

Now, why isn't everyone who tries drugs addicted to drugs? Well, there's multiple factors which affect addiction potential. These have to do with the agent itself. Some agents are more or less likely to make a person addicted. They're obviously host factors which contribute to vulnerability to addiction, and there are also some environmental issues. Now, as far as the agent goes, anything that's commercially available and therefore subject to advertising, and in this case, alcohol and tobacco are very important. The more commercially available something is, the more likely someone is to try it, and the more likely someone is to try it, the more likely they are to become addicted to it. In other words, if you never try something, you can never become addicted to it. As far as route of administration, the faster something gets to your reward center, the more likely it is to be addicting, and likewise, the faster it is eliminated from your system, the more likely it is to be addicting. So, if something can be given intravenously or inhaled, like injecting a drug or snorting it, or smoking it, it tends to be much more addicting than something that's taken orally, has to be absorbed through the digestive tract, and has a slower onset of action and a slower offset of action. Things that have a very short half-life are more addicting because the craving and withdrawal tends to happen more speedily and satiety is an important factor. There also seem to be some intrinsic features of the drug, as we said earlier. Drugs that are more likely to cause dopamine release are more likely to become addicting. Now, obviously there are multiple factors in hosts, which make them more or less likely to become addicted. There have been many twin and family studies that have shown a genetic predisposition to addiction, although the genetics of it is not simple. It seems to be related primarily to dopamine receptor type and also it is found on multiple chromosomes and it is not a very simple genetically transferred trait. Also, the presence or absence of any underlying psychiatric disorder seems to make a patient more likely to be addicted, and there's a concept called hedonic tone, which is basically how rewarded are you in the first place with your life? In other words, if you have lots of things in your life which you find rewarding, your temptation to take addicting drugs is probably lower than patients who don't have a significant reward experience in their life, and so therefore are more vulnerable to addiction. From an environmental standpoint, different cultures have different tolerance to both drug or alcohol use and intoxication. Religious background as well plays a role. Things like Jehovah Witness and religions like that which don't tolerate drug or alcohol use, and also there are socioeconomic factors in that drug use costs money, and for instance, cocaine used to be the drug of wealthy people, but as cocaine became available in the crack form and was much less expensive, it has now become a very popular drug, and the cheaper a drug is, the more likely people are to use it. Now, why don't people just stop using drugs? The addiction circuit and the reward circuit is a very powerful part of our brain from an evolutionary standpoint. And once the behaviors take place that are associated around drug use, they tend to hijack this reward system and all the normal pleasures in life no longer seem as rewarding. There's also data to suggest that these reward pathways are altered in a fairly chronic, and some people feel, a permanent way. Importantly, human beings aren't lab animals. In other words, if you have a lab animal that gets addicted to a compound but you give them an antagonist, the lab animals very quickly stop using the drug. However, if you give antagonists to human beings, human beings tend to stop taking the antagonist and go back to their drug use. We have the ability to rationalize,

we have the ability to deny, and this makes it very difficult to control the craving and compulsion that comes with drug use. Also, very importantly there becomes a blurring of the difference between the cue and the actual reward. In other words, when people are trying to stay sober from alcohol and see beer commercials on TV every 5 minutes during a sporting event, they may not be drinking, but the continuous visual cue starts to release dopamine in the reward center and starts that whole memory cascade involved, which really amplifies craving. The cues associated with drug use are frequently very difficult to avoid. Generally, people who are addicted, their entire recreational life revolves around drug use, and many of the cues associated with drug use are patients' family and friends. Also, obviously stresses are multifactorial early in recovery. People have family stress, financial stress, frequently health-related stresses and as we talked about earlier, stress is a very common trigger to relapse. Now, there are positive and negative reinforcing events which tend to continue the cycle of drug use, and avoiding the negative consequences of drug dependence and withdrawal obviously plays a role. But if avoiding the negative consequences of withdrawal was the primary motivator of relapse, having patients go through detox would be the answer. Once patients are detoxed and