Benzodiazepine dependence

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Benzodiazepine dependence or benzodiazepine addiction is the condition when a person is dependent on benzodiazepine drugs. Dependence can either be a psychological dependence (addiction) or a physical dependence or a combination of the two. Physical dependence occurs when a person becomes tolerant to benzodiazepines and as a result of the physiological tolerance they develop a physical dependence which can manifest itself upon dosage reduction or withdrawal as the benzodiazepine withdrawal syndrome. Addiction or what it is sometimes referred to as psychological dependence includes people who misuse and/or crave the drug not to relieve withdrawal symptoms but to experience its euphoric and/or intoxicating effects. Addiction to benzodiazepines can also include people who are not abusing benzodiazepines but take them as prescribed who psychologically can't stop taking benzodiazepines despite the drug causing harm. It is important to distinguish between addiction and drug abuse of benzodiazepines and normal physical dependence on benzodiazepines. Physical dependence typically occurs from long term prescribed use but drug abuse and/or addiction does not typically occur in prescribed users.\[1\][2]

Therapeutic dose dependence is the largest category of people dependent on benzodiazepines. These individuals typically do not escalate their doses to high levels or abuse their medication. Smaller groups include patients who escalate their dosage to higher levels and also illicit drug misusers. It is unclear exactly how many people illicitly abuse benzodiazepines. Tolerance develops within days or weeks to the anticonvulsant, hypnotic, muscle relaxant and after 4 months there is little evidence that benzodiazepines retain their anxiolytic properties. Some authors however disagree and feel that benzodiazepines retain their anxiolytic properties.\[3\] Long-term benzodiazepine treatment may remain necessary in certain clinical conditions.\[4\]

Benzodiazepines can be addictive and induce dependence even at low doses, with 23% becoming addicted within 3 months of use. Benzodiazepine addiction is considered a public health problem. Approximately 68.5% of prescriptions of benzodiazepines originate from local health centers, with psychiatry and general hospitals accounting for 10% each. A survey of general practitioners reported that the reason for initiating benzodiazepines was due to an empathy for the patients suffering and a lack of other therapeutic options rather than patients demanding them. However, long term use was more commonly at the insistence of the patient, presumably because physical dependence and/or addiction had developed.\[5\][6][7] Prescribing levels of benzodiazepines have been declining, primarily due to concerns of dependence. In the short-term benzodiazepines are the most effective drugs for acute anxiety or insomnia. With longer-term use other therapies, both pharmacological and psychotherapeutic, become more effective. This is in part due to other forms of therapy becoming more effective with time but also because tolerance develops to all of the pharmacological actions of benzodiazepines.\[8\][9]
Definition

Benzodiazepine dependence is the condition which commonly develops as the result of repeated ingestion of benzodiazepine drugs. It can include both a physical dependence as well as a psychological dependence and is typified by a withdrawal syndrome upon a fall in blood plasma levels of benzodiazepines, eg during dose reduction or abrupt withdrawal.\[10]\n
Signs and symptoms

The signs and symptoms of benzodiazepine dependence include feeling unable to cope without the drug, unsuccessful attempts to cut down or stop benzodiazepine use, tolerance to the effects of benzodiazepines and withdrawal symptoms when not taking the drug. Some withdrawal symptoms that may appear include; anxiety, depressed mood, depersonalisation, derealisation, sleep disturbance, hypersensitivity to touch and pain, tremor, shakiness, muscular aches, pains, twitches and headache.\[11]\n
Benzodiazepine dependence and withdrawal has been associated with suicide and self harming behaviors, especially in young people. The Department of Health substance misuse guidelines recommends monitoring for mood disorder in those who are dependent on or withdrawing from benzodiazepines.\[12]\n
Risk factors

Benzodiazepine dependence is a frequent complication when they are prescribed for or taken for longer than four weeks, with physical dependence and withdrawal symptoms being the most common problem, but also occasionally drug-seeking behavior. Withdrawal symptoms include anxiety, perceptual disturbances, distortion of all the senses, dysphoria and, in rare cases, psychosis and epileptic seizures.\[13]\n
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The risk factors for benzodiazepine dependence are long-term use beyond four weeks, use of high doses and use of potent short-acting benzodiazepines, dependent personalities and those prone to drug abuse.[13] Use of short-acting benzodiazepines leads to repeated withdrawal effects which is alleviated by the next dose; this reinforces in the individual the dependence.[11]

