Benzodiazepine and z-drug withdrawal

Last revised in April 2015

Changes

Last revised in April 2015

**April 2015** — minor update. Update to the text to reflect a new law on drugs and impaired driving [Department for Transport, 2014 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

**July 2013** — reviewed. A literature search was conducted in May 2013 to identify evidence-based guidelines, UK policy, systematic reviews, and key RCTs published since the last revision of this topic. No major changes to recommendations have been made.

Previous changes

**February 2013** — minor update. The 2013 QIPP options for local implementation have been added to this topic [NICE, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

**August 2011** — minor update. Updates the information on the frequency of prescribing of benzodiazepines and z-drugs, based on an MHRA update [MHRA, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)], and a publication commissioned by the Department of Health [National Addiction Centre et al. 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]. Also a new node has been added to background information (Definition (/benzodiazepine-and-z-drug-withdrawal#backgroundsub)). Issued in September 2011.

**March 2009** — minor amendment to wording in the section on Driving (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:7). Issued in April 2009.

**November 2008 to March 2009** — converted from CKS guidance to CKS topic structure. The evidence-base has been reviewed in detail, and recommendations are more clearly justified and transparently linked to the supporting evidence. There are no major changes to the recommendations.


This guidance has been reviewed and updated following a full literature review. The scope of the guidance has changed. It now covers the assessment of a person who is being prescribed long-term benzodiazepines or z-drugs and offers advice on how to withdraw them from these treatments, and no longer covers withdrawal from illicit benzodiazepine use. Several new management sections have now been included, such as how to support the person during and after withdrawal, and how to manage someone who does not want to stop benzodiazepines or z-drugs. A more detailed evidence section to support the recommendations has been included. The guidance title has changed from Hypnotic or anxiolytic dependence to Benzodiazepine and z-drug withdrawal.
Update

New evidence

Evidence-based guidelines
No new evidence-based guidelines since 1 May 2013.

HTAs (Health Technology Assessments)
No new HTAs since 1 May 2013.

Economic appraisals
No new economic appraisals relevant to England since 1 May 2013.

Systematic reviews and meta-analyses
Systematic reviews published since the last revision of this topic:


Primary evidence
No new randomized controlled trials published in the major journals since 1 May 2013.

New policies
No new national policies or guidelines since 1 May 2013.

New safety alerts
No new safety alerts since 1 May 2013.

Changes in product availability
No changes in product availability since 1 May 2013.

Goals

- To assess suitability for benzodiazepine or z-drug withdrawal
- To manage benzodiazepine or z-drug withdrawal, including switching to diazepam
- To manage withdrawal symptoms
- To provide appropriate advice to people wishing to withdraw from these drugs

QIPP - Options for local implementation

- Hypnotics:
  - Review and, where appropriate, revise prescribing of hypnotics to ensure that it is line with national guidance.
Definition

What are benzodiazepines and z-drugs?

- **Benzodiazepines** are gamma-aminobutyric acid (GABA) receptor agonists which have hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties [National Addiction Centre et al., 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]. The British National Formulary groups benzodiazepines into hypnotics and anxiolytics [BNF, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].
  - **Hypnotics** are used for short term treatment of insomnia and include nitrazepam, loprazolam, lormetazolam, and temazepam.
  - **Anxiolytics** are effective in alleviating anxiety states and include chlordiazepoxide, diazepam, lorazepam, and oxazepam.
  - Some anxiolytics may have other indications, for example [BNF, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]:
    - Diazepam can also be prescribed as an adjunct in acute alcohol withdrawal, status epilepticus, and insomnia.
    - Oxazepam and lorazepam can also be prescribed for insomnia.
  - **Z-drugs** are non-benzodiazepine hypnotics, developed with the intention of overcoming some of the adverse effects of benzodiazepines (such as next-day sedation, dependence and withdrawal), but there is no firm evidence of differences in the effect of z-drugs and shorter-acting benzodiazepines. Like benzodiazepines, they are also GABA receptor agonists.
    - The three z-drugs available in the UK are zaleplon, zolpidem and zopiclone.

[National Addiction Centre et al., 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Frequency of prescribing

How commonly are benzodiazepines and z-drugs prescribed?

- Despite warnings regarding the long-term use of benzodiazepines (/benzodiazepine-and-z-drug-withdrawal#background) or z-drugs (/benzodiazepine-and-z-drug-withdrawal#background), millions of prescriptions are still issued for these drugs in primary care each year [National Addiction Centre et al., 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]. Of concern, 56% of prescriptions for the three most commonly prescribed benzodiazepines were for people older than 65 years of age [DH, 2004 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

However, dispensing data for benzodiazepines show:
- An overall substantial decrease in dispensing of benzodiazepines in England from 1991 to 2009. This is mostly accounted for by the decrease in dispensing of hypnotic benzodiazepines.
- An overall increase in dispensing of anxiolytic benzodiazepines in England from 1991 to 2009. However, this increase was less marked than the total decrease in all benzodiazepine dispensing in that period.
  - There was a small decrease in anxiolytic benzodiazepine dispensing between 2004 and 2006, but this could have been due to the publication of the NICE clinical guidelines on anxiety in 2004.
- An overall trend of decreasing benzodiazepine dispensing from 1980 to 1990, which when combined to the data above, shows a 51.3% decrease in total benzodiazepine dispensing.
  - The 1980 to 1990 data was noted separately due to differences in data collection over this decade, limiting the comparability with the 1991 to 2009 figures.

Dispensing data for z-drugs show:
- An increase in the dispensing of z-drugs in England from 1991 to 2009.
  - This increase does not mirror nor proportionally reflect the decrease in hypnotic benzodiazepine dispensing.
  - This increase could have been due to people being switched from hypnotic benzodiazepines to z-drugs.
  - A decrease in total hypnotic dispensing (z-drugs and benzodiazepines) in England from 1991 to 2009.
- Although dispensing and prescribing are not directly comparable, the data above are still a useful indication of the frequency of prescribing.

[MHRA, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); National Addiction Centre et al., 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]

Reasons for stopping

Why should people on long-term benzodiazepines or z-drugs be advised to stop?

