

= Amphetamine =

Amphetamine ( contracted from alpha ? methylphenethylamine ) is a potent central nervous system ( CNS ) stimulant that is used in the treatment of attention deficit hyperactivity disorder ( ADHD ) , narcolepsy , and obesity . Amphetamine was discovered in 1887 and exists as two enantiomers : levoamphetamine and dextroamphetamine . Amphetamine properly refers to a specific chemical , the racemic free base , which is equal parts of the two enantiomers , levoamphetamine and dextroamphetamine , in their pure amine forms . However , the term is frequently used informally to refer to any combination of the enantiomers , or to either of them alone . Historically , it has been used to treat nasal congestion and depression . Amphetamine is also used as an athletic performance enhancer and cognitive enhancer , and recreationally as an aphrodisiac and euphoriant . It is a prescription drug in many countries , and unauthorized possession and distribution of amphetamine are often tightly controlled due to the significant health risks associated with recreational use .

The first pharmaceutical amphetamine was Benzedrine , a brand which was used to treat a variety of conditions . Currently , pharmaceutical amphetamine is prescribed as racemic amphetamine , Adderall , dextroamphetamine , or the inactive prodrug lisdexamfetamine . Amphetamine , through activation of a trace amine receptor , increases monoamine and excitatory neurotransmitter activity in the brain , with its most pronounced effects targeting the catecholamine neurotransmitters norepinephrine and dopamine .

At therapeutic doses , amphetamine causes emotional and cognitive effects such as euphoria , change in desire for sex , increased wakefulness , and improved cognitive control . It induces physical effects such as decreased reaction time , fatigue resistance , and increased muscle strength . Larger doses of amphetamine may impair cognitive function and induce rapid muscle breakdown . Drug addiction is a serious risk with large recreational doses but is unlikely to arise from typical long @-@ term medical use at therapeutic doses . Very high doses can result in psychosis ( e.g. , delusions and paranoia ) which rarely occurs at therapeutic doses even during long @-@ term use . Recreational doses are generally much larger than prescribed therapeutic doses and carry a far greater risk of serious side effects .

Amphetamine belongs to the phenethylamine class . It is also the parent compound of its own structural class , the substituted amphetamines , which includes prominent substances such as bupropion , cathinone , MDMA ( ecstasy ) , and methamphetamine . As a member of the phenethylamine class , amphetamine is also chemically related to the naturally occurring trace amine neuromodulators , specifically phenethylamine and N @-@ methylphenethylamine , both of which are produced within the human body . Phenethylamine is the parent compound of amphetamine , while N @-@ methylphenethylamine is a constitutional isomer that differs only in the placement of the methyl group .

= = Uses = =

= = = Medical = = =

Amphetamine is used to treat attention deficit hyperactivity disorder ( ADHD ) , narcolepsy ( a sleep disorder ) , and obesity , and is sometimes prescribed off @-@ label for its past medical indications , such as depression . Long @-@ term amphetamine exposure at sufficiently high doses in some animal species is known to produce abnormal dopamine system development or nerve damage , but , in humans with ADHD , pharmaceutical amphetamines appear to improve brain development and nerve growth . Reviews of magnetic resonance imaging ( MRI ) studies suggest that long @-@ term treatment with amphetamine decreases abnormalities in brain structure and function found in subjects with ADHD , and improves function in several parts of the brain , such as the right caudate nucleus of the basal ganglia .

Reviews of clinical stimulant research have established the safety and effectiveness of long @-@

term amphetamine use for ADHD . Controlled trials spanning two years have demonstrated treatment effectiveness and safety . One review highlighted a nine @-@ month randomized controlled trial in children with ADHD that found an average increase of 4 @.@ 5 IQ points , continued increases in attention , and continued decreases in disruptive behaviors and hyperactivity .

Current models of ADHD suggest that it is associated with functional impairments in some of the brain 's neurotransmitter systems ; these functional impairments involve impaired dopamine neurotransmission in the mesocorticolimbic projection and norepinephrine neurotransmission in the locus coeruleus and prefrontal cortex . Psychostimulants like methylphenidate and amphetamine are effective in treating ADHD because they increase neurotransmitter activity in these systems . Approximately 80 % of those who use these stimulants see improvements in ADHD symptoms . Children with ADHD who use stimulant medications generally have better relationships with peers and family members , perform better in school , are less distractible and impulsive , and have longer attention spans . The Cochrane Collaboration 's reviews on the treatment of ADHD in children , adolescents , and adults with pharmaceutical amphetamines stated that while these drugs improve short @-@ term symptoms , they have higher discontinuation rates than non @-@ stimulant medications due to their adverse side effects . A Cochrane Collaboration review on the treatment of ADHD in children with tic disorders such as Tourette syndrome indicated that stimulants in general do not make tics worse , but high doses of dextroamphetamine could exacerbate tics in some individuals .

