Drugs, Doses, and Biodistribution

Alcohol, Caffeine, and Adderall

Group 7
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Background: Alcohol

The main compounds in an alcoholic beverage are ethanol and water. Ethanol (C_2H_6O) is a short organic molecule that is composed of two carbons and a hydroxyl (OH) group, all with single bonds (Figure 1). The presence of the OH group makes the molecule polar and therefore soluble in water (IARC 1988). If folded along the carbon backbone, the two sides mirror each other, meaning ethanol has a plane of symmetry and is achiral. There are two main receptors alcohol binds to: gamma-aminobutyric acid (GABA) receptors and *N*-methyl-D-aspartate (NMDA) receptors. To GABA, alcohol is an agonist meaning it has the same effect as a typical signal. The GABA receptor promotes the release of dopamine and serotonin when alcohol is consumed (Bardi 2002). Additionally, alcohol is an antagonist to the NMDA receptor, which is located in the brain and influences memory (Krystal et al. 2003). Damage to the receptor can cause neurodegenerative and cognitive disorders (Dutta, 2020). Consuming alcohol initially can cause feelings of euphoria, calmness, and relaxation. The chemical also slows processing which can lead to confusion and difficulty processing emotions which can cause anger, anxiety, and depression. Alcohol is often used as a mechanism to cope and can cause dependence which can worsen depression, stress, and anxiety (Mental Health Foundation, n.d.). Long-term excessive drinking has many physical effects. Alcohol causes an increase in blood pressure, which can lead to a greater risk of heart attacks and strokes. Infections, especially in the liver, are also a side effect of excessive drinking. It is time-consuming and difficult for the liver to break down alcohol which causes the buildup of fat. Lastly, alcohol is one of the main contributors to cancer as it damages and prevents cell repair, preventing signals between cells causing excess division and allowing harmful chemicals to be absorbed by cells (Nidirect Government Services 2017; Cancer Research UK 2018).

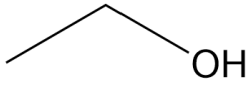

Figure 1: The molecular structure of ethanol (ChemDraw 2024).

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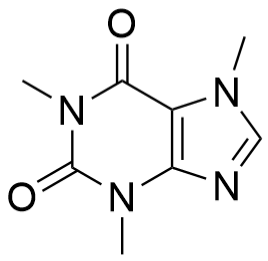
Background: Caffeine

Caffeine is one of the most widely used drugs globally and belongs to the methylxanthine class (Fiani et al. 2021). Its chemical structure features a purine ring system, which is a bicyclic structure that contains nitrogen atoms. The core of this stimulant is formed by a purine base known as xanthine, with three methyl groups attached to nitrogen positions at 1, 3, and 7 as shown in Figure 2 (Karuppagounder et al. 2021). This drug is achiral and does not have a plane of symmetry (Musale and Landomery 2012). As well, caffeine does not have a carbon that is bonded to four different groups and so its stereoisomers are identical.

Caffeine acts as a nonselective antagonist for the G-protein-coupled A1 and A2A adenosine receptors (Fredholm et al. 1999). This prevents adenosine, a purine nucleoside that inhibits neural activity, from binding to the receptors. Instead, caffeine can bind to them due to its structural similarity without activating the receptors (Riberio and Sebastião 2010). This inhibition of adenosine allows for increased neural activity while indirectly promoting the release of neurotransmitters like dopamine and norepinephrine (Institute of Medicine (US) Committee on Military Nutrition Research 2001). The increase in the activation of the central nervous system allows for greater focus, while the inhibition of adenosine reduces the perception of fatigue. The release of dopamine improves the mood of the user. Caffeine also affects the pituitary gland which leads to the stimulation of the adrenal glands to release epinephrine, causing an increase in heart rate and blood pressure. It acts as a mild diuretic as it prevents sodium reabsorption in the proximal and distal tubules. As a result, this increases free water excretion (Zhang et al. 2015). However, if taken in excessive amounts, caffeine can impact regular sleep patterns, cardiovascular and bone health, as well as increase symptoms of anxiety (Institute of Medicine (US) Committee on Military Nutrition Research 2001).



Caffeine

Figure 2: The molecular structure of caffeine, 1,3,7-trimethylpurine-2,6-dione (ChemDraw 2024)

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Background: Adderall

Adderall is a drug commonly used to treat attention-deficit hyperactivity disorder (ADHD) and sometimes narcolepsy. Its main purpose is to improve focus, attention, and impulse control by increasing the availability of specific neurotransmitters in the brain (Gordon 2017). However, because of its stimulant properties, it carries a risk of misuse which can lead to addiction.

Adderall mainly consists of amphetamine salts, which have one chiral centre and two enantiomers: dextroamphetamine and levoamphetamine (Figure 3). Adderall is approximately 25% l-amphetamine–the “left-handed” enantiomer–and 75% d-amphetamine– the “right-handed” enantiomer (Gordon 2017). It has a three-carbon chain with a benzene ring on the first carbon and an amine on the second carbon (National Center for Biotechnology Information 2005). This amine makes amphetamine polar, which is important when analyzing its cellular interactions.

Amphetamine acts as a central nervous system stimulant and its overall function is to increase the number of monoamines, such as dopamine, norepinephrine, and serotonin, in the synaptic cleft (Martin and Le 2023). Through their respective transporters: DAT, NET, and SERT, amphetamine is transported into the presynaptic neuron. Then, the amphetamine molecules inhibit vesicular monoamine transporter 2 (VMAT2). VMAT2 is a protein that stores monoamines in vesicles in the presynaptic neuron (Wu et al. 2023). Amphetamine’s blocking of VMAT2 eventually allows for more monoamines to be released into the synaptic cleft and then bind to the postsynaptic neuron (Figure 4). Other mechanisms include inhibiting the metabolism of monoamines by inhibiting monoamine oxidase and preventing DAT’s, NET’s, and SERT’s reuptake of monoamines by stimulating an intracellular receptor called TAAR1. Overall, Adderall is an indirect agonist of monoamine release into the synaptic cleft.

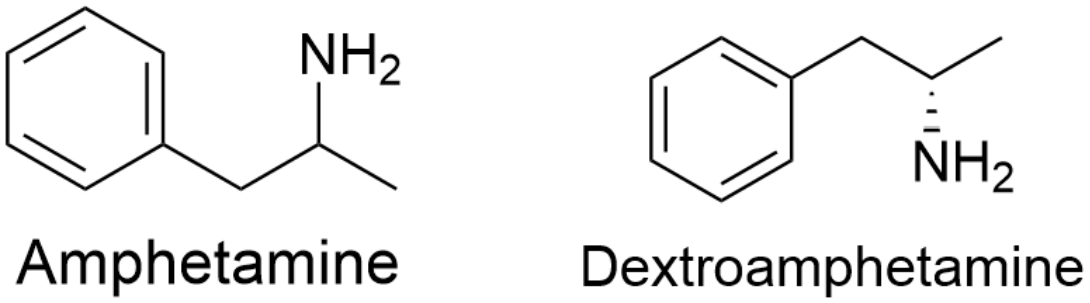

Figure 3: The chemical structure of enantiomers amphetamine and dextroamphetamine (1-phenylpropan-2-amine) (ChemDraw 2024).

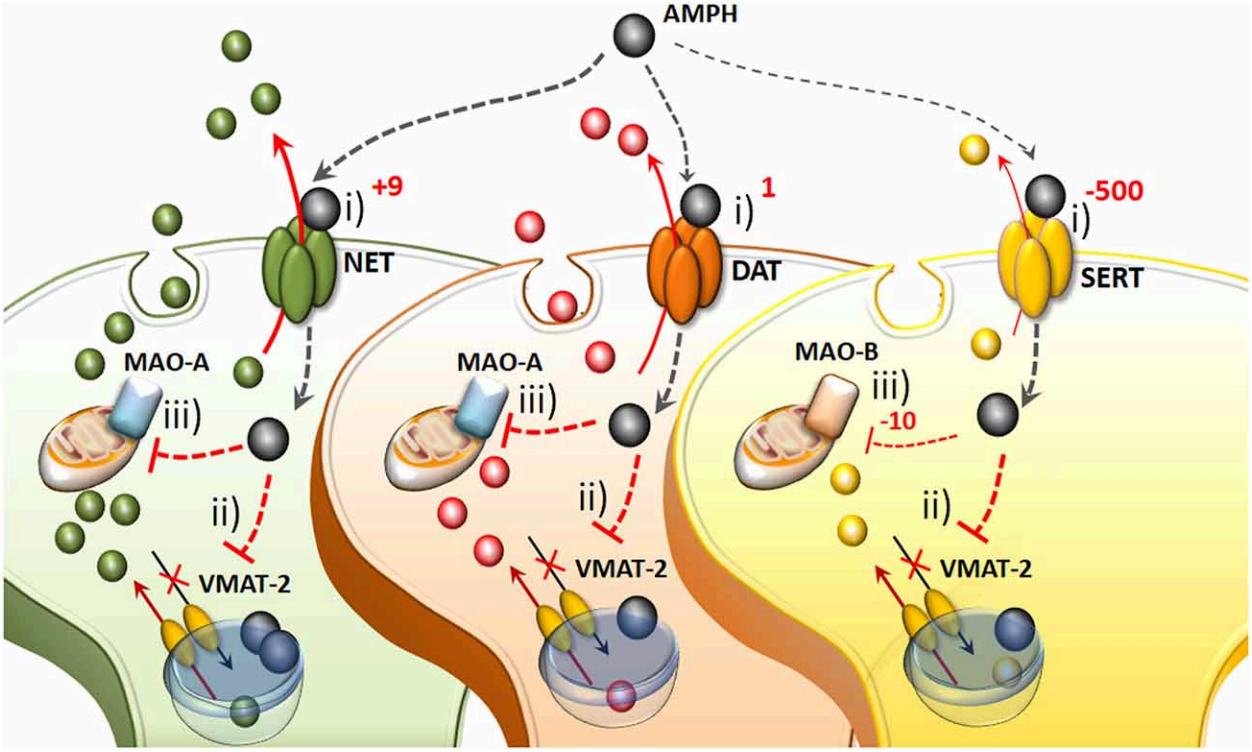

Figure 4: Amphetamine (AMPH) is transported into the presynaptic neuron via monoamine transporters DAT, NET, and SERT. Inside the presynaptic neuron, AMPH inhibits VMAT2 and MAO. AMPH also makes DAT, NET, and SERT reverse their transportation direction and push monoamines into the synaptic cleft (Ferrucci et al. 2019).

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Modelling the Pharmacokinetics of Adderall

First Order Kinetics

The metabolism of amphetamine, the compound that Adderall is made of, follows first-order kinetics. This means that the rate of elimination of Adderall remains constant and does not depend on the amount of amphetamine in the body (Baggot, Davis 1973). This is the case because the maximum velocity (V_{max}) of the reaction that metabolizes amphetamine is not rate-limiting (Vree 1973). Given this, it is possible to model the elimination of Adderall in mg over time (*t*) in hours with a constant unitless rate (*r*) based on half-life using Equation 1.

$$a_{t+1} = ra_t \tag{1}$$

Adderall is composed of a 3:1 ratio of two salt isomers: d-amphetamine and l-amphetamine. D-amphetamine has an average half-life of approximately 10.385 hours. The l-isomer has a longer average half-life of approximately 12.65 hours (Food and Drug Administration 2007).

For d-amphetamine, the rate of elimination per hour is equal to $e^{-\frac{ln(2)}{10.385}}$. L-amphetamine has a rate of elimination of $e^{-\frac{ln(2)}{12.65}}$ (see Appendix for calculations). Since Adderall metabolism follows first-order kinetics, these will be the rates per hour regardless of the initial amount of Adderall consumed (Figure 5).

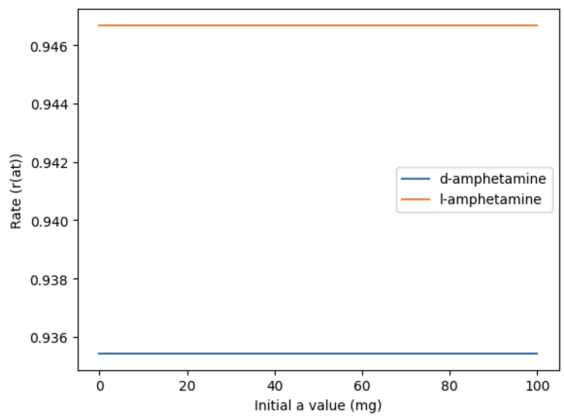

Figure 5: Plot of the elimination rate of the two amphetamine isomers showing that the rates are independent of the initial amount of Adderall.

