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Adderall

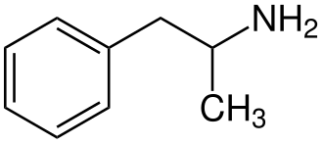
Adderall and **Mydayis**[4] are trade names[note 2] for a combination drug called **mixed amphetamine salts** containing four salts of amphetamine. The mixture is composed of equal parts racemic amphetamine and dextroamphetamine, which produces a (3:1) ratio between dextroamphetamine and levoamphetamine, the two enantiomers of amphetamine. Both enantiomers are stimulants, but differ enough to give Adderall an effects profile distinct from those of racemic amphetamine or dextroamphetamine,[1][2] which are marketed as Evekeo and Dexedrine/Zenzedi, respectively.[1][6][7] Adderall is used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. It is also used as an athletic performance enhancer, cognitive enhancer, appetite suppressant, and recreationally as a euphoriant. It is a central nervous system (CNS) stimulant of the phenethylamine class.[1]

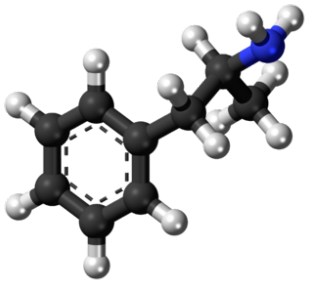
Adderall is generally well tolerated and effective in treating the symptoms of ADHD and narcolepsy. At therapeutic doses, Adderall causes emotional and cognitive effects such as euphoria, change in sex drive (loss of sex drive), increased wakefulness, and improved cognitive control. At these doses, it induces physical effects such as a faster reaction time, fatigue resistance, and increased muscle strength. In contrast, much larger doses of Adderall can impair cognitive control, cause rapid muscle breakdown, provoke panic attacks, or induce a psychosis (e.g., paranoia, delusions, hallucinations). The side effects of Adderall vary widely among individuals, but most commonly include insomnia, dry mouth, loss of appetite, and weight loss. The risk of developing an addiction or dependence is insignificant when Adderall is used as prescribed at fairly low daily doses, such as those used for treating ADHD; however, the routine use of Adderall in larger daily doses poses a significant risk of addiction or dependence due to the pronounced reinforcing effects that are present at high doses. Recreational doses of amphetamine are generally much larger than prescribed therapeutic doses, and carry a far greater risk of serious adverse effects.[sources 1]

The two amphetamine enantiomers that compose Adderall (levoamphetamine and dextroamphetamine) alleviate the symptoms of ADHD and narcolepsy by increasing the activity of the neurotransmitters norepinephrine and dopamine in the brain, which results in part from their interactions with human trace amine-associated receptor 1 (hTAAR1) and vesicular monoamine transporter 2 (VMAT2) in neurons. Dextroamphetamine is a more potent CNS stimulant than levoamphetamine, but levoamphetamine has slightly stronger cardiovascular and peripheral effects and a longer elimination half-life than dextroamphetamine. The levoamphetamine component of Adderall has been reported to improve the treatment response in some individuals relative to dextroamphetamine alone. Adderall's active ingredient, amphetamine, shares many chemical and pharmacological properties with the human trace amines, particularly phenethylamine and *N*-methylphenethylamine, the latter of which is a positional isomer of amphetamine.[sources 2] In 2019, Adderall was the 24th most commonly prescribed medication in the United States, with more than 24 million prescriptions.[27][28]

Contents

Amphetamine/dextroamphetamine salt mixture (1:1)[note 1]





Top: racemic amphetamine skeleton
Bottom: *(D)*-amphetamine ball-and-stick model

Combination of	
amphetamine aspartate monohydrate	25% – stimulant (12.5% levo; 12.5% dextro)
amphetamine sulfate	25% – stimulant (12.5% levo; 12.5% dextro)
dextroamphetamine saccharate	25% – stimulant (0% levo; 25% dextro)
dextroamphetamine sulfate	25% – stimulant (0% levo; 25% dextro)
Clinical data	
Trade names	Adderall, Adderall XR, Mydayis
Other names	Mixed amphetamine salts; MAS
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/Adderall.html)
MedlinePlus	a601234 (https://medlineplus.gov/druginfo/meds/a601234.html)
License data	US DailyMed: Adderall (https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=Adderall) US FDA: Adderall (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=Adderall&SearchType=BasicSearch)
Dependence liability	Moderate[3]
Routes of administration	Oral, insufflation, rectal, sublingual
Drug class	CNS stimulant

ATC code	N06BA02 (WHO (https://www.whocc.no/atc_ddd_index/?code=N06BA02)) N06BA01 (WHO (https://www.whocc.no/atc_ddd_index/?code=N06BA01))
Legal status	
Legal status	AU: S8 (Controlled drug) CA: Schedule I DE: Anlage III (Special prescription form required) NZ: Class B UK: Class B US: Schedule II UN: Psychotropic Schedule II
Identifiers	
CAS Number	300-62-9 (https://commonchemistry.cas.org/detail?cas_rn=300-62-9) ✓ 51-64-9 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=51-64-9&title=)
PubChem CID	3007 (https://pubchem.ncbi.nlm.nih.gov/compound/3007)
IUPHAR/BPS	4804 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4804)
DrugBank	DB00182 (https://www.drugbank.ca/drugs/DB00182) ✓
ChemSpider	13852819 (https://www.chemspider.com/Chemical-Structure.13852819.html) ✓
UNII	CK833KGX7E (https://precision.fda.gov/uniisearch/srs/unii/CK833KGX7E)
KEGG	D11624 (https://www.kegg.jp/entry/D11624) ✓
ChEBI	CHEBI:2679 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:2679) ✓
ChEMBL	ChEMBL405 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL405) ✓
	(verify)

Uses

Medical

Adderall is used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy (a sleep disorder).[29][9] Long-term amphetamine exposure at sufficiently high doses in some animal species is known to produce abnormal dopamine system development or nerve damage,[30][31] but in humans with ADHD, pharmaceutical amphetamines at therapeutic dosages appear to improve brain development and nerve growth.[32][33][34] 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.[32][33][34]

Reviews of clinical stimulant research have established the safety and effectiveness of long-term continuous amphetamine use for the treatment of ADHD.[35][36][37] Randomized controlled trials of continuous stimulant therapy for the treatment of ADHD spanning 2 years have demonstrated treatment effectiveness and safety.[35][36] Two reviews have indicated that long-term continuous stimulant therapy for ADHD is effective for reducing the core symptoms of ADHD (i.e., hyperactivity, inattention, and impulsivity), enhancing quality of life and academic achievement, and producing improvements in a large number of functional outcomes[note 3] across 9 categories of outcomes related to academics, antisocial behavior, driving, non-medicinal drug use, obesity, occupation, self-esteem, service use (i.e., academic, occupational, health, financial, and legal services), and social function.[35][37] One review highlighted a nine-month randomized controlled trial of amphetamine treatment for ADHD in children that found an average increase of 4.5 IQ points, continued increases in attention, and continued decreases in disruptive behaviors and hyperactivity.[36] Another review indicated that, based upon the longest follow-up studies conducted to date, lifetime stimulant therapy that begins during childhood is continuously effective for controlling ADHD symptoms and reduces the risk of developing a substance use disorder as an adult.[35]

Current models of ADHD suggest that it is associated with functional impairments in some of the brain's neurotransmitter systems;[19] these functional impairments involve impaired dopamine neurotransmission in the mesocorticolimbic projection and norepinephrine neurotransmission in the noradrenergic projections from the

locus coeruleus to the prefrontal cortex.[19] Psychostimulants like methylphenidate and amphetamine are effective in treating ADHD because they increase neurotransmitter activity in these systems.[10][19][38] Approximately 80% of those who use these stimulants see improvements in ADHD symptoms.[39] 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.[40][41] The Cochrane reviews[note 4] on the treatment of ADHD in children, adolescents, and adults with pharmaceutical amphetamines stated that short-term studies have demonstrated that these drugs decrease the severity of symptoms, but they have higher discontinuation rates than non-stimulant medications due to their adverse side effects.[43][44] A Cochrane 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.[45]


30 capsules of 10 mg Adderall XR


A group of 20 mg Adderall tablets, some broken in half, with a lengthwise-folded US dollar bill along the bottom (3.07 inches; 7.8 cm) for size comparison

Available forms

Adderall is available as immediate-release (IR) tablets or two different extended-release (XR) formulations.[9][46] The extended-release capsules are generally used in the morning.[47] A shorter, 12-hour extended-release formulation is available under the brand Adderall XR and is designed to provide a therapeutic effect and plasma concentrations identical to taking two doses 4 hours apart.[46] The longer extended-release formulation, approved for 16 hours, is available under the brand Mydayis. In the United States, the immediate and extended release formulations of Adderall are both available as generic drugs,[48][49] while Mydayis is available only as a brand-name drug.