= = = Enhancing performance = = =

In 2015 , a systematic review and a meta @-@ analysis of high quality clinical trials found that , when used at low ( therapeutic ) doses , amphetamine produces modest , unambiguous improvements in cognition , including working memory , episodic memory , inhibitory control and some aspects of attention , in normal healthy adults ; the cognition @-@ enhancing effects of amphetamine are known to occur through its indirect activation of both dopamine receptor D1 and adrenoceptor ?2 in the prefrontal cortex . A systematic review from 2014 noted that low doses of amphetamine also improve memory consolidation , in turn leading to improved recall of information . Therapeutic doses of amphetamine also enhance cortical network efficiency , an effect which mediates improvements in working memory in all individuals . Amphetamine and other ADHD stimulants also improve task saliency ( motivation to perform a task ) and increase arousal ( wakefulness ) , in turn promoting goal @-@ directed behavior . Stimulants such as amphetamine can improve performance on difficult and boring tasks and are used by some students as a study and test @-@ taking aid . Based upon studies of self @-@ reported illicit stimulant use , 5 ? 35 % of college students use diverted ADHD stimulants , which are primarily used for performance enhancement rather than as recreational drugs . However , high amphetamine doses that are above the therapeutic range can interfere with working memory and other aspects of cognitive control .

Amphetamine is used by some athletes for its psychological and athletic performance @-@ enhancing effects , such as increased endurance and alertness ; however , non @-@ medical amphetamine use is prohibited at sporting events that are regulated by collegiate , national , and international anti @-@ doping agencies . In healthy people at oral therapeutic doses , amphetamine has been shown to increase muscle strength , acceleration , athletic performance in anaerobic conditions , and endurance ( i.e. , it delays the onset of fatigue ) , while improving reaction time . Amphetamine improves endurance and reaction time primarily through reuptake inhibition and effluxion of dopamine in the central nervous system . Amphetamine and other dopaminergic drugs also increase power output at fixed levels of perceived exertion by overriding a " safety switch " that allows the core temperature limit to increase in order to access a reserve capacity that is normally off @-@ limits . At therapeutic doses , the adverse effects of amphetamine do not impede athletic performance ; however , at much higher doses , amphetamine can induce effects that severely impair performance , such as rapid muscle breakdown and elevated body temperature .

## = = Contraindications = =

According to the International Programme on Chemical Safety ( IPCS ) and United States Food and Drug Administration ( USFDA ) , amphetamine is contraindicated in people with a history of drug abuse , heart disease , severe agitation , or severe anxiety . It is also contraindicated in people currently experiencing arteriosclerosis ( hardening of the arteries ) , glaucoma ( increased eye pressure ) , hyperthyroidism ( excessive production of thyroid hormone ) , or moderate to severe hypertension . People who have experienced allergic reactions to other stimulants in the past or who are taking monoamine oxidase inhibitors ( MAOIs ) are advised not to take amphetamine , although safe concurrent use of amphetamine and monoamine oxidase inhibitors has been documented . These agencies also state that anyone with anorexia nervosa , bipolar disorder , depression , hypertension , liver or kidney problems , mania , psychosis , Raynaud 's phenomenon , seizures , thyroid problems , tics , or Tourette syndrome should monitor their symptoms while taking amphetamine . Evidence from human studies indicates that therapeutic amphetamine use does not cause developmental abnormalities in the fetus or newborns ( i.e. , it is not a human teratogen ) , but amphetamine abuse does pose risks to the fetus . Amphetamine has also been shown to pass into breast milk , so the IPCS and USFDA advise mothers to avoid breastfeeding when using it . Due to the potential for reversible growth impairments , the USFDA advises monitoring the height and weight of children and adolescents prescribed an amphetamine pharmaceutical .

## = = Side effects = =

The side effects of amphetamine are varied , and the amount of amphetamine used is the primary factor in determining the likelihood and severity of side effects . Amphetamine products such as Adderall , Dexedrine , and their generic equivalents are currently approved by the USFDA for long @-@ term therapeutic use . Recreational use of amphetamine generally involves much larger doses , which have a greater risk of serious side effects than dosages used for therapeutic reasons .

## = = = Physical = = =

At normal therapeutic doses , the physical side effects of amphetamine vary widely by age and from person to person . Cardiovascular side effects can include hypertension or hypotension from a vasovagal response , Raynaud 's phenomenon ( reduced blood flow to extremities ) , and tachycardia ( increased heart rate ) . Sexual side effects in males may include erectile dysfunction , frequent erections , or prolonged erections . Abdominal side effects may include abdominal pain , appetite loss , nausea , and weight loss . Other potential side effects include blurred vision , dry mouth , excessive grinding of the teeth , nosebleed , profuse sweating , rhinitis medicamentosa ( drug @-@ induced nasal congestion ) , reduced seizure threshold , and tics ( a type of movement disorder ) . Dangerous physical side effects are rare at typical pharmaceutical doses .

Amphetamine stimulates the medullary respiratory centers , producing faster and deeper breaths . In a normal person at therapeutic doses , this effect is usually not noticeable , but when respiration is already compromised , it may be evident . Amphetamine also induces contraction in the urinary bladder sphincter , the muscle which controls urination , which can result in difficulty urinating . This effect can be useful in treating bed wetting and loss of bladder control . The effects of amphetamine on the gastrointestinal tract are unpredictable . If intestinal activity is high , amphetamine may reduce gastrointestinal motility ( the rate at which content moves through the digestive system ) ; however , amphetamine may increase motility when the smooth muscle of the tract is relaxed . Amphetamine also has a slight analgesic effect and can enhance the pain relieving effects of opioids .

