 ng/mL at 1.5 hours. A single oral dose of 10 mg hydrocodone given to five subjects resulted in an average peak serum concentration of 24 ng/mL at 1.5 hours, declining to 7 ng/mL by 8 hours (Baselt, 2020).

In 36 healthy volunteers, 45 mg of extended-release hydrocodone was administered as a single dose or twice daily for 6 days. Plasma C_{max} was higher (125.4 vs 57.2 ng/mL), and T_{max} occurred earlier (5.0 vs 8.0 hours), with multi-dose administration compared to the single dose. Steady state concentrations were achieved within five days of twice-daily administration of extended-release hydrocodone (Darwish et al., 2015).

A single oral dose of 90 mg extended-release hydrocodone was given to 40 healthy subjects, or several doses were given to 43 healthy subjects for 10 days. Doses were administered to both fed and fasted subjects. Single dose plasma C_{max} was 40 percent higher under fed versus fasted conditions. In contrast, the multi-dose study showed that the effect of food was much less at steady state (Bond, 2017).

Hydromorphone

A single oral dose of 4 mg hydromorphone was given to six subjects resulting in an average peak plasma concentration of 22 ng/mL at 0.8 to 1.5 hours (Baselt, 2001).

A single 8 mg oral dose of the immediate-release tablet given to 12 subjects resulted in an average peak plasma concentration of 4.7 ng/mL at 0.8 to 1 hour (Angst, 2001). In the same study, a single 8, 16, or 32 mg sustained-release oral dose given to 12 subjects resulted in average peak plasma concentrations of 0.7 ng/mL, 1.5 ng/mL, and 2.4 ng/mL, respectively, at 9 to 13.5 hours. A single 4 mg intramuscular dose given to two subjects resulted in peak urinary total hydromorphone concentrations of 3,900 to 4,300 ng/mL at 6.4 to 7.0 hours (Baselt, 2020).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Hydrocodone pKa 8.9; hydromorphone pKa 8.2

A single oral dose of 20 mg hydrocodone given to 12 subjects resulted in an average C_{max} of 208 ng/mL (61.7 to 626 ng/mL) for hydrocodone, 12.8 ng/mL (3.6 to 27.0 ng/mL) for norhydrocodone, and 6.4 ng/mL (2.6 to 18.2 ng/mL) for dihydrocodeine. The time to first detection in the oral fluid samples was 0.25-0.5 hours, and peak oral fluid concentrations for hydrocodone were observed at 8 to 14 hours (Desrosiers & Huestis, 2019). In another study, the first detection time after an oral dose of 20 mg hydrocodone was at 0.27 hours and the last detection time was 29.8 hours; for norhydrocodone it was 0.54 hours and 18 hours; and for dihydrocodeine it was 1.15 hours and 17.8 hours, respectively (Lee, 2018).

Concentrations of hydrocodone were determined in oral fluid specimens from 1,843 chronic pain patients, with an average concentration of 178.4 ng/mL (median 67.8; range 1.0 to 33,438 ng/mL). Norhydrocodone concentrations were detected in 1,454 oral fluid specimens with an average concentration of 23.3 ng/mL (median 10.5; range 1.0 to 611.4 ng/mL). Hydromorphone concentrations were detected in 304 oral fluid specimens with an average concentration of 305.6 ng/mL (median 2.7; range 1.0 to 67,019 ng/mL) (Heltsley et al., 2011).

General Effects

Hydrocodone and hydromorphone have similar effects. The pharmacological effects of these drugs depend on the dose, route of administration, experience of the user, and tolerance.

Table 50 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 50. Physiological, motor, and cognitive side effects of hydrocodone or hydromorphone consumption

Physiological	Motor (behavioral)	Cognitive
• Relief from pain • Constricted pupils • Dry throat • Nausea • Constipation • Headache • Hypotension • Lightheadedness • Sedation • Weakness • Sweating • Vertigo • Flushing	• Drowsiness • Dizziness • Lethargy • Confusion • Itching	• Euphoria

Other adverse effects may include dysphoria, agitation, nervousness, decreased appetite, seizures, hallucinations, double or blurred vision, involuntary muscle jerking, and sleep disturbances (Baselt, 2020; AAC, 2021; LiverTox, 2019; PDR, 2021; Stoops et al., 2012).

Duration of Effects

Onset of effects with oral hydrocodone is 10 to 30 minutes; effects peak at 30 to 60 minutes and last 4 to 8 hours. Effects following extended-release dosing last 14 to 16 hours.

Onset of effects with oral hydromorphone is 15 to 30 minutes and effects last 3 to 5 hours. Onset of effects following intravenous administration is less than 5 minutes, while onset of extended-release hydromorphone is 6 hours and effects last 13 hours.

Tolerance, Dependence, and Withdrawal Effects

Withdrawal effects may include yawning, nausea, vomiting, abdominal pain, anxiety, depression, goose bump skin, muscle and joint pain, runny nose, lacrimation, sweating, chills, mydriasis, irritability, restlessness, and insomnia (Patterson, 2021; PDR, 2021).

Driving-Related Studies

Laboratory Studies

A single oral dose of 1 or 3 mg hydromorphone or placebo was given to eight people with previous heavy use of drugs. Performance testing occurred over the following 5 hours and included sedation self-rating, circular lights, visual search, arithmetic, digit symbol substitution, and card sorting. The 3 mg dose increased subjective sedation and both doses impaired performance on the visual search task (Baselt, 2001).

A single intravenous dose of 2, 4, or 6 mg hydromorphone or placebo was given to five former opioid users. Pupillary response and sedation self-rating were tested over the following 2 hours. Hydromorphone caused a dose-related constriction of the pupils and increased subjective sedation (Baselt, 2001).

Cumulative intravenous dosing of 0.3, 1, and 2.3 mg hydromorphone were given to 16 healthy adults over a 4-hour period. Performance testing occurred over the following 3 hour and included sedation self-rating, Maddox wing, tracking, reaction time (auditory), semantic recognition, digit symbol substitution, and pupillary response. Hydromorphone increased subjective self-sedation, constricted pupils, and caused dose-related impairment for the Maddox wing, tracking, and digit symbol substitution tasks (Baselt, 2001).

Simulated Driving Studies

A single oral dose of 10 mg/325 mg hydrocodone/acetaminophen or placebo was given to eight healthy adults. Subject performance was evaluated using a driving simulator in various scenarios (urban, rural, straight, curvy, different speed limits, day- and night-time). Driving started 3 hours post dose. There were no significant detrimental effects on steering, deviation from lane position, lane departures, or speed with this modest hydrocodone dose (Brown, 2018).

Interactions With Ethanol

A single dose of 50 mg hydrocodone extended-release was given to 30 subjects, followed by 240 mL of either 20 percent ethanol, 40 percent ethanol, or placebo (Farr, 2015). Following the combined administration of hydrocodone extended-release and 40 percent ethanol, the C_{max} of hydrocodone was 2.3-fold higher compared to placebo (average 109 versus 46.3 ng/mL), and T_{max} was reached in less than half the time (median 2.43 versus 6.16 hours). No significant differences were observed with the 20 percent ethanol treatment.

Interactions With Other Drugs

Information not available.

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 51 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 51. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	Little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

References and Recommended Reading

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Methadone

Methadone hydrochloride is a white crystalline powder or colorless crystals.

Synonyms

Dolophine Hydrochloride, Methadose, Methadone Hydrochloride Intensol

Source

Methadone is a synthetic opioid analgesic and is a Schedule II controlled substance. Methadone is available by prescription as oral solutions (1 to 2 mg/mL), tablets (5 to 10 mg), dispersible tablets (40 mg), or injectable solutions (10 mg/mL).

Drug Class

Narcotic analgesic

Uses

Clinical

Methadone is an analgesic prescribed for the relief of moderate to severe pain and is used in treatment of opioid use disorder. Compared to morphine, methadone has a much longer duration of action, effectively suppressing opioid withdrawal symptoms for an extended period of time with repeated administration.

Non-Clinical

Methadone is misused for its sedative and analgesic effects.

Potency, Purity, and Dose

Available as the racemic mixture, or *l*-methadone is 8 to 50 times more potent than the s- or *d*-isomer. For relief of severe acute pain, the usual adult dose is 2.5 to 10 mg every 3 to 4 hours. For methadone maintenance the daily dose is generally 60 to 80 mg, but can vary from 30 to 120 mg. Tolerant people may ingest daily doses of 160 mg. For detoxification treatment an initial oral dose of 15 to 20 mg is administered, with an additional dose if withdrawal symptoms are not suppressed; a stabilizing dose of 40 mg in single or divided dosages is prescribed for 2 to 3 weeks, then the dose is gradually decreased. Concurrent use of other prescription medication is common.

Route of Administration

Oral ingestion, intravenous, intramuscular, or subcutaneous injection.

Pharmacodynamics

Methadone is a long-acting μ-opioid receptor agonist with potent central analgesic, sedative, and antitussive actions. Methadone inhibits ascending pain pathways, alters perception of and response to pain (dissociative effect), and produces generalized CNS depression. Respiratory

depression also occurs due to complete blockade of respiratory centers to pCO_2. s-methadone lacks significant respiratory depressive action and addiction liability.

Pharmacokinetics

When administered orally, methadone is rapidly absorbed from the gastrointestinal tract and can be detected in the blood within 30 minutes. Oral bioavailability varies from 41 to 99 percent (average ~79%) and plasma protein binding is 60 to 90 percent. After repeated administration there is gradual accumulation in tissues. As for most lipid soluble drugs, a large between and within subject variability is observed. The half-life (R)-methadone is 28.5 to 47 hours (average 37.5 hours), and 18.5 to 45.7 hours (average 28.6 hours) for s-methadone. Methadone undergoes extensive biotransformation in the liver primarily to two inactive metabolites, 2-ethylidene-1-5-dimethyl-3.3diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3- diphenyl-1-pyrroline (EMDP), through N-demethylation and cyclization. These are eliminated in urine and in bile. In total, nine metabolites have been identified including two minor active metabolites, methadol, and normethadol. The percentage of a dose excreted in the urine as unchanged methadone and EDDP will vary with the pH of the urine. Urinary excretion of unchanged parent drug is 5 to 50 percent and EDDP 3 to 25 percent.

Blood to Plasma Concentration Ratio

Reported values range from 0.70-0.80.

Interpretation of Blood Concentrations

Methadone can be detected in plasma within 30 minutes following oral ingestion, reaching a peak concentration at ~4 hours. Average EDDP concentration are ~15 percent that of methadone. There is often a large overlap between reported therapeutic (30 to 560 ng/mL) and fatal concentrations (60 to 3,100 ng/mL). Peak serum concentrations following a single oral dose of 15 mg were 75 ng/mL, 860 ng/mL for 100 mg, and 830 ng/mL for 120 mg; all at 4 hours. Chronic oral administration of 100 to 200 mg to tolerant subjects produced average peak plasma concentrations of 830 ng/mL at 4 hours, decreasing to 460 ng/mL at 24 hours. Peak plasma methadone concentrations of 34 ng/mL were obtained at 50 minutes following intramuscular injection of 10 mg, while intravenous administration of 10 mg produced concentrations of 96 ng/mL at 34 minutes. Concentrations greater than 100 ng/mL are required for prevention of opioid withdrawal symptoms. In cancer patients treated for pain relief and sedation, methadone concentrations were 350 ± 180 ng/mL (Baselt, 2020).

OF(S) to Blood Concentration Ratio

2.9 (*n*=11; median 1.8; range 0.69 to 7.1) (Langel et al., 2014)

2.2 (*n*=6) (Gjerde et al., 2010)

2.0 (*n*=22; range 0.49-7.39) (Strand et al., 2019)

0.77 (*n*=46; range 0.13 to 1.97) (Desrosiers & Huestis, 2019)

Interpretation of OF(S) Test Results

Methadone pKa 8.3

In 16 opioid-dependent pregnant women receiving methadone doses of 30 to 110 mg/day, methadone concentrations in oral fluid ranged from 5.2-78,255 ng/mL for methadone and 1.0 to 1,791 ng/mL for EDDP (Desrosiers & Huestis, 2019).

Concentrations of methadone were determined in oral fluid specimens from 462 chronic pain patients with an average methadone concentration of 615.5 ng/mL (median 63.8; range 2.1 to 239,080 ng/mL). EDDP concentrations were detected in 400 specimens with an average concentration of 28.3 ng/mL (median 7.3; range 1.0 to 3,446.4 ng/mL; Heltsley et al., 2011).

General Effects

The pharmacological effects of methadone depend on the dose, route of administration, experience of the user, and tolerance. Table 52 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 52. Physiological, motor, and cognitive side effects of methadone

Physiological	Motor (behavioral)	Cognitive
• Analgesia • Headache • Dry mouth • Facial flushing • Nausea • Constipation • Respiratory depression • Muscle flaccidity • Constricted pupils • Decreased heart rate • Sweating • Sedation • Sleep disorders	• Drowsiness • Dizziness • Lightheadedness • Depressed reflexes • Stupor	• Euphoria • Altered sensory perception • Alteration in cognitive and sensory efficiency • Lack of concentration • Mood swings

Infrequent adverse effects include urticaria, hypersensitivity reaction, shock, and pulmonary edema. Signs of overdose can include slow, shallow breathing, respiratory depression, clammy skin, convulsions, extreme somnolence, apnea, circulatory collapse, cardiac arrest, coma, and possible death (Baselt, 2020; Felder et al., 1999; Gordon & Appel, 1998; PDR, 2021).

Duration of Effects

Onset of analgesia occurs 10 to 20 minutes following parenteral administration and 30 to 60 minutes after oral administration. Oral administration results in slower onset, lower peak concentration, and longer duration of action. Following single oral doses, effects may last 6 to 8 hours, increasing to 22 to 48 hours in cases of chronic administration.

Tolerance, Dependence, and Withdrawal Effects

Upon repeated administration, tolerance may develop to the nauseant, miotic, sedative, respiratory depressant, and cardiovascular effects of methadone. Tolerance develops more slowly to methadone than to morphine in some patients. Methadone can produce physiological and psychological dependence and has the potential for being abused. Withdrawal symptoms are like those of other opioids but are slower in onset and last longer. Symptoms include watery eyes, yawning, runny nose, nausea, loss of appetite, diarrhea, cramps, muscle aches, dysphoria, restlessness, irritability, anxiety, pupillary dilation, piloerection, tremors, chills, sweating, increased sensitivity to pain, insomnia, and tachycardia (Florimbio, 2021; PDR, 2021).

Driving-Related Studies

In healthy, non-methadone using volunteers, single doses of methadone may impair driving ability. Numerous European studies of long-term methadone maintenance patients have shown that appropriately administered methadone does not cause significant psychomotor or cognitive impairment when administered regularly and when the subject abstains from all other drugs (Berghaus et al., 1993; Chesher, 1985; Friedel & Berghaus; 1995; Hauri-Bionda et al., 1998).

Laboratory Studies

In general, laboratory studies have shown that non-tolerant people receiving single doses of methadone exhibit dose-dependent reductions in reaction time, visual acuity, information processing, and sedation; however, significant psychomotor impairments are seldom evident when tolerant subjects have been tested, including performance deficits in reaction time, attention, and peripheral vision. In most experimental clinical trials, psychophysical performance tests have yielded the same results for methadone substitution patients as for control groups. Nevertheless, variable results have been observed. Attention and perception tasks have been impaired in methadone maintenance patients, but sociodemographic factors may have played a role. In patients receiving 35 to 85 mg methadone daily, significant impairment was measured on attention, perception, and learning tasks but there was no reaction time deficit. In patients receiving a daily average of 63 mg methadone, significant impairment in distance perception, attention span, and time perception was observed. No significant adverse effects were measured with people with opioid use disorder stabilized for 3 months to 1 year on daily oral doses of methadone (Baselt, 2001; Hauri-Bionda, 1998; Joo, 1994).

Interactions With Ethanol

Eight opioid-dependent patients stabilized on methadone were given either 100 percent or 150 percent of their daily methadone dose in addition to 0.25 or 0.50 g/kg ethanol or placebo. The 150 percent increased methadone dose was used to assess the effect of an acute increase in methadone dose. When performance tasks were compared from before to after drug administration, the results suggested reduced accuracy and slowed response at the elevated methadone dose. Although an acute increase in methadone and a moderate dose of ethanol can impair distinct aspects of performance, there was no significant interaction between the two drugs for any outcome (Kleykamp, 2015).

Interactions With Other Drugs

There are additive CNS depressive effects with concurrent use of sedatives, hypnotics, tranquilizers, other narcotic analgesics, tricyclic antidepressants, ethanol, and other CNS depressant drugs, resulting in exaggerated respiratory depression and sedation. Methadone may potentiate the deleterious effects of ethanol. Pentazocine, nalbuphine, butorphanol, and buprenorphine are partial agonists and will behave as antagonists in the presence of methadone, resulting in the precipitation of withdrawal symptoms. Rifampin reduces blood concentrations of methadone and may lead to withdrawal. Blood levels of desipramine have increased with concurrent methadone therapy. SSRIs can increase plasma/blood concentrations of methadone (PDR, 2021).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 53 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 53. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	Little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include muscle tone flaccidity, droopy eyelids, drowsiness, depressed reflexes, and dry mouth.