Elimination of One Dose

Modelling the elimination of a single dose of Adderall can be achieved through a discrete-time dynamical system (DTDS). Cobwebbing the individual updating functions of each isomer with their proportions of the initial dose and plotting the solution sets shows the elimination of one dose. Equation 2 is the updating function of a single dose of d-amphetamine in one-hour time intervals while Equation 3 shows the same DTDS for l-amphetamine. By this model, for a single dose of 50 mg, it would take approximately 63 hours for the total amount of amphetamine in the body to fall below 1 mg (Figure 6).

$$a_{t+1} = e^{-\frac{ln(2)}{10.385}} a_t \tag{2}$$

$$a_{t+1} = e^{-\frac{ln(2)}{12.65}} a_t \tag{3}$$

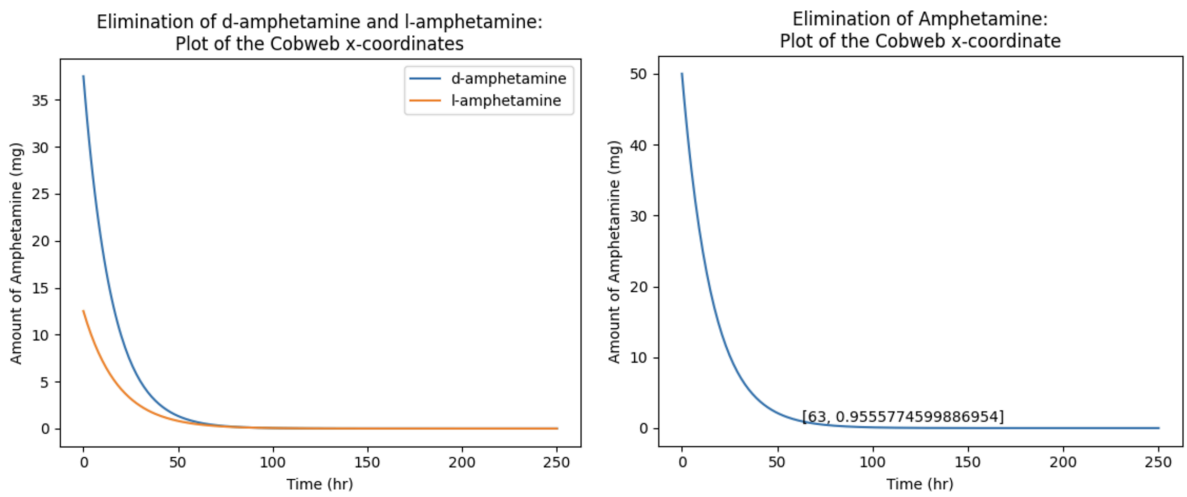

Figure 6: The curves of elimination of one 50 mg dose of Adderall. The first graph shows Adderall split into d-amphetamine and l-amphetamine, and the second graph shows the combination of the two salts. The indicated point is where the amount of Adderall remaining falls below 1 mg.

To further support this model of elimination, raw data from Cody et al. 2004's study shows the elimination of amphetamine in urine (ng/mL) over time after a 20mg dose was administered. Plotting the data reveals a similar pattern to the one observed in the DTDS (see Figure 7).

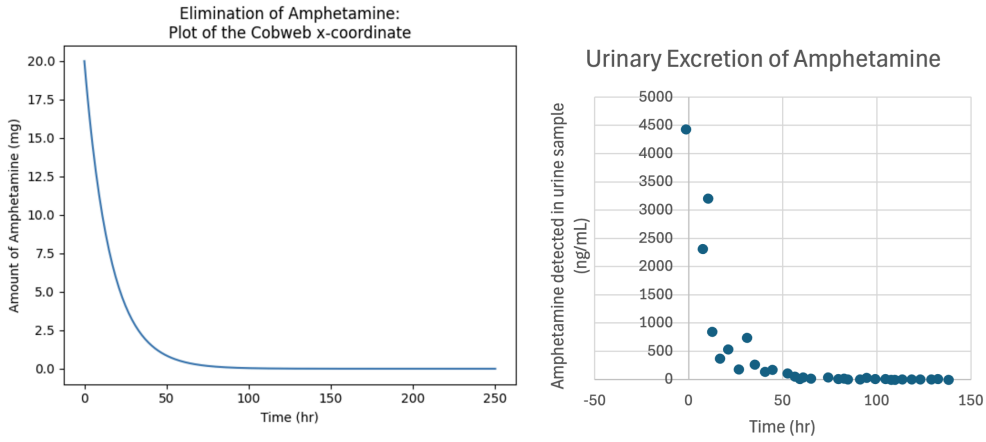

Figure 7: A comparison between the proposed DTDS and plotted raw data from Cody et al. 2004.

Modeling Elimination and Consumption

Prescriptions of Adderall usually instruct a dose to be taken every 24 hours. As illustrated by Figure 6, by the 24-hour mark, not all of the amphetamine from the initial dose has been eliminated. Due to this fact, to assess the safety requirements of a dose it is important to look beyond hourly elimination, to daily maximum amounts.

One of Adderall's physiological effects is an increased amount of norepinephrine. Too high of a dose can cause vasoconstriction and an increase in heart rate, stroke volume, and skeletal muscle blood volume. Due to these cardiovascular side effects, overdose is possible at a minimum of 1.5 mg/kg for humans (Fitzgerald and Bronstein 2013). The average American adult weighs approximately 84.051 kg (National Center for Health Statistics 2023). Based on this average, any amount of Adderall in the body at one time more than 126 mg can be dangerous (see Appendix for calculations).

To see if taking a specific daily dose can cause an overdose, one must use a new DTDS to model the daily maximum amounts of amphetamine in the body after each dose. To model this, Equation 2 and Equation 3 were modified to account for a new dose (*d*) every 24 hours. Equation 4 describes the DTDS of elimination and consumption of d-amphetamine over time (*t*) in days, while Equation 5, shows the same for the l-amphetamine.

$$a_{t+1} = e^{-\frac{24ln(2)}{10.385}} a_t + d \tag{4}$$

$$a_{t+1} = e^{-\frac{24ln(2)}{12.65}} a_t + d \tag{5}$$

To solve for the equilibrium algebraically, a weighted half-life of approximately 11 hours can be used (see Appendix for calculations). Equation 6 shows the DTDS with the weighted half-life. The equilibrium is obtained when a_t is equal to the amount at the next time interval:

$$a_{t+1} = e^{-\frac{24ln(2)}{11}} a_t + d \tag{6}$$

Since, $a_{t+1} = a_t$

$$a_t = e^{-\frac{24ln(2)}{11}} a_t + d$$

$$a_t = \frac{d}{1-e^{-\frac{24ln(2)}{11}}}$$

For $d = 30\ mg$:

$$a_t \approx 38.48$$

For $d = 100\ mg$:

$$a_t \approx 128.27\ mg$$

One *d* value for a safe outcome is 30 mg, a commonly prescribed daily dose (Food and Drug Administration 2007). One *d* value for a dangerous outcome is 100 mg. Although only taking a single dose of 100 mg would be safe for the average person, the equilibrium amount of 128.27 mg reached after multiple doses would be dangerous.

Plotting these updating functions with $a_0 = d = 30$ mg and cobwebbing with the diagonal produced an equilibrium value of approximately 38.43 mg. This gives a stable equilibrium since the cobwebbing moves towards the point of equilibrium as opposed to away from it. This makes sense when looking at the plot of solutions from the DTDS since the values stabilize over time (Figure 8).

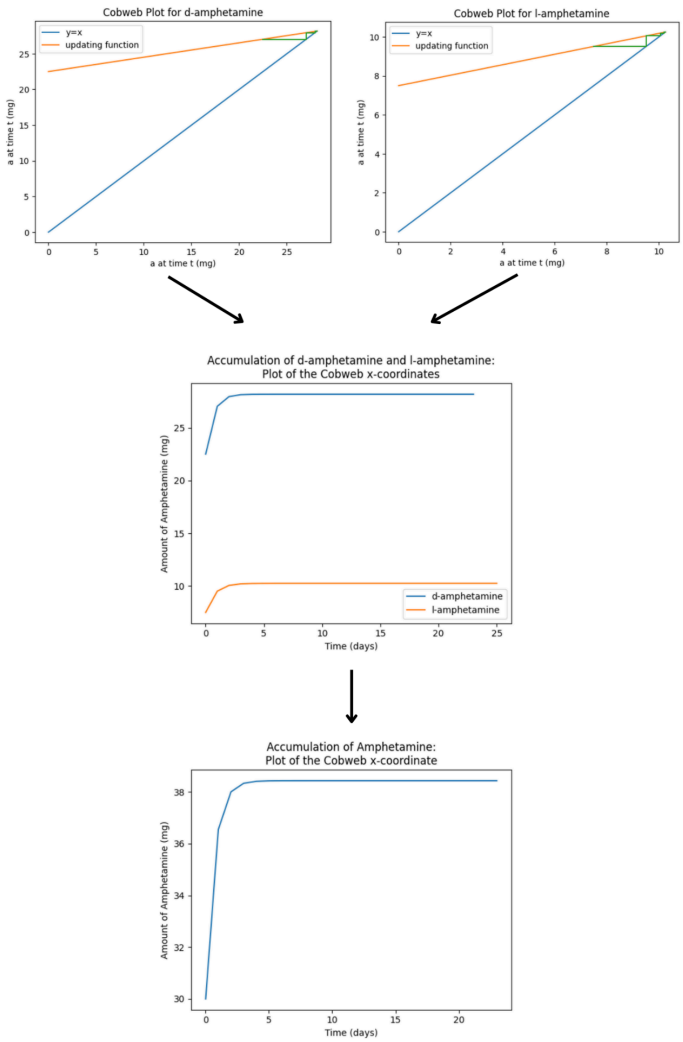

Figure 8: Analysis of accumulation of 30 mg daily doses. The first two plots show the cobwebbing for the updating functions of d-amphetamine and l-amphetamine from their respective initial values. The third graph plots the x-coordinates obtained from the cobwebbing for both salts. This shows the maximum amount of each salt in the body per day. The final graph shows the cumulative maximums leading to an equilibrium of 38.43 mg as returned by the code (see Appendix).

For $a_0 = d = 100$ mg, plotting the same functions gives an equilibrium value of approximately 128.10 mg, which is no longer a safe dose and can lead to an overdose (Figure 9). This is likely an accurate prediction of what would happen to a person when taking this large of a daily dose.

