Benzodiazepine Dependence

The first benzodiazepine was marketed in 1959. It was described as a ‘minor tranquilliser’ and an alternative to barbiturates. Benzodiazepines act by enhancing the effect of gamma-aminobutyric acid on the GABA-A receptor, thereby resulting in CNS depression. They are anxiolytic, hypnotic, anticonvulsant and muscle relaxants. They also cause psychomotor retardation.

They are useful in the short term. They are indicated for short-term relief (2-4 weeks maximum) of insomnia or anxiety where it is severe, disabling or causing unacceptable distress. [1] Specific benzodiazepines are also used for prolonged seizures, some forms of epilepsy, palliative care, surgery and withdrawal from alcohol. However, long-term use (possibly even after a few weeks) is associated with dependence, tolerance and withdrawal syndrome.

Following advice from the Committee on Safety of Medicines (CSM) in 1988, the overall prescribing of benzodiazepines has markedly reduced. [2] Since this time the recommendation for duration of use has been 2-4 weeks. [3] Recreational use of benzodiazepines is also an increasing problem. Statistics from the Health and Social Care Information Centre (HSCIC) for England in 2013 suggest they represent 1% of drugs used as adjuncts to drugs of primary dependence in the UK. [4] As drugs of abuse, they are mainly used to augment a “high” experienced from another drug, or alleviate the negative effects. [5]

Good practice for prescribing benzodiazepines [1, 6]

- Do not prescribe benzodiazepines in someone with a history of drug misuse and dependence.
- Prescribe the lowest possible doses of benzodiazepines and only prescribe for 2-4 weeks. It is important to remember that patients can get withdrawal symptoms between doses if they are given short-acting benzodiazepines.
- Use the lowest dose which will control the symptoms, for the shortest possible time.
- Use only for severe or disabling anxiety or insomnia.
- Use of benzodiazepines for short-term mild anxiety is inappropriate. National Institute for Health and Care Excellence (NICE) guidelines state a benzodiazepine should not be used for treatment of generalised anxiety disorder. [7, 8]
- Where used as a hypnotic, advise intermittent use if possible.
- Taper off gradually when stopping benzodiazepines.
- Where possible, use alternatives to benzodiazepines, such as non-pharmacological strategies, and medication with less risk of dependence. See the separate articles Insomnia and Generalised Anxiety Disorder for options.
- Advise patients of the risk of dependence and impaired reaction times. Advise that this may affect ability to drive or operate machinery. Also advise that effects of alcohol may be exacerbated.
- Elderly patients are particularly prone to adverse effects of benzodiazepines and, therefore, there is a need to be even more cautious when prescribing.
- Be aware that benzodiazepines cross the placenta, and may lead to neonatal side-effects. [9]

Definitions of problems related to use of benzodiazepines [10, 11]

The ICD-10, maintained by the World Health Organization (WHO) - has the following classifications/definitions:

Harmful use
A pattern of psychoactive substance use that is causing damage to the mental or physical health of the user.
Dependence
A cluster of physiological, behavioural, and cognitive phenomena as manifested by three (or more) of the following, occurring within a 12-month period:

- A strong desire or sense of compulsion to take benzodiazepines.
- Difficulties in controlling benzodiazepine consumption in terms of its onset, termination, or levels of use.
- A physiological withdrawal when benzodiazepines use has ceased or has been reduced.
- Evidence of tolerance, such that increased doses of benzodiazepines are required in order to achieve effects originally produced by lower doses.
- Progressive neglect of alternative pleasures or interests because of benzodiazepine use, increased amount of time necessary to obtain or take the substance or to recover from its effects.
- Persisting with benzodiazepine use despite clear evidence of overtly harmful consequences.

Withdrawal state
A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a substance after repeated, and usually prolonged and/or high-dose, use of that substance. Onset and course of the withdrawal state are time-limited and are related to the type of substance and the dose being used immediately before abstinence. The withdrawal state may be complicated by convulsions.

Unintentional abuse or dependence may occur when individuals start taking a benzodiazepine appropriately for a diagnosed disorder, but end up taking them for longer or in higher doses than intended. The condition for which they were originally prescribed may have settled, but they continue to take the benzodiazepine to prevent withdrawal effects, or for other perceived benefits.

Reasons for stopping benzodiazepines\textsuperscript{[2]}

- Tolerance develops so they are no longer effective for the condition for which they were prescribed.
- Dependence may develop, so that stopping will result in withdrawal symptoms, and the end result is long-term continuation in order to avoid withdrawal syndromes.
- Prevention of adverse effects such as cognitive and psychomotor impairment, depression, irritability, loss of concentration and emotional blunting.
- Reduce risk of falls in the elderly.
- Reduce risk of accidents while driving.
- Avoid potential interaction with other medication and with alcohol.

Possible outcomes on stopping benzodiazepines\textsuperscript{[1]}

- Recurrence of original disorder.
- Rebound symptoms - last a few days.
- Withdrawal syndrome:
  - Common symptoms: increased anxiety, tremor, irritability, restlessness, depression, dizziness, sweating, insomnia, nightmares, abdominal pain, tachycardia and hypertension (usually mild).
  - Serious symptoms: seizures, delirium, confusion. Usually due to abrupt withdrawal.
  - Other symptoms: anorexia, nausea, tinnitus, excessive sensitivity to light and sound, depersonalisation and derealisation.