References and Recommended Reading

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Mitragynine

Mitragynine is one of numerous alkaloids contained in the leaves of the kratom tree. The leaves are dark green, glossy, and ovate-acuminate in shape. Each leaf typically has 12 to 17 veins, which can be red, green, or white in color. Kratom powder is a fine, loose powder usually green in color but possibly brown, red, or orange depending on the strain.

Synonyms

Mitragyna speciosa. Kratom.

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

The kratom tree is native to Malaysia, Thailand, and Indonesia, New Guinea, the Philippines, and parts of Africa. It is a leafy tree that grows up to 25 meters (82 feet) tall. Kratom is available as raw leaves, crushed or powdered leaves, liquid extracts, capsules, and tablets. Paste-like extracts and resins are prepared by boiling off the water from aqueous leaf suspensions. Various preparations can be purchased online or from outlets. Kratom is not a Federally scheduled compound under the United States Controlled Substance Act, however, it is controlled in several States.

Drug Class

CNS effects are dose-dependent. At lower doses can be a stimulant; at higher doses can be a depressant; narcotic analgesic

Uses

Clinical

Kratom is not currently approved by the Food and Drug Administration for the treatment of any condition.

Non-Clinical

People may use kratom as a supplement for its stimulant and analgesic effects: to relieve chronic pain, reduce depression and anxiety, fight fatigue and improve work performance/productivity, treat diarrhea and fever, as a substitute for other opioid drugs, and to alleviate withdrawal from illicit drugs or prescription opioid medication. It is also misused to increase energy, sociability, and produce feelings of happiness, well-being, relaxation, and euphoria. People may also use kratom, as opposed to other opioids, to bypass routine drug tests which may not selectively test for mitragynine. Other opioids and benzodiazepines are often co-abused with mitragynine.

Potency, Purity, and Dose

Fifty-four distinct alkaloids have been isolated from the leaves of *Mitragyna speciosa*. Mitragynine and 7-hydroxymitragynine comprise 66 percent and 2 percent of the total alkaloid content, respectively, and are thought to be responsible for the majority of kratom's opioid-like effects. The content of mitragynine and 7-hydroxymitragynine in unadulterated kratom preparations can be in the range of 1 to 2 percent and 0.02-0.33 percent mass, respectively.

However, these concentrations can vary from strain to strain depending on the geographical origin of the plant, environmental conditions, plant maturity, and harvesting times. Plants from Indonesia contain higher levels of mitragynine than those from Malaysia and Thailand. Kratom varieties with red-veined leaves (typically in Thailand) are reported to be more sedating than those with green or white veins, which are reportedly more stimulating. Since kratom preparations are not regulated, they often have unknown concentrations and purities of mitragynine and 7-hydromitragynine. Substantially higher concentrations of 7-hydroxymitragynine have been found in some kratom products -- up to 500 percent higher -- suggesting artificial addition of 7-hydroxymitragynine to these products (Lydecker et al., 2016). Kratom "cough syrup" preparations in Southeast Asia have contained codeine, diphenhydramine, or other medications.

Users typically chew 3 to 20 fresh leaves at a time, providing an approximate dose of 2 to 15 mg mitragynine. This is often repeated 2 to 3 times a day. An 8 g dose of raw kratom consumed by a 70 kg subject is estimated to equate to 120 to 180 mg mitragynine and 1.1 to 3.4 mg 7-hydroxymitragynine. Doses for addicted subjects can range from 14 to 42 g of kratom per day.

Route of Administration

Kratom leaves can be chewed raw or dried and added to hot water and consumed as a tea. Kratom can be orally ingested in powder, capsules, or tablet form. Extracts and dried leaves can be smoked or mixed with food to counteract its bitter taste. Mitragynine is also available for use in vaporizers and for intravenous administration.

Pharmacodynamics

Mitragynine and 7-hydroxymitragynine are both partial agonists of the μ-, κ- and δ-opioid receptors in the CNS. 7-hydroxymitragynine, while present in the plant in much smaller quantities than mitragynine, has greater opioid agonist activity than either mitragynine or morphine; 7-hydroxymitragynine reportedly has a potency 13-times higher than morphine and 46 times higher than mitragynine. The analgesia induced by mitragynine appears to depend largely on the formation of 7-hydroxymitragynine as a metabolite rather than the parent compound itself. Both mitragynine and 7-hydroxymitragynine are G protein-based agonists of the μ-opioid receptor and are therefore classified as "atypical opioids." Mitragynine also has an affinity for α_2 adrenergic, dopamine D_2, serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_7, and adenosine A_2 receptors.

Pharmacokinetics

The oral bioavailability of mitragynine is 3 percent and greater than 90 percent is protein bound in plasma. Mitragynine has demonstrated biphasic elimination from plasma, suggesting distribution into tissue compartments. The volume of distribution is ~38 L/kg. Both mitragynine and 7-hydroxymitragynine readily cross the blood brain barrier. Following oral consumption, mitragynine has an elimination half-life of 17 to 29 hours. Mitragynine undergoes extensive hepatic metabolism and at least nine metabolites have been identified. 7-hydroxymitragynine, an alkaloid contained within kratom leaves, is also an active metabolite of mitragynine. Mitragynine is primarily eliminated in the urine with less than 0.2 percent detected as the unchanged parent compound. Most pharmacokinetic data are derived from studies on chronic users and may be different in occasional users.

Blood to Plasma Concentration Ratio

Data not available.

Interpretation of Blood Concentrations

Nine healthy adult male chronic users were administered single daily oral doses of 6 to 12 mg for 7 days, followed by a final dose of 6 to 23 mg on the 8th day. Peak plasma concentrations at 0.8 hours after the last dose ranged from 18.5 to 105 ng/mL. C_{max} increased proportionally with dose. The lowest C_{max} (18.5 ng/mL) came from a low loading dose of ~10 mg while the highest C_{max} (105 ng/mL) came from the highest loading dose of 23 mg. T_{max} was determined to be 0.83 hours (Trakulsrichai et al., 2015).

In 1,001 blood samples testing positive for mitragynine, from various case types, concentrations ranged from 5.6 to 29,000 ng/mL (average 410 ± 1,124; median 130 ng/mL). Once the 29,000 ng/mL is removed, the average concentration was 381 ± 668 ng/mL. In a subset of these cases, mitragynine concentrations in 18 suspected impaired driving cases ranged from 11 to 490 ng/mL (average 106 ± 117 ng/mL, median 75 ng/mL (Papsun et al., 2019).

In a review of 156 deaths associated with the use of kratom, blood concentrations in 71 of these cases ranged from 0.89 to 16,000 ng/mL (average 853 ng/mL). 7-hydroxymitragynine was only measured in five cases and averaged 662 ng/mL (range 9 to 2,800 ng/mL). Most mitragynine-related cases reported in the literature involved other substances detected, namely other opioids, benzodiazepines, and ethanol (Corkery et al., 2019).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

Mitragynine pKa 7.3.

General Effects

It is often reported that the effects of kratom produces a combination of stimulant and opioid effects with stimulatory effects predominating at lower doses and sedative/analgesic effects being more pronounced at higher doses. A low to moderate dose (1 to 5 g of kratom leaves) is reported to produce mild stimulant effects (e.g., alertness, euphoria); moderate to high doses (5 to 15 g) produce euphoriant and opioid-like effects (e.g., analgesia); and high doses (> 15 g) produce sedative and analgesic effects (White, 2018). However, in a study of 63 daily kratom users, kratom produced both stimulatory and sedative effects and there were no significant differences associated with the dose consumed. The subjects in this study drank either less than or greater than 3 glasses of kratom juice per day (75 to 85 mg kratom per drink) (Singh et al., 2019).

Table 54 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 54. Physiological, motor, and cognitive side effects of kratom consumption

Physiological	Motor (behavioral)	Cognitive
• Elevated blood pressure • Elevated pulse • Analgesia • Constipation • Fever reduction • Decreased appetite • Weight loss • Hyperpigmentation • Dark-colored urine • Light-colored stool • Tongue numbness (tea drinking)	• Relaxation • Increased sociability • Increased energy • Relief of fatigue • Improved productivity	• Euphoria • Feeling of well-being • Alertness • Reduced depression • Reduced anxiety

Other adverse effects may include nausea, vomiting, abdominal pain, agitation, irritability, restlessness, tremors, insomnia, anxiety, drowsiness, lethargy, confusion, and sweating. Serious clinical effects, often observed with higher and/or chronic doses, can include hepatitis, liver toxicity, seizure, respiratory depression, bradycardia, respiratory arrest, and coma. Kratom toxicity is presumed to resemble an opioid toxidrome – depressed respiratory function, decreased mental status, hypotension, and hypothermia (Walker, 2021; Alsarraf et al., 2019; Baselt, 2020; Corkery et al., 2019; Kruegel et al., 2019; Logan et al., 2017; Papsun et al., 2019; Post et al., 2019; Singh et al., 2014, Singh et al., 2019).

Duration of Effects

Following oral consumption, onset of effects may be felt within 5 to 20 minutes, with full effects apparent at 30 to 60 minutes. Effects have been described as strongest at 2 to 4 hours after ingestion and can last 5-7 hours. Weak effects can be felt up to a day later. Some effects, such as increased blood pressure and heart rate, can be delayed approximately 8 hours after drinking kratom tea.

Tolerance, Dependence, and Withdrawal Effects

Chronic kratom use can lead to tolerance, cross-tolerance to other opioids, physical dependence, addiction, cravings, and withdrawal symptoms. Kratom tolerance develops slower than for morphine and may have lower potential for addiction. However, 7-hydroxymitragynine has a higher abuse potential and is often elevated in kratom preparations. Tolerance generally occurred after 3 months but can occur after several weeks (Alsarraf, 2019). Over 50 percent of people consuming an average of 277 mg orally on a chronic basis developed physical dependence; cessation of use caused withdrawal symptoms of myalgia, fever, restlessness, rhinitis, and insomnia (Singh et al., 2014).

Reported withdrawal symptoms are like those described for traditional opioids but are milder and overlap with some adverse effects. Symptoms of kratom withdrawal generally develop within 6

to 12 hours after last reported use. Physical symptoms include decreased appetite, weight loss, decreased libido, insomnia, myalgia, jerky movement of limbs, watery eyes and nose, runny nose, dry mouth, hot flushes, hypertension, fever, nausea, frequent micturition, diarrhea, diaphoresis, and abdominal cramps. Psychological symptoms can include cravings, dysphoria, nervousness, restlessness, tension, anger, hostility, irritability, aggression, and sadness. Mental confusion, delusion, and hallucinations have also been reported (Walker, 2021; Bin Abdullah, 2020; Hartley et al, 2021; Vento et al, 2021; White, 2018).

Driving-Related Studies

Case Reports

A 38-year-old male driver made an abrupt steering correction and crossed the yellow line. He appeared anxious and had bloodshot eyes. He displayed clues on the HGN and WAT tests. Mitragynine was detected at 99 ng/mL in blood, and amphetamine was also detected at 140 ng/mL (Papsun et al., 2019).

A 39-year-old male driver was observed swerving between lanes and the shoulder and almost struck another vehicle. He admitted using kratom daily. His pupils were pinpoint, his eyes were bouncing/twitching, and he was unable to focus. Mitragynine was detected at 69 ng/mL in blood, along with cocaine at 360 ng/mL and benzoylecgonine at 2,000 ng/mL (Papsun et al., 2019).

A 37-year-old female driver nearly struck an oncoming vehicle. She displayed the following signs during a DRE evaluation: eyelid and body tremors, twitching, unsteadiness on feet, swaying, severe leg tremors, poor balance, rapid and slurred speech, elevated blood pressure and heart rate, decreased body temperature, no HGN or VGN, lack of convergence, and dilated pupils. The DRE officer reported a CNS stimulant and cannabis. The driver's blood was qualitatively positive for mitragynine and citalopram, while amphetamine was detected at 52 ng/mL (Wright, 2018).

Interactions With Ethanol

Information not available.

Interactions With Other Drugs

Combined use of mitragynine with opioids can cause over-sedation or potential respiratory depression (Meireles, 2019).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

Data not available; however, the indicators in Table 55 are the most consistent with mitragynine use. Variation observed may be due to individual reaction, dose taken and drug interactions.

Table 55. DEC program profile most consistent with mitragynine use

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	normal to constricted	little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Analytical Considerations

Mitragynine is stable for up to 7 days in preserved blood at room temperature and up to 30 days when refrigerated or frozen. Loss of > 20 percent of mitragynine was observed from 30 to 90 days across all temperature settings, and especially at room and refrigerated temperatures. Overall, mitragynine stability declines markedly after 30 days. Additionally, mitragynine concentrations may also be influenced by inadequate resolution of mitragynine from its diastereomers, potentially leading to falsely elevated concentrations (Papsun, 2019).

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Morphine, Heroin, and Codeine

In its pure form, morphine is a white crystalline powder or colorless or white acicular crystals; Heroin varies in color from white to dark brown due to impurities, or it may appear as a black tar-like material. Codeine is a colorless crystal or a white crystalline powder.

Synonyms

Morphine: Astramorph, Duramorph, Infumorph, Kadian, Morphine Sulfate, MSIR, MS-Contin, Oramorph SR, Roxanol

Heroin: diacetylmorphine, diamorphine

Codeine: ingredient in Tylenol#3, several cough preparations

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Morphine is a naturally occurring substance extracted from the seedpod of the poppy plant, *Papavar somniferum*. Morphine concentration in opium can range from 4 to 21 percent. An alternate method of harvesting morphine is by the industrial poppy straw process of extracting alkaloids from the mature dried plant, which produces a fine brownish powder. Morphine is a Schedule II controlled substance and is available in a variety of prescription forms: injectables (0.5 to 25 mg/mL strength); oral solutions (2 to 20 mg/mL); immediate and controlled release tablets and capsules (15 to 200 mg); and suppositories (5 to 30 mg).

Heroin is a Schedule I controlled substance and is produced from morphine by acetylation at the 3 and 6 positions. Most of the heroin sold in the United States originates from Southeast Asia, South America (Columbia), and Mexico. Low-purity Mexican black tar heroin is most common on the West Coast, while high purity Columbian heroin dominates in the East and most mid-western States. However, illicit fentanyl has contaminated or replaced heroin in many locales across the United States.

Codeine is a morphine product obtained from opium that is listed as a Schedule III, IV, or V controlled substance, depending on the formulation. Codeine is available as the phosphate or sulfate salt, either alone or in combination with other drugs such as non-opioid analgesics and antihistamines. It is available in 15, 30 and 60 mg tablets.

Drug Class

Narcotic analgesic

Uses

Clinical

Morphine is used for the relief of moderate to severe pain in both acute and chronic pain management. It can also be used to sedate a patient pre-operatively and to facilitate the induction of anesthesia. Heroin has no currently accepted medical uses in the United States; however, it has both analgesic and antitussive properties. Codeine is effective as a cough suppressant and is also used for analgesia.

Non-Clinical

Heroin is used to produce intense euphoria; morphine is misused to produce a feeling of euphoria, to reduce anxiety, and for self-medication of pain; and codeine is misused for its euphoric, drowsiness and relaxation purposes.

Potency, Purity, and Dose

The dosage of morphine is patient dependent. A usual adult oral dose of morphine is 60 to 120 mg daily in divided doses, or up to 400 mg daily in opioid tolerant patients. For non-clinical purposes, daily heroin doses of 5 to 1,500 mg have been reported, with an average daily dose of 300 to 500 mg. People who use heroin may inject 2 to 4 times per day. Depending on the demographic region in the United States, the street purity of heroin can range from 11-72 percent (average purity is ~38%). Heroin may be cut with inert or toxic bulking agents such as sugars, starch, powdered milk, and quinine. Throughout the country, heroin has been adulterated with illicit fentanyl which confers a greater risk of overdose due to its higher potency. In many United States locales, heroin has become difficult to find as it has essentially been replaced by illicit fentanyl. Heroin may also be mixed with methamphetamine or cocaine ("speedball") and injected; or co-administered with alprazolam, ecstasy (MDMA), crack cocaine, or diphenhydramine. Codeine is one-sixth to one-tenth as potent an analgesic as morphine. For pain relief, typical doses of codeine range from 15 to 60 mg orally every 4 hours, with a total daily dose of 60 to 240 mg.

Route of Administration

Morphine: Oral, intramuscular, intravenous, rectal, epidural, and intrathecal administration. Morphine tablets may be crushed and injected, while opium can be smoked.

Heroin: Smoked, snorted, intravenous ("mainlining"), and subcutaneous ("skin popping") administration. Black tar heroin is typically dissolved, diluted, and injected, while higher purity heroin is often snorted or smoked.