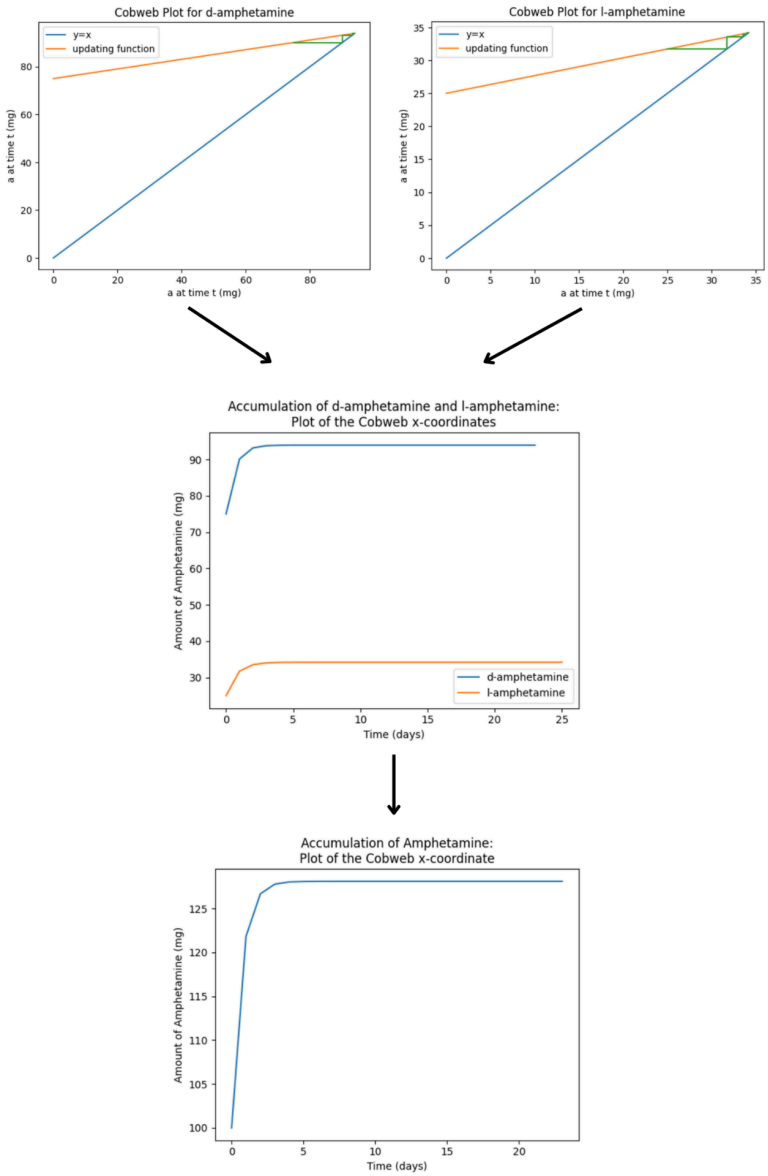

Figure 9: Analysis of accumulation of 100 mg daily doses. The pathway to the final equilibrium graph follows the same algorithm as in Figure 8.

Additionally, the inverse of the Adderall elimination and consumption DTDS can provide useful information (Figure 10). The given elimination and consumption model will take the current amount of Adderall in the body as the input, and output the amount of Adderall in the body at the next time interval. The inverse would take the current amount of Adderall and output the amount at the previous time interval. If the amount of Adderall in the body at equilibrium is known, the initial amount can be found recursively. One practical situation in which this inverse function may be useful is in a clinical setting where, if the current or equilibrium amount of Adderall in a patient's body is known, the amount of Adderall at a previous time or at the beginning can be found for any testing or record-keeping purposes. Also, the updating function and its inverse have the same equilibrium. This is because the equilibrium of a DTDS is found by finding its intersection with the y = x line. A function's inverse will be its reflection over the line y = x, so it will intersect the y = x line at the same point as the original function.

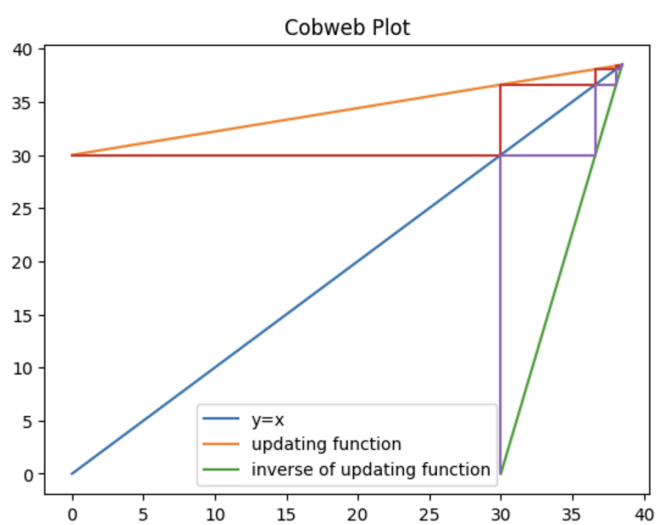

Figure 10: Cobwebbing of the updating function of elimination and consumption of Adderall using the weighted average half-life and its inverse with $a_0 = 0$ and $d = 100$. Both functions will have the same equilibrium amount, as shown by how they intersect the blue y = x line at the same point.

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Life Science

Cell types

Long-term use of the stimulant drug Adderall can affect the central nervous system (CNS) in numerous ways. This may result in a number of alterations to cellular activity and thus physiological function (Nyberg 2014).

Prolonged use of Adderall can impact dopaminergic neurons (DA neurons), glial cells and endothelial cells. Distributed throughout the brain, DA neurons generate the neurotransmitter dopamine (DA) and carry out a variety of tasks including: hormone regulation, sensory information processing, and motor control (Speranza et al. 2021). DA-producing neurons are found in the ventral midbrain, specifically among the amacrine cells in the retina and in the telencephalon, the frontal part of the brain. The dopaminergic system plays a key role in behavioural regulation as well as the regulation of learning and memory-related neural mechanisms. These DA neurons manage three large neural circuits in the mammalian CNS: the nigrostriatal, mesolimbic, and mesocortical pathways as shown in Figure 11. The development of motor skills and movement control are influenced by the nigrostriatal pathway. The mesolimbic pathway has a link to addiction. Finally, the mesocortical pathway influences decisions and behaviours related to the prefrontal cortex, an area of the brain essential for decision-making. ADHD or a lack of focus might result from DA deficiency in this part of the brain.

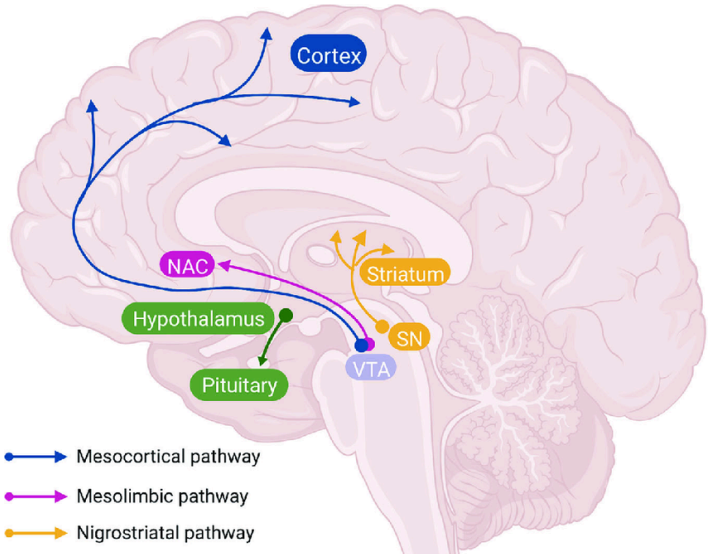

Figure 11: The three dopaminergic pathways in the brain are the mesocortical (blue), mesolimbic (pink), and nigrostriatal (yellow) pathways. The mesocortical pathway travels from the ventral tegmental area (VTA) neurons to the cortex. While the mesolimbic pathway travels from the same area to the nucleus accumbens (NAC). The nigrostriatal pathway to the striatum from the substantia nigra (SN) (Xu and Yang 2024).

Glial cells maintain homeostasis and support neurons by assisting maturing neurons to their destination and creating the myelin sheath around axons (Molnar and Gair 2015). Since Adderall increases the cortical glial fibrillary acidic protein, a filament protein that offers structural support, it also affects these cells (Koriem and El-Soury 2024). Prolonged Adderall usage especially affects astrocytes, a type of glial cells which are in charge of preserving the blood-brain barrier and controlling neurotransmitter levels (Fort and Cain 2023). Long-term use of Adderall alters the structure and function of these support roles, making them less effective.

Lastly, the endothelial cells that surround the blood vessels in the brain, are also affected by the misuse of this substance (Fitzgerald and Bronstein 2013). Long-term usage of Adderall

may weaken the blood-brain barrier, increasing its permeability, which could lead to neurotoxicity.

Physiological systems affected

DA and norepinephrine (NE) systems are affected by the long-term use of Adderall (Bell, Jachimowski, and Lewis 2019). For the DA system, extended usage may result in DA depletion and changed receptor density, which may influence mood, motivation, and cognitive abilities. For this reason, chronic use may be associated with depression, anxiety, and even drug dependence (Uddin et al. 2017). Moreover, like DA, NE levels can become dysregulated, which can lead to symptoms like elevated blood pressure, agitation, and an accelerated heartbeat. The body's stress response system may also be impacted by prolonged overuse (Malik et al. 2021). In terms of cognitive process, Adderall can improve focus and attention in the short term, but long-term use can harm executive function, memory, and learning (Weyandt et al. 2018). Neurotransmitter depletion or receptor desensitisation may impair cognitive processes that depend on synaptic plasticity, the change in neuron connection and effective neurotransmission (Risan and Ali 2024; Bassi et al. 2019). In regards to long-term effects on mood regulation, excessive use of Adderall over time may cause anxiety, irritability, mood changes, or paranoia (Green 2019). The imbalance in the DA and serotonin neurotransmitter systems, which control emotions, is partially to blame for this.

An additional risk of long-term use of Adderall is addiction. Chronic Adderall use can alter the DA system, one of the brain's reward pathways. This results in dependency and withdrawal symptoms that further impair mood and cognitive function.

Long-term Adderall usage in younger people may affect brain development and neuroplasticity, especially in areas related to concentration, impulse control, and decision-making (Steiner and Van Waes 2013). Decision-making and behaviour regulation may be permanently impacted by alterations in the prefrontal cortex, a region that plays a significant role in executive function (Spencer, Devilbiss, and Berridge 2015; van Gaalen et al. 2006).

The stimulating effects of Adderall can interfere with sleep cycles (L.Yaremchuk and Wardrop 2010). Chronic sleep disturbance can have detrimental impacts on the CNS. This can result in exhaustion, cognitive decline, and long-term disturbances of circadian rhythms. These are crucial for preserving the health of the brain as a whole.

Homeostasis

As the user continues to abuse Adderall, the body strays further from homeostasis. Prolonged exposure to this drug may lead to neurotoxicity and damage structures that are part of the CNS (Berman et al. 2009). Currently, there is evidence that high doses of amphetamine in animal subjects can lead to the damage of DA neurons that supply the dorsal striatum. High doses cause neural damage leading to a deficit in markers like DA. Although the mechanisms have not been identified to their full extent, there are some hypotheses. Strong evidence points to the high levels of cytoplasmic DA that are present due to the disruptions in vesicular storage caused by amphetamine (Basmadjian et al. 2021). The oxidation of these species, shown in Figure 12, may begin the process of microglial activation. If microglial cells are activated frequently, it may contribute to the degeneration of DA nerve endings. This process is usually followed by astroglial activation which increases the levels of proinflammatory cytokines. This

can lead to inflammation of the brain which when studied in rodents was found in the striatum, hippocampus, thalamus, and parietal cortex, areas of the brain that have dopaminergic endings (Tucker 2021).

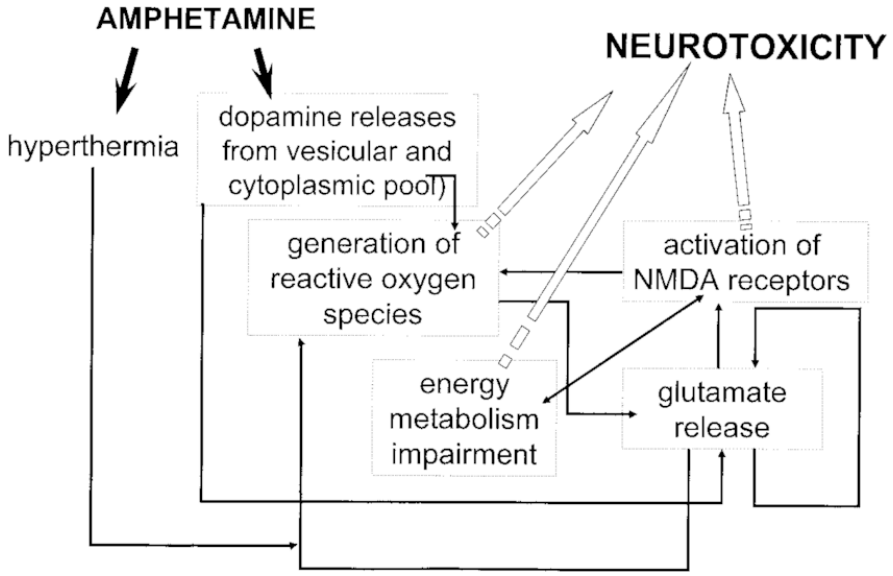

Figure 12: These high levels of DA contribute to the accumulation of reactive oxygen species. As well, an increased influx in Ca^{2+} can contribute to the formation of reactive nitrogen species. These compounds oxidise and change the function of important cellular components like lipids and proteins. This AMPH-induced oxidative stress has a key role in neurotoxicity (Basmadjian et al. 2021).