Enhancing performance

Cognitive 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 yet unambiguous improvements in cognition, including working memory, long-term episodic memory, inhibitory control, and some aspects of attention, in normal healthy adults;[50][51] these cognition-enhancing effects of amphetamine are known to be partially mediated through the indirect activation of both dopamine receptor D_1 and adrenoceptor α_2 in the prefrontal cortex.[10][50] A systematic review from 2014 found that low doses of amphetamine also improve memory consolidation, in turn leading to improved recall of information.[52] Therapeutic doses of amphetamine also enhance cortical network efficiency, an effect which mediates improvements in working memory in all individuals.[10][53] Amphetamine and other ADHD stimulants also improve task saliency (motivation to perform a task) and increase arousal (wakefulness), in turn promoting goal-directed behavior.[10][54][55] 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.[10][55][56] Based upon studies of self-reported illicit stimulant use, 5–35% of college students use diverted ADHD stimulants, which are primarily used for enhancement of academic performance rather than as recreational drugs.[57][58][59] However, high amphetamine doses that are above the therapeutic range can interfere with working memory and other aspects of cognitive control.[10][55]

Physical performance

Amphetamine is used by some athletes for its psychological and athletic performance-enhancing effects, such as increased endurance and alertness;[11][23] however, non-medical amphetamine use is prohibited at sporting events that are regulated by collegiate, national, and international anti-doping agencies.[60][61] 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.[11][62][63] Amphetamine improves endurance and reaction time primarily through reuptake inhibition and release of dopamine in the central nervous system.[62][63][64] Amphetamine and other dopaminergic drugs also increase power output at fixed levels of perceived exertion by overriding a "safety switch", allowing the core temperature limit to increase in order to access a reserve capacity that is normally off-limits.[63][65][66] At therapeutic doses, the adverse effects of amphetamine do not impede athletic performance;[11][62] however, at much higher doses, amphetamine can induce effects that severely impair performance, such as rapid muscle breakdown and elevated body temperature.[12][62]

Adderall has been banned in the National Football League (NFL), Major League Baseball (MLB), National Basketball Association (NBA), and the National Collegiate Athletics Association (NCAA).[67] In leagues such as the NFL, there is a very rigorous process required to obtain an exemption to this rule even when the athlete has been medically prescribed the drug by their physician.[67]

Recreational

Adderall has high potential for misuse as a recreational drug.[68][69][70] Adderall tablets can either be swallowed, crushed and snorted, or dissolved in water and injected.[71] Injection into the bloodstream can be dangerous because insoluble fillers within the tablets can block small blood vessels.[71]

Many postsecondary students have reported using Adderall for study purposes in different parts of the developed world.[70] Among these students, some of the risk factors for misusing ADHD stimulants recreationally include: possessing deviant personality characteristics (i.e., exhibiting delinquent or deviant behavior), inadequate accommodation of disability, basing one's self-worth on external validation, low self-efficacy, earning poor grades, and having an untreated mental health disorder.[70]

Contraindications

According to the International Programme on Chemical Safety (IPCS) and the United States Food and Drug Administration (USFDA),[note 5] amphetamine is contraindicated in people with a history of drug abuse,[note 6] cardiovascular disease, severe agitation, or severe anxiety.[74][75][76] It is also contraindicated in individuals with advanced arteriosclerosis (hardening of the arteries), glaucoma (increased eye pressure), hyperthyroidism (excessive production of thyroid hormone), or moderate to severe hypertension.[74][75][76] These agencies indicate that people who have experienced allergic reactions to other stimulants or who are taking monoamine oxidase inhibitors (MAOIs) should not take amphetamine,[74][75][76] although safe concurrent use of amphetamine and monoamine oxidase inhibitors has been documented.[77][78] 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.[75][76] 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.[76] Amphetamine has also been shown to pass into breast milk, so the IPCS and the USFDA advise mothers to avoid breastfeeding when using it.[75][76] Due to the potential for reversible growth impairments,[note 7] the USFDA advises monitoring the height and weight of children and adolescents prescribed an amphetamine pharmaceutical.[75]

Adverse effects

The adverse side effects of Adderall are many and varied, but the amount of substance consumed is the primary factor in determining the likelihood and severity of side effects.[12][23] Adderall is currently approved for long-term therapeutic use by the USFDA.[12] Recreational use of Adderall generally involves far larger doses and is therefore significantly more dangerous, involving a much greater risk of serious adverse drug effects than dosages used for therapeutic purposes.[23]

Physical

Cardiovascular side effects can include hypertension or hypotension from a vasovagal response, Raynaud's phenomenon (reduced blood flow to the hands and feet), and tachycardia (increased heart rate).[12][23][82] Sexual side effects in males may include erectile dysfunction, frequent erections, or prolonged erections.[12] Gastrointestinal side effects may include abdominal pain, constipation, diarrhea, and nausea.[3][12][83] Other potential physical side effects include appetite loss, blurred vision, dry mouth, excessive grinding of the teeth, nosebleed, profuse sweating, rhinitis medicamentosa (drug-induced nasal congestion), reduced seizure threshold, tics (a type of movement disorder), and weight loss.[sources 3] Dangerous physical side effects are rare at typical pharmaceutical doses.[23]

Amphetamine stimulates the medullary respiratory centers, producing faster and deeper breaths.[23] In a normal person at therapeutic doses, this effect is usually not noticeable, but when respiration is already compromised, it may be evident.[23] Amphetamine also induces contraction in the urinary bladder sphincter, the muscle which controls urination, which can result in difficulty urinating.[23] This effect can be useful in treating bed wetting and loss of bladder control.[23] The effects of amphetamine on the gastrointestinal tract are unpredictable.[23] If intestinal activity is high, amphetamine may reduce gastrointestinal motility (the rate at which content moves through the digestive system);[23] however, amphetamine may increase motility when the smooth muscle of the tract is relaxed.[23] Amphetamine also has a slight analgesic effect and can enhance the pain relieving effects of opioids.[3][23]

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.[sources 4] However, amphetamine pharmaceuticals are contraindicated in individuals with cardiovascular disease.[sources 5]

Psychological

At normal therapeutic doses, the most common psychological side effects of amphetamine include increased alertness, apprehension, concentration, initiative, self-confidence and sociability, mood swings (elated mood

followed by mildly depressed mood), insomnia or wakefulness, and decreased sense of fatigue.[12][23] Less common side effects include anxiety, change in libido, grandiosity, irritability, repetitive or obsessive behaviors, and restlessness;[sources 6] these effects depend on the user's personality and current mental state.[23] Amphetamine psychosis (e.g., delusions and paranoia) can occur in heavy users.[12][13][91] Although very rare, this psychosis can also occur at therapeutic doses during long-term therapy.[12][91][14] According to the USFDA, "there is no systematic evidence" that stimulants produce aggressive behavior or hostility.[12]

Amphetamine has also been shown to produce a conditioned place preference in humans taking therapeutic doses,[43][92] meaning that individuals acquire a preference for spending time in places where they have previously used amphetamine.[92][93]

Reinforcement disorders

Addiction

Addiction is a serious risk with heavy recreational amphetamine use, but is unlikely to occur from long-term medical use at therapeutic doses;[35][15][16] in fact, lifetime stimulant therapy for ADHD that begins during childhood reduces the risk of developing substance use disorders as an adult.[35] 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.[104][105] Individuals who frequently self-administer high doses of amphetamine have a high risk of developing an amphetamine addiction, since chronic use at high doses gradually increases the level of accumbal ΔFosB, a "molecular switch" and "master control protein" for addiction.[94][106][107] Once nucleus accumbens ΔFosB is sufficiently overexpressed, it begins to increase the severity of addictive behavior (i.e., compulsive drug-seeking) with further increases in its expression.[106][108] 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.[109][110] Sustained aerobic exercise on a regular basis also appears to be an effective treatment for amphetamine addiction; [sources 7] exercise therapy improves clinical treatment outcomes and may be used as an adjunct therapy with behavioral therapies for addiction.[109][111]

Addiction and dependence glossary[93][94][95][96]

- **addiction** – a biopsychosocial disorder characterized by persistent use of drugs (including alcohol) despite substantial harm and adverse consequences
- **addictive drug** – psychoactive substances that with repeated use are associated with significantly higher rates of substance use disorders, due in large part to the drug's effect on brain reward systems
- **dependence** – an adaptive state associated with a withdrawal syndrome upon cessation of repeated exposure to a stimulus (e.g., drug intake)
- **drug sensitization** or **reverse tolerance** – the escalating effect of a drug resulting from repeated administration at a given dose
- **drug withdrawal** – symptoms that occur upon cessation of repeated drug use
- **physical dependence** – dependence that involves persistent physical–somatic withdrawal symptoms (e.g., fatigue and delirium tremens)
- **psychological dependence** – dependence that involves emotional–motivational withdrawal symptoms (e.g., dysphoria and anhedonia)
- **reinforcing stimuli** – stimuli that increase the probability of repeating behaviors paired with them
- **rewarding stimuli** – stimuli

Biomolecular mechanisms

Chronic use of amphetamine at excessive doses causes alterations in gene expression in the mesocorticolimbic projection, which arise through transcriptional and epigenetic mechanisms.[107][112][113] The most important transcription factors[note 8] that produce these alterations are *Delta FBJ murine osteosarcoma viral oncogene homolog B* (ΔFosB), *cAMP response element binding protein* (CREB), and *nuclear factor-kappa B* (NF-κB).[107] ΔFosB is the most significant biomolecular mechanism in addiction because ΔFosB overexpression (i.e., an abnormally high level of gene expression which produces a pronounced gene-related phenotype) in the D1-type medium spiny neurons in the nucleus accumbens is necessary and sufficient[note 9] for many of the neural adaptations and regulates multiple behavioral effects (e.g., reward sensitization and escalating drug self-administration) involved in addiction.[94][106][107] Once ΔFosB is sufficiently overexpressed, it induces an addictive state that becomes increasingly more severe with further increases in ΔFosB expression.[94][106] It has been implicated in addictions to alcohol, cannabinoids, cocaine, methylphenidate, nicotine, opioids, phencyclidine, propofol, and substituted amphetamines, among others.[sources 8]

ΔJunD, a transcription factor, and G9a, a histone methyltransferase enzyme, both oppose the function of ΔFosB and inhibit increases in its expression.[94][107][117] Sufficiently overexpressing ΔJunD 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 ΔFosB).[107] Similarly, accumbal G9a hyperexpression results in markedly increased histone 3 lysine residue 9 dimethylation (H3K9me2) and blocks the induction of ΔFosB-mediated neural and behavioral plasticity by chronic drug use,[sources 9] which occurs via H3K9me2-mediated repression of transcription factors for ΔFosB and H3K9me2-mediated repression of various ΔFosB transcriptional targets (e.g., CDK5).[107][117][118] ΔFosB also plays an important role in regulating behavioral responses to natural rewards, such as palatable food, sex, and exercise.[108][107][121] Since both natural rewards and addictive drugs induce the expression of ΔFosB (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.[108][107] Consequently, ΔFosB is the most significant factor involved in both amphetamine addiction and amphetamine-induced sexual addictions, which are compulsive sexual behaviors that result from

excessive sexual activity and amphetamine use.[108][122][123] These sexual addictions are associated with a dopamine dysregulation syndrome which occurs in some patients taking dopaminergic drugs.[108][121]

The effects of amphetamine on gene regulation are both dose- and route-dependent.[113] Most of the research on gene regulation and addiction is based upon animal studies with intravenous amphetamine administration at very high doses.[113] 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.[113] This suggests that medical use of amphetamine does not significantly affect gene regulation.[113]

