Session 5

The Science of Addiction
October 17, 2018

I'm writing this while on summer vacation in the Berkshires. Yesterday I had the perfect day. I got up at sunrise, and made my french roast coffee in the french press. Then my Newfie Beowulf and I went for a swim together across the lake and back. We went inside and I toweled him off and brushed him out and then made breakfast for Cindy and I, topped off with yogurt and fresh raspberries which I found in our bushes at the edge of the lawn. I've been terrified that I wouldn't complete this syllabus by September so I was relieved to work on this chapter for a few hours and get a lot done. In the afternoon Cindy and I drove up to Williamstown to do a little shopping and visit Mass MoCA art museum. They had a wonderful multimedia exhibition by Laurie Anderson complete with a virtual reality experience. In Williamstown, Cindy found some birthday gifts for a friend of ours and I got a couple of great sports coats on sale, 80% off! We had dinner with friends at our favorite restaurant in Lenox and Cindy and I celebrated by going to bed early.

Now you might think me a bit daft for describing a summer day, but it illustrates some points about the science of addiction. The human brain is designed to maximize survival in a very uncertain world. As a strategy, it uses novelty seeking (raspberries, museum and shopping) to find new and useful things together with relying on proven successful strategies of the past (daily swim, favorite restaurant). The brain is very complex and there is much that scientists do not yet understand, but there has been good progress over the past twenty years at understanding the mechanisms in the brain that correlate with our experiences of pleasure, pain, motivation, fear and anxiety. These moods of the mind which correlate with neural circuits in the brain are key to our survival. It is avoidance of the anxiety, fear and terror that I feel when I contemplate preparing twelve sessions of this class that motivates me to do the research and write it up, and the corresponding relief I feel when I finish a session is sublime. The delight that I feel when I discover a wonderful new thing like the first fresh raspberries of the season gets wired into my brain, which records the pleasure, the location and the season, so that next year my brain will remind me to go look for those raspberries. Similarly, shopping is most likely the use of neural circuitry that evolved during our hunter-gatherer days, when we explored the environment looking for good things to eat. Spending time with my dog, especially grooming behavior triggers a reward in me which is related to the social bonding that monkeys do when they pick insects off each others' fur. Social bonding as with pets, with one's mate and by sharing food with friends is a crucial component of human survival; we're social animals and cannot survive alone.

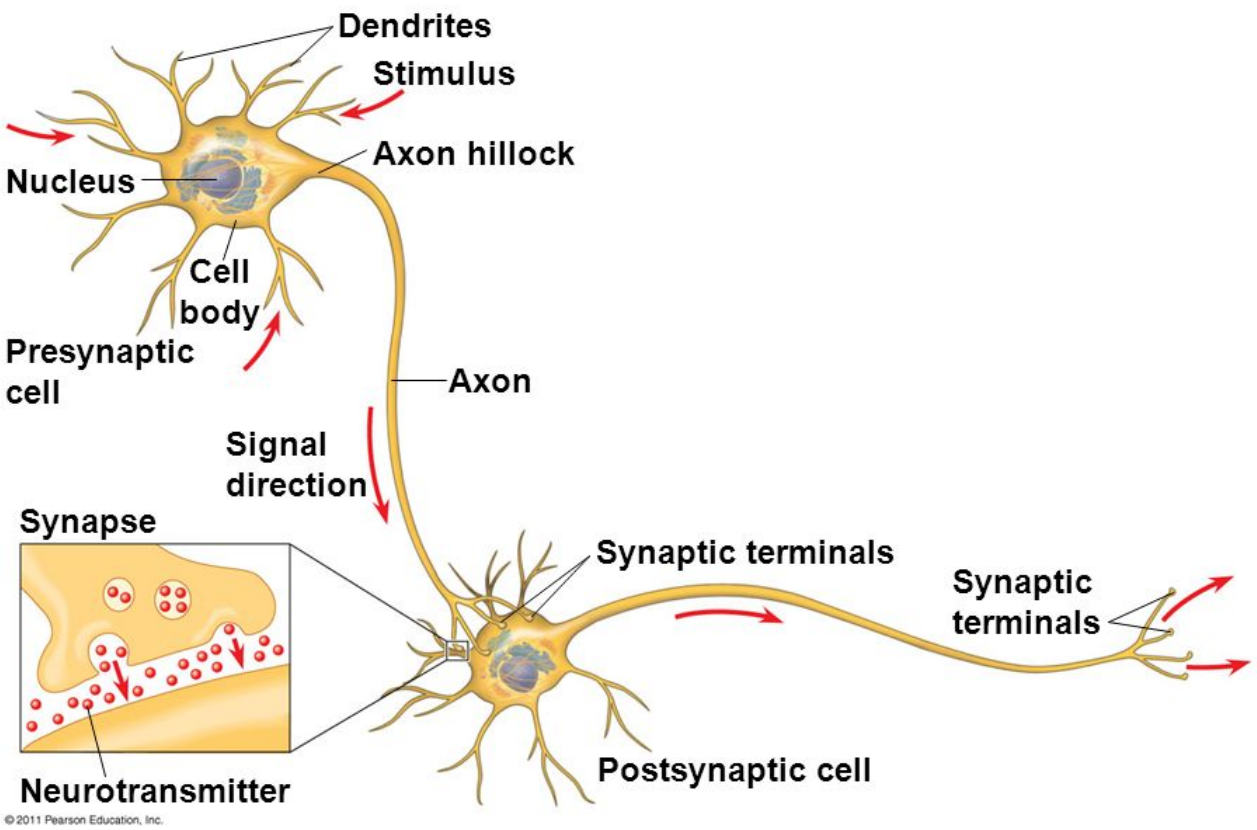
So what does any of this have to do with drug addiction? As it turns out, addiction to drugs, or shopping, gambling, internet games, sex, or food, all rely on well understood reward/motivation and stress/pain avoidance pathways in the brain. Any addiction is a learned behavior in which a wonderful new experience is repeated over and over and becomes an ingrained habit which becomes more and more difficult to break. The American Society of Addiction Medicine defines addiction as “a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.”

“Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.”

I think most people, including myself, find addicts’ pursuit of their addiction to the point of self harm to be bizarre and alien. Why can’t they just stop? It’s as if they were possessed by the devil. But it is important to note that addictive behavior is just an exaggeration of normal behavior; it is a result of the brain doing what it was designed to do. Drug or sex or food or gambling addictions can be so strong as to be pathological and that pathology or self harm is an important part of the definition of addiction. But we all engage in repetitive, compulsive behaviors that would be classified as addictions but for their lack of self harm. Many people compulsively play sports or musical instruments or collect things or even lead study groups at HILR; these behaviors are socially acceptable even though they use the same brain biology as addictions. Let’s take a look at that brain biology, without getting too technical.