**Background**

Benzodiazepines are regarded as potentially addictive drugs. A psychological and physical dependence can develop in as short as a few weeks but may take years to develop in other individuals. Patients wanting to withdraw from benzodiazepines typically receive little advice or support.[14] Benzodiazepines are usually only prescribed short-term as there is little justification for their prescribing long-term.[15] Some doctors however, disagree and believe long-term use beyond 4 weeks is sometimes justified, although there is little data to support this viewpoint.[8] Such viewpoints are a minority in the medical literature.[16]

Tolerance occurs rapidly to the sleep inducing effects of benzodiazepines but takes several months to develop to the anxiolytic effects. The anticonvulsant and muscle relaxant effects last for a few weeks before tolerance occurs in most individuals. Tolerance results in a change in the desensitization of the GABA receptors and an increased sensitization of the excitatory neurotransmitter system, glutamate such as NMDA glutamate receptors. These changes occur as a result of the body trying to overcome the drug's effects. Other changes which occur are the reduction of the number of GABA receptors (internalization) as well as possibly long term changes in gene transcription coding of brain cells. The differing speed at which tolerance occurs to the therapeutic effects of benzodiazepines can be explained by the speed of changes in the range of neurotransmitter systems and sub systems which are altered by chronic benzodiazepine use. The various neurotransmitter systems and subsystems may reverse tolerance at different speeds thus explaining the prolonged nature of some withdrawal symptoms. As a result of a physical dependence which develops due to tolerance a characteristic benzodiazepine withdrawal syndrome often occurs after removal of the drug or a reduction in dosage.[17] Changes in the expression of neuropeptides such as corticotropin-releasing hormone and neuropeptide Y may play a role in benzodiazepine dependence.[18]

Symptom severity is worse with the use of high doses, or with benzodiazepines of high potency or short half life. Other cross tolerant sedative hypnotics, such as barbiturates or alcohol increase the risk of benzodiazepine dependence.[19] Similar to opioids use for pain, therapeutic use of benzodiazepines rarely leads to a substance use disorder.[20]

Approximately twice as many women as men are prescribed benzodiazepines. It is believed that this is largely because men typically turned to alcohol to cope with stress and women to prescription drugs. Biased perception of women by male doctors may also play a role in increased prescribing rates to women. Increased anxiety features in women does not account for the wide gap alone between men and women.[21]

**Tolerance and physical dependence**

*Main article: Benzodiazepine withdrawal syndrome*

**Physical dependence**

Regular use of benzodiazepines at prescribed levels for six weeks was found to produce a significant risk of dependence, with resultant withdrawal symptoms appearing on abrupt discontinuation in a study assessing diazepam and buspirone. However, with abrupt withdrawal after six weeks of treatment with buspirone, no withdrawal symptoms developed.[22] Various studies have shown between 20–100% of patients prescribed benzodiazepines at therapeutic dosages long term are physically dependent and will experience withdrawal
A physical dependence develops more quickly with higher potency benzodiazepines such as alprazolam (Xanax) than with lower potency benzodiazepines such as chlordiazepoxide (Librium).

Previously, physical dependence on benzodiazepines was largely thought to occur only in people on high-therapeutic-dose ranges and low- or normal-dose dependence was not suspected until the 1970s; and it wasn't until the early 1980s that it was confirmed.

However, low-dose dependence is now a recognized clinical disadvantage of benzodiazepines and severe withdrawal syndromes can occur from these low doses of benzodiazepines even after gradual dose reduction. Low dose dependence has now been clearly demonstrated in both animal studies and human studies.

In an animal study of four baboons on low-dose benzodiazepine treatment, three out of the four baboons demonstrated physical dependence and developed flumazenil-precipitated withdrawal symptoms after only two weeks of low-dose benzodiazepine treatment. Furthermore, the baboons on low-dose therapy did not develop more severe flumazenil-precipitated withdrawal symptoms when low-dose benzodiazepine therapy was continued over a period of 6–10 months, suggesting rapid onset of tolerance and dependence with benzodiazepines and suggesting that physical dependence was complete after two weeks of chronic, low-dose benzodiazepine treatment.