Once the dose reaches beyond the therapeutic amount, the mesolimbic pathways become affected by the greater concentrations of dopamine. Regions like the nucleus accumbens, the reward-processing part of the brain, are affected. As the substance is used at higher doses, it leads to a general decrease in the strength of the DA circuits, which leads to a decreased euphoric effect that the individual seeks during non-medical use. As they continue to increase the dosage to combat the tolerance, it worsens the damaged dopamine circuitry, furthering the body from homeostasis.

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Opioids: Morphine, Codeine, and Heroin

Chemical Structure

Morphine, codeine, and heroin are all drugs of the opioid class. They all have three organic rings, one of which is a benzene ring. Although they seem similar, these molecules are each unique due to differences in functional groups. They all contain an ether that connects its benzene ring to a cyclohexene. Additionally, all three of the molecules contain a tertiary amine on the central ring. This amine is unusual because one of its hydrogens is from the methane subgroup connected to the same ring. Both the amine and ether are polar subunits. Morphine ($C_{17}H_{19}NO_3$) differs from the rest by the presence of two additional polar subunits: alcohol on the benzene, creating a phenol group, and alcohol on the hexene ring. Instead of alcohol on its benzene, codeine ($C_{18}H_{21}NO_3$) has an additional ether. Lastly, located in the same place as the other molecules, heroin ($C_{21}H_{23}NO_5$) has acetyl groups, another polar subunit (Figure 13).

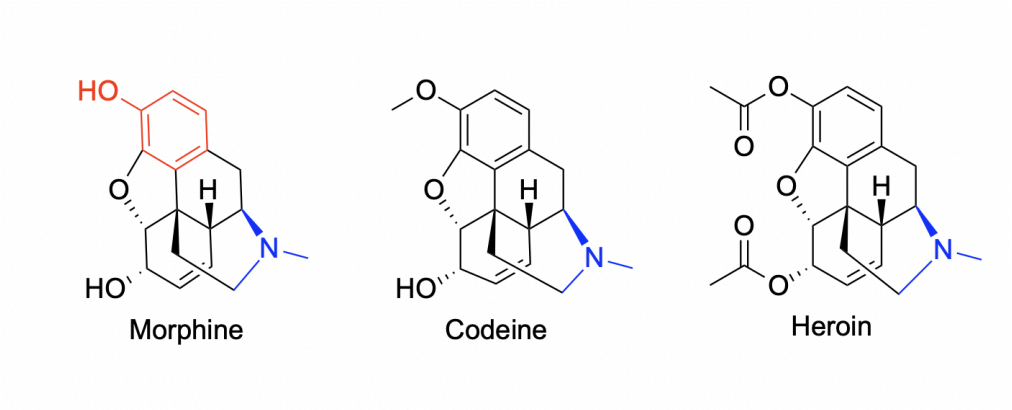

Figure 13: The molecular structures of morphine, codeine, and heroin. Phenol groups are indicated in red and amine groups are indicated in blue (ChemDraw 2024).

Morphine at Different pH Levels

Table 1 of Avdeef et al. 1996 shows the phenolic and amine pK_a values for morphine, codeine, and heroin. pK_a represents the strength of an acid. It is especially useful in understanding large organic molecules, such as opioids, since different functional groups can have different pK_as and will ionize at different conditions. The relationship between pK_a and pH is also important to consider. When the environmental pH is equal to the pK_a of a molecule or a functional group, the reaction mixture has equal concentrations of the acid and conjugate base. When pH < pK_a, the reaction mixture consists mostly of the acid, and inversely when pH > pK_a, it consists mostly of the conjugate base. Using phenolic and amine pK_a, the structure of the most abundant form of morphine at different pH levels can be predicted.

Morphine has one phenol group, as seen in red in Figure 13. Phenolic pK_a refers to the ionization of a phenol group ($RC_6H_5OH_{(aq)}$), as seen in Equation 7.

$$RC_6H_5OH_{(aq)} + H_2O_{(l)} \rightleftharpoons RC_6H_5O^-_{(aq)} + H_3O^+_{(aq)} \tag{7}$$

The phenolic pK_a of morphine is 9.26. From this value, three conclusions can be drawn. For pH = 9.26, the concentration of $RC_6H_5OH_{(aq)}$ is equal to the concentration of $RC_6H_5O^-_{(aq)}$. For pH < 9.26, the concentration of $RC_6H_5OH_{(aq)}$ is greater than the concentration of $RC_6H_5O^-_{(aq)}$. For pH > 9.26, the concentration of $RC_6H_5OH_{(aq)}$ is less than the concentration of $RC_6H_5O^-_{(aq)}$.

The amine pK_a of morphine is more complicated to interpret. The pK_a value refers to the protonated amine, $R_2NH_2{}^+_{(aq)}$, as opposed to the neutral amine, $R_2NH_{(aq)}$. Equation 8 shows the two ionizations of $R_2NH_2{}^+_{(aq)}$. It is polyprotic since it contains multiple hydrogen atoms.

$$R_2NH^+_{2(aq)} + H_2O_{(l)} \rightleftharpoons R_2NH_{(aq)} + H_3O^+_{(aq)}$$
$$R_2NH_{(aq)} + H_2O_{(l)} \rightleftharpoons R_2NN^-_{(aq)} + H_3O^+_{(aq)} \quad (8)$$

$R_2NH_2^+{}_{(aq)}$ in morphine has a pK_a of 8.18, but $R_2NH_{(aq)}$ has a pK_a of approximately 40 causing the second ionization to be highly improbable, especially in the human body (Avdeef et al. 1996; Schwartz and Light, n.d.). From morphine's amine pK_a of 8.18, three conclusions can be made. For pH = 8.18, the concentration of $R_2NH_2^+{}_{(aq)}$ is equal to the concentration of $R_2NH_{(aq)}$. For pH < 8.18, the concentration of $R_2NH_2^+{}_{(aq)}$ is greater than concentration of $R_2NH_{(aq)}$. For pH > 8.18, the concentration of $R_2NH_2^+{}_{(aq)}$ is less than concentration of $R_2NH_{(aq)}$. Figure 14 summarizes the predictions of morphine's structure at different pHs based on both the phenolic and amine pK_as.

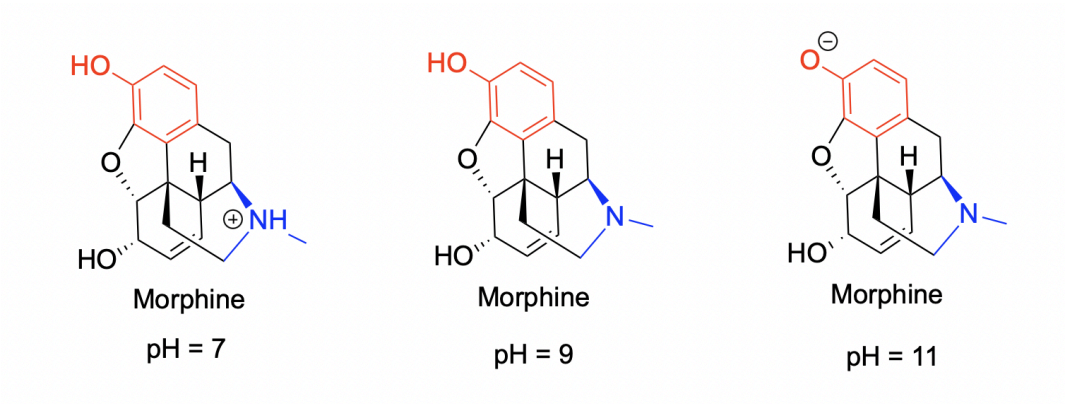

Figure 14: A comparison between the structure of morphine at pH = 7, pH = 9, and pH = 11. At pH = 7, morphine has a neutral phenol group and a protonated amine. At pH = 9, both the phenol and amine are neutral. At pH = 11, the phenol group is ionized and the amine group is neutral (ChemDraw 2024).

Heroin and codeine also contain amine groups similar to morphine. When comparing the amine pK_as of the three molecules, heroin has the lowest amine pK_a of 7.95. This means that its amine group is the strongest acid or, in other words, the least basic.

Lipophilicity of Morphine and Heroin

Table 2 of Avdeef et al. 1996 compares the *logP* and $logD_{7.4}$ values of morphine, heroin, and codeine. These values relate to the octanol/water partition coefficient (K_{ow}); the measure of the lipophilicity of a substance. The general equation for the ionization of an acid (Equation 9*)* allows for definitions of *logP* and *logD*.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^- \tag{9}$$

The partition coefficient, *P*, works as an effective measurement for species that do not undergo ionization, but overlooks the ionized form of a given *HA* (Equation 10).

$$P = \frac{[HA]_O}{[HA]_W} \tag{10}$$

The distribution coefficient, *D*, is similar to *P* but takes into account the ionized product (Equation 11). This makes *logD* dependent on the environmental pH and the pK_a of the substance. This relationship can be seen in Equation 12.

$$D = \frac{[HA]_O + [A^-]_O}{[HA]_W + [A^-]_W} \tag{11}$$

$$logD = logP - pK_a + pH \tag{12}$$

Measuring *logD* is important for pharmacology because lipophilicity affects whether a large molecule can enter a cell's phospholipid membrane by passive diffusion instead of active transport. If *logD* is positive, the species is more lipophilic, but if *logD* is negative, then the species is more hydrophilic and cannot enter a cell (Kah and Brown 2008).

An especially important measurement for medicine is $logD_{7.4}$, or the lipophilicity of a drug at a pH of 7.4, which is the average pH of blood (Palmer 2008). Knowing the lipophilicity of a drug in the blood is important to understanding its absorption.

Even though heroin is converted into morphine in the brain creating an identical physiological effect, Table 2 in Avdeef et al. 1996 helps explain why heroin is more addictive than morphine, especially by injection. Morphine has a $logD_{7.4}$ of -0.07, making it more hydrophilic in the blood. Alternatively, heroin has a $logD_{7.4}$ of +0.85, making it more lipophilic and allowing it to pass through the blood-brain barrier by passive diffusion. From the same injected quantity of heroin and morphine, more heroin diffuses through the blood-brain barrier. This causes a higher concentration of morphine to be absorbed by the brain in the form of heroin, making it more addictive.

Methadone: The Morphine Rule

Methadone is a synthetic drug manufactured for detoxification. It has a similar but weaker effect as opioids and, during treatment, doses are slowly reduced to minimize withdrawal symptoms ("Treating Opiate Addiction, Part I: Detoxification and Maintenance" 2005). These similar effects are due to similar structural properties to opioids (Figure 15). Both methadone and opioid drugs have benzene rings and an amine group; compounds that have these characteristics

are considered to follow the morphine rule. The structural similarities allow methadone to bind to the opioid receptors, act as an agonist, and be used for detoxification (Liu et al. 1999).

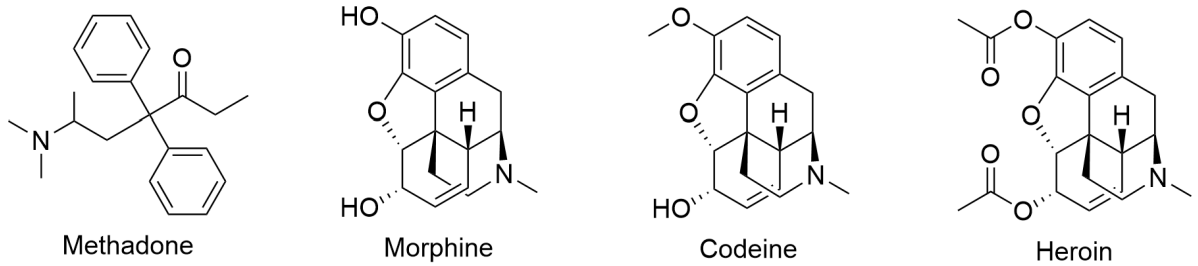

Figure 15: Comparison between the chemical structure of methadone to morphine, codeine, and heroin (ChemDraw 2024).

