Benzine can be inhaled to produce mind-altering effects.

Benzoapyrene dihydrodial exposide A substance associated with *tobacco* smoke that causes cancer.

Benzocaine Local anastethics used in tablets against soar throat and in ointments against itching and pain. Although not poisonous, some people become sensitive to it over prolonged or frequent use. Use of benzocaine may cause a blood disorder (methemoglobinemia) in infants and small children. A minimum of 5% benzocaine is required in a compound to be effective.

Benzocaine is used as adulterating substance for cocaine. And is sometimes sold as cocaine in streets because it can easy be mistaken for *cocaine* even of an experienced user as it gives the same numbing effect on the tongue when it is tried. Benzocaine is also used in *cocaine* lookalikes often together with procaine. Benzocaine has however no *euphoric* properties.

Benzodiapin *Chlordiazepoxide* or *Chlordiazepoxide hydrochloride*.

Benzodiazepan *Chlordiazepoxide*.

Benzodiazepin *Chlordiazepoxide* or *Chlordiazepoxide hydrochloride*.

BENZODIAZEPINES

Introduction
History
Chemistry and pharmacology
Effects, tolerance, withdrawal and overdose
Misuse patterns
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Prevention

BENZODIAZEPINES Introduction One of a group of structurally related drugs used mainly as sedatives/hypnotics muscle relaxants, and anti-epileptics, and once referred to by the now-deprecated term "minor tranquillizers". These agents are believed to produce therapeutic effects by potentiating the action of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter.

Benzodiazepines were introduced as safer alternatives to *barbiturates*. They do not suppress REM sleep to the same extent as *barbiturates*, but have a significant potential for physical and psychological dependence and misuse.

Short-acting benzodiazepines include *halazepam* and *triazolam*, both with rapid onset of action; *alprazolam*, *flunitrazepam*, *nitrazepam*, *lorazepam*, and *temazepam*, with intermediate onset; and *oxazepam*, with slow onset. Profound anterograde amnesia ("blackout" and paranoia have been reported with *triazolam*, as well as rebound insomnia and anxiety. Many clinicians have encountered particularly difficult problems on discontinuing treatment with *alprazolam*.

Long-acting benzodiazepines include *diazepam* (with the fastest onset of action), *clorazepate* (also fast onset), *chlordiazepoxide* (intermediate onset), *flurazepam* (slow onset), and *prazepam* (slowest onset). The long-acting benzodiazepines may produce a cumulative disabling effect and are more likely than the short-acting agents to cause daytime sedation and motor impairment.

Even when benzodiazepines are taken in therapeutic doses, their abrupt discontinuation induces a *withdrawal* syndrome in up to 50% of people treated for 6 months or longer. Symptoms are more intense with shorter-acting preparations; with the long-acting benzodiazepines, *withdrawal* symptoms appear one or two weeks after discontinuation and last longer, but are less intense. As with other sedatives, a schedule of slow *detoxification* is necessary to avoid serious complications such as *withdrawal* seizures Some benzodiazepines have been used in combination with other psychoactive substances to accentuate *euphoria*, e g 40-80 mg of *diazepam* taken shortly before or immediatly after a daily maintenance dose of *methadone*. Benzodiazepines are frequently misused in conjunction with *alcohol* or in opioid dependence see multiple drug use).

Fatal *overdose* is rare with any benzodiazepine unless it is taken concurrently with *alcohol* or other central nervous system *depressants*.

BENZODIAZEPINES History Leo H Sternbach, a chemist employed by the pharmaceutical company Hoffman-La Roche, investigated 1955 a substance chlordiazepoxide that had been synthesized already 1947. He noticed that when a certain dose of chlordiazepoxide was given to a mouse it would loosen its grip on an inclined wire screen and fall to the floor of the test cage. When the mouse was given *barbiturates* it promptly fell asleep but when given chlordiazepoxide it continued to walk around sniffing the cage in a normal manner. This led to further investigations and chlordiazepoxide was considered as an almost perfect selective "antianxiety" drug that produced less drowsiness than the *barbiturates* and had a larger safety marginal before *overdose* death occurred. Chlordiazepoxide was introduced 1960 under the trade name Librium, followed five years later by *diazepam* under the tradename *Valium*. The introduction of benzodiazepines was an immediate medical and commercial success. They rapidly became the most widely used *sedative*-hypnotics worldwide. The marketing was aggressive.

