This is a very busy slide. But the reward path that we were talking about starts in the anterior bed nucleus here. It runs through the hypothalamus to the ventral tegmental area. The ventral tegmental area connects to the nucleus accumbens, which has very important connections to both the ventral pallidum, the frontal cortex -- which is the gateway to the higher lobes in humans -- and also the hippocampus and amygdala, which are very important in memory, and especially emotional memories. Another important part of the reward circuit is here in the brainstem where the periaqueductal gray area, the lateral tegmentum and the locus coeruleus are involved in some of the autonomic function that takes place with these medications.

Now how do these addictive drugs cause the release of dopamine in the reward center? Well starting with alcohol, alcohol affects 4 very important aspects of the homeostatic inhibitory mechanism on dopamine-releasing pathways in the reward center. In other words, these sensory filters that are built into our reward center are blocked by alcohol. First of all, it stimulates a GABA receptor. This is a protein complex in the cell membrane that allows chloride into the cell and makes it less likely to fire. And so it inhibits these inhibitors, and it causes the downstream release of dopamine. It also very importantly blocks the NMDA receptor, which is where glutamate binds, which is a major excitatory neurotransmitter in the brain. Because it blocks this excitatory receptor it, again, inhibits these inhibitors and allows dopamine to be released downstream.

Alcohol also causes the release of endorphins that stimulate the mu opiate receptor. This likewise has an inhibitory effect on these inhibitors. And this appears to be a major site of reward from alcohol. It also, importantly, causes the release of endocannabinoids, which we will talk about later, and stimulates the cannabinoid-1 receptor, likewise inhibiting these inhibitors and enhancing the release of dopamine downstream.

Benzodiazepines and phenobarbital both stimulate this same GABA receptor and have an effect very similar to alcohol. By inhibiting these inhibitors, they cause the release of dopamine. And this is how these 2 compounds also have their sedative and hypnotic effects.

We make 3 endogenous opiates in our ventral nervous system, and these are very important compounds that modulate multiple functions in our nervous system. There are 3 different types of opiate receptors: the mu receptor for endorphins, the delta receptor for enkephalins and the kappa receptor for dynorphins. On our topic today, the mu receptor is the most important one. And stimulation of the mu receptor in the reward center blocks energy production via adenylyl cyclase and cyclic AMP. As previously discussed this inhibits these inhibitors and causes the downstream release of dopamine. By also stimulating the mu receptors in the periaqueductal gray area, this is where opiates cause their analgesic effect that's in the brainstem. And also by stimulating these adrenergic neurons in the locus coeruleus, that's what causes the autonomic effects of both respiratory depression and also gastrointestinal effects of opiates. Opiates also appear to cause release of endocannabinoids, which stimulate

that same CB1 receptor and inhibits the inhibitor and enhances dopamine release.

Now speaking of endocannabinoids, it wasn't until 1990 that the first cannabinoid receptors were discovered and cloned. And as people long suspected, our bodies do produce endogenous cannabinoids, which are found throughout the CNS. The most important of the two receptors are the CB1s receptor. This is found throughout the CNS and in especially high concentrations in this limbic system, the basal ganglia and the hippocampus. It is also found in the liver and gut. There are CB2 receptors, which are still being researched. These are localized primarily in our immune system. These inhibitory receptors reduce cyclic AMP formation, somewhat like the mu receptor. And they reduce protein kinase activity in gene expression. They tend to counteract the activation of this glutamate NMDA receptor, which is an excitatory receptor, and are felt to have a neuroprotective effect in our nervous system. And they seem to play a very important role in feeding and appetite behaviors, which seems to be the biological source of what people call the "munchies."

Now there are 2 endocannabinoids which have been fairly well identified. Both of them are arachidonic acid derivatives. One is anandamide and the other is 2-Arachidonoylglycerol, or what's called 2-AG in the literature. CB1 antagonists were developed and were found to decrease hunger. They also decrease caloric intake; inhibit the dopamine release in the reward system in response to multiple drugs of abuse, including alcohol, opiates, nicotine and cannabis; and seem to have great promise as a relapse prevention medication. There seems to be a close reciprocal relationship between endocannabinoids and endorphin systems. Agonists both increase reward, and antagonists decrease reward and decrease cue-related phenomena.

Unfortunately Rimonabant, which was the first of the CB1 antagonists to be released in Europe as an appetite suppressant medication, caused a significant degree of emotional upset, depression and suicidality. And so after a very short period of time these CB1 antagonists were taken off of the market. And also unfortunately, several compounds which were still in development were taken out of experimental trials. We are all hoping that this is not the end of the endocannabinoid research, but there do not seem to be any CB1 antagonists on the horizon.