In another animal study, physical dependence was demonstrated with withdrawal signs appearing after only seven days of low-dose benzodiazepine treatment and withdrawal signs appeared after only three days after high-dose treatment, which demonstrated the extremely rapid development of tolerance and dependence on benzodiazepines, at least in baboons. It was also found that previous exposure to benzodiazepines sensitized baboons to the development of physical dependence.

In humans, chronic, low-therapeutic-dose dependence was demonstrated in experimentally precipitated withdrawal using flumazenil to show physical dependence and withdrawal signs. Withdrawal symptoms experienced by the chronic therapeutic low-dose subjects included increased ratings of dizziness, blurred vision, heart pounding, feelings of unreality, pins and needles, nausea, sweatiness, noises louder than usual, jitteriness, things moving, sensitivity to touch. Healthy control subjects who were not dependent on benzodiazepines exhibited no benzodiazepine withdrawal-like effects or notable side effects.

In another study of 34 low-dose benzodiazepine users, physiological dependence was demonstrated by the appearance of withdrawal symptoms in 100% of those who received flumazenil whereas those receiving placebo experienced no withdrawal signs. It was also found that those dependent on low doses of benzodiazepines with a history of panic attacks were at an increased risk of suffering panic attacks due to flumazenil precipitated benzodiazepine withdrawal.

It has been estimated that 30–45% of chronic low dose benzodiazepine users are dependent and it has been recommended that benzodiazepines even at low dosage be prescribed for a maximum of 7–14 days to avoid dependence.

Some controversy remains, however, in the medical literature as to the exact nature of low-dose dependence and the difficulty in getting patients to discontinue their benzodiazepines, with some papers attributing the problem to predominantly drug-seeking behavior and drug craving, whereas other papers have found the opposite, attributing the problem to a problem of physical dependence with drug-seeking and craving not being typical of low-dose benzodiazepine users.

**Tolerance**

Tolerance occurs to the muscle relaxant, anticonvulsant and sleep inducing effects of benzodiazepines and
upon cessation a benzodiazepine withdrawal syndrome occurs. This can lead to benzodiazepines being taken for longer than originally intended as people continue to take the drugs over a long period of time to suppress withdrawal symptoms. Some people abuse benzodiazepines at very high doses and devote a lot of time in doing so and satisfy the diagnostic criteria in DSM IV for substance abuse and dependence. Another group of people include those who are on low to moderate therapeutic doses of benzodiazepines who do not abuse their benzodiazepines but develop a tolerance and benzodiazepine dependence.[37] A considerable number of individuals using benzodiazepines for insomnia escalate their dosage, sometimes above therapeutic prescribing dose levels. Tolerance to the anxiolytic effect of benzodiazepines has been clearly demonstrated in rats. In humans there is little evidence that benzodiazepines retain their anti-anxiety effects beyond four months of continuous treatment; there is evidence which suggests that long-term use of benzodiazepines may actually worsen anxiety which in turn may lead to dosage escalation, with one study finding 25% of patients escalated their dosage. Some authors however, consider benzodiazepines to be effective long-term, however, it is more likely that the drugs are acting to prevent rebound anxiety withdrawal effects. Tolerance to the anticonvulsant and muscle relaxing effects of benzodiazepines occurs within a few weeks in most patients.[3]

Tolerance in humans to the anxiolytic effects of benzodiazepines develops over a period of 3 months. Tolerance to the anxiolytic effect of benzodiazepines also occurs in animals. The study found that tolerance does not occur at the GABA binding site on the GABA_A receptor but that tolerance occurs at the benzodiazepine site on the GABA_A receptor.[38][39] A study of the benzodiazepine drug mexazolam found it to be no more effective than placebo after three weeks of use.[40]

**Cross tolerance**

Benzodiazepines share a similar mechanism of action with various sedative compounds that act by enhancing the GABA_A receptor. Cross tolerance means that one drug will alleviate the withdrawal effects of another. It also means that tolerance of one drug will result in tolerance of another similarly-acting drug. Benzodiazepines are often used for this reason to detoxify alcohol-dependent patients and can have life-saving properties in preventing and/or treating severe life-threatening withdrawal syndromes from alcohol, such as delirium tremens. However, although benzodiazepines can be very useful in the acute detoxification of alcoholics, benzodiazepines in themselves act as positive reinforcers in alcoholics, by increasing the desire for alcohol. Low doses of benzodiazepines were found to significantly increase the level of alcohol consumed in alcoholics.[41]