USFDA @-@ commissioned studies from 2011 indicate that in children , young adults , and adults there is no association between serious adverse cardiovascular events ( sudden death , heart attack , and stroke ) and the medical use of amphetamine or other ADHD stimulants .

## == Psychological ==

Common psychological effects of therapeutic doses can include increased alertness , apprehension , concentration , decreased sense of fatigue , mood swings ( elated mood followed by mildly depressed mood ) , increased initiative , insomnia or wakefulness , self @-@ confidence , and sociability . Less common side effects include anxiety , change in libido , grandiosity , irritability , repetitive or obsessive behaviors , and restlessness ; these effects depend on the user 's personality and current mental state . Amphetamine psychosis ( e.g. , delusions and paranoia ) can occur in heavy users . Although very rare , this psychosis can also occur at therapeutic doses during long @-@ term therapy . According to the USFDA , " there is no systematic evidence " that stimulants produce aggressive behavior or hostility .

Amphetamine has also been shown to produce a conditioned place preference in humans taking therapeutic doses , meaning that individuals acquire a preference for spending time in places where they have previously used amphetamine .

## == Overdose ==

An amphetamine overdose can lead to many different symptoms , but is rarely fatal with appropriate care . The severity of overdose symptoms increases with dosage and decreases with drug tolerance to amphetamine . Tolerant individuals have been known to take as much as 5 grams of amphetamine in a day , which is roughly 100 times the maximum daily therapeutic dose . Symptoms of a moderate and extremely large overdose are listed below ; fatal amphetamine poisoning usually also involves convulsions and coma . In 2013 , overdose on amphetamine , methamphetamine , and other compounds implicated in an " amphetamine use disorder " resulted in an estimated 3 @,@ 788 deaths worldwide ( 3 @,@ 425 ? 4 @,@ 145 deaths , 95 % confidence ) .

Pathological overactivation of the mesolimbic pathway , a dopamine pathway that connects the ventral tegmental area to the nucleus accumbens , plays a central role in amphetamine addiction . Individuals who frequently overdose on amphetamine during recreational use have a high risk of developing an amphetamine addiction , since repeated overdoses gradually increase the level of accumbal ?FosB , a " molecular switch " and " master control protein " for addiction . Once nucleus accumbens ?FosB is sufficiently overexpressed , it begins to increase the severity of addictive behavior ( i.e. , compulsive drug @-@ seeking ) with further increases in its expression . While there are currently no effective drugs for treating amphetamine addiction , regularly engaging in sustained aerobic exercise appears to reduce the risk of developing such an addiction . Sustained aerobic exercise on a regular basis also appears to be an effective treatment for amphetamine addiction ; exercise therapy improves clinical treatment outcomes and may be used as a combination therapy with cognitive behavioral therapy , which is currently the best clinical treatment available .

## == Addiction ==

Addiction is a serious risk with heavy recreational amphetamine use but is unlikely to arise from typical long @-@ term medical use at therapeutic doses . Drug tolerance develops rapidly in amphetamine abuse ( i.e. , a recreational amphetamine overdose ) , so periods of extended use require increasingly larger doses of the drug in order to achieve the same effect .

## === Biomolecular mechanisms ===

Current models of addiction from chronic drug use involve alterations in gene expression in certain parts of the brain , particularly the nucleus accumbens . The most important transcription factors that produce these alterations are ?FosB , cAMP response element binding protein ( CREB ) , and nuclear factor kappa B ( NF @-@ ?B ) . ?FosB plays a crucial role in the development of drug addictions , since its overexpression in D1 @-@ type medium spiny neurons in the nucleus accumbens is necessary and sufficient for most of the behavioral and neural adaptations that arise

from addiction . Once  $\Delta$ FosB is sufficiently overexpressed , it induces an addictive state that becomes increasingly more severe with further increases in  $\Delta$ FosB expression . It has been implicated in addictions to alcohol , cannabinoids , cocaine , methylphenidate , nicotine , opioids , phencyclidine , propofol , and substituted amphetamines , among others .

$\Delta$ JunD , a transcription factor , and G9a , a histone methyltransferase enzyme , both directly oppose the induction of  $\Delta$ FosB in the nucleus accumbens ( i.e. , they oppose increases in its expression ) . Sufficiently overexpressing  $\Delta$ JunD in the nucleus accumbens with viral vectors can completely block many of the neural and behavioral alterations seen in chronic drug abuse ( i.e. , the alterations mediated by  $\Delta$ FosB ) .  $\Delta$ FosB also plays an important role in regulating behavioral responses to natural rewards , such as palatable food , sex , and exercise . Since both natural rewards and addictive drugs induce expression of  $\Delta$ FosB ( i.e. , they cause the brain to produce more of it ) , chronic acquisition of these rewards can result in a similar pathological state of addiction . Consequently ,  $\Delta$ FosB is the most significant factor involved in both amphetamine addiction and amphetamine @-@ induced sex addictions , which are compulsive sexual behaviors that result from excessive sexual activity and amphetamine use . These sex addictions are associated with a dopamine dysregulation syndrome which occurs in some patients taking dopaminergic drugs .

