

The diagnosis and management of benzodiazepine dependence

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Purpose of review

Despite repeated recommendations to limit benzodiazepines to short-term use (2–4 weeks), doctors worldwide are still prescribing them for months or years. This over-prescribing has resulted in large populations of long-term users who have become dependent on benzodiazepines and has also led to leakage of benzodiazepines into the illicit drug market. This review outlines the risks of long-term benzodiazepine use, gives guidelines on the management of benzodiazepine withdrawal and suggests ways in which dependence can be prevented.

Recent findings

Recent literature shows that benzodiazepines have all the characteristics of drugs of dependence and that they are inappropriately prescribed for many patients, including those with physical and psychiatric problems, elderly residents of care homes and those with comorbid alcohol and substance abuse. Many trials have investigated methods of benzodiazepine withdrawal, of which the keystones are gradual dosage tapering and psychological support when necessary. Several studies have shown that mental and physical health and cognitive performance improve after withdrawal, especially in elderly patients taking benzodiazepine hypnotics, who comprise a large proportion of the dependent population.

Summary

Benzodiazepine dependence could be prevented by adherence to recommendations for short-term prescribing (2–4 weeks only when possible). Withdrawal of benzodiazepines from dependent patients is feasible and need not be traumatic if judiciously, and often individually, managed.

Keywords

benzodiazepine dependence, benzodiazepine withdrawal, prevention of dependence

Abbreviation

GABA γ -aminobutyric acid

Introduction

Since their introduction in the 1950s, benzodiazepines appear to have passed their zenith of medical popularity. However, they are still prescribed excessively and often inappropriately. With their reputation perhaps approaching a nadir, at least as prescribed medications for long-term use, it is timely to review approaches to the diagnosis and management of dependence on these drugs.

The benzodiazepine bonanza

In the late 1970s benzodiazepines became the most commonly prescribed of all drugs in the world. Their range of actions – sedative/hypnotic, anxiolytic, anti-convulsant and muscle relaxant – combined with low toxicity and alleged lack of dependence potential seemed to make them ideal medications for many common conditions (Table 1). The drugs were prescribed long term, often for many years, for complaints such as anxiety, depression, insomnia and ordinary life stresses. Benzodiazepines were undoubtedly efficacious at first for these conditions, and apparently harmless – but there was a sting in the tail.

By the early 1980s long-term prescribed users themselves had realized that the drugs tended to lose their efficacy over time and instead became associated with adverse effects. In particular, patients found it difficult to stop taking benzodiazepines because of withdrawal reactions and many complained that they had become ‘addicted’ [1•]. Controlled clinical trials among such patients [2–4] demonstrated beyond doubt that withdrawal symptoms, even from regular ‘therapeutic’ doses of benzodiazepines, were real and that they indicated dependence on the drugs.

Changing definitions of dependence

That benzodiazepines could cause physical dependence was accepted by the medical profession on the basis that a withdrawal syndrome occurred on cessation of regular use, and doctors were advised to reserve them for short-term use in minimal dosage [5,6]. However, definitions of drug dependence changed in the 1990s. Previously, dependence had been defined in terms of

Curr Opin Psychiatry 18:249–255.

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Current Opinion in Psychiatry 2005, 18:249–255

Table 1. Therapeutic actions of benzodiazepines (in short-term use)

Action	Clinical use
Anxiolytic – relief of anxiety	Anxiety and panic disorders, phobias Agitated psychoses
Hypnotic – promotion of sleep	Insomnia
Myorelaxant – muscle relaxation	Muscle spasms, spastic disorders
Anticonvulsant – stops fits, convulsions	Fits due to drug poisoning, some forms of epilepsy, alcohol withdrawal
Amnesia – impairment of short-term memory	Premedication for operations, sedation for minor surgical operations

the development of drug tolerance and a withdrawal syndrome on cessation, but in current classification systems these two features alone are no longer considered sufficient for the diagnosis. Present criteria for substance dependence [7] include tolerance, escalation of dosage, continued use despite efforts to stop and knowledge of adverse effects, other behavioural features, and a withdrawal syndrome (Table 2). Benzodiazepines meet all these criteria.

Tolerance and dosage escalation

Tolerance to benzodiazepines develops at different rates and to different degrees for the various actions. Tolerance to hypnotic effects develops rapidly, within a few days or weeks of regular use. Studies in elderly patients indicate that, when taken over long periods, benzodiazepines have little effect on sleep [8,9^{••},10[•]]. Although some poor sleepers report continued efficacy of benzodiazepine hypnotics, possibly because they prevent rebound insomnia (a withdrawal effect), clinical experience shows that a considerable proportion of hypnotic users gradually increase their dosage, sometimes to above recommended levels. It is not uncommon for insomniacs to be taking two or more nightly benzodiazepines concurrently [11^{••},12[•]].

Tolerance to the anxiolytic effects of benzodiazepines develops more slowly, over a few months, and clinical

observations show that long-term use does little to control, and may even aggravate, anxiety [13]. There is also evidence of dosage escalation in anxiolytic users. In one clinical study over 25% of the patients were taking two benzodiazepines, the second having been added to the prescription when the first ceased to be effective [13]. Although some authors recommend long-term use of benzodiazepine anxiolytics for certain conditions [14,15], it is likely that the drugs are preventing withdrawal symptoms rather than reducing anxiety [16].

Tolerance to the anticonvulsant effects of benzodiazepines occurs within a few weeks in a high proportion of patients with epilepsy [17] and also to the muscular relaxant effects when used in patients with spastic disorders. Of particular clinical importance, however, is the finding that little tolerance develops to the amnesic effects and other cognitive impairments caused by benzodiazepines. Studies of long-term users have shown deficits in learning, memory, attention and visuospatial ability. A metaanalysis of 13 research studies revealed moderate–large deficits in all 12 of the cognitive domains tested in long-term benzodiazepine users compared with controls [18^{••}]. Such effects are most marked in the elderly in whom they may suggest dementia [19]. Improvement occurs when the drugs are stopped, but it may be slow and perhaps incomplete [20^{••},21].

Escalation of dosage and chronic use of benzodiazepines cause additional adverse effects including depression, excessive sedation, leading to falls and fractures, road traffic and other accidents (especially when combined with alcohol), and the insidious development of increasing psychological and physical symptoms [13,16,21,22, 23[•]–25[•]]. Again, the elderly are most vulnerable to these effects, especially if taking multiple medications [26^{••}]. Furthermore, benzodiazepines can be lethal in overdose [27,28[•]].

Withdrawal syndrome

The existence of a benzodiazepine withdrawal syndrome has been abundantly demonstrated [2–4,29,30]. The

Table 2. Criteria for substance dependence^a

1	Tolerance as defined by either a need for markedly increased amounts of the substance to achieve the clinical effect, or markedly diminished effect with continued use of the same amount of the substance
2	Withdrawal as defined by either the characteristic withdrawal syndrome for the substance, or the same or similar substance is taken to avoid withdrawal symptoms
3	The substance is taken in larger amounts or over a longer period than was intended
4	There is a persistent desire or unsuccessful attempts to cut down or control substance use
5	Time is spent in activities necessary to obtain the substance (e.g. visiting multiple doctors)
6	Important activities are given up or reduced because of substance use
7	The substance use is continued despite knowledge of having a problem caused or exacerbated by the substance

^aA maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the above, occurring at any time in the same 12-month period. Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, copyright 2000. American Psychiatric Association [7].

Table 3. Some common benzodiazepine withdrawal symptoms

Symptoms common to all anxiety states	Symptoms less common in anxiety states – relatively specific to benzodiazepine withdrawal ^a
Anxiety, panic attacks, agoraphobia	Perceptual distortions, sense of movement
Insomnia, nightmares	Depersonalization, derealization
Depression, dysphoria	Hallucinations (visual, auditory)
Excitability, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light headedness	Formication (skin 'crawling')
Weakness 'jelly legs'	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness	Tinnitus
Sweating, night sweats	Psychotic symptoms ^a
Palpitations	Confusion, delirium ^a
Blurred or double vision	Convulsions ^a

^aUsually only on rapid or abrupt withdrawal from high doses of benzodiazepines.

syndrome can be mild and short-lived or severe and sometimes protracted [31]. Symptoms include many that are common to anxiety states in general, as well as some more characteristic of benzodiazepine withdrawal (Table 3). Severity is often associated with prolonged or high-dose use, short-acting potent benzodiazepines, certain personality types and anxiety/neuroticism [32,33]. The reported incidence varies between 30 and 100% in different studies, but up to 50% of long-term users decline to participate in, or drop out of, withdrawal studies [4,34,35]. Withdrawal symptoms prolong benzodiazepine use, which often continues for years after the initial indication for the drug has passed. Many long-term users, aware that the drugs are no longer effective or are causing adverse effects, have tried to stop but have been unsuccessful because of the emergence of withdrawal symptoms [13].

Mechanisms of tolerance and withdrawal

The pharmacological mechanisms underlying benzodiazepine tolerance and withdrawal are complex and still not clear. Present knowledge has recently been reviewed in detail [36,37]. Tolerance to chronic benzodiazepine administration appears to result from neuroadaptive processes involving both desensitization of inhibitory γ -aminobutyric acid (GABA) receptors and sensitization of excitatory glutamergic receptors. Both these systems include multiple receptor subtypes. Changes in GABA receptors may include conformational alterations towards a low affinity state for GABA and uncoupling of benzodiazepine receptors from their sites on certain GABA_A receptors, followed by internalization and perhaps long-term effects on intraneural gene transcription [36,38^{*}]. Changes in the glutamergic system may include sensitization of *N*-methyl-D-aspartate (NMDA) and possibly other receptors

[1^{**},37]. These adaptations could occur on different time scales depending on the receptor subtype and brain region involved, thus accounting for the differing rates of development of tolerance to various benzodiazepine actions.

Rapid or abrupt withdrawal of the benzodiazepine once tolerance has developed exposes the recipient to the consequences of all these drug-induced adaptations. The result is underactivity of inhibitory GABA functions and a surge in excitatory nervous activity, giving rise to many of the benzodiazepine withdrawal symptoms shown in Table 3. The various receptor changes occurring during tolerance may be slow to reverse and may do so at different rates, possibly explaining the variable time of emergence and duration of individual withdrawal symptoms and sometimes protracted nature of benzodiazepine withdrawal [31].

Diagnosis of benzodiazepine dependence

The key signs of benzodiazepine dependence are withdrawal symptoms on dosage reduction or discontinuation. However, dependence can often be inferred in continuing benzodiazepine users from a history of long-term use, reliance on regular prescriptions, dosage escalation, unsuccessful attempts to cut down or stop drug use, and high anxiety levels [39^{*},40^{*},41,42^{**},43]. Chronic benzodiazepine users with a history of other drug or alcohol dependence are also likely to be dependent [44]. Unfortunately, long-term prescription of benzodiazepines continues today [45^{*}] and maintains several overlapping populations of benzodiazepine-dependent users.

Benzodiazepine-dependent populations

There are three overlapping types of benzodiazepine-dependent populations.

Therapeutic dose dependence

The largest population of benzodiazepine-dependent patients comprises long-term users who have inadvertently become dependent as a result of regular repeat prescriptions over months or years. The size of this population is estimated as 500 000 to 1 million in the UK, 4 million in the US [1^{**}] and several million worldwide [46]. It is likely that at least 50% of these users are dependent. A considerable proportion of these patients are elderly females taking benzodiazepine hypnotics [8,9^{**}] and it is noteworthy that prescriptions for hypnotics (including drugs with similar actions such as zopiclone) have not declined despite a reduction in prescriptions for benzodiazepine anxiolytics [39^{*}]. Other long-term prescribed users who are likely to be dependent are patients with physical and psychiatric problems and elderly residents of care homes [46,47^{*},48^{*},49,50^{*}].

Prescribed high-dose dependence

A minority of patients who start on prescribed benzodiazepines escalate their dosage excessively. At first they may persuade their doctors to increase prescriptions, but on reaching the prescriber's limits, they may attend several doctors or hospital departments to obtain further supplies. When other sources fail they may resort to 'street' benzodiazepines.

Recreational benzodiazepine abuse

The use of benzodiazepines as recreational drugs is a growing problem [16]. The size of this population is unknown but estimates suggest about 200 000 people in the UK alone (population 55 million) and similar or higher proportions in the US, Europe, Australia and other countries. Benzodiazepines commonly form part of a polysubstance abuse pattern. They are taken by at least half of opiate, amphetamine, cocaine and other illegal drug users worldwide and by alcoholics [1^{••},51]. Other users include patients with mental illness and comorbid other substance abuse [48[•],49]. Some people use benzodiazepines as their primary recreational drug, bingeing intermittently on high doses or injecting intravenously with risk of gangrene, HIV and hepatitis C [51].

