Amphetamines: Useful Stimulant or Dangerous Drug

Imagine a powerful class of drugs that has the ability to affect various people in all of the following situations. The first is a college student, we’ll call him Jimmy, is an avid student of a high achieving university who is up late night studying for an exam. Slowly fatigue from the day settles in and Jimmy decides to take an Adderall pill he was prescribed to keep alert and help prep for his test. Second we have a bodybuilder, 2013 Mr. 212 Olympia Flex Lewis. In preparation for an the upcoming Arnold Classic bodybuilding show Flex begins taking a supplement EPA in order to assist in the heavy weight loss needed to get to low body fat for the event. The third is television’s Walter White, from the Grammy award winning show Breaking Bad. White, a chemistry teacher and cancer survivor, pays his way through treatments with a chemistry kit in the back of an RV making blue crystals and selling in the illicit drug trade. Fourth is the infamous, Rudy Eugene, a Miami man whom in was the perpetrator in the cannibalistic attack of a homeless man in 2012. Eugene was suspected to be high on a new synthetic street drug known as “Bat Salts” for their resemblance to aromatic salts. So what do these four people all have in common? Well, they all have a direct relation with a class of chemicals known as Substituted Amphetamines, based on the original amphetamine molecule.

Amphetamine (C₉H₁₃N) is a relatively simple molecule (take out - as drugs go), consisting of an aromatic ring with a propyl group which has an amine substituted at the beta position. It has a well-developed history beginning in 1887 when it was first synthesized by Jewish/Romanian chemist Lazar Edeleanu at the University of Berlin. Edeleanu received his Ph.D in Chemistry within the same year for the discovery of amphetamine and his ability to find synthetic methods to build the compound. Although Edeleanu was able to synthesize amphetamine, the physiological properties of the drug were above his capabilities which left this determination to be found by Gordon Alles 40 years later. Alles resynthesized the compound and reported it to have symptomatic (adrenal imitating) properties; which contributed to the pharmaceutical uses of Amphetamine to become widespread.
Amphetamine was first used as a pharmaceutical drug as an inhaled decongestant sold by Smith, Kline and French under the brand name Benzedrine. As a small molecule (low molecular weight) and relatively non-polar, it is able to diffuse through the blood-brain barrier and act as a powerful stimulant to the Central Nervous System. A 2001 study found that Amphetamine is a full agonist of the G protein coupled receptor (GPCR) known as trace amine-associated receptor 1 (TAAR1). TAAR1 is critical in the regulation of brain monoamines which are often hormones or neurotransmitters. Activating TAAR1 in turn activates adenylyl cyclase resulting in increased cyclic adenosine monophosphate cAMP within the neuron, activating dopamine transporter (DAT) and causing the release of several neurotransmitters. Some of these transmitters are dopamine, serotonin which is related to happiness, and norepinephrine which is a precursor to Adrenaline. Additionally, acetylcholine can be released which is associated with memory and nerve function while histamine relates to inflammation.

Amphetamine is also an agonist of CART (cocaine amphetamine regulated transcript), a neuropeptide responsible partly for hunger, stress, and reward behavior. At high doses, Amphetamine also inhibits MAO-B, an enzyme responsible for metabolism of dopamine and phenethylamine, which results in even greater concentrations of these neurotransmitters in the synaptic cleft between neurons which increases attentiveness, motivation and mood. With so many mechanisms involved, it is easy to see how Amphetamine has so many
pharmacodynamic effects on the body.