- **People on long-term benzodiazepines or z-drugs should be advised to stop because** [Ashton, 2005 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]:
  - **Tolerance to these drugs progressively reduces their effectiveness for the treatment of insomnia or anxiety.**
    - Tolerance to the hypnotic effects of benzodiazepine may be rapid, and may occur within a few days or weeks of regular use.
    - Tolerance to the anxiolytic effects is slower and appears over a few months of use.
    - In contrast, little tolerance develops to the amnesic effects or other cognitive impairments caused by benzodiazepines.
  - **Dependence may develop, and continuing treatment may serve only to prevent withdrawal symptoms.**
Dependence is more likely to develop with long-term use, high doses, more potent or shorter-acting benzodiazepines, and a history of anxiety problems. The severity of withdrawal symptoms will depend on the degree of dependence.

Common withdrawal symptoms include insomnia, anxiety, irritability, restlessness, agitation, depression, tremor, panic attacks, dizziness, and perceptual disturbances (for example hypersensitivity to physical, visual, and auditory stimuli).

Less common, but more medicinally serious, withdrawal symptoms include seizure (associated with abruptly stopping high doses of benzodiazepines with or without alcohol use), delirium, and psychosis.

Other benefits of stopping these drugs include:
- Avoiding the adverse effects (for example, cognitive and psychomotor impairment, depression, emotional blunting, and, less commonly, paradoxical excitation with increased anxiety, irritability, or hyperactive or aggressive behaviour).
- Reducing the risk of a road traffic accident, as benzodiazepines can impair driving performance [Department for Transport, 2003 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; DTB, 2004 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; DVLA, 2013 /benzodiazepine-and-z-drug-withdrawal#references/-368725];
- Minimizing the risk of drug interactions (for example, with alcohol or other drugs with sedative actions, increasing cognitive and psychomotor impairment).

Older people are more vulnerable to the adverse effects of benzodiazepines (for example, increased risk of falls, fractured hips, impaired cognitive function and memory which may be wrongly diagnosed as dementia, and occasionally, paradoxical excitement) [DTB, 2004 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Heather et al, 2004 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Ashton, 2005 /benzodiazepine-and-z-drug-withdrawal#references/-368725];
- Stopping long-term benzodiazepines in elderly people has been found to improve their working memory and reaction times, increase levels of alertness, and improve concentration [Curran et al, 2003 /benzodiazepine-and-z-drug-withdrawal#references/-368725].

Effectiveness of intervening

What is the effectiveness of intervening?

- For most people in a primary care setting, 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 [Bashir et al, 1994 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Heathet al, 2004 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Ashton, 2005 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Gorrels et al, 2005 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Lader et al, 2009 /benzodiazepine-and-z-drug-withdrawal#references/-368725]; Salonoia et al, 2010 /benzodiazepine-and-z-drug-withdrawal#references/-368725].
- CKS identified a recently published systematic review (search date August 2010) which assessed the effectiveness of minimal interventions to reduce the long term use of benzodiazepines in primary care [Mugunthan et al, 2011 /benzodiazepine-and-z-drug-withdrawal#references/-368725]. Minimal interventions were defined as: a letter, self-help information, or consultation with a GP. The primary outcome measured was benzodiazepine usage; measured by prescription records. Three randomised (unblinded, but used objective prescription records) controlled trials were included in this review. The main results were:
  - Reduction in benzodiazepine consumption — pooled results from three trials (n = 615) found that when compared to usual care, minimal intervention significantly reduced benzodiazepine consumption at 6 months follow up risk, ratio (RR); 2.04 (95% CI 1.5–2.8, p < 0.008).
  - Cessation of benzodiazepines — pooled results from three trials (n = 615) found that when compared to usual care, minimal intervention significantly reduced benzodiazepine consumption at 6 months follow up, RR; 2.3 (95% CI 1.32–4.2, p = 0.008).

Scenario: Benzodiazepine and z-drug withdrawal

Age from 16 years onwards

Assessment

How do I assess someone who wants to stop benzodiazepines or z-drugs?

- Assess whether this is a suitable time for the person to stop taking the drugs.
  - The chances of success are improved when a person’s physical and psychological health and personal circumstances are stable. In some circumstances it may be more appropriate to wait until other problems are resolved or improved before starting drug withdrawal.
- Enquire about:
  - Symptoms of depression. Withdrawing these drugs can worsen symptoms of clinical depression. The priority is to manage depression first, before attempting drug withdrawal — see the CKS topic on Depression (/depression).
  - Symptoms of anxiety — see the CKS topic on Generalized anxiety disorder (/generalized-anxiety-disorder). Withdrawing treatment when significant symptoms of anxiety are present is likely to make symptoms worse and is therefore unlikely to succeed. However, when symptoms are reasonably well controlled and stable it may be possible to attempt careful drug withdrawal.
  - Symptoms of long-term insomnia. If insomnia is severe, consider treating this with non-drug treatments prior to starting withdrawal of a benzodiazepine or z-drug — see the CKS topic on Insomnia (/insomnia).
  - Any medical problems and whether these are well controlled and stable. If problems are causing significant distress, consider
managing these first, prior to starting withdrawal of benzodiazepines or z-drugs.

- Consider whether the withdrawal of the benzodiazepine or z-drug can be appropriately managed in primary care.
  - People are considered suitable if they:
    - Are willing, committed, and compliant, and have adequate social support.
    - Have no previous history of complicated drug withdrawal.
    - Are able to attend regular reviews.
  - Consider seeking specialist advice or referral to a specialist centre for people with:
    - A history of alcohol or other drug use or dependence.
    - Concurrent, severe medical or psychiatric disorder or personality disorder.
    - A history of drug withdrawal seizures — these generally occur in people who suddenly stop high doses of the drugs. Slow tapering is recommended for these individuals.