Brain biology

Figure 48.4

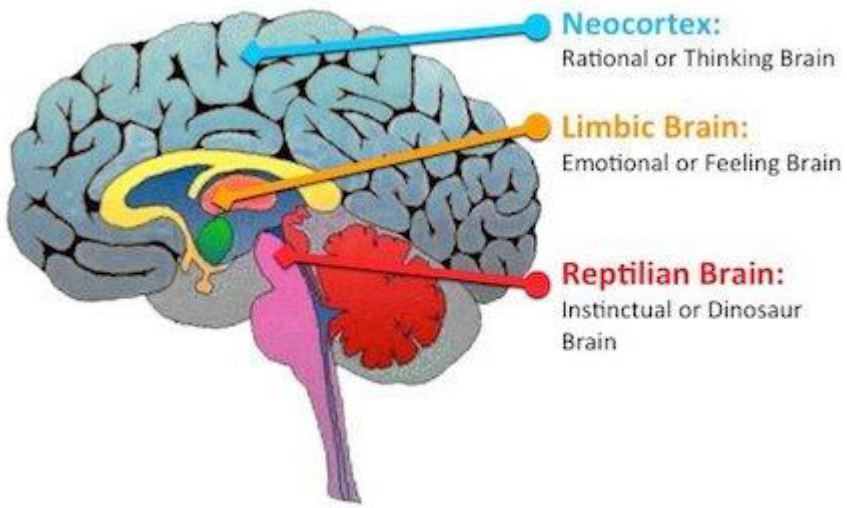


How nerves communicate with each other **(https://slideplayer.com/slide/9054503/%20)**

The brain has a great number of nerve cells, on the order of 100 billion **(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776484/)** . Each of these nerve cells has hundreds to thousands of branches that touch other nerve cells, and hundreds to thousands of other nerve cells touch each nerve so there are on the order of 150 trillion connections between nerve cells in the brain. When nerves are excited, they depolarize **(https://en.wikipedia.org/wiki/Depolarization)** and a wave of electricity travels from the cell body out to each of the nerve's branches. The connection point between one nerve and another is called a synapse. When the wave of electricity reaches the end of a branch at the synapse the excited nerve releases some chemicals called neurotransmitters which are picked up by the

receiving nerve. If enough branches touching a nerve fire at once, the receiving nerve may also fire, and electrical waves can pass from neuron to neuron in what are three dimensional electrical circuits.

The brain isn't just a giant hodgepodge of interconnected neurons, but rather the neurons are organized into interconnected structures. Often the nerves in the same structure use the same neurotransmitter to communicate to other neurons. There are many different types of nerves and many different neurotransmitters. One you may have heard of is serotonin. 10% of Americans (https://well.blogs.nytimes.com/2013/08/12/a-glut-of-antidepressants/) take antidepressants like Prozac; among women in their 40's and 50's the percentage is one in four. Prozac is among the class of drugs called selective serotonin reuptake inhibitors, or SSRI's. These drugs are thought to work by reducing the reuptake of the neurotransmitter serotonin in the synapse after it is released from a serotonin neuron, thus increasing the effect of that neuron on the neuron it is connected to. Serotonergic neurons are located in the brainstem, the most primitive part of the brain and it is thought that they play a role in skewing perceptions toward a pleasant interperetation (http://rstb.royalsocietypublishing.org/content/368/1615/20120407.short) . In this way they may help relieve anxiety and depression.



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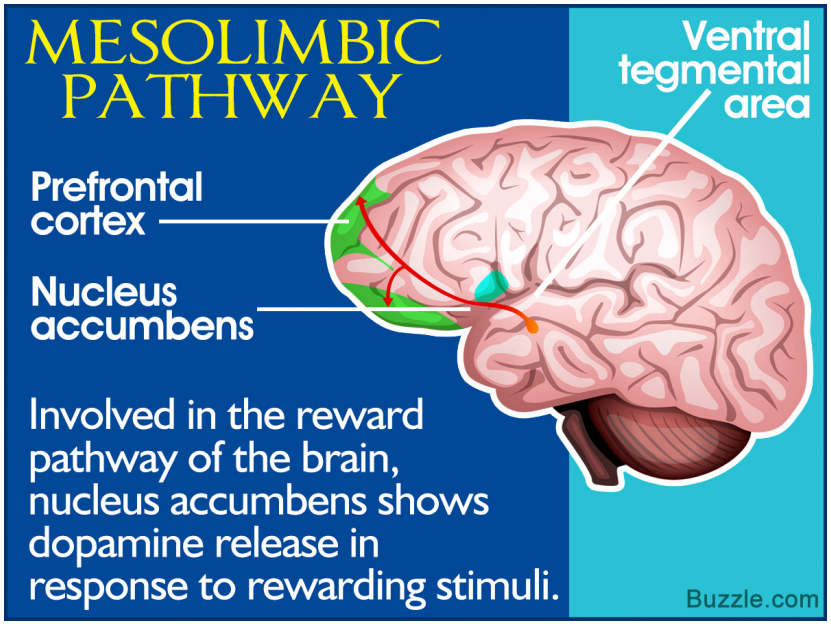
Brains evolved through evolution from the simple to the complex. Reptilian brains are pretty primitive but they get the job done. Mammalian brains are more complicated than those of reptiles, but what evolution did was to keep the reptilian brain and add limbic circuits for emotional responses on top of it. Human brains are much like other mammals except for the fact that we've got huge cortexes - the outermost part of the brain that allows us to utilize language and abstract thought. The human cortex has 19% of the nerve cells in the brain but 82% of the brain's mass **(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776484/)**. We may pride ourselves on how enlightened and rational we are, but that might be overstating the case; it's more correct to say that our cortex provides us with a thin veneer of civility and rationalization over a savage reptilian core.