Reasons given for taking benzodiazepines recreationally are that they enhance the 'high' obtained from illicit drugs, alleviate withdrawal effects, serve as 'downers' from the effects of stimulant drugs ('uppers') and also produce a 'kick' when taken alone in high doses or injected intravenously. Many illicit benzodiazepine users become dependent and show typical withdrawal symptoms which can be severe [52,53]. The tragedy of recreational benzodiazepine abuse is that it is largely iatrogenic, resulting from widespread overprescription of benzodiazepines which increased their general availability. Major sources of illicit benzodiazepines are from general practitioner prescriptions and thefts from chemists or pharmaceutical warehouses [51]. They are available on the black market [54[•]] and can be obtained on the Internet.

Management of benzodiazepine withdrawal

Because of the adverse effects, lack of efficacy and socio-economic costs of continued benzodiazepine use, long-term users have for many years been advised to withdraw if possible or at least to reduce dosage [5,45[•]]. However, benzodiazepine withdrawal has often been badly managed and has acquired a reputation as a traumatic process for both patients and doctors. This reputation is largely undeserved if the process is carried out judiciously. The management of withdrawal has been reviewed by many authors [1^{••},55–57,58[•]]. All agree that the key strategies for successful discontinuation are gradual dosage tapering and psychological support if necessary.

Dosage reduction

The rate of dosage reduction varies for different types of benzodiazepine patients.

Therapeutic dose users

Benzodiazepine dosage should be tapered gradually since abrupt withdrawal, especially from high doses, can precipitate convulsions, acute psychotic states and other severe reactions (Table 3). The recommended rate of tapering for patients on therapeutic doses of benzodiazepine is withdrawal in steps of about one-eighth to one-tenth of the daily dose every 1–2 weeks [59[•],60]. Over-rapid tapering such as fixed dosage reductions of 25–50% every 1 or 2 weeks or faster, especially in patients taking potent or rapidly eliminated benzodiazepines (Table 4), increases the likelihood of other withdrawal symptoms, dropouts from trials, need for psychological support and later relapse [11^{••},12[•],35]. For this reason, the rate of withdrawal should be individually adjusted to the patient's needs, taking into account factors such as dosage and type of benzodiazepine, reasons for prescription, lifestyle, personality, environmental stresses and amount of available support. Various authors have suggested optimal times of 6–8 weeks for withdrawal but some patients may require a year or more [1^{••},59[•]]. Ideally, after receiving advice and information from the physician and giving full consent, the patient should be in control of his/her own personal reduction rate and proceed at whatever pace is tolerable. A personalized approach is likely to result in fewer patients dropping out or declining to participate in withdrawal trials.

In general practice settings, even minimal intervention such as a letter with an information sheet or a single brief consultation can be effective in reducing or stopping benzodiazepine use without adverse effects. In one

Table 4. Approximate equivalent doses and elimination half-lives of benzodiazepines

Benzodiazepine	Approximately equivalent dosage (mg) ^a	Elimination half-life (h) (active metabolite)
Alprazolam	0.5	6–12
Chlordiazepoxide	25	5–30 (36–200)
Clonazepam	0.5	18–50
Diazepam	10	20–100 (36–200)
Flunitrazepam	1	18–26 (36–200)
Flurazepam	15–30	(40–250)
Loprazolam	1	6–12
Lorazepam	1	10–20
Lormetazepam	1	10–12
Nitrazepam	10	15–38
Oxazepam	20	4–15
Temazepam	20	8–22

^aClinical potency for hypnotic or anxiolytic effects may vary between individuals; equivalent doses are approximate.

controlled study of 191 mainly elderly long-term hypnotic users, within 6 months such measures resulted in significant dosage reduction or complete cessation [9^{••}]. The advice in the letter sent to patients was simply 'try reducing by half a tablet every few weeks'. Those who reduced dosage by 25% or more showed improvement in mental and physical health, reported no withdrawal symptoms or sleep problems, and required fewer medical consultations. In another controlled general practice study, 192 elderly hypnotic users underwent a tapered dosage programme over 8–9 weeks using placebo [8]. Eighty percent had successfully withdrawn by 6 months. These patients showed improvements in cognitive and psychomotor performance and did not differ in sleep or withdrawal symptoms from a control group who continued taking benzodiazepines.