**Basis for recommendation**

These recommendations are in line with published reviews and guidelines on managing benzodiazepine dependence and are based on expert opinion [Lader and Russell, 1993 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Mant and Walsh, 1997 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2002b (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Australian Government Department of Health and Ageing, 2004 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Taylor et al, 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

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**Managing someone who wants to stop**

**How do I manage someone who wants to stop benzodiazepines or z-drugs?**

- Decide if the person can stop their current benzodiazepine or z-drug without changing to diazepam.
  - **Switching to diazepam** is recommended for:
    - People using the short-acting potent benzodiazepines (that is, alprazolam and lorazepam).
    - People using preparations that do not easily allow for small reductions in dose (that is alprazolam, flurazepam, loprazolam and lormetazepam).
    - People taking temazepam or nitrazepam who choose to withdraw from diazepam after discussing the advantages and disadvantages.
    - People experiencing difficulty or who are likely to experience difficulty withdrawing directly from temazepam, nitrazepam, or z-drugs, due to a high degree of dependency (associated with long duration of treatment, high doses, and a history of anxiety problems).
  - **Seek specialist advice (preferably from a hepatic specialist) before switching to diazepam in people with hepatic dysfunction** as diazepam may accumulate to a toxic level in these individuals. An alternative benzodiazepine without active metabolites (such as oxazepam) may be preferred.
  - For information on converting to diazepam, see Switching to diazepam (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:2).
  - **Negotiate a gradual drug withdrawal schedule (dose tapering) that is flexible.** Be guided by the person in making adjustments so that they remain comfortable with the withdrawal.
    - Titrate the drug withdrawal according to the severity of withdrawal symptoms.
    - Drug withdrawal may take 3 months to a year or longer. Some people may be able to withdraw in less time.
  - For information on withdrawing and advice to give people, see Withdrawing a benzodiazepine or z-drug (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:3) and Advice (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:3).
  - **Review frequently, to detect and manage problems early and to provide advice and encouragement during and after the drug withdrawal.**
    - For further information, see Managing withdrawal symptoms (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:4).
  - **If they did not succeed on their first attempt, encourage the person to try again.**
    - Remind the person that reducing benzodiazepine dosage, even if this falls short of complete drug withdrawal, can still be beneficial.
    - If another attempt is considered, reassess (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation) the person first, and treat any underlying problems (such as depression) before trying again.

**Basis for recommendation**

These recommendations are in line with published reviews and guidelines on managing benzodiazepine dependence and are based on expert opinion and limited evidence [CSM, 1988 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Lader and Russell, 1993 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Mant and Walsh, 1997 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2002b (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Australian Government Department of Health and Ageing, 2004 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Lader et al, 2009 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Lingford-Hughes et al, 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Taylor et al, 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); BNF 65, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].
Although less well-studied, given that they work similarly, the same approach as for withdrawing benzodiazepines has been recommended for withdrawing z-drugs [Ashton, 2002c (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

These recommendations also apply to older people; they can stop benzodiazepines as successfully as younger people [Ashton, 2002b (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]. Benzodiazepine withdrawal is particularly important for older people as they are more prone to their adverse effects and have more to gain from benzodiazepine cessation, see Reasons for stopping (/benzodiazepine-and-z-drug-withdrawal#backgroundsub:2).

Gradual withdrawal of benzodiazepines and z-drugs

Although good quality evidence (/benzodiazepine-and-z-drug-withdrawal#supportingevidence1) for this is lacking, withdrawing benzodiazepines gradually is recommended to allow a smooth, gradual fall in the level of drugs in the blood, thus minimizing withdrawal symptoms [Ashton, 2005 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Lader et al. 2009 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Lingford-Hughes et al. 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); BNF 65, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Abrupt drug withdrawal can produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens [Lader et al. 2009 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); BNF 65, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]. This is more likely in people taking high doses, although seizures or psychosis may occur when other predisposing factors are also present [Schweizer and Rickels, 1998 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2005 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

As the optimal speed or duration of dose reduction is unknown [Lader et al. 2009 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Lingford-Hughes et al. 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)], drug withdrawal should be guided by individual choice and severity of withdrawal symptoms.

Gradual drug withdrawal is also recommended for people dependent on z-drugs as the manufacturers of these drugs warn that abrupt termination of treatment can lead to withdrawal symptoms, particularly in people taking high doses [ABPI Medicines Compendium, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); ABPI Medicines Compendium, 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); APB Medicines Compendium, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]

Switching to diazepam

Despite the lack of good quality evidence, switching to diazepam is recommended for some people — particularly if they have difficulty withdrawing or if they are on short-acting, potent benzodiazepines [Ashton, 2002b (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2005 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Taylor et al. 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); BNF 65, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Diazepam is preferred because:
- It possesses a long half-life (20–100 hours), thus avoiding sharp fluctuations in plasma level.
- It is available in a variety of strengths and formulations. This facilitates stepwise dose substitution from other benzodiazepines or z-drugs and allows for small incremental reductions in dosage (especially at low doses).
- The National Institute for Health and Care Excellence does not recommend the substitution of z-drugs for people who are being withdrawn from benzodiazepines as this is not supported by available evidence of reduced potential for dependency [NICE, 2004 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Switching to diazepam
How do I switch from a benzodiazepine or a z-drug to diazepam?

Information on the approximate dose equivalents of diazepam for a number of benzodiazepines and z-drugs can be found in Additional information (/benzodiazepine-and-z-drug-withdrawal#scenarioclarification).

Be aware that this information should only be used as a guide.
- Exact dose substitution is not possible, due to:
  - Differences in potency between different benzodiazepines and z-drugs.
  - Wide variation in the half-life and response to these drugs (such as the degree of sedation) between different individuals (for example, the elderly and people with hepatic impairment).
- Consequently, a complete dose substitution may not always be required, depending on the individual response (to avoid excessive sedation).

Switching to diazepam is best carried out gradually, usually in a stepwise fashion.
- Consider making the first switch in the night-time dose to avoid daytime sedation.
- For examples of switching for the three most common hypnotics and an anxiolytic (lorazepam), see Additional information (/benzodiazepine-and-z-drug-withdrawal#scenarioclarification).
- For information on switching for other benzodiazepines or z-drugs, see the Ashton Manual (http://www.benzo.org.uk/manual/bzsched.htm) (available online at www.benzo.org.uk (http:/www.benzo.org.uk)).

Dose withdrawal may be started when conversion to diazepam is complete.
Dose conversion to diazepam:

  - Alprazolam 0.25 mg
  - Chlordiazepoxide 15 mg
  - Clobazam 10 mg
  - Clonazepam 0.25 mg
  - Loprazolam 0.5 mg to 1.0 mg
  - Lorazepam 0.5 mg
  - Lorazepam 0.5 mg to 1.0 mg
  - Nortriptyline 5 mg
  - Oxazepam 15 mg
  - Temazepam 10 mg
  - Zaleplon 10 mg
  - Zopiclone 7.5 mg
  - Zolpidem 10 mg

- These equivalents are based on clinical experience and may vary between individuals [Ashton, 2002a](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725); Lader et al, 2009 ([benzodiazepine-and-z-drug-withdrawal#references/-368725](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725)).

