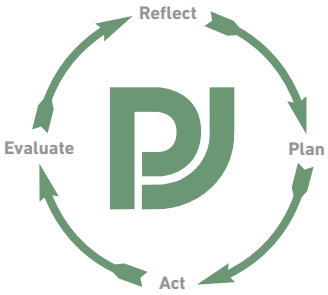
Dependence on benzodiazepines or Z-drugs: having that conversation

Many patients take benzodiazepines or Z-drugs for longer than recommended. Do you have the background information to explain the benefits of reviewing treatment?

GRAHAM PARSONS *DIPCOMMPHARM, BPHARM, PRESCRIBER WITHIN THE PLYMOUTH SPECIALIST ADDICTION SERVICE AND MEDICINES MANAGEMENT PHARMACIST SPECIALISING IN SUBSTANCE MISUSE, NHS DEVON, PLYMOUTH AND TORBAY WESTERN LOCALITY*

DIANE DIEDERICH/ISTOCKPHOTO.COM



REFLECT

1 Read the scenario in the Panel below. What advice would you give to this patient?
2 How is dependence on benzodiazepines or Z-drugs defined?
3 How is dependency treated and what are the benefits?

Before reading on, think about how this article may help you to do your job better.

BENZODIAZEPINES were introduced in the 1960s as a tranquilliser that would reduce barbiturate-related deaths. Their use increased dramatically during the 60s and 70s and by 1975 sales of benzodiazepines accounted for about 10 per cent of all prescriptions in the US.[1]

In the UK about 15 per cent of all prescriptions in the latter part of the 20th century were reported to be for hypnotics and anxiolytics but since then the use of benzodiazepines has fallen by about 35 per cent.[2]

Z-drugs (zaleplon, zolpidem and zopiclone) were introduced in the 1980s for the treatment of insomnia and with the aim of overcoming some of the disadvantages of benzodiazepines, namely, next day sedation ("hangover effect"), dependence and withdrawal syndrome.[3] Some reports have suggested that GPs favour them as safer and more effective than benzodiazepines.[2] From 1991 to 2009 dispensing trends suggest that a large proportion of the hypnotic benzodiazepine prescribing switched to Z-drug prescribing, with the latter overtaking the former in 2006.[2]

Having that conversation

There were over 10.5 million prescriptions dispensed for benzodiazepines in England in 2009 and over 5.7 million prescriptions for Z-drugs. The same report calculated that most prescriptions dispensed between 1991 and 2009 were repeat prescriptions (benzodiazepines 93.9 per cent and Z-drugs 84.8 per cent).[2]

Pharmacists are in an ideal position to support patients in recovery from benzodiazepine and Z-drug dependency and this article should give readers the background information they need to do so. However, how can pharmacists open a conversation about the issue and how can they encourage patients to think about coming off these drugs? You might consider, when issuing repeat prescriptions, letting patients know that these medicines are recommended for short-term use only. It may also be helpful to educate patients of the risks of long-term use and the benefits of stopping. Panel 1 contains suggested points.

Pharmacists can use medicines use reviews as well as opportunistic discussions when medicines are handed out to patients to broach the subject and provide brief advice. Look out for patients who are taking other anti-anxiety medicines or who self-declare issues that may be related to the benzodiazepine or Z-drug use, such as morning sedation or falls.

SCENARIO

John, aged 58 years, has been a patient at your pharmacy for five years. He has been taking zopiclone (7.5mg at night) for three years, following the death of his father, and lorazepam 1mg twice a day for 15 years, following a period of severe anxiety. During a medicines use review he says he is fed up of having to take tablets to manage his life and wants to know about stopping these medicines.

Mechanisms

Benzodiazepines work by enhancing the transmission of the

inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the central nervous system. This "damping down" of the central nervous system results in a hypnotic, anxiolytic, anticonvulsant and muscle relaxant action.

The BNF categorises benzodiazepines as either hypnotic or anxiolytic. In general, hypnotic agents are used for the treatment of short-term insomnia and have shorter half-lives to reduce the risk of morning sedation. Examples include lormetazepam and temazepam. Anxiolytics used for the short-term treatment of anxiety often have longer half-lives than the hypnotic benzodiazepines. Examples include alprazolam and chlordiazepoxide. Panel 2 gives some examples of long-, intermediate- and short-acting benzodiazepines.