Brain Circuits of Pleasure and Motivation



https://bodytomy.com/structure-function-of-nucleus-accumbens **(https://bodytomy.com/structure-function-of-nucleus-accumbens)**

A very particular part of our brains plays a key role in addiction, as well as pleasure and motivation. It is called the reward system **(https://en.wikipedia.org/wiki/Reward_system)**, or mesolimbic pathway, or the mesocorticolimbic projection **(https://en.wikipedia.org/wiki/Dopaminergic_pathways#Mesocorticolimbic_projection)**. It starts with the Ventral Tegmental Area (VTA **(https://en.wikipedia.org/wiki/Ventral_tegmental_area)**) which is a part of the mammalian midbrain or limbic system. The VTA receives

signals from all over the brain, upper cortical, limbic midbrain, and lower reptilian brain and projects primarily to two areas: the nucleus accumbens, which is a kidney bean shaped area in the mid-brain and the prefrontal cortex. The nucleus accumbens (https://en.wikipedia.org/wiki/Nucleus_accumbens) is often described as the pleasure center of the brain, although there are other areas of the brain which when stimulated produce pleasure. When the nucleus accumbens is excited by nerves from the VTA or from an electrode implanted into the brain (https://en.wikipedia.org/wiki/Brain_stimulation_reward), humans will feel pleasure and euphoria. The nucleus accumbens projects to a variety of other midbrain structures. The VTA also connects to the prefrontal cortex; this is the last part of the cortex to develop in adults in their late teens and twenties and is thought to be associated with executive function (https://en.wikipedia.org/wiki/Executive_functions) behaviors such as planning complex behaviors, self control, focusing attention, impulse control, maintaining socially acceptable behaviors and orchestrating thoughts and behaviors in conformance with internal goals.

The neurotransmitter that is released from ventral tegmental area nerves onto the nucleus accumbens and prefrontal cortex is called dopamine, and the reward system, or mesolimbic pathway is often called the dopaminergic pathway (https://en.wikipedia.org/wiki/Dopaminergic_pathways#Mesocorticolimbic_projection). This is important for our story because all of the behavioral addictions and all of the addictive drugs cause release of dopamine in the reward system.

While activity in the mesolimbic pathway correlates with feelings of pleasure or euphoria, the system is more complicated than that. There is some evidence that the pathway is more related to motivation and anticipation for a reward (https://en.wikipedia.org/wiki/Mesolimbic_pathway#Function), or desire (http://jonlieffmd.com/blog/human-brain/pleasure-circuits-in-the-brain). The mesolimbic pathway can be activated by the placebo effect (http://www.jneurosci.org/content/29/15/4882), highlighting the interplay between higher level cortical functions and the midbrain. It is clear that the mesolimbic pathway is activated when a reward is found (sports coats, 80% off!), and this memory is strongly encoded in cortical memory. When cues in the environment associated with the reward are noticed, the brain will activate the mesolimbic pathway in anticipation of or desire for an additional reward.

Endogenous Drugs

Some drugs, like opiates and marijuana work by activating receptors in the brain. Why would the brain have opiate receptors? The receptors in the brain weren't designed for opium, they were designed for brain chemicals called endorphins: the name is a contraction

of “endogenous” or natural, and “morphine”. It may be just coincidence that molecules like morphine activate endorphin receptors in the brain or it might be an evolutionary adaptation by the opium poppy to prevent animals from eating it, or to encourage humans to cultivate poppies. Endorphins are hormones produced in the brain and pituitary gland; they are released under various circumstances. Endorphins can act as natural analgesics; they block pain signals in the spinal cord (https://en.wikipedia.org/wiki/Opioid_receptor).

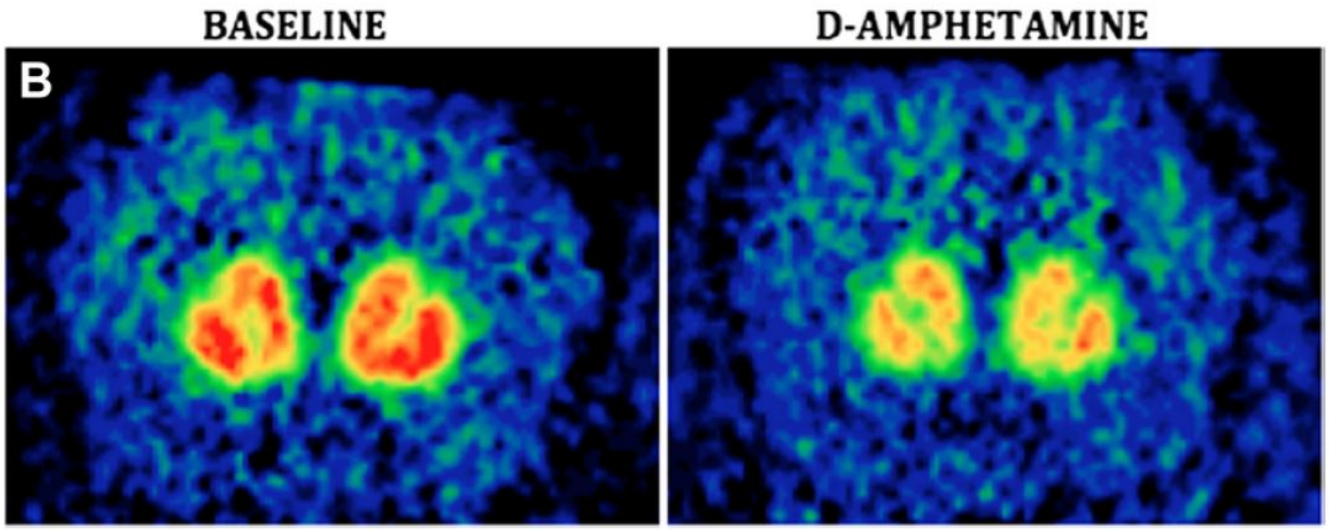
There are also many opioid receptors in the mesolimbic pathway and release of endorphins can create a feeling of relaxation or happiness; endorphins moderate psychic pain as well as physical pain by activating the mesolimbic pathway. Oxytocin is another powerful hormone produced in the pituitary gland that plays a key role in social relations, pair bonding and maternal bonding. Oxytocin increases sensitivity to endorphins (https://www.sciencedirect.com/science/article/pii/0091305787905338) and the combination of oxytocin and endorphins help produce the euphoria and **strong bond between nursing mother and infant** (https://canvas.harvard.edu/courses/41939/files/6223031/download)  (https://canvas.harvard.edu/courses/41939/files/6223031/download). There is some evidence that alterations in the dopamine system (https://www.sciencedaily.com/releases/2015/01/150130092921.htm) or in the oxytocin receptor gene (https://www.ncbi.nlm.nih.gov/pubmed/25092245) may be responsible for some cases of autism spectrum disorder.

Endocannabinoids are endogenous neurotransmitters whose receptors are also activated by marijuana. Endocannabinoids (https://en.wikipedia.org/wiki/Endocannabinoid_system) are found throughout the body, but especially in the intestines and midbrain, and play a role in mediating appetite, mood, and analgesia. In the past, scientists hypothesized that endorphins were responsible for the euphoria after exercise known as a runner’s high. It is now thought that runner’s high is caused by a specific endocannabinoid, anandamide (https://en.wikipedia.org/wiki/Neurobiological_effects_of_physical_exercise#Anandamide) which has receptors in the nucleus accumbens. Anandamide (https://en.wikipedia.org/wiki/Anandamide) may be an active ingredient in chocolate and is thought to be responsible for the analgesic effect of Tylenol (https://en.wikipedia.org/wiki/Paracetamol#Mechanism_of_action).