- Diazepam is available in a variety of strengths (2 mg, 5 mg, and 10 mg) and formulations (scored tablets or liquid) to facilitate switching.

**Examples of switching schedules from the three commonest hypnotics to diazepam [Ashton, 2002c](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725):**

- **From temazepam 10 mg to diazepam 5 mg:**
  - Week 1: convert temazepam 10 mg straight to diazepam 5 mg.

- **From temazepam 20 mg to diazepam 10 mg:**
  - Week 1: convert temazepam 20 mg to temazepam 10 mg and diazepam 5 mg.
  - Week 2: convert remaining temazepam 10 mg to diazepam 5 mg, giving a total diazepam dose of 10 mg daily.

- **From nitrazepam 5 mg to diazepam 5 mg:**
  - Week 1: convert nitrazepam 5 mg straight to diazepam 5 mg.

- **From nitrazepam 10 mg to diazepam 10 mg:**
  - Week 1: convert nitrazepam 10 mg to nitrazepam 5 mg and diazepam 5 mg.
  - Week 2: convert remaining nitrazepam 5 mg to diazepam 5 mg, giving a total diazepam dose of 10 mg daily.

- **From zopiclone 7.5 mg to diazepam 5 mg:**
  - Week 1: convert zopiclone 7.5 mg straight to diazepam 5 mg.

- **From zopiclone 15 mg to diazepam 10 mg:**
  - Week 1: convert zopiclone 15 mg to zopiclone 7.5 mg and diazepam 5 mg.
  - Week 2: convert remaining zopiclone 7.5 mg to diazepam 5 mg, giving a total diazepam dose of 10 mg daily.

**Example of a conversion of an anxiolytic (lorazepam 1 mg three times daily) to diazepam [Ashton, 2002c](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725):**

- **Week 1:**
  - Morning: lorazepam 1 mg.
  - Midday: lorazepam 1 mg.
  - Evening: lorazepam 1 mg.

- **Week 2:**
  - Morning: lorazepam 1 mg.
  - Midday: lorazepam 1 mg.
  - Evening: lorazepam 0.5 mg plus diazepam 5 mg.

- **Week 3:**
  - Morning: lorazepam 0.5 mg plus diazepam 5 mg.
  - Midday: lorazepam 1 mg.
  - Evening: lorazepam 0.5 mg plus diazepam 5 mg.

- **Week 4:**
  - Morning: lorazepam 0.5 mg plus diazepam 5 mg.
  - Midday: lorazepam 1 mg.
  - Evening: diazepam 10 mg.

- **Week 5:**
  - Morning: diazepam 10 mg.
Midday: lorazepam 1 mg.
Evening: diazepam 10 mg.

**Week 6:**
- Morning: diazepam 10 mg.
- Midday: lorazepam 0.5 mg plus diazepam 5 mg.
- Evening: diazepam 10 mg.

**Week 7:**
- Morning: diazepam 10 mg.
- Midday: diazepam 10 mg.
- Evening: diazepam 10 mg.

**Week 8:**
- Start diazepam withdrawal.

### Basis for recommendation

These recommendations are in line with published reviews and guidelines on switching different benzodiazepines to diazepam and are based on expert opinion [Mant and Walsh, 1997](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725); Ashton, 2002b [benzodiazepine-and-z-drug-withdrawal#references/-368725]; Australian Government Department of Health and Ageing, 2004 [benzodiazepine-and-z-drug-withdrawal#references/-368725]; Lader et al, 2009 [benzodiazepine-and-z-drug-withdrawal#references/-368725]; Taylor et al, 2012 [benzodiazepine-and-z-drug-withdrawal#references/-368725]; BNF 65, 2013 [benzodiazepine-and-z-drug-withdrawal#references/-368725].

### Switching to diazepam

- Despite the lack of good quality evidence, switching to diazepam is recommended for some people. It possesses a long half-life (20–100 hours), thus avoiding sharp fluctuations in plasma level. For further information, see Managing someone who wants to stop [benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:1].

### Examples of benzodiazepine and z-drug substitution schedules

- These are adapted from the Ashton Manual [http://www.benzo.org.uk/manual/bzsched.html](http://www.benzo.org.uk/manual/bzsched.html) [Ashton, 2002c](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725). This widely published manual was developed on the basis of clinical experience of managing people withdrawing from benzodiazepines and z-drugs in an English specialist clinic over a 12-year period.

### Withdrawing a benzodiazepine or z-drug

**How should I withdraw a benzodiazepine or a z-drug?**

- **Withdrawal should be gradual** (dose tapering, such as 5–10% reduction every 1–2 weeks, or an eighth of the dose fortnightly, with a slower reduction at lower doses), and titrated according to the severity of withdrawal symptoms.
  - This may take 3–4 months to a year or longer. Some people may be able to withdraw in less time.
  - For advice on withdrawal, see Advice [benzodiazepine-and-z-drug-withdrawal#scenarioclarification:1].

- **Withdrawal may be undertaken with or without switching to diazepam [benzodiazepine-and-z-drug-withdrawal#scenarioclarification:2].**
  - See Additional information [benzodiazepine-and-z-drug-withdrawal#scenarioclarification:1] for examples of withdrawal schedules. These should be tailored to meet individual needs.
  - For more information on withdrawal schedules for other benzodiazepines and z-drugs, see the Ashton Manual [http://www.benzo.org.uk/manual/bzsched.html](http://www.benzo.org.uk/manual/bzsched.html) (available online at [www.benzo.org.uk](http://www.benzo.org.uk)).

### Additional information


- Diazepam is available in a variety of strengths (2 mg, 5 mg, and 10 mg) and formulations (scored tablets or liquid) to facilitate dose reduction, particularly at lower doses.

### Suggested withdrawal schedule for diazepam

- Midday: lorazepam 1 mg.
- Evening: diazepam 10 mg.

**Week 6:**
- Morning: diazepam 10 mg.
- Midday: lorazepam 0.5 mg plus diazepam 5 mg.
- Evening: diazepam 10 mg.

**Week 7:**
- Morning: diazepam 10 mg.
- Midday: diazepam 10 mg.
- Evening: diazepam 10 mg.

**Week 8:**
- Start diazepam withdrawal.
Benzodiazepine and z-drug withdrawal - NICE CKS

From diazepam 40 mg per day or less:
- Reduce dose by 2–4 mg every 1–2 weeks until reaching 20 mg per day, then
- Reduce dose by 1–2 mg every 1–2 weeks until reaching 10 mg per day, then
- Reduce dose by 1 mg every 1–2 weeks until reaching 5 mg per day, then
- Reduce dose by 0.5–1 mg every 1–2 weeks until completely stopped.

Estimated total withdrawal time:
- From diazepam 40 mg per day: 30–60 weeks.
- From diazepam 20 mg per day: 20–40 weeks.

Suggested withdrawal schedules for temazepam, nitrazepam, and zopiclone without diazepam conversion

From temazepam 20 mg daily or less:
- Reduce daily dose by a quarter of a 10 mg tablet (2.5 mg) every 2 weeks.
- The target dose for when to stop is when the person is taking only a quarter of a 10 mg tablet as a daily dose.
- If stopping is not possible at the target dose, offer temazepam liquid (10 mg/5 mL) and an oral syringe to achieve further reductions.
- Estimated total withdrawal time: 16–20 weeks or longer.

From nitrazepam 10 mg daily or less:
- Reduce the daily daily dose by a quarter of a 5 mg tablet (1.25 mg) every 2 weeks.
- The target dose for when to stop is when the person is taking only a quarter of a 5 mg tablet as a daily dose.
- If stopping is not possible at the target dose, offer nitrazepam (2.5 mg/5 mL) liquid and an oral syringe to achieve further reductions.
- Estimated total withdrawal time: 16–20 weeks or longer.

From zopiclone 7.5 mg per day or less:
- Reduce the daily dose by half of a 3.75 mg tablet (1.875 mg) every 2 weeks.
- The target dose for when to stop is when the person is taking only half of a 3.75 mg tablet.
- If stopping is not possible at the target dose, one option is to convert to diazepam to complete the withdrawal, although this is controversial.
- Estimated total withdrawal time: 16–20 weeks or longer.

Basis for recommendation


Withdrawal z-drugs

Although less well studied, given that they work similarly, the same approach for withdrawing benzodiazepines has been recommended as for withdrawing z-drugs [Ashton, 2002c](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725).

Basis for gradual drug withdrawal

Despite the lack of good quality evidence ([benzodiazepine-and-z-drug-withdrawal#supportingevidence1](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!supportingevidence1)), gradual withdrawal of benzodiazepines is recommended to allow a smooth, gradual fall in blood-drug level, thus minimizing withdrawal symptoms. For further information, see [Managing someone who wants to stop ([benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:1](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!scenariorecommendation:1)).

Time required for drug withdrawal

Although some experts have recommended drug withdrawal over 8–12 weeks, or longer (such as 6 months) if the person has tried to stop before but failed [Lader et al, 2009](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725); Ashton et al, 2009 ([benzodiazepine-and-z-drug-withdrawal#references/-368725](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725)); BNF 65, 2013 ([benzodiazepine-and-z-drug-withdrawal#references/-368725](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725)).

Consequently, no specified time frame has been recommended as drug withdrawal should be titrated according to the severity of withdrawal symptoms and individual preference. However, it is recommended that the person should not be tempted to prolong the drug withdrawal to an extremely slow rate towards the end [Ashton, 2002b](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725); Lader et al, 2009 ([benzodiazepine-and-z-drug-withdrawal#references/-368725](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725)).

Examples of drug withdrawal schedules

These are adapted from the [Ashton Manual](https://www.benzo.org.uk/manual/bzsched.htm)[Ashton, 2002c](https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#!references/-368725).
Managing withdrawal symptoms

How should I manage withdrawal symptoms?

- **Review frequently** to detect and manage problems early, and to provide encouragement and reassurance during and after drug withdrawal.

- **Manage anxiety.**
  - Explain that anxiety is the most common acute withdrawal symptom.
  - Reassure that anxiety is likely to be temporary.

- **Consider slowing or suspending withdrawal until symptoms become manageable.**

- **Consider additional use of non-drug treatments**.

  - **Adjunct drug therapy should not be routinely prescribed** but may be considered:
    - Propranolol: for severe, physical symptoms of anxiety (such as palpitations, tremor, and sweating) only if other measures fail.
    - Antidepressants: only if depression or panic disorder coexist or emerge during drug withdrawal.
    - Do not prescribe antipsychotics which may aggravate withdrawal symptoms.

  - Seek specialist advice if symptoms are severe or difficult to manage.

- **Manage depression.**
  - If depression emerges or coexists with withdrawal symptoms:
    - Consider suspending drug withdrawal until the depression resolves.
  - See the CKS topic on Depression for further information on the management of depression.

- **Manage insomnia.**
  - Non-drug treatments have proved to be beneficial in managing long-term insomnia and should be considered for all people with long-term insomnia problems — see the CKS topic on Insomnia.

Additional information

- **Non-drug treatments for managing anxiety include** [Ashton, 2002d; Lader and Russell, 1993; Mart and Walsh, 1997; Ashton, 2002b; Australian Government Department of Health and Ageing, 2004; Taylor et al, 2012]:
  - Behaviour therapy — this may require referral to a counselling service, psychologist, or local mental health team — for example:
    - Relaxation techniques (such as progressive muscular relaxation and controlled breathing techniques).
    - More specialized psychological interventions (such as cognitive behavioural therapy) if symptoms are severe or protracted.
  - It should be noted that benzodiazepines may impair the learning of new skills, including strategies for coping with stress. During or after drug withdrawal, the person may be in a vulnerable state and less able to deal with stressful situations.
  - Exercise (tailored to the person’s capabilities) and other techniques (such as yoga and meditation).
  - Complementary or alternative therapies (such as aromatherapy, massage, and reflexology).

Basis for recommendation

These recommendations are in line with published reviews and guidelines on managing benzodiazepine dependence and are based on expert opinion and limited evidence [Lader and Russell, 1993; Mart and Walsh, 1997; Ashton, 2002b; Australian Government Department of Health and Ageing, 2004; Taylor et al, 2012].