Z-drugs are known as non-benzodiazepine hypnotics. They exert an agonist effect at the GABA receptor complex, "damping down" the CNS in a similar manner to benzodiazepines. However, their elimination half-lives of between one and 6.5 hours has been promoted as an advantage because this limits hangover effects. The Z-drugs are licensed for the short-term treatment of insomnia only.

Adverse effects

The adverse effects of benzodiazepines and Z-drugs are well documented. The main side effects of benzodiazepines are:

- Drowsiness and light headiness that can persist the next day
- Confusion and ataxia (particularly in the elderly)
- Amnesia
- Paradoxical increase in aggression
- Muscle weakness

The main side effects of Z-drugs include:

- Taste disturbance (zopiclone only)
- Dizziness
- Drowsiness
- Amnesia
- Confusion
- Light-headiness
- Paradoxical effects
- Nausea

The latest edition of the BNF and summaries of product characteristics contain more comprehensive information.

The long-term effects of benzodiazepines and Z-drugs merit further consideration because an understanding of these is critical when discussing the benefits and disadvantages of reducing and stopping the drug.

Long-term negative effects include:

- Failure to manage the underlying emotional disorder (eg, grief or anxiety)
- Increased anxiety (Anxiety can be reduced in 40 to 60 per cent of long-term users when the benzodiazepine is stopped.)
- Over-sedation, especially in the elderly, which may contribute to falls and fractures
- Long-term cognitive effects (Moderate to large deficits in all 12 cognitive domains have been demonstrated in long-term benzodiazepine users compared with controls. These have been shown to improve following withdrawal of the benzodiazepine.)
- Emotional blunting (Long-term benzodiazepine use can inhibit arousal, resulting in individuals being unable to feel normal emotional highs and lows.)
- Agoraphobia

A recent matched cohort survival analysis in *BMJ Open* has also indicated a greater than threefold increase in the hazards of death with prescriptions for hypnotics and a small increase in the risk of cancer where more than 132 hypnotic pills were taken each year (HR=1.35, 95 per cent CI 1.18 to 1.55).[4]

The major factor predicting the risk of abuse of an individual benzodiazepine is its speed of onset. Rapid onset drugs (eg, diazepam) provide faster positive subjective effects compared with those with a slower onset of action (eg, oxazepam) so are more likely to be abused.

Although prescribing should not exceed two to four weeks, the minimum time needed to become dependent and experience withdrawal syndrome (see below) is less well defined.

Dependency

Benzodiazepine dependency is a well established phenomenon. Studies in the early 1960s confirmed the potential of these drugs to cause a physical dependence state when given in high doses for several weeks.[1] This initial work was supported by case reports in the medical literature. In 1980, the Committee on the Review of Medicines looked at the evidence on long-term benzodiazepine use. It concluded that there was a low risk of dependence on these agents although there was "little evidence" for the efficacy of benzodiazepines for the treatment of anxiety after four months.[5]

However, following this review, the number of publications on benzodiazepines and their adverse effects rose substantially. Interest in the media and a large scale legal action brought against Wyeth and Roche in 1986 led to the Committee on Safety of Medicine (CSM) reviewing the risk of dependence and withdrawal from benzodiazepines in 1988. They concluded that dependence and withdrawal symptoms did occur and recommended that:[6]

- Benzodiazepines should be used for two to four weeks only
- Benzodiazepines should not be used for mild anxiety or insomnia
- The lowest dose to control symptoms should be used
- Treatment should be tapered off gradually

These recommendations are still relevant today.

Zaleplon should be used for up to two weeks only, compared with four weeks for the two other Z-drugs. Evidence for Z-drug dependency is less well established. A review by Reed *et al*[2] found increasing reports of misuse (eg, intoxication or regular excessive consumption) but prevalence in the UK could not be determined from the data.