their withdrawal symptoms resolve, we could discharge them and their problems would be over. Well, as we all know, detox is not the answer, and it appears to be the craving that drives the continued use of substances and is the biggest problem, as far as relapse prevention. The drug reward causes much more intense compulsive habit than the natural pleasures in life. As we previously said, your reward system basically gets hijacked by the drug and so the normal activities in life, such as your family, your friends, work, nothing is as rewarding or as important as taking the drug again. And there's an intense need for and focus on repeating the drug experience. As we previously talked about, our intellect allows us to deny that we have a problem, and also rationalize why using the drugs despite obvious harm is an option. There's the concept that's talked about now called the protracted abstinence syndrome. And this is related to this chronic dysregulation of the brain's motivational system. There's in recovery, an underactivity of the reward system, which is characterized by low dopamine levels, low endogenous opioid levels, and very high glutamate states. There's also overactivity of what's called the anti-reward system, which is this norepinephrine system, and so norepinephrine levels are high, and corticotropin releasing factor levels are high, and so patients live basically with hyperactivity in their brain stress system. Once again, detox is easy and the million dollar question is relapse prevention. So, what can we do to try and help patients stay sober once they've gone through detox? Far and away, the most effective tool in helping prevent relapse are cognitive behavioral therapies. This cognitive approach reframes how the addict relates to and views their world. Very importantly, it deconditions the addicted patient to the cues that elicit craving. It allows for social rehabilitation, which reduces stress, and also provides a new social structure without the cues that the patient previously associated with drug addiction, and these most importantly are involved in 12-step programs, which assist with the guilt, remorse, and repair of relationships. In fact, this is so effective, most studies that look at the medications we're going to talk about, use cognitive behavioral therapy as their placebo. And most drugs are compared to patients in cognitive behavioral therapy with and without the drug. Now, having said that, there are medications that can be added to cognitive behavioral therapies that enhance relapse

prevention. To begin with alcohol, there's the old-time Antabuse, which has been around since the 1940s. Most people are familiar with this. Alcohol is metabolized to acetaldehyde and then very quickly to acetate, which is an innocuous medication. Disulfiram inhibits an enzyme that breaks down acetaldehyde so therefore, acetaldehyde builds up in your system and this causes very unpleasant nausea, vomiting, flushing, and headaches. Once you take disulfiram, this enzyme is blocked for 5 to 7 days, so therefore, it's very good for the impulsive use in alcohol. The patient needs to be alcohol-free for 72 hours, or else the little bit of acetaldehyde in their system can make them sick. The dose is fairly simple, 250 milligrams once a day, but very importantly, compliance is a problem. And the reason is that disulfiram use does not address the craving that we talked about. If patients do take this, and I have to say I have a number of patients who have taken it for many years, they call it their insurance policy. It works for some people, but if it was the answer for alcohol addiction, we would all be prescribing it all the time. Patients who do take this medication need to have their livers checked periodically, because it is metabolized in the liver. Naltrexone was a medication that was originally designed for opiate abuse. It blocks the mu-receptor as an antagonist, and therefore, it blocks the dopamine release associated with alcohol, and blocks its rewarding effect. It tends to ameliorate the glutamate and noradrenergic-mediated release of dopamine with cue or stress. And it has been shown to statistically reduce drinking days, volume of drinks, increased time to first drink, and the number of abstinent days compared to placebo groups. The biggest problem with naltrexone is compliance, in that because it blocks this mu-receptor, it reduces dopamine release, and so most people find it dysphorigenic. The dose is 50 milligrams once a day; however, there is a depot form available, and 380 milligrams can be given monthly. Campral, which has been out for 6 to 7 years now, indirectly blocks the glutamate effect at the NMDA receptor and tends to offset this chronic imbalance between the GABA and glutamate system. It reduces the so-called chronic withdrawal symptoms, and also tends to reduce cue-related relapse. It's got a very good safety profile. It's very well tolerated, it's safe, even if patients relapse and drink a fair amount of alcohol. It can be used in conjunction with naltrexone and can be shown to have an additive effect. The one drawback is the dose is two 330 milligram tablets 3 times a day by mouth, but motivated patients will take it. It has had some disappointing results in some recent large trials compared to naltrexone alone and placebo. However, in view of its good safety profile and ease of use, it certainly is worth a trial in patients early in recovery. Topamax, and other medications such as Lioresal or baclofen that stimulate the GABA-B receptor, has also been found to reduce dopamine release with alcohol use and limit its reward. It also tends to offset that GABA-glutamate system imbalance and reduce the so-called chronic withdrawal symptoms. It has been shown in studies to reduce drinking days, drinks per day, increase of the time to the first drink, and also the number of abstinent days. The dose is 25 milligrams once a day to begin with, and can be titrated up to 300 milligrams a day. The big drawback is it tends to be fairly sedating, and so you need to increase the dose very slowly to avoid this cognitive dysfunction. And patients have to be cautioned that there is an additive effect between alcohol's sedating effect and Topamax. Topamax is also metabolized in the liver, and if it's being used, most liver enzymes should be checked as well. Now, opiate abusers, again, have a chronically and perhaps permanently altered endogenous opiate pathway, and so the

biggest problem is chronic dysphoria, this chronic withdrawal syndrome, and significant craving. A chronic use of opiate antagonists tends to regulate this dysfunction back towards "normal." If you look at the one-year recovery rates after opiate detox, patients who try to go drug-free have a 5 to 30% chance of being sober in one year. With naltrexone, the numbers are slightly better, and the biggest problem, as I talked about, is noncompliance due to dysphoria. If you use an opiate, that should be opioid, antagonist therapy, you can improve these numbers up to 50 to 80%, and this is why methadone and buprenorphine are such popular relapse-prevention medications. Naltrexone, again, was originally developed for opiate addiction. It is a mu-receptor antagonist, and therefore blocks the rewarding effects of opiate use. Patients must be drug-free for 7 days or this medication will precipitate a withdrawal syndrome. They tend to be dysphorigenic and again, early drop-out is a problem. The depot form is available and tends to help, as far as compliance goes. And this is a very good medication for people who absolutely, positively have to be drug-free, such as medical providers, nurses, doctors, airline pilots, drug or police enforcement agents. One problem is that once you're taking naltrexone, opiate analgesics for pain control can be a problem. So, if a patient happens to break their arm after they've had a depot dose of naltrexone, it's going to be very difficult to give them pain control with opiates. Also, a very important factor that I remind our patients, you can still get the autonomic effect of opiates and some patients try to overwhelm the naltrexone with high doses of opiates, and this has led to serious overdoses and even death. Now, mu-receptor agonists tend to mitigate the chronic withdrawal syndrome, and these are primarily methadone and buprenorphine. They have been shown to significantly reduce the rate of mortality, IV drug use, crime, and HIV infection, as well as relapse, and they've also been shown to increase the rate of employment, health parameters and social function among people with opiate addiction. Methadone is a long-acting once-a-day drug, and therefore, it can be given in both supervised and unsupervised dosing. It has a fairly low abuse potential primarily because of its long action. As we talked about earlier, the quicker something comes in and out of your system, the more likely it is to be rewarding and addicting. Methadone has a very slow onset and a very slow offset. The dose is titrated to reduce or eliminate withdrawal symptoms and craving, and it tends to restore the physiologic dysfunction back toward normal. In the right dose, it tends to be minimally sedating. Constipation is an issue, but tends to respond to stool softeners and fiber supplement. One drawback is it does tend to affect libido, but this is something that patients tend to adapt to. Buprenorphine was approved in 2002 and it can be administered in an office setting by qualified physicians. One hurdle that is continuing to be worked on is each physician is not allowed to have more than 30 patients on their panel. It's a partial mu-receptor agonist, which means it will precipitate withdrawal symptoms in heroine or methadone users. Patients need to be drug-free for 72 hours before starting. It is combined with naloxone because when buprenorphine came out initially, addicts found that if they ground it up, they could inject it and get some opiate effect, so adding naloxone, if patients try to use it intravenously, it precipitates withdrawal. Also, naloxone has a bitter taste, which prevents people from combining multiple doses and abusing it orally. It has been shown to be equally effective in moderate doses to methadone, although patients who have high methadone requirements, it does not seem to be as effective. These are patients generally in the 80 to 100 milligram per day. Now, nicotine