Amphetamine mechanism of action at nerve synapses

Primarily, the increase in dopamine available for brain neurons results in an overall increase in focus, memory retention, an increase in stamina or endurance, and increased initiative. These effects are the reason why Amphetamine, as a sulfate salt under the drug name Adderall is prescribed as a treatment for attention deficit hyperactive disorder (ADHD). Adderall is a racemic mixture of dextroamphetamine and levoamphetamine (the D and L forms of the drug). Interestingly, it was found that dextroamphetamine form has a stronger effect on the CNS while the levoamphetamine form has a stronger effect on the somatic neurons and norepinephrine. Also, the dextro form is more rapidly metabolized with a shorter half-life then the levo form. Hence, Adderall is administered as a racemic mixture of 50/50 for an even effect throughout the body and to have a prolonged effect between the two half-lives, and this is why restlessness ensues after the neurological effects seem to have worn off from the drug. Adderall as an Amphetamine sulfate is a weak base with a pKa of around 10. Hence, it is more likely to be protonated in an acidic environment which results in charged drug and less uptake through diffusion via cell membrane in the stomach lining or intestinal epithelial lining. For this reason, Adderall is often instructed to be taken with a base or stomach-acid inhibitor to improve absorption in the stomach and reduce excretion through the kidneys, which allows for the lengthening of the half-life and increased effectiveness. Several studies on
effectiveness of Adderall on ADHD children have shown that it helps to improve attention and decrease disruptive behaviors associated with the disorder. An average IQ improvement of 4.5 following regular usage was observed. Another study has also shown long-term usage to help improve the brain abnormalities associated with ADHD, such as improved function in the right caudate nucleus. There are additional affects that the drug can provide that can help children with ADHD who wish to have more than improved memory function.

As a drug that inhibits increased cognitive function and memory retention, it should not come as a surprise that Adderall has began to become widely abused by university students who do not have a prescription, at doses that are higher than the recommended therapeutic dose. But, this non-prescribed abuse does have its risks. Firstly, longterm non-monitored usage often carries a high risk of addiction. Because of the administration of the levo form, higher doses of Amphetamine (Adderall) can cause heart related issues from the adrenergic effects of the norepinephrine. These effects include high blood pressure, heart palpitations, or even low blood pressure from adverse effects. Regular and improper use of this drug has been shown to produce sexual dysfunction in males, causing erectile dysfunction or in some cases even the opposite issue of prolonged unwanted erections. Heavier doses have been shown to hinder regular memory function and cognitive control. This often ensues the unregulated party to continue to take additional doses to achieve desired effect to no avail. With cases of heavy abuse, such as the partaking of high doses for extended periods of time (finals week for instance), Amphetamine can induce permanent psychosis for which up to 15% of users never recover from. The psychosis can include delusion, hallucination, paranoia and extreme insomnia. Due to its effect on the CART production and hence feeding behavior, Adderall has been shown to reduce appetite to extreme lows, which can result in muscle breakdown/excessive weight-loss if the food intake is not maintained to adequate levels. This latter effect is often unnoticed by the ingesting party until weight-loss has already set in. This weight-loss effect is closely related to another naturally occurring substituted amphetamine.

Ephedrine, is a type of substituted Amphetamine from the herb ma huang (Ephedra sinica) that is found in China which has been used as a herbal remedy for thousands of years. It has a hydroxyl group at the alpha positioned carbon of the propyl chain and an additional methyl group attached to the nitrogen. This results in four possible racemates from the two chiral centers. The Ephedra plant species has both Ephedrine (1R,2S or 1S, 2R) and Pseudoephedrine (1R,1R or 1S,1S) as natural products. With the addition of the hydroxyl group, this makes Ephedrine far more polar than unsubstituted Amphetamine and therefore far less viable to enter the blood brain barrier. This means Ephedra is almost entirely sympathomimetic and has hardly any CNS effects. As such it was often marketed as a heavy stimulant and appetite suppressant used for weightloss in dietary fitness supplements like the ones mentioned in the story regarding Flex Lewis. During the 80’s and 90’s it was used by weightlifters, bodybuilders, fitness enthusiasts, and professional athletes to alter their speed and performance, but it was found to also be able to assist them in making a specific weight class if
his/her sport required cutting weight. Ephedrine also has a hunger reducing effect in addition to somatic effects. When taken the increase in average heart rate results in and increase in oxygen uptake throughout the day and therefore more calories are metabolized throughout the day. However, after it was found to be potentially dangerous, with over 18,000 reports of adverse effects in 2004 alone, the USFDA restricted its usage and distribution heavily. Currently, it is almost exclusively sold as a decongestant and cough suppressant in cold medicine in very low doses. The sale of Ephedrine is very restricted, with the average pharmacy only being allowed to sell 9 grams of pseudoephedrine per month, regardless of the overall number of customers or demand. This is because Ephedrine and Pseudoephedrine are the most widely sought after products for the production of another substituted amphetamine, the illicit street drug Methamphetamine.