For some patients, particularly those taking benzodiazepines for anxiety or using potent benzodiazepines (lorazepam, alprazolam, clonazepam) (Table 4), there are advantages in conducting the withdrawal by using diazepam. The slow elimination of this drug ensures a gradual fall in blood concentration while its availability in low-dosage forms permits small dosage reductions. Conversion from other benzodiazepines to diazepam can be conducted in stages, and it is important to allow for equivalent potencies between different benzodiazepines (Table 4). Full details and examples of withdrawal schedules from different benzodiazepines at various doses are available on the Internet [57] and other references [1^{••},56,60].

High-dose abusers

A different withdrawal approach is required for high-dose benzodiazepine abusers in whom benzodiazepine use often forms a part of polydrug abuse pattern. These patients may need in-patient detoxification for the primary drug and a fairly rapid withdrawal of the benzodiazepine, with diazepam substitution and tapering over 2–3 weeks being usual [52,53]. The development of convulsions can usually be prevented by moderate doses of diazepam (10 mg), but some authors report benefit from carbamazepine [61,62].

Adjuvant drugs

Many drugs have been investigated for their ability to attenuate benzodiazepine withdrawal symptoms, but none has proved generally useful for patients dependent on therapeutic doses [1^{••}]. Drugs tested include antidepressants [34,63], β -blockers [4], buspirone [64,65], carbamazepine and other anticonvulsants [61,62,66[•]], flumazenil [1^{••},67,68], captodiamine [69[•]], gabapentin [70] and others are under investigation [71,72[•],73[•]]. Nonbenzodiazepine GABA receptor agonists such as zopiclone relieve withdrawal symptoms but are contra-

indicated since they have the same disadvantages as benzodiazepines [74[•]].

Psychological support

The degree of psychological support required during withdrawal is variable and may range from a single brief consultation or letter [9^{••}] to more formal cognitive, behavioural or other therapies directed towards anxiety management and stress-coping strategies [1^{••},56]. Support when needed should be available both during and after withdrawal since patients may remain vulnerable to stress for some months. Information about withdrawal symptoms should be supplied and referral to a support organization is often helpful.

Outcome of withdrawal

With carefully managed withdrawal and adequate psychological support in motivated patients, the success rate for stopping benzodiazepines can be 70–80% [8,13,34,35]. Successful cessation need not be affected by duration of use, type or dosage of benzodiazepines, severity of symptoms, psychiatric history or personality disorder, although symptom severity is greater in anxious individuals [13,32,33,65]. Relapse rates 1–5 years after withdrawal vary between 8 and 57% in different studies [8,11^{••},13,34,75] but are probably minimized by using individualized withdrawal programmes. Some patients revert temporarily to benzodiazepine use after withdrawal but most stop again or considerably reduce dosage [34,75].

Conclusion

Prevention of benzodiazepine dependence can be achieved by adherence to official recommendations to limit prescriptions to short-term use (2–4 weeks), or as intermittent brief courses or occasional doses [5,6]. Although prescribing of benzodiazepines has declined substantially since 1988, 30% of GP prescriptions in the UK are still for 56 or more tablets [45[•]] and many physicians in Europe, the US and Australia continue to prescribe them long term. Particular care should be taken in prescribing benzodiazepines for vulnerable patients such as those with alcohol or drug dependence, and doctors should be aware that prescriptions may enter the illicit market. Benzodiazepines are not indicated for long-term treatment of depression and when used for chronic psychiatric conditions such as schizophrenia, bipolar affective disorder, anxiety disorders and chronic insomnia, clinicians should examine the risk–benefit ratio at an early stage so that the risks of dependence can be balanced against any therapeutic benefits [76–79,80[•]]. Finally, doctors should avoid using nonbenzodiazepine hypnotics and anxiolytics such as zopiclone, zolpidem and zaleplon in benzodiazepine-dependent patients since these drugs can also cause dependence and abuse.

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