However, alcoholics dependent on benzodiazepines should not be abruptly withdrawn but be very slowly withdrawn from benzodiazepines as over-rapid withdrawal is likely to produce severe anxiety or panic, which is well known for being a relapse risk factor in recovering alcoholics.[42]

There is also cross tolerance between alcohol, the benzodiazepines, the barbiturates and the nonbenzodiazepine drugs, corticosteroids which all act by enhancing the GABA_A receptor's function via modulating the chloride ion channel function of the GABA_A receptor.[43][44][45][46][47]

Neuroactive steroids e.g. progesterone and its active metabolite allopregnanolone are positive modulators of the GABA_A receptor and are cross tolerant with benzodiazepines.[48] The active metabolite of progesterone has been found to enhance the binding of benzodiazepines to the benzodiazepine binding sites on the GABA_A receptor.[49] The cross-tolerance between GABA_A receptor positive modulators occurs because of the similar mechanism of action and the subunit changes which occur from chronic use from one or more of these compounds in expressed receptor isoforms. Abrupt withdrawal from any of these compounds, e.g. barbiturates, benzodiazepines, alcohol, corticosteroids, neuroactive steroids and nonbenzodiazepines, precipitate similar withdrawal effects characterized by central nervous system hyper-excitability resulting in symptoms such as increased seizure susceptibility and anxiety.[50] While many of the neuroactive steroids do not produce full tolerance to their therapeutic effects, cross-tolerance to benzodiazepines still occurs as had been demonstrated
between the neuroactive steroid ganaxolone and diazepam. Alterations of levels of neuroactive steroids in the body during the menstrual cycle, menopause, pregnancy and stressful circumstances can lead to a reduction in the effectiveness of benzodiazepines and a reduced therapeutic effect. During withdrawal of neuroactive steroids benzodiazepines become less effective.\[51\]

**Mechanism**

The increased GABA inhibition caused by benzodiazepines is balanced by neuroadaptations which result in decreased GABA inhibition and increased excitability of the glutamate system. When benzodiazepines are stopped, these neuroadaptations are "unmasked" leading to excitability of the nervous system and the appearance of withdrawal symptoms.\[37\]

Ethanol (alcohol), also has a similar very similar mechanism of tolerance and withdrawal as benzodiazepines, involving the GABA\(\alpha\), NMDA and AMPA receptors. As with benzodiazepines kindling also occurs with alcohol after repeated withdrawals. The research into kindling, a phenomenon which results in increased sensitivity of the nervous system due to multiple acute withdrawals with for example increased seizures, has primarily focused on alcohol. It is suspected that similar to alcohol, repeated benzodiazepine withdrawals may result in similar neuronal kindling with resultant increased neuro-excitability. There is no evidence that "drug holidays" or periods of abstinence reduced the risk of dependence; there is evidence from animal studies that such an approach does not prevent dependence from happening. Use of short-acting benzodiazepines is associated with interdose withdrawal symptoms; kindling has clinical relevance with regard to benzodiazepines; for example, there is an increasing shift to use of benzodiazepines with a shorter half life and intermitant use which can result in interdose withdrawal and rebound effects. Animal studies have shown that repeated withdrawal from benzodiazepines leads to increasingly severe withdrawal symptoms, including an increased risk of seizures; the glutamate system is believed to play an important role in this kindling phenomena with AMPA receptors which are a subtype of glutamate receptors being altered by repeated withdrawals from benzodiazepines. The changes which occur after withdrawal in AMPA receptors in animals have been found in regions of the brain which govern anxiety and seizure threshold; thus kindling may result in increased severity of anxiety and a lowered seizure threshold during repeated withdrawal. Changes in the glutamate system and GABA system may play an important role at different time points during benzodiazepine and withdrawal.\[37\]

The shift of benzodiazepine receptors to an inverse agonist state after chronic treatment, leads the brain to be more sensitive to excitatory drugs or stimuli. Excessive glutamate activity, can result in excitotoxicity which may result in neurodegeneration. The glutamate receptor subtype NMDA is well known for its role in causing excito-neurotoxicity. The glutamate receptor subtype AMPA is believed to play an important role in neuronal kindling as well as excitotoxicity during withdrawal from alcohol as well as benzodiazepines. NMDA receptors are involved in the tolerance of some effects of benzodiazepines.\[37\]