The effects of amphetamine on gene regulation are both dose- and route @-@ dependent . Most of the research on gene regulation and addiction is based upon animal studies with intravenous amphetamine administration at very high doses . The few studies that have used equivalent ( weight @-@ adjusted ) human therapeutic doses and oral administration show that these changes , if they occur , are relatively minor . This suggests that medical use of amphetamine does not significantly affect gene regulation .

=== Pharmacological treatments ===

As of May 2014 , there is no effective pharmacotherapy for amphetamine addiction . Reviews from 2015 and 2016 indicated that TAAR1 @-@ selective agonists have significant therapeutic potential as a treatment for psychostimulant addictions ; however , as of February 2016 , the only compounds which are known to function as TAAR1 @-@ selective agonists are experimental drugs . Amphetamine addiction is largely mediated through increased activation of dopamine receptors and co @-@ localized NMDA receptors in the nucleus accumbens ; magnesium ions inhibit NMDA receptors by blocking the receptor calcium channel . One review suggested that , based upon animal testing , pathological ( addiction @-@ inducing ) psychostimulant use significantly reduces the level of intracellular magnesium throughout the brain . Supplemental magnesium treatment has been shown to reduce amphetamine self @-@ administration ( i.e. , doses given to oneself ) in humans , but it is not an effective monotherapy for amphetamine addiction .

=== Behavioral treatments ===

Cognitive behavioral therapy is currently the most effective clinical treatment for psychostimulant addictions . Additionally , research on the neurobiological effects of physical exercise suggests that daily aerobic exercise , especially endurance exercise ( e.g. , marathon running ) , prevents the development of drug addiction and is an effective adjunct therapy ( i.e. , a supplemental treatment ) for amphetamine addiction . Exercise leads to better treatment outcomes when used as an adjunct treatment , particularly for psychostimulant addictions . In particular , aerobic exercise decreases psychostimulant self @-@ administration , reduces the reinstatement ( i.e. , relapse ) of drug @-@ seeking , and induces increased dopamine receptor D2 ( DRD2 ) density in the striatum . This is the opposite of pathological stimulant use , which induces decreased striatal DRD2 density . One review noted that exercise may also prevent the development of a drug addiction by altering  $\Delta$ FosB or c @-@ Fos immunoreactivity in the striatum or other parts of the reward system .

=== Dependence and withdrawal ===

According to another Cochrane Collaboration review on withdrawal in individuals who compulsively use amphetamine and methamphetamine , " when chronic heavy users abruptly discontinue amphetamine use , many report a time @-@ limited withdrawal syndrome that occurs within 24 hours of their last dose . " This review noted that withdrawal symptoms in chronic , high @-@ dose users are frequent , occurring in up to 87 @. @ 6 % of cases , and persist for three to four weeks with a marked " crash " phase occurring during the first week . Amphetamine withdrawal symptoms can include anxiety , drug craving , depressed mood , fatigue , increased appetite , increased movement or decreased movement , lack of motivation , sleeplessness or sleepiness , and lucid dreams . The review indicated that withdrawal symptoms are associated with the degree of dependence , suggesting that therapeutic use would result in far milder discontinuation symptoms . Manufacturer prescribing information does not indicate the presence of withdrawal symptoms following discontinuation of amphetamine use after an extended period at therapeutic doses .

= = = Toxicity and psychosis = = =

In rodents and primates , sufficiently high doses of amphetamine cause dopaminergic neurotoxicity , or damage to dopamine neurons , which is characterized by reduced transporter and receptor function . There is no evidence that amphetamine is directly neurotoxic in humans . However , large doses of amphetamine may cause indirect neurotoxicity as a result of increased oxidative stress from reactive oxygen species and autoxidation of dopamine .

A severe amphetamine overdose can result in a stimulant psychosis that may involve a variety of symptoms , such as paranoia and delusions . A Cochrane Collaboration review on treatment for amphetamine , dextroamphetamine , and methamphetamine psychosis states that about 5 ? 15 % of users fail to recover completely . According to the same review , there is at least one trial that shows antipsychotic medications effectively resolve the symptoms of acute amphetamine psychosis . Psychosis very rarely arises from therapeutic use .

= = Interactions = =

Many types of substances are known to interact with amphetamine , resulting in altered drug action or metabolism of amphetamine , the interacting substance , or both . Inhibitors of the enzymes that metabolize amphetamine ( e.g. , CYP2D6 and flavin @-@ containing monooxygenase 3 ) will prolong its elimination half @-@ life , meaning that its effects will last longer . Amphetamine also interacts with MAOIs , particularly monoamine oxidase A inhibitors , since both MAOIs and amphetamine increase plasma catecholamines ( i.e. , norepinephrine and dopamine ) ; therefore , concurrent use of both is dangerous . Amphetamine modulates the activity of most psychoactive drugs . In particular , amphetamine may decrease the effects of sedatives and depressants and increase the effects of stimulants and antidepressants . Amphetamine may also decrease the effects of antihypertensives and antipsychotics due to its effects on blood pressure and dopamine respectively . In general , there is no significant interaction when consuming amphetamine with food , but the pH of gastrointestinal content and urine affects the absorption and excretion of amphetamine , respectively . Acidic substances reduce the absorption of amphetamine and increase urinary excretion , and alkaline substances do the opposite . Due to the effect pH has on absorption , amphetamine also interacts with gastric acid reducers such as proton pump inhibitors and H2 antihistamines , which increase gastrointestinal pH ( i.e. , make it less acidic ) .