The manufacturers of all three Z-drugs warn of tolerance, dependence and withdrawal symptoms, and the National Institute for Health and Clinical Excellence has said that "use of these agents for extended periods is associated with increased likelihood of dependence".[3] Yet some commentators have argued that the abuse potential of Z-drugs is lower than with benzodiazepines, based on early warning systems from other countries and their different pharmacological profile — patients report less of a buzz, rush or high, and generally do not experience desirable dopey

PANEL 1: PATIENT EDUCATION*

- Benzodiazepines and Z-drugs are not the long-term answer to anxiety or insomnia.
- Studies have shown that long-term benzodiazepine use can impair memory and mental function and that memory and mental function improved when benzodiazepines were stopped. Use in people over the age of 65 years has been linked to a 50 per cent increase in risk of dementia within 15 years.[11]
- Long-term benzodiazepine use has been linked with an increased risk of car crashes.
- Studies indicate that long-term benzodiazepine use is related to an increased risk of hip fractures in older people.
- Coming off benzodiazepines will increase your levels of alertness and vitality and improve your physical and social functioning.
- A study has found that stopping treatment has no long-term adverse effects on sleeping or anxiety symptoms.

*These points have been adapted from an information leaflet "Stopping benzodiazepines and Z-drugs", available from Patient.co.uk. This may be printed off and supplied to patients.

The author will be available to answer questions on this topic until 29 October 2012

Ask the expert

www.pjonline.com/expert

KEY POINTS

- Benzodiazepine and Z-drug prescribing should not exceed four weeks.
- Rapid onset drugs (eg, diazepam) are more likely to be abused than slower onset drugs (eg, oxazepam).
- It is argued that the abuse potential of Z-drugs is lower than benzodiazepines
- Long-term benzodiazepines should not be stopped suddenly — the withdrawal syndrome can be severe. A treatment plan for withdrawal is needed.
- Benefits of stopping long-term benzodiazepines include improved memory and mental function and physical and social functioning.

feelings or sedation on drug onset.[7] Nevertheless, treatment protocols for dependency remain similar for the benzodiazepines and Z-drugs (see later).

For short-term treatment of insomnia in patients over 55 years melatonin may be an option.

Is the patient dependent?

Addiction to benzodiazepines and Z-drugs is defined in the same way as addiction to any other drug using the International Classification of Disease 10th Edition (ICD-10). A diagnosis of dependency is met if a patient has experienced at least three of the six criteria in Panel 3 in the past 12 months. There are two drug-related criteria, two consequences of use criteria and two physiological criteria.

Neither controlled use of a therapeutic dose nor binge use of high doses constitutes dependence per se but patients seeking help to manage either of these issues should be provided with an appropriate treatment plan to support them (see later).

The benzodiazepine withdrawal state is a well defined set of symptoms (see Figure 1). It has been estimated that long-term use can result in withdrawal symptoms in 30–45 per cent of users and this can occur after three to six weeks of therapeutic doses. The severity of the syndrome can range from mild and short-lived to severe and protracted, lasting for six to 12 months or more before gradually reducing. This can occur in up to 15 per cent of patients who come off benzodiazepines.

The risks of symptoms occurring have been shown to increase if there are any of the following factors:

- Use for over four months
- High doses (ie, greater than therapeutic doses)
- Use of high-potency benzodiazepines with a short or intermediate half-life (eg, lorazepam)
- Chronic psychiatric and personality problems
- Chronic physical health problems
- A history of current or past alcohol or other sedative-hypnotic dependence, or a family history of these

PANEL 2: DURATIONS OF ACTION

Long-acting benzodiazepines	Intermediate-acting benzodiazepines	Short-acting benzodiazepines
Chlordiazepoxide*	Nitrazepam†	Lorazepam‡ǀ
Clobazam*		Lormetazepam†
Diazepam‡		Oxazepam*
Flurazepam†		Temazepam†

*Indicated for anxiety; † Indicated for insomnia; ‡ Indicated for anxiety or insomnia