The benzodiazepines were important innova-

tions in the treatment of anxiety disorders and they were rapidly replacing barbiturates, bromides, opioids which were more toxic and had more serious side effects. One of the mayor advantages compared with these older substances was that benzodiazepines were a lot safer. The number of fatal *overdose*s fell considerably when benzodiazepines were introduced.

The benzodiazepines became so popular that they influenced the whole concept and acceptance of drug-taking. Rolling Stones sang about "Mother´s little helper" and it became widely accepted to use benzodiazepines even for minor problems with anxiety and sleeping disorders. The health care professionals were so enthusiastic of the fairly "safe" therapeutic index (the amount needed to induce sedation was much lower than the amount that would cause *overdose*) and the relatively mild side-effects that they promoted a wide use that was accompanied by intense marketing from the pharmaceutical industry.

After a few years the darker sides of the benzodiazepines where reported: the lengthy time it lasted in the body, the ability to induce *addiction* even at low levels of use, the severity of *withdrawal* symptoms and the frequent use of the substance in combination with *alcohol* and other drugs.

Beginning in the 1970 a wave of criticism against what was claimed as the over-prescription of benzodiazepines. Self help groups of people dependent on benzodiazepines was formed. The benzodiazepines was placed under international control in the UN Convention on Psychotropic drugs 1971. In the 1980 a book written by the American journalist Barbara Gordon "*I am dancing as fast as I can*" played an important role in forming a political opinion against the "overprescription". In the media several cases of persons who had became violent after use of especially short-acting benzodiazepines were reported. There were also several reports on low-dose dependency. Mainly middle-aged women who had taken low therapeutic doses of benzodiazepines reported severe *withdrawal* problems and rebound effects. There were also a more ideological critisism of the frequent use of benzodiazepines for "normal" crises. It was strongly questioned whether it was good practice to prescribe benzodiazepines in life-crises such as divorces, deaths of close relatives, minor family problems or workplace problems and sleeping disturbances. The idea of the critics where that these problems will only be contained, prolonged and worsened by "sedating" them with benzodiazepines.

The use of benzodiazepines is still controversial. While almost all health care professionals agree on the good of their relaxing, sleep-inducing and mucle-relaxant effects and their relative safety, it is still controversial how broad the indications shall be. The more psychoanalytic and psychotherapeutic oriented professionals are generally more restrictive in this sence.

In the 1990 the use of benzodiazepines has culminated in many industrialized countries. The use of Selective Serotenine Reuptake Inhibitors, though they act in a whole different way has partly taken over as the substances of choice especially in treatment of depressions and anxiety.

BENZODIAZEPINES Chemistry and pharmacology All substances in this group has a center of benzodiazdepine. They interact with or act as the naturally occurring neurotransmitter in the brain called gamma amino butyric acid, or GABA for short. GABA is one of the most important inhibitory neurotransmitters. Benzodiazepines greatly increase the actions of GABA and also influence other sedating neurotransmitters such as serotonin and dopamine. The effect is selective and does not influence the whole central nervous system.

There have been intensive efforts to isolate an endogenous benzodiazepine-like substance from brain tissue, this has so far not succeeded, but a *diazepam* binding inhibitor (DBI) peptide has been isolated.

Benzodiazepines is eliminated through the liver and through the kidneys, the elimination time is relatively long, it takes for example about a week for most of the *diazepam* (*Valium*) to leave it. The breakdown-process can be especially long in elderly persons where there is a risk for cumulation.

PLASMA HALF LIFE OF BENZODIAZEPINES

Chemical name	**Halflife (hours)**
Very long acting	
Flurazepam	90 - 200
Halazepam	30 - 200
Prazepam	30 - 200
Intermediate acting	
Chlordiazepoxide	7 - 46
Diazepam	14 - 90
Clonazepam	19 - 50
Short acting	
Temazepam	5 - 20
Alprazolam	6 - 20
Oxazepam	6 - 24
Lorazepam	9 - 22
Extremly short acting	
Triazolam	2 - 6

BENZODIAZEPINES Effects, tolerance,

withdrawal syndrome and overdose A therapeutic dose of benzodiazepines (i.e., medically prescribed) can relieve anxiety and insomnia. They also have a significant muscle-relaxant effect.