Codeine: Oral administration.

Pharmacodynamics

Morphine produces its major effects on the CNS primarily through μ-opioid receptors. Morphine is a strong agonist at this receptor, which was originally named after morphine (its best-known ligand). Morphine is also a weak agonist at κ- and δ-opioid receptors. μ_1-opioid receptors are involved in pain modulation, analgesia, respiratory depression, miosis, euphoria, and decreased gastrointestinal activity; μ_2- opioid receptors are involved in respiratory depression, drowsiness, nausea, and mental clouding; κ- opioid receptors are involved in analgesia, diuresis, sedation, dysphoria, mild respiratory depression, and miosis; and δ- opioid receptors are involved in analgesia, dysphoria, delusions, and hallucinations. Heroin has little affinity for opioid receptors and most of its pharmacology resides in its metabolism to active metabolites, namely 6-acetylmorphine, morphine, and morphine-6-glucuronide. Codeine is a weak μ and δ agonist.

Pharmacokinetics

The oral bioavailability of morphine is 20 to 40 percent and 30 to 35 percent is bound in plasma. The volume of distribution is 1.0 L/kg. Morphine has a short half-life of 1.5-7 hours and is primarily glucuroconjugated at positions 3- and 6-, to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), respectively. A small amount (5%) is demethylated to normorphine. M6G is an active metabolite with a higher potency than morphine and can accumulate following chronic administration or in renally impaired people. The half-life of M6G is 4 ± 1.5 hours. Close to 90 percent of a single morphine dose is eliminated in the 72-hour urine, with 75 percent present as M3G and less than 10 percent as unchanged morphine. Morphine itself is also a metabolite of codeine, ethylmorphine, heroin, and pholcodine.

Heroin has an extremely short elimination half-life of 2 to 6 minutes and is metabolized to 6-acetylmorphine and morphine. The half-life of 6-acetylmorphine is 6 to 25 minutes. Both heroin and 6-acetylmorphine are more lipid soluble than morphine and enter the brain more readily. Codeine is well absorbed orally, is 7 to 25 percent plasma protein bound and has a half-life of 2 to 4 hours. The volume of distribution is 2.5 to 3.5 L/kg. Codeine is metabolized to morphine and norcodeine. Over 95 percent of a single dose is excreted in the urine within 48 hours, mostly as free or conjugated codeine, and the conjugated forms of morphine and norcodeine.

Blood to Plasma Concentration Ratio

Morphine: 1.02

M6G: 0.57

M3G: 0.59

Codeine: 0.87-0.90

Interpretation of Blood Concentrations

Tolerance makes interpretation of blood or plasma morphine concentrations extremely difficult. Peak plasma morphine concentrations occur within an hour of oral administration and within 5 minutes following intravenous injection. Average plasma concentrations of 65 ng/mL are necessary for adequate therapeutic analgesia in ambulatory patients. Anesthetic concentrations can reach beyond 2,000 ng/mL in surgical patients.

A single intravenous dose of 8.75 mg/70 kg morphine resulted in an average serum concentration of 44 ng/mL at 0.5 minutes, declining to 20 ng/mL by 2 hours. A single intramuscular dose of 8.75 mg/70 kg morphine resulted in an average serum concentration of 70 ng/mL at 10 to 20 minutes, declining to 20 ng/mL by 4 hours. Chronic dosing of oral doses of 15 mg morphine every 6 hours for 5 days resulted in average steady-state plasma morphine concentrations of 14 ng/mL (Baselt, 2001).

Following a single 12 mg intravenous dose of heroin, a peak heroin concentration of 141 ng/mL was obtained at 2 minutes, while the 6-acetylmorphine and morphine concentrations were 151 and 44 ng/mL, respectively. A single 5 mg intravenous dose of heroin produced a peak plasma morphine concentration of 35 ng/mL at 25 minutes, while intravenous doses of 150 to 200 mg have produced plasma morphine concentrations of up to 300 ng/mL (Baselt, 2020).

Intranasal administration of 12 mg heroin in six subjects produced average peak concentrations of 16 ng/mL heroin in plasma within 5 minutes; 14 ng/mL of 6-acetylmorphine at ~5 to 10 minutes; and 19 ng/mL of morphine at ~5 minutes to 1.5 hours (Cone, 1993).

The following cases are summarized in Baselt, 2020: Two subjects received a single oral dose of 15 mg codeine, resulting in an average peak serum concentration of 30 ng/mL at 2 hours. Seventeen subjects received a single oral dose of 30 mg codeine, resulting in an average peak plasma concentration of 38 ng/mL at 0.5 hours, declining to 18 ng/mL by 4 hours. Twenty subjects received a single oral dose of 60 mg codeine, resulting in an average peak plasma concentration of 134 ng/mL at 1 hour. A single oral dose of 120 mg codeine resulted in an average peak plasma concentration of 470 ng/mL at 1.2 hours. Similarly, 12 subjects received single oral doses of 60 and 120 mg codeine, resulting in average peak plasma concentrations of codeine of 120.8 ± 14.8 at 60 minutes following the 60 mg dose and 265.8 ± 28.8 ng/mL for the 120 mg dose. At 105 minutes post-dose, codeine concentrations were 114.1 ± 9.1 and 229.6 ± 17.8 ng/mL, respectively. Plasma concentrations of both doses declined to less than 15 ng/mL at 11 hours post-dose. Morphine concentrations were not detected for either dose in most subjects.

OF(S) to Blood Concentration Ratio

Morphine: average 9.8 (*n*=32; median 6.4; range 0.58 to 37) (Langel et al., 2014)

Morphine: 6.8 (*n*=10) (Gjerde et al., 2010)

Codeine: average 8.8 (*n*=41; median 4.8; range 0.17 to 47) (Langel et al., 2014)

Codeine: 11.4 (*n*=7) (Gjerde et al., 2010)

Interpretation of OF(S) Test Results

Morphine pKa 8.1; codeine pKa 8.2; heroin pKa 7.6

Concentrations of morphine were determined in oral fluid specimens from 619 pain patients, with an average concentration of 416.8 ng/mL (median 18.1; range 1.0 to 130,570 ng/mL).

Codeine concentrations were detected in 136 pain patients with an average concentration of 127.4 ng/mL (median 7.5; range 1.0 to 4,732.1 ng/mL). Norcodeine concentrations were detected in 55 pain patients, with an average concentration of 32.1 ng/mL (median 6.3; range 1.0 to 342.3 ng/mL; Heltsley et al., 2011).

Subjects received three ascending doses of both smoked and intravenous heroin. Heroin and 6-acetylmorphine were both detected in the first oral fluid samples that were collected at 2 minutes, for both routes. Peak heroin concentrations were achieved in 2 to 5 minutes after intravenous dosing and ranged from 6 to 30 ng/mL (doses 10 to 12 mg); peak heroin concentrations at 2 minutes after smoked heroin ranged from 3,534 to 20,580 ng/mL (doses 2.6 to 5.2 mg). Heroin concentrations declined slowly after smoking (last detection times ranged from 4 to 24 hours) whereas heroin declined rapidly after intravenous administration, within 1 hour. Following smoked and intravenous administration of heroin (2.6 g), heroin first appeared in oral fluid at 0.04 hours, with a last detection time of 6.5 hours; 6-acetylmorphine first appeared at 0.04 hours, with a last detection time of 1.9 hours; and morphine first appeared at 0.4 hours, with a last detection time of 3.5 hours (Jenkins et al., 1995).

In 25 subjects undergoing detoxification, oral fluid samples were collected for up to 10 days. For participants with positive findings of opiates in oral fluid, detection time ranged from 0 to 1 days for codeine, 0 to 3 days for morphine, and 0 to 8 days for 6-acetylmorphine. For three of the subjects, morphine negative specimens were interspersed with morphine-positive specimens (Vindenes et al., 2014).

Nineteen subjects received single doses of oral 60 mg and 120 mg/70 kg codeine capsules. The average codeine C_{max} was 639 ng/mL (range 184 to 1,289 ng/mL) for the low dose and 1,599 ng/mL (range 620 to 3,350 ng/mL) for the higher dose. The average norcodeine C_{max} were 17 ng/mL (range 3.9 to 58 ng/mL) and 47 ng/mL (10 to 191 ng/mL), respectively. Morphine was not detected (Desrosiers & Huestis, 2019).

After an oral dose of 15.7 mg poppy seeds, morphine was first detected in oral fluid at 0.5 hours, with a last detection time of 5 hours. The average morphine C_{max} was 34 ng/mL (range 11.9 to 99.9 ng/mL). Following a second dose of poppy seeds, the last detection time was 15 hours. The average morphine C_{max} following this second dose was 9.5 ng/mL (1.1 to 32.6 ng/mL). After an oral dose of 60 mg or 120 mg/70 kg codeine, codeine first appeared in oral fluid at 0.4-0.5 hours, with a last detection time of 21.1 to 21.6 hours (Lee, 2018).

General Effects

Effects depend heavily on the dose of morphine or heroin, the route of administration, and previous exposure/tolerance. Following an intravenous dose of heroin, the user generally feels an intense surge of euphoria ("rush") accompanied by a warm flushing of the skin, dry mouth, and heavy extremities. The user then alternates between a wakeful and drowsy state ("on the nod").

Table 56 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher doses are consumed.

Table 56. Physiological, motor, and cognitive side effects of morphine, heroin, and codeine consumption

Physiological	Motor (behavioral)	Cognitive
• Analgesia • Depressed heart rate • Respiratory depression • Nausea & vomiting • Reduced gastrointestinal motility • Constipation • Urinary retention • Flushing of face & neck • Cramping • Sweating	• Relaxation • Drowsiness • Lethargy • Self-absorption • Diminished reflexes • Depressed consciousness	• Euphoria • Feeling of well-being • Mental clouding ('mental fog') • Inability to concentrate • Delirium

Physiological	Motor (behavioral)	Cognitive
• Pupils fixed & constricted		

Other adverse effects may include apathy, lessened physical activity, constipation, tremors, itching, bradycardia, severe respiratory depression, and pulmonary complications such as pneumonia. Medical complications among illicit drug users arise primarily from adulterants found in drugs and in non-sterile injecting practices, and may include skin, lung, and brain abscesses, scarring (or sclerosis) of veins, and endocarditis. When untreated, overdose precipitates slow, shallow breathing, clammy skin, convulsions, extreme somnolence, severe respiratory depression, apnea, circulatory collapse, cardiac arrest, coma, and death (Baselt, 2020; Feldon et al., 2011; Mason, 1977; PDR, 2021).

Duration of Effects

Depending on the morphine dose and the route of administration, onset of effects is within 15 to 60 minutes and effects may last 4 to 6 hours. The duration of analgesia increases progressively with age although the degree of analgesia remains unchanged. Following heroin use, the intense euphoria lasts from 45 seconds to several minutes, peak effects last 1 to 2 hours, and the overall effects wear off in 3 to 5 hours, depending on dose.

Tolerance, Dependence, and Withdrawal Effects

Both morphine and heroin have high physical and psychological dependence. With regular use, tolerance develops early to the duration and intensity of euphoria and analgesia. Withdrawal symptoms may occur if use is abruptly stopped or reduced. Withdrawal typically begins within 6 to 12 hours after the last dose and may last 5 to 10 days. Early symptoms include watery eyes, runny nose, yawning, and sweating. Major withdrawal symptoms peak from 48-72 hours after the last dose and include drug craving, restlessness, irritability, dysphoria, loss of appetite, tremors, repeated sneezing, diarrhea, nausea and vomiting, elevated heart rate and blood pressure, chills alternating with flushing and excessive sweating, goose-flesh (piloerection), abdominal cramps, body aches, muscle and bone pain, muscle spasms, insomnia, and severe depression (Miller, 2021; Patterson, 2021; Gjerde & Mørland, 1991; PDR, 2021).

Driving-Related Studies

Laboratory Studies

Laboratory studies have shown that morphine may cause sedation and psychomotor impairment following single oral or intravenous doses in healthy volunteers, as well as current/past opiate users and cancer patients. Effects often peaked at 1 to 2 hours and persisted up to 4 to 6 hours. Effects and other symptoms have included slowed reaction time, reduced memory, pupil constriction, and self-rated sedation, intoxication and/or fatigue. Similar findings have been observed after intravenous heroin (2.5 to 12 mg) was administered to former heroin/narcotic users (Baselt, 2001).

In a summary of five laboratory studies on former opioid/heroin addicts, heroin was shown to cause dose-related subjective sedation and miosis, and performance decrements on visual

reaction time with higher doses. However, a large range of cognitive and/or psychomotor tasks were not included in any of the studies. The doses included single intravenous doses of 2.4 to 12 mg and intranasal doses of 6 to 12 mg (Baselt, 2001).

In a review article of single intravenous doses of morphine, morphine was found in some studies to impair reaction time, attention, and visual functions. Tests on visual functions and attention seemed to be more sensitive to morphine administration than reaction time. Overall, it was estimated that at plasma morphine concentrations at or below 14.3 ng/mL, there are very few effects on traffic-relevant performance tasks (Strand et al., 2017).

A summary of 15 laboratory studies demonstrated morphine causes dose-related subjective sedation and pupillary constriction. Morphine also caused impaired performance on most tasks and on the driving simulator, although a significant difference was not always measured. Test subjects across the studies included former opioid or heroin addicts, recreational drug users, cancer or chronic pain patients, and healthy subjects. Morphine doses across the studies included single intravenous doses of 6 to 20 mg, single intramuscular doses of 15 to 30 mg, single oral doses of 10 to 15 mg, and daily oral doses of sustained-release morphine at 30 to 11,000 mg. Performance tests included reaction time (auditory/visual), pupillary response, tapping rate, visual acuity, short story, arithmetic, letter recognition, tracking, Maddox wing testing, digit symbol substitution, critical flicker fusion, body sway, and sedation self-rating. The overall effect of morphine on cancer or chronic pain patients appeared less pronounced (Baselt, 2001).

A summary of four laboratory studies on healthy subjects demonstrated codeine did not cause impaired performance, and typically only caused an increase in subjective sedation, vertigo, or sluggishness with higher doses. Performance tests across the studies included paired words, word list recall, critical flicker fusion, digit symbol substitution, critical tracking, visual acuity, choice reaction time, Maddox wing testing, connect-the-dots, and sedation self-rating. Oral codeine doses ranged from 25 to 120 mg (Baselt, 2020).

Simulated Driving Studies

In a video driving simulator study, 20 patients treated with long-term codeine for chronic pain (average 180 mg/day) were compared to 20 chronic pain patients not treated with codeine, and 20 healthy controls. Testing was performed 1 and 5^{+} hours after the last codeine dose and the primary outcome measures were reaction time and number of missed reactions. The long-term codeine treated patients performed no differently than the non-codeine treated patients. Compared to healthy controls, the reaction times were significantly slower for the two chronic pain groups, in both rural and urban driving scenarios, and they were almost twice as likely to miss reactions to traffic signs (Nilsen et al., 2011).

Case Reports

Opiates, alone or in combination with other drugs, were detected in 2,573 impaired driving subjects in Sweden. Morphine was detected in 2,029 subjects with average blood concentrations of 46 ng/mL (median 30; highest 1,130 ng/mL); codeine was detected in 1,391 subjects with average blood concentrations of 47 ng/mL (median 10, highest 2,400 ng/mL); and 6-acetylmorphine was detected in 52 subjects with average blood concentrations of 15 ng/mL (median 10, highest 100 ng/mL). In subjects where heroin had been taken, the average morphine/codeine ratio in blood was 7.5 (median 6.7) (Jones et al., 2008).

Baselt (2001) summarized the case of a chronic heroin user who took a brief stop on a long-distance drive and administered heroin intravenously. The subject fell asleep at the wheel nearly 3 hours later, drove off the road, and overturned his vehicle. Approximately 3 hours after the crash, morphine was detected in the subject's blood at 15 ng/mL.

Interactions With Ethanol

Ethanol increases the CNS effects of morphine such as sedation, drowsiness, and decreased motor skills.

A single oral dose of 25 mg codeine or placebo was given to 70 healthy subjects, in addition to 0.5 g/kg ethanol or placebo. Subjects were tested on a driving simulator during the following 0.5 to 1.2 hour period. Ethanol and codeine alone each demonstrated performance decrements (e.g., increased collisions and off-road excursions), the combined effect of ethanol and codeine was not greater than that of codeine alone (Baselt, 2001).

A single oral dose of 25 mg codeine or placebo was given to healthy volunteers, in addition to 0.5 g/kg ethanol or placebo. Subjects were tested on a driving simulator for 40 minutes, starting 30 minutes after dosing. Primary outcome measures included self-assessment of performance, reaction time to emergency situations, and changes in steering, distance, and speed. Alcohol alone increased the frequency of collisions and made the subjects prone to ignore instructions and traffic rules. Codeine potentiated alcohol in the number of collisions, serious steering errors and ignoring traffic rules (Linnoila & Mattila, 1973).