Adaptational changes at the GABA\(\alpha\) benzodiazepine receptor complex do not fully explain tolerance, dependence and withdrawal from benzodiazepines. Other receptor complexes are believed to be involved, in particular the excitatory glutamate system. The involvement of glutamate in benzodiazepine dependence explains long-term potentiation as well as neuro kindling phenomena. Tolerance is defined as a loss of pharmacological effects after a repeated or regular use of a drug. Use of a short-acting benzodiazepine at night as a sleeping pill causes repeated acute dependence followed by acute withdrawal. There is some evidence that a prior history of CNS depressant dependence eg alcohol increases the risk of dependence on benzodiazepines. Tolerance to drugs is commonly believed to be due to receptor down-regulation (decrease in number), however, there is very limited evidence to support this and comes from animal studies using very high doses. Instead other mechanisms are believed to play a more important role in the development of benzodiazepine dependence, such as receptor uncoupling which may lead to prolonged comformational changes in the receptors or altered subunit composition of the receptors.\[37\]
Animal studies have found that glutameric changes as a result of benzodiazepine use, are responsible for a delayed withdrawal syndrome, which in mice peaks 3 days after cessation of benzodiazepines. This was demonstrated by the ability to avoid the withdrawal syndrome by the administration of AMPA antagonists. It is believed that different different glutamate subreceptors eg NMDA and AMPA are responsible for different stages/time points of the withdrawal syndrome. NMDA receptors are upregulated in the brain as a result of benzodiazepine tolerance. AMPA receptors are also involved in benzodiazepine tolerance and withdrawal.[37][52][52] Tolerance to the anticonvulsant effect of benzodiazepines also develops in both humans and animals.[53][54] A decrease in benzodiazepine binding sites in the brain may also occur as part of benzodiazepine tolerance.[55]

Patients taking daily benzodiazepine drugs have a reduced sensitivity to further additional doses of benzodiazepines.[56] Tolerance to benzodiazepines can be demonstrated by injecting diazepam into long-term users. In normal subjects increases in growth hormone occurs whereas in benzodiazepine tolerant individuals this effect is blunted.[57]

**Physiology of withdrawal**

Withdrawal symptoms are a normal response in individuals who have chronically used benzodiazepines, and an adverse effect and result of drug tolerance. Symptoms typically emerge when dosage of the drug is reduced. GABA is the second most common neurotransmitter in the central nervous system (after glutamate,[58][59][60]) and by far the most abundant inhibitory neurotransmitter; roughly one-quarter to one-third of synapses use GABA.[61] The use of benzodiazepines has a profound effect on almost every aspect of brain and body function, either directly or indirectly.[62]

Benzodiazepines cause a decrease in norepinephrine (noradrenaline), serotonin, acetylcholine and dopamine. These neurotransmitters are needed for normal memory, mood, muscle tone and coordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control. With chronic benzodiazepine use, tolerance develops rapidly to most of its effects, so that when benzodiazepines are withdrawn, various neurotransmitter systems go into overdrive due to the lack of inhibitory GABA-ergic activity. Withdrawal symptoms then emerge as a result, and persist until the nervous system physically reverses the adaptions (physical dependence) which have occurred in the CNS.[62]

Withdrawal symptoms typically consist of a mirror image of the drug’s effects: sedative effects and suppression of REM and SWS stages of sleep can be replaced by insomnia, nightmares, and hypnogogic hallucinations; its antianxiety effects are replaced with anxiety and panic; muscle relaxant effects are replaced with muscular spasms or cramps; and anticonvulsant effects with seizures, especially in cold turkey or overly-rapid withdrawal.[62]

Benzodiazepine withdrawal represents in part excitotoxicity to brain neurons.[63] Rebound activity of the hypothalamic-pituitary-adrenocortical axis also plays an important role in the severity of benzodiazepine withdrawal.[64] Tolerance and the resultant withdrawal syndrome may be due to alterations in gene expression which results in long term changes in the function of the GABAergic neuronal system.[65][66]

Studies in mice have found that discontinuation of benzodiazepines leads to decreased agonist affinity and increased inverse agonist affinity of the benzodiazepine receptors, essentially causing the receptors to reverse their natural function. This may explain at least in part the cause of the benzodiazepine withdrawal effects. This change in receptor sensitivity may be due to receptor uncoupling.[67] During withdrawal from full or partial agonists, changes occur in benzodiazepine receptor with upregulation of some receptor subtypes and down regulation of other receptor subtypes.[68]
Withdrawal

