



The Road to Tranquilizers and Benzodiazepines: Short Overview

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Benzodiazepines have significant value in medicine to treat anxiety, sleep, seizures, muscle spasms, etc. But the origin of tranquilizers dates back to the beginning of alcohol.

Alcohol

The first "medicine" to treat anxiety and used in religious and cultural activities was alcohol. The first traces of alcohol from fermented beverages in jugs dates back to the Stonge Age in 10,000 BC, suggesting that it was available even then.

The first evidence of wine was 7000 BC in China fermented from rice, honey, and fruit. Beer originated in the Middle East at about the same time.

Even the Pilgrims on the Mayflower drank "Ship's Beer" as the main source of hydration, up to a gallon per person daily, with an alcohol content of 6%. The beer did not contain bacteria like barrel water and thus it was safer to drink to prevent diarrhea. Some suggest that Plymouth Rock was the Pilgrim's landing site due to diminishing beer reserves remaining after two months at sea.

Today, alcohol consumption is common around the world. In the United States around one hundred bottles of wine-equivalents per person are consumed annually. While that may seem excessive, the US does not hold the title of highest consumption per person. That title goes to Romania, with the US ranking in the top third of countries around the world.

According to NIAAA (2022), a "standard drink" in the United States contains 0.6 ounces of ethanol. In 2021 the national annual per capita consumption rate was 2.51 gallons of pure ethanol which equates to an average of 535 drinks per year!

Opium

Opium is derived from opium poppy and can be traced back to 2100 BC. It was used as a treatment for surgery and later for cholera and dysentery ailments. Opium eventually became a commodity for sale from China like silk and porcelain objects. It became a drug of abuse as usage spread from the ruling class to the working class prompting the British East India Company to begin moving tons of opium



into China. The opium trade eventually resulted in two Opium Wars in the 1800s between Great Britain and China. During this time period, it was claimed as many as one-third of the population were addicted to opium, presumably because it was considered the national social drug for relaxation. Of course, the US began to import opium as well where it became a social drug as well and the basis for pain treatment such as morphine and codeine. Later came hydrocodone, oxycodone, and fentanyl which are current day drugs of abuse.

Barbiturates

The development of pharmaceutical chemicals to treat anxiety, induce sleep, etc. has a much shorter history when compared to opium. The first barbiturate was synthesized in 1864 by Adolf van Baeyer. Barbiturates were not commercially used until 1904 to treat psychiatric and neurologic disorders. Subsequently, more than 2500 barbiturates were created but only a handful of barbiturates are still available for treatment today. From the 1920s until the 1950s, barbiturates were the only sedative/hypnotics available. Phenobarbital became the drug to treat epilepsy and butobarbital became the anti-anxiety drug. These drugs become lethal when mixed with alcohol and cause severe withdrawal effects when discontinuing their use.

Barbiturates are associated with the 1950s as they were used in conjunction with alcohol in entertainment/show business. This combination was highlighted by Jacqueline Susann in the 1966 book "Valley of the Dolls" (Dolls was a slang term used for barbiturates and amphetamines during that period). The combination of barbiturates and alcohol is a very deadly combination. This was the case with Marily Monroe in 1962 with barbiturates listed as her cause of death. Because of the potential deadly outcomes, this led to the development of an additional group of compounds which were safer and more effective. They are known as the benzodiazepines.

Benzodiazepines

The use of barbiturates was a major step forward for the treatment of anxiety, but it also had serious side effects which could be fatal. The first benzodiazepine called Librium (chlordiazepoxide) was synthesized in 1955. By 1960 Librium was widely distributed which then led to the development of Valium (diazepam) in 1963. The development of Valium created a whole new class of compounds with various uses, but they had addictive properties with extended use. Benzodiazepines can be used for a variety of purposes including treatment for anxiety, seizures, insomnia, and muscle spasms.

Over the last 65 years many benzodiazepines have been synthesized for specific purposes resulting in a variety of variations and strengths. Today, CRL offers two panels to fulfill the employer testing requirements. The first group identified below as the "**7-Panel**" were the original benzodiazepines.

As newer benzodiazepines became available, a more inclusive panel of benzodiazepines referred to as "**Extended Benzodiazepines**" was created. The extended benzodiazepine panel also includes the non-



FDA approved list of illicit benzodiazepines which are only available via the internet from Europe and Dark Web sources. The illicit benzodiazepines are frequently used by employees because they are not included in most workplace drug testing panels. At CRL, we have the ability to report illicit benzodiazepines in our extended benzodiazepine panel.

The illicit benzodiazepines names are often remarkably close to the legal version (i.e., FDA approved) and it is common for the drug name to end with "lam." The designers are all more powerful than their FDA approved counterparts which leads to significant impairment on the job sites.

7-Panel Benzodiazepines	Extended Benzodiazepines	
Alprazolam	Nitrazepam	Lormetazepam
Oxazepam	Clonazepam	Diazepam
Flurazepam	Bromazepam	Halazepam
Lorazepam	Midazolam	Flunitrazepam*
Temazepam	Alprazolam	8-Aminoclonazolam*
Nordiazepam	Triazolam	Etizolam*
Diazepam	Estazolam	Flualprazolam*
	Oxazepam	Flubromazolam*
	Flurazepam	Clobazam*
	Lorazepam	Bromazolam*
	Temazepam	Phenazepam*
	Nordiazepam	
*Illicit Benzodiazepines		

The metabolism of these drugs is often quite complex (see flow chart following) and several have common metabolites due to the metabolism by the liver. Thankfully, MROs are familiar with how Benzodiazepines metabolize and can easily match with the prescriptions provided by the donor.





Oxidative and nonoxidative metabolism of benzodiazepines

The overall positivity rate for benzodiazepines at CRL is about 0.5% per month. By far, the most popular benzodiazepines are alprazolam (Xanax) and diazepam (Valium). They are also some of the oldest, inexpensive, and considered relatively safe from addiction when used in moderation for short periods of time.

To select your benzodiazepine panel, please contact your CRL sales associate.