Drugs and Addictive Behaviors

It is now understood that all drugs which produce euphoria (not including hallucinogens) as well as addictive behaviors such as gambling, sex, eating, video gaming, exercise etc, all release dopamine in the mesolimbic system, exciting the nucleus accumbens and alerting the prefrontal cortex that this activity is important. Some drugs release dopamine directly: amphetamines release dopamine and inhibit its reuptake, cocaine inhibits dopamine reuptake. Marijuana and opioids activate the mesolimbic pathway directly, through endocannabinoid and endorphin receptors. Nicotine and alcohol and even caffeine (http://www.jneurosci.org/content/22/15/6321) activate other neurotransmitter pathways which indirectly activate the mesolimbic pathway.

The extent of activation can be measured directly with imaging studies which can measure dopamine release and number of dopamine receptors:



Imaging study showing dopamine activation by amphetamine in nucleus accumbens (https://canvas.harvard.edu/courses/41939/files/6223043/download?wrap=1)
(https://canvas.harvard.edu/courses/41939/files/6223043/download?wrap=1)

The importance of the mesolimbic dopamine pathways to addiction is demonstrated by patients with Parkinson's disease. Parkinson's causes a loss of control of movement and it is caused by loss of dopaminergic neurons in motor circuits in the midbrain. A common treatment is to prescribe drugs which increase the amount of dopamine in these nerves. However, the treatment also increases dopamine output in the mesolimbic pathway; as a result Parkinson's patients often develop behavioral addictions such as pathological gambling **(https://www.sciencedirect.com/science/article/pii/S089662730900124X)**; up to 8% of Parkinson's patients develop gambling addictions as compared to 1% of the general population.

Neurobiology of Addiction

We are now ready to examine an explanation for addiction **(https://en.wikipedia.org/wiki/Addiction)**. As with any brain research, this is a simplified view of an extraordinarily complex system but it is well supported with evidence and highly explanatory. I've borrowed this section primarily from two papers by the preeminent addiction researcher, George Koob. The papers are **The Neurobiology of Addiction: Where We Have Been and Where We Are Going (https://canvas.harvard.edu/courses/41939/files/6223044/download?**

wrap=1) (https://canvas.harvard.edu/courses/41939/files/6223044/download?wrap=1) and Neuroclinical Framework for the Role of Stress in Addiction (https://canvas.harvard.edu/courses/41939/files/6223049/download?wrap=1) (https://canvas.harvard.edu/courses/41939/files/6223049/download?wrap=1). An addiction, be it a drug addiction or behavioral addiction usually starts with the reward system: a person takes a drug, or perhaps gambles, and finds the results intensely pleasurable and rewarding. When this happens the ventral tegmental area tells the prefrontal cortex that this is an important behavior and the brain takes notice. If possible, the person will repeat the behavior, and the reward will be repeated and the associations of behavior with that reward will be strengthened with repetition. However, over time the intense pleasure will lessen; this is called tolerance. Tolerance is nature's way of telling your brain not to get so excited. While the first raspberry find of the season may be sublime, at the end of raspberry season they've become ho-hum, and you start looking for new exciting stimuli like apples. The stronger the repeated source of pleasure the faster and stronger tolerance can build up. The brain has lots of inhibitory circuits that strive to achieve homeostasis, or equilibrium. If you push the brain strongly toward pleasure, it will dampen down the pleasure circuits. This makes sense from an evolutionary perspective; if we were happy all the time we wouldn't be continually striving to achieve more successful rewards. In drug addiction, tolerance causes people to find that they need more and more of the drug to achieve the same "high". The tolerance feedback mechanism includes a protein transcription factor called ΔFosB (http://rstb.royalsocietypublishing.org/content/363/1507/3245). When the mesolimbic system is activated, ΔFosB is produced and it acts on the nerves to reduce dopamine output and reduce the number of dopamine receptors. The more the mesolimbic system is activated, the more it becomes suppressed.

There is another key brain circuit which mediates addiction, called the hypothalamus-pituitary-adrenal or HPA axis (https://en.wikipedia.org/wiki/Hypothalamic%E2%80%93pituitary%E2%80%93adrenal_axis). This system causes a stress response through the release of stress hormones such as cortisol. In some sense, it is the opposite of the reward system. The HPA axis can be activated by any number of physical or psychological stressors. One mechanism for HPA activation is release of an endorphin like molecule named dynorphin (https://en.wikipedia.org/wiki/Dynorphin). Dynorphin is released from the mesolimbic system when activated by ΔFosB. Dynorphin seems to act oppositely to other endorphins: it activates the HPA axis, causing anxiety and psychological stress. The more the mesolimbic system is activated, by euphoriant drugs for example, the more anxiety and stress is produced. This is shown by in a diagram from Koob:

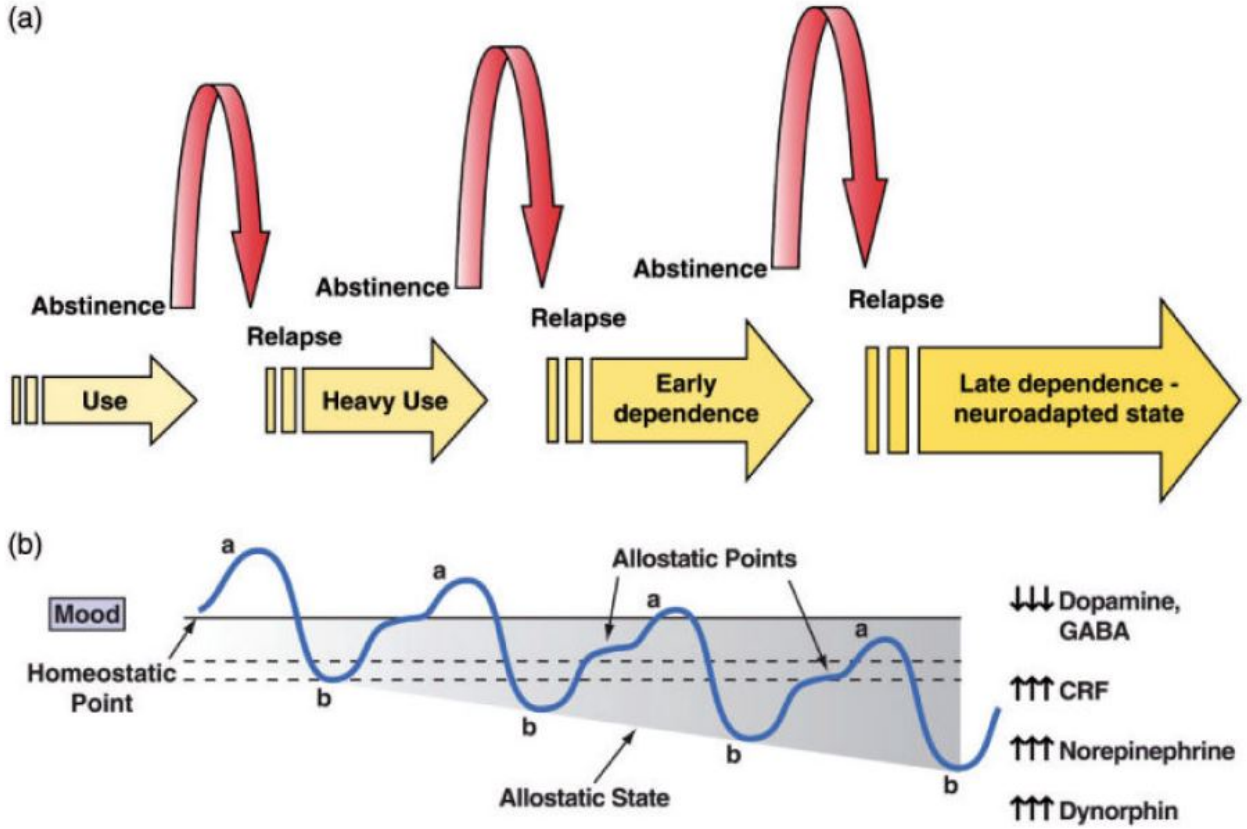


Figure 3.(a) Schematic of the progression of drug and alcohol dependence over time, illustrating the shift in underlying motivational mechanisms. From initial, positive-reinforcing, pleasurable effects of drugs and alcohol, the addiction process progresses over time to being maintained by negative-reinforcing relief from a negative emotional state. Neuroadaptations that encompass the recruitment of extra-hypothalamic CRF systems are key to this shift (taken with permission from Heilig and Koob88). (b) The a-process represents a positive hedonic or positive mood state, and the b-process represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be the sum of both the a-process and the b-process. An individual who experiences a positive hedonic mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain the a-process. An appropriate counter-adaptive opponent process (b-process) that balances the activational process (a-process) does not lead to an allostatic state. The changes in the affective stimulus (state) in an individual with repeated frequent drug use may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction (see text). Notice that the apparent b-process never returns to the original homeostatic level before drug taking begins again, thus creating a greater and greater allostatic state in the brain reward system. The counteradaptive opponent-process (b-process) does not balance the activational process (a-process) but in fact shows a residual hysteresis. Although these changes that are illustrated in the figure are exaggerated and condensed over time, the hypothesis is that even during post-detoxification (a period of “protracted abstinence”), the reward system still bears allostatic changes.

From the diagram above we see that what starts out as a pleasurable activity for the addict over time changes into a situation where the normal state without the drug or behavior stimulus includes increasing amounts of anxiety, stress and depression. Over time the addict ceases to take the drug to get high, but feels the need for the drug just to feel normal. Some drugs, such as opiates cause physical withdrawal: runny nose, pains, sweats, and feelings of flu. However it is not the alleviation of physical symptoms that drive the addict's behavior so much as the avoidance of severe mental stress. The reduction in overall mood is compounded by the addict's place in society. The addict feels psychic pain: shame from his actions, social isolation and rejection and hopelessness. These cause stress, make the mood disregulation worse, and only increase the desire for the drug or addictive behavior.

Addictions are a learned behavior; just like practicing the piano, the repetitive cycles of positive reinforcement, and as tolerance builds up, negative reinforcement, strengthen the learned behavior so that over time it becomes a strongly ingrained habit. When drug addicts see visual cues which remind them of their addiction such as a billboard for a glass of wine or a friend they used to drink with, the cortex activates the ventral tegmental area which triggers anticipation in the mesolimbic pathway. This can cause feedback in prefrontal cortical loops so that the addict soon has strong cravings for their drug or behavior; the person can be consumed with desire for the drug and has intrusive thoughts about how to get it. To add insult to injury, after a period of addiction there is a reduction of grey matter in the prefrontal cortex; the addict loses some degree of executive function. Addicts are less able to control their impulses and defer short term rewards for later rewards. A survey of addicts' families showed that they felt the number one factor in their loved one's addiction was lack of willpower **(https://news.gallup.com/poll/24094/Addicts-Family-Members-Say-Lack-Willpower-Top-Addiction-Factor.aspx?g_source=link_NEWSV9&g_medium=TOPIC&g_campaign=item_&g_content=Addicts%27%2520Family%2520Members%2520Say%2520Lack%2520of%2520Willpower%2520Top%2520Addiction%2520Factor)**. The lack of willpower is not because the addict is a bad person, it is because the addiction has changed their brain. When an addict stops his addictive behavior, it can take a very long time to reverse the changes in the brain. In-patient rehab treatments often last 30 days, but the compulsions, cravings and lack of impulse control can last for years. **Studies of rhesus monkeys (https://canvas.harvard.edu/courses/41939/files/6223043/download)**  **(https://canvas.harvard.edu/courses/41939/files/6223043/download)** showed that after only one week of cocaine usage, dopamine receptors in the mesolimbic pathway were reduced by 20% and stayed that way for a year after abstinence. They say that once you learn to ride a bicycle, you never forget; unfortunately the same applies to addictions. This article from the Boston Globe **(https://www.bostonglobe.com/ideas/2018/07/21/should-law-based-luck/mnlC0EaMl13hrPfuXvl8wl/story.html)** questions the degree to which addicts have free will.

Predispositions to Addictive Behavior

What causes people to become addicts? That subject has been debated for a long time. In the 1920's the scientific consensus was that addicts started with a psychopathic personality. That view has shifted; David Courtwright in Dark Paradise (https://www.amazon.com/Dark-Paradise-History-Addiction-America/dp/0674005856/ref=sr_1_1?ie=UTF8&qid=1531418108&sr=8-1&keywords=dark+paradise+david+courtwright) says *"Over and over again the epidemiologic data affirm a simple truth: those groups who, for whatever reason, have had the greatest exposure to opiates have had the highest rates of opiate addiction."* The 20% addiction rate among Saigon's intelligentsia during French rule would seem to support his view. The view that drugs themselves cause addiction and anyone can become addicted has led to Nancy Reagan's "Just Say No" campaign and the trillion dollar failed attempt at drug interdiction.