= = Pharmacology = =

= = = Pharmacodynamics = = =

Amphetamine exerts its behavioral effects by altering the use of monoamines as neuronal signals in

the brain , primarily in catecholamine neurons in the reward and executive function pathways of the brain . The concentrations of the main neurotransmitters involved in reward circuitry and executive functioning , dopamine and norepinephrine , increase dramatically in a dose @-@ dependent manner by amphetamine due to its effects on monoamine transporters . The reinforcing and task saliency effects of amphetamine are mostly due to enhanced dopaminergic activity in the mesolimbic pathway .

Amphetamine has been identified as a potent full agonist of trace amine @-@ associated receptor 1 ( TAAR1 ) , a Gs @-@ coupled and Gq @-@ coupled G protein @-@ coupled receptor ( GPCR ) discovered in 2001 , which is important for regulation of brain monoamines . Activation of TAAR1 increases cAMP production via adenylyl cyclase activation and inhibits monoamine transporter function . Monoamine autoreceptors ( e.g. , D2 short , presynaptic ?2 , and presynaptic 5 @-@ HT1A ) have the opposite effect of TAAR1 , and together these receptors provide a regulatory system for monoamines . Notably , amphetamine and trace amines bind to TAAR1 , but not monoamine autoreceptors . Imaging studies indicate that monoamine reuptake inhibition by amphetamine and trace amines is site specific and depends upon the presence of TAAR1 co @-@ localization in the associated monoamine neurons . As of 2010 , co @-@ localization of TAAR1 and the dopamine transporter ( DAT ) has been visualized in rhesus monkeys , but co @-@ localization of TAAR1 with the norepinephrine transporter ( NET ) and the serotonin transporter ( SERT ) has only been evidenced by messenger RNA ( mRNA ) expression .

In addition to the neuronal monoamine transporters , amphetamine also inhibits both vesicular monoamine transporters , VMAT1 and VMAT2 , as well as SLC1A1 , SLC22A3 , and SLC22A5 . SLC1A1 is excitatory amino acid transporter 3 ( EAAT3 ) , a glutamate transporter located in neurons , SLC22A3 is an extraneuronal monoamine transporter that is present in astrocytes , and SLC22A5 is a high @-@ affinity carnitine transporter . Amphetamine is known to strongly induce cocaine- and amphetamine @-@ regulated transcript ( CART ) gene expression , a neuropeptide involved in feeding behavior , stress , and reward , which induces observable increases in neuronal development and survival in vitro . The CART receptor has yet to be identified , but there is significant evidence that CART binds to a unique Gi / Go @-@ coupled GPCR . Amphetamine also inhibits monoamine oxidase at very high doses , resulting in less dopamine and phenethylamine metabolism and consequently higher concentrations of synaptic monoamines . In humans , the only post @-@ synaptic receptor at which amphetamine is known to bind is the 5 @-@ HT1A receptor , where it acts as an agonist with micromolar affinity .

The full profile of amphetamine 's short @-@ term drug effects in humans is mostly derived through increased cellular communication or neurotransmission of dopamine , serotonin , norepinephrine , epinephrine , histamine , CART peptides , acetylcholine , endogenous opioids , adrenocorticotrophic hormone , corticosteroids , and glutamate , which it effects through interactions with CART , 5 @-@ HT1A , EAAT3 , TAAR1 , VMAT1 , VMAT2 , and possibly other biological targets .

Dextroamphetamine is a more potent agonist of TAAR1 than levoamphetamine . Consequently , dextroamphetamine produces greater CNS stimulation than levoamphetamine , roughly three to four times more , but levoamphetamine has slightly stronger cardiovascular and peripheral effects .

== == Dopamine == ==

In certain brain regions , amphetamine increases the concentration of dopamine in the synaptic cleft . Amphetamine can enter the presynaptic neuron either through DAT or by diffusing across the neuronal membrane directly . As a consequence of DAT uptake , amphetamine produces competitive reuptake inhibition at the transporter . Upon entering the presynaptic neuron , amphetamine activates TAAR1 which , through protein kinase A ( PKA ) and protein kinase C ( PKC ) signaling , causes DAT phosphorylation . Phosphorylation by either protein kinase can result in DAT internalization ( non @-@ competitive reuptake inhibition ) , but PKC @-@ mediated phosphorylation alone induces reverse transporter function ( dopamine efflux ) . Amphetamine is also known to increase intracellular calcium , an effect which is associated with DAT phosphorylation through an unidentified Ca2 + / calmodulin @-@ dependent protein kinase ( CAMK

) -dependent pathway , in turn producing dopamine efflux . Through direct activation of G protein @-@ coupled inwardly @-@ rectifying potassium channels , TAAR1 reduces the firing rate of postsynaptic dopamine neurons , preventing a hyper @-@ dopaminergic state .