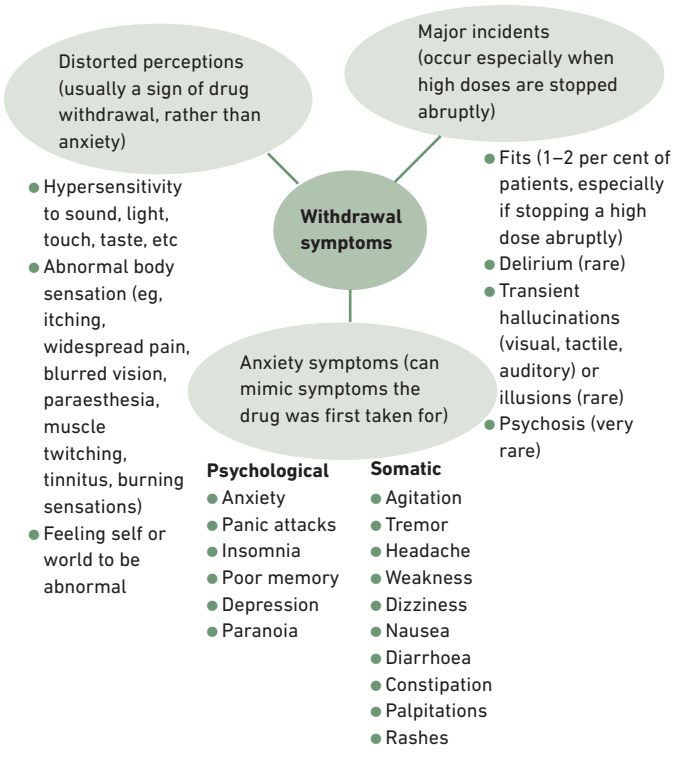


Figure 1: Symptoms of withdrawal from benzodiazepines

PANEL 3: CRITERIA FOR DEPENDENCY

- Compulsion or cravings to take benzodiazepines or Z-drugs
- Difficulties in controlling benzodiazepine or Z-drug use
- Progressive neglect of alternative pleasures or interests due to benzodiazepine or Z-drug use
- Persistent benzodiazepine or Z-drug use despite harmful consequences
- Characteristic benzodiazepine or Z-drug withdrawal state
- Evidence of tolerance to benzodiazepines or Z-drugs

Resources

- Sleep hygiene advice can be found in a previous CPD article "Insomnia and its management", available on PJ Online.
- There is a wealth of information for both patients and healthcare professionals on benzodiazepine addiction, withdrawal and recovery at www.benzo.org.uk.

Treatment of dependency

Once dependency has been established and the patient has consented to treatment, a treatment plan can be agreed for withdrawal. The outcome is to minimise the impact of withdrawal symptoms and support the patient in his or her recovery with a package of care that provides psycho-social support in addition to pharmacological support. It is vital that patients develop effective therapeutic relationships with all healthcare professionals involved in their care and are actively involved in developing their care plans.

The conventional treatment plan outlined in the BNF[6] is to:

1. Convert patients to an equivalent dose of diazepam preferably taken at night (see Panel 4). The long half-life of diazepam provides a smooth withdrawal profile and its multiple strengths and formulations (tablets and liquid) allow clinicians and patients to establish a flexible plan. Taking the dose at night reduces the risk of next-day sedation.
2. Reduce the dose by an eighth every two to three weeks and if symptoms occur, maintain the dose until they improve. This allows a controlled reduction and opportunities for review and reflection if withdrawal symptoms emerge.
3. Reduce the dose further in smaller steps — it is better to reduce slowly rather than too quickly.
4. Stop completely (Note that the period needed for withdrawal can vary from about four weeks to a year or more.)

However, there are some caveats to these recommendations. Dose conversion information should be considered as a guide only, due to inter-patient variability, and switching should be carried out cautiously and in a step-wise manner. In addition, the dose reduction should always be tailored to the individual and

agreed — no patient should be pressured into a reduction, especially if he or she has developed an iatrogenic dependency (as opposed to illicit use). A patient taking diazepam for one year at a therapeutic dose may require a different approach from someone taking supratherapeutic doses for 10 years and who has a complex psychiatric history. Some patients may also want to reduce using the current benzodiazepine or Z-drug they are taking.

In a review of the evidence this year, the British Association of Psychopharmacology states that switching from a short half-life benzodiazepine to a long half-life benzodiazepine before gradual dose tapering does not receive much support in the literature.[10] Nevertheless, it accepts that this may be an appropriate strategy if problematic withdrawal symptoms occur.