**Adjunct drug therapy**

- **Use of adjunct drug therapy to assist benzodiazepine withdrawal is not routinely recommended** because there is no good evidence to support its use.

- **Although propranolol is recommended by the British National Formulary** for managing withdrawal symptoms when other measures have failed, the evidence for its effectiveness is poor.

**Adjunct psychological intervention**
Advice
What should I advise people undergoing withdrawal?

- Advise that drug withdrawal should be gradual to minimize the risk of withdrawal effects.
- Offer reassurance that the person will be in control of the drug withdrawal and that they can proceed at a rate that suits them. Drug withdrawal may take 3 months to a year or longer if necessary. Some people may be able to withdraw in less time.
- If the person reaches a difficult point in the drug withdrawal schedule, maintain the current dose for a few weeks if necessary. Try to avoid going backwards and increasing the dosage again if possible.
- Avoid taking extra tablets in times of stress.
- Avoid compensating for benzodiazepines or z-drugs by increasing the intake of alcohol or other drugs (prescription, non-prescription, or illicit drugs) or smoking.
- Stopping the last few milligrams is often seen as being particularly difficult.
  - Reassure the person that this is usually an unfounded fear derived from long-term psychological dependence on benzodiazepines.
  - Warn the person not to be tempted to prolong the drug withdrawal to an extremely slow rate towards the end (such as reducing by 0.25 mg diazepam each month). Advise the person to consider stopping completely when they reach an appropriate low dose (such as diazepam 1 mg daily).
- Give information on withdrawal symptoms.
  - With slow tapering, many people experience few or no withdrawal symptoms.
  - If withdrawal symptoms are present with slow tapering, some users will have lost all their symptoms by the end of the drug withdrawal schedule. For most people, symptoms will disappear within a few months.
  - Only a very small number of people will suffer from protracted withdrawal symptoms which will gradually improve over a year or longer.
  - Inform the person that nearly all the acute symptoms of withdrawal are those of anxiety.
  - Explain that some of the withdrawal symptoms may be similar to the original complaint and do not indicate a return of this.
  - It is not possible to estimate the severity and duration of withdrawal symptoms as these will depend on a number of factors (such as severity of dependence and speed of withdrawal).
  - For information on managing withdrawal symptoms, see Managing withdrawal symptoms (/benzodiazepine-and-z-drug-withdrawal#scenariorecommendation:4).
- Reassure the person that they can try again if they did not succeed at their first attempt.
- Remind the person that reducing benzodiazepine dosage, even if this falls short of complete drug withdrawal, can still be beneficial.

Basis for recommendation

These recommendations are pragmatic advice and are based on expert opinion [Mant and Walsh, 1997 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2002b (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Australian Government Department of Health and Ageing, 2004 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Taylor et al, 2012 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Managing someone who does not want to stop
How do I manage someone who does not want to stop taking benzodiazepines or z-drugs?

- Do not pressurize the person to stop if they are not motivated to do so.
- Listen to the person, and address any concerns they have about stopping.
  - Explain that for most people who withdraw from treatment slowly, symptoms are mild and can usually be effectively managed by other means.
  - Reassure the person that they will be in control of the drug withdrawal and that they can proceed at a rate that suits them.
- Discuss the benefits of stopping the drug.
  - The discussion should include an explanation of tolerance, adverse effects, and the risks of continuing the drug. See Reasons for stopping (/benzodiazepine-and-z-drug-withdrawal#backgroundsub:2) for further information.
- Review at a later date if appropriate, and reassess the person’s motivation to stop.
- In people who remain concerned about stopping treatment despite explanation and reassurance, persuading them to try a small reduction in dose may help them realize that their concerns are unfounded.
Basis for recommendation

These recommendations are based on expert opinion [Lader and Russell, 1993 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Mant and Walsh, 1997 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2002b (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Australian Government Department of Health and Ageing, 2004 (/benzodiazepine-and-z-drug-withdrawal#references/-368725); Ashton, 2011 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Driving

Should a person with benzodiazepine or z-drug dependency drive?

- The following advice should be given to people who take benzodiazepines:
  - You should not drive if you feel drowsy, dizzy, unable to concentrate or make decisions.
  - It is now an offence to drive if you have more than a specified amount of benzodiazepine in your body whether your driving is impaired or not.
  - Roadside drug screening tests have been introduced into the UK since March 2015. These test the saliva for drugs that impair driving. If you have a positive roadside drug test for benzodiazepines, the police may ask you to provide a blood sample to measure the amount of benzodiazepine in your body.
  - If you are found to have more than the specified amount of benzodiazepine, as long as your driving is not impaired, you are taking your medicine on the advice of your GP, or your pharmacist, you will be able to raise a ‘statutory defence’ and the police may not prosecute you.
  - It may be helpful to keep evidence with you while you are driving, that you are taking a benzodiazepine in accordance with medical advice. Suitable evidence may include: your medication box with the pharmacy label on, or the other half of your prescription with the list of medicines prescribed by your doctor.
- The DVLA provides no advice for people taking z-drugs.
- For more information, see the 'At a glance guide (https://www.gov.uk/government/publications/at-a-glance)' available on the DVLA website (https://www.gov.uk/government/organisations/driver-and-vehicle-licensing-agency).

Basis for recommendation

These recommendations are based on the At a glance guide to the current standards of fitness to drive published by the Driver and Vehicle Licensing Agency [DVLA, 2013 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)]; and advice issued by the Department of Transport [Department for Transport, 2014 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].

Search strategy

Scope of search

A literature search was conducted for guidelines, systematic reviews and randomized controlled trials on the primary care management of benzodiazepine and z-drug withdrawal.

Search dates

October 2008 - May 2013

Key search terms

Various combinations of searches were carried out. The terms listed below are the core search terms that were used for Medline.

- exp Substance Withdrawal Syndrome/, withdrawal$.tw.

Table 1. Key to search terms.