Interactions With Other Drugs

There is a higher risk of respiratory depression, hypotension, and profound sedation or coma with concurrent treatment or use of other CNS depressant drugs such as benzodiazepines, barbiturates, hypnotics, tricyclic antidepressants, general anesthetics, monoamine oxidase inhibitors (MAOIs), and antihistamines. Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Small doses of amphetamine substantially increase the analgesia and euphoriant effects of morphine and may decrease its sedative effects. Antidepressants may enhance morphine's analgesia. Partial agonists such as buprenorphine, nalbuphine, butorphanol, and pentazocine will precipitate morphine withdrawal (PDR, 2021).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 57 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 57. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	None	constricted	little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include presence of fresh injection marks, track marks, flaccid muscle tone, droopy eyelids, drowsiness or being "on-the-nod," and low raspy slow speech.

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Oxycodone and Oxymorphone

Oxycodone hydrochloride salt is a white crystalline powder. Oxymorphone hydrochloride salt is a white crystal or white to off-white powder.

Synonyms

Oxycodone: OxyContin, and as an ingredient of Percodan and Percocet

Oxymorphone: Opana, Opana ER, Numorphan

Source

Oxycodone and oxymorphone are both Schedule II controlled substances. Oxycodone is a semisynthetic opioid prepared from thebaine and is available as a hydrochloride or terephthalate salt. Prescription products include immediate-release tablets in strengths of 2.5 and 5 mg; sustained-release tablets in strengths of 10, 20, 40, and 80 mg; and solutions of 1 and 20 mg/L for oral administration.

Oxymorphone is also a semisynthetic opioid prepared from thebaine. It is available as the hydrochloride salt in 1 and 1.5 mg/mL ampules for intramuscular or subcutaneous administration and in a 5 mg suppository for rectal administration. Immediate-release oral tablets are available in strengths of 5 to 10 mg. Although Opana ER was taken off the market in the United States in 2017, a generic version of the extended-release formulation is available as tablets in strengths of 5 to 40 mg.

Drug Class

Narcotic analgesic

Uses

Clinical

Both oxycodone and oxymorphone are used for the relief and management of acute and chronic, moderate to severe pain.

Non-Clinical

People self-administer recommended or higher than recommended doses to achieve euphoric highs, intoxication, relaxation, anxiolysis, and pain relief.

Potency, Purity, and Dose

Oxycodone has 1.5 times the analgesic potency of morphine. Single oral doses of immediate-release oxycodone tablets in non-tolerant adults typically range from 2.5 to 5 mg, taken every 6 hours, whereas patients with chronic pain may ingest daily doses of 20 to 160 mg in divided doses. For moderate-severe pain, patients may take 10 to 30 mg every 4 hours.

Oxymorphone has 6 to 10 times the potency of morphine. Extended-release tablets are to be taken every 12 hours.

Pharmacodynamics

Oxycodone is a highly selective full agonist at the μ-opioid receptor and has much lower affinity for δ- and κ-opioid receptors. Oxymorphone is a strong μ-opioid agonist, with far less affinity for δ-opioid receptors; in high doses, oxymorphone can produce some binding to κ-opioid receptors.

Pharmacokinetics

Oxycodone has moderate oral bioavailability (60 to 87%) and is 38 to 45 percent plasma protein bound. The volume of distribution is 2.6 L/kg. Following oral and intramuscular administration, the elimination half-life ranges from 3 to 6 hours. Oxycodone is metabolized by *O*-demethylation to oxymorphone and by *N*-demethylation to noroxycodone. Approximately 30 to 60 percent of a single dose is excreted in the urine as free (5 to 10%) and conjugated (10 to 30%) oxycodone, and conjugated oxymorphone (13 to 14%). All main metabolites are active to some degree; however, as a metabolite, oxymorphone is responsible for only ~16 percent and 4.5 percent of oxycodone's analgesic effect following oral and intravenous administration, respectively.

Oxymorphone has lower overall bioavailability: oral (10%), buccal (28%), sublingual (35 to 40%), and intranasal (43%). Renally impaired patients may have a 57 to 65 percent increase in bioavailability, and food can increase the rate of absorption by as much as 50 percent. Only 10 percent is plasma protein bound and the volume of distribution is approximately 2 to 4 L/kg. Following oral administration, the elimination half-life ranges from 7 to 9.5 hours. Oxymorphone is extensively metabolized to the 6α - and 6β -hydroxy metabolites (6-oxymorphol), followed by conjugation. Two major metabolites are oxymorphone-3-glucuronide and 6-OH-oxymorphone, with the former being the major metabolite detected in urine. Approximately 90 percent of an administered dose is eliminated in the urine within 5 days, with approximately 1 percent of a dose excreted as unchanged oxymorphone.

Blood to Plasma Concentration Ratio

Reported value of 1.3.

Interpretation of Blood Concentrations

A single oral dose of 10 mg oxycodone given to 12 subjects resulted in an average peak plasma concentration of 30 ng/mL at 0.8 to 2.5 hours. A single oral dose of 20 mg controlled-release oxycodone given to 28 adults resulted in an average peak plasma concentration of 23.2 ng/mL at 3.2 hours, 15 ng/mL for noroxycodone at 4.3 hours, and 1 ng/mL for oxymorphone at 4.5 hours. Subjects receiving single oral doses of 40 or 80 mg controlled-release oxycodone achieved average peak plasma concentrations of 39 and 99 μg/L, respectively. A single oral dose of 20 mg oxycodone/70 kg given to nine subjects resulted in average peak plasma oxycodone concentrations of 38 ng/mL at an average T_{max} of 1.0 hour. Steady state concentrations are typically achieved after 3 days of therapeutic daily dosing (Baselt, 2001; PDR, 2021).

A single oral dose of 0.28 mg/kg oxycodone given to nine healthy subjects resulted in an average maximum plasma concentration of 38 ± 14 ng/mL at a median of 1.0 hours (range 0.5 to 1.0 hours). Maximum plasma concentrations of noroxycodone averaged 14.78 ± 6.69 ng/mL at a median of 0.75 hours (range 0.25 to 2.0 hours; Poyhia, 1992). A single intramuscular dose of 0.14 mg/kg oxycodone given to the same nine subjects resulted in an average maximum plasma

concentration of 34 ± 10 ng/mL at a median of 1.0 hour (range 0.5 to 1.5 hours). Maximum plasma concentrations of noroxycodone averaged 4.0 ± 0.87 ng/mL at a median of 1.75 hours (range 0.75 to 5.0 hours). Plasma concentrations of oxycodone were below the assay limit (3 ng/mL) in all samples at 24 hours after the drug was given. Plasma concentrations of the metabolite oxymorphone were below the limit of assay (0.5 ng/mL) following both treatments.

A single oral dose of 5, 10, or 20 mg immediate-release oxymorphone given to 23 healthy subjects resulted in average peak plasma concentrations of 1.1, 1.9, and 4.4 ng/mL, respectively, at 0.5 hours (Baselt, 2020). Twice daily doses of oral 20 or 40 mg extended-release oxymorphone were given to 21 healthy subjects for 3 days, resulting in average peak plasma oxymorphone concentrations after the first dose of 1.2 and 2.6 ng/mL, respectively, at 2.5 to 4.0 hours. After the second dose, average peak plasma oxymorphone concentrations were 2.5 and 4.5 ng/mL, respectively, at 1.3 to 3.5 hours (PDR, 2021).

Older patients (≥ 65 years) may experience a 40 percent increase in plasma oxymorphone concentrations with the extended-release tablets. Food can also increase the rate of absorption of oxymorphone and increase the C_{max} by 38 percent (PDR, 2021).

OF(S) to Blood Concentration Ratio

Oxycodone: average 14.9 (*n*=94) (Heiskanen et al., 2015)

Interpretation of OF(S) Test Results

Oxycodone pKa 8.5; oxymorphone pKa 8.5

A single oral dose of 20 mg controlled-release oxycodone was given to 12 subjects. Average C_{max} was 133 ng/mL (range 49.2 to 219 ng/mL) for oxycodone; 18.7 ng/mL (range 10.3 to 31.8 ng/mL) for noroxycodone; and 1.6 ng/mL (range 1.2 to 2.4 ng/mL) for oxymorphone. Oxycodone was first seen in oral fluid within 15 to 30 minutes and the last detection times ranged from 12 to 28 hours (Desrosiers & Huestis, 2019).

In a study of 6,441 chronic pain patients from 231 pain clinics in the United States, concentrations of oxycodone were determined in oral fluid specimens from 1,847 pain patients, with an average concentration of 613.2 ng/mL (median 120.1 mL; range 1.0 to 239,870 ng/mL). Noroxycodone concentrations were detected in 1,952 oral fluid specimens with an average concentration of 135.7 ng/mL (median 48.5; range 1.0 to 6,896.5 ng/mL). Oxymorphone was detected in 1,046 oral fluid specimens with an average concentration of 24.7 ng/mL (median 4.2 ng/mL; range 1.0 to 6,130 ng/mL; Heltsley et al., 2011).

General Effects

The pharmacological effects of oxycodone and oxymorphone depend on the dose, route of administration, experience of the user, and tolerance. Table 58 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 58. Physiological, motor, and cognitive side effects of oxycodone and oxymorphone consumption

Physiological	Motor (behavioral)	Cognitive
• Reduced sensitivity to pain/pain relief • Constipation • Nausea and vomiting • Dry mouth • Sweating • Constricted pupils • Urine retention • Low blood pressure • Headache • Weakness	• Relaxation • Anxiolysis • Dizziness • Somnolence • Itching	• Euphoria • Reduced alertness

Other adverse effects may include loss of appetite, nervousness, abdominal pain, diarrhea, shallow breathing, slow heart rate, cold and clammy skin, pyrexia, anxiety, and stupor. High doses may cause agitation, disorientation, lethargy, fatigue, depression, flushing, dysphoria, edema, insomnia, hallucinations, coma, respiratory depression, and blurred vision (Baselt, 2020; PDR, 2021; Schoedel et al., 2010; Verster et al., 2006).

Duration of Effects

Oxycodone: Onset of pain relief following administration of immediate release oral tablet is 10 to 15 minutes and lasts 3 to 6 hours. Onset for controlled release is 1 hour and lasts 10 to 12 hours.

Oxymorphone: Onset for pain relief is felt within 5 to 10 minutes after intravenous administration and 15 to 30 minutes after oral administration. Main effects last 3 to 4 hours after administration of immediate release form, 12 hours after extended release, and 3 to 5 hours after intravenous or intramuscular forms.

Tolerance, Dependence, and Withdrawal Effects

Withdrawal effects can include yawning, anxiety, panic attacks, nausea, insomnia, muscular pain and aches, muscular weakness, fever, flu-like symptoms, runny nose, restlessness, and watery eyes (Savard, H., 2021; PDR 2021).

Driving-Related Studies

Laboratory Studies

A single intramuscular dose of 9.1 mg oxycodone/70 kg or placebo was given to nine healthy adults. Performance testing occurred at 1.5, 3.0, and 4.5 hours post dose and included digit symbol substitution, critical flicker fusion, Maddox wing testing, tapping rate, body sway, divided attention (tracking/choice reaction time), and sedation self-rating. Average plasma concentrations were 22 ng/mL at 1.5 hours, decreasing to 11 ng/mL at 3.0 hours. Oxycodone impaired performance on the critical flicker fusion, Maddox wing testing, body sway, and choice

reaction time tasks and increased subjective sedation. Effects peaked at 1.5 hours and persisted for as long as 4.5 hours (Baselt, 2001).

A single oral dose of 19.6 mg oxycodone/70 kg or placebo was given to nine healthy adults. Performance testing occurred at 1, 2.5, 5, and 8 hours post dose and included digit symbol substitution, critical flicker fusion, pupillary response, Maddox wing testing, and sedation self-rating. Oxycodone caused decremental effects for all measures, with the critical flicker fusion decrease and subjective sedation persisting for up to 5 hours. Constricted pupils were maximal at 1 hour (Poyhia et al., 1992).

A single oral dose of 20 mg of prolonged-release oxycodone or placebo was given to 10 healthy adults. Performance testing occurred at 1, 2, 4, 8, 12, and 24 hours post dose and included Maddox wing testing, digit symbol substitution, critical flicker fusion, pupillary response and sedation self-rating. Average peak plasma oxycodone concentrations were 20 ng/mL at 2.3 hours. Oxycodone adversely affected performance on the Maddox wing testing, and critical flicker fusion tasks, and caused constricted pupils and subjective sedation. Miosis and sedation were still present at 8 hours (Baselt, 2001).

Driving Studies

A single dose of 5/325 mg or 10/650 mg oxycodone/acetaminophen or placebo was given to 18 healthy subjects. Performance tests included driving ability, memory functioning, psychomotor performance, pupil size, and mood. One hour after dosing, subjects performed a standardized driving test during normal traffic. Other tests were performed 2.5 hours after dosing, while mood and pupil size were assessed on several occasions. Oxycodone/acetaminophen did not significantly affect performance in any test. However, subjects reported that significantly more effort was needed to perform the driving test while using oxycodone and that they experienced increased sedation and reduced alertness. The lack of impairment may have been related to the participants reporting increased effort during driving. Pupil size was decreased significantly. There was no significant effect on driving performances, although reduced alertness and increased mental effort were observed in a dose-dependent manner (Verster, 2006).

A single oral dose of 30 or 60 mg controlled-release oxycodone, or a single oral dose of 15 or 30 mg extended-released oxymorphone, or placebo, were given to 35 healthy nondependent recreational opioid users. Divided attention tasks (reaction time, lane travel, accuracy) were tested at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dose, and pupil size, sedation, and mood effects were tested at similar times. Both oxycodone doses produced significant effects on all tasks, compared to placebo, except false alarms. Peak cognitive and psychomotor impairment was greater with controlled-release oxycodone than the extended-release oxymorphone for reaction time (hit latency), tracking accuracy, and target accuracy. There was greater impairment for target accuracy, manual tracking, root mean square (RMS) diagonal distance, furthest distance, and reaction time. Both drugs produced miosis, dizziness, drowsiness, relaxation, dysphoria, and sedation. Overall, the effects observed on all divided attention measures were more pronounced with controlled-release oxycodone than the extended-release oxymorphone (Schoedel, 2010).

Interactions With Ethanol

Ethanol may increase plasma oxymorphone concentrations (PDR, 2021). The combination of ethanol and oxycodone in healthy subjects can enhance drug-liking actions, increase drug-taking behavior, and increase euphoria (Jann, 2014).

Interactions With Other Drugs

Amitriptyline alone caused no significant decremental effects relative to placebo; however, it enhanced the performance decrements caused by oxycodone on the digit symbol substitution and critical flicker fusion tasks (Baselt, 2001).

A single oral dose of 0, 2.5, or 5 mg dronabinol was given to 10 healthy subjects 1 hour before a single dose of 0, 5 or 10 mg oral oxycodone. Oxycodone produced constricted pupils and analgesic responses, whereas dronabinol did not. Depending on the dose combination, dronabinol either reduced or did not alter oxycodone analgesia. However, dronabinol increased oxycodone subjective effects such as drug liking and rating of a "high." The authors concluded that dronabinol did not enhance the analgesic effects of oxycodone but increased its abuse-related and impairment-related subjective effects (Babalonis, 2019).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 59 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 59. DEC program profile of a narcotic analgesic.

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	little to no reaction	Down	down	down

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.

Other characteristic indicators may include flaccid muscle tone, droopy eyelids, drowsiness or "on-the-nod," and low raspy slow speech.

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Tramadol

Tramadol is a white crystalline powder.

Synonyms

Ultram, Ultram ER, Ultracet (with acetaminophen), Ryzolt

Source

Tramadol is classified as a Schedule IV controlled substance in the United States. It is available as a hydrochloride salt in 37.5 to 50 mg normal release tablets or capsules; 50 to 400 mg extended-release tablets and capsules. A 50 mg/mL strength solution for parenteral injection is not commercially available in the United States.

Drug Class

Narcotic analgesic

Uses

Clinical

Tramadol is a synthetic opioid used clinically as a narcotic analgesic. Its principal indication is for the relief of moderately severe pain.

Non-Clinical

Tramadol is misused at high doses to produce feelings of well-being and pleasure, euphoria, a state of relaxation, and sleepiness.

Potency, Purity, and Dose

Tramadol is equipotent to codeine but causes less respiratory depression and much less abuse potential. It has approximately one tenth the potency of morphine. Daily doses are typically 50 to 100 mg normal release tramadol taken every 4 to 6 hours or extended-release tramadol taken every 12 to 24 hours. A daily maximum of 400 mg is recommended. The metabolite, *O*-desmethyltramadol, has approximately six times the potency of tramadol.