Alternatives to diazepam may also not have the dosage form flexibilities to formulate a suitable community detoxification programme . For example, lorazepam 1mg (equivalent to 10mg diazepam) is only available as 1mg or 2.5mg tablet or 4mg/ml (1ml ampoule) injection. The BAP approach is also supported by Prodigy's information on benzodiazepine and Z-drug withdrawal.[9]

It is also of vital importance that the clinician establishes the primary reason for taking the benzodiazepine or Z-drug and that the re-emergence of this or any secondary problems are recognised and a plan for their management established. This should include non-pharmacological management strategies such as:

- Psycho-education to ensure the patient is aware of the issues of long-term benzodiazepine or Z-drug use, understands how the withdrawal plan will progress and what he or she might expect during the process, and knows how to manage these withdrawals (eg, relaxation techniques) and whom to contact for support
- Additional psychological therapies (eg, group cognitive behavioural therapy has been shown to increase cessation rates compared with both routine care [OR=3.38, CI 1.86-6.12] and gradual dose reduction alone [OR=1.82, CI 1.25-2.67])[10]
- Advice on sleep hygiene rather than more pharmacotherapy is recommended as the best approach for people with insomnia during withdrawal of a misused substance[10] (see Resources, p401)
- Support for self-care, which may include details of self-help groups in the locality or nationally (see Signposting)

Additional pharmacotherapies should not routinely be prescribed and show no benefit over gradual dose reduction alone in a meta-analysis (OR=1.3, CI=0.97–1.73).[10] However, if depression emerges or co-exists with the withdrawal symptoms the clinician should consider suspending the withdrawal and managing the depression in line with current guidelines.[9]

Advice you can give

With reference to the Scenario, (p399), John has affirmed that he would like to reduce or stop his benzodiazepine and Z-drug use but he should be advised not to stop his medicines suddenly due to the risk of significant withdrawal effects, including seizures. He may initially be supported with some information and literature on stopping benzodiazepines. Both Battle Against Tranquillisers and the Council for Involuntary Tranquilliser Addiction (see Signposting) provide information for patients considering benzodiazepine or Z-drug withdrawal. He should be encouraged to see his GP to discuss his concerns and so that his full medical history can be considered before any community detoxification programme is started. If the GP does not think he or she can manage this programme he or she may want to seek advice from a local specialist prescribing service for support or refer John directly. This service can also be useful for community pharmacists because it should be able to supply further information on referral pathways and networks for patients seeking support.

Helpful tips you can give patients like John include waiting until any crisis has passed and stress levels are as low as possible, starting withdrawal while on holiday (away from pressures) and consider telling family or friends so they can give him encouragement and support during his community detoxification.

In John's case it would be advisable for the GP or clinic to convert his medicines to 25mg diazepam considering that he is taking both a benzodiazepine and a Z-drug and to devise a schedule of reduction that John is comfortable with. He should be supplied with local and national support network s and could be signposted to local groups to support his recovery from his anxiety disorder. His GP or clinic may also wish to refer John to the local Improving Access to Psychological Treatments (IAPT) service for some further psychological treatments.

John will probably be collecting prescriptions from the pharmacy regularly during this withdrawal programme and the pharmacy team should give him plenty of practical support and positive affirmation during this period.

Signposting

- Battle Against Tranquillisers (www.bataid.org) is a registered charity offering a range of support and educational services. These are available to users of tranquillisers and sleeping pills.
- The Council for Involuntary Tranquilliser Addiction (CITA; www.citawithdrawal.org.uk) is a charity providing support and information for individuals, families, friends and professional advisors dealing with prescribed tranquillisers, sleeping tablets, and antidepressants.

References available online

PANEL 4: DOSE EQUIVALENTS 5MG DIAZEPAM

Benzodiazepine	BNF equivalent	Prodigy equivalent dose[9]
Alprazolam		0.25mg
Chlordiazepoxide	15mg	
Clobazam		10mg
Flurazepam		15mg
Loprazolam	0.5mg (to 1mg)	
Lorazepam		0.5mg
Lormetazepam	0.5mg (to 1mg)	
Nitrazepam	5mg	
Oxazepam	15mg	
Temazepam	10mg	
Zaleplon	10mg	
Zolpidem	10mg	
Zopiclone	7.5mg	

Available online until 12 November 2012

Check your learning

www.pjonline.com/expert

PRACTICE POINTS

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist's CPD portfolio.

1. Ask about side effects of benzodiazepines in medicines use reviews.
2. Highlight the benefits of stopping benzodiazepines to patients with repeat prescriptions.
3. Advise patients newly prescribed Z-drugs or benzodiazepines for insomnia that it is best to have some nights when they do not take a tablet, not to use the tablets for more than two weeks and that using more tablets than this can make them less effective and can result in dependence.

Consider making this activity one of your nine CPD entries.