Effects of Short-Acting vs. Long-Acting Drugs on the Brain

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RJ Oenbrink DO

Certain medications are notable for their effect on the brain.

Amphetamines ("uppers, speed") are used therapeutically to treat Attention Deficit conditions and Depression. They have also been used to treat obesity due to their appetite suppressing effects. Safer drugs are now available that are *analogues*; similar in effect but safer without the level of risk of the original parent drug.

Benzodiazepines (Alprazolam [Xanax], Clonazepam [Klonopin], Diazepam [Valium] & Lorazepam [Ativan]) and Barbiturates have the opposite effect, causing sedation (tranquilizers) and sleep, calming high-anxiety states, terminating seizures and as an adjunct in treating depression.

Opiates are derived from the opium poppy. Drugs of this class are mainly used to treat pain states. There are a variety of analogues to Morphine which is the parent of this class of drugs.

All of these drugs work by affecting certain receptors found in different regions of the brain. Think of a lock and key model: the drug acts as a key, the receptors are located on the membranes of different cell types in different areas of the brain and spinal cord. Typically a key enters a lock. If it's the correct key for that lock, it turns allowing the lock to open. Certain other keys may fit into the lock without turning thus blocking the lock if the correct key becomes available. These locks and keys are to small to be seen with the most powerful microscope; they function at the molecular level. The keys tend to bounce around, binding to the locks until another key may come along and bump it out of the lock. Certain keys may stick stronger to a lock receptor, being less likely to be bumped away from the receptor site. Often, there is more than one receptor (lock) on a cell for a given drug. Morphine has several known receptors; delta, kappa, mu are examples of these different locks that the morphine key fits into. One receptor may cause diminished pain perception, another may cause nausea and vomiting, yet another is responsible for the state of euphoria that morphine is known to induce.

The various analogues will have varying strengths of binding affinity to the different receptors available: a drug with a weak affinity to the mu receptor can be pushed away by a different drug with a stronger binding affinity thus triggering the effect of that receptor. Some drugs will bind with one receptor and activate it, while binding with a different receptor but not activating (thus blocking) it.

When these drugs are used for a long period of time the brain responds to high concentration of "keys (drugs)" by making more receptors (locks) to keep up with all of the available keys/drugs. When those drugs are no longer available the brain responds with withdrawal symptoms.

Tolerance describes the brain's response to prolonged effect of to many keys/drugs. More receptors are made by the brain. More drug is then necessary for the therapeutic/ desired effect. *Dependence* is another affect of this excess of drug; if the drug is not available to the brain in the concentrations formerly available then the brain goes through the withdrawal process.

Typically the withdrawal symptom will be the opposite of the therapeutic effect of the drug involved. Abrupt withdrawal of a tranquilizer will induce anxiety/irritability initially, later it may induce seizures that can be lethal. Withdrawal from Alcohol, Barbiturates, and Benzodiazepines can cause death from seizure states.

Withdrawal from opiates causes the "cold turkey" spectrum of symptoms with goose bumps, nausea, vomiting, tremors, pain, yawning, runny nose, diarrhea, cramps and sweats. Patients typically wish they'd die from the misery of opiate withdrawal. Fortunately the withdrawal symptoms rarely last more than forty eight hours or so and are not lethal (despite what the patients may wish for at the time of their suffering).

The symptoms of withdrawal can be lessened in intensity by lengthening the process: slowly reducing the dose of the drug over a period of time will cause milder symptoms of withdrawal but for a longer period of time.

It's also important to understand that Dependence/Tolerance/Withdrawal is not the same as *Addiction*. Addiction doesn't define how the brain is responding to presence of these drug/keys per se. Addiction is a set of complex behaviors found in addiction-susceptible people (not everybody is equally susceptible to the problem of addiction, even when given drugs that get other folks addicted). Addiction presents itself as frequent demands for more medication, higher and/or more frequent doses of the medication etc. Addiction is not confined to any one class of drugs. If a patient has alcohol addiction or a history of misuse/abuse of alcohol, they are at MUCH higher risk of addiction to drugs of the classes mentioned above.

Another key concept to understand is that while the medications above (not intended to be a complete list) are associated with Dependence/Tolerance/Withdrawal, not all drugs are prone to these problems. It's also important to understand that some drugs correct chemical imbalances in the brain while other drugs simply "mask" the symptoms caused by that imbalance. The imbalance is still present; the symptoms are less severe. The imbalance can even worsen over time while the symptoms are masked by higher doses of the drug being used to control the symptoms. Typically medications used to correct a chemical imbalance do not cause Dependence/Tolerance/Withdrawal. While it may take a long time for symptoms to appear, it typically takes longer for the underlying imbalance to be corrected: it's usually necessary to take the healing therapeutic drugs longer than the symptoms are present to allow proper healing of the brain.