Some examples: *alprazolam* is used to treat patents subjects to panic attacks, triazolam is used to treat insomnia, *diazepam* is used to control seizures such as those that occur during severe *alcohol* or *barbiturate withdrawal*.

Benzodiazepines are commonly used as premedication before surgeries. The. benzodiazepines has also very powerful anti-epileptic properties, but the effect wears off within a few months and they are therefore rarely used for long term treatment of epilepsy. Especially *diazepam* and *clonazepam* is the drug of choice for treating life-threat conditions of status epilepticus.

Generally, benzodiazepines are well tolerated and have a wide margin of safety. But some people may experience drowsiness, lethargy dizziness or difficulty with co-ordination.

High doses lead to heavier sedation and can impair both mental sharpness and physical co-ordination. Lower doses are recommended for older people and for those with some chronic diseases, since they may be more sensitive to medications and may metabolize them more slowly. It has also been suggested that benzodiazepines can impair the ability to learn and remember new information.

Studies show that anti-anxiety agents, even when correctly prescribed, may interfere with the ability of some users to perform certain physical, intellectual and perceptual functions. Most side-effects usually occur early in treatment and wane over time.

For these reasons, individuals should assess their response to benzodiazepines before they operate a motor vehicle or engage in tasks requiring concentration and co-ordination. Such activities may become more dangerous if benzodiazepines are used together with *alcohol* and/or other sedative hypnotics or antihistamines (found in many cold, cough and allergy remedies).

Because some benzodiazepines (such as *diazepam* and *flurazepam*) are metabolized and eliminated from the body quite slowly, the medication can accumulate in body tissues with long-term use and may heighten such effects as lethargy in some individuals. Some users may feel drowsy or "hung over," even on the day after they take the medication. Seniors, in particular, may be at increased risk of falls, fractures and confusion.

Tolerance and Dependence

Tolerance is the need to increase the dose of a drug to maintain the desired effects. Tolerance to the anxiety-relieving effects of benzodiazepines is uncommon and most individuals do not increase their benzodiazepine dose. But tolerance to the *sedative* and other effects of benzodiazepines can develop in some people with regular use. When the liver becomes more efficient in processing the drug, tolerance develops since more benzodiazepines is needed to achieve the same effect.

Risk of physical dependence increases if benzodiazepines are taken regularly (e.g., daily)for more than a few months, especially at higher than normal doses. However, problems have been reported after shorter periods of use. The user's body adapts to the presence of the medication and experiences *withdrawal* symptoms when use is stopped. The frequency and severity of these symptoms depend on the dosage, the duration of use, and whether the medication is stopped abruptly or tapered off.

Stopping abruptly can bring on such symptoms as trouble sleeping, gastrointestinal upset, feeling unwell, loss of appetite, sweating, trembling, weakness, anxiety, and changes in perception (e.g.numbness and altered sensitivity to light, sound and smells). In rare cases after high doses, psychosis and convulsions may occur.

After high dose , continuous use for about two months, or lower-dose for a year or more, *withdrawal* can be severe.

First there will be craving fro the drug, then more anxiety, sleep disturbances. pacing the floor, tremulous movements and even *hallucinations* and temporary loss of vision or hearing, seizures and convulsions. The symptoms continue and peak in the first to to third weeks.

The onset and severity of *withdrawal* are often more marked for benzodiazepines that are rapidly eliminated from the body (e.g., triazolam, alprazolam) than for those that are slowly eliminated (e.g., *diazepam*).

It is highly advisable to gradually taper the benzodiazepine dose to minimize discomfort, especially after long-term use. Gradual discontinuation of the medication is preferred, but it may not entirely eliminate *withdrawal* symptoms.