addiction, as we've all experienced, is a very, very difficult addiction to manage. Up to 75% of smokers want to quit and in fact, a third try to quit each year, but only 3-5% succeed. The biggest problem with nicotine is it's dosed continuously throughout the day. If you take ten puffs on each cigarette, and smoke 20 cigarettes a day, you're basically dosing yourself with nicotine 200 times a day. There's no other drug of abuse that's used 200 times a day. As a result, you tend to pair nicotine use with every single aspect of your life. People smoke when they're talking on the phone, people smoke when they're drinking coffee, people smoke when they're driving in the car. The biggest problem too is that nicotine has a unique ability to modulate a wide variety of moods. If you feel tired and smoke, you get a little more energy. If you're feeling tense and stressed and smoke, you'll feel more relaxed. Also, very importantly, smoking is an oral gratification, which makes the habit very difficult to shake. It also, unfortunately, causes weight loss, which is a primary factor in many young people starting smoking. Having said all this though, any type of pharmacotherapy tends to double your rate of success. The original medication available for nicotine relapse prevention was nicotine gum. The nicotinic replacement therapy gives you a low tonic dose of nicotine, which increases the number of nicotinic receptors in that desensitized state and reduces the withdrawal symptom. As time goes by, the number of receptors slowly decreases, and the craving and the need for nicotine gradually goes down. The original delivery system was the so-called nicotine gum, though if anybody has ever tried it, it's not a gum, but more of a resin. It comes in 2 to 4 milligram doses. The resin is chewed and then parked. You can either take it out of your mouth or park it in your cheek, and it allows the patient to self-titrate the nicotine dose to their symptoms. Most people use 10 to 15 pieces per day and the biggest drawback is for many people it caused mouth irritation. The nicotine patch came along fairly shortly after this, and it comes in 7 to 21 milligram doses. It's changed once a day, and after several weeks, the dose is gradually decreased. If patients have sleep disturbance, removing the patch at bedtime will frequently help. Interestingly, heavy smokers may require more than one patch per day. We have many patients that start out with a 21 milligram patch, and if they're continuing to have symptoms, we'll add a 7 milligram patch to that. A big drawback is adhesive irritation. This can be minimized or eliminated by rotating the site where the patch is applied. And we're always asked, "I have heart problems, will the nicotine patch give me a heart attack?" It's been shown to be very safe in coronary artery disease patients, and in fact, it's much safer than smoking a cigarette. Bupropion, which is marketed as Wellbutrin or Zyban, is a monocyclic antidepressant, and inhibits the reuptake of dopamine and norepinephrine in parts of the central nervous system. Its effect on nicotine withdrawal does not seem to work by its antidepressant effect, however. But it seems to antagonize the nicotinic acetylcholine receptor and decreases the reward of smoking. It has an additive effect with nicotine replacement therapy. Interestingly, it tends to minimize the weight gain commonly seen with smoking cessation. The initial dose is 150 milligram once a day for 3 days, then increased to twice daily. The biggest drawback is it cannot be used in patients with a history of seizures. Chantix, or varenicline, is the newest drug in our armamentarium as far as nicotine relapse prevention. It's a partial agonist at the nicotinic acetylcholine receptor, which means it occupies the receptor and reduces and eliminates this reward of smoking, but its mild stimulation reduces withdrawal symptoms. It comes in a starter pack. The initial dose is a half milligram daily for 3 days,

then a half milligram twice daily for 5 days, and then up to the full dose, which is 1 milligram twice daily. It has been shown to be better than bupropion and, or nicotine replacement therapy in clinical trials. The major side effects are nausea, headache and insomnia. As most people are probably aware, there is now a black-box warning on Chantix because studies have shown that there is an increased rate of anxiety, depression, and even suicidality, not only among patients with underlying psychiatric disorders, but among patients who had no previous psychiatric symptoms. I always warn patients about this now, and this is another sign that anytime you tinker with these powerful evolutionary parts of your brain, you're playing with very powerful forces. Pharmacotherapy for cocaine and amphetamines unfortunately has been very disappointing. There have been multiple medical trials using SSRIs, tricyclics, MAO inhibitors, naltrexone, Campral, anticonvulsants, none of them have been shown to be better than placebo, and so we're left with intense psychosocial treatment as we talked about before. There have been attempts to develop products using immunotherapy. Basically patients are vaccinated against cocaine, and the theory is, if you have immunoglobulins floating around in your system, you smoke or inject cocaine, these immunoglobulins grab the cocaine before it gets to your central nervous system and therefore reduces the reward associated with stimulant use. These unfortunately have never come to fruition and I think are still in animal trial.