Long-term use of benzodiazepines leads to increasing physical and mental health problems and as a result withdrawal is recommended for many long-term users. The withdrawal syndrome from benzodiazepines can range from a mild and short lasting syndrome to a prolonged and severe syndrome. Withdrawal symptoms leads to continued use of benzodiazepines for many years, long after the original reason for taking benzodiazepines has passed. Many patients know that the benzodiazepines no longer work for them but are unable to discontinue benzodiazepines because of withdrawal symptoms.[62]

Withdrawal symptoms can emerge despite slow reduction but can be reduced by a slower rate of withdrawal. As a result, withdrawal rates have been recommended to be customized to each individual patient. The time needed to withdraw can vary from a couple of months to a year or more and often depends on length of use, dosage taken, lifestyle, health, social and environmental stress factors.[62]

Diazepam is often recommended due to its long elimination half life and also because of its availability in low potency doses. The non-benzodiazepine Z drugs such as zolpidem, zaleplon and zopiclone should not be used as a replacement for benzodiazepines as they have a similar mechanism of action and can induce a similar dependence. The pharmacological mechanism of benzodiazepine tolerance and dependence is the internalization (removal) of receptor site in the brain and changes in gene transcription codes in the brain.[62]

With long-term use and during withdrawal of benzodiazepines treatment emergent depression and emotional blunting may emerge and sometimes also suicidal ideation. There is evidence that the higher the dose used the more likely it is benzodiazepine use will induce these feelings. Reducing the dose or discontinuing benzodiazepines may be indicated in such cases. Withdrawal symptoms can persist for quite some time after discontinuing benzodiazepines. Some common protracted withdrawal symptoms include anxiety, depression and insomnia and physical symptoms such as gastrointestinal, neurologic and musculoskeletal effects. The protracted withdrawal state may still occur despite slow titration of dosage. It is believed that the protracted withdrawal effects are due to persisting neuroadapations.[9]

The Committee on the Review of Medicines (UK)

The Committee on the Review of Medicines carried out a review into benzodiazepines due to significant concerns of tolerance, drug dependence and benzodiazepine withdrawal problems and other adverse effects. The committee found that benzodiazepines do not have any antidepressant or analgesic properties and are therefore unsuitable treatments for conditions such as depression, tension headaches and dysmenorrhea. Benzodiazepines are also not beneficial in the treatment of psychosis. The committee also recommended against benzodiazepines being used in the treatment of anxiety or insomnia in children.[39]

The committee was in agreement with the Institute of Medicine (USA) and the conclusions of a study carried out by the White House Office of Drug Policy and the National Institute on Drug Abuse (USA) that there was little evidence that long term use of benzodiazepine hypnotics were beneficial in the treatment of insomnia due to the development of tolerance. Benzodiazepines tended to lose their sleep promoting properties within 3–14 days of continuous use and in the treatment of anxiety the committee found that there was little convincing evidence that benzodiazepines retained efficacy in the treatment of anxiety after 4 months of continuous use due to the development of tolerance.[39]

The committee found that the regular use of benzodiazepines caused the development of dependence characterized by tolerance to the therapeutic effects of benzodiazepines and the development of the benzodiazepine withdrawal syndrome including symptoms such as anxiety, apprehension, tremors, insomnia, nausea, and vomiting upon cessation of benzodiazepine use. Withdrawal symptoms tended to develop within 24 hours upon cessation of short acting; and 3–10 days after cessation of longer acting benzodiazepines. Withdrawal effects could occur after treatment lasting only 2 weeks at therapeutic dose levels, however
withdrawal effects tended to occur with habitual use beyond 2 weeks and were more likely the higher the dose. The withdrawal symptoms may appear to be similar to the original condition.[39]

The committee recommended that all benzodiazepine treatment be withdrawn gradually and recommended that benzodiazepine treatment be used only in carefully selected patients and that therapy be limited to short term use only. It was noted in the review that alcohol can potentiate the central nervous system depressant effects of benzodiazepines and should be avoided. The central nervous system depressant effects of benzodiazepines may make driving or operating machinery dangerous and the elderly are more prone to these adverse effects. In the neonate high single doses or repeated low doses have been reported to produce hypotonia, poor suckling, and hypothermia in the neonate and irregularities in the fetal heart. The committee recommended that benzodiazepines should be avoided in lactation.[39]