There are also several reports on low-dose dependence on benzodiazepines in low or even very low doses. Persons who have taken benzodiazepines for a long time in therapeutic doses have reported *withdrawal* symptoms, anxiety and rebound effects. They are usually mild as a few sleepless nights but can also be severe with headache, muscle pain, and over sensitivity for sound and light. The users are often frightened especially when it is combined with rebound-effects for example that

the anxiety for a life trauma for which the medication originally was taken is returning.
Low-dose dependence is however controversial and is not included in most diagnostic system.
The persistence of benzodiazepines in the body from low or regular doses taken over long time results not only in prolonged *withdrawal* symptoms but also in symptoms that erratically come and go in cycles separated by 2 to 10 days. These symptoms are called protracted *withdrawal* syndrome and may persist for several months after the drug use has been discontinued.
If several *depressant* drugs is used the combination can cause a much greater reaction than simply the sum of the effects. When *alcohol* and diazepam is taken together, the liver is so busy metabolizing *alcohol* that the strength of the diazepam and its breakdown products pass through the body in a much greater strength.
Benzodiazepines also exhibit cross dependence and cross tolerance between different as well as similar chemical drug classes such as *alcohol*, *barbiturates* chlormetiazole and opioids.
Toxic Effects and overdoses
Symptoms of overdose include drowsiness, loss of consciousness, depressed breathing, coma and death if left untreated.
While it usually takes 50-100 pills to cause a serious overdose, street versions of the drugs, sometimes misrepresented and sold as Quaaludes can be so strong that 5-10 pills could cause severe reactions.
While death rarely results from benzodiazepine *overdose* alone, these medications may be fatal when used in combination with *alcohol* and other drugs that depress the central nervous system.
People do die from just a few pills of benzodiazepines and a modest amount of *alcohol.*

BENZODIAZEPINES Misuse patterns The misuse of benzodiazepines has a very broad spectrum. It spans from older women who are on very low dose presciptions of benzodiazepines and experince that they are dependent on the drug and can not live without it to people highly physically adiicted to doses 10 to 20 times the normal daily dose and introvenous drug addicts who uses benzodiazepines in combination with *cocaine* or *heroin*.
Amfetamine and *cocaine* users use benzodiazepines to calm down from excess stimulation and mildering the crash.
Heroin addicts use often benzodiazepines as a substitute when they can not get opiates and alcoholics are frequently using benzodiazepines in combination with *alcohol* or as a self-medication to prevent life-threatening *withdrawal* symptoms as convulsions. Methadone patiens in some cases use benzodiazepines as their drug of choice.
BENZODIAZEPINES Treatment A slow descalation over at least 4-6 weeks is strongly recommended to avoid the sometimes severe *withdrawal* symptoms. If the dependence on benzodiazepines is one of the main problems for the individual counceling, group therapy and contact with self-help groups gives often the best results.
For many patiens especially persons who have got their initial benzoadiazepines in connection with a life-crise such as a dicvorce, a death of a relative etc it can be necessary with individual or group-therapy for a year or more.
For a small group av patients eg persons with borderline syndromes, and certain types of severe anxiety the dependence on benzodiazepines even over a very long time is a lesser probem compared with the underlying diagnosis. To these persons it can be counterproductive and inhuman to force them to withdraw from their medication. They need the help of benzodiazepines as well as other psyciatric help. Moralizing over their drug dependence is counter productive.
BENZODIAZEPINES Prevention Benzodiazepines were put under international control in the 1971 UN convention on psychotropic drugs., the reason was the rapid spread of misuse.
Most nations has restricted the preisciptions of benzodiazepines. It has been done by narrowing the indications and by educationg the medical professionals.
Common rules and recommendations on benzodiazepines often include restrictions and carefulness when to prescribing benzodiazepines to certain gruops such as:
- young persons, especially young persons in different maternity crisis.
- patients with anxiety if not other measures are taken simultaniously.
- patients that the phisichen not has a good perosnal knowledge of.
- patients with known substance misuse history or spouce with known substance misuse.
The doses and durationm of medication are often recommended to be limited
A common method of getting large amounts of benzodiazepines used by addicts is to go to tens or seometiomes hundreds of physichans and obtain prescriptions for real or fake sympotoms or to "buy" pills or prescriptions dirctly from medical professionals or perons wokring in the pharmacetutical industry. As computers are introduced in pharmacies and

drug stores it is nowdays easy to impliment control systems on both patiens and physicans but many such ssystems has been stopped by intersts groups the pharmaceutical industry often motivatd by a concern for the right of privacy.

As the interational trade has increased smuggling of pharmaceutical products esopecially from Latin America and Eastern Europe

It has also been common to invclude education on benzodiazepines in the drug educations in schools. A common way to start the use of benzodiazepines is by getting them from a friend or a family member,.teenage girls often get them from their mothers.