Amphetamine is also a substrate for the presynaptic vesicular monoamine transporter , VMAT2 . Following amphetamine uptake at VMAT2 , the synaptic vesicle releases dopamine molecules into the cytosol in exchange . Subsequently , the cytosolic dopamine molecules exit the presynaptic neuron via reverse transport at DAT .

=== Norepinephrine ===

Similar to dopamine , amphetamine dose @-@ dependently increases the level of synaptic norepinephrine , the direct precursor of epinephrine . Based upon neuronal TAAR1 mRNA expression , amphetamine is thought to affect norepinephrine analogously to dopamine . In other words , amphetamine induces TAAR1 @-@ mediated efflux and non @-@ competitive reuptake inhibition at phosphorylated NET , competitive NET reuptake inhibition , and norepinephrine release from VMAT2 .

=== Serotonin ===

Amphetamine exerts analogous , yet less pronounced , effects on serotonin as on dopamine and norepinephrine . Amphetamine affects serotonin via VMAT2 and , like norepinephrine , is thought to phosphorylate SERT via TAAR1 . Like dopamine , amphetamine has low , micromolar affinity at the human 5 @-@ HT1A receptor .

=== Other neurotransmitters , peptides , and hormones ===

Amphetamine has no direct effect on acetylcholine neurotransmission , but several studies have noted that acetylcholine release increases after its use . In lab animals , amphetamine increases acetylcholine levels in certain brain regions as a downstream effect . In humans , a similar phenomenon occurs via the ghrelin @-@ mediated cholinergic ? dopaminergic reward link in the ventral tegmental area . Acute amphetamine administration in humans also increases endogenous opioid release in several brain structures in the reward system . Extracellular levels of glutamate , the primary excitatory neurotransmitter in the brain , have been shown to increase upon exposure to amphetamine . This cotransmission effect was found in the mesolimbic pathway , an area of the brain implicated in reward , where amphetamine is known to affect dopamine neurotransmission .

Amphetamine also induces the selective release of histamine from mast cells and efflux from histaminergic neurons through VMAT2 . Acute amphetamine administration can also increase adrenocorticotrophic hormone and corticosteroid levels in blood plasma by stimulating the hypothalamic ? pituitary ? adrenal axis .

=== Pharmacokinetics ===

The oral bioavailability of amphetamine varies with gastrointestinal pH ; it is well absorbed from the gut , and bioavailability is typically over 75 % for dextroamphetamine . Amphetamine is a weak base with a pKa of 9 ? 10 ; consequently , when the pH is basic , more of the drug is in its lipid soluble free base form , and more is absorbed through the lipid @-@ rich cell membranes of the gut epithelium . Conversely , an acidic pH means the drug is predominantly in a water @-@ soluble cationic ( salt ) form , and less is absorbed . Approximately 15 ? 40 % of amphetamine circulating in the bloodstream is bound to plasma proteins .

The half @-@ life of amphetamine enantiomers differ and vary with urine pH . At normal urine pH , the half @-@ lives of dextroamphetamine and levoamphetamine are 9 ? 11 hours and 11 ? 14 hours , respectively . An acidic diet will reduce the enantiomer half @-@ lives to 8 ? 11 hours ; an alkaline diet will increase the range to 16 ? 31 hours . The immediate @-@ release and extended



release variants of salts of both isomers reach peak plasma concentrations at 3 hours and 7 hours post @-@ dose respectively . Amphetamine is eliminated via the kidneys , with 30 ? 40 % of the drug being excreted unchanged at normal urinary pH . When the urinary pH is basic , amphetamine is in its free base form , so less is excreted . When urine pH is abnormal , the urinary recovery of amphetamine may range from a low of 1 % to a high of 75 % , depending mostly upon whether urine is too basic or acidic , respectively . Amphetamine is usually eliminated within two days of the last oral dose . Apparent half @-@ life and duration of effect increase with repeated use and accumulation of the drug .

The prodrug lisdexamfetamine is not as sensitive to pH as amphetamine when being absorbed in the gastrointestinal tract ; following absorption into the blood stream , it is converted by red blood cell @-@ associated enzymes to dextroamphetamine via hydrolysis . The elimination half @-@ life of lisdexamfetamine is generally less than one hour .

