

Benzodiazepines: benefits versus risks

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Benzodiazepines act on the central nervous system and can be prescribed for various medical conditions. They are usually classified by their duration of action. Patients using long-term benzodiazepines are at risk of dependence and tolerance. Benzodiazepines may also worsen or mask symptoms of depression and may cause cognitive and psychomotor impairment. Therefore, benzodiazepines should not be prescribed in the absence of a clear indication. When prescribed, benzodiazepines should be prescribed in as low a dose as possible and long-term patients should be reviewed regularly.

Introduction

Benzodiazepines are drugs which depress activity in the part of the brain which controls emotion by promoting the action of a chemical called gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, thus preventing excessive brain activity that causes anxiety.¹ Benzodiazepines can be prescribed for various medical conditions which include anxiety, insomnia, alcohol withdrawal, seizure control, muscle relaxation and to induce amnesia for uncomfortable procedures. They can also be given before administration of an anaesthetic, e.g. prior to surgery. Benzodiazepines act on the central nervous system resulting in sedation and muscle relaxation, and lower anxiety levels.² Benzodiazepines are usually classified by their duration of action as indicated in Table 1.

Uses of Benzodiazepines

Anxiety

Benzodiazepines should be prescribed primarily for the short-term relief of severe anxiety when this is resulting in significant distress or problems in social functioning. Benzodiazepines are effective anxiolytic drugs having an immediate onset of action⁴, with their maximum benefit shown in the first few weeks of treatment. Thus they may offer a period of respite whilst other more indicated treatments such as antidepressants have time to act. Long-term prescription of benzodiazepines may be considered desirable in certain circumstances when other alternatives are considered less appropriate than the use of benzodiazepines. This may be in conditions such as chronic treatment-resistant anxiety or in patients who have confirmed dependency and are unable to withdraw successfully. Rarely, benzodiazepines may be prescribed in the long term as maintenance

treatment in patients who would otherwise consume illicit benzodiazepines. In situations where anxiety is complicated by other illnesses such as schizophrenia, the risk of dependence may be considered acceptable because of the severity of the other disorder. Benzodiazepines may also be used as adjunctive treatment in the initial management of acute mania where sedation is a priority.^{5,6} In other instances there is much less evidence to support the use of benzodiazepines.

Depression

Depression is not a primary indication for prescribing benzodiazepines. Benzodiazepines may only be prescribed for depression if the latter is accompanied by anxiety or severe distress for short-term relief when the patient is subject to extreme distress. They do not have a specific antidepressant effect,⁴ and may offer early symptomatic relief while antidepressants have time to act, or cover the initial increase in anxiety that may occur when some antidepressants are prescribed.

Sleep

Benzodiazepines are effective hypnotics for the short-term treatment of insomnia⁷ if given in sufficient doses.⁸ Again, they should be used intermittently for 2 to 4 weeks and at the lowest dose while more appropriate long-term treatments are instituted, if the problem is long-term.^{7,8} Primary causes of insomnia, such as depression or substance misuse, should be excluded.⁷

Anticonvulsant and muscle relaxant actions

Benzodiazepines have anticonvulsant and muscle relaxant properties. These are often valuable, particularly in the emergency treatment of epilepsy and the management of spasticity or muscle spasms.

Excitement, agitation and severe psychotic disturbance

Patients with excitement, agitation and severe psychotic disturbance may be prescribed short-term benzodiazepines to obtain rapid tranquillisation or as an adjunct to their antipsychotic drugs. The dose and duration of such treatment needs to be monitored closely.

Table 1: Duration of action of benzodiazepines³

Ultra-short acting	Short-acting $t_{1/2}$ less than 6 hours	Intermediate-acting $t_{1/2}$ 6-24 hours	Long-acting $t_{1/2}$ greater than 24 hours
Midazolam	Zopiclone Zolpidem	Alprazolam Lorazepam Temazepam	Diazepam Flurazepam

Risks of Benzodiazepines**Dependence**

Long-term use of benzodiazepines can result in dependence. Dependence on benzodiazepines is mainly manifest by withdrawal symptoms and even seizures on abrupt cessation.^{2,7} These symptoms may sometimes be prolonged and they may be hard to distinguish from other anxiety-related disorders such as panic disorder. Symptoms usually develop after three days of benzodiazepine cessation, although they can appear earlier with short-acting varieties.² Short-acting benzodiazepines are more likely to lead to a withdrawal syndrome than long-acting ones.⁹ Therefore, to reduce the risk of dependence on benzodiazepines, these should not be prescribed regularly for longer than one month, and ideally be given on as-required basis and intermittently every few days.⁷

Tolerance

Tolerance can develop with continued use of benzodiazepines. Tolerance to the hypnotic effects tends to develop rapidly whereby patients are initially relieved from insomnia, but this is followed by a gradual loss of efficacy. Tolerance to the anxiolytic effect develops at a slower rate, but there is little evidence to indicate that benzodiazepines retain their efficacy after four to six months of regular use.^{10,11}

Depression

Benzodiazepines may worsen or mask symptoms of depression. Consequently this may deny the patient the opportunity of effective antidepressant medication. Moreover it may result in disinhibition

which may lead to suicide attempts. Therefore, a benzodiazepine should only be prescribed for a brief concomitant period with an effective antidepressant, such as a tricyclic antidepressant (TCA) or a selective serotonin re-uptake inhibitor (SSRI), followed by a clinical review within 2 weeks. Augmenting an antidepressant with another antidepressant should be considered for patients whose depression is treatment resistant and who are prepared to tolerate side effects. However, there is insufficient evidence to recommend the use of benzodiazepine augmentation of antidepressants.⁴

Misuse

Death rarely results from benzodiazepine abuse alone.² However, a proportion of the population may abuse benzodiazepines as part of a wider drug and alcohol problem. Therefore, doctors should be aware that medications they prescribe may fall into the wrong hands. Maintenance benzodiazepines given to addicts are often used to supplement illicit sources.

Cognitive impairment

Benzodiazepines may cause cognitive impairment, mainly involving memory disturbance and subtle learning impairment. Cognitive impairment may not allow patients to make an optimum response to a situation which they may be facing. In cases of loss or bereavement the psychological adjustment to this trauma may also be inhibited by benzodiazepines. On the other hand, short-term symptomatic relief of benzodiazepines may aid the natural healing process.⁷

Disinhibition

Extreme caution should be used in prescribing benzodiazepines in patients with severe personality disorders. Studies have shown that use of benzodiazepines in such patients may increase the incidence of suicidal behaviour. Moreover, combination with alcohol is common and dangerous. The use of benzodiazepines in this category of patient may facilitate aggