● Potentiatally DANGEROUS Pro-tips that will raise your tolerance, or worse.

1. ⚠️ If you ingest an antacid or baking soda 10 minutes prior to your oral dose of (active) amphetamine-based meds then the bioavailability *dramatically* increased through increased absorption.

2. ⚠️ If you also take reuptake inhibitor, such as 10 mg Ritalin, about 30 minutes before the same oral medication then you'll put the bi-directional monoamine Transporter into *simultaneous overdrive*.

3. ⚠️⚠️ If you take it after an MAOI then it will be *very* potentiated and for much longer.

4. ⚠️ A CYP2D6 Inhibitor will make even stronger again, such as:

- Amiodarone (Cordarone)
- Bupropion (Wellbutrin)

- Chlorpheniramine (Chlor-Trimeton)
- Chloroquine (Aralen)
- Chlorpromazine (Thorazine)
- Cinacalcet (Sensipar)
- Diphenhydramine (Benadryl)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Halofantrine (Halfan)
- Haloperidol (Haldol)
- Imatinib (Gleevec)
- Paroxetine (Paxil)
- Perphenazine (Trilafon)
- Propafenone (Rythmol)
- Propoxyphene (Darvon)
- Quinacrine (Atabrine)
- Quinidine (Quinidex, etc)
- Quinine
- Terbinafine (Lamisil)

👉 Stolen from https://go.drugbank.com/drugs/DB00182

● Summary

Amphetamine is a CNS stimulant and sympathomimetic agent indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

● Background

Amphetamine, a compound discovered over 100 years ago, is one of the more restricted controlled drugs. It was previously used for a large variety of conditions and this changed until this point where its use is highly restricted. Amphetamine, with the chemical formula alpha-methylphenethylamine, was discovered in 1910 and first synthesized by 1927. After being proven to reduce drug-induced anesthesia and produce arousal and insomnia, amphetamine racemic mix was registered by Smith, Kline and French in 1935. Amphetamine structure presents one chiral center and it exists in the form of dextro- and levo-isomers.

During World War II, amphetamine was used to promote wakefulness in the soldiers. This use

derived into a large overproduction of amphetamine and all the surplus after the war finalized ended up in the black market, producing the initiation of the illicit abuse.

3D image is at https://go.drugbank.com/structures/DB00182/image.svg

Chemical Formula: C9H13N

- Synonyms
  - alpha-Methylbenzeneethaneamine
  - Amfetamina
  - Amfetamine
  - Amfetaminum
  - Amphetamine
  - beta-Aminopropylbenzene

- beta-Phenylisopropylamin
- Desoxynorephedrine
- rac-amphetamine

----- PHARMACOLOGY -----

● Indication

Amphetamine is indicated for the treatment of attention-deficit/hyperactivity disorders (ADHD) as well as for the treatment of central nervous system disorders such as narcolepsy.

ADHD is a complex disorder associated with the substantial heterogeneity in etiology, clinical presentation, and treatment outcome.

ADHD comes from a complex interplay between interdependent genetic and non-genetic factors which cause complex mental disorders in children and teenagers.

On the other hand, narcolepsy is a chronic sleep disorder typically resenting during adolescence and characterized by excessive daytime sleepiness.

Amphetamine is also being used nowadays off-label for the treatment of obesity, depression and chronic pain.

● Pharmacodynamics

From its mechanism of action, it has been demonstrated that amphetamine augments the concentration of noradrenaline in the prefrontal cortex and dopamine in the striatum on a dose and time-dependent manner. The indistinct release of neurotransmitters which include adrenaline is known to produce cardiovascular side effects.

There are old reports of a cognitive enhancement related to the administration of amphetamine in which improvements in

intelligence test scores were reported.

In ADHD, amphetamine has been largely showed to produce remarkable improvements in school performance, behavior, and demeanor.1 The effect was shown to be produced through both racemic forms and to this date, the use of racemic forms 3:1 (D:L) is very common.

The therapeutic effect of amphetamine on serotonin does not seem to have a significant clinical effect on ADHD as observed on comparative studies with amphetamine and fenfluramine, a powerful serotonin releasing factor. However, the indirect effect on serotonin might have an effect on the depression and anxiety profile of ADHD.

Studies regarding the illicit use of amphetamine in which heavy consumers were studied proved the generation of a paranoid state which flagged this drug as a psychiatric danger compound.This observation was supported by the continuous reports of misuse in patients under depression.

- Mechanism of action

It is important to consider that amphetamine has a very similar structure to the catecholamine neurotransmitters mainly on the presence of a long planar conformation, the presence of an aromatic ring and nitrogen in the aryl side chain.

Amphetamine, as well as other catecholamines, is taken into presynaptic nerve terminals by the association with two sodium ions and one chloride ion.

The complex of the amphetamine with the ions is actively transported by monoamine reuptake transporters.

As amphetamine acts competitively with the endogenous monoamines, the greater the number of amphetamines the more internalized amphetamine will be found.

Once inside the presynaptic terminal,

amphetamine displaces other monoamines to be stored by VMAT2 which produces the pumping of the neurotransmitters into the synapse by a process called retro-transport.

This process of release of neurotransmitters is approximately fourfold more potent in the d-isomer for the release of dopamine.

The mechanism of action of amphetamine is complemented by the inhibition of the reuptake and of monoamine oxidase which acts synergistically to produce a significant increase the monoamine concentration.

This activity is not done as an inhibitor per se but more as a competitive substrate and thus, amphetamine is known to be a weak dopamine reuptake inhibitor, moderate noradrenaline reuptake inhibitor and very weak serotonin reuptake inhibitor.

From this specific action, the l-isomer is known to be significantly less potent.

Lastly, * amphetamine is known to be an inhibitor of the mitochondrial-bound enzyme MAO which is the catalytic enzyme in charge of degrading all the excess of neurotransmitters. This mechanism of action is often overpassed as amphetamine is a weak MAO inhibitor but this mechanism cannot be dismissed.

- Human target actions

Synaptic vesicular amine transporter: inhibitor

Sodium-dependent dopamine transporter: negative modulator

Cocaine- and amphetamine-regulated transcript protein: agonist

TAAR1 or Trace amine-associated receptor 1: agonist

Monoamine oxidase: inhibitor

Sodium-dependent noradrenaline transporter: agonist

• Substrate:

Alpha adrenergic receptor: agonist

Beta adrenergic receptor: agonist

Dopamine D2 receptor: binder

Amine oxidase [flavin-containing] B: inhibitor

Sodium-dependent serotonin transporter: binder

● Absorption

Amphetamine is well absorbed in the gut and as it is a weak base hence the more basic the environment the more of the drug is found in a lipid-soluble form and the absorption through lipid-rich cell membranes is highly favored.

The peak response of amphetamine occurs 1-3

hours after oral administration and approximately 15 minutes after injection and it presents a bioavailability of over 75%.

Complete amphetamine absorption is usually done after 4-6 hours.

- Volume of distribution

Amphetamine is reported to have a high volume of distribution of 4 L/kg.

- Protein binding

The reported protein binding of amphetamine is relatively low and register to be of 20%.

- Metabolism

Amphetamine is known to be metabolized by the liver under the action of the CYP2D6. The metabolic pathway of amphetamine is mainly defined by aromatic hydroxylation, aliphatic hydroxylation, and n-dealkylation.

The formed metabolites in this pathway are 4-hydroxyamphetamine, 4-hydroxynorephedrine, hippuric acid, benzoic acid, benzyl methyl ketone, and p-hydroxyamphetamine which is known to be a potent hallucinogen.

However, a significant part of the original compound remains unchanged.

- Route of elimination

The elimination of amphetamine is mainly via the urine from which about 40% of the excreted dose is found as unchanged amphetamine. About 90% of the administered amphetamine is eliminated 3 days after oral administration.

The rate of elimination of amphetamine highly depends on the urine pH in which acidic pH will produce a higher excretion of amphetamine and basic pH produces a lower excretion.

- Half-life

The half-life of amphetamine highly depends on the isomer. For d-amphetamine, the reported half-life is of approximately 9-11 hours while for l-amphetamine the half-life is reported to be of 11-14 hours. The urine pH can modify this pharmacokinetic parameter which can vary from 7 hours in acid urine to 34 hours for alkaline urine.

- Clearance

The reported normal clearance rate is of 0.7 L.h/kg. This clearance has been shown to get significantly reduced in patients with renal impairment reaching a value of 0.4 L.h/kg.

- Toxicity

The mean lethal serum concentration is reported to be of 6.4 mg/l. Acute amphetamine overdose can lead to hyperthermia, respiratory depression, seizures, metabolic acidosis, renal failure, hepatic injury, and coma.

Some of the neurologic effects have been shown to be agitation, aggressive behavior, irritability, headache, and hallucinations.

In the cardiovascular site, there have been reports of arrhythmia, cardiomyopathy, myocardial infarction or ischemic stroke.

Lastly, in the GI tract, there are reports if abdominal pain, vomiting, diarrhea, cramps, anorexia and GI hemorrhage. A dose of 1-2 g of amphetamine is known to cause severe intoxication but some chronic abusers can report usage of even 5-15 g per day.

In animal studies, there is no evidence of carcinogenic potential, not clastogenic or to affect fertility or early embryonic development.