Benzodiazepine Overdose and Withdrawal Are Essentially Never Fatal

2014-11-10 by Zak Fallows

Caveat: Benzodiazepines are very dangerous when mixed with other sedating drugs such as alcohol and opioids. Drug mixtures that include benzodiazepines are very often fatal. Benzodiazepines do enhance the lethality of alcohol and opioids. The point of this document is that benzodiazepines *by themselves* are essentially never fatal.

Disclaimer: Benzodiazepines are powerful and dangerous prescription-only medications. Use benzodiazepines only as directed by a competent physician, and be totally honest with your physician.

Summary:

Benzodiazepines are **extremely safe** when compared to other sedatives such as ethanol and barbiturates. Benzodiazepines do not cause classical addiction, whereas ethanol and barbiturates do. Benzodiazepines are essentially never fatal in overdose, whereas ethanol and barbiturates are extremely dangerous in overdose. Benzodiazepine withdrawal is essentially never fatal, although ethanol withdrawal is often fatal. There are very rare exceptions, these are discussed below.

Benzodiazepines Are Superior to Ethanol and Barbiturates in Three Ways:

1. Less euphoric, no risk of classical addiction (except in former alcoholics)
2. Overdose is essentially never fatal (except when drugs are mixed)
3. Withdrawal is much milder, and is essentially never fatal (with very rare exceptions)

Mechanisms of Action:

All three drug classes (benzodiazepines, barbiturates, and ethanol) bind to $GABA_A$ receptors and act as positive allosteric modulators. The $GABA_A$ receptor is a complex of 5 protein subunits arranged in a circle with a chloride ion channel in the middle. When GABA binds, the chloride channel opens, chloride ions flow into the neuron, and the neuron becomes inhibited. $GABA_A$ receptors are thus inhibitory, and GABA (the natural ligand) is an inhibitory neurotransmitter. Benzodiazepines, barbiturates, and ethanol all amplify the inhibitory signal sent by the $GABA_A$ receptor, they all increase chloride influx and thus cause inhibition. Benzodiazepines, barbiturates, and ethanol are sedatives, because they cause widespread neuronal inhibition, leading to unconsciousness and coma in higher doses.

Benzodiazepines bind to the $GABA_A$ receptor complex at the benzodiazepine binding site. This site is different than the GABA binding site, it is located in a physically separate location on the large five-protein receptor complex. Sometimes I might say that benzodiazepines are $GABA_A$ receptor agonists, but this is slightly inaccurate because benzodiazepines do **not** bind to the same site as GABA. It is more precise to say that benzodiazepines are benzodiazepine receptor agonists, and the benzodiazepine receptor is a part of the $GABA_A$ receptor complex. Alternatively, you can say that benzodiazepines are $GABA_A$ receptor positive allosteric modulators.

Barbiturates are very similar to benzodiazepines in mechanism, they bind to the $GABA_A$ receptor complex at a separate site. The barbiturate binding site is different than both the GABA binding site and the benzodiazepine binding site.

Ethanol binds to the $GABA_A$ receptor complex at yet another distinct binding site. There is evidence that the ethanol binding site is directly adjacent to the benzodiazepine binding site, located only a few atoms away. However, **ethanol has several additional mechanisms of action.** Ethanol binds to and modulates several neuronal ion channels, mostly with inhibitory effects but sometimes with excitatory effects. This is one reason that low doses of ethanol can have paradoxical stimulant effects, despite the fact that ethanol is mostly a sedative.

Example Drugs:

You should memorize a few example drugs. Here they are:

Benzodiazepines: Valium (diazepam), Klonopin (clonazepam), Xanax (alprazolam).

Barbiturates: Phenobarbital, pentobarbital, secobarbital.

Addiction and Euphoria:

Benzodiazepines do **not** cause classical addiction, except possibly in alcoholics. Benzodiazepines are not addictive. Benzodiazepines do cause withdrawal, but many non-addictive drugs cause withdrawal. Blood pressure medications such as beta blockers cause withdrawal, but beta blockers are non-addictive. Remember that withdrawal is not related to the definition of addiction.