Pharmacological treatments

As of December 2019, there is no effective pharmacotherapy for amphetamine addiction.[124][125][126] Reviews from 2015 and 2016 indicated that TAAR1-selective agonists have significant therapeutic potential as a treatment for psychostimulant addictions;[127][128] however, as of February 2016, the only compounds which are known to function as TAAR1-selective agonists are experimental drugs.[127][128] Amphetamine addiction is largely mediated through increased activation of dopamine receptors and co-localized NMDA receptors[note 10] in the nucleus accumbens;[105] magnesium ions inhibit NMDA receptors by blocking the receptor calcium channel.[105][129] One review suggested that, based upon animal testing, pathological (addiction-inducing) psychostimulant use significantly reduces the level of intracellular magnesium throughout the brain.[105] Supplemental magnesium[note 11] 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.[105]

A systematic review and meta-analysis from 2019 assessed the efficacy of 17 different pharmacotherapies used in randomized controlled trials (RCTs) for amphetamine and methamphetamine addiction;[125] it found only low-strength evidence that methylphenidate might reduce amphetamine or methamphetamine self-administration.[125] There was low- to moderate-strength evidence of no benefit for most of the other medications used in RCTs, which included antidepressants (bupropion, mirtazapine, sertraline), antipsychotics (aripiprazole), anticonvulsants (topiramate, baclofen, gabapentin), naltrexone, varenicline, citicoline, ondansetron, prometa, riluzole, atomoxetine, dextroamphetamine, and modafinil.[125]

Behavioral treatments

A 2018 systematic review and network meta-analysis of 50 trials involving 12 different psychosocial interventions for amphetamine, methamphetamine, or cocaine addiction found that combination therapy with both contingency management and community reinforcement approach had the highest efficacy (i.e., abstinence rate) and acceptability (i.e., lowest dropout rate).[130] Other treatment modalities examined in the analysis included monotherapy with contingency management or community reinforcement approach, cognitive behavioral therapy, 12-step programs, non-contingent reward-based therapies, psychodynamic therapy, and other combination therapies involving these.[130]

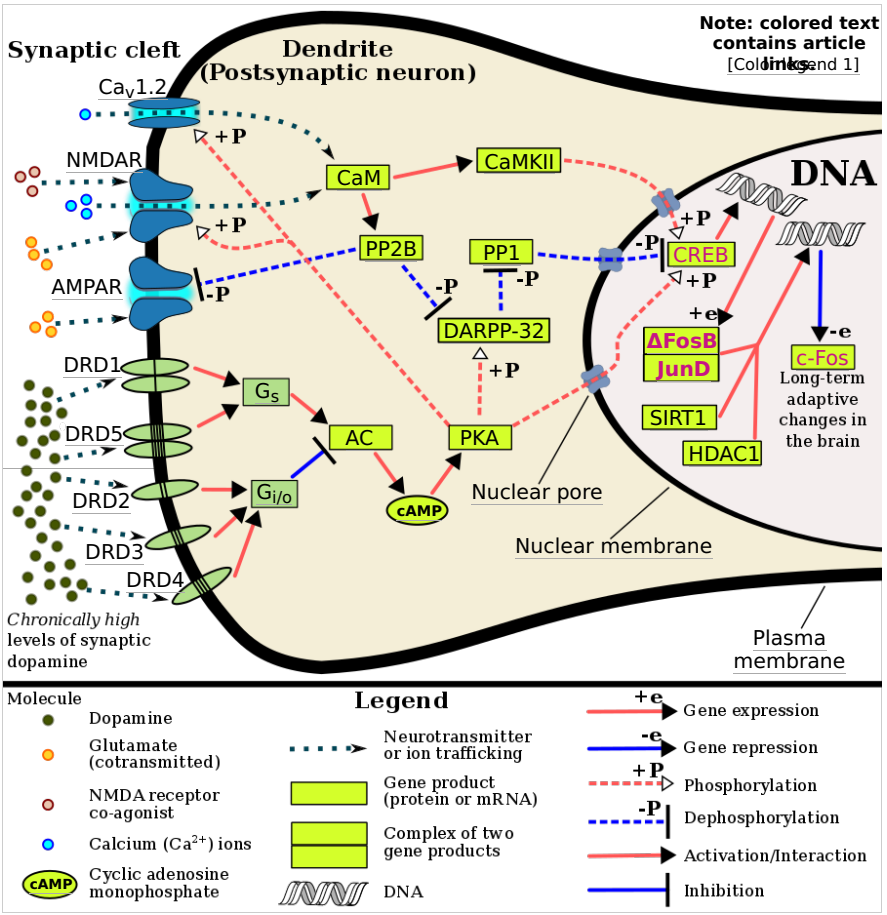
Additionally, research on the neurobiological effects of physical exercise suggests that daily aerobic exercise, especially endurance exercise (e.g., marathon running), prevents the development of drug addiction and is an effective adjunct therapy (i.e., a supplemental treatment) for amphetamine addiction.[sources 7] Exercise leads to better treatment outcomes when used as an adjunct treatment, particularly for psychostimulant addictions.[109][111][131] In particular, aerobic exercise decreases psychostimulant self-administration, reduces the reinstatement (i.e., relapse) of drug-seeking, and induces increased dopamine receptor D_2 (DRD2) density in the striatum.[108][131] This is the opposite of pathological stimulant use, which induces decreased striatal DRD2 density.[108] One review noted that exercise may also prevent the development of a drug addiction by altering ΔFosB or c-Fos immunoreactivity in the striatum or other parts of the reward system.[110]

that the brain interprets as intrinsically positive and desirable or as something to approach
- **sensitization** – an amplified response to a stimulus resulting from repeated exposure to it
- **substance use disorder** – a condition in which the use of substances leads to clinically and functionally significant impairment or distress
- **tolerance** – the diminishing effect of a drug resulting from repeated administration at a given dose

Transcription factor glossary

- **gene expression** – the process by which information from a gene is used in the synthesis of a functional gene product such as a protein
- **transcription** – the process of making messenger RNA (mRNA) from a DNA template by RNA polymerase
- **transcription factor** – a protein that binds to DNA and regulates gene expression by promoting or suppressing transcription
- **transcriptional regulation** – *controlling* the rate of gene transcription for example by helping or hindering RNA polymerase binding to DNA
- **upregulation**, **activation**, or **promotion** – *increase* the rate of gene transcription
- **downregulation**, **repression**, or **suppression** – *decrease* the rate of gene transcription
- **coactivator** – a protein (or a small molecule) that works with transcription factors to *increase* the rate of gene transcription
- **corepressor** – a protein (or a small molecule) that works with transcription factors to *decrease* the rate of gene transcription
- **response element** – a specific sequence of DNA that a transcription factor binds to

Signaling cascade in the nucleus accumbens that results in amphetamine addiction



This diagram depicts the signaling events in the brain's reward center that are induced by chronic high-dose exposure to psychostimulants that increase the concentration of synaptic dopamine, like amphetamine, methamphetamine, and phenethylamine. Following presynaptic dopamine and glutamate co-release by such psychostimulants,[97][98] postsynaptic receptors for these neurotransmitters trigger internal signaling events through a cAMP-dependent pathway and a calcium-dependent pathway that ultimately result in increased CREB phosphorylation.[97][99][100] Phosphorylated CREB increases levels of ΔFosB, which in turn represses the c-Fos gene with the help of corepressors;[97][101][102] c-Fos repression acts as a molecular switch that enables the accumulation of ΔFosB in the neuron.[103] A highly stable (phosphorylated) form of ΔFosB, one that persists in neurons for 1–2 months, slowly accumulates following repeated high-dose exposure to stimulants through this process.[101][102] ΔFosB functions as "one of the master control proteins" that produces addiction-related structural changes in the brain, and upon sufficient accumulation, with the help of its downstream targets (e.g., nuclear factor kappa B), it induces an addictive state.[101][102]

Summary of addiction-related plasticity

Form of neuroplasticity or behavioral plasticity	Type of reinforcer						Sources
	Opiates	Psychostimulants	High fat or sugar food	Sexual intercourse	Physical exercise (aerobic)	Environmental enrichment	
ΔFosB expression in nucleus accumbens D1-type MSNs	↑	↑	↑	↑	↑	↑	[108]
Behavioral plasticity							
Escalation of intake	Yes	Yes	Yes				[108]
Psychostimulant cross-sensitization	Yes	Not applicable	Yes	Yes	Attenuated	Attenuated	[108]
Psychostimulant self-administration	↑	↑	↓		↓	↓	[108]

Psychostimulant conditioned place preference	↑	↑	↓	↑	↓	↑	[108]
Reinstatement of drug-seeking behavior	↑	↑			↓	↓	[108]
Neurochemical plasticity							
CREB phosphorylation in the nucleus accumbens	↓	↓	↓		↓	↓	[108]
Sensitized dopamine response in the nucleus accumbens	No	Yes	No	Yes			[108]
Altered striatal dopamine signaling	↓DRD2, ↑DRD3	↑DRD1, ↓DRD2, ↑DRD3	↑DRD1, ↓DRD2, ↑DRD3		↑DRD2	↑DRD2	[108]
Altered striatal opioid signaling	No change or ↑μ-opioid receptors	↑μ-opioid receptors ↑κ-opioid receptors	↑μ-opioid receptors	↑μ-opioid receptors	No change	No change	[108]
Changes in striatal opioid peptides	↑dynorphin No change: enkephalin	↑dynorphin	↓enkephalin		↑dynorphin	↑dynorphin	[108]
Mesocorticolimbic synaptic plasticity							
Number of dendrites in the nucleus accumbens	↓	↑		↑			[108]
Dendritic spine density in the nucleus accumbens	↓	↑		↑			[108]

Dependence and withdrawal

Drug tolerance develops rapidly in amphetamine abuse (i.e., recreational amphetamine use), so periods of extended abuse require increasingly larger doses of the drug in order to achieve the same effect.[132][133] According to a Cochrane 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."[134] This review noted that withdrawal symptoms in chronic, high-dose users are frequent, occurring in roughly 88% of cases, and persist for 3–4 weeks with a marked "crash" phase occurring during the first week.[134] 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.[134] The review indicated that the severity of withdrawal symptoms is positively correlated with the age of the individual and the extent of their dependence.[134] Mild withdrawal symptoms from the discontinuation of amphetamine treatment at therapeutic doses can be avoided by tapering the dose.[3]

Overdose

An amphetamine overdose can lead to many different symptoms, but is rarely fatal with appropriate care.[135][76][136] The severity of overdose symptoms increases with dosage and decreases with drug tolerance to amphetamine.[137][76] 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.[76] Symptoms of a moderate and extremely large overdose are listed below; fatal amphetamine poisoning usually also involves convulsions and coma.[75][137] 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).[note 12][138]

Overdose symptoms by system

System	Minor or moderate overdose[75][137][76]	Severe overdose[sources 10]
Cardiovascular	▪ Abnormal heartbeat ▪ High or low blood pressure	▪ Cardiogenic shock (heart not pumping enough blood) ▪ Cerebral hemorrhage (bleeding in the brain) ▪ Circulatory collapse (partial or complete failure of the circulatory system)
Central nervous system	▪ Confusion ▪ Abnormally fast reflexes ▪ Severe agitation ▪ Tremor (involuntary muscle twitching)	▪ Acute amphetamine psychosis (e.g., delusions and paranoia) ▪ Compulsive and repetitive movement ▪ Serotonin syndrome (excessive serotonergic nerve activity) ▪ Sympathomimetic toxidrome (excessive adrenergic nerve activity)
Musculoskeletal	▪ Muscle pain	▪ Rhabdomyolysis (rapid muscle breakdown)
Respiratory	▪ Rapid breathing	▪ Pulmonary edema (fluid accumulation in the lungs) ▪ Pulmonary hypertension (high blood pressure in the arteries of the lung) ▪ Respiratory alkalosis (reduced blood CO_2)
Urinary	▪ Painful urination ▪ Urinary retention (inability to urinate)	▪ No urine production ▪ Kidney failure
Other	▪ Elevated body temperature ▪ Mydriasis (dilated pupils)	▪ Elevated or low blood potassium ▪ Hyperpyrexia (extremely elevated core body temperature) ▪ Metabolic acidosis (excessively acidic bodily fluids)

Interactions

- Monoamine oxidase inhibitors (MAOIs) taken with amphetamine may result in a hypertensive crisis if taken within two weeks after last use of an MAOI type drug.[141]
- Inhibitors of enzymes that directly metabolize amphetamine (particularly CYP2D6 and FMO3) will prolong the elimination of amphetamine and increase drug effects.[141][142][143]
- Serotonergic drugs (such as most antidepressants) co-administered with amphetamine increases the risk of serotonin syndrome.[143]
- Stimulants and antidepressants (sedatives and depressants) may increase (decrease) the drug effects of amphetamine, and vice versa.[141]
- Gastrointestinal and urinary pH affect the absorption and elimination of amphetamine, respectively. Gastrointestinal alkalizing (acidifying) agents increase the absorption of amphetamine. Urinary alkalizing (acidifying) agents increase concentration of non-ionized (ionized) species, decreasing (increasing) urinary excretion.[141]
- Proton-pump inhibitors (PPIs) modify the absorption of Adderall XR and Mydayis.[141][143]
- Zinc supplementation may reduce the minimum effective dose of amphetamine when it is used for the treatment of ADHD.[note 13][147]

Pharmacology

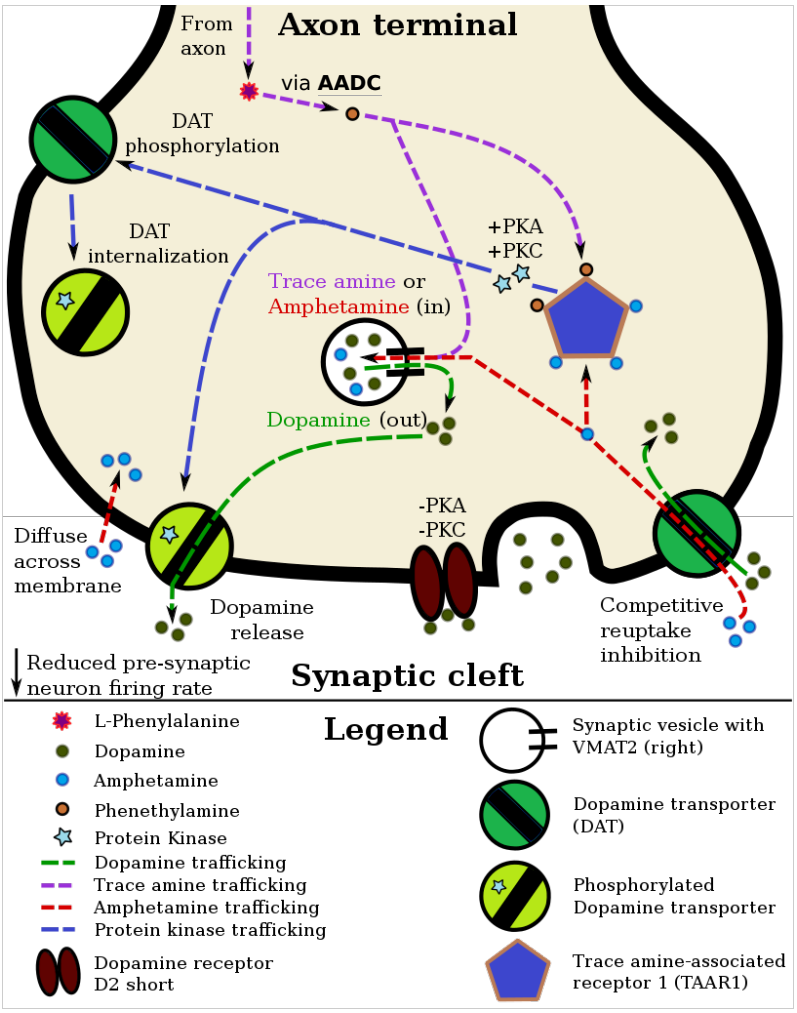
Mechanism of action

Amphetamine, the active ingredient of Adderall, works primarily by increasing the activity of the neurotransmitters dopamine and norepinephrine in the brain.[19][38] It also triggers the release of several other hormones (e.g., epinephrine) and neurotransmitters (e.g., serotonin and histamine) as well as the synthesis of certain neuropeptides (e.g., cocaine and amphetamine regulated transcript (CART) peptides).[21][153] Both active ingredients of Adderall, dextroamphetamine and levoamphetamine, bind to the same biological targets,[23][24] but their binding affinities (that is, potency) differ somewhat.[23][24] Dextroamphetamine and

levoamphetamine are both potent full agonists (activating compounds) of trace amine-associated receptor 1 (TAAR1) and interact with vesicular monoamine transporter 2 (VMAT2), with dextroamphetamine being the more potent agonist of TAAR1.[24] Consequently, dextroamphetamine produces more CNS stimulation than levoamphetamine;[24][154] however, levoamphetamine has slightly greater cardiovascular and peripheral effects.[23] It has been reported that certain children have a better clinical response to levoamphetamine.[25][26]

In the absence of amphetamine, VMAT2 will normally move monoamines (e.g., dopamine, histamine, serotonin, norepinephrine, etc.) from the intracellular fluid of a monoamine neuron into its synaptic vesicles, which store neurotransmitters for later release (via exocytosis) into the synaptic cleft.[21] When amphetamine enters a neuron and interacts with VMAT2, the transporter reverses its direction of transport, thereby releasing stored monoamines inside synaptic vesicles back into the neuron's intracellular fluid.[21] Meanwhile, when amphetamine activates TAAR1, the receptor causes the neuron's cell membrane-bound monoamine transporters (i.e., the dopamine transporter, norepinephrine transporter, or serotonin transporter) to either stop transporting monoamines altogether (via transporter internalization) or transport monoamines out of the neuron;[20] in other words, the reversed membrane transporter will push dopamine, norepinephrine, and serotonin out of the neuron's intracellular fluid and into the synaptic cleft.[20] In summary, by interacting with both VMAT2 and TAAR1, amphetamine releases neurotransmitters from synaptic vesicles (the effect from VMAT2) into the intracellular fluid where they subsequently exit the neuron through the membrane-bound, reversed monoamine transporters (the effect from TAAR1).[20][21]

Pharmacodynamics of amphetamine in a dopamine neuron



Amphetamine enters the presynaptic neuron across the neuronal membrane or through DAT.[20] Once inside, it binds to TAAR1 or enters synaptic vesicles through VMAT2.[20][21] When amphetamine enters synaptic vesicles through VMAT2, it collapses the vesicular pH gradient, which in turn causes dopamine to be released into the cytosol (light tan-colored area) through VMAT2.[21][148] When amphetamine binds to TAAR1, it reduces the firing rate of the dopamine neuron via potassium channels and activates protein kinase A (PKA) and protein kinase C (PKC), which subsequently phosphorylates DAT.[20][149][150] PKA-phosphorylation causes DAT to withdraw into the presynaptic neuron (internalize) and cease transport.[20] PKC-phosphorylated DAT may either operate in reverse or, like PKA-phosphorylated DAT, internalize and cease transport.[20] Amphetamine is also known to increase intracellular calcium, an effect which is associated with DAT phosphorylation through a CAMKIIα-dependent pathway, in turn producing dopamine efflux.[151][152]

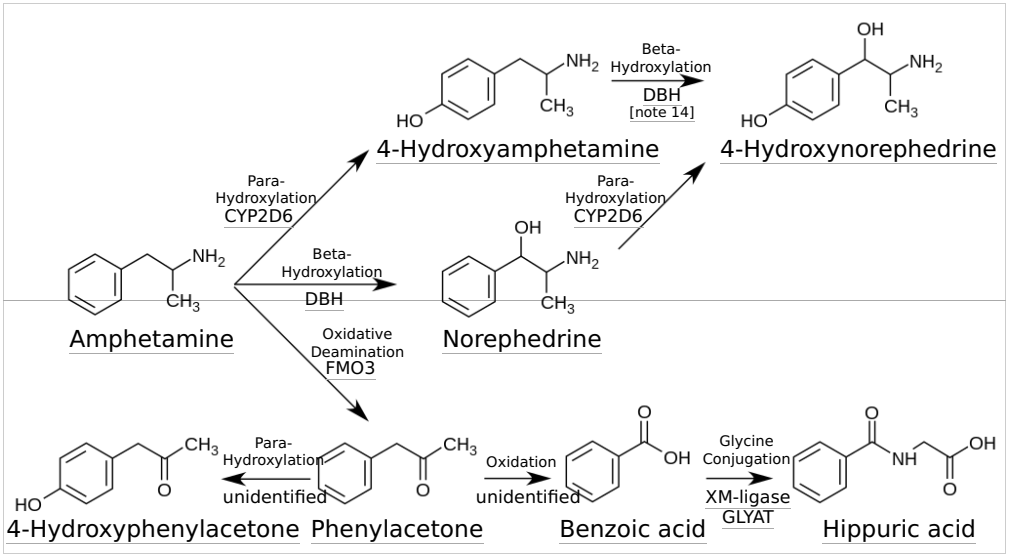
Pharmacokinetics

The oral bioavailability of amphetamine varies with gastrointestinal pH;[12] it is well absorbed from the gut, and bioavailability is typically over 75% for dextroamphetamine.[155] Amphetamine is a weak base with a pK_a of 9.9;[156] 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.[156][12] Conversely, an acidic pH means the drug is predominantly in a water-soluble cationic (salt) form, and less is absorbed.[156] Approximately 20% of amphetamine circulating in the bloodstream is bound to plasma proteins.[157] Following absorption, amphetamine readily distributes into most tissues in the body, with high concentrations occurring in cerebrospinal fluid and brain tissue.[158]