Methamphetamine is Amphetamine that is methylated at the amine itself. It is currently a Schedule II drug, a ranking system set by the USFDA. All non-prescription based sales are highly prohibited with heavy punishment if a illicit drug dealer is convicted. Methamphetamine has many street names and is most commonly referred to as: crystal meth, meth, speed, crystal, ice, shards, glass, crank, jib, tweak, rock, tina, cold, yaba in Thailand, as well as shabu or shaboo in China. With an extra methyl group that helps electronically stabilize the amine group, Methamphetamine is more hydrophobic than regular amphetamine, which allows it to readily diffuse through the blood-brain barrier. This means that Meth has a much greater CNS effect than Adderall and binds more tightly to certain receptors than regular amphetamine. As one might already assume, Methamphetamine has many more CNS side effects. It has been shown to be directly neurotoxic to dopaminergic and serotonin neurons. Therefore, prolonged usage causes direct damage to the brain, memory function due to dopaminergic neuron damage. Damage to the serotonin neurons can cause extreme or sometimes permanent depression in users. Methamphetamine is also slightly more addictive than unsubstituted Amphetamine due to enhanced CNS effects and having a stronger binding to brain neurons then Amphetamine. Methamphetamine also carries a much higher risk of permanent psychosis then unsubstituted Amphetamine. Unregulated usage is usually in proportions way higher than therapeutic recommended precautionary doses.

Methamphetamine was first synthesized in 1893 by Nagai Nagayoshi, a Japanese chemist who made it by reducing Ephedrine. Thereafter, in 1919 crystal meth (the salt form) was synthesized by Akira Ogata, another Japanese chemist. He did this by a process that is still used today, a reduction of Ephedrine via red phosphorus and hydroiodic acid. Interestingly enough, during World War II, both Axis and Allied forces would administer methamphetamine to the soldiers for the stimulant and performance enhancing benefits. During this time, they would feed the soldiers chocolate laced with the drug and in Germany it was known as Fliegerschocolade (Flying chocolate) because it made you feel like you were flying. This would induce fearless effect on them, making them fear death less. CNS side effects would take place on the battlefield such as hallucinations paranoia etc. It was also interesting to note at this time that Adolf Hitler himself
used Methamphetamine. He is believed to have smoked and used
methamphetamine personally beforehand, but there is documented evidence that
he was given intravenous meth injections during the war from 1942 until his
death in 1945. This is a possible explanation for the erratic psychotic behavior he
exuded during these years but that is left up to speculation. Since that time, Meth
has been banned in the Controlled Substances Act, which led to the production
of Meth taken into the underground illicit street market.

Today, crystal methamphetamine can be synthesized in multiple ways which are
convenient for non-industrial production. The most common is the Nagai method
mentioned before using red-P and hydroiodic acid. In this method, the hydroxyl
group is rapidly protonated by the HI, which results in the iodide attacking the
intermediate resulting in iodoephedrine. The phosphorous absorbs the iodide to
form phosphorous triiodide, which decomposes to phosphoric acid and HI again.
Another route uses hypophosphourous acid or phosphorous acid directly instead
of red phosphorous. This method results in a much greater yield but is also
exponentially more dangerous as toxic phosphine gas is a byproduct of the
reaction. Another procedure uses phenylacetone and reductive amination with
methylamine. Another simple method is a one-pot synthesis using ground
pseudoephedrine with NH₄NO₃ , water, and a hydrophobic solvent such as
Coleman fuel from lanterns. To this mixture, Lye (NaOH) and lithium from
batteries are added. This method, although quick and single-pot (meaning only
one flask is needed for synthesis), is very dangerous and requires careful
attention. Hydrochloride (HCL) gas is produced as a byproduct, so pressure can
accumulate and the reaction can get out of control, often leading to cracked glass
(contaminant exposure) or fire outbreak from uncontrolled reaction. As one would
expect, most of the methods used are dangerous and produce harmful
byproducts which waste management of Meth labs has become a problem in
areas where meth production occurs such as Fresno County in central California.

**Synthetic Pathways to Methamphetamine**
It has been shown that Amphetamines and substituted amphetamines are potent CNS stimulants that should not be taken lightly. It is amazing how a simple group substitution can dramatically change the pharmacodynamic effect of a drug when going from amphetamine to ephedrine or ephedrine to methamphetamine.
Works Cited