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Environmental Impact of an Adderall Spill

Along with other drugs, Adderall's production and disposal present environmental concerns. Adderall contains amphetamine salts, which can pollute from both point and nonpoint sources (Loague and Corwin 2006). Pharmaceutical chemicals that are difficult for conventional treatment plants to completely eliminate are frequently released into wastewater by Adderall manufacturers. As a result, water bodies and surrounding ecosystems become substantially contaminated. Furthermore, improper disposal methods, such as flushing away unused or expired prescription drugs or discarding them with regular trash, causes more widespread nonpoint source pollution when chemicals escape into soil and water systems. This extensive pollution impacts aquatic life in several ways, including hormone disruption, altered reproduction, and even increased antibiotic resistance in bacteria (UN Environment Programme 2018).

Adderall’s behaviour in the environment relies on its chemical structure and environmental conditions like soil composition (Cody 2008). Amphetamines dissolve in water which increases their likelihood of infiltrating soil and entering groundwater systems, potentially impacting human use and the water cycle.

Contamination of groundwater is a major environmental concern. Groundwater can become contaminated by chemicals from improperly disposing of pharmaceuticals or factory leaks, endangering agricultural irrigation and drinking water supplies (Harvey 2016). Stricter regulations concerning pharmaceutical manufacture and waste disposal must be required to reduce these risks. Knowing how aquifers and subsurface geology affect the movement of pollutants is crucial for assessing the environmental effects of Adderall pollution (Candela et al. 2016). Since the permeability and porosity of the bedrock directly affect the movement of

contaminated groundwater, determining the affected area's geological composition is essential (Banzhaf, Krein, and Scheytt 2012).

Geological Composition

Due to their high porosity and permeability, as seen in Figure 16, aquifers, especially unconfined ones, can carry water pollutants over great distances. In many parts of Ontario, particularly the Greater Toronto Area, the bedrock is composed primarily of sandstone and limestone, which would allow the chemical components of Adderall to travel into aquifers with effective flow paths (Foubister 2023). The considerable geological variations and frequent fractures and weathering within limestone aquifers allow complex transport channels and fluctuating groundwater flow rates (Ghasemizadeh et al. 2012). High-flow zones produced by weathering in upper limestone levels can quickly spread pollutants like Adderall into larger groundwater systems.

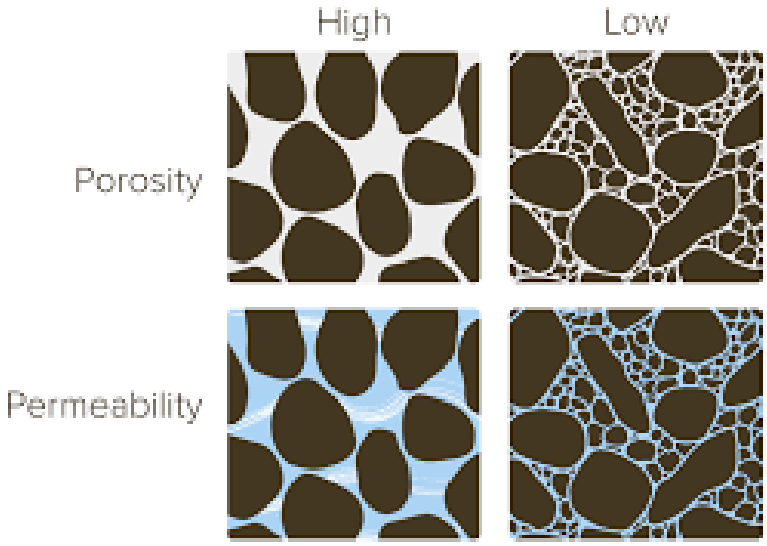

Figure 16: Diagram depicting the effect of variations in porosity and permeability on water flow. High porosity and permeability in bedrock formations allow a greater flow of water. This can explain the contamination of Adderall in these subsurfaces (Walker n.d.).

Similarly, groundwater can migrate both horizontally and vertically through sandstone aquifers, which are renowned for being porous and permeable (Edmunds and Smedley 2000). Contaminants may move across sandstone's networked pores with ease, and geological processes like fracturing can increase this mobility further.

The spread of amphetamine into deeper groundwater supplies may be worsened by vertical transport through faults, which is frequently linked to glacial movements in Canadian bedrock (Rivera and Calderhead 2022). These features make sandstone and limestone aquifers crucial areas when monitoring for drug contamination.

Groundwater Zones

The four main factors affecting groundwater flow are recharge areas, discharge areas, and unsaturated and saturated zones, as seen in Figure 17 (Zemann, Majewsky, and Wolf 2016). Precipitation in topographically elevated regions such as hills or mountains, serves as recharge zones in rainy climates, allowing water to seep into the soil. In this instance, the unsaturated zone, where air and water are present in the pore spaces between sediments, is where water is initially located. Contaminants like Adderall may dissolve and go down through this area due to gravity, especially in places with permeable soils.

The saturated zone lies underneath the unsaturated zone and has pore spaces that are completely filled with water (Drewes et al. 2007). Once Adderall enters this zone, it will flow toward discharge sites such as lakes, marshes, or streams along the hydraulic gradient of the groundwater. These discharge areas allow groundwater to flow out of the system, and potentially contaminate surface water ecosystems. How much Adderall moves and how long it lasts depends

on its rate of breakdown, absorption into soil, and interactions with organic molecules (Einsiedl, Radke, and Maloszewski 2010).

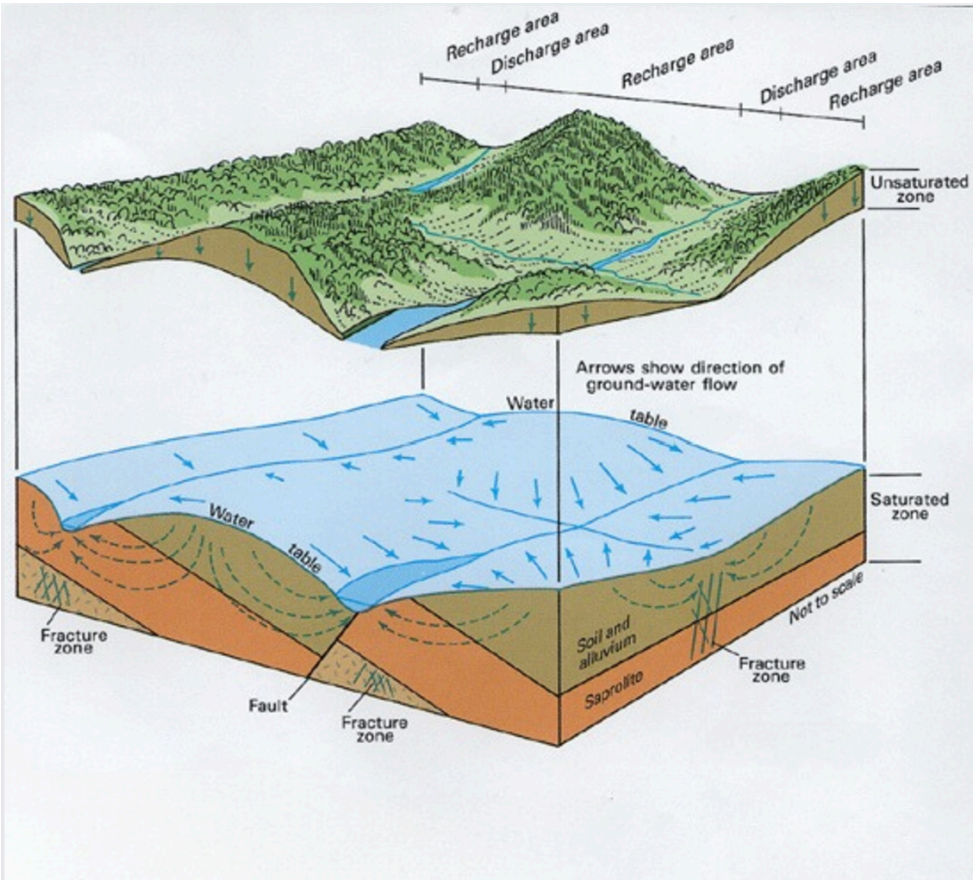

Figure 17: This diagram displays the flow of water in various directions based on the zone. Recharge areas are shown to have higher elevations, where precipitation can flow into the soil. Discharge areas have lower elevation, meaning groundwater flows at surface level (United States Geological Survey n.d.).

When assessing the environmental concerns, it is important to consider how close a possible Adderall contamination site is to areas of recharge and outflow. Recharge zones are usually found at higher elevations that receive a lot of precipitation. They allow water and any dissolved contaminants to seep into the soil and reach the groundwater. To determine how long it will take for the contamination to reach discharge zones and possibly impact crops or aquatic life, the rate of groundwater flow must also be evaluated. It is known that amphetamines impact

microbial activity and plant growth in soil and water habitats, endangering biodiversity (Cary Institute of Ecosystem Studies 2016).

Monitoring Contamination Pathways

Investigating the transport of drugs like Adderall in groundwater, especially in locating possible contamination pathways, may benefit from the use of ground penetrating radar (GPR) as seen in Figure 18 (GPRS 2024). Although GPR cannot directly detect Adderall, it can assist in mapping the previously mentioned subsurface features that affect the movement of contaminants and groundwater, such as rock and soil fractures or porous zones (West Coast Tank Recovery 2024). This could identify possible areas of Adderall accumulation.

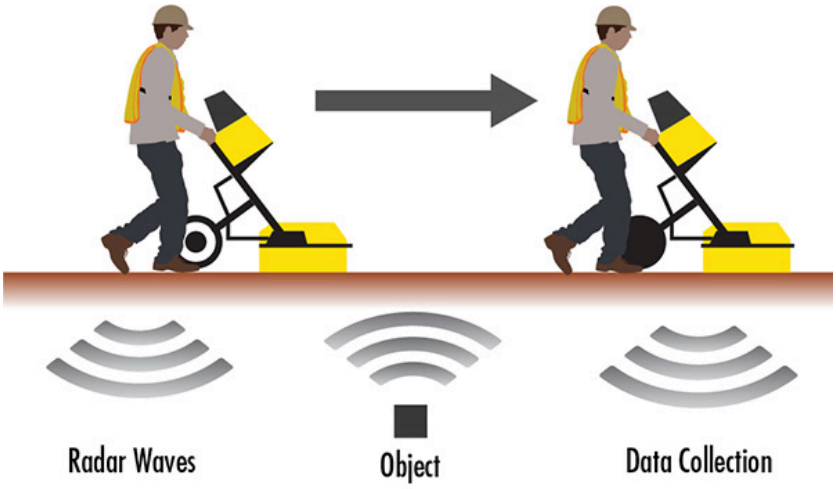

Figure 18: GPR helps map subsurface features through the use of RADAR. This can help make predictions for areas of pharmaceutical contamination (KCI Technologies n.d.).

GPR can be used alongside groundwater samples to pinpoint impacted areas and monitor the flow of pollutants for a more accurate analysis (QED Environmental Systems n.d.). Groundwater sampling involves collecting water from boreholes or wells. Samples are collected

at different depths and sites to evaluate groundwater quality and find materials like pharmaceuticals. These samples are examined in a laboratory to detect and measure contaminants using methods like chromatography. The findings guide the mapping of pollution patterns, the understanding of groundwater flow, and the planning of remediation operations.

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Body Pressures

Pressure is measured as the force experienced over a surface area (Magder 2018). Although this concept is most often associated with fluids in systems, pressures can also be applied to the human body. The human body itself is a system that contains many internal pressures that must stay within normal ranges to maintain homeostasis. The pressures which are discussed in this paper include arterial blood pressure (BP), intraocular eye pressure (IOP), and intracranial pressure (ICP). These pressures are sensitive to change, especially after the administration of drugs like caffeine, alcohol, and Adderall (amphetamine) into the body.

