

THE HISTORY OF HYPNOTICS

Understanding the Three Major Eras of Sleeping Pills

This timeline is designed to help make sense of the very uncollected history of hypnotic medications, commonly known as sleeping pills. The three major eras within this classification, distinguished by chemical composition, effects, and/or marketing plans, are explained here through the key drugs that composed their histories. The selected dates focus on the ebb and flow of these drugs as well as their presence and affect on hypnotics as a whole. Hypnotic medications are some of the world's all-time top selling drugs (Valium, Halcion, Ambien, etc), yet their stories remain fairly unknown. The aim of this work is to help correct some of that.

ICON KEY

- Drugs
- Commercial Release
- Lawsuit
- Regulation/Classification
- Increase
- Decrease
- Peak
- Death Statistics
- Overdose
- Dependency
- Withdrawal
- Psychosis/ Mental State

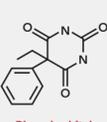
PRE-BARBITURATE PERIOD | **BARBITURATE ERA** | **TRANSITIONAL PERIOD** | **BENZODIAZEPINE ERA**

1864 Adolf von Baeyer synthesizes the parent compound of all barbiturates, malonylurea (barbituric acid). The name barbiturate may be reference to Baeyer's friend Barbara, though some say it is due to the discovery falling on St. Barbara's Day, while others claim it is due to the barbed appearance of the crystals of the compound.	1869 Chloral hydrate, (commonly known as "knock-out" drops), a derivative of ethyl alcohol, is introduced as a synthetic sedative-hypnotic. This is the introduction of hypnotic drugs.	1879 Edouard Grimaux, a French chemist, develops and perfects the synthesis process. This allows for future mass development of barbiturate derivatives.	1881 Diethyl-barbituric acid (barbital, or malonal, or gonalal) is synthesized by Max Conrad and M. Guthzeit	1902 Barbital is synthesized for clinical use by Emil Fischer and Jacob von Mering for the German pharmaceutical company Bayer.	1903 Barbital's discovery is published and the license for commercial use is obtained.	1904 Barbital is released under the brand name Veronal. It has hypnotic, sedative, and anticonvulsant properties.	1911 Phenobarbital is synthesized by Heinrich Hörlein as part of a group assembled by Fischer and von Mering to create barbital analogs. In total they create 18 variations of the drug.	1912 Phenobarbital is released by Bayer under the brand name Luminal. Phenobarbital's six carbon ring phenyl side chain structure becomes the prototype for long-duration barbiturates, mainly used as anticonvulsants.	1923 Amobarbital is synthesized by the US pharmaceutical company Eli Lilly and released under the brand name Amytal. It's discovered that when gradually administered intravenously Amytal can relax a person's inhibitions and act as a "truth serum."	1929 California enacts the first laws to regulate barbiturate distribution. Despite the ever increasing popularity and amount of variants barbiturate issues with dependence and fatal overdose cannot be eliminated.	1936 Even with increased legal regulation production of barbiturates in the US rises by 400% from 1933-1936.	1950 Meprobamate is synthesized by Frank M. Berger and Bernard Ludwig for the US pharmaceutical company Wallace Laboratories. This is the first major breakthrough since the introduction of barbiturates in treating anxiety and related conditions, mainly due to its lower risks of addiction.	1955 Meprobamate is released under the brand name Miltown and marketed as a tranquilizer for anxiety, tension, and muscle spasms. Months after its release meprobamate is the best selling drug in the US. Barbiturate production peaks with 900,000 pounds produced.	1957 One third of all prescriptions in the US are for either of the two forms of meprobamate, Miltown or Equanil. Chlordiazepoxide, the first benzodiazepine, is synthesized by Leo Sternbach and Lowell Randall for the US pharmaceutical company Hoffmann-LaRoche.	1960 Meprobamate is discovered to have issues with dependence and withdrawal, similar to those of barbiturates. Chlordiazepoxide is released under the brand name Librium and promises to be a safer alternative to meprobamate.	1963 Between 1957-1963 there were 8,469 cases of barbiturate related overdoses in New York City. 1,165 of these were fatal. The first case of the effects of chlordiazepoxide appears in scientific literature and notes fatalities in the drug's safety claims. Diazepam, synthesized by Leo Sternbach for Hoffmann-LaRoche, is released under the brand name Valium. It's stronger, shorter in effect, and has better anxiolytic and sedative separation compared to chlordiazepoxide.	1964 Librium gains popularity and overtakes meprobamate's leading position.	1965 Meprobamate is reclassified as a sedative, which puts federal restrictions on prescribing and refilling it. The Drug Abuse Control Act (DACA) is enacted in the US and immediately takes legal action against Librium and Valium. Benzodiazepines are now the world's most prescribed drug.	1966 Valium gains popularity and begins to take over Librium's sales.	1968 Valium becomes the most prescribed drug in the world. The Advisory Council Campaign in Britain creates restrictions on barbiturates in an effort to decrease their use. Between 1965-1970 prescriptions for benzodiazepine increase 110% while prescriptions for the whole of psychotropic drugs only increase by 9%.	1970 Between 1965-1970 12,354 deaths in the UK were attributed directly to barbiturates. The American Medical Association's Council on Librium to be a superior drug in terms of efficacy to meprobamate. This ends any remaining usefulness for meprobamate. Valium and Librium's combined sales account for \$200 million of Hoffmann-LaRoche's yearly \$280 million in US sales.	1971 The National Health Service (UK) uses Hoffmann-LaRoche over high costs paid by the government due to the mass consumption of their drugs. Hoffmann-LaRoche lose and pay £4 million (roughly \$10 million) to the National Health Service. The popularity and financial success of benzodiazepines can be largely credited to it being the first type of drug to have major marketing campaigns by the manufacturers.	1972 Valium prescriptions reach 50 million written per year. This is up from 4 million prescriptions during the drug's first year at market in 1963. 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Z-DRUG ERA