The half-lives of amphetamine enantiomers differ and vary with urine pH.[156] At normal urine pH, the half-lives of dextroamphetamine and levoamphetamine are 9–11 hours and 11–14 hours, respectively.[156] Highly acidic urine will reduce the enantiomer half-lives to 7 hours;[158] highly alkaline urine will increase the half-lives up to 34 hours.[158] 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.[156] Amphetamine is eliminated via the kidneys, with 30–40% of the drug being excreted unchanged at normal urinary pH.[156] When the urinary pH is basic, amphetamine is in its free base form, so less is excreted.[156] 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.[156] Following oral administration, amphetamine appears in urine within 3 hours.[158] Roughly 90% of ingested amphetamine is eliminated 3 days after the last oral dose.[158]

CYP2D6, dopamine β-hydroxylase (DBH), flavin-containing monooxygenase 3 (FMO3), butyrate-CoA ligase (XM-ligase), and glycine *N*-acyltransferase (GLYAT) are the enzymes known to metabolize amphetamine or its metabolites in humans.[sources 11] Amphetamine has a variety of excreted metabolic products, including 4-hydroxyamphetamine, 4-hydroxynorephedrine, 4-hydroxyphenylacetone, benzoic acid, hippuric acid, norephedrine, and phenylacetone.[156][159] Among these metabolites, the active sympathomimetics are 4-hydroxyamphetamine,[160] 4-hydroxynorephedrine,[161] and norephedrine.[162] The main metabolic pathways involve aromatic para-hydroxylation, aliphatic alpha- and beta-hydroxylation, *N*-oxidation, *N*-dealkylation, and deamination.[156][163] The known metabolic pathways, detectable metabolites, and metabolizing enzymes in humans include the following:

Metabolic pathways of amphetamine in humans[sources 11]



The primary active metabolites of amphetamine are 4-hydroxyamphetamine and norephedrine;[159] at normal urine pH, about 30–40% of amphetamine is excreted unchanged and roughly 50% is excreted as the inactive metabolites (bottom row).[156] The remaining 10–20% is excreted as the active metabolites.[156] Benzoic acid is metabolized by XM-ligase into an intermediate product, benzoyl-CoA, which is then metabolized by GLYAT into hippuric acid.[168]

Pharmacomicrobiomics

The human metagenome (i.e., the genetic composition of an individual and all microorganisms that reside on or within the individual's body) varies considerably between individuals.[172][173] Since the total number of microbial and viral cells in the human body (over 100 trillion) greatly outnumbers human cells (tens of trillions),[note 15][172][174] there is considerable potential for interactions between drugs and an individual's microbiome, including: drugs altering the composition of the human microbiome, drug metabolism by microbial enzymes modifying the drug's pharmacokinetic profile, and microbial drug metabolism affecting a drug's clinical efficacy and toxicity profile.[172][173][175] The field that studies these interactions is known as pharmacomicrobiomics.[172]

Similar to most biomolecules and other orally administered xenobiotics (i.e., drugs), amphetamine is predicted to undergo promiscuous metabolism by human gastrointestinal microbiota (primarily bacteria) prior to absorption into the blood stream.[175] The first amphetamine-metabolizing microbial enzyme, tyramine oxidase from a strain of *E. coli* commonly found in the human gut, was identified in 2019.[175] This enzyme was found to metabolize amphetamine, tyramine, and phenethylamine with roughly the same binding affinity for all three compounds.[175]

Related endogenous compounds

Amphetamine has a very similar structure and function to the endogenous trace amines, which are naturally occurring neuromodulator molecules produced in the human body and brain.[20][22][176] 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).[20][22][177] 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.[22][177] In turn, *N*-methylphenethylamine is metabolized from phenethylamine by phenylethanolamine *N*-methyltransferase, the same enzyme that metabolizes norepinephrine into epinephrine.[22][177] Like amphetamine, both phenethylamine and *N*-methylphenethylamine regulate monoamine neurotransmission via TAAR1;[20][176][177] unlike amphetamine, both of these substances are broken down by monoamine oxidase B, and therefore have a shorter half-life than amphetamine.[22][177]

History, society, and culture

History

The pharmaceutical company Rexar reformulated their popular weight loss drug Obetrol following its mandatory withdrawal from the market in 1973 under the Kefauver Harris Amendment to the Federal Food, Drug, and Cosmetic Act due to the results of the Drug Efficacy Study Implementation (DESI) program (which indicated a lack of efficacy). The new formulation simply replaced the two methamphetamine components with dextroamphetamine and amphetamine components of the same weight (the other two original dextroamphetamine and amphetamine components were preserved), preserved the Obetrol branding, and despite it lacking FDA approval, it still made it onto the market and was marketed and sold by Rexar for many years.

In 1994 Richwood Pharmaceuticals acquired Rexar and began promoting Obetrol as a treatment for ADHD (and later narcolepsy as well), now marketed under the new brand name of Adderall, a contraction of the phrase "A.D.D. for All" intended to convey that "it was meant to be kind of an inclusive thing" for marketing purposes.[178] The FDA cited the company for numerous significant CGMP violations related to Obetrol discovered during routine inspections following the acquisition (including issuing a formal warning letter for the violations), then later issued a second formal warning letter to Richwood Pharmaceuticals specifically due to violations of "the new drug and misbranding provisions of the FD&C Act". Following extended discussions with Richwood Pharmaceuticals regarding the resolution of a large number of issues related to the company's numerous violations of FDA regulations, the FDA formally approved the first Obetrol labeling/sNDA revisions in 1996, including a name change to Adderall and a restoration of its status as an approved drug product.[179][180] In 1997 Richwood Pharmaceuticals was acquired by Shire Pharmaceuticals in a $186 million transaction.[178]

Richwood Pharmaceuticals, which later merged with Shire plc, introduced the current Adderall brand in 1996 as an instant-release tablet.[181] In 2006, Shire agreed to sell rights to the Adderall name for the instant-release form of the medication to Duramed Pharmaceuticals.[182] DuraMed Pharmaceuticals was acquired by Teva Pharmaceuticals in 2008 during their acquisition of Barr Pharmaceuticals, including Barr's Duramed division.[183]

The first generic version of Adderall IR was introduced to market in 2002.[5] Later on, Barr and Shire reached a settlement agreement permitting Barr to offer a generic form of the extended-release drug beginning in April 2009.[5][184]

Commercial formulation

Chemically, Adderall is a mixture of four amphetamine salts; specifically, it is composed of equal parts (by mass) of amphetamine aspartate monohydrate, amphetamine sulfate, dextroamphetamine sulfate, and dextroamphetamine saccharate.[46] This drug mixture has slightly stronger CNS effects than racemic amphetamine due to the higher proportion of dextroamphetamine.[20][23] Adderall is produced as both an immediate release (IR) and extended release (XR) formulation.[5][9][46] As of December 2013, ten different companies produced generic Adderall IR, while Teva Pharmaceutical Industries, Actavis, and Barr Pharmaceuticals manufactured generic Adderall XR.[5] As of 2013, Shire plc, the company that held the original patent for Adderall and Adderall XR, still manufactured brand name Adderall XR, but not Adderall IR.[5]

Comparison to other formulations

Adderall is one of several formulations of pharmaceutical amphetamine, including singular or mixed enantiomers and as an enantiomer prodrug. The table below compares these medications (based on US approved forms):

Amphetamine base in marketed amphetamine medications

drug		formula	molar mass [note 16] (g/mol)		amphetamine base [note 17] (percent)			amphetamine base in equal doses (30 mg dose)		doses with equal base content [note 18]
			total	base	total	dextro-	levo-	dextro-	levo-	
dextroamphetamine sulfate[186][187]		$(C_9H_{13}N)_2•H_2SO_4$	368.49	270.41	73.38%	73.38%	—	22.0 mg	—	30.0 mg
amphetamine sulfate[188]		$(C_9H_{13}N)_2•H_2SO_4$	368.49	270.41	73.38%	36.69%	36.69%	11.0 mg	11.0 mg	30.0 mg
Adderall					62.57%	47.49%	15.08%	14.2 mg	4.5 mg	35.2 mg
25%	dextroamphetamine sulfate[186][187]	$(C_9H_{13}N)_2•H_2SO_4$	368.49	270.41	73.38%	73.38%	—			
25%	amphetamine sulfate[188]	$(C_9H_{13}N)_2•H_2SO_4$	368.49	270.41	73.38%	36.69%	36.69%			
25%	dextroamphetamine saccharate[189]	$(C_9H_{13}N)_2•C_6H_{10}O_8$	480.55	270.41	56.27%	56.27%	—			
25%	amphetamine aspartate monohydrate[190]	$(C_9H_{13}N)•C_4H_7NO_4•H_2O$	286.32	135.21	47.22%	23.61%	23.61%			
lisdexamfetamine dimesylate[191]		$C_{15}H_{25}N_3O•(CH_4O_3S)_2$	455.49	135.21	29.68%	29.68%	—	8.9 mg	—	74.2 mg
amphetamine base suspension[83]		$C_9H_{13}N$	135.21	135.21	100%	76.19%	23.81%	22.9 mg	7.1 mg	22.0 mg

Legal status

- In Canada, amphetamines are in Schedule I of the Controlled Drugs and Substances Act, and can only be obtained by prescription.[192]
- In Japan, the use, production, and import of any medicine containing amphetamine are prohibited.[193]
- In South Korea, amphetamines are prohibited.[194]
- In Taiwan, amphetamines including Adderall are Schedule 2 drugs with a minimum five years prison term for possession.[195] Only Ritalin can be legally prescribed for treatment of ADHD.
- In Thailand, amphetamines are classified as Type 1 Narcotics.[196]
- In the United Kingdom, amphetamines are regarded as Class B drugs. The maximum penalty for unauthorized possession is five years in prison and an unlimited fine. The maximum penalty for illegal supply is 14 years in prison and an unlimited fine.[197]
- In the United States, amphetamine is a Schedule II prescription drug, classified as a CNS stimulant.[198]
- Internationally, amphetamine is in Schedule II of the Convention on Psychotropic Substances.[199][200]

See also

- Dextroamphetamine
- Levoamphetamine
- Lisdexamfetamine
- Methylphenidate

Explanatory notes

1. Salts of racemic amphetamine and dextroamphetamine are mixed in a (1:1) ratio to produce this drug. Because the racemate is composed of equal parts dextroamphetamine and levoamphetamine, this drug can also be described as a mixture of the *D* and *(L)*-enantiomers of amphetamine in a (3:1) ratio, although none of the components of the mixture are levoamphetamine salts.[1][2]
2. The trade name **Adderall** is used primarily throughout this article because the four-salt composition of the drug makes its nonproprietary name (dextroamphetamine sulfate 25%, dextroamphetamine saccharate 25%, amphetamine sulfate 25%, and amphetamine aspartate 25%) excessively lengthy.[5] **Mydayis** is a relatively new trade name that is not commonly used to refer generally to the mixture.[4]

3. The ADHD-related outcome domains with the greatest proportion of significantly improved outcomes from long-term continuous stimulant therapy include academics (≈55% of academic outcomes improved), driving (100% of driving outcomes improved), non-medical drug use (47% of addiction-related outcomes improved), obesity (≈65% of obesity-related outcomes improved), self-esteem (50% of self-esteem outcomes improved), and social function (67% of social function outcomes improved).[37]

   The largest effect sizes for outcome improvements from long-term stimulant therapy occur in the domains involving academics (e.g., grade point average, achievement test scores, length of education, and education level), self-esteem (e.g., self-esteem questionnaire assessments, number of suicide attempts, and suicide rates), and social function (e.g., peer nomination scores, social skills, and quality of peer, family, and romantic relationships).[37]

   Long-term combination therapy for ADHD (i.e., treatment with both a stimulant and behavioral therapy) produces even larger effect sizes for outcome improvements and improves a larger proportion of outcomes across each domain compared to long-term stimulant therapy alone.[37]
4. Cochrane reviews are high quality meta-analytic systematic reviews of randomized controlled trials.[42]
5. The statements supported by the USFDA come from prescribing information, which is the copyrighted intellectual property of the manufacturer and approved by the USFDA. USFDA contraindications are not necessarily intended to limit medical practice but limit claims by pharmaceutical companies.[72]
6. According to one review, amphetamine can be prescribed to individuals with a history of abuse provided that appropriate medication controls are employed, such as requiring daily pick-ups of the medication from the prescribing physician.[73]
7. In individuals who experience sub-normal height and weight gains, a rebound to normal levels is expected to occur if stimulant therapy is briefly interrupted.[79][80][81] The average reduction in final adult height from 3 years of continuous stimulant therapy is 2 cm.[81]
8. Transcription factors are proteins that increase or decrease the expression of specific genes.[114]
9. In simpler terms, this *necessary and sufficient* relationship means that ΔFosB overexpression in the nucleus accumbens and addiction-related behavioral and neural adaptations always occur together and never occur alone.
10. NMDA receptors are voltage-dependent ligand-gated ion channels that requires simultaneous binding of glutamate and a co-agonist (D-serine or glycine) to open the ion channel.[129]
11. The review indicated that magnesium L-aspartate and magnesium chloride produce significant changes in addictive behavior;[105] other forms of magnesium were not mentioned.
12. The 95% confidence interval indicates that there is a 95% probability that the true number of deaths lies between 3,425 and 4,145.
13. The human dopamine transporter contains a high affinity extracellular zinc binding site which, upon zinc binding, inhibits dopamine reuptake and amplifies amphetamine-induced dopamine efflux *in vitro*.[144][145][146] The human serotonin transporter and norepinephrine transporter do not contain zinc binding sites.[146]
14. 4-Hydroxyamphetamine has been shown to be metabolized into 4-hydroxynorephedrine by dopamine beta-hydroxylase (DBH) *in vitro* and it is presumed to be metabolized similarly *in vivo*.[164][167] Evidence from studies that measured the effect of serum DBH concentrations on 4-hydroxyamphetamine metabolism in humans suggests that a different enzyme may mediate the conversion of 4-hydroxyamphetamine to 4-hydroxynorephedrine;[167][169] however, other evidence from animal studies suggests that this reaction is catalyzed by DBH in synaptic vesicles within noradrenergic neurons in the brain.[170][171]
15. There is substantial variation in microbiome composition and microbial concentrations by anatomical site.[172][173] Fluid from the human colon – which contains the highest concentration of microbes of any anatomical site – contains approximately one trillion (10^12) bacterial cells/ml.[172]
16. For uniformity, molar masses were calculated using the Lenntech Molecular Weight Calculator[185] and were within 0.01 g/mol of published pharmaceutical values.
17. Amphetamine base percentage = molecular $mass_{base}$ / molecular $mass_{total}$. Amphetamine base percentage for Adderall = sum of component percentages / 4.
18. dose = (1 / amphetamine base percentage) × scaling factor = (molecular $mass_{total}$ / molecular $mass_{base}$) × scaling factor. The values in this column were scaled to a 30 mg dose of dextroamphetamine sulfate. *Due to pharmacological differences between these medications (e.g., differences in the release, absorption, conversion, concentration, differing effects of enantiomers, half-life, etc.), the listed values should not be considered equipotent doses.*

Image legend

1.
   - Ion channel
   - G proteins & linked receptors
   - (Text color) Transcription factors

Reference notes

1. [8][9][10][11][12][13][14][15][16][17][18]
2. [19][20][21][22][23][24][25][26]

3. [3][12][23][82][83][84]
4. [85][86][87][88]
5. [12][89][85][87]
6. [8][12][23][90]
7. [108][109][110][111][131]
8. [106][108][107][115][116]
9. [107][118][119][120]
10. [139][75][137][136][140]
11. [156][164][165][142][166][159][167][168]

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    Beyond these general permissive effects, dopamine (acting via D1 receptors) and norepinephrine (acting at several receptors) can, at optimal levels, enhance working memory and aspects of attention."

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Physiologic and performance effects
• Amphetamines increase dopamine/norepinephrine release and inhibit their reuptake, leading to central nervous system (CNS) stimulation
• Amphetamines seem to enhance athletic performance in anaerobic conditions 39 40
• Improved reaction time
• Increased muscle strength and delayed muscle fatigue
• Increased acceleration
• Increased alertness and attention to task"
12. "Adderall XR- dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate and amphetamine aspartate capsule, extended release" (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aff45863-ffe1-4d4f-8acf-c7081512a6c0). *DailyMed*. Shire US Inc. 17 July 2019. Retrieved 22 December 2019.
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About 5–15% of the users who develop an amphetamine psychosis fail to recover completely (Hofmann 1983) ...
Findings from one trial indicate use of antipsychotic medications effectively resolves symptoms of acute amphetamine psychosis.
psychotic symptoms of individuals with amphetamine psychosis may be due exclusively to heavy use of the drug or heavy use of the drug may exacerbate an underlying vulnerability to schizophrenia."
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Figure 3: Treatment benefit by treatment type and outcome group (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340791/figure/pone.0116407.g003/)
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Table 9.2 Dextroamphetamine formulations of stimulant medication
Dexedrine [Peak:2–3 h] [Duration:5–6 h] ...
Adderall [Peak:2–3 h] [Duration:5–7 h]
Dexedrine spansules [Peak:7–8 h] [Duration:12 h] ...
Adderall XR [Peak:7–8 h] [Duration:12 h]
Vyvanse [Peak:3–4 h] [Duration:12 h]"
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DOSAGE FORMS AND STRENGTHS
Extended-release oral suspension contains 2.5 mg amphetamine base equivalents per mL."
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– Nasal decongestants:
– Sympathomimetic:
• Amphetamine"
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Figure 2: Psychostimulant-induced signaling events (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834246/figure/DialoguesClinNeurosci-11-257-g002/)
98. Broussard JI (January 2012). "Co-transmission of dopamine and glutamate" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3250102). *The Journal of General Physiology*. **139** (1): 93–96. doi:10.1085/jgp.201110659 (https://doi.org/10.1085%2Fjgp.201110659). PMC 3250102 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3250102). PMID 22200950 (https://pubmed.ncbi.nlm.nih.gov/22200950). "Coincident and convergent input often induces plasticity on a postsynaptic neuron. The NAc integrates processed information about the environment from basolateral amygdala, hippocampus, and prefrontal cortex (PFC), as well as projections from midbrain dopamine neurons. Previous studies have demonstrated how dopamine modulates this integrative process. For example, high frequency stimulation potentiates hippocampal inputs to the NAc while simultaneously depressing PFC synapses (Goto and Grace, 2005). The converse was also shown to be true; stimulation at PFC potentiates PFC–NAc synapses but depresses hippocampal–NAc synapses. In light of the new functional evidence of midbrain dopamine/glutamate co-transmission (references above), new experiments of NAc function will have to test whether midbrain glutamatergic inputs bias or filter either limbic or cortical inputs to guide goal-directed behavior."
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Figure 4: Epigenetic basis of drug regulation of gene expression (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272277/figure/F4/)
102. Nestler EJ (December 2012). "Transcriptional mechanisms of drug addiction" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3569166). *Clinical Psychopharmacology and Neuroscience*. **10** (3): 136–143. doi:10.9758/cpn.2012.10.3.136 (https://doi.org/10.9758%2Fcpn.2012.10.3.136). PMC 3569166 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3569166). PMID 23430970 (https://pubmed.ncbi.nlm.nih.gov/23430970). "The 35-37 kD ΔFosB isoforms accumulate with chronic drug exposure due to their extraordinarily long half-lives. ... As a result of its stability, the ΔFosB protein persists in neurons for at least several weeks after cessation of drug exposure. ... ΔFosB overexpression in nucleus accumbens induces NFκB ... In contrast, the ability of ΔFosB to repress the c-Fos gene occurs in concert with the recruitment of a histone deacetylase and presumably several other repressive proteins such as a repressive histone methyltransferase"
103. Nestler EJ (October 2008). "Transcriptional mechanisms of addiction: Role of ΔFosB" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2607320). *Philosophical Transactions of the Royal Society B: Biological Sciences*. **363** (1507): 3245–3255. doi:10.1098/rstb.2008.0067 (https://doi.org/10.1098%2Frstb.2008.0067). PMC 2607320 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2607320). PMID 18640924 (https://pubmed.ncbi.nlm.nih.gov/18640924). "Recent evidence has shown that ΔFosB also represses the c-fos gene that helps create the molecular switch—from the induction of several short-lived Fos family proteins after acute drug exposure to the predominant accumulation of ΔFosB after chronic drug exposure"
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108. Olsen CM (December 2011). "Natural rewards, neuroplasticity, and non-drug addictions" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139704). *Neuropharmacology*. **61** (7): 1109–1122. doi:10.1016/j.neuropharm.2011.03.010 (https://doi.org/10.1016%2Fj.neuropharm.2011.03.010). PMC 3139704 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139704). PMID 21459101 (https://pubmed.ncbi.nlm.nih.gov/21459101). "Similar to environmental enrichment, studies have found that exercise reduces self-administration and relapse to drugs of abuse (Cosgrove et al., 2002; Zlebnik et al., 2010). There is also some evidence that these preclinical findings translate to human populations, as exercise reduces withdrawal symptoms and relapse in abstinent smokers (Daniel et al., 2006; Prochaska et al., 2008), and one drug recovery program has seen success in participants that train for and compete in a marathon as part of the program (Butler, 2005). ... In humans, the role of dopamine signaling in incentive-sensitization processes has recently been highlighted by the observation of a dopamine dysregulation syndrome in some patients taking dopaminergic drugs. This syndrome is characterized by a medication-induced increase in (or compulsive) engagement in non-drug rewards such as gambling, shopping, or sex (Evans et al., 2006; Aiken, 2007; Lader, 2008)."