<table>
<thead>
<tr>
<th>Search commands</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>indicates a MeSH subject heading with all subheadings selected</td>
</tr>
<tr>
<td>.tw</td>
<td>indicates a search for a term in the title or abstract</td>
</tr>
<tr>
<td>exp</td>
<td>indicates that the MeSH subject heading was exploded to include the narrower, more specific terms beneath it in the MeSH</td>
</tr>
</tbody>
</table>
$ indicates that the search term was truncated (e.g. wart$ searches for wart and warts)

Topic specific literature search sources
- Benzo.org.uk (http://www.benzo.org.uk)

Sources of guidelines
- National Institute for Health and Care Excellence (NICE) (http://www.nice.org.uk)
- Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk)
- Royal College of Physicians (http://www.rcplondon.ac.uk/)
- Royal College of General Practitioners (http://www.rcgp.org.uk/)
- Royal College of Nursing (http://www.rcn.org.uk/development/practice/clinicalguidelines)
- NICE Evidence (https://www.evidence.nhs.uk/topics/)
- Health Protection Agency (http://www.hpa.org.uk)
- World Health Organization (http://www.who.int)
- National Guidelines Clearinghouse (http://www.guideline.gov)
- Guidelines International Network (http://www.g-i-n.net)
- TRIP database (http://www.tripdatabase.com)
- GAIN (http://www.gain-ni.org/index.php/audits/guidelines)
- NHS Scotland National Patient Pathways (http://www.pathways.scot.nhs.uk/)
- New Zealand Guidelines Group (http://www.nzgg.org.nz)
- Agency for Healthcare Research and Quality (http://www.ahrq.gov)
- Institute for Clinical Systems Improvement (http://www.icsi.org)
- National Health and Medical Research Council (Australia) (http://www.nhmrc.gov.au/publications/index.htm)
- Royal Australian College of General Practitioners (http://www.racgp.org.au/your-practice/guidelines)
- British Columbia Medical Association (http://www.health.gov.bc.ca/gpsa/index.html)
- Canadian Medical Association (http://www.cma.ca/index.php/ci_id/54316/s_id/1.htm)
- Alberta Medical Association (http://www.topalbertadoctors.org/cpgs.php)
- University of Michigan Medical School (http://ocpd.med.umich.edu/cme/self-study/)
- Singapore Ministry of Health (http://www.moh.gov.sg/content/moh_web/home/Publications/guidelines/cpg.html)
- National Resource for Infection Control (http://www.nric.org.uk)
- Patient UK Guideline links (http://www.patient.co.uk/guidelines.asp)
- UK Ambulance Service Clinical Practice Guidelines (http://www2.warwick.ac.uk/fac/med/research/hrsi/emergencycare/jrcalc_2008/guidelines/)
- Medline (with guideline filter)
- Driver and Vehicle Licensing Agency (http://www.dft.gov.uk/dvla/medical/ataglance.aspx)
- NHS Health at Work (http://www.nhshealthatwork.co.uk/oh-guidelines.asp) (occupational health practice)

Sources of systematic reviews and meta-analyses
- The Cochrane Library (http://www.thecochranelibrary.com):
  - Systematic reviews
  - Protocols
  - Database of Abstracts of Reviews of Effects
  - Medline (with systematic review filter)
  - EMBASE (with systematic review filter)

Sources of health technology assessments and economic appraisals
- NIHR Health Technology Assessment programme (http://www.hta.ac.uk/)
- The Cochrane Library (http://www.thecochranelibrary.com):
  - NHS Economic Evaluations
  - Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca)
- International Network of Agencies for Health Technology Assessment (http://www.inahta.org)

Sources of randomized controlled trials
- The Cochrane Library (http://www.thecochranelibrary.com):
  - Central Register of Controlled Trials
  - Medline (with randomized controlled trial filter)
  - EMBASE (with randomized controlled trial filter)

Sources of evidence based reviews and evidence summaries
Gradual dose reduction

Evidence on gradual dose reduction for benzodiazepine withdrawal

For people withdrawing from benzodiazepines, there is very limited evidence that gradual withdrawal is more preferable than abrupt withdrawal in terms of reducing symptoms and improving cessation rate.

- A meta-analysis (search date: up to 2007, month unspecified) evaluating treatment approaches for benzodiazepine discontinuation identified only one small study (n = 107) which found that engagement in a programme of gradual dose reduction was more effective than routine care (odds ratio 5.96, 95% CI 2.08 to 17.11) [Parr et al, 2009 (/benzodiazepine-and-z-drug-withdrawal#!references/-368725)].

Psychological interventions

Evidence on psychological interventions for benzodiazepine withdrawal

Limited evidence from two meta-analyses indicates that gradual benzodiazepine withdrawal combined with psychological interventions is more effective than usual care or gradual withdrawal alone. However, the results should be interpreted with caution as the studies were generally small and heterogeneous.

- One meta-analysis (search date: up to September 2004) compared systematic discontinuation programmes (guided by a physician or psychologist) with psychotherapy against systematic discontinuation programmes alone [Voshaar et al, 2006 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].
  - Pooled results from five studies (n = 342) found the addition of cognitive behavioural therapy (CBT) increased the discontinuation rate (pooled Odds Ratio [OR] 1.8, 95% CI 1.1 to 2.9, p = 0.01). However, significant heterogeneity exists between the studies (p < 0.001).
  - Only two of these studies were comparable, involving 115 people on low dose benzodiazepine for insomnia in a psychiatric outpatient setting. Pooled analysis indicated the combination to be more effective (pooled OR 5.5, 95% CI 2.3 to 14.2, p < 0.001; test for heterogeneity p = 1.00).
  - A second meta-analysis (search date: up to 2007, month unspecified) examined the effectiveness of psychological interventions (including CBT) when combined with a strategy of gradual dose reduction [Parr et al, 2009 (/benzodiazepine-and-z-drug-withdrawal#references/-368725)].
  - Gradual dose reduction with psychological interventions versus routine care:
    - Three studies (n = 354) found gradual dose reduction combined with psychological interventions (relaxation training, psycho-education, teaching strategies) resulted in higher benzodiazepine cessation rates than routine care (OR 3.38, 95% CI 1.86 to 6.12).
    - Only one small study (n = 20) provided follow-up data and found that benefits of the psychological intervention were maintained (OR 13.5,
Pharmacological interventions
Evidence on pharmacological interventions for benzodiazepine withdrawal

Two meta-analyses did not support the use of adjunct drug therapy to improve benzodiazepine withdrawal rate or to reduce withdrawal symptoms. The number of studies that met inclusion criteria was low and they were generally small in size with high drop out rates.