Cannabis: The active ingredient is tetrahydrocannabinol, which is known as THC. By stimulating the CB1 receptor it inhibits the inhibitor and causes dopamine release in the reward center. It also appears to release endorphins by activating the mu receptor, and this also seems to enhance its dopamine release.

Now stimulants such as cocaine and amphetamine have a different effect on the nervous system than those compounds we have talked previous that inhibit the filtering system. They all enhance monoamine neurotransmitter activity by inhibiting the monoamine reuptake transporters in the synapse. In other words, dopamine is released. And instead of being very rapidly taken back up to the presynaptic nerve cell, the transmitter is inhibited and so the dopamine has a longer duration and an

increased concentration in the synapse. This dopamine release causes the reward related to stimulants. Norenephrine, which is another monoamine, causes the physiological arousal. And serotonin, which a third monoamine neurotransmitter affected by stimulants, causes its mood elevation effect.

Nicotine works on receptors which are found throughout the central nervous system, and stimulation of this receptor causes sodium, potassium and calcium ions to enter the cell and enhances depolarization. And this results in the release of many neurotransmitters, including dopamine, in the reward center.

Now having gone over how these have an effect on the reward center, how do these effects cause the withdrawal syndromes that we are all so familiar with? Looking at alcohol, the chronic stimulation of these GABA receptors -- which are - if you think of them as a braking effect on the nerve cell -- leads to a downregulation of the protein on the cell surface. If you sudden decrease or eliminate alcohol in the system, the lack of the braking effect causes hyperexcitability and lowers the seizure threshold. Very similarly, chronic blockade of the NMDA receptor leads to an upregulation of this protein on the cell surface. And if you suddenly take away or decrease the amount of drug in the system, it leads to hyperexcitability and lowers the seizure threshold. This upregulation of the stimulatory glutamate receptor and downregulation of the braking or GABA receptor is the basis of why patients who are chronically dependent on alcohol can walk around with an alcohol level of 300 or 400 but still be awake. It also is the biological basis for patients beginning to show withdrawal symptoms while their alcohol levels are still in the 200 to 300 range.

The autonomic hyperactivity is mediated by an increased noradrenergic effect in the locus coeruleus. And if you give a benzodiazepine or phenobarbital, which stimulates the GABA receptor, it blunts the effect and lowers - and increases the seizure threshold and resolves the hyperexcitability associated with alcohol withdrawal.

Now, chronic stimulation of the mu receptor with opiate abuse leads to an internalization of this receptor from the cell surface and also upregulation of the energy systems in the nerve cell. So if the dose of opiate is decreased or drug use is stopped, this leads to an increased firing in the autonomic nervous system, hyperesthesia -- which means things are more painful than they were to begin with -- and also profound dysphoria since the dopamine level in this reward system drops dramatically. If you administer an opiate agonist such as methadone or buprenorphine, it mitigates these withdrawal symptoms. Clonidine, which we use in conjunction with opiate agonists during the withdrawal phase, diminishes the noradrenergic effects that we see in the locus coeruleus.

Cannabis: There was a great debate for many years about whether cannabis caused any withdrawal symptoms at all and also whether cannabis was even addicting. But it turns out that if you chronically stimulate the cannabinoid-1 receptor, it leads to decreased receptor density on the cell surface and decreased receptor sensitivity. Sudden cessation after heavy use or administration of an antagonist to these receptors

leads to symptoms of irritability, nervousness, restlessness, loss of appetite, sleep difficulties and dysphoria. And so cannabis does have a withdrawal syndrome. However, due to its very slow elimination and accumulation in fat cells, these withdrawal symptoms are fairly attenuated. And it's interesting. They are very similar to, but much less severe than, opiate withdrawal symptoms.

Cocaine and stimulants have no actual withdrawal syndrome in that they don't work on a receptor, and therefore there is no up- or downregulation. However, they all deplete dopamine from the reward center, and reduction or absence of stimulant drugs causes very severe dysphoria due to low dopamine levels in the reward center and also profound drug craving. Also seen due to their stimulatory effects are sleep disturbances and fatigue.

Now nicotine -- as we said previously -- stimulates multiple nicotinic acetylcholine receptors throughout the central nervous system. And if you chronically stimulate these receptors and cause relative desensitization, the body tends to upgrade the number of cell receptors on the neuron surfaces. If you cut back or eliminate nicotine in the system, fewer of these receptors are in the desensitized state, and it causes hyperexcitability across the central nervous system. This leads to increased appetite, irritability, difficulty concentrating, restlessness and fairly intense craving for nicotine. If you give a nicotine administration through a patch or a lozenge, or if you give a nicotine - nicotinic agonist, these symptoms are eliminated.