Another very important concept to understand is the time-course of these medications, a term referred to as *pharmacokinetics*. Cocaine is widely known as a drug that causes a lot of problems. During the disco era in the 70's cocaine was widely used by

“snorting” it into the nose. From there it was absorbed into the bloodstream where it went to the heart, then to the lungs, back to the heart and finally to the target organ; the brain.

Unfortunately there’s another form of cocaine referred to as “Crack”. Same drug. Different delivery system. MUCH MUCH more addictive! Virtually nobody can use crack without becoming addicted. Pharmacokinetics is the reason. The faster the drug causes effect the more addicting it tends to be. Crack is smoked. The drug enters the lungs, goes right to the heart then to the brain. The effect of the drug is felt before the crack pipe is removed from the users mouth--the effect is IMMEDIATE. There is less dilution with blood from other parts of the body as the drug passes from the veins to the heart, through the lungs, back to the heart then to the target organ. The more rapidly the effect is given the stronger the reinforcement to continue the drug. Lab animals have had wires placed in the pleasure centers of their brain, given a button to push to get an immediate dose of pleasure. The animals will ignore food, water, opportunities for procreation and everything else to keep pushing the button and getting the immediate pleasure reward until they die. THAT is a strong reinforcing statement to describe the power of addiction.

The same drug that causes intense addiction with rapid repeated delivery can be used more safely, despite inherent addiction potential if it has a slower onset and longer duration of action. An example to use to help understand that would be to place a 1-pound weight on your head. That weight on the head won’t cause any pain or other problems at all. You can go days with a one lb weight on your head without much notice. As an alternative, take the weight off of your head and replace it with an equal amount of force given for one second every 6 hours; 4 times daily. Doing the math; 1 lb/second X 60 seconds = 60 lbs/minute X 60 = 3600 lbs/hr X 6 hours = 21,600 lbs of force to be delivered to your brain 4 times daily. THAT is a real kick in your head!

Think of the brain damage that would be caused! Repeated impacts over short periods of time are harmful. Now consider that the impact is not something that is curing a chemical imbalance, but only masking the symptoms of that imbalance! Lots of further damage is being done despite the relative absence of symptoms--other than when tolerance and dependence develop causing the dose and frequency of dosing to be increased to maintain the desired effect.

Let’s stop though and recall that there is still suffering going on with the absence of the medication that is desired. What is the solution to this conundrum?

Low doses of a medically necessary medication, directed by a licensed provider, given in a sustained manner over as long a period as possible will provide the therapeutic benefit with a much lower risk.

What are the risks of these medications?

If you've ever noticed the worm in a bottle of Tequila you won't be surprised to know that alcohol is a poison. It can embalm you among other problems, it causes damage to every organ and tissue that is exposed to it, cirrhosis to the liver, "wet brain" damage, heart damage, kidney damage, muscle damage, the list goes on and on.

Amphetamines cause brain problems, heart problems, blood pressure problems, weight loss, poor health and a variety of other issues

Tobacco products are very addictive. They have their own commonly recognized toxicities. There are about 500 toxins in every cigarette, pinch of snuff or dose of tobacco (heresy to mention this in a tobacco state, but true nonetheless). There is a less toxic form that is advertised as only having one poison; E-cigarettes, Nicorette gum, inhalers, lozenges, patches--all available without a prescription.

Benzodiazepines effect the Gama Amino Barbituric Acid (GABA) receptor in the brain. This is the same receptor that alcohol affects. Think of these drugs as alcohol in tablet form. Although they are less toxic to most tissues, they are still linked to bad effects in the brain including increased risk of falling down (with the broken bones common in elderly people, alcoholics and tobacco users who are at greatest risk; hip fracture is actually a good marker for death within 24 months in the elderly). Memory and cognitive (thinking ability) loss is very common with these drugs. This leads to frequent diagnosis' of premature dementia and nursing home placement which typically will be permanent (of course, hitting the same receptor, alcohol use will do the same thing in the aging population). Sleep architecture distortion is another problem with this class of drugs. Sleep is a very complex pattern in the brain. Numerous stages of sleep exist with Rapid Eye Movement (when dreams occur) as important structural frameworks of how and what the brain processes from the previous day. Disrupting the natural architecture long enough can cause memory loss, behavioral changes, cognitive problems eventually leading to full blown psychosis and loss of touch with reality (psychiatric hospitalization may soon follow).

Opiates/pain relievers cause constipation immediately. Later effects will include alterations in the sleep/wake state, memory loss, loss of warning pain that can alter behavior to prevent further damage (you don't want to try to walk on a broken bone!). These drugs are very prone to inducing addiction issues as well. People generally have different susceptibilities to addiction. Short-term use of a highly addictive substances such as crack cocaine will addict pretty much anybody with the first dose. Opiates used in the short-acting form are much more prone to long-acting forms and are more likely to cause eventual addiction even in people who ordinarily wouldn't be as prone to becoming addicted.

Please listen to your provider as he discusses the options to treat your medical problems. We want to help you and all of our patients. We took an oath in training; "Primum non nocere"; "First, do no harm". We don't want to be talked into hurting even the most demanding patient!