1975 DACA wins a decade of court battles and Librium and Valium are now Schedule IV controlled substances. Benzodiazepines stop being the world's most prescribed drug.	1976 Zopiclone, the first Z-drug, is synthesized by the Danish pharmaceutical company Rhône-Poulenc.	1977 The US consumes 8,000 tons of benzodiazepines. Benzodiazepines are now classified as hypnotics, sedatives, and anxiolytics.	1978 Valium has its peak year with 2.3 million pills sold, generating a profit of \$600 million. Valium is now the most widely used and most profitable prescription drug to have existed. It will stay here until the arrival of Ambien. Jean-Pierre Kaplan and Pascal George synthesize zolpidem for the French pharmaceutical company Synthelabo (now Sanofi).	1979 Benzodiazepine prescriptions fall from 100 million in 1975 to 70 million.	1981 Valium is no longer the world's most prescribed drug.	1982 Triazolam is synthesized by the US pharmaceutical company Upjohn and released under the name Halcion. Halcion quickly becomes the world's best selling sleep-aid.	1984 At The request of the World Health Organization (WHO) the United Nations Commission on Narcotic Drugs (UNCOD) declares that all benzodiazepines are now Schedule IV controlled substances.	1985 Research on zolpidem is accelerated when a lab researcher who is preparing samples of the drug for human testing accidentally swallows a teaspoon sized amount and instantly falls asleep. Zolpidem is effective at reaching the brain so quickly due to its molecular tail of nitrogen, oxygen, and carbon. LSD has the same tail.	1986 Zopiclone becomes available in Europe via Danish pharmaceutical company Rhône-Poulenc.	1988 Halcion has its peak year with 9 million prescriptions and \$265 million in sales.	1989 Ilo Marie Grundberg sues Upjohn after shooting her sleeping mother eight times in the head and neck with a .22-caliber pistol right after slipping a birthday card into her mother's hand, her birthday was the following day, while on Halcion. Upjohn loses the case the is forced to note that Halcion's side effects include: - Psychosis - Organic brain damage - Bizarre and profoundly disturbing behavior - Suicide - Homicide - Aggressive assaultive behavior - Amnesia - Panic Sales of Halcion fall in the US and the drug is banned in the UK.	1993 Zolpidem is released in the US under the brand name Ambien and is distributed through a collaboration between Synthelabo and the US pharmaceutical company Searle (which is now part of Pfizer). Ambien manufacturers take advantage of the recent Halcion disaster and help achieve initial sales success by marketing their drug as safer than Halcion and just as effective.	1994 All reported deaths directly attributed to benzodiazepines from 1980-1989 in the UK are analyzed: - 265.5 total prescriptions - 1576 total deaths - 5.9 deaths/million - 56.5% one substance - 37.5% alcohol present - 53.8% suicides - 20.4% fatal accidents - 25.8% undetermined	1998 Ambien's popularity and reputation for being a benign drug helps to normalize the opinion that it is safe for treatment of insomnia. "We had to change consumer perception about the sleep category in general to eliminate the stigma." Kathy Gulisti (Searle exec.)	1999 The Fatal Toxicity Index (FTI) (based on the ratio of rates of deaths to prescriptions, and use of drug agents prone to dependence and abuse. Now a prescription for these drugs requires a copy be held by the doctor, the pharmacy, and the NY State Department. Benzodiazepine prescriptions drop by 50%. This returns people to more dangerous options like barbiturates, opioids, or bromides.	2004 South African coma patient Louis Viljoen, starts talking for the first time in five years just 25 minutes after being fed Ambien to treat his spasms. Since this discovery several other stroke and coma victims have been helped by Ambien. Any effects typically wear off with the drug though. More prescriptions have been written for Ambien than all benzodiazepines combined.	2006 A manufacturer's estimate states that Ambien has been taken 12 billion times worldwide and is worth \$2 billion in US sales. The annual diagnosis of insomnia rises from less than one million in 1993 to over five million.	2007 The patent to zolpidem, Ambien's key compound, ends and gives way to a flood of generics. The FDA requests warnings on all Z-drugs for complex side effect behaviors that may happen in a sleep state, often with amnesia of the event. Including: - Sleep-driving - Preparing and eating food - Making phone calls - Having sex	2010 Valium is now only the 13th most popular psychiatric drug in the world, with 14 million prescriptions each year.	2012 Over 4,000 deaths/year are linked directly to Z-Drugs. These deaths are not directly caused by the drugs, but by circumstances caused by being on them.	2014 The US Food and Drug Administration (FDA) approves suvorexant, to be released under the brand name Belsomra, for Merck. It is a first-in-class insomnia drug that was approved after dosages were lowered to satisfy safety concerns.
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BARBITURATES