- A meta-analysis (search date: up to September 2004) which compared systematic discontinuation programmes (that is, treatment strategies guided by a physician or psychologist) either with adjunct drug therapy or placebo found no good evidence for pharmacological interventions for benzodiazepine withdrawal [Voshaar et al, 2006://benzodiazepine-and-z-drug-withdrawal#references/-368725].
  - The meta-analysis did not support adding carbamazepine (three trials, n = 94), trazodone (two trials, n = 98), buspirone (five trials, n = 193), and propranolol (three trials, n = 71) as the results were not statistically significant compared with placebo.
  - Addition of imipramine produced a higher discontinuation success rate (pooled odds ratio [OR] 2.3, 95% CI 1.1 to 9.4) but this was only based on two small studies (n = 47 and n = 28).
  - Although results for sodium valproate, flumazenil, and melatonin were statistically significant, further research is required as the analysis was based on small, single studies (n = 27-40).
- A more recent meta-analysis (search date: up to 2007, month unspecified) also found no benefit in the use of adjunct drug therapy [Parr et al, 2009://benzodiazepine-and-z-drug-withdrawal#references/-368725].
  - Pooled results of trials involving people undergoing gradual withdrawal found no additional benefit (as measured by the percentage of people who ceased benzodiazepine use) between the drug and placebo groups at:
    - Post-treatment (14 studies, n = 927): OR 1.30, 95% CI 0.97 to 1.73.
    - Follow-up (five studies, n = 389): OR 1.30, 95% CI 0.77 to 2.20.
  - In contrast, pooled results from three studies (n = 260) found that abrupt substitution of drug treatment was actually less effective than gradual dose reduction (OR 0.30, 95% CI 0.14 to 0.64), and no more effective than abrupt reduction alone (OR 1.69, 95% CI 0.60 to 4.74).
  - These pooled results should be viewed with caution given that the authors acknowledged substantial variability in participant numbers, types of treatment, and dose reduction regimens between studies.

Benzodiazepine and z-drug withdrawal - Summary

- Benzodiazepines are gamma-aminobutyric acid (GABA) receptor agonists which have hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties. Benzodiazepines can be grouped into hypnotics and anxiolytics.
  - Hypnotics are used for short term treatment of insomnia and include nitrazepam, loprazolam, lormetazolam, and temazepam.
  - Anxiolytics are effective in alleviating anxiety states and include diazepam, oxazepam, lorazepam, alprazolam, and cloridiazepoxide.
- Z-drugs are non-benzodiazepine hypnotics, developed to overcome some of the adverse effects of benzodiazepines (such as next-day sedation, dependence, and withdrawal). Like benzodiazepines, they are also GABA receptor agonists.
  - The three z-drugs available in the UK are zaleplon, zolpidem, and zopiclone.
  - Despite warnings regarding the long-term use of benzodiazepines or z-drugs, millions of prescriptions are still issued for these drugs in primary care each year.
- People on long-term benzodiazepines or z-drugs should be advised to stop because:
  - Tolerance to these drugs progressively reduces their effectiveness for the treatment of insomnia or anxiety.
  - Dependence may develop, and continuing treatment may serve only to prevent withdrawal symptoms.
  - Other benefits of stopping these drugs include:
    - Avoiding the adverse effects (e.g. depression and increased anxiety).
    - Reducing the risk of a road traffic accident, as benzodiazepines can impair driving performance.
    - Minimizing the risk of drug interactions (e.g. with alcohol or other drugs with sedative actions).
  - If a person wishes to stop taking benzodiazepines or z-drugs:
    - An assessment should be carried out to determine whether it is a suitable time for them to stop, and whether they have symptoms of depression, anxiety, long term insomnia, or any other medical problems.
    - Consideration should be given to whether withdrawal can be appropriately managed in primary care.
    - A decision should be made regarding whether the person can stop their current drug without changing to diazepam. Withdrawal may be undertaken with or without switching to diazepam.
    - A gradual drug withdrawal schedule (dose tapering) that is flexible should be negotiated. The person should guide adjustments so that they remain comfortable with the withdrawal.

https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#scenario
Reviews should be frequent to detect and manage problems early and to provide advice and encouragement during and after the drug withdrawal.
If a person does not succeed on their first attempt, they should be encouraged to try again.
If a person does not want to stop taking benzodiazepines or z-drugs:
- They should not be pressurized.
- They should be listened to and have any concerns they have about stopping addressed.
- The benefits of stopping should be discussed.
- A review should be arranged for a later date, if appropriate.
- **Driving**
  - People who take British National Formulary (BNF) recommended doses of benzodiazepines or z-drugs and have no evidence of impairment do not need to inform the DVLA.
  - However, the non-prescribed use of benzodiazepines and/or the use of supra-therapeutic dosage, whether in a substance withdrawal/maintenance programme or otherwise, constitutes misuse/dependency for licensing purposes and will lead to licence refusal or revocation.

Have I got the right topic?

Age from 16 years onwards

This CKS topic covers the assessment of a person who is being prescribed long-term benzodiazepines or z-drugs, and offers advice on managing withdrawal of treatment.

This CKS topic does not cover the management of people taking benzodiazepines with illicit drugs, the management of people who are dependent on other drugs (including alcohol), the management of overdose, or the management of dependence in neonates, children, or pregnancy.

There are separate CKS topics on Alcohol - problem drinking (/alcohol-problem-drinking), Depression (/depression), Insomnia (/insomnia), Opioid dependence (/opioid-dependence), and Smoking cessation (/smoking-cessation).

The target audience for this CKS topic is healthcare professionals working within the NHS in the UK, and providing first contact or primary health care.

How up-to-date is this topic?

- Changes
- Update

Goals and outcome measures

- Goals
- QIPP - Options for local implementation

Background information

- Definition
- Frequency of prescribing
- Reasons for stopping
- Effectiveness of intervening

Management

- **Scenario: Benzodiazepine and z-drug withdrawal (/benzodiazepine-and-z-drug-withdrawal#scenario)**: covers the assessment of a person who is being prescribed long-term benzodiazepines or z-drugs, and offers advice on managing withdrawal of treatment.

How this topic was developed

- Search strategy
References


https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#scenario
Benzodiazepine and z-drug withdrawal - NICE CKS


https://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal#scenario
Supporting evidence
Evidence on strategies for discontinuing long-term benzodiazepine use

- Gradual dose reduction
- Psychological interventions
- Pharmacological interventions