Pharmacodynamics

Tramadol is a weak μ-opioid receptor agonist and to a lesser extent an agonist at δ- and κ-opioid receptors. Tramadol inhibits serotonin and norepinephrine reuptake and is an antagonist at serotonin 5-$HT2_C$ receptors, M1 and M3 muscarinic acetylcholine receptors and α7 nicotinic acetylcholine receptors. Tramadol exists as a racemic mixture – the positive (+) enantiomer inhibits serotonin reuptake while the negative (-) enantiomer inhibits norepinephrine reuptake. Both enantiomers are weak agonists of the μ-opioid receptor. *O*-desmethyltramadol has a much stronger binding affinity to the μ-opioid receptor than tramadol.

Pharmacokinetics

Tramadol has moderate oral bioavailability (68%) and is approximately 15 to 20 percent plasma protein bound. The volume of distribution is 2.6 to 2.9 L/kg. Following oral administration of immediate release formulations, the elimination half-life ranges from 4.3 to 6.7 hours. Tramadol is metabolized via *N*- and *O*-demethylation, followed by conjugation with glucuronic acid and sulfate. Main metabolites include nortramadol, *O*-desmethyltramadol, and *O*-desmethylnortramadol. Approximately 90 percent of an administered dose is eliminated in the urine over 3 days, with approximately 29 percent of a dose excreted as unchanged tramadol. The half-life of *O*-desmethyltramadol is approximately 6.3 to 9.5 hours.

Blood to Plasma Concentration Ratio

Reported value of 1.1.

Interpretation of Blood Concentrations

The following studies are summarized in Baselt (2020).

A single oral dose of 100 mg tramadol given to 10 subjects resulted in an average peak serum concentration of 280 ng/mL at 2 hours. A single oral dose of 50 mg extended-release tramadol dose given to 24 healthy subjects resulted in an average peak plasma tramadol concentration of 107 ng/mL at 3.3 hours and an average peak plasma O-desmethyltramadol concentration of 80 ng/mL at 7.6 hours. Times to reach maximum concentration were 7.6 and 8.5 hours, respectively.

A single intramuscular dose of 80 mg was given once daily for 3 days to 10 healthy adults. Average peak plasma tramadol concentrations of 40 ng/mL were reached at 1.1 hours after the first dose, and 263 ng/mL at 0.8 hours after the last dose. A single oral dose of 100 mg tramadol given to 10 healthy subjects resulted in average peak serum tramadol concentrations of 280 ng/mL at 2 hours post-dose.

Oral doses of 50 mg normal release tramadol were given thrice daily for 2 days to 2 sets of 8 subjects (Baselt, 2020). Resulting average peak plasma tramadol and *O*-desmethyltramadol concentrations were 231 and 60 ng/mL, respectively, in eight extensive cytochrome P450 CYP2D6 metabolizers; and 315 and 26 ng/mL, respectively, in eight poor metabolizers. Single oral doses of 100 or 200 mg extended-release tramadol were given to 27 healthy subjects. Average peak plasma concentrations of 91 and 197 ng/mL were reached at 9 hours and 6 hours, respectively, for tramadol; and 20 and 43 ng/mL at 12 hours and 8 hours, respectively, for *O*-desmethyltramadol.

A single intravenous injection of 100 mg tramadol was given to five healthy subjects, resulting in average peak plasma concentrations of 613 ng/mL (range 182 to 1,047 ng/mL) at 0.25 hours, declining to 409 ng/mL by 2 hours, and 158 ng/mL after 8 hours. Steady state is typically achieved within 2 days, and some accumulation occurs with chronic administration.

OF(S) to Blood Concentration Ratio

Tramadol: average 13 (*n*=22; median 11, range 1.4 to 34) (Langel et al., 2014)

Interpretation of OF(S) Test Results

Tramadol pKa 9.4

A single oral dose of 50 mg tramadol was given to 12 subjects. Resulting median C_{max} oral fluid concentrations were 1,181 ng/mL (range 459 to 3,905 ng/mL) for tramadol and 43 ng/mL (range 2 to 158 ng/mL) for *O*-desmethyltramadol. Lower oral fluid concentrations were reported in intermediate-slow metabolizers. The last detection times were at least 48 hours for tramadol and up to 32 hours for *O*-desmethyltramadol (Desrosiers & Huestis, 2019).

In a study of 6,441 chronic pain patients from 231 pain clinics in the United States, concentrations of tramadol were determined in oral fluid specimens from 149 patients, with an average concentration of 918.8 ng/mL (median 237.6; range 20.0 to 58,083 ng/mL). *N*-desalkyltramadol was detected in 118 oral fluid specimens with an average concentration of 357.5 ng/mL (median 194.4; range 21.0 to 13,522 ng/mL). *O*-desalkyltramadol was detected in 284 oral fluid specimens with an average concentration of 207.8 ng/mL (median 85.7; range 20.1 to 2,845.8 ng/mL) (Heltsley et al., 2011).

General Effects

Tramadol produces effects comparable to a prototypical opioid but with less respiratory depression and constipation than other opioids. The pharmacological effects of tramadol depend on the dose, route of administration, experience of the user, genetic variability, drug-drug interactions, and tolerance. Table 60 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 60. Physiological, motor, and cognitive side effects of tramadol consumption

Physiological	Motor (behavioral)	Cognitive
• Pain relief • Constricted pupils • Constipation • Nausea • Dry mouth • Indigestion • Headache	• Relaxation • Dizziness • Drowsiness • Itching	• Euphoria • Sense of well-being • Reduced alertness

Other adverse effects may include vomiting, abdominal pain, somnolence, vertigo, loss of appetite, hypoglycemia, seizures, agitation, hypertension, anxiety, flushing, twitch, dysphoria, and insomnia. Adverse effects are more common during initial treatment than during maintenance therapy (Baselt, 2020; Golightly et al., 2017; Grond & Sablozki, 2004; Langley et al., 2010; Matouskova et al., 2011; PDR, 2021; Stoops et al., 2012).

Duration of Effects

Onset of pain relief within 1 hour following oral administration. Peak effects occur from 2 to 4 hours and last up to 6 hours. Miosis is evident within 2.5 hours after a tramadol dose and persists at least 6 hours post dose.

Tolerance, Dependence, and Withdrawal Effects

Withdrawal symptoms can include numbness, tingling, stiffness, insomnia, paresthesia, tinnitus, hallucinations, paranoia, extreme anxiety, panic attacks, and confusion. Onset of withdrawal effects typically occur within 12 to 20 hours of the last dose; however, compared to other opioids, withdrawal from tramadol often lasts 7 or more days (AAC, 2021; PDR, 2021).

Driving-Related Studies

Laboratory Studies

A single oral dose of 75 mg tramadol or placebo was given to 17 healthy subjects who were then tested for tracking ability on six occasions over the following 2 hours. Tramadol produced no significant effect on tracking. In contrast, a single oral dose of 100 mg tramadol impaired tracking performance throughout a 12-hour study period in 20 healthy subjects (Baselt, 2001).

Single intramuscular doses of 0, 75, 150, or 300 mg tramadol were given to 12 former narcotic addicts. Pupillary reaction and sedation self-rating were tested on 10 occasions over the next 12 hours. The 300 mg tramadol dose was subjectively detected as an opiate, but no other significant effects were observed (Baselt, 2001).

Epidemiological Studies

In a study determining the risk of motor vehicle crashes associated with individual medications in a population of drivers ≥ 65 years, drivers consuming tramadol were at a significantly increased risk (adjusted odds ratio11.41; 95 percent confidence interval (CI) 1.27 to 102.15 (Rudisill et al., 2016).

Case Reports

Blood specimens from 83 suspected impaired drivers contained an average of 390 ng/mL tramadol (range 10 to 5,360 ng/mL; Clarkson et al., 2004). Blood from another 105 people arrested for impaired driving averaged 850 ng/mL for tramadol (Jones et al., 2007). Two drivers injured in collisions had blood tramadol concentrations of 494 and 986 ng/mL (Baselt, 2020).

Interactions With Ethanol

Ethanol may cause a gradual inhibition of the active pharmaceutical ingredient released in controlled-release tramadol tablets (Dragomiroiu et al., 2015).

Interactions With Other Drugs

Naloxone precipitates opioid withdrawal symptoms among subjects maintained on oral tramadol (Stoops et al., 2012). Tramadol is primarily metabolized to *O*-desmethyltramadol by CYP2D6; the many drugs that inhibit CYP2D6 activity can limit the analgesic effects of tramadol. Use in conjugation with other serotonergic xenobiotics can result in serotonin syndrome.

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

The indicators in Table 61 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 61. DEC program profile of a narcotic analgesic.

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; HGN: vertical gaze nystagmus; LOC: lack of convergence.

Most subjects will experience constricted pupils; however, dilated pupils have been observed in up to 30 percent of subjects.

References and Recommended Reading

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Novel Synthetic Opioids

Novel Synthetic Opioids (NSO) are a class of drugs that are designed to provide pain relief, mimicking naturally occurring opioids such as morphine, and are used recreationally to produce a euphoric high. Novel Synthetic Opioids are typically highly potent and include the fentanyl analogs and other miscellaneous drugs such as AH-7921, U-47700, and MT-45. NSOs include compounds manufactured by pharmaceutical companies for medical use and compounds manufactured illegally in clandestine labs and distributed through the illicit drug market. NSOs are frequently detected in biological fluids in combination with other drugs.

Fentanyl Analogs

Well over 1,000 distinct fentanyl analogs have been identified and described. Examples include carfentanil, furanylfentanyl, acetylfentanyl, alfentanil, sufentanil, methylfentanyl, butyrfentanyl, cyclopropylfentanyl, *para*-fluoroisobutyrfentanyl, and methoxyacetylfentanyl. In the United States, "fentanyl-related substances" were placed on the list of Schedule I drugs in 2018.

Carfentanil

Carfentanil (Wildnil) is a Schedule II drug approved as a general anesthetic in veterinary use for large animals. It is estimated to be 10,000 times more potent than morphine and 100 times more potent than fentanyl. In seized drug materials, it is often found in combination with heroin, fentanyl, and other fentanyl analogs. In 55 cases of suspected impaired driving in which carfentanil was detected, carfentanil was the only drug detected in four cases, and was most commonly detected with other opioids (73 percent of cases), benzodiazepines (43%), and stimulants (29%) (Tiscione & Allford, 2018).

Carfentanil is a strong agonist at μ-opioid receptors with stronger affinity at μ_1 than at the μ_2 receptors. It is a weaker agonist at κ- and δ-receptors. Carfentanil is extensively metabolized and at least 12 metabolites have been identified. Commonly described effects following the administration of carfentanil include analgesia, sedation, depressed cough reflex, miosis, dizziness, drowsiness, bradycardia, hypotension, muscle rigidity, coma, and respiratory depression (Baselt, 2020; Logan et al., 2017).

In 26 suspected impaired driving cases testing positive for various fentanyl analogs, carfentanil was detected in 14 cases with concentrations ranging from 0.11 to 2.7 ng/mL, with a further three cases with concentrations under the limit of quantitation (0.10 ng/mL). If the two highest carfentanil concentrations are excluded (1.3 and 2.7 ng/mL), the average and median carfentanil concentrations observed were 0.23 and 0.19 ng/mL, respectively (Sofalvi et al., 2017).

Furanylfentanyl

Furanylfentanyl is a Schedule I fentanyl analog with a potency similar[22] to that of fentanyl. It is available in solutions, powders, tablets, and capsules and can be used via oral, intranasal, intravenous, and inhalational routes. Commonly used doses include 0.5 to 1.0 mg for oral administration and 0.4-0.8 mg for intranasal administration. Effects last 1 to 3 hours and include somnolence, muscle rigidity, hypotension, pulmonary edema, respiratory depression, seizure, and coma. At least 14 metabolites have been detected.

[22] Reports range from one-fifth to seven times the potency of fentanyl in the literature.

Two subjects admitted to an emergency department with apnea and cyanosis had serum concentrations of furanylfentanyl at 4.4 and 148 ng/mL; both had other synthetic drugs detected in their serum (Logan et al., 2017). In 26 cases of suspected impaired driving, in which the people tested positive for various fentanyl analogs, 2-furanylfentanyl was detected in two cases with concentrations of 0.12 and 1.4 ng/mL. A further 17 of the cases were positive for carfentanil, as described in the carfentanil section above. Fentanyl was detected in nine cases with concentrations ranging from 1.0 to 9.9 ng/mL (average 5.1 ng/mL; median 4.9 ng/mL); norfentanyl was detected in 12 cases with concentrations ranging from 0.1 to 3.5 ng/mL (average & median 1.2 ng/mL); and two cases were positive for 3-methoxyfentanyl at 0.93 and 2.8 ng/mL (Sofalvi et al., 2017).

Acetylfentanyl

Acetylfentanyl is a Schedule I opioid that is approximately 15 times more potent than morphine. It is available as a powder and has been identified in counterfeit Xanax tablets and other mislabeled pills. Acetylfentanyl can be administered orally, intranasally, and intravenously, and common oral doses are 3 to 5 mg. Effects observed following acetylfentanyl use include euphoria, analgesia, miosis, hypotension, altered mental status, respiratory depression, and hypoxemia. At least 32 metabolites have been identified.

In seven intoxication cases presenting to an emergency department, serum concentrations of acetylfentanyl ranged from 0.6 to 51.6 ng/mL (average 18.2 ng/mL, median 14.8 ng/mL). Common symptoms included miosis, respiratory depression, agitation, and delirium (Logan et al., 2017).

Miscellaneous NSOs

Miscellaneous NSOs include U-47700, AH-7921, and MT-45. They are promoted as heroin or oxycodone substitutes and are often found to be combined with other psychoactive substances such as synthetic cathinones, synthetic cannabinoids, antidepressants, and antipsychotics. Effects of these NSOs resemble an opioid toxidrome with miosis, respiratory depression, and CNS depression.

U-47700

U-47700 is a Schedule I drug. It is a structural isomer of AH-7921 and is approximately 7 to 8 times more potent than morphine. It binds primarily to the μ-opioid receptor with high affinity, much less affinity for the κ-opioid receptor, and poor affinity for δ-opioid receptor. U-47700 is typically sold as a powder or liquid and can be taken orally, rectally, intranasally, or smoked, with common doses of 5 to 20 mg reported. The duration of action is approximately 5-7 hours when taken orally, 3 to 4 hours when snorted, and 1 to 2 hours when intravenously injected.

Effects of U-47700 use include somnolence, miosis, respiratory depression, apnea, cyanosis, and depressed consciousness. The following three cases were summarized in Logan et al., 2017: A 26-year-old male was found unresponsive with cyanosis and agonal respirations; his urine contained 0.1 ng/mL of U-47700. A 41-year-old female was found unresponsive, and her admission serum was positive for U-47700 and fentanyl at 7.6 ng/mL and 15 ng/mL, respectively. A 23-year-old female was found unresponsive and cyanotic; her admission serum and urine were 228 ng/mL and 394 ng/mL, respectively.

AH-7921

AH-7921 is a Schedule I agonist at the μ-opioid receptor, with some affinity for the κ-opioid receptor. It is available in powders and capsules for oral administration in doses of 10 to 100 mg. AH-7921 can also be taken intranasally or intravenously. Effects last up to 6 hours and can include sedation, analgesia, hypothermia, addictive behavior, nausea, vertigo, alertness, tremors, and respiratory depression. It may be sold online as "doxylam."

MT-45

MT-45 is a Schedule I drug structurally unrelated to morphine and other opioid-receptor agonists and appears to influence both opioid and non-opioid receptors. It is approximately equipotent to morphine in terms of analgesic properties. It is available as a racemic mixture, with the S(+) isomer having greater potency than either the racemate or the R(-) isomer. MT-45 is typically sold online as a "research chemical" and has been combined with other synthetic compounds in chemical and herbal products. It can be taken orally, intranasally, intravenously, and intramuscularly and common oral doses are 50 to 250 mg, depending on tolerance. A range of moderate to severe adverse effects have been reported following the use of MT-45 including nausea, itching, CNS depression, sudden hearing loss, dissociative-type symptoms, loss of smell and taste, alopecia, hair depigmentation, vision impairment, apnea, decreased respiratory rate, cyanosis, neurological disturbances such as paresthesias in the hands and/or feet, and coma.

In reports of non-fatal intoxications involving MT-45, 11 subjects had reported blood concentrations ranging from 6 to 344 ng/mL. Respiratory and CNS depression (unconsciousness) were commonly reported (Logan et al., 2017).

Drug Evaluation and Classification Program Category

Narcotic analgesic

Drug Evaluation and Classification Program Profile

DEC profiles for individual novel opioids have not been established. The indicators in Table 62 are those of a narcotic analgesic. Variation may be observed due to the novel opioid and dose consumed, individual reaction, and drug interactions.

Table 62. DEC program profile of a narcotic analgesic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
none	none	none	constricted	little to no reaction	down	down	down

HGN: horizontal gaze nystagmus; HGN: vertical gaze nystagmus; LOC: lack of convergence.