CYP2D6 , dopamine ? @-@ hydroxylase , flavin @-@ containing monooxygenase 3 , butyrate @-@ CoA ligase , and glycine N @-@ acyltransferase are the enzymes known to metabolize amphetamine or its metabolites in humans . Amphetamine has a variety of excreted metabolic products , including 4 @-@ hydroxyamphetamine , 4 @-@ hydroxynorephedrine , 4 @-@ hydroxyphenylacetone , benzoic acid , hippuric acid , norephedrine , and phenylacetone . Among these metabolites , the active sympathomimetics are 4 ? hydroxyamphetamine , 4 ? hydroxynorephedrine , and norephedrine . The main metabolic pathways involve aromatic para @-@ hydroxylation , aliphatic alpha- and beta @-@ hydroxylation , N @-@ oxidation , N @-@ dealkylation , and deamination . The known pathways and detectable metabolites in humans include the following :

== Related endogenous compounds ==

Amphetamine has a very similar structure and function to the endogenous trace amines , which are naturally occurring neurotransmitter molecules produced in the human body and brain . Among this group , the most closely related compounds are phenethylamine , the parent compound of amphetamine , and N @-@ methylphenethylamine , an isomer of amphetamine ( i.e. , it has an identical molecular formula ) . In humans , phenethylamine is produced directly from L @-@ phenylalanine by the aromatic amino acid decarboxylase ( AADC ) enzyme , which converts L @-@ DOPA into dopamine as well . In turn , N ? methylphenethylamine is metabolized from phenethylamine by phenylethanolamine N @-@ methyltransferase , the same enzyme that metabolizes norepinephrine into epinephrine . Like amphetamine , both phenethylamine and N ? methylphenethylamine regulate monoamine neurotransmission via TAAR1 ; unlike amphetamine , both of these substances are broken down by monoamine oxidase B , and therefore have a shorter half @-@ life than amphetamine .

== Physical and chemical properties ==

Amphetamine is a methyl homolog of the mammalian neurotransmitter phenethylamine with the chemical formula C<sub>9</sub>H<sub>13</sub>N . The carbon atom adjacent to the primary amine is a stereogenic center , and amphetamine is composed of a racemic 1 : 1 mixture of two enantiomeric mirror images . This racemic mixture can be separated into its optical isomers : levoamphetamine and dextroamphetamine . Physically , at room temperature , the pure free base of amphetamine is a mobile , colorless , and volatile liquid with a characteristically strong amine odor , and acrid , burning taste . Frequently prepared solid salts of amphetamine include amphetamine aspartate , hydrochloride , phosphate , saccharate , and sulfate , the last of which is the most common amphetamine salt . Amphetamine is also the parent compound of its own structural class , which includes a number of psychoactive derivatives . In organic chemistry , amphetamine is an excellent chiral ligand for the stereoselective synthesis of 1 @,@ 1'-bi @-@ 2 @-@ naphthol .

== Substituted derivatives ==

The substituted derivatives of amphetamine, or "substituted amphetamines", are a broad range of chemicals that contain amphetamine as a "backbone"; specifically, this chemical class includes derivative compounds that are formed by replacing one or more hydrogen atoms in the amphetamine core structure with substituents. The class includes amphetamine itself, stimulants like methamphetamine, serotonergic empathogens like MDMA, and decongestants like ephedrine, among other subgroups.

#### == Synthesis ==

Since the first preparation was reported in 1887, numerous synthetic routes to amphetamine have been developed. The most common route of both legal and illicit amphetamine synthesis employs a non @-@ metal reduction known as the Leuckart reaction (method 1). In the first step, a reaction between phenylacetone and formamide, either using additional formic acid or formamide itself as a reducing agent, yields N @-@ formylamphetamine. This intermediate is then hydrolyzed using hydrochloric acid, and subsequently basified, extracted with organic solvent, concentrated, and distilled to yield the free base. The free base is then dissolved in an organic solvent, sulfuric acid added, and amphetamine precipitates out as the sulfate salt.

A number of chiral resolutions have been developed to separate the two enantiomers of amphetamine. For example, racemic amphetamine can be treated with d @-@ tartaric acid to form a diastereoisomeric salt which is fractionally crystallized to yield dextroamphetamine. Chiral resolution remains the most economical method for obtaining optically pure amphetamine on a large scale. In addition, several enantioselective syntheses of amphetamine have been developed. In one example, optically pure (R) -1 @-@ phenyl @-@ ethanamine is condensed with phenylacetone to yield a chiral Schiff base. In the key step, this intermediate is reduced by catalytic hydrogenation with a transfer of chirality to the carbon atom alpha to the amino group. Cleavage of the benzylic amine bond by hydrogenation yields optically pure dextroamphetamine.

A large number of alternative synthetic routes to amphetamine have been developed based on classic organic reactions. One example is the Friedel-Crafts alkylation of chlorobenzene by allyl chloride to yield beta chloropropylbenzene which is then reacted with ammonia to produce racemic amphetamine (method 2). Another example employs the Ritter reaction (method 3). In this route, allylbenzene is reacted with acetonitrile in sulfuric acid to yield an organosulfate which in turn is treated with sodium hydroxide to give amphetamine via an acetamide intermediate. A third route starts with ethyl 3 @-@ oxobutanoate which through a double alkylation with methyl iodide followed by benzyl chloride can be converted into 2 @-@ methyl @-@ 3 @-@ phenyl @-@ propanoic acid. This synthetic intermediate can be transformed into amphetamine using either a Hofmann or Curtius rearrangement (method 4).