An alternate view highlights that almost all American adults (https://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf) are exposed to addictive drugs but only a small percentage become addicted, thus pointing to other biological or social causes. This view has been popularized by Dr. Gabor Maté (https://drgabormate.com/) in his book In the Realm of Hungry Ghosts: Close Encounters with Addiction (https://www.amazon.com/Realm-Hungry-Ghosts-Encounters-Addiction/dp/155643880X/ref=sr_1_1?ie=UTF8&qid=1531418586&sr=8-1&keywords=gabor+mate+in+the+realm+of+hungry+ghosts) and by Bruce Alexander (the Rat Park experimenter) in his book The Globalization of Addiction: A Study In Poverty of the Spirit (https://www.amazon.com/Globalization-Addiction-Study-Poverty-Spirit/dp/0199588716/ref=sr_1_1?s=books&ie=UTF8&qid=1531418863&sr=1-1&keywords=bruce+alexander). Dr. Maté was a general practitioner tending to the needs of hundreds of cocaine and heroin addicts in Vancouver for twelve years and views addiction as a response to psychic pain. *"If you want to understand addiction you can't look at what's wrong with the addiction, you have to look at what's right about it. In other words what is the addict getting from the addiction that they otherwise wouldn't have. And what addicts get are relief from pain, a sense of peace, a sense of control, a sense of calmness (very temporarily), and the question is why are these qualities missing from their lives; what happened to them? … So if you want to ask the question of why people are in pain, you can't look at their genetics. You have to look at their lives. And in the case of my patients, my highly addicted patients it's very clear why they're in pain: because they've been abused all their lives. They began life as abused children. All the women I worked with over a twelve year period, hundreds of them, they had all been sexually abused as children. And the men had been traumatized as well. The men had been sexually abused, neglected, physically abused, abandoned, and emotionally hurt over and over again."* Maté tells the story of Serena, a Native American woman who was born to a fifteen year old mother who left the family to become a drug addict in Vancouver. Serena was raised by her alcoholic grandmother who was the only person who loved her. Starting at age seven Serena was sexually abused by her grandfather and uncle; when she tried to force them to stop at age eleven they threatened to rape her younger brother unless she submitted. At

age fifteen Serena took $400 in savings and ran away to Vancouver to find her mother. Her mother injected her with heroin, stole her $400 and sold her to a pimp who maintained her addiction and prostituted her. Can we blame her for using drugs?

There has been criticism of Dr. Maté for reducing the cause of drug addiction to childhood trauma. Especially in the current opioid epidemic there are many stories of great children raised in loving households whose lives were destroyed by addiction. However, the teenage years can be traumatic for anybody as people try to navigate a complex social scene. The pain of social rejection can be severe and is ameliorated with drugs, and social pain and rejection, together with underdeveloped executive function may explain some of these cases.

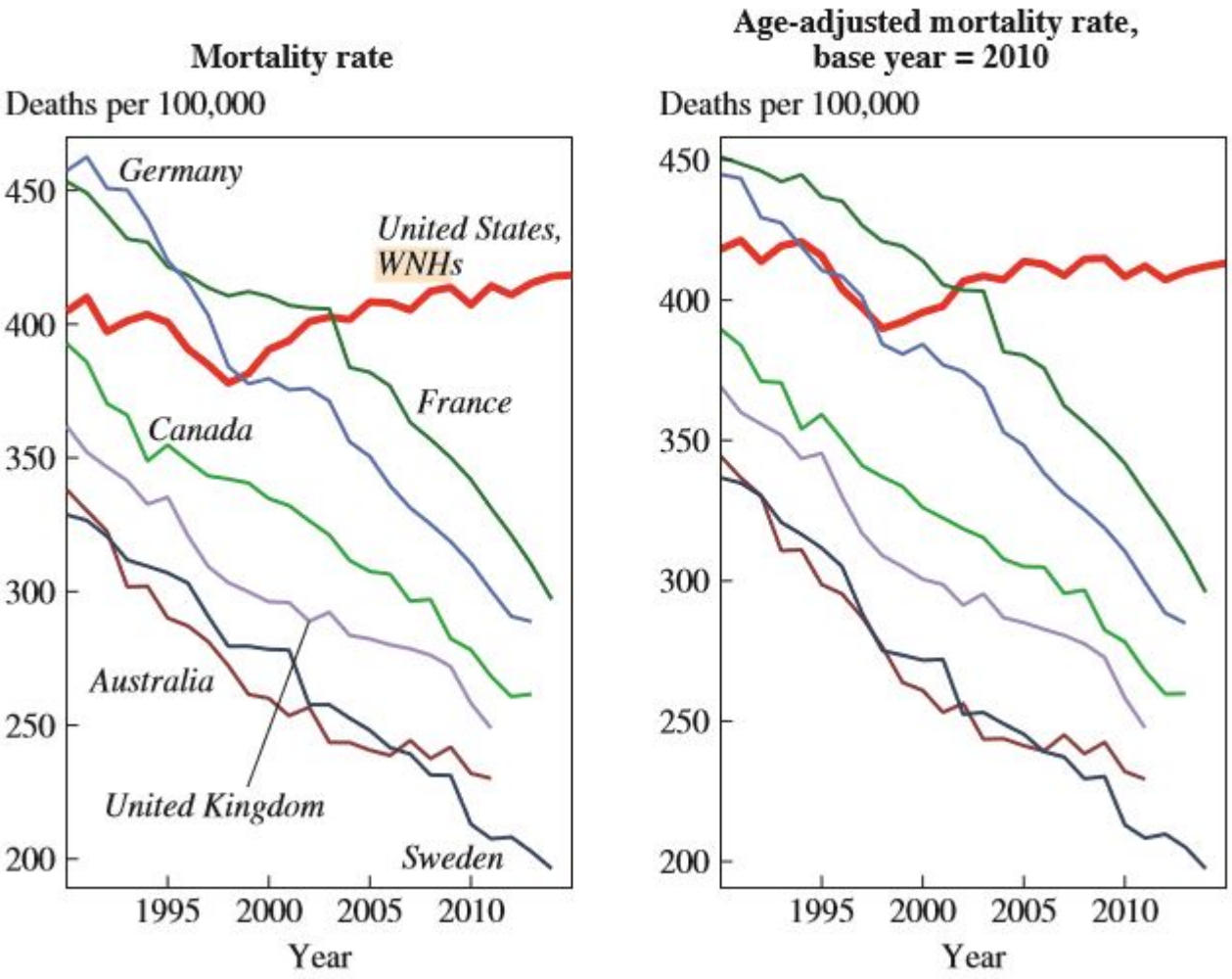
An outcome study of people with adverse childhood experiences found that only 3.5% of people with four or more adverse childhood experiences **(https://www.psychologytoday.com/us/blog/addiction-in-society/201112/the-seductive-dangerous-allure-gabor-mat?page=2&destination=node/81431)** became involved in intravenous drug use, so many people with adverse childhoods find other ways to cope or are for some reason more resilient. On the other hand, the author of the study, Vincent Felitti, found that each adverse childhood experience (abuse, neglect, mental illness, substance abuse or criminality among family members) increased the likelihood of teenage drug use between two and four times, and that one half to two thirds of drug problems could be traced to adverse childhood experiences **(http://www.theannainstitute.org/ACE%20folder%20for%20website/19CNID.pdf)**. A study of non-abusing children from alcoholic households showed that their brains had much higher stress responses **(https://www.ncbi.nlm.nih.gov/pubmed/9862555)** than normal and attributed it to diminished number of opioid receptors in the mesolimbic pathway. Trauma can be passed down from generation to generation, perhaps through epigenetics, according to a recent study **(https://medicalxpress.com/news/2018-07-parents-severe-trauma-stresses-childhood.html)**. A recent US Surgeon General's report on drug addiction stated that of the 20.8 million American adults with a substance use disorder, 41.7% also had mental illness **(https://addiction.surgeongeneral.gov/sites/default/files/surgeon-generals-report.pdf)**, suggesting a self medication reason for substance abuse, or alternatively, that substance abuse can lead to mental illness.