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Phencyclidine (PCP)

PCP is a white, crystalline powder (contaminants may cause tan to brown color); or a clear, yellowish liquid.

Synonyms

1-phenylcyclohexylpiperidine

Refer to the DEA website for a list of common street names (www.dea.gov/factsheets).

Source

Synthetic chemical made in clandestine laboratories or diverted from veterinary sources. PCP is currently a Schedule II controlled substance. In illicit synthesis, piperidine is reacted with cyanide and cyclohexanone to make piperidinocyclohexanecarbonitrile (PCC), which is then reacted with phenylmagnesium bromide to make PCP. PCP can be mixed with dyes and sold in a variety of tablets, capsules, and colored powders. PCP is also sold as a liquid in small shaker bottles. PCP analogs are also available: cyclohexamine (PCE), phenylcyclohexylpyrrolidine (PHP), phenylcyclopentylpiperidine (PCPP), and thienylcyclohexylpiperidine (TCP).

Drug Class

Hallucinogen; dissociative anesthetic; psychotomimetic; sedative-hypnotic

Uses

Clinical

Formerly used as a surgical anesthetic; however, there is no current legitimate medical use in humans. PCP may be used in veterinary medicine as an anesthetic or tranquilizer.

Non-Clinical

PCP is misused as a psychedelic and hallucinogen.

Potency, Purity, and Dose

At doses of 1 to 3 mg, PCP is typically injected or smoked by applying to plant material. The liquid can be sprinkled on tobacco or marijuana then smoked, or the cigarettes or joints themselves can be dipped in PCP solution; the resulting PCP dose can therefore vary widely. Higher doses (2 to 10 mg) are typically taken by oral ingestion. Due to difficulty of synthesis, street preparations have highly variable concentrations of PCP and byproducts. PCC, the PCP precursor, is found in approximately 20 percent of illicit samples and is more toxic than PCP as it releases cyanide. Abuse of PCP precursors or analog chemicals leads to similar or more devastating pharmacological effects than PCP. PCP is often administered or mixed with other drugs such as crack cocaine, cocaine hydrochloride, and marijuana.

Route of Administration

Smoked, intravenous injection, snorted, added as eye drops, oral ingestion, and transdermal absorption.

Pharmacodynamics

PCP is a non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist, and blocks dopamine reuptake and elevates synaptic dopamine levels. It has high affinity to sites in the cortex and limbic structures. PCP acts as a dissociative anesthetic which can lead to sedation, loss of consciousness, agitation, psychosis, and a lack of sensation of pain.

Pharmacokinetics

PCP is well absorbed following all routes of administration, although when smoked, approximately 50 percent of PCP is converted to an inactive thermal degradation product. At low doses (~1 mg), PCP has an oral bioavailability of 72 percent and a volume of distribution of approximately 6.2 L/kg, with plasma binding of 65 percent. It is highly lipid soluble, mainly stored in fat and brain tissue. Its half-life ranges from 7 to 46 hours (average 21 hours). PCP is extensively metabolized to inactive metabolites by a variety of metabolic routes.

Blood to Plasma Concentration Ratio

Reported values of 0.94 and 1.0.

Interpretation of Blood Concentrations

There is no direct correlation between PCP concentration and behavioral or physical findings. Blood levels peak 1 to 4 hours after ingestion. Average peak plasma concentrations of 2.7 and 2.9 ng/mL were achieved after a 1 mg oral and intravenous dose, respectively (Cook et al., 1982). PCP concentrations ranged from 0.3 to 143 ng/mL in 63 patients presenting to a psychiatric hospital emergency room and were associated with a wide variety of psychotic clinical pictures resembling mania, depression, or schizophrenia. All these patients had at least one manifestation of toxic psychosis and/or acute delirium, in addition to other symptoms (Yago et al., 1981). In another series, plasma PCP concentrations ranged up to 812 ng/mL in 22 patients with nonfatal PCP intoxication. The most common physical findings were combativeness-agitation (64%), depressed level of consciousness (50%), hypertension (43%), miosis (43%), and tachycardia (43 percent; Bailey, 1979).

OF(S) to Blood Concentration Ratio

Data not available.

Interpretation of OF(S) Test Results

PCP pKa 8.5

General Effects

The pharmacological effects of phencyclidine are usually dose dependent. Table 63 provides a range of effects, including side effects that subjects may experience.

Table 63. Physiological, motor, and cognitive side effects of PCP consumption

Physiological	Motor (behavioral)	Cognitive
• Increased heart rate • Increased blood pressure • Flushing • Profuse sweating • Generalized numbness of extremities • Blurred vision • Marked analgesia • Sedation • Nystagmus • Grimacing facial expression • Anesthesia	• Calmness • Lethargy • Disorientation • Speech difficulties • Ataxia • Agitation • Combativeness or violence • Stupor • Feelings of strength and invulnerability • Depressed level of consciousness	• Euphoria • Lack of concentration • Changes in body awareness • Distorted sensory perceptions • Illusions and hallucinations • Disordered thinking • Memory loss

In the anesthetized state, the patient remains conscious with a staring gaze and rigid muscles.

Other adverse effects may include excessive salivation, nausea, vomiting, amnesia, combativeness, severe anxiety, paranoia, flashbacks, seizures, coma, and death. PCP can simulate schizophrenic-like symptomatology such as flattened affect, dissociative thought disorder, depersonalization, and catatonic states. Long periods of use may lead to memory loss, difficulties with speech and thinking, depression, weight loss, liver function abnormalities, and rhabdomyolysis (Bailey, 1979; Barton et al., 1981; Baselt, 2020; Hess et al., 1993; Kesner et al., 1993; McCarron et al., 1981; Pradhan, 1984; Rappolt et al., 1980; Rawson et al., 1981; Yago et al., 1981).

Duration of Effects

Onset of effects is very rapid when smoked or injected (1 to 5 minutes) and are delayed when snorted or orally ingested (30 minutes), with a gradual decline of major effects over 4 to 6 hours. A return to "normal" may take up to 24 hours. Consciousness is regained within 10 to 60 minutes following intravenous administration, with a prolonged recovery period of 3 to 18 hours. Long-term psychological effects are possible, and PCP may precipitate a psychotic reaction lasting a month or more that appears clinically like schizophrenia.

Tolerance, Dependence, and Withdrawal Effects

Most PCP users administer the drug intermittently, although daily use has been reported and tolerance may develop. PCP can be addicting, and use can lead to psychological dependence, craving, and drug seeking behavior. Upon abrupt discontinuation, physical distress, agitation, increased body temperature, rhabdomyolysis, seizures, lack of energy, and depression have been reported. Long periods of use may lead to memory loss, difficulties with speech and thinking, depression, and weight loss. These can last up to a year after cessation of use (AAC, 2021; Rawson et al., 1981).

Driving-Related Studies

Laboratory Studies

Laboratory studies have shown that PCP causes disorientation, drowsiness, dizziness, ataxia, double or blurred vision, body image changes, disorganization of thoughts, combativeness, impairment of eye-hand coordination, memory impairment, paresthesia, slowed reaction time, and distorted perceptions of space. Effects generally occur within 1-hour post oral dose. Subjective sensation of intoxication has been reported up to 8 hours and slowed reaction time up to 14 hours (Pradhan, 1984).

Case Reports

Fifty-six subjects were arrested for erratic driving and were evaluated by a drug recognition expert. All subjects were judged to be driving under the influence of PCP, and blood PCP concentrations ranged from 12 to 118 ng/mL (average 51 ng/mL; Kunsman et al., 1997). Similarly, blood PCP concentrations ranged from 5 to 180 ng/mL (average 30 ng/mL) in one study of 152 subjects arrested for driving under the influence and ranged from 25 to 118 ng/mL (average 67 ng/mL) in another 11 impaired drivers (Baselt, 2001).

Interactions With Ethanol

Information not available.

Interactions With Other Drugs

Benzodiazepines can decrease hypertensive effects and treat seizure activity due to PCP intoxication. PCP may enhance effects of other CNS depressants like barbiturates and ethanol.

Drug Evaluation and Classification Program Category

Dissociative anesthetic

Drug Evaluation and Classification Program Profile

The indicators in Table 64 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 64. DEC program profile of a dissociative anesthetic

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present*	present	present	normal	normal	elevated	elevated	elevated

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* typically with an early onset.

Other characteristic indicators may include rigid muscles, trance-like state or blank stare, sudden turn to violence, cyclic behavior between trance-like state and combativeness/violence, lack of response to painful stimuli, sweating, and incomplete or delayed verbal responses.

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Trazodone

Trazodone is a white, odorless, crystalline powder.

Synonyms

Desyrel, Trittico, Oleptro; Trazorel (Canada)

Source

Available as the hydrochloride salt as 50, 100, 150 and 300 mg immediate-release tablets or capsules. Also available as 75 to 300 mg extended-release tablets and a 50 mg/5 mL syrup (oral administration). Trazodone is not currently scheduled under the United States Controlled Substance Act.

Drug Class

CNS depressant, depressant; antidepressant

Uses

Clinical

Trazodone is approved for the treatment of major depressive disorder. It is also used commonly for conditions such as primary or secondary insomnia, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and obsessive-compulsive disorder. Other off-label uses include the treatment of chronic pain, benzodiazepine, and/or ethanol dependence; degenerative diseases of the CNS such as dementia; erectile dysfunction; and second line treatment of post-traumatic stress disorder.

Non-Clinical

Trazodone is misused to attain a high and for relaxation, increased energy, and elevated mood.

Potency, Purity, and Dose

As an antidepressant, typical daily trazodone doses of 150 to 400 mg are taken in single or divided doses. Lower doses of 25 to 100 mg are used for hypnotic purposes. Higher doses of up to 600 mg may be given to more severely depressed patients in an inpatient setting.

Route of Administration

Primarily oral. Less common routes include snorting crushed tablets and heating tablets until boiling, then inhaling the vapor.

Pharmacodynamics

Trazodone is a mixed serotonergic agonist/antagonist with adrenolytic activity. It is a serotonin reuptake inhibitor and a 5-HT_{2A} receptor antagonist, which leads to increased synaptic levels of serotonin (5-HT) and norepinephrine. It is also an antagonist at 5-HT_{2B} receptors, a partial agonist of 5-HT_{1A} receptors, and inhibits postsynaptic α_1- and presynaptic α_2-adrenergic receptors. Trazodone has a potent affinity for 5-HT_{2C} receptors, but it is unclear what activity it

has at this site. It also blocks histamine H_1 receptors and has low anticholinergic and dopaminergic activity. Trazodone's active metabolite, m-chlorophenylpiperizine (m-CPP), also has potent pre- and post-synaptic serotonergic effects. m-CPP inhibits the serotonin transporter, promotes the release of cytosolic 5-HT, antagonizes the $5\text{-}HT_{2A}$ receptor, and is a partial agonist of $5\text{-}HT_{1A}$ and $5\text{-}HT_{2C}$ receptors.

Pharmacokinetics

Trazodone is rapidly absorbed with an oral bioavailability of 65 to 80 percent and is 90 to 95 percent bound to plasma proteins. Peak plasma concentrations are attained 1 to 2 hours following dosage with an immediate-release tablet. It has a volume of distribution of 0.8 L/kg and does not sequester in tissues to any extent. Trazodone is extensively metabolized to primarily m-CPP, beta-(3-oxo-s-triazolic(4-3a)pyridine-2-yl) propionic acid, and their glucuronides. Approximately 75 percent of a dose is excreted as urinary metabolites, with only approximately 1 percent excreted as unchanged parent drug. The half-life of trazodone ranges from 3 to 7 hours, while the elimination half-life of m-CPP ranges from 2 to 12 hours. Decreased clearance of trazodone occurs in older adults, resulting in increased concentrations and adverse effects.

Blood to Plasma Concentration Ratio

Reported values range from 0.6-0.7.

Interpretation of Blood Concentrations

Following a single oral dose of 100 mg immediate-release trazodone in 12 healthy adults, an average peak plasma concentration of 1.1 mg/L was reached at 2 hours (Baselt, 2020). A single oral dose of 100 mg immediate-release or 100 mg controlled-release resulted in peak plasma concentrations of trazodone of 1.6 mg/L at 1.55 hours and 1.0 mg/L at 3.2 hours, respectively (Mittur, 2011). Following single oral doses of 150 mg immediate-release trazodone in four healthy adults, an average peak plasma trazodone concentration of 2.0 mg/L and a m-CPP concentration of 0.01 mg/L were attained in 2 to 4 hours. Single oral doses of 150 or 300 mg extended-release trazodone in 45 healthy adults resulted in average peak plasma concentrations of 0.5 and 1.2 mg/L, respectively, at 6 to 7 hours for trazodone. The corresponding peak plasma m-CPP concentrations were 0.006 and 0.014 mg/L, respectively, at 11 to 12 hours (Baselt, 2020).

Peak plasma steady state concentrations following oral administration of trazodone were 1.35 mg/L for 50 mg twice daily, 2.63 mg/L for 100 mg twice daily, and 3.10 mg/L for 150 mg twice daily. At these doses, the trough steady-state plasma concentrations were 0.26, 0.58, and 0.89 mg/L, respectively, at 12-hours post-dose (Mittur, 2011).

Patients with major depression were administered 150 mg immediate-release trazodone daily for 3 weeks; steady state plasma concentrations of trazodone and mCPP were 0.62 and 0.056 mg/L, respectively. Following 300 mg daily oral doses of normal- or extended-release trazodone in 27 healthy adults for seven days, average steady-state peak plasma concentrations of 3.1 and 1.8 mg/L, respectively, were obtained for trazodone at 8.0 to 8.3 hours. Corresponding concentrations of the metabolite m-CPP were 0.034 and 0.026 mg/L, respectively, at 8.0 to 8.7 hours (Baselt, 2020).

Average doses of 354 mg/day (range 150 to 500 mg/day) given to 23 depressed, older patients resulted in average plasma steady state trazodone concentrations of 1.5 mg/L (range 0.24 to 4.9

mg/L) (Baselt, 2020). Owing to reduced clearance in older adults, plasma concentrations of trazodone are typically greater than in younger subjects for 8 hours or longer after a single oral dose (Mittur, 2011).

OF(S) to Blood Concentration Ratio

Average 0.31 (n=28; median 0.24; range 0.080 to 0.77) (Langel et al., 2014).

Interpretation of OF(S) Test Results

Trazodone pKa 6.1

General Effects

At low doses (25 to 100 mg), trazodone induces and maintains physiological sleep without causing residual sedation in the morning. An antidepressant effect occurs at higher doses (150 to 600 mg). Table 65 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 65. Physiological, motor, and cognitive side effects of trazodone consumption

Physiological	Motor (behavioral)	Cognitive
• Dry mouth • Headache • Postural hypotension • Sedation	• Increased energy • Dizziness	• Euphoria • Elevated mood • Reduced anxiety

Other adverse effects may include daytime sleepiness, excessive sedation, headache, dizziness, hypotension, postural hypotension, nausea, sweating, drowsiness, confusion, fatigue, incoordination, weakness, anxiety, disorientation, ataxia, tremor, numbness, disturbed concentration, blurred vision, miosis, insomnia, memory impairment, and psychomotor impairment. Less common adverse effects include gastric distress, diarrhea, delirium, hallucinations, anorexia, hepatotoxicity, priapism, and cardiac arrhythmias. m-CPP exerts behavioral effects consistent with serotonergic activity, including headache, panic, anxiety, dysphoria, psychosis, sleep disruption, and anorexia (Baselt, 2020; Bossini et al., 2015; Longmore et al., 1988; Mittur, 2011; PDR, 2021).

Duration of Effects

Onset of effects is typically 30 minutes following oral administration of the immediate-release formulation, and the primary effects last approximately 6 hours. There should be no residual effects the morning after an evening dose of 25 to 100 mg trazodone.

Tolerance, Dependence, and Withdrawal Effects

Tolerance can occur for both trazodone and m-CPP after 1 to 2 weeks of oral administration. Physical dependence can develop after 6 to 8 weeks; however, overall trazodone has low abuse potential. Withdrawal symptoms may include anxiety, agitation, and sleep disturbances (PDR, 2021).

Driving-Related Studies

Laboratory Studies

The following studies are summarized in Baselt (2001).