Blood Pressure

Blood pressure is measured in units of millimetres of mercury (mmHg) and requires two numbers for an accurate reading (Magder 2018). The systolic pressure measures the pressure in the arteries as the heart pumps blood while the diastolic pressure measures the pressure between heartbeats. When measuring pressure in a fluid-filled system, it is key to factor in the gravitational component because it can cause a variation in results. This variation can be seen in Figure 19 and can be attributed to Equation 13, where h represents the height which changes depending on which part of the body's blood pressure is measured. The main factor of arterial pressure is the stretch of the arterial walls from the blood volume they contain. In systole, the volume rises because the amount of blood rushing in exceeds the blood rushing out. This volume falls after the peak.

$$\Delta P = \Delta h \rho g \tag{13}$$

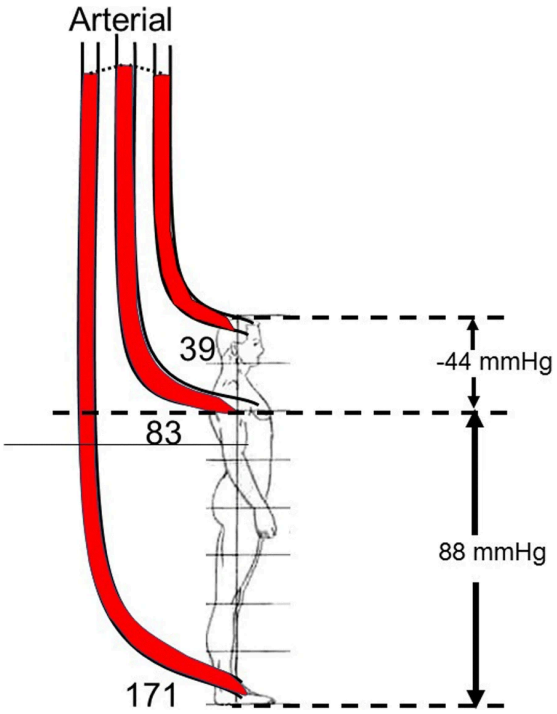

Figure 19: The gravitational potential energy in mm Hg is recorded on the right. When the transducer is moved around the body, the mean arterial pressure changes as shown on the left. The large differences show how gravity has a significant impact on pressure in the human body when measured upright (Magder 2018).

Based on these factors, the normal blood pressure of an individual should be within the range of <120/80 mmHg (Lüscher 2018). If blood pressure falls in a range of 120–129/80 mmHg, it is considered elevated, while a range of 130–139/80–89 mmHg is stage 1 hypertension. Finally blood pressure of ≥140/≥90 mmHg is classified as stage 2 hypertension. For blood pressure lower than 90/60 mmHg, this is classified as hypotension (National Heart, Lung, and Blood Institute 2022). However, there are exceptions to these ranges, as on an individual basis, people have different resting blood pressures based on genetics, lifestyle, and their health condition (Ram 2023).

The use of substances like caffeine, alcohol and amphetamine can set off the delicate balance in the body and affect arterial blood pressure. According to the European Food Safety

Authority (EFSA), a caffeine dose of 80 mg to 300 mg can cause a 3-8mmHg increase in mean systolic BP and a diastolic increase of 4-6 mmHg (Giuseppe et al. 2019). Alcohol also showed an increase in BP which can be explained by increased noradrenaline in the body from the alcohol, which stimulates the adrenergic receptors in the heart, leading to an increased BP (Tasnim et al. 2020). Amphetamine works similarly as it causes the release of norepinephrine which affects the α–Adrenergic receptor site (Fitzgerald and Bronstein 2013). This causes vasoconstriction and thus an increase in BP.

Intraocular Pressure

Another significant pressure found in the body is intraocular pressure (IOP) which is maintained by the production and outflow of fluids (Machiele et al. 2024). The aqueous humour, a fluid that supports the lens, determines the force exerted on the internal surface area of the eye. This pressure can be calculated using the Goldmann equation as shown in Equation 14. The pressure is given in mmHg, where *F* is the aqueous humour flow rate, *C* represents its outflow , and *P* is the episcleral venous pressure. The normal range for the IOP is 10 to 21 mm Hg. However, if the pressure exceeds 21 mmHg, it is classified as ocular hypertension. When this occurs, the risk of glaucoma increases significantly. Ocular hypotony is more uncommon but happens when IOP is less than 7mmHg.

$$IOP = \frac{F}{C} + P \tag{14}$$

Both caffeine and alcohol increase IOP but through different methods. Caffeine induces an IOP rise with a peak in the IOP change 90 minutes after ingestion (Audrey Yan 2024). When

adenosine receptors are antagonised by the caffeine, it prevents the outflow of the aqueous humour, which leads to increased intraocular pressure. Alcohol also leads to an increased IOP, with one of the hypotheses being that this effect is caused by chronic drinking and the release of cortisol. As discussed previously, this increases BP, which is a risk factor for high IOP (Grant et al. 2023). Unlike the other substances, the research on the effect of Adderall on IOP is not conclusive.

Intracranial Pressure

Intracranial pressure (ICP) is the pressure measured in the cranial vault, composed of three main components; the brain, cerebrospinal fluid (CSF), and blood (Pinto, Tadi, and Adeyinka 2024). This rigid compartment is a closed system that must balance cerebral blood inflow and outflow to maintain a normal ICP. Based on the Monro-Kellie hypothesis, changes in the volume of one of the components will lead to an opposite change in the other two components (Bothwell, Janigro, and Patabendige 2019). However, if the body cannot offset the change in one of the components, the volume will increase, leading to an increase in ICP as shown in Figure 20 (Yuh and Dillion 2010; Bothwell, Janigro, and Patabendige 2019). Normal conditions range from 7 to 15 mm Hg in a supine position, but treatment is only considered when ICP is above 20 mmHg (Munakomi and Das 2024; Yuh and Dillion 2010). Intracranial hypertension can be classified in the range of 20 to 30 mmHg, which is mild but if above 40 mmHg, it is life-threatening. Intracranial hypotension is when the ICP is below the expected range. Intracranial pressure is relatively equal to the intraspinal pressure and both can be approximated by the opening pressure of a lumbar puncture.

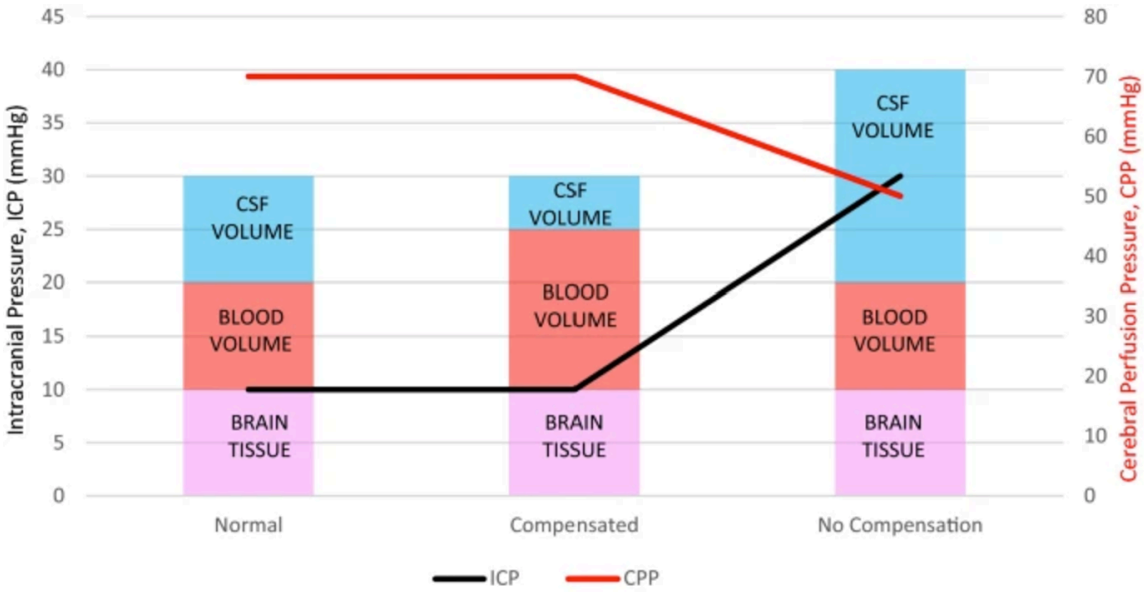

Figure 20: The relationship between the three components: blood, CSF, and brain tissue in the cranium. If one component does not compensate for the other, ICP rises. An increase in ICP can lead to central nervous system issues like hydrocephalus, stroke, and blindness (Bothwell, Janigro, and Patabendige 2019).

The brain is the control centre of the body, so ICP must remain constant for normal regulatory function. However, caffeine and alcohol can induce negative effects on the ICP. Caffeine has been found to reduce cerebral blood flow by around 10 to 20% (Bláha et al. 2009). This leads to the conclusion that caffeine must decrease the ICP, since the volume of the fluid decreases, the pressure must also decrease within this cavity. However, the opposite is true for alcohol as a study found that alcohol increases blood flow from around 8% to 24%. This may lead to increased ICP due to the rising amounts of CSF. Sufficient research on the effects of Adderall on ICP has not been conducted to understand how this drug impacts this aspect of brain health (Harbeck-Seu et al. 2011).

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ACE Inhibitors

RAAS and ACE Inhibitors

The body's blood pressure is regulated by the renin-angiotensin-aldosterone system (RAAS). This system includes many hormones such as angiotensin II which is catalysed by the renin enzyme from angiotensin I. Angiotensin II inhibits baroreflex, the negative feedback loop for high blood pressure (Maryam, Varghese, and B 2024). High blood pressure or hypertension, is a serious diagnosis that can lead to other cardiac conditions such as stroke, heart attack, and heart failure (Herman et al. 2024). Various prescriptions known as ACE inhibitors prevent the catalyzing of angiotensin I into angiotensin II, allowing for negative feedback to occur (Herman et al. 2024).

Applying Pascal's Principle

In the RAAS, angiotensin II binds and signals the kidneys. The hormone promotes the reuptake of ions and water in the nephron. This retention, among other factors, causes an increase in blood pressure and blood volume (Maryam, Varghese, and B 2024). The purpose of the nephron is to filter toxic molecules and waste from the blood (Hawk, n.d.). The flow of fluid through the nephron can be better understood using Pascal's principle and the concept of hydrostatic pressure. The pressure in a fluid is the hydrostatic pressure. Pressure is directly proportional to depth, therefore as depth increases hydrostatic pressure increases. This can be seen with Equation 15 where h is depth, g is the acceleration due to gravity, and ρ is the density of the fluid. As shown in Figure 21, confined liquid pressure is constant at equal heights and an increase in pressure at a specific point causes an increase in pressure throughout the liquid. This

principle of fluid dynamics is known as Pascal's principle. Additionally, as pressure is added to a system, the change in pressure is related to the displacement of the liquid, the acceleration due to gravity, and the density of the fluid.

$$\Delta P = \rho g h \tag{15}$$

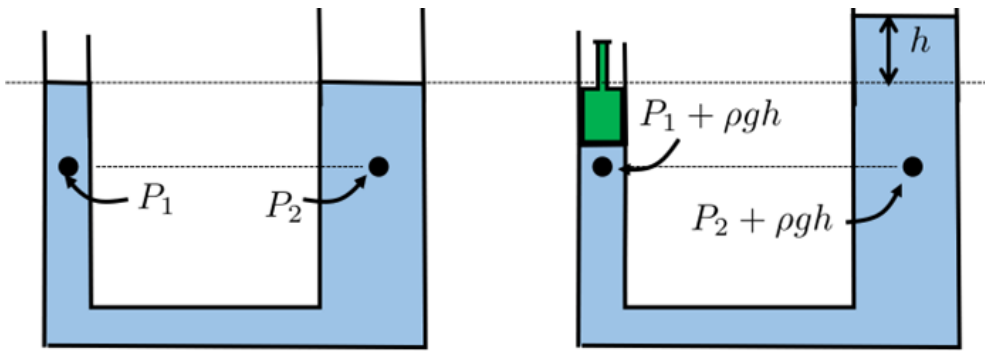

Figure 21: Image displays that $P_1 = P_2$ at equal heights. As pressure is added, the new pressure is a combination of the original pressure and the change in height of the liquid multiplied by its density and acceleration due to gravity.

Figure 22 is a diagram of a nephron. According to Pascal's principle, there is more pressure in the loop of Henle because it is at a lower height. The change in pressure is proportional to the density and displacement of the fluid. Alternatively, the movement of a fluid is proportional to pressure divided by fluid density. The fluid in the nephron is not static and is constantly moving. This movement is the result of hydrostatic pressure caused by the beating of the heart (Biga et al. 2019). As the heart contracts, additional pressure is applied throughout the nephron causing the fluid to move through.