People who are heavily dependent on benzodiazepines will often claim to be addicted, but further questioning shows that they are not addicted. They have complete control over their drug taking behavior. They make a logical decision to take drugs in order to avoid withdrawal. This is very similar to a person with type I diabetes, who makes a logical decision to take insulin so that they will not die. The diabetic is heavily dependent on insulin, but they are not addicted to insulin. In contrast, many alcoholics will say, "I can't have just one drink – if I have one drink, then I have ten more." Alcoholics talk about being physically incapable of self-restraint, and in a sense they are. The alcoholic brain has been rewired in ways that are detectable using PET scans, fMRI, and at autopsy. The rewiring in an alcoholic brain is very similar to that seen in a heroin or cocaine addict.

In contrast to benzodiazepines, ethanol and barbiturates are both classically addictive. This is somewhat predictable, because most people report that ethanol and barbiturates cause significant euphoria, whereas benzodiazepines cause much less euphoria.

Ethanol and barbiturates probably cause addiction by binding to presynaptic $GABA_A$ autoreceptors on GABA-releasing neurons in the ventral tegmental area (VTA). Ethanol and barbiturates act as agonists at these $GABA_A$ autoreceptors, thus decreasing the release of GABA. A decrease of GABA in the VTA leads to increased activity in the dopamine-releasing cells in the VTA. Many dopamine-releasing cells in the VTA project axons to the nucleus accumbens

(NAcc), so ethanol or barbiturates in the VTA ultimately lead to increased dopamine release in the NAcc. Remember that dopamine release in the NAcc is necessary and sufficient to cause classical addiction.

Benzodiazepines do not seem to cause dopamine release in the NAcc, and benzodiazepines do not cause classical addiction. This may be because benzodiazepines, ethanol, and barbiturates are each most active at different $GABA_A$ receptor subtypes. Ethanol and barbiturates may be preferentially active at $GABA_A$ receptor subtypes that serve as presynaptic autoreceptors in the VTA. Agonism at these $GABA_A$ receptors tends to increase dopamine release, as discussed above. In contrast, benzodiazepines may be more active at $GABA_A$ receptors that are located postsynaptically on dopamine-releasing cells in the VTA. Agonism at these $GABA_A$ receptors tends to decrease dopamine release. Depending on the balance of affinity and intrinsic efficacy at various $GABA_A$ receptor subtypes, a $GABA_A$ receptor agonist can be addictive (like ethanol and barbiturates) or non-addictive (like benzodiazepines).

Note that ethanol has additional mechanisms of action. Ethanol has actions on potassium channels that seem to cause dopamine release in the NAcc.

Overdose:

Benzodiazepine overdose is essentially never fatal, unless the benzodiazepine is mixed with another sedating drug such as ethanol or an opioid. There are a few very rare exceptions. For example, taking over 100 tablets of the benzodiazepine triazolam and then passing out face down in the mud will cause suffocation and death. (F. Moriya and Y. Hashimoto, Leg Med [Tokyo], March 2003, pages S91-S95, PMID: 12935561)

Every year, thousands of Americans attempt to kill themselves by taking massive overdoses of benzodiazepines. Unless they mix in other drugs, these suicide attempts essentially never lead to death. In a typical case, a patient might swallow two months' worth of Valium and then go to sleep. The patient will typically wake up after 36 hours feeling very drowsy, hungry, thirsty, and having soiled themself.

In contrast, ethanol overdose and barbiturate overdose are both very often fatal. Ethanol and barbiturates both tend to suppress breathing. It is not entirely clear why barbiturate overdose is so much more dangerous than benzodiazepine overdose, because both classes of drugs act at the $GABA_A$ receptor complex in similar ways. It has been suggested that a large dose of a barbiturate will cause the $GABA_A$ receptor chloride channel to open even in the absence of GABA, but a benzodiazepine can only open the $GABA_A$ receptor chloride channel if GABA is also present. If this is true, then benzodiazepines are fundamentally less efficacious than barbiturates. Clinical experience seems to support this view: barbiturates can induce a deeper coma than benzodiazepines, and barbiturates can sedate some patients with delirium tremens due to alcohol withdrawal even when benzodiazepines are ineffective.