- A single oral dose of 23 or 47 mg/70kg trazodone or placebo were given to 10 healthy adults, followed by performance testing at 1-, 3-, and 5-hours post-dose. Trazodone caused subjective sedation, increased the evoked potential (brain response time to stimuli), decreased pupil size, and impaired taping rate and symbol copying in a dose-related manner.
- A single oral dose of 100 mg trazodone or placebo were given to 15 healthy older adults, followed by performance testing at 1.5- and 3.5-hours post-dose. Trazodone impaired performance on critical tracking task only.
- A single oral dose of controlled-release or immediate-release 100 mg trazodone or placebo were given to 8 healthy adults, followed by testing at 2-, 4-, 6- and 8-hours post-dose. Trazodone caused subjective sedation and increased digit cancellation time during the 2 to 6 hours period, and dry mouth and miosis was also reported.
- Daily oral doses of 100 mg trazodone or placebo were given to 14 healthy adults for 7 days. Performance tests were administered on 6 occasions over 8 hours on days 1 and 7. Tests included critical flicker fusion, manual dexterity, and sedation self-rating. Trazodone impaired performance on all three tasks on both testing days, although diminished impairing effects were observed on day 7.
- Single oral doses of either 100 or 200 mg trazodone or placebo were given to 10 healthy adults, followed by performance testing at 2- and 4-hours post-dose. The 200 mg trazodone caused subjective sedation and impaired performance on digit span, digit symbol substitution, and choice reaction time for up to 4 hours.
- Daily oral doses of 100 mg or placebo were given to 12 healthy adults for 1 week, followed by daily doses of 200 mg for a second week. Performance tests were administered at 2 hours post-dose on days 1, 8, and 14. Trazodone caused marked subjective sedation and impairment on memory and psychomotor tasks following the daily doses. The impairing effects tended to increase during the 2-week period, with the higher trazodone dose.
- Single oral doses of 50, 100, or 200 mg trazodone or placebo were given to 7 healthy adults. Performance tests were administered on 9 occasions over the next 6 hours. The higher 200 mg dose caused subjective sedation at 2 to 4 hours post-dose and impaired digit symbol substitution performance at 2.5 hours post-dose.
- Twice daily doses of 150 to 200 mg trazodone were given to eight depressed patients for 5 weeks. Performance tests were administered to subjects in the morning prior to drug administration at the end of each week. Trazodone lowered the critical flicker fusion threshold but improved performance on the word list recall task.

Simulated and On-the-Road Driving Studies

Nightly oral doses of 25 mg trazodone were given to 19 healthy males for 8 days. Performance tests, using a driving simulator, were administered to subjects at baseline and during the next day on days 2 and 9. Trazodone did not affect driving performance (road tracking, car following, and harsh braking) or cognitive functions on either day of testing, demonstrating no detrimental residual daytime effects at a relatively low dose (Sasada et al., 2013).

Nightly oral doses of 50 mg trazodone were given to 16 adult insomniacs for 7 nights. Subjective effects, equilibrium (anterior/posterior body sway), short-term memory, verbal learning, simulated driving, and muscle endurance were assessed the morning after days 1 and 7 of drug administration. Trazodone produced small but significant impairments of short-term memory, verbal learning, equilibrium, and arm muscle endurance across time-points. No significant effects on driving speed or errors occurred (Roth et al., 2011).

A single oral dose of 50 mg trazodone or placebo were given to 10 healthy females, followed by 0.5 g/kg ethanol or placebo 1 hour later. Brake reaction time in a moving vehicle was tested on subjects 30 min after the ethanol dose. Trazodone alone impaired performance on this task and the combination of trazodone and ethanol caused an even greater performance decrement (Baselt, 2001).

A single 100 mg trazodone was given to 30 healthy adults and SFST were administered at 2 hours post-dose. No statistical differences in overall SFST failure rates were observed between the trazodone group and a control group of 10 people given 650 mg of acetaminophen. However, the number of individual impairment clues detected were significantly increased for 100 mg trazodone compared to baseline, and the trazodone group showed a trend for a greater number of overall failure rates for the combined SFST scores. The trazodone group exhibited more impairment clues within the individual tests of the SFTSs, particularly the walk and turn and one leg stand tests (Ip et al., 2013).

Case Reports

Average blood trazodone concentrations of 0.23 mg/L (range 0.06 to 0.72) were detected in 14 drivers stopped for routine survey purposes, while two drivers injured in traffic collisions had blood trazodone concentrations of 0.46 and 0.99 mg/L (Baselt, 2020).

Interactions With Ethanol

The combined effects of trazodone with ethanol have only been studied using low doses of trazodone (50 to 100 mg). A single oral dose of 50 mg trazodone or placebo was administered to 10 healthy females, followed by 0.5 g/kg ethanol or placebo 1 hour later. Performance tests were given at 1.5 and 4 hours post-ethanol dose. Trazodone alone impaired performance on the critical flicker fusion, reaction time, and Maddox wing testing tasks at 4 hours. The combination of trazodone and ethanol caused subjective sedation as well as impaired ocular control, increased sedative activity, impaired reaction time, and impaired total motor movement at 1.5 hours. The combined effects were consistent with potentiation (Baselt, 2001).

A single oral dose of 100 mg trazodone or placebo and 0.5 mL/kg ethanol or placebo were given to six healthy adults. Performance tests were given on four occasions over the next 4 hours. Average peak plasma trazodone concentrations were 1.37 mg/L at 1.3 hours, while average peak blood ethanol concentration was 0.035 percent at 1.5 hours post-ingestion. Trazodone alone

caused a profound depressant effect on critical flicker fusion, choice reaction time, manual dexterity, and subjective sedation. Ethanol enhanced the impairing effects of trazodone on manual dexterity (Baselt, 2001).

A single oral dose of 100 mg trazodone or placebo were given to 24 healthy older adults, followed by 0.5 g/kg ethanol or placebo 1.5 hours later. Performance tests were administered at 2, 3, 4, and 6 hours after the trazodone dose. Trazodone alone impaired performance on reaction time, word list recall, number recall, continuous performance, choice reaction time, critical flicker fusion, body sway and mood self-rating. Ethanol potentiated the impairment observed (Baselt, 2001).

Interactions With Other Drugs

Excessive sedation has been reported with the combined use of low dose trazodone (25 to 75 mg) to treat insomnia associated with fluoxetine (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 66 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 66. DEC program profile of a CNS depressant.

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include behavior like other CNS depressants such as sedation, lack of balance and coordination, and disorientation. Note that pupil size may also be constricted.

References and Recommended Reading

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Z-Drugs: Zolpidem, Zaleplon, Zopiclone, and Eszopiclone

Zolpidem is a white to off-white crystalline powder.

Synonyms

Ambien (zolpidem); Sonata (zaleplon); Imovane (zopiclone); Lunesta (eszopiclone)

Source

Zolpidem is available by prescription and is a Schedule IV controlled substance. Ambien (zolpidem) is available in strengths of 5 mg and 10 mg (white and pink oval tablets, respectively). Ambien CR is an extended-release preparation of zolpidem available in 6.25 mg and 12.5 mg (brown and purple circular tablets, respectively). Generic zolpidem is also available in the above formulations. Sonata contains zaleplon (5 or 10 mg capsules). Imovane contains zopiclone (7.5 mg tablets) and is no longer commercially available in the United States. Zopiclone's active stereoisomer, Lunesta (eszopiclone) is available in 1 mg, 2 mg, and 3 mg tablets.

Drug Class

Non-benzodiazepine sedative-hypnotic; CNS depressant; sleep aid; $GABA_A$ agonizing imidazopyridine

Uses

Clinical

Zolpidem is a non-benzodiazepine hypnotic used in short-term treatment (up to 4 weeks) of insomnia. Zaleplon, zopiclone and eszopiclone also are reported for the treatment of insomnia.

Non-Clinical

People may misuse these drugs to self-treat sleep disorders and for their sedating effects.

Potency, Purity, and Dose

Recommended zolpidem dose is 5 to 10 mg immediately before bedtime. Recommended nighttime zaleplon, zopiclone and eszopiclone doses are 5 to 20 mg, 3.75 to 15 mg, and 1 to 3 mg, respectively.

Route of Administration

Oral

Pharmacodynamics

While zolpidem has a chemical structure unrelated to benzodiazepines, it is a $GABA_A$ receptor agonist and shares some of the pharmacological properties of benzodiazepines. Zolpidem preferentially binds to receptors containing an α1 subunit (also known as BZ1- or ω1-receptor subtypes). Zolpidem shortens sleep latency and prolongs total sleep time in patients with insomnia but has little effect on the stages of sleep in normal subjects. It also has weak anticonvulsant properties. Zaleplon binds preferentially to α1, but also to α2 and α3; zopiclone

binds equally to α1 and α2; and eszopiclone has similar affinity for α1, α2, α3, and α5 receptor subunits.

Pharmacokinetics

Zolpidem is absorbed readily from the gastrointestinal tract in its immediate-release preparation. First-pass hepatic metabolism results in an oral bioavailability of 70 percent, and 92.5 percent is bound in plasma. Immediate-release zolpidem has a short elimination half-life (2.5 to 2.6 hours), which is reduced in children (~ 1.4 hours) and increased in older adults (~ 2.8 hours) and patients with hepatic cirrhosis (~ 9.9 hours). Peak plasma concentrations are detected at 1.5 to 2.5 hours. Peak concentrations are decreased with food and increased in patients with hepatic insufficiency. Zaleplon has a bioavailability of 30 percent and has a shorter half-life (0.8 to 1.2 hours) compared to zolpidem. Zopiclone has a longer half-life (3.5 to 6.5 hours) compared to zolpidem. Eszopiclone also has a longer half-life than zolpidem (6 hours in healthy adults, ~ 9 hours in older adults).

Blood to Plasma Concentration Ratio

Zolpidem: 0.6 to 0.8

Zaleplon: 1.0

Zopiclone: 1.0

Eszopiclone 0.8

Interpretation of Blood Concentrations

Single doses of 5 mg zolpidem resulted in average peak concentrations of 60 ng/mL at 1.6 hours; 10 mg produced 120 ng/mL at 1.6 hours; 15 mg produced 200 ng/mL at 1.5 hours; and 20 mg produced 230 ng/mL at 2.1 hours. Single oral doses of 5 or 10 mg zolpidem given to 45 healthy adults resulted in average peak plasma zolpidem concentrations of 59 ng/mL and 121 ng/mL, respectively (PDR, 2021).

A single oral dose of 5 mg zaleplon given to 23 healthy subjects resulted in an average peak serum zaleplon concentration of 15 ng/mL at 0.8 hours, declining to < 3 ng/mL by 4 hours. A single oral dose of 15 mg zopiclone given to 12 healthy adults resulted in an average peak plasma concentration of 131 ng/mL at 1.6 hours. A single oral dose of 2 mg and 3 mg of eszopiclone given to 39 to 40 healthy adults resulted in average peak plasma concentrations of 25 ng/mL and 43 ng/mL, respectively, at 1 hour (Baselt, 2001).

OF(S) to Blood Concentration Ratio

Zolpidem: average 0.43 (*n*=21; median 0.28; range 0.051 to 1.8) (Langel et al., 2014)

Zopiclone: average 2.5 (*n*=6; median 2.4; range 1.3 to 4.7) (Langel et al., 2014)

Interpretation of OF(S) Test Results

Zolpidem pKa of 6.2; zopiclone 6.7; eszopiclone 6.89

Zolpidem was detected in a random oral fluid sample at a concentration of 51 ng/mL (Smink et al., 2006).

General Effects

The pharmacological effects of zolpidem, zaleplon, zopiclone and eszopiclone depend on the dose, experience of the user, and tolerance. Table 67 provides a range of effects, including side effects that subjects may experience. In general, these effects are more common and intensified when higher than therapeutic doses are consumed.

Table 67. Physiological, motor, and cognitive side effects of z-drugs

Physiological	Motor (behavioral)	Cognitive
• Nausea • Sedation • Ataxia	• Dizziness • Lightheadedness • Confusion • Slow and slurred speech • Slow reflexes • Ataxia	• Amnesia • Memory impairment • Lack of concentration

Other adverse effects may include somnolence, vertigo, headache, fatigue, cognitive deficits, and impairment of consciousness ranging from somnolence to light coma. Infrequently reported side effects include agitation, depressive syndrome, detachment, nightmares, hallucination, leg cramp, paresthesia, speech disorder, double vision, dry mouth, and diarrhea. Hangover effects are unlikely with zolpidem, although morning-after anterograde amnesia may occur. The Food and Drug Administration responded to reports of complex sleep behaviors after zolpidem use, including sleep-walking and sleep-driving by requiring a boxed warning that these behaviors may results after zolpidem use and cause injury or death (Poceta, 2011). In overdose, patients mainly suffer somnolence and drowsiness, pinpoint pupils, respiratory depression, and in extreme cases, coma, and respiratory failure (Baselt, 2020; DeClerk & Bissebe, 1997; Garnier et al., 1994; Hindmarch et al., 2001; Isawa et al., 2000; Lheureux et al., 1990; Logan & Couper, 2001; Mattila et al., 1998; PDR, 2021; Rush, 1998; Troy et al., 2000).

Duration of Effects

Following 10 to 20 mg oral doses of zolpidem, effects can last up to 4 to 5 hours (dose-dependent). There are generally no residual effects the morning after a nighttime dose of zolpidem. Sedation may extend for 8 to 16 hours following intoxication. Zaleplon has a more rapid onset and shorter duration of effects compared to zolpidem, while zopiclone and eszopiclone have longer duration of effects.

Tolerance, Dependence, and Withdrawal Effects

Tolerance and dependency are not typically detected after 4 weeks of therapeutic use; however, tolerance may develop with chronic use. There is some evidence of tolerance and physical dependency observed with chronic administration of zolpidem in animal models. There is no reliable data documenting the occurrence of withdrawal symptoms following discontinuation of zolpidem, but evidence of fatigue, nausea/vomiting, flushing, lightheadedness, stomach cramps, panic attack, nervousness, and rebound insomnia may constitute a withdrawal syndrome (PDR, 2021).

Driving-Related Studies

Laboratory Studies

In laboratory studies, single oral doses of zolpidem (5 to 30 mg) have been shown to cause significant impairment of psychomotor functions for the first 4 to 5 hours following ingestion but is relatively free of residual effects the morning after nighttime dosing (10 hours post-dose). Single oral doses of zaleplon (10 to 20 mg) have been shown to cause significant impairment of psychomotor abilities for the first 1 to 2 hours following ingestion but have not been shown to cause impairment or residual sedation 3 hours or more post-dose. Single oral doses of zopiclone (2.5 to 10 mg) have been shown to cause significant impairment of psychomotor performance for up to 5 hours post-dose, with some residual impairment still observable at 10 or more hours post-dose (Baselt, 2001).

On-the-Road Driving Studies

Within the first 4 to 5 hours, zolpidem can produce significantly impaired coordinative, reactive, and cognitive skills following single oral doses of 10 to 20 mg. However, no significant residual adverse effects were observed during a 1.5-hour driving test on a rural road, 10 to 12 hours after zolpidem administration (Baselt, 2001).

A single oral dose of 10 mg or 20 mg zaleplon, or placebo, was given to 28 healthy adults at bedtime or after 5 hours of sleep. Five hours later, subjects drove a 100 km highway circuit at constant speed and steady lateral position. Zaleplon did not cause significant adverse effects at either 5 or 10 hours post dosing, at either dose (Baselt, 2001).

In a two-part controlled, crossover study, a single oral dose of 10 mg zaleplon, 7.5 mg zopiclone, and placebo were given to 30 healthy adults. Testing included a highway driving test, laboratory tests (word learning, critical tracking, divided attention), and subjective assessments of sleep, mood and driving ability. Highway driving began 10 hours after drug intake. Zaleplon's residual effects did not differ significantly from those of placebo in any test; however, zopiclone had significant residual effects on driving, divided attention, and memory at 10 hours post-dose (Vermeeren et al., 2002).

Case reports: In five reported cases of driving impairment in which zolpidem was the only drug detected, blood concentrations of zolpidem ranged from 80 to 1,400 ng/mL (average 650 ng/mL). Symptoms and observed behavior included erratic driving (weaving, lane travel), slow and slurred speech, longer reaction times, dazed appearance, disorientation, confusion, loss of balance and coordination, loss of short-term memory, blacking out, somnolence, dilated pupils, double vision, poor performance on field sobriety tests, poor attention, and an inability to stand or walk unassisted (Logan & Couper, 2000). In another six reported cases of driving under the influence of zolpidem, blood concentrations ranged from 100 to 730 ng/mL (average 310 ng/mL). The subjects were involved in automobile crashes or were seen to have driven erratically, and symptoms included slow and slurred speech, ataxia, unsteady gait, confusion, and disorientation (Meeker & Baselt, 1996).

An average blood zolpidem concentration of 310 ng/mL was detected in 148 impaired driving subjects, while an average blood zopiclone concentration of 99 ng/mL was found in 111 drivers (Jones et al., 2007). In five impaired driving cases, an average blood zaleplon concentration of 100 ng/mL was detected (Baselt, 2020).

Interactions With Ethanol

Twenty-four healthy subjects received a single oral dose of either 10 or 15 mg zolpidem, followed by an ethanol dose sufficient to produce a blood ethanol concentration of .08 g/dL. Performance (divided attention, information processing, immediate memory, and sustained attention) was tested at 45 minutes, 130 minutes, and 230 minutes post-treatment. Performance on all tasks was significantly impaired with ethanol alone, zolpidem alone, and the combination of the two drugs at 45 minutes. The combination of ethanol and zolpidem still impaired divided attention at 230 minutes. In general, additive effects of ethanol were detected with 10 mg zolpidem but not with 15 mg zolpidem. Ethanol produced an increase in self-reported sedation/intoxication, dysphoria, and negative drug effects of zolpidem (Wilkinson, 1995; Wilkinson, 1998).