A significant number of amphetamine syntheses feature a reduction of a nitro, imine, oxime or other nitrogen @-@ containing functional groups. In one such example, a Knoevenagel condensation of benzaldehyde with nitroethane yields phenyl @-@ 2 @-@ nitropropene. The double bond and nitro group of this intermediate is reduced using either catalytic hydrogenation or by treatment with lithium aluminium hydride (method 5). Another method is the reaction of phenylacetone with ammonia, producing an imine intermediate that is reduced to the primary amine using hydrogen over a palladium catalyst or lithium aluminum hydride (method 6).

#### == Detection in body fluids ==

Amphetamine is frequently measured in urine or blood as part of a drug test for sports, employment, poisoning diagnostics, and forensics. Techniques such as immunoassay, which is the most common form of amphetamine test, may cross @-@ react with a number of sympathomimetic drugs. Chromatographic methods specific for amphetamine are employed to prevent false positive results. Chiral separation techniques may be employed to help distinguish the source of the drug, whether prescription amphetamine, prescription amphetamine prodrugs, (e.g.

, selegiline ) , over @-@ the @-@ counter drug products that contain levomethamphetamine , or illicitly obtained substituted amphetamines . Several prescription drugs produce amphetamine as a metabolite , including benzphetamine , clobenzorex , famprofazone , fenproporex , lisdexamfetamine , mesocarb , methamphetamine , prenylamine , and selegiline , among others . These compounds may produce positive results for amphetamine on drug tests . Amphetamine is generally only detectable by a standard drug test for approximately 24 hours , although a high dose may be detectable for two to four days .

For the assays , a study noted that an enzyme multiplied immunoassay technique ( EMIT ) assay for amphetamine and methamphetamine may produce more false positives than liquid chromatography ? tandem mass spectrometry . Gas chromatography ? mass spectrometry ( GC ? MS ) of amphetamine and methamphetamine with the derivatizing agent ( S ) - ( ? ) -trifluoroacetylpropyl chloride allows for the detection of methamphetamine in urine . GC ? MS of amphetamine and methamphetamine with the chiral derivatizing agent Mosher 's acid chloride allows for the detection of both dextroamphetamine and dextromethamphetamine in urine . Hence , the latter method may be used on samples that test positive using other methods to help distinguish between the various sources of the drug .

= = History , society , and culture = =

Amphetamine was first synthesized in 1887 in Germany by Romanian chemist Laz?r Edeleanu who named it phenylisopropylamine ; its stimulant effects remained unknown until 1927 , when it was independently resynthesized by Gordon Alles and reported to have sympathomimetic properties . Amphetamine had no pharmacological use until 1934 , when Smith , Kline and French began selling it as an inhaler under the trade name Benzedrine as a decongestant . Benzedrine sulfate was introduced three years later and found a wide variety of medical applications , including narcolepsy . During World War II , amphetamine and methamphetamine were used extensively by both the Allied and Axis forces for their stimulant and performance @-@ enhancing effects . As the addictive properties of the drug became known , governments began to place strict controls on the sale of amphetamine . For example , during the early 1970s in the United States , amphetamine became a schedule II controlled substance under the Controlled Substances Act . In spite of strict government controls , amphetamine has been used legally or illicitly by people from a variety of backgrounds , including authors , musicians , mathematicians , and athletes .

Amphetamine is still illegally synthesized today in clandestine labs and sold on the black market , primarily in European countries . Among European Union ( EU ) member states , 1 @.@ 2 million young adults used illicit amphetamine or methamphetamine in 2013 . During 2012 , approximately 5 @.@ 9 metric tons of illicit amphetamine were seized within EU member states ; the " street price " of illicit amphetamine within the EU ranged from ? 6 ? 38 per gram during the same period . Outside Europe , the illicit market for amphetamine is much smaller than the market for methamphetamine and MDMA .

= = = Legal status = = =

As a result of the United Nations 1971 Convention on Psychotropic Substances , amphetamine became a schedule II controlled substance , as defined in the treaty , in all ( 183 ) state parties . Consequently , it is heavily regulated in most countries . Some countries , such as South Korea and Japan , have banned substituted amphetamines even for medical use . In other nations , such as Canada ( schedule I drug ) , the Netherlands ( List I drug ) , the United States ( schedule II drug ) , Australia ( schedule 8 ) , Thailand ( category 1 narcotic ) , and United Kingdom ( class B drug ) , amphetamine is in a restrictive national drug schedule that allows for its use as a medical treatment .

= = = Pharmaceutical products = = =

Several currently prescribed amphetamine formulations contain both enantiomers , including Adderall , Dyanavel XR , and Evekeo , the last of which is racemic amphetamine sulfate . Amphetamine is also prescribed in enantiopure and prodrug form as dextroamphetamine and lisdexamfetamine respectively . Lisdexamfetamine is structurally different from amphetamine , and is inactive until it metabolizes into dextroamphetamine . The free base of racemic amphetamine was previously available as Benzedrine , Psychedrine , and Sympatedrine . Levoamphetamine was previously available as Cydril . Many current amphetamine pharmaceuticals are salts due to the comparatively high volatility of the free base . However , oral suspension and orally disintegrating tablet ( ODT ) dosage forms composed of the free base were introduced in 2015 and 2016 . Some of the current brands and their generic equivalents are listed below .

= = Reference notes = =