A huge number of scientific papers state or imply that benzodiazepines cause fatal overdoses, but these papers are misleading. These papers are invariably lists of drug overdose statistics compiled from various sources. The largest problem is that they count a fatal benzodiazepine

overdose even when other drugs were also involved, most often ethanol or opioids. The thought process goes like this:

> "Let's test the blood in this corpse for drugs… Okay, the blood tests positive for heroin, alprazolam [a benzodiazepine], alcohol, THC, methamphetamine, and cocaine. THC lingers for a long time, we can ignore that. The methamphetamine and cocaine levels are low, let's ignore those. The levels of heroin, alprazolam, and alcohol are all quite high. Larry, put three more tick marks on the board: one heroin death, one benzodiazepine death, and one alcohol death. Okay, next corpse."

This type of double-counting and triple-counting is extremely common, especially in papers which report hundreds or thousands of fatal benzodiazepine overdoses.

However, some papers refuse to double-count, so they pick a single "primary cause of death" for each fatality. In this case, the authors will sometimes say that a patient died of a benzodiazepine overdose because the benzodiazepine level was extremely high, and they will ignore the moderate level of heroin and the moderate level of alcohol. I think this is misleading. The benzodiazepine level may be very high, but it is not the "primary cause of death" because even very high doses of benzodiazepines do not cause death. The alcohol and heroin played a crucial role, and that is often ignored.

Another problem is that reports from coroners and medical examiners are often of very low quality. Coroners in particular often have no scientific or medical qualifications. In many parts of the US, coroners need less training than hair stylists. There is a PBS *Frontline* episode about this issue. Many coroners operate like this:

> "The police found her corpse in bed, there was a suicide note, and there was an empty bottle of Valium on the floor nearby. The family says the suicide note matches her handwriting, and they say she was depressed. Larry, put 'benzodiazepine overdose' on the death certificate. Let's not do any blood tests, those are expensive. Oh and Larry, put 'accidental death' on the death certificate, the mother said she doesn't want it to say suicide. They're Catholic, you understand."

In reality, this woman may have been smothered with a pillow. Many coroners and medical examiners are very incompetent. This was actually a murder, it looked like suicide, and they intentionally misrepresented it as an accident. And the whole thing gets blamed on benzodiazepines.

The absurdity of the claim that benzodiazepine overdose kills thousands of Americans each year becomes patently obvious when you look for actual case reports of fatal benzodiazepine overdose. There are almost none. The paper cited above by F. Moriya and Y. Hashimoto is a genuine case report of a fatal benzodiazepine overdose, but cases like this are extremely rare. Fatal cat bites are more common.

Withdrawal:

Benzodiazepine withdrawal is essentially never fatal. There are only two case reports of fatal benzodiazepine withdrawal in the scientific literature. Tens of millions of people have gone through benzodiazepine withdrawal, and only two of them have died. One of the case reports is

here: M.A. Lann and D.K. Molina, Am J Forensic Med Pathol, June 2009, pages 177-179, PMID: 19465812.

In contrast, ethanol withdrawal is often fatal, and barbiturate withdrawal also seems to be fairly fatal, although the data are more limited. Benzodiazepine withdrawal is quite mild compared to ethanol and barbiturate withdrawal.

Benzodiazepine withdrawal does sometimes cause seizures, and if you have a seizure while driving you could crash the car and die.

Benzodiazepine withdrawal is unusually dangerous for former alcoholics. Alcohol withdrawal causes delirium tremens, a condition that is often fatal. Delirium tremens gets progressively worse each time you experience it. An alcoholic who has suffered delirium tremens five times in the past is more likely to get delirium tremens again, the symptoms will start more quickly after they stop drinking alcohol, and the symptoms will be more severe. If that alcoholic is taking a benzodiazepine on a daily basis, then abruptly stopping the benzodiazepine may trigger delirium tremens. It is not known why delirium tremens gets progressively worse each time you experience it, but it must cause permanent changes in the brain. Because of these permanent changes, former alcoholics must be more careful when discontinuing benzodiazepines. Even including former alcoholics, there have only been two fatal cases of benzodiazepine withdrawal. Only two cases.