Bruce Alexander goes further than Gabor Maté, and views the epidemic of drug abuse as caused by social dislocation caused by a breakdown in traditional social networks in our society. Alexander points out that the vast number of people who take opiates either for pain control or experimentally do not experience euphoria or even pleasure. But for some, their first experience with heroin is transcendent. Lenny Bruce likened heroin to kissing God. One addict said when she first did heroin, she felt like a warm, soft hug, like a mother hugging her baby. Alexander suggests that those people who respond strongly to opiates are feeling psychic pain, or social dislocation, and he points to the example of 90% of the Vietnam GI heroin addicts who easily gave up their addiction when they

returned stateside and resumed their life and relationships. Alexander's theory is also supported by the geographical distribution of the current opiate epidemic which has hit small town America especially hard in places like Ohio, Indiana and Kentucky. These states have also suffered disproportionately from loss of manufacturing jobs to globalization. We'll look more deeply at the current opiate crisis in Session 10.

Bruce Alexander's indictment of modern society as causing widespread poverty of the spirit is controversial, but recently gained support from a paper by Anne Case and Angus Deaton called Mortality and Morbidity in the 21st Century. **(https://www.brookings.edu/wp-content/uploads/2017/08/casetextsp17bpea.pdf)** They report that starting around the year 2000, the mortality rate among middle aged white non-Hispanic Americans reversed trend and started rising:

Figure 3. All-Cause Mortality by Country for Age 45–54, 1990–2015



Case and Deaton trace the mortality rise to increase in deaths by drugs, alcohol, or suicide, and term these “deaths of despair”, attributed to economic disadvantage especially among white non-HIspanics without a college education, together with the failure of religion and social networks. Case and Deaton’s conclusions were disputed in a recent paper titled **Deaths of Despair or Drug Problems? (https://bfi.uchicago.edu/sites/default/files/research/drugmort2.pdf)**, which shows that the increase in opiate deaths between 2000 and 2015 was not correlated with economic deterioration over the same time period. However, something is going on: between 2008 and 2015 the number of hospital admittances of children for suicidal thoughts has tripled **(https://www.nytimes.com/2018/05/16/well/family/suicide-adolescents-hospital.html?module=WatchingPortal&region=c-column-middle-**

span-region&pgType=Homepage&action=click&mediaId=none&state=standard&contentPlacement=6&version=internal&contentCollection=www.nytimes.com&contentId=https%3A%2F%2Fwww.nytimes.com%2F2018%2F05%2F16%2Fwell%2Ffamily%2Fsuicide-adolescents-hospital.html&eventName=Watching-article-click) , and the overall rate of death by suicide has increased by 25% since 1999 (https://www.nytimes.com/2018/06/23/opinion/sunday/suicide-rate-existential-crisis.html?hpw&rref=opinion&action=click&pgtype=Homepage&module=well-region&region=bottom-well&WT.nav=bottom-well) .

Addiction Treatment

A student paper (https://web.stanford.edu/class/e297c/poverty_prejudice/paradox/htele.html) recently gave three explanations for drug addiction:

The **Colonial or Moralist view** considers the drug user to be sinful and morally defective. The drug itself is not the problem. The moralist's drug policy entails punitive measures for users. Drug use is a crime. Reagan's "zero tolerance" policy on drug use is an excellent example of a moralist drug policy.

Second, the **Temperance view** considers the drug itself, as an addictive substance and the cause of addiction. The supply of drugs is a public hazard. According to the temperance view, drug policy should focus on drug smugglers and drug dealers as the root of drug addiction. U S drug policy has largely been influenced by the temperance view of addiction.

Third, the **Disease concept** views addiction as being a treatable disease. Neither the drug user, nor the drug supplier is responsible for drug addiction. The disease concept calls for a drug policy that focuses on drug treatment and rehabilitation. Clinton, for example embraced the disease concept and increased funding for treatment programs.

This session focusing on the science of addiction has tended toward the disease concept of addiction, which is the most prevalent view in the medical establishment today. But if addiction is a treatable disease, how do you treat it? That is not settled science; there are a wide variety of divergent opinions and the "cure rate" for most addiction treatments is poor. Many addicts go to rehab a dozen times or more before they die or enter prolonged recovery. The National Institute on Drug Abuse defines addiction as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences, and most addiction treatment professionals emphasize that relapsing after treatment is par for the course. However, a survey of 42,000 Americans showed that eventually most drug addicts will finally quit their addictions. The average duration of addiction prior to voluntary cessation is 8.6 years for opiates (https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1964-01-01_1_page002.html) , 4 years for cocaine, 6

years for marijuana, 16 years for alcohol, and 25 years for tobacco (https://www.researchgate.net/publication/236654790_Addiction_and_Choice_Theory_and_New_Data) . Thus most opiate or cocaine addicts who start in their teens or early twenties will become ex-addicts by the time they're thirty.

Methadone Maintenance Therapy

Perhaps the most successful treatment for opiate addiction is maintaining the addiction. Methadone clinics were established across the United States under Richard Nixon and they allow addicts to function normally in society by swallowing methadone once per day. Because methadone taken orally is absorbed slowly, and because methadone has a much longer half life in the body than heroin or morphine, the addict will not get a rush of pleasure, nor will he go into withdrawal. Methadone maintenance patients may stay on maintenance indefinitely, some addicts are able to slowly wean themselves off the drug as they rebuild their lives. As of 2006, there were about 1,400 methadone clinics serving 254,000 patients in the United States; this is about 2.5 times the number when the programs were first introduced in 1972-1973. Methadone maintenance is controversial; critics take a moralist approach in claiming that addicts are just substituting one addiction for another. Other critics point to overdose deaths when methadone patients take other drugs such as heroin or benzodiazepines. And almost nobody wants a methadone clinic in their neighborhood because addicts are "undesirable."