The committee recommended that withdrawal from benzodiazepines should be gradual as abrupt withdrawal from high doses of benzodiazepines may cause confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. Abrupt withdrawal from lower doses may cause depression, nervousness, rebound insomnia, irritability, sweating, and diarrhea.[39]

In the elderly

See also: Benzodiazepine withdrawal syndrome#Elderly

Long term use and benzodiazepine dependence is a serious problem in the elderly. Failure to treat benzodiazepine dependence in the elderly can cause serious medical complications.[69] The elderly have less cognitive reserve and are more sensitive to the short, (e.g. in between dose withdrawal) and protracted withdrawal effects of benzodiazepines, as well as the side effects both from short-term and long-term use. This can lead to excessive contact with their doctor. Research has found that withdrawing elderly people from benzodiazepines leads to a significant reduction in doctor visits per year, presumably due to an elimination of drug side effects and withdrawal effects.[9]

Tobacco and alcohol are the most common substance that elderly people get a dependence on or misuse. The next most common substance that elderly people develop a drug dependence to and/or misuse is benzodiazepines. Drug induced cognitive problems can have serious consequences for elderly people and can lead to confusional states and "pseudo-dementia". About 10% of elderly patients referred to memory clinics actually have a drug induced cause which most often is benzodiazepines. Benzodiazepines have also been linked to an increased risk of road traffic accidents and falls in the elderly. The long term effects of benzodiazepines are still not fully understood in the elderly or any age group. Long term benzodiazepine use is associated with attentional and visuospatial functional impairments. Withdrawal from benzodiazepines can lead to improved alertness and decreased forgetfulness in the elderly. Withdrawal led to statistical significant improvements in memory function and performance related skills in those who withdrew successfully from benzodiazepines whereas those who remained on benzodiazepines experienced worsening symptoms. People who had withdrawn from benzodiazepines also felt their sleep was more refreshing making statements such as "I feel sharper when I wake up" or "I feel better, more awake", or "It used to take me an hour to fully wake up." This suggests that benzodiazepines may actually make insomnia worse in the elderly.[70]

Prevention

Letter to patients

Sending a letter to patients warning of the adverse effects of long term use of benzodiazepines and recommending dosage reduction has been found to be successful and a cost effective strategy in reducing benzodiazepine consumption in general practice. Within a year of the letter going out there was found to be a
17% fall in the number of benzodiazepines being prescribed, with 5% of patients having totally discontinued benzodiazepines.[71][72] A study in Holland reported a higher success rate by sending a letter to patients who are benzodiazepine dependent. The results of the Dutch study reported 11.3% of patients discontinuing benzodiazepines completely within a year.[73]

**Pharmacist intervention programs**

A study found that pharmacists providing educational sessions for medical staff at nursing homes for the elderly combined with medicine audits and feedback cycles combined with an interdisciplinary sedative review resulted in a large reduction in both the number of residents taking benzodiazepines or antipsychotics at all as well as an overall reduction in total dosage.[74]