In premarketing studies, zaleplon potentiated the CNS effects of ethanol for at least 2 to 4 hours (PDR, 2020).

Interactions With Other Drugs

Imipramine has an additive effect of decreased alertness; chlorpromazine has an additive effect of decreased alertness and decreased psychomotor performance; ritonavir decreases clearance though inhibiting cytochrome P450 CYP3A hydroxylation; ketoconazole also decreases clearance; and flumazenil is an effective and therapeutic pharmacodynamic antagonist. Other CNS depressant drugs may potentiate the effects of zolpidem. Zopiclone has additional performance decrements when concurrently taken with ethanol, carbamazepine, and diazepam (PDR, 2021).

Drug Evaluation and Classification Program Category

CNS depressant

Drug Evaluation and Classification Program Profile

The indicators in Table 68 are the most consistent with the category; however, there may be variation due to individual reaction, dose taken, and drug interactions.

Table 68. DEC program profile of a CNS depressant

HGN	VGN	LOC	Pupil size	Reaction to light	Pulse rate	Blood pressure	Body temp
present	present*	present	normal	slow	down	down	normal

HGN: horizontal gaze nystagmus; VGN: vertical gaze nystagmus; LOC: lack of convergence.
* present in high doses.

Other characteristic indicators may include slow and slurred speech, and somnolence.

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Drug Combinations

Drug combinations are commonly encountered in suspected impaired driving cases, because of two or more medications being prescribed and/or a subject self-administering medications and/or drugs. In combination, medication and drug effect profiles can differ depending on the specific combination, whether one agent is taken in a larger dose than the other, or when one agent is taken before another. The following sections briefly outline those studies that have researched the effects of specific drug and drug class combinations.

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Drug Combination 1: Ethanol and Cannabis

A commonly encountered drug combination in arrested impaired driving subjects is ethanol and Δ^9-tetrahydrocannabinol (Δ^9-THC)/cannabis. While ethanol is a CNS depressant, cannabis has a spectrum of behavioral effects preventing its classification as solely a stimulant, sedative, or hallucinogen. While low doses of ethanol and cannabis may not affect psychomotor function when used alone, they may still impair performance when used together. The combined use of ethanol and cannabis in occasional cannabis users has repeatedly been shown to increase the magnitude of cognitive and motor impairments in an additive manner (Ramaekers, 2011). Ethanol and cannabis share many behavioral effects such as euphoria, analgesia, sedation, and cognitive and motor dysfunction. Therefore, a combination of the two in occasional cannabis users may additively alter the magnitude of cognitive and motor impairment.

In a study of 22 healthy volunteers receiving low to moderate doses of Δ^9-THC (1.24 or 2.64%), subjects who consumed alcohol (0.35 or 0.70 g/kg) experienced marijuana-like side effects more quickly, reported more episodes of euphoria, and had higher plasma Δ^9-THC concentrations as compared to the use of placebo ethanol (Lukas & Orozco, 2001). The research suggests that alcohol "may increase the absorption of Δ^9-THC resulting in an increase in the positive subjective mood effects of smoked marijuana and contributing to the popularity of the drug combination."

Hartman et al. (2016a) also determined that ethanol increased Δ^9-THC concentrations when the two drugs were consumed concurrently. A single inhaled dose of 2.9 percent Δ^9-THC (low), 6.7 percent Δ^9-THC (high), or placebo was given to 18 occasional cannabis users via a vaporizer, over 10 min *ad libitum*, either with or without a low-dose of ethanol (.05 g/dL). The median maximum plasma concentration, at 0.17 hours, was 38.2 ng/mL (range, 11.4 to 137) for the 2.9 or 6.7 percent Δ^9-THC dose in the absence of ethanol and 47.9 ng/mL (range, 13.0 to 210) in the presence of ethanol. Another key finding was that the alcohol T_{max} occurred significantly later when Δ^9-THC and alcohol were co-administered, as opposed to alcohol alone, consistent with Δ^9-THC slowing gastric emptying, although this was not directly tested. While many toxicologists back-extrapolate the alcohol concentration to the time of a crash or enforcement stop, this standard calculation may not be accurate when cannabis is co-ingested with alcohol. Because alcohol is primarily absorbed from the small intestine, T_{max} was found to be delayed when cannabis was present.

In the same study, subjects drove a simulator course especially constructed to be sensitive to the effects of cannabis for 45 minutes, 0.5 to 1.3 hours post-inhalation, with a focus on standard deviations of lateral position (SDLP,[23], lane weave), steering angle, lane departures/minute, and maximum lateral acceleration (Hartman et al., 2015). Cannabis and alcohol were both shown to increase SDLP. Blood Δ^9-THC concentrations of 8.2 and 13.1 ng/mL during driving increased SDLP like 0.05 and 0.08g/210L breath ethanol concentrations (BrAC), respectively. Note that these Δ^9-THC concentrations were present at the time of driving, 0.5 to 1.3 hours post-inhalation, and were not the expected Δ^9-THC concentrations at times when blood is typically collected in real-life driving incidents, 1.4 to 4 hours after a crash or traffic stop (Huestis & Smith, 2018). Overall, the cannabis and alcohol SDLP effects were additive rather than synergistic.

[23] While there may be statistically significant changes in performance with measures such as SDLP, there may not be meaningful differences when related to real-world driving.

Cannabis effects on driving longitudinal control with and without alcohol, relative to Δ^9-THC blood concentrations, were also evaluated (Hartman et al., 2016). Occasional cannabis smokers drank placebo or low-dose alcohol, and inhaled 500 mg placebo, 2.9 percent, or 6.7 percent Δ^9-THC vaporized cannabis over 10 minutes *ad libitum* in separate sessions. After cannabis smoking, participants performed simulated drives at the National Advanced Driving Simulator (located at the University of Iowa) 0.5 to 1.3 hours post-inhalation. Average speed relative to the road limit, standard deviation (SD) of speed, percent time spent > 10 percent above/below the speed limit, longitudinal acceleration, and ability to maintain headway relative to a lead vehicle were studied with blood Δ^9-THC and BrAC. In 18 completing drivers, Δ^9-THC was associated with decreased average speed, increased percent of low speed and increased average following distance during headway maintenance. BrAC was associated with increased SD speed and increased percent speed high, whereas Δ^9-THC was not. The data also suggested that cannabis mitigated drivers' tendency to drive faster with alcohol. Cannabis was associated with slower driving and greater headway, suggesting a possible awareness of impairment and attempt to compensate. People who consume concurrent cannabis and alcohol may experience more elevated or rising alcohol concentrations longer than with alcohol alone, thereby increasing the driving risk.

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Drug Combination 2: Opioid and Stimulant

Heroin and cocaine taken together, a "speedball," is a common opioid and stimulant combination administered by drug users. The combination is often taken to augment the euphoric high felt and/or reduce the crash of cocaine, taking the "edge" off negative effects. Heroin and amphetamines are another common opioid and stimulant combination. *d*-Amphetamine is known to enhance the analgesic effect of morphine and reduce side effects compared to morphine alone (e.g., less sedation, respiratory depression, and hypotension). In many parts of the country, fentanyl has replaced heroin in cases where opioids and stimulants are used simultaneously.

Single doses of intravenous cocaine (0, 8, 16, 32 mg/70kg) and morphine (0, 5, 10 mg/70kg), alone and in combination, were given to nine healthy, non-dependent cocaine-heroin users (Foltin, 1992). Both cocaine and morphine alone significantly increased peak heart rate and systolic and diastolic blood pressure. Peak cardiovascular effects occurred within 6 minutes of drug administration and as expected, the cardiovascular effects of cocaine were larger and longer in duration than for morphine. When both drugs were administered together, all users described an initial stimulant rush of cocaine, followed by a prolonged opioid high. The ratings for this 'high' were greater and of longer duration than that experienced by either drug alone. When increasing doses of cocaine were administered with morphine, users felt less sedation compared to the same morphine dose without cocaine. Neither cocaine nor morphine altered the plasma concentration observed with the other drug. The overall results suggested that in combination, cocaine and morphine produced a profile of both opioid and stimulant effects instead of an alteration in the effects produced by either drug alone.

Single intramuscular doses of morphine sulfate (0, 12.5, 20, and 32 mg/70 kg) and *d*-amphetamine sulfate (0, 12.5, 20, and 32 mg/70 kg) were administered to 10 non-dependent substance users (Jasinski, 1986). The drugs were also administered to subjects in combination, in equal doses of either 0, 7.8, 12.5, or 20 mg/70 kg. Both drugs alone increased the subjective feeling of euphoria, and together the drugs produced greater euphoria than that produced by either drug alone. *d*-Amphetamine also produced less "skin itching" and "turning of the stomach" than did morphine but produced more subjective feelings of "nervousness" and "drive." Unlike with morphine, *d*-amphetamine was not associated with vomiting, "nodding," "sleepiness," scratching, or "coasting." Many of these subjective feelings were greater with the drug combination compared to either morphine or *d*-amphetamine alone. *d*-Amphetamine alone produced pupillary dilation, increased respiratory rate, elevated body temp, elevated systolic and diastolic blood pressure, increased pulse rate in low doses, and reflex bradycardia with increasing doses. Morphine alone produced constricted pupils and lowered respiratory rate, but produced no significant effects on body temperature, pulse rate, or systolic and diastolic blood pressure. Like the previously described study, less sedation was recorded with the morphine-amphetamine combination than with morphine alone. Other physiological effects were also mutually antagonized when the two drugs were taken together. *d*-Amphetamine antagonized the pupillary constriction and respiratory depression of morphine, while morphine antagonized the elevation in body temperature and the reflex bradycardia produced by *d*-amphetamine. While morphine had little effect on normal body temperature itself, it was able to block the thermogenic effect of *d*-amphetamine. In contrast, morphine had little effect on the elevated blood pressure produced by *d*-amphetamine.

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Drug Combination 3: Opioid and Depressant

Opioids and benzodiazepines are both classes of CNS depressants with significant respiratory depression occurring through two different pharmacological mechanisms. When taken individually, together, or in combination with ethanol (another CNS depressant), these agents can produce marked sedation, loss of consciousness, and coma. In combination with ethanol, increased CNS depression occurs with additional pharmacokinetic and pharmacodynamic interactions between opioids and benzodiazepines (Jann et al., 2014).

Among opioid users, the risk of overdose increases markedly when other CNS depressants (e.g., benzodiazepines, muscle relaxants, gabapentinoids) are co-prescribed (Gomes et al., 2017; Park et al., 2015). The risk of overdose death goes up by almost a factor of four in people who use both opioids and benzodiazepines (Park et al., 2015). Although gabapentinoids are frequently used to avoid escalating opioid doses, the use of gabapentin with opioids doubles the risk of fatal overdose as compared with the use of opioids alone (Gomes et al., 2017). These examples illustrate the synergistic effect of opioids and other CNS depressants in producing sedation and respiratory depression.

In a study on the drug-drug interactions between opioids and benzodiazepines, using physiologically based pharmacokinetic modeling and simulation, Ji et al., (2019) surmised that pharmacodynamics may play a more important role than pharmacokinetics in causing drug-drug interactions between opioids and benzodiazepines.

Compared to buprenorphine alone (average dose of 11.1 mg), the addition of 40 mg diazepam increased the following: strength of drug effect, sedation, liking of drug effect, over 6 hours post dose; and increased visual reaction time (a measure of sensory-motor performance), digit symbol substitution (decrease in coding skills), and cancellation time (measure of focused attention; Gudin et al., 2015).

Eight healthy subjects received a single oral dose of 1 mg alprazolam and 10 mg/325 mg hydrocodone/acetaminophen or placebo (Brown et al., 2018). Subject performance was tested using a driving simulator in various scenarios (urban, rural, straight, curvy, different speed limits, day- and night-time). Driving started 3 hours post dose. A statistical analysis failed to reveal significant interactions between these modest alprazolam and hydrocodone doses and the authors found little evidence for drug interactions. Although minor effects were observed, the effects of the opioid were much less pronounced than the effect of the benzodiazepine.

The coadministration of diazepam, to methadone-maintained patients, has been demonstrated to increase the "high" and users' reports of liking (Horsfall & Sprague, 2017; Spiga et al., 2001). This is likely to be related to either the enhancement of μ_1-opioid receptors or through the potentiation of the dopaminergic effects of the opioids within the nucleus accumbens.

With respect to the use of ethanol and opioids, several studies have shown that concurrent use of ethanol increases the maximum plasma concentration of certain opioids and decreases the time to peak concentrations (i.e., increase C_{max} and decrease T_{max}), per Gudin et al. (2015). In 14 subjects, 0.3 g/kg ethanol or 10 mg oxycodone, or a combination of both, were studied. Subjective effects were measured at approximate peak concentrations of both drugs. The combination of ethanol and oxycodone significantly increased the following subjective feelings – "spaced out," "difficultly concentrating," "dreamy," "floating," "pleasant bodily sensations,"

"not in control of thought," "like drug," and "take again." These effects were larger than those felt with ethanol or oxycodone alone and were significantly different from placebo.

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Drug Combination 4: Stimulant and Depressant

People frequently use benzodiazepines (e.g., alprazolam) to lessen the impact of agitation, insomnia, and withdrawal symptoms of stimulant drugs such as methamphetamine and cocaine.

Studies have demonstrated neurobiological disturbances to central $GABA_A$ activity following chronic stimulant use, and that positive modulation of $GABA_A$ receptors attenuate the neurochemical and behavioral response to stimulant drugs such as methamphetamine. A history of cocaine use also modified the anxiolytic and locomotor response to benzodiazepines in rodents, and subject ratings following lorazepam administration in a clinical study. $GABA_A$ receptor-positive modulation by benzodiazepines attenuate the dopaminergic response to stimulant drugs, which is believed to play a critical role in their abuse-related effects. A study in rats showed that acute lorazepam administration attenuated cocaine-induced increases in dopamine in the striatum.

In humans, concurrent administration of alprazolam attenuated the discriminative-stimulus and some of the positive subject-rated effects of d-amphetamine in non-stimulant dependent subjects.

The effects of concurrent use of methamphetamine and alprazolam were studied among eight stimulant-dependent subjects during an inpatient study in which ascending intranasal doses of methamphetamine (0, 5, 10, 20, and 30 mg) were administered after 4 days of alprazolam extended-release maintenance (0 and 1 mg/day). Intranasal methamphetamine produced prototypical effects such as elevated cardiovascular signs and increased positive subjective ratings. Alprazolam extended-release produced small, but orderly, reductions in some of the subjective effects of methamphetamine. It also reduced the increase in cardiovascular signs (Lile et al., 2015).

There is a significant effect of methamphetamine on both systolic and diastolic blood pressure and heart rate. Alprazolam XR reduced heart rate and systolic blood pressure at the 10 mg dose of methamphetamine. There was no effect of methamphetamine on oral temperature. Methamphetamine significantly increased the digit symbol substitution score (increased number of attempts and increased correct attempts). Alprazolam significantly decreased the digit symbol substitution score for methamphetamine. A significant main effect of methamphetamine was observed on the drug-effect questionnaire. Methamphetamine generally increased ratings in a dose-dependent manner. Alprazolam reduced ratings for effects such as “any effect,” “stimulated,” “rush,” and “high.” Alprazolam also reduced scores for nervous-anxious and shaky-jittery (Lile et al., 2015).

Hoiseth et al. (2014) aimed to compare the impairment among apprehended drivers in whom a combination of amphetamines (methamphetamine and/or amphetamine) was detected, as judged by a clinical test of impairment (CTI) performed by a trained physician. The study compared amphetamines-only results, benzodiazepine-only cases, and cases containing a combination of the two drug classes. No other drugs were detected in these groups. Significantly more drivers were judged as impaired in the combined group (n=777), compared with both the amphetamines alone (n=267, p<0.001) and benzodiazepine alone (n=153, p=0.008). The percentage of drivers judged as impaired (mildly, moderately, or considerably) was 75 percent in the benzodiazepine-only group, 64 percent in the amphetamines-only group, and 84 percent among cases where benzodiazepines and amphetamines were detected in combination. The concentrations of the drugs were higher to significantly higher in the single drug groups, compared with the combined group. The authors concluded that their study demonstrated that during real-life driving, those

influenced by both amphetamines and benzodiazepines are more impaired, as judged by the CTI, than with those influenced by only one of the drug classes.

References and Recommended Reading

Høiseth, G., Andås, H., Bachs, L., & Mørland, J. (2014). Impairment due to amphetamines and benzodiazepines, alone and in combination. *Drug and Alcohol Dependence*, *145*:174-179.

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