Many special units dealing with benzodiazepine misuse has been established. They tend to reach middle aged soially functioning middle age women that are not alikely to show up at a regular drug abuse unit.

In many countrises self-help groups has been formed. Volontary organisations on benzodiazepine misuse working with treatment and opinion making now exist in most industrialized countries.

The use of benzodiazepines are still controversial in many countires. Self help groups and mass-media often point out the misuse of benzodiazepines as a very widespread and hidden problem. They also often point out that presciption of benzodiazepines often are performed routinely, symptom-oriented and that the important REM-sleep are disturbed and crises are contained rather than penetrated.

The advocates of extensive use of benzodiazepines in the medical profession as well as in the pharmaceutical industry points out that the majority of the millions of benzodiazepine users do not have any problems with them and that the critics not take in to account the massive suffering of, anxiety, depressions, tensions and sleeping-problems that the benzodiazepines at least partly counteract. The relative safety of the drugs are also udnerlined.

Several national concensus conference on benzodiazepines has been arranged. But the differing opinions on benzodiazepines seems to depend on basic views on mental health, psychiatry, psychopharmacology and the society as a whole. Most medical professionals tend to have a pragmatic view between these exterms. Hardly no one defends routin high-dose presciptions. and very few would never use them in the therapeutic arsenal. As in almost all other medical practice the answer is to find a reasonable balance for the individual patient.

Benzoilmorfina Spanish for *Benzoylmorphine*.

Benzol *Benzene*.

Benzolecgonina *Ecgonine benzoylester*.

Benzolone *Amfetamine sulfate*.

Benzopin *Diazepam*.

Benzoposan *Dexamfetamine hydrochloride*.

Benzopyrene dihydrodial exposide A substance associated with *tobacco* smoke that causes cancer.

Benzorphanol *Levophenacylmorphan*.

Benzotraine *Oxazepam*.

Benzotran *Oxazepam*.

Benzoyl-1-ekgonin-metylester *Cocaine*.

Benzoylecgonine *Ecgonine benzoylester*.

Benzoylecgonine ethylester *Ecgonine benzoylethylester*.

Benzoylecgoninmethylester *Cocaine*.

Benzoylekgonin *Ecgonine benzoylester*.

Benzoylmethylecgonin, -e *Cocaine*.

Benzoylmetylekgonin *Cocaine*.

Benzoylmorphine $C_{24}H_{23}NO_4$. An ester of *morphine* with benzoic acid under international control according to the UN Single Convention 1961 and its amendments, Schedule I. Molecular weight: 389.5. Percentage of anhydrous base: 100. See: *Opioids*.

Benzphetamin, -e, -um *Benzfetamine*.

Benzpropamin, -e, -um *Amfetamine*.

Benzpropaminum phosphoricum *Amfetamine phosphate*.

Benzyl-3 morphine *Benzylmorphine*.

Benzylmorphine $C_{24}H_{23}NO_3$. Derivative of *morphine* under international control according to the UN Single Convention 1961 and its amendments, Schedule I. Molecular weight: 375.5. Percentage of anhydrous base: 100. See: *Opioids*.

Benzylmorphine hydrochloride $C_{24}H_{23}NO_3$ HCl. Derivative of *morphine* under international control according to the UN Single Convention 1961 and its amendments, Schedule I. Molecular weight: 411. 9. Percentage of anhydrous base: 91. 2. See: *Opioids*.

Benzylmorphine methylsulfonate $C_{24}H_{23}NO_3$ CH_3SO_3H. Derivative of *morphine* under international control according to the UN Single Convention 1961 and its amendments, Schedule I. Molecular weight: 471. 5. Percentage of anhydrous base: 79.6. See: *Opioids*.

Benzylmorphine myristic acid ester *Myrophine*.

Benzylmorphine myristyl ester *Myrophine*.

Benzylmorphinmyristat *Myrophine*.

Benzylmorphinyl miristate *Myrophine*.

Benzyloxyethylnorpethidine *Benzethidine*.

Benzéthidine French term for *Benzethidine*.

Bephen *Phenobarbital*.

Beplete Drug containing more than one ac-