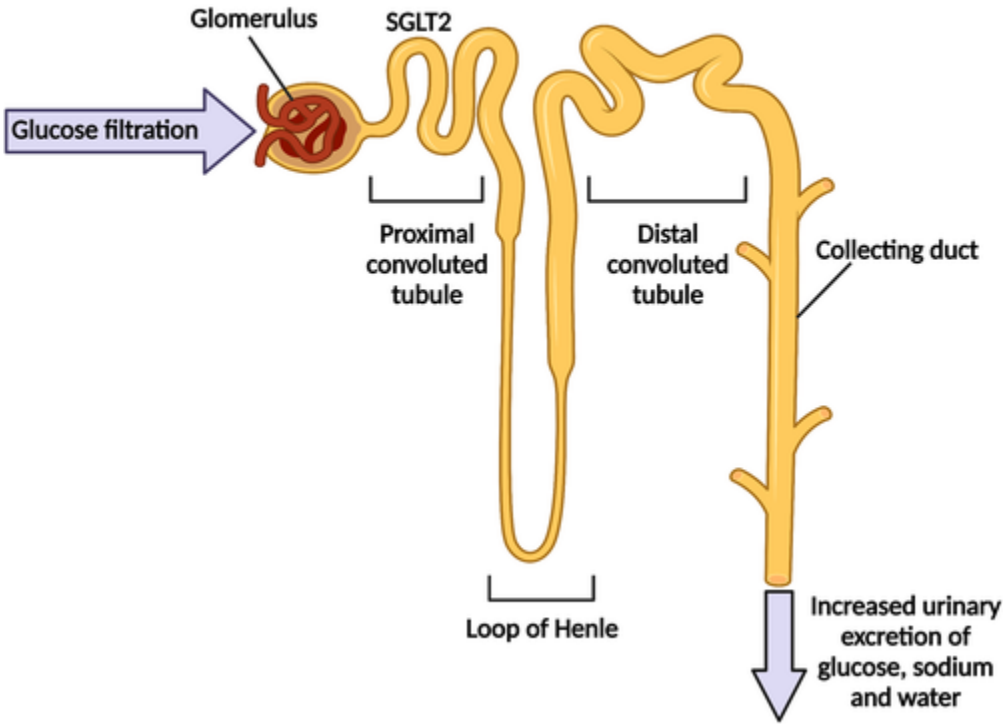

Figure 22: Fluid starts in the Bowman's capsule and travels through the various parts of the nephron. This movement is a result of hydrostatic pressure (Tiwary et al. 2022).

As stated previously, the nephron is the filtration system and has selective permeability. The movement of molecules through the nephron wall, which acts as the container, causes this application of Pascal's principle to be non-ideal (Hawk, n.d.). When passive diffusion is not considered, the nephron could be an ideal situation to apply Pascal's principle.

Applying Bernoulli's Equation

Hypertension creates a greater force within the blood vessels causing poor circulation (National Heart, Lung, and Blood Institute 2022). To understand circulation and pressure in blood vessels, Bernoulli's equation can be used (Equation 16). In this equation ρ is the density of the fluid, v is the fluid's velocity, h is the height at which energy is measured, and P is the work

done by pressure. Bernoulli's equation states that the total energy of a liquid is conserved but can be transferred between types of energy. The SI units used in Bernolli's equation are J/m^3, energy per volume. The total energy is composed of kinetic energy, gravitational energy, and work, which in the case of liquids, is done by the pressure. As one of the variables changes, the others change too because energy is conserved and the total initial energy must equal the total final energy.

$$\frac{1}{2}\rho v_i^2 + \rho g h_i + P_i = \frac{1}{2}\rho g v_f^2 + \rho g h_f + P_f \tag{16}$$

Figure 23 displays a blood vessel under hypertensive conditions and normal conditions. It can be seen that the cross-section is narrower in hypertensive conditions and pressure is high. ACE inhibitors decrease pressure. This means the initial pressure in the blood does not equal the final pressure. For Bernoulli's equation to hold, there must be a change in the blood's kinetic or gravitational energy. Since Figure 23 is in the same location, height is the same in the initial and final conditions, keeping gravitational potential energy constant on both sides of the equation. If gravitational potential energy does not change, the kinetic energy must increase as pressure decreases. Kinetic energy is impacted by the density of the blood, which is relatively constant, and the blood's velocity. According to Bernoulli's equation as ACE inhibitors decrease pressure, the velocity of blood increases.

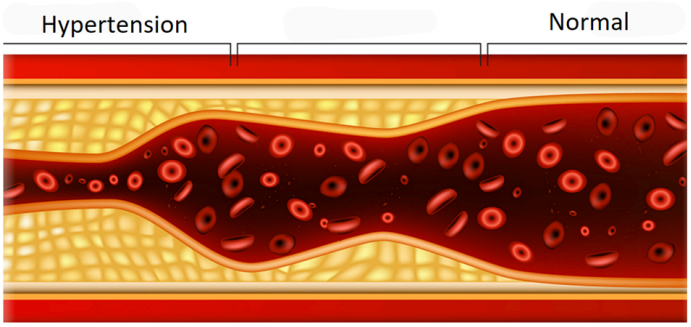

Figure 23: A display of blood vessels under hypertensive conditions and normal conditions. The narrower the blood vessel the more pressure there is (Raghu 2021).

Although Bernoulli's equation can be applied to better understand the energy transfer in blood, this is an ideal situation because the equation is applied to non-viscous fluids (OpenStax CNX n.d.). In reality, blood has viscosity and some energy will be lost due to friction.

Angiotensin II is an important enzyme but can also have adverse effects such as hypertension. ACE inhibitors can treat hypertension by preventing the production of angiotensin II. Using various physics concepts, such as Pascal's principle and Bernoulli's equation, the effects of hypertension and ACE inhibitors can be better understood, even though they do not follow ideal conditions in the body.

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Appendix

Finding the rate of elimination (r) for d-amphetamine:

$$a_t = e^{kt} a_0$$

$$\frac{a_0}{2} = e^{k(10.385)} a_0$$

$$\frac{1}{2} = e^{10.385k}$$

$$k = \frac{-ln(2)}{10.385}$$

$$r = e^{\frac{-ln(2)}{10.385}}$$

Finding the rate of elimination (r) for l-amphetamine:

$$a_t = e^{kt} a_0$$

$$\frac{a_0}{2} = e^{k(12.65)} a_0$$

$$\frac{1}{2} = e^{12.65k}$$

$$k = \frac{-ln(2)}{12.65}$$

$$r = e^{\frac{-ln(2)}{12.65}}$$

Finding the minimum dangerous daily dose of Adderall:

$$a_{t+1} = e^{-\frac{24ln(2)}{11}} a_t + d$$

$$126 = e^{-\frac{24\,ln(2)}{11}} (126) + d$$

$$d = 126 - e^{-\frac{24\,ln(2)}{11}} (126)$$

$$d = 98.23\,mg$$

Finding the weighted-average half-life:

$$t_{1/2-average} = (t_{1/2-d-amphetamine})(3/4) + (t_{1/2-l-amphetamine})(1/4)$$

$$t_{1/2-average} = (10.385)(3/4) + (12.65)(1/4)$$

$$t_{1/2-average} = 10.95 \approx 11$$

Code:

Full code can be accessed through GitHub here: https://github.com/KathrineMondshain/rp2

```
[1] '''
    By Group 7: Kathrine Mondshain, Sulagna Nandi, Nour Al-Sakka, Ella Seymour, Tessa Sigi
    This code creates a DTDS model for the elimination and consumption of Adderall
    '''
    import numpy as np
    import matplotlib.pyplot as plt
    from collections import OrderedDict
```

```
[2] #This section graphs the rate of elimination of Adderall. It is constant so it is the same for all initial amounts

    #This is for the weighted average half-life
    halflife = 11
    r = np.exp(-np.log(2) / halflife)

    '''
    r = np.exp(-np.log(2) / halflife)
    R_d = []

    for i in range(0,1000):
      R.append(r)

    x_graph = np.linspace(0,100,1000)
    plt.plot(x_graph,R)
    '''

    #This is for the half-lives of d-AMPH and l-AMPH
    halflife_d_amph = 10.385
    halflife_l_amph = 12.65
    #Rates are defined
    r_d_amph = np.exp(-np.log(2) / halflife_d_amph)
    r_l_amph = np.exp(-np.log(2) / halflife_l_amph)
    R_d = []
    R_l = []

    for i in range(0,1000):
      R_d.append(r_d_amph)
      R_l.append(r_l_amph)

    #Creates plot of both rates
    x_graph = np.linspace(0,100,1000)
    plt.plot(x_graph,R_d, label = "d-amphetamine")
    plt.plot(x_graph,R_l, label = "l-amphetamine")
    plt.ylabel("Rate (r(at))")
    plt.xlabel("Initial a value (mg)")
    plt.legend()
```

```
[3] #This section is not directly included in the documentation. It models the elimination of Adderall with the weighted average half-life

    def adderall_updating_approx(x): #Updating function for elimination by hour using weighted average half-life
      return x * r

    #Code modified from DTDS lesson
    def plot_cobwebbing_approx(f, a0, steps):
        cobwebs_x=[a0] #starting x-value
        cobwebs_y=[f(a0)] #starting y-value

        for i in range(1,steps):
            if i%2==1: #if the step i is odd
                cobwebs_x.append(cobwebs_y[i-1]) #append the same values along the diagonal y=x
                cobwebs_y.append(cobwebs_y[i-1])
            elif i%2==0: #if the step i is even
                cobwebs_x.append(cobwebs_y[i-1]) #append the same x-value, but "move up" to the updating curve.
                cobwebs_y.append(f(cobwebs_x[i]))


        xvalues=np.linspace(0,max(cobwebs_x), 500) #linspace for plotting
        plt.title("Cobweb Plot")
        plt.plot(xvalues,xvalues, label="y=x") #plot the diagonal y=x
        plt.plot(xvalues, f(xvalues), label="updating function") #plot the updating function

        plt.plot(cobwebs_x,cobwebs_y) #plot the cobwebs
        for x,y in zip(list(np.around(np.array(cobwebs_x),2)),list(np.around(np.array(cobwebs_y),2))): #add some labels
            label = f"({x},{y})"

        plt.legend()
        plt.draw()

        plt.figure()

        distinct_solutions=list(OrderedDict.fromkeys(cobwebs_x))#get the x-components of the cobwebs to plot the solution. This orders them and deletes repeats
        plt.title("Plot of the Cobweb x-coordinates")

        plt.plot(list(range(len(distinct_solutions))),distinct_solutions) #plots the solution set.

    plot_cobwebbing_approx(adderall_updating_approx, 30, 500) # a0 = 30 mg
```

```
# This section models the daily maximum amounts of amphetamine based on the approximate half-life
d = 30
r_per_day = np.exp(-24*np.log(2) / halflife)

#Code modified from DTDS lesson
def plot_cobwebbing_plusD_approx(f, a0, steps):
  cobwebs_x=[a0] #starting x-value
  cobwebs_y=[f(a0)] #starting y-value

  for i in range(1,steps):
      if i%2==1: #if the step i is odd
          cobwebs_x.append(cobwebs_y[i-1]) #append the same values along the diagonal y=x
          cobwebs_y.append(cobwebs_y[i-1])
      elif i%2==0: #if the step i is even
          cobwebs_x.append(cobwebs_y[i-1]) #append the same x-value, but "move up" to the updating curve.
          cobwebs_y.append(f(cobwebs_x[i]))

  xvalues=np.linspace(0,max(cobwebs_x), 500) #linspace for plotting
  plt.title("Cobweb Plot")
  plt.plot(xvalues,xvalues, label="y=x") #plot the diagonal y=x
  plt.plot(xvalues, f(xvalues), label="updating function") #plot the updating function

  plt.plot(cobwebs_x,cobwebs_y) #plot the cobwebs
  for x,y in zip(list(np.around(np.array(cobwebs_x),2)),list(np.around(np.array(cobwebs_y),2))): #add some labels
      label = f"({x},{y})"

  plt.ylabel("a at time t (mg)")
  plt.xlabel("a at time t (mg)")

  plt.legend()
  plt.draw()

  plt.figure()

  distinct_solutions=list(OrderedDict.fromkeys(cobwebs_x))#get the x-components of the cobwebs to plot the solution. This orders them and deletes repeats
  plt.title("Plot of the Cobweb x-coordinates")

  plt.plot(list(range(len(distinct_solutions))),distinct_solutions) #plots the solution set.

  plt.draw()

  plt.show()

def adderall_updating_plusD_approx(x):
    return x * r_per_day + d

plot_cobwebbing_plusD_approx(adderall_updating_plusD_approx, 30, 1000)
```

```
[5] # This section models the daily maximum amounts of d-AMPH and l-AMPH with doses every 24 hours.

    d = 100
    # Rates have been modified to account for 24 hour time steps
    r_per_day_d = np.exp(-24*np.log(2) / halflife_d_amph)
    r_per_day_l = np.exp(-24*np.log(2) / halflife_l_amph)

    #Code modified from DTDS lesson
    def plot_cobwebbing_exact(f, g, a0, steps): # Has two functions in parameter for the two different updating functions

        d = a0

        #D-AMPH
        cobwebs_d_x=[a0*(3/4)] #starting x-value weighted for ratio of d-AMPH : l-AMPH
        cobwebs_d_y=[f(a0*(3/4))] #starting y-value

        for i in range(1,steps):
            if i%2==1: #if the step i is odd
                cobwebs_d_x.append(cobwebs_d_y[i-1]) #append the same values along the diagonal y=x
                cobwebs_d_y.append(cobwebs_d_y[i-1])
            elif i%2==0: #if the step i is even
                cobwebs_d_x.append(cobwebs_d_y[i-1]) #append the same x-value, but "move up" to the updating curve.
                cobwebs_d_y.append(f(cobwebs_d_x[i]))

        xvalues_d=np.linspace(0,max(cobwebs_d_x), 500) #linspace for plotting
        plt.title("Cobweb Plot for d-amphetamine")
        plt.plot(xvalues_d,xvalues_d, label="y=x") #plot the diagonal y=x
        plt.plot(xvalues_d, f(xvalues_d), label="updating function") #plot the updating function

        plt.plot(cobwebs_d_x,cobwebs_d_y) #plot the cobwebs
        for x,y in zip(list(np.around(np.array(cobwebs_d_x),2)),list(np.around(np.array(cobwebs_d_y),2))):
            label = f"({x},{y})"

        plt.ylabel("a at time t (mg)")
        plt.xlabel("a at time t (mg)")

        plt.legend()
        plt.draw()

        plt.figure()

        #L-AMPH
        cobwebs_l_x=[a0*(1/4)] #starting x-value weighted for ratio of d-AMPH : l-AMPH
        cobwebs_l_y=[g(a0*(1/4))] #starting y-value
```

```
[5]     for i in range(1,steps):
            if i%2==1: #if the step i is odd
                cobwebs_l_x.append(cobwebs_l_y[i-1]) #append the same values along the diagonal y=x
                cobwebs_l_y.append(cobwebs_l_y[i-1])
            elif i%2==0: #if the step i is even
                cobwebs_l_x.append(cobwebs_l_y[i-1]) #append the same x-value, but "move up" to the updating curve.
                cobwebs_l_y.append(g(cobwebs_l_x[i]))

        xvalues_l=np.linspace(0,max(cobwebs_l_x), 500) #linspace for plotting
        plt.title("Cobweb Plot for l-amphetamine")
        plt.plot(xvalues_l,xvalues_l, label="y=x") #plot the diagonal y=x
        plt.plot(xvalues_l, g(xvalues_l), label="updating function") #plot the updating function


        plt.plot(cobwebs_l_x,cobwebs_l_y) #plot the cobwebs
        for x,y in zip(list(np.around(np.array(cobwebs_l_x),2)),list(np.around(np.array(cobwebs_l_y),2))):
            label = f"({x},{y})"

        plt.ylabel("a at time t (mg)")
        plt.xlabel("a at time t (mg)")

        plt.legend()
        plt.draw()

        plt.figure()

        #Creates lists of solution sets for d-AMPH and l-AMPH
        distinct_solutions_d=list(OrderedDict.fromkeys(cobwebs_d_x))
        distinct_solutions_l=list(OrderedDict.fromkeys(cobwebs_l_x))

        #Plots both solution sets
        plt.title("Accumulatuion of d-amphetamine and l-amphetamine:\nPlot of the Cobweb x-coordinates")
        plt.ylabel("Amount of Amphetamine (mg)")
        plt.xlabel("Time (days)")

        plt.plot(list(range(len(distinct_solutions_d))),distinct_solutions_d, label="d-amphetamine") #plots the solution set.
        plt.plot(list(range(len(distinct_solutions_l))),distinct_solutions_l, label="l-amphetamine") #plots the solution set.


        plt.legend()

        plt.draw()

        plt.show()

        plt.figure()
```

```
        #Plots cumulative solution sets of d-AMPH and l-AMPH together
        plt.title("Accumulation of Amphetamine:\nPlot of the Cobweb x-coordinate")
        plt.ylabel("Amount of Amphetamine (mg)")
        plt.xlabel("Time (days)")

        solutions_together = [] #list of combined solutions
        for i in range(len(distinct_solutions_d)):
          solutions_together.append(distinct_solutions_d[i] + distinct_solutions_l[i]) #appends combination to combined solutions list

        plt.plot(list(range(len(distinct_solutions_d))),solutions_together) #plots the solution set.

        print(solutions_together) #Prints solutions as list

        plt.draw()

        plt.show()

    #Updating function for d-AMPH
    def adderall_updating_d_plusD(x):
        return x * r_per_day_d + (3/4)*d

    #Updating function for l-AMPH
    def adderall_updating_l_plusD(x):
        return x * r_per_day_l + (1/4)*d

    plot_cobwebbing_exact(adderall_updating_d_plusD, adderall_updating_l_plusD, 100, 50)
```

```
[6] # This section models the elimination of a single dose of Adderall as d-AMPH and l-AMPH over time (hrs)

    def adderall_updating_d(x): # Updating function for d-AMPH
        return x * r_d_amph

    def adderall_updating_l(x): # Updating function for l-AMPH
        return x * r_l_amph

    #Code modified from DTDS lesson
    def plot_cobwebbing_exact_singleDose(f, g, a0, steps,endValue):
        d = a0

        #D-AMPH
        cobwebs_d_x=[a0*(3/4)] #starting x-value weighted for ratio of d-AMPH : l-AMPH
        cobwebs_d_y=[f(a0*(3/4))] #starting y-value

        for i in range(1,steps):
            if i%2==1: #if the step i is odd
                cobwebs_d_x.append(cobwebs_d_y[i-1]) #append the same values along the diagonal y=x
                cobwebs_d_y.append(cobwebs_d_y[i-1])
            elif i%2==0: #if the step i is even
                cobwebs_d_x.append(cobwebs_d_y[i-1]) #append the same x-value, but "move up" to the updating curve.
                cobwebs_d_y.append(f(cobwebs_d_x[i]))
        #No graph, just collects values from cobwebbing

        #L-AMPH
        cobwebs_l_x=[a0*(1/4)] #starting x-value weighted for ratio of d-AMPH : l-AMPH
        cobwebs_l_y=[g(a0*(1/4))] #starting y-value

        for i in range(1,steps):
            if i%2==1: #if the step i is odd
                cobwebs_l_x.append(cobwebs_l_y[i-1]) #append the same values along the diagonal y=x
                cobwebs_l_y.append(cobwebs_l_y[i-1])
            elif i%2==0: #if the step i is even
                cobwebs_l_x.append(cobwebs_l_y[i-1]) #append the same x-value, but "move up" to the updating curve.
                cobwebs_l_y.append(g(cobwebs_l_x[i]))
        #No graph, just collects values from cobwebbing

        #Plots d-AMPH and l-AMPH hourly elimination
        distinct_solutions_d=list(OrderedDict.fromkeys(cobwebs_d_x))#get the x-components of the cobwebs to plot the solution. This orders them and deletes repeats
        distinct_solutions_l=list(OrderedDict.fromkeys(cobwebs_l_x))#get the x-components of the cobwebs to plot the solution. This orders them and deletes repeats

        plt.title("Elimination of d-amphetamine and l-amphetamine:\nPlot of the Cobweb x-coordinates")
        plt.ylabel("Amount of Amphetamine (mg)")
        plt.xlabel("Time (hr)")
```

```
        plt.plot(list(range(len(distinct_solutions_d))),distinct_solutions_d, label="d-amphetamine")
        plt.plot(list(range(len(distinct_solutions_l))),distinct_solutions_l, label="l-amphetamine")

        plt.legend()

        plt.draw()

        plt.show()

        plt.figure()

        #Plots the total elimination curves for amphetamine
        plt.title("Elimination of Amphetamine:\nPlot of the Cobweb x-coordinate")
        plt.ylabel("Amount of Amphetamine (mg)")
        plt.xlabel("Time (hr)")

        solutions_together = []
        for i in range(len(distinct_solutions_d)):
          solutions_together.append(distinct_solutions_d[i] + distinct_solutions_l[i]) #Appends combination of two solution lists for each index i

        plt.plot(list(range(len(distinct_solutions_d))),solutions_together) #plots the solution set.

        for i in range(len(solutions_together)):
          if solutions_together[i] < endValue:
            #plt.annotate(str([i,solutions_together[i]]),[i,solutions_together[i]]) #Plots a point where the amount of Adderall falls below the inputted end value
            print("The amount of total amphetamine falls below 1mg at t = ", i) #Prints out time where the amount of Adderall falls below the inputted end value
            break;

        plt.draw()

        plt.show()

    plot_cobwebbing_exact_singleDose(adderall_updating_d, adderall_updating_l, 50, 500, 1) #a0 = 50 mg
```

```
#This section compares the updating function and its cobwebbing to its inverse and its cobwebbing to help visualize the information that the inverse tells us
#Code modified from DTDS lesson
def plot_cobwebbing_with_inverse(f, a0, steps):

    #Updating function
    cobwebs_x=[a0] #starting x-value
    cobwebs_y=[f(a0)] #starting y-value

    #Inverse function, x and y swapped
    cobwebs_x_inverse=[f(a0)] #starting x-value
    cobwebs_y_inverse=[a0] #starting y-value

    for i in range(1,steps):
        if i%2==1: #if the step i is odd
            #Updating function
            cobwebs_x.append(cobwebs_y[i-1])
            cobwebs_y.append(cobwebs_y[i-1])
            #Inverse
            cobwebs_y_inverse.append(cobwebs_y[i-1])
            cobwebs_x_inverse.append(cobwebs_y[i-1])
        elif i%2==0: #if the step i is even
            #Updating function
            cobwebs_x.append(cobwebs_y[i-1])
            cobwebs_y.append(f(cobwebs_x[i]))
            #Inverse: x and y swapped
            cobwebs_y_inverse.append(cobwebs_y[i-1])
            cobwebs_x_inverse.append(f(cobwebs_y[i-1]))

    #Plots the updating function, its cobwebbing, the inverse, and its cobwebbing
    xvalues=np.linspace(0,max(cobwebs_x), 500) #linspace for plotting
    plt.title("Cobweb Plot")
    plt.plot(xvalues,xvalues, label="y=x") #plot the diagonal y=x
    plt.plot(xvalues, f(xvalues), label="updating function") #plot the updating function
    plt.plot(f(xvalues), xvalues, label="inverse of updating function") #plot the inverse

    plt.plot(cobwebs_x,cobwebs_y) #plot the cobwebs
    for x,y in zip(list(np.around(np.array(cobwebs_x),2)),list(np.around(np.array(cobwebs_y),2))): #add some labels
        label = f"({x},{y})"

    plt.plot(cobwebs_x_inverse,cobwebs_y_inverse) #plot the cobwebs for the inverse
    for x,y in zip(list(np.around(np.array(cobwebs_x_inverse),2)),list(np.around(np.array(cobwebs_y_inverse),2))): #add some labels
        label = f"({x},{y})"

    plt.legend()
    plt.draw()

plot_cobwebbing_with_inverse(adderall_updating_plusD_approx, 0, 100) #a0 = 0 mg, d = 100
```