Suboxone Maintenance Therapy

Suboxone (buprenorphine/naloxone (https://en.wikipedia.org/wiki/Buprenorphine/naloxone)) is an opiate maintenance treatment which can be prescribed in pill form, obviating the need for daily visits to a clinic. Buprenorphine is a long lasting opiate like methadone. It is combined with an opiate antagonist, naloxone, because naloxone is deactivated in the stomach, but if the combination pill is injected the naloxone will block the opiate receptors and prevent the addict from getting high; this is a clever way to prevent intravenous misuse. While Suboxone would seem to be a promising approach with $1.5 billion in annual sales, there are Federal restrictions on doctors' ability to prescribe the drug, insurance companies unwillingness to pay for it, and some degree of illicit use (https://www.nytimes.com/2013/11/17/health/in-demand-in-clinics-and-on-the-street-bupe-can-be-savior-or-menace.html) that has prevented the approach from being used more widely. The DEA has recently been threatening to prosecute pharmacies (https://drugabuse.com/the-vicious-attack-against-suboxone-continues/) that fill suboxone prescriptions. Here is a poignant story (https://www.nytimes.com/2018/06/23/health/opioid-addiction-suboxone-treatment.html?

hpw&rref=health&action=click&pgtype=Homepage&module=well-region&region=bottom-well&WT.nav=bottom-well) about a suboxone clinic on the front line of the opiate epidemic.

Twelve Step Programs

Twelve Step programs (https://en.wikipedia.org/wiki/Twelve-step_program) began with the founding of Alcoholics Anonymous (https://en.wikipedia.org/wiki/Alcoholics_Anonymous) by Bill Wilson and Bob Smith in 1935, and have since expanded to other domains such as Narcotics Anonymous (https://en.wikipedia.org/wiki/Narcotics_Anonymous) and Gamblers Anonymous (https://en.wikipedia.org/wiki/Gamblers_Anonymous) . The philosophy of these programs which are based on abstinence and group membership form the basis of the vast majority of rehab programs today in the United States. These programs are based on the dogma from the "Big Book (https://en.wikipedia.org/wiki/Alcoholics_Anonymous#The_Big_Book,_the_Twelve_Steps_and_the_Twelve_Traditions) " in which members admit that they are powerless over alcohol and need help from a "higher power". They seek guidance and strength through prayer and meditation from God or a Higher Power of their own understanding; take a moral inventory with care to include resentments; list and become ready to remove character defects; list and make amends to those harmed; continue to take a moral inventory, pray, meditate, and try to help other alcoholics recover. Surveys have shown that 75% members who attend meetings at least once per week for two years are clean of drug or alcohol use at that point in time, although they may well have fallen off the wagon several times during the two years Another report showed that 95% of members dropped out of the program within 12 months (https://www.theatlantic.com/health/archive/2014/03/the-surprising-failures-of-12-steps/284616/) .

There are many critics of twelve step programs, who do not share the religious beliefs, the lack of evidence based treatment, or the group's prohibition of all anti-addiction medication. As you might expect some of these programs are havens for drug pushers and sexual predators who prey on the vulnerability of members. These criticisms and more can be found at the Orange Papers (https://www.orange-papers.info/) .

Abstinence Medication

Antabuse (disulfiram (https://en.wikipedia.org/wiki/Disulfiram)) is a medication which causes a severe hangover when any amounts of alcohol are ingested. Antabuse can stay in the body for up to two weeks, so it inhibits alcoholics from breaking their sobriety. Naltrexone (https://en.wikipedia.org/wiki/Naltrexone) is a drug which blocks opiate receptors from being activated. It is taken by pill once per day, although a once per month injection is better for opiate addicts because they could get high by skipping their pill that day.

Somewhat surprisingly, naltrexone can help some alcoholics cut down by blocking the cravings for alcohol arising in the mesolimbic pathway. When used for alcoholics, it is known as the Sinclair method (https://en.wikipedia.org/wiki/Alcoholism#Sinclair_method) ; here is a moving testimonial (https://www.youtube.com/watch?v=6EghiY_s2ts) . This highlights the concept that alcohol addiction is in some sense an opiate addiction of the addict's endorphins.

New and Better Treatments

Insurers and government spends $20 billion per year (https://www.nytimes.com/2008/12/23/health/23reha.html) in the United States on rehab programs. A lot of this money is spent on revolving door programs with no doctor, little efficacy, and outright fraud (https://www.nbcnews.com/feature/megyn-kelly/florida-s-billion-dollar-drug-treatment-industry-plagued-overdoses-fraud-n773376) (see also this fraud report (https://www.statnews.com/2017/07/07/opioid-insurance-fraud/)). But states like Oregon are starting to tighten up on spending and direct it to only the most promising programs with proven evidence outcomes. The psychiatric field has developed some talk based methods such as cognitive behavioral therapy (https://en.wikipedia.org/wiki/Cognitive_behavioral_therapy) and dialectical behavioral therapy (https://en.wikipedia.org/wiki/Dialectical_behavior_therapy) . There are some new approaches which seem promising. Tech companies are experimenting with on-line treatment (https://www.wired.com/story/addiction-rehab-is-broken-can-technology-fix-it/) . New experimental treatment with psilocybin (https://www.pharmaceutical-journal.com/news-and-analysis/features/psychedelics-entering-a-new-age-of-addiction-therapy/20066899.article?firstPass=false) , ibogaine (https://www.bbc.com/news/magazine-17666589) , ayahuasca (http://www.eurekaselect.com/111922/article) and other hallucinogens (https://www.nytimes.com/interactive/2018/05/15/magazine/health-issue-my-adventures-with-hallucinogenic-drugs-medicine.html) , have been reported to help addicts quit their addictions in a very short period of time. A small study of 15 long term smokers found that 80% had quit smoking six months after one guided hallucinogenic trip, a rate far better than any other smoking cessation method. If we have time, we'll look at some of these promising approaches in more detail in Session 12.

Preparation

Please read the text above and click through the hyperlinks and read whichever of them look interesting. Please email me with any questions or topics that you would like to discuss in class. Please send the email no later than the day before class, to ocurme@gmail.com (mailto:ocurme@gmail.com) .

Additional Resources

List resources