Management of benzodiazepine dependence\textsuperscript{[2, 12]}

Assessment

- Is this the right time to start a withdrawal programme? It is less likely to be effective if there are significant stresses, social problems, medical problems, etc.
- Does the person wish to stop using benzodiazepines or reduce the dose? Motivation will increase the chances of success, and whether the person wishes to stop or not will guide the management plan.
- Has the problem for which the benzodiazepine was originally used resolved? If there are still symptoms of anxiety, insomnia or depression, these should be addressed prior to attempting to withdraw from benzodiazepines.
- Are they using benzodiazepines regularly? Have there been symptoms when the benzodiazepines are reduced or stopped? Do they fit the ICD-10 criteria for dependence or harmful use?
- Is there comorbidity? For example, those with concurrent substance abuse, significant psychiatric illness or serious medical illness may require input from specialists in those fields. It may not be possible in these cases to manage withdrawal in primary care.
- Assess which category the person fits:
  - "Therapeutic" dose users: those on long-term benzodiazepines at therapeutic doses, usually initially prescribed for insomnia or anxiety.
  - Those who misuse their prescription or obtain medication in other ways. This group tends to use high doses and may also abuse other substances.

Management of benzodiazepine dependence in "therapeutic" users who wish to stop

- Only make a diagnosis of dependence if the patient fits the above criteria.
- Begin with advisory letters and patient information. Minimal motivational interventions by GPs, such as a single consultation, or writing a letter, have been found to be effective.\textsuperscript{[13]}
Try consultation with GP and practice nurse; provide education on why benzodiazepines are harmful when used chronically. Explain the difficulties that may arise with continued prescribing.

Gradual dose reduction:
- Tailor the regime to the needs of the patient. Negotiate a schedule which is flexible. Adjust the withdrawal rate if necessary, depending on severity of symptoms.
- Withdrawal may take three months to a year.
- Some but not all may benefit from switching to a longer-acting benzodiazepine (diazepam) before reducing the dose. Longer-acting benzodiazepines are less likely to produce rapid onset of withdrawal symptoms. This may sometimes be useful for those on short-acting potent benzodiazepines such as lorazepam and alprazolam, or those preparations which do not allow for small changes in dose. Use the benzodiazepine conversion equivalence table below.
- Gradually reduce the dose. Several examples of regimes that can be used are given by NICE Clinical Knowledge Summaries (CKS). [2]
- Have regular contact and consider only prescribing for a week at a time.

Other psychological therapies - consider in all patients - eg, cognitive behavioural therapy and supportive therapies. Success rates have been shown to be higher in those receiving additional psychological therapies. [14] Relaxation techniques may also be helpful.

Adjunct medication is not usually recommended but in some cases may be necessary:
- Propranolol may be used to help with symptoms of anxiety where other measures fail.
- Antidepressants - only appropriate if depression and/or panic disorder develop during withdrawal.
- Melatonin occasionally has a role for those with insomnia.
- Short-term flumazenil infusions (used in severe cases). [15, 16]

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Dose equivalent to diazepam 5 mg</th>
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<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>15 mg</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>5 mg</td>
</tr>
<tr>
<td>Temazepam</td>
<td>10 mg</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Clobazam</td>
<td>10 mg</td>
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<tr>
<td>Loprazolam</td>
<td>0.5-1 mg</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>0.5-1 mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

Management of benzodiazepine dependence in those who do not wish to stop
- Do not put pressure on a person to stop if they do not wish to do so. Discuss their concerns.
- Explain and reassure where possible. Tell them the reduction regime can be adjusted to a rate which suits them.
- Explain the benefits of stopping benzodiazepines.
- Review and reassess motivation at a later date.
- Consider compromising on a small reduction in dose. If there are no ill effects from this reduction, this may help to allay fears.

Management of benzodiazepine dependence in illicit or high-dose users
- Does the patient abuse other drugs - eg, alcohol, cannabis, opiates? Drug screens may be appropriate.
- Educate the patient - cover the problems with abusing benzodiazepines, offer support and assistance, advise them on methods available to stop abusing benzodiazepines - eg, graded reduction.
- Alternative therapy, such as cognitive behavioural therapy (CBT) or relaxation therapy may be offered for their insomnia.
- If the patient agrees to reduce benzodiazepines then a signed contract may help them to commit.
- There is no need to match self-reported high doses used illicitly. Doses greater than the equivalent of diazepam 30 mg per day should rarely be prescribed. [17]
- This is often a situation better managed by specialist substance abuse teams than in primary care.
- Carbamazepine is sometimes used to manage withdrawal symptoms in specialist units.
• Regular follow-up: this will be based on how each individual patient does. If the patient is developing withdrawal symptoms frequently then they will need to be seen more often. Otherwise, review weekly as the dose of benzodiazepine is tapered.

Further reading & references

- The Ashton Manual Supplement; benzoz.org.uk, 2011

1. British National Formulary
2. Benzodiazepine and z-drug withdrawal; NICE CKS, July 2013 (UK access only)
3. Drug Safety Update: Addiction to benzodiazepines and codeine; Medicines and Healthcare products Regulatory Agency (MHRA), July 2011
4. ONS Statistics on Drug Misuse: England 2013; Health and Social Care Information Centre
7. Generalised anxiety disorder and panic disorder in adults: management; NICE Clinical Guideline (January 2011)
8. Anxiety disorders; NICE Quality Standards, Feb 2014
10. Darker CD, Sweeney BP, Barry JM, Farrell MF; Psychosocial interventions for benzodiazepine harmful use, abuse or dependence (Protocol). Cochrane Database of Systematic Reviews 2012
11. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines; F10-F19 Mental and behavioural disorders due to psychoactive substance use. World Health Organization