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There is accelerating evidence that physical exercise is a useful treatment for preventing and reducing drug addiction ... In some individuals, exercise has its own rewarding effects, and a behavioral economic interaction may occur, such that physical and social rewards of exercise can substitute for the rewarding effects of drug abuse. ... The value of this form of treatment for drug addiction in laboratory animals and humans is that exercise, if it can substitute for the rewarding effects of drugs, could be self-maintained over an extended period of time. Work to date in [laboratory animals and humans] regarding exercise as a treatment for drug addiction supports this hypothesis. ... Animal and human research on physical exercise as a treatment for stimulant addiction indicates that this is one of the most promising treatments on the horizon."
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41. "Adderall XR Prescribing Information" (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021303s026lbl.pdf) (PDF). *United States Food and Drug Administration*. December 2013. pp. 8–10. Archived (https://web.archive.org/web/20131230233702/http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021303s026lbl.pdf) (PDF) from the original on 30 December 2013. Retrieved 30 December 2013.
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Table 5: N-containing drugs and xenobiotics oxygenated by FMO (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1828602/table/T5/)

43. "Mydayis Prescribing Information" (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022063s000lbl.pdf) (PDF). *United States Food and Drug Administration*. Shire US Inc. June 2017. pp. 1–21. Archived (https://web.archive.org/web/20190609083453/https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022063s000lbl.pdf) (PDF) from the original on 9 June 2019. Retrieved 8 August 2017.
44. Krause J (April 2008). "SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder". *Expert Rev. Neurother*. **8** (4): 611–625. doi:10.1586/14737175.8.4.611 (https://doi.org/10.1586%2F14737175.8.4.611). PMID 18416663 (https://pubmed.ncbi.nlm.nih.gov/18416663). S2CID 24589993 (https://api.semanticscholar.org/CorpusID:24589993). "Zinc binds at ... extracellular sites of the DAT [103], serving as a DAT inhibitor. In this context, controlled double-blind studies in children are of interest, which showed positive effects of zinc [supplementation] on symptoms of ADHD [105,106]. It should be stated that at this time [supplementation] with zinc is not integrated in any ADHD treatment algorithm."
45. Sulzer D (February 2011). "How addictive drugs disrupt presynaptic dopamine neurotransmission" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065181). *Neuron*. **69** (4): 628–649. doi:10.1016/j.neuron.2011.02.010 (https://doi.org/10.1016%2Fj.neuron.2011.02.010). PMC 3065181 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065181). PMID 21338876 (https://pubmed.ncbi.nlm.nih.gov/21338876). "They did not confirm the predicted straightforward relationship between uptake and release, but rather that some compounds including AMPH were better releasers than substrates for uptake. Zinc, moreover, stimulates efflux of intracellular [3H]DA despite its concomitant inhibition of uptake (Scholze et al., 2002)."
46. Scholze P, Nørregaard L, Singer EA, Freissmuth M, Gether U, Sitte HH (June 2002). "The role of zinc ions in reverse transport mediated by monoamine transporters" (https://doi.org/10.1074%2Fjbc.M112265200). *J. Biol. Chem*. **277** (24): 21505–21513. doi:10.1074/jbc.M112265200 (https://doi.org/10.1074%2Fjbc.M112265200). PMID 11940571 (https://pubmed.ncbi.nlm.nih.gov/11940571). "The human dopamine transporter (hDAT) contains an endogenous high affinity Zn^{2+} binding site with three coordinating residues on its extracellular face (His193, His375, and Glu396). ... Although Zn^{2+} inhibited uptake, Zn^{2+} facilitated [3H]MPP+ release induced by amphetamine, MPP+, or K+-induced depolarization specifically at hDAT but not at the human serotonin and the norepinephrine transporter (hNET). ... Surprisingly, this amphetamine-elicited efflux was markedly enhanced, rather than inhibited, by the addition of 10 μM Zn^{2+} to the superfusion buffer (Fig. 2 A, open squares). We stress that Zn^{2+} per se did not affect basal efflux (Fig. 2 A). ... In many brain regions, Zn^{2+} is stored in synaptic vesicles and co-released together with glutamate; under basal conditions, the extracellular levels of Zn^{2+} are low (~10 nM; see Refs. 39, 40). Upon neuronal stimulation, however, Zn^{2+} is co-released with the neurotransmitters and, consequently, the free Zn^{2+} concentration may transiently reach values that range from 10–20 μM (10) up to 300 μM (11). The concentrations of Zn^{2+} shown in this study, required for the stimulation of dopamine release (as well as inhibition of uptake), covered this physiologically relevant range, with maximum stimulation occurring at 3–30 μM. It is therefore conceivable that the action of Zn^{2+} on hDAT does not merely reflect a biochemical peculiarity but that it is physiologically relevant. ... Thus, when Zn^{2+} is co-released with glutamate, it may greatly augment the efflux of dopamine."
47. Scassellati C, Bonvicini C, Faraone SV, Gennarelli M (October 2012). "Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses". *J. Am. Acad. Child Adolesc. Psychiatry*. **51** (10): 1003–1019.e20. doi:10.1016/j.jaac.2012.08.015 (https://doi.org/10.1016%2Fj.jaac.2012.08.015). PMID 23021477 (https://pubmed.ncbi.nlm.nih.gov/23021477). "Although we did not find a sufficient number of studies suitable for a meta-analysis of PEA and ADHD, three studies[20,57,58] confirmed that urinary levels of PEA were significantly lower in patients with ADHD compared with controls. ... Administration of D-amphetamine and methylphenidate resulted in a markedly increased urinary excretion of PEA,[20,60] suggesting that ADHD treatments normalize PEA levels. ... Similarly, urinary biogenic trace amine PEA levels could be a biomarker for the diagnosis of ADHD,[20,57,58] for treatment efficacy,[20,60] and associated with symptoms of inattentivenesss.[59] ... With regard to zinc supplementation, a placebo controlled trial reported that doses up to 30 mg/day of zinc were safe for at least 8 weeks, but the clinical effect was equivocal except for the finding of a 37% reduction in amphetamine optimal dose with 30 mg per day of zinc.[110]"
48. Sulzer D, Cragg SJ, Rice ME (August 2016). "Striatal dopamine neurotransmission: regulation of release and uptake" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4850498). *Basal Ganglia*. **6** (3): 123–148. doi:10.1016/j.baga.2016.02.001 (https://doi.org/10.1016%2Fj.baga.2016.02.001). PMC 4850498 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4850498). PMID 27141430 (https://pubmed.ncbi.nlm.nih.gov/27141430). "Despite the challenges in determining synaptic vesicle pH, the proton gradient across the vesicle membrane is of fundamental importance for its function. Exposure of isolated catecholamine vesicles to protonophores collapses the pH gradient and rapidly redistributes transmitter from inside to outside the vesicle. ... Amphetamine and its derivatives like methamphetamine are weak base compounds that are the only widely used class of drugs known to elicit transmitter release by a non-exocytic mechanism. As substrates for both DAT and VMAT, amphetamines can be taken up to the cytosol and then sequestered in vesicles, where they act to collapse the vesicular pH gradient."
49. Ledonne A, Berretta N, Davoli A, Rizzo GR, Bernardi G, Mercuri NB (July 2011). "Electrophysiological effects of trace amines on mesencephalic dopaminergic neurons" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131148). *Front. Syst. Neurosci*. **5**: 56. doi:10.3389/fnsys.2011.00056 (https://doi.org/10.3389%2Ffnsys.2011.00056). PMC 3131148 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131148). PMID 21772817 (https://pubmed.ncbi.nlm.nih.gov/21772817). "Three important new aspects of TAs action have recently emerged: (a) inhibition of firing due to increased release of dopamine; (b) reduction of D2 and GABAB receptor-mediated inhibitory responses (excitatory effects due to disinhibition); and (c) a direct TA1 receptor-mediated activation of GIRK channels which produce cell membrane hyperpolarization."
50. "TAAR1" (http://genatlas.medecine.univ-paris5.fr/fiche.php?symbol=TAAR1). *GenAtlas*. University of Paris. 28 January 2012. Retrieved 29 May 2014. " • tonically activates inwardly rectifying K(+) channels, which reduces the basal firing frequency of dopamine (DA) neurons of the ventral tegmental area (VTA)"