Description
Barbiturates are a group of central nervous system (CNS) depressants which produce effects ranging from mild sedation to general anesthesia.

Side Effects/Problems
Adverse reactions include drowsiness, sedation, in-coordination followed by respiratory depression, headache, gastrointestinal disturbances, confusion, and memory impairment.

Legal Status
Barbiturates are classified as Schedule II, III, and IV depressants under the Controlled Substances Act in the US as well as being internationally monitored.

Forms
Tablets
Capsules
Injectables
Elixir
Suppositories

Common Barbiturates
Drug Name (Brand Name)
Street Names
Amobarbital (Amytal)
Blue Devils
Blue Heavens
Blue Velvet
Barbital/Barbitone (Veronal)
Pentobarbital (Nembutal)
Abbots
Mexican Yellows
Yellow Jackets
Phenobarbital (Luminal)
Goof Balls
Purple Hearts
Secobarbital (Seconal)
Lillies
Pink Ladies
Red Birds
Red Devils
Reds
Secobarbital and Amobarbital (Tuinal)
Double Trouble
Gorilla Pills
Rainbows
Toies

BENZODIAZEPINES



Description
Benzodiazepines are a group of CNS depressants which induce feelings of calm, drowsiness, and sleep. Compared to barbiturates they have a lower tendency to cause a potentially fatal CNS depression.

Side Effects/Problems
The combined use of alcohol and benzodiazepines increases the risk of a fatal overdose, as both act as CNS depressants. A similar fatal interaction can occur when opiates and benzodiazepines are taken together as part of a pattern of polydrug use.

Legal Status
Benzodiazepines are classified as a Schedule IV depressant under the Controlled Substance Act in the US as well as being internationally monitored.

Forms
Tablets
Capsules
Injectables
Suppositories

Common Benzodiazepines
Drug Name (Brand Name)
Street Names
Alprazolam (Xanax)
Bike Parts
Handlebars
Totem Poles
Xannies
Clonazepam (Klonopin)
K-Pins
Chlordiazepoxide (Librium)
Diazepam (Valium)
Dead Flower Power
Foolfoos
Mother's Little Helpers
Valley Girls
Flunitrazepam (Rohypnol)
Date-Rape Drug
Roofties
Lorazepam (Ativan)
Atties
Lozies
Temazepam (Restoril)
Mazzies
Triazolam (Halcion)
Upjohns

Z-DRUGS

Description
Z-drugs (or non-benzodiazepines) are a group of CNS depressants which produce effects similar to those of benzodiazepines. They have more specific effects due to their chemical design and are the first drug group designed to only treat issues of sleep.

Side Effects/Problems
Adverse reactions include headache, gastrointestinal upset, dizziness, pruritis (itching), visual disturbance, xerostomia (dry mouth), hemolytic anemia (not enough red blood cells), methemoglobinemia (an abnormal amount of methemoglobin), hallucinations, psychosis, tolerance, dependence, and withdrawal.

Legal Status
Available through prescription.

Forms
Tablets
Capsules

Common Z-Drugs
Drug Name (Brand Name)
Street Names
Zaleplon (Sonata)
Zolpidem (Ambien)
A minus
Zombie Pills
Zopiclone (Imovane)
Zopiclone (Lunesta)
Zopiclone derivative

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