**Cognitive behavioral therapy**

Nitrazepam, temazepam and zopiclone are the most frequently prescribed hypnotics in the UK. Hypnotic drugs are of poor value for the management of chronic insomnia. Hypnotic drug consumption has been shown to reduce work performance, increase absenteeism, increase road traffic accidents, increase morbidity, increase mortality and is associated with an increased incidence of deliberate self harm. In the elderly, increases in falls and fractures associated with sedative hypnotic drug use has been found. It is widely accepted that hypnotic drug usage beyond 4 weeks is undesirable for all age groups of patients. Many continuous hypnotic users exhibit disturbed sleep as a consequence of tolerance but experience worsening rebound or withdrawal insomnia when the dose is reduced too quickly which compounds the problem of chronic hypnotic drug use. Cognitive behavioral therapy has been found to be more effective for the long term management of insomnia than sedative hypnotic drugs. No formal withdrawal programs for benzodiazepines exists with local providers in the UK. Meta-analysis of published data on psychological treatments for insomnia show a success rate between 70 and 80%. A large scale trial utilizing cognitive behavioral therapy in chronic users of sedative hypnotics including nitrazepam, temazepam and zopiclone found CBT to be a significantly more effective long term treatment for chronic insomnia than sedative hypnotic drugs. Persisting improvements in sleep quality, sleep onset latency, increased total sleep, improvements in sleep efficiency, significant improvements in vitality, physical and mental health at 3, 6 and 12 month follow ups was found in those receiving CBT. A marked reduction in total sedative hypnotic drug use was found in those receiving CBT, with 33% reporting zero hypnotic drug use. Age has been found not to be a barrier to successful outcome of CBT. It was concluded that CBT for the management of chronic insomnia was flexible, practical and a cost effective treatment and it was also concluded that CBT leads to a reduction of benzodiazepine drug intake in a significant number of patients.[75] Chronic use of hypnotic medications is not recommended due to their adverse effects on health and the risk of dependence. A gradual taper is usual clinical course in getting people off of benzodiazepines but even with gradual reduction a large proportion of people fail to stop taking benzodiazepines. The elderly are particularly sensitive to the adverse effects of hypnotic medications. A clinical trial in elderly people dependent on benzodiazepine hypnotics showed that the addition of CBT to a gradual benzodiazepine reduction program increased the success rate of discontinuing benzodiazepine hypnotic drugs from 38% to 77% and at the 12 month follow-up from 24% to 70%. The paper concluded that CBT is an effective tool for reducing hypnotic use in the elderly and reducing the adverse health effects that are associated with hypnotics such as drug dependence, cognitive impairments and increased road traffic accidents.[76]

A study of patients undergoing benzodiazepine withdrawal who had a diagnosis of generalized anxiety disorder showed that those who received CBT had a very high success rate of discontinuing benzodiazepines compared to those who did not receive CBT. This success rate was maintained at the 12 month follow up. Furthermore in patients who had discontinued benzodiazepines it was found that they no longer met the diagnosis of general anxiety disorder and that patients no longer meeting the diagnosis of general anxiety disorder was higher in the group who received CBT. Thus CBT can be an effective tool to add to a gradual benzodiazepine dosage reduction program leading to improved and sustained mental health benefits.[77]
Misuse and addiction

See also: Benzodiazepine drug misuse

Benzodiazepines are one of the largest classes of abused drugs; they are classed as schedule IV controlled drugs because of their recognized medical uses.[78]

Benzodiazepines can cause serious addiction problems. A survey in Senegal of doctors found that many doctors feel that their training and knowledge of benzodiazepines is generally poor. Due to the serious concerns of addiction national governments were recommended to urgently seek to raise knowledge via training about the addictive nature of benzodiazepines and appropriate prescribing of benzodiazepines.[79]

Another study in Dakar found that almost one fifth of doctors ignored prescribing guidelines regarding short term use of benzodiazepines and almost three quarters of doctors regarded their training and knowledge of benzodiazepines to be inadequate. More training regarding benzodiazepines has been recommended for doctors.[80]

A six-year study on 51 Vietnam veterans who were drug abusers of either mainly stimulants (11 people), mainly opiates (26 people) or mainly benzodiazepines (14 people) was carried out to assess psychiatric symptoms related to the specific drugs of abuse. After six years, opiate abusers had little change in psychiatric symptomatology; 5 of the stimulant users had developed psychosis, and 8 of the benzodiazepine users had developed depression. Therefore, long-term benzodiazepine abuse and dependence seems to carry a negative effect on mental health, with a significant risk of causing depression.[81]

Benzodiazepines are also sometimes abused intranasally.[82]

In the elderly, alcohol and benzodiazepines are the most commonly abused substances. Abuse of sedative hypnotics such as alcohol or benzodiazepines is more problematic in the elderly because they are more sensitive to the adverse effects and experience a more severe withdrawal syndrome with withdrawal related delerium being more common in the elderly than in younger patients.[83]

See also

- Benzodiazepine
- Benzodiazepine withdrawal syndrome
- Long term effects of benzodiazepines
- Alcohol withdrawal syndrome
- Long term effects of alcohol
- SSRI discontinuation syndrome
- Drug related crime

References


External links

- Benzodiazepines: How they work and how to withdraw by Professor Heather Ashton (http://www.benzo.org.uk/manual/)
- Benzodiazepine dependence (http://www.dmoz.org/Health/Mental_Health/Disorders/Substance_Related/Support_Groups/) at the Open Directory Project


Categories: Pharmacology | Drug addiction | Drug rehabilitation | Neurology | Psychiatry | Substance-related disorders | Syndromes | Benzodiazepines

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