151. Underhill SM, Wheeler DS, Li M, Watts SD, Ingram SL, Amara SG (July 2014). "Amphetamine modulates excitatory neurotransmission through endocytosis of the glutamate transporter EAAT3 in dopamine neurons" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159050). *Neuron*. **83** (2): 404–416. doi:10.1016/j.neuron.2014.05.043 (https://doi.org/10.1016%2Fj.neuron.2014.05.043). PMC 4159050 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159050). PMID 25033183 (https://pubmed.ncbi.nlm.nih.gov/25033183). "AMPH also increases intracellular calcium (Gnegy et al., 2004) that is associated with calmodulin/CamKII activation (Wei et al., 2007) and modulation and trafficking of the DAT (Fog et al., 2006; Sakrikar et al., 2012). ... For example, AMPH increases extracellular glutamate in various brain regions including the striatum, VTA and NAc (Del Arco et al., 1999; Kim et al., 1981; Mora and Porras, 1993; Xue et al., 1996), but it has not been established whether this change can be explained by increased synaptic release or by reduced clearance of glutamate. ... DHK-sensitive, EAAT2 uptake was not altered by AMPH (Figure 1A). The remaining glutamate transport in these midbrain cultures is likely mediated by EAAT3 and this component was significantly decreased by AMPH"
152. Vaughan RA, Foster JD (September 2013). "Mechanisms of dopamine transporter regulation in normal and disease states" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3831354). *Trends Pharmacol. Sci*. **34** (9): 489–496. doi:10.1016/j.tips.2013.07.005 (https://doi.org/10.1016%2Fj.tips.2013.07.005). PMC 3831354 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3831354). PMID 23968642 (https://pubmed.ncbi.nlm.nih.gov/23968642). "AMPH and METH also stimulate DA efflux, which is thought to be a crucial element in their addictive properties [80], although the mechanisms do not appear to be identical for each drug [81]. These processes are PKCβ– and CaMK–dependent [72, 82], and PKCβ knock-out mice display decreased AMPH-induced efflux that correlates with reduced AMPH-induced locomotion [72]."
153. "Amphetamine: Biomolecular Interactions and Pathways" (https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3007#x301). *PubChem Compound*. National Center for Biotechnology Information. Archived (https://web.archive.org/web/20131013122604/http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3007#x301) from the original on 13 October 2013. Retrieved 13 October 2013.
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155. Wishart DS, Djombou Feunang Y, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Iynkkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C, Wilson M. "Dextroamphetamine | DrugBank Online" (https://go.drugbank.com/drugs/DB01576). *DrugBank*. 5.0.
156. "Adderall XR Prescribing Information" (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021303s026lbl.pdf) (PDF). *United States Food and Drug Administration*. Shire US Inc. December 2013. pp. 12–13. Retrieved 30 December 2013.
157. Wishart DS, Djombou Feunang Y, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Iynkkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C, Wilson M. "Amphetamine | DrugBank Online" (https://go.drugbank.com/drugs/DB00182). *DrugBank*. 5.0.
158. "Metabolism/Pharmacokinetics". *Amphetamine* (https://web.archive.org/web/20171002194327/https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/cgi-bin/sis/search2/f?.%2Ftemp%2F~mdjW95%3A1%3AFULL). *United States National Library of Medicine – Toxicology Data Network*. Hazardous Substances Data Bank. Archived from the original (http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+300-62-9) on 2 October 2017. Retrieved 2 October 2017. "Duration of effect varies depending on agent and urine pH. Excretion is enhanced in more acidic urine. Half-life is 7 to 34 hours and is, in part, dependent on urine pH (half-life is longer with alkaline urine). ... Amphetamines are distributed into most body tissues with high concentrations occurring in the brain and CSF. Amphetamine appears in the urine within about 3 hours following oral administration. ... Three days after a dose of (+ or -)-amphetamine, human subjects had excreted 91% of the (14)C in the urine"
159. Santagati NA, Ferrara G, Marrazzo A, Ronsisvalle G (September 2002). "Simultaneous determination of amphetamine and one of its metabolites by HPLC with electrochemical detection". *Journal of Pharmaceutical and Biomedical Analysis*. **30** (2): 247–255. doi:10.1016/S0731-7085(02)00330-8 (https://doi.org/10.1016%2FS0731-7085%2802%2900330-8). PMID 12191709 (https://pubmed.ncbi.nlm.nih.gov/12191709).
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65. Taylor KB (January 1974). "Dopamine-beta-hydroxylase. Stereochemical course of the reaction" (http://www.jbc.org/content/249/2/454.full.pdf) (PDF). *Journal of Biological Chemistry*. **249** (2): 454–458. PMID 4809526 (https://pubmed.ncbi.nlm.nih.gov/4809526). Retrieved 6 November 2014. "Dopamine-β-hydroxylase catalyzed the removal of the pro-R hydrogen atom and the production of 1-norephedrine, (2*S*,1*R*)-2-amino-1-hydroxyl-1-phenylpropane, from d-amphetamine."
66. Cashman JR, Xiong YN, Xu L, Janowsky A (March 1999). "N-oxygenation of amphetamine and methamphetamine by the human flavin-containing monooxygenase (form 3): role in bioactivation and detoxication". *Journal of Pharmacology and Experimental Therapeutics*. **288** (3): 1251–1260. PMID 10027866 (https://pubmed.ncbi.nlm.nih.gov/10027866).
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68. Badenhorst CP, van der Sluis R, Erasmus E, van Dijk AA (September 2013). "Glycine conjugation: importance in metabolism, the role of glycine N-acyltransferase, and factors that influence interindividual variation". *Expert Opinion on Drug Metabolism & Toxicology*. **9** (9): 1139–1153. doi:10.1517/17425255.2013.796929 (https://doi.org/10.1517%2F17425255.2013.796929). PMID 23650932 (https://pubmed.ncbi.nlm.nih.gov/23650932). "Figure 1. Glycine conjugation of benzoic acid. The glycine conjugation pathway consists of two steps. First benzoate is ligated to CoASH to form the high-energy benzoyl-CoA thioester. This reaction is catalyzed by the HXM-A and HXM-B medium-chain acid:CoA ligases and requires energy in the form of ATP. ... The benzoyl-CoA is then conjugated to glycine by GLYAT to form hippuric acid, releasing CoASH. In addition to the factors listed in the boxes, the levels of ATP, CoASH, and glycine may influence the overall rate of the glycine conjugation pathway."
69. Horwitz D, Alexander RW, Lovenberg W, Keiser HR (May 1973). "Human serum dopamine-β-hydroxylase. Relationship to hypertension and sympathetic activity". *Circulation Research*. **32** (5): 594–599. doi:10.1161/01.RES.32.5.594 (https://doi.org/10.1161%2F01.RES.32.5.594). PMID 4713201 (https://pubmed.ncbi.nlm.nih.gov/4713201). "The biologic significance of the different levels of serum DβH activity was studied in two ways. First, in vivo ability to β-hydroxylate the synthetic substrate hydroxyamphetamine was compared in two subjects with low serum DβH activity and two subjects with average activity. ... In one study, hydroxyamphetamine (Paredrine), a synthetic substrate for DβH, was administered to subjects with either low or average levels of serum DβH activity. The percent of the drug hydroxylated to hydroxynorephedrine was comparable in all subjects (6.5-9.62) (Table 3)."
70. Freeman JJ, Sulser F (December 1974). "Formation of p-hydroxynorephedrine in brain following intraventricular administration of p-hydroxyamphetamine". *Neuropharmacology*. **13** (12): 1187–1190. doi:10.1016/0028-3908(74)90069-0 (https://doi.org/10.1016%2F0028-3908%2874%2990069-0). PMID 4457764 (https://pubmed.ncbi.nlm.nih.gov/4457764). "In species where aromatic hydroxylation of amphetamine is the major metabolic pathway, *p*-hydroxyamphetamine (POH) and *p*-hydroxynorephedrine (PHN) may contribute to the pharmacological profile of the parent drug. ... The location of the *p*-hydroxylation and β-hydroxylation reactions is important in species where aromatic hydroxylation of amphetamine is the predominant pathway of metabolism. Following systemic administration of amphetamine to rats, POH has been found in urine and in plasma.
The observed lack of a significant accumulation of PHN in brain following the intraventricular administration of (+)-amphetamine and the formation of appreciable amounts of PHN from (+)-POH in brain tissue in vivo supports the view that the aromatic hydroxylation of amphetamine following its systemic administration occurs predominantly in the periphery, and that POH is then transported through the blood-brain barrier, taken up by noradrenergic neurones in brain where (+)-POH is converted in the storage vesicles by dopamine β-hydroxylase to PHN."
71. Matsuda LA, Hanson GR, Gibb JW (December 1989). "Neurochemical effects of amphetamine metabolites on central dopaminergic and serotonergic systems". *Journal of Pharmacology and Experimental Therapeutics*. **251** (3): 901–908. PMID 2600821 (https://pubmed.ncbi.nlm.nih.gov/2600821). "The metabolism of *p*-OHA to *p*-OHNor is well documented and dopamine-β hydroxylase present in noradrenergic neurons could easily convert *p*-OHA to *p*-OHNor after intraventricular administration."

172. ElRakaiby M, Dutilh BE, Rizkallah MR, Boleij A, Cole JN, Aziz RK (July 2014). "Pharmacomicrobiomics: the impact of human microbiome variations on systems pharmacology and personalized therapeutics" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086029). *Omics*. **18** (7): 402–414. doi:10.1089/omi.2014.0018 (https://doi.org/10.1089%2Fomi.2014.0018). PMC 4086029 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086029). PMID 24785449 (https://pubmed.ncbi.nlm.nih.gov/24785449). "The hundred trillion microbes and viruses residing in every human body, which outnumber human cells and contribute at least 100 times more genes than those encoded on the human genome (Ley et al., 2006), offer an immense accessory pool for inter-individual genetic variation that has been underestimated and largely unexplored (Savage, 1977; Medini et al., 2008; Minot et al., 2011; Wylie et al., 2012). ... Meanwhile, a wealth of literature has long been available about the biotransformation of xenobiotics, notably by gut bacteria (reviewed in Sousa et al., 2008; Rizkallah et al., 2010; Johnson et al., 2012; Haiser and Turnbaugh, 2013). This valuable information is predominantly about drug metabolism by unknown human-associated microbes; however, only a few cases of inter-individual microbiome variations have been documented [e.g., digoxin (Mathan et al., 1989) and acetaminophen (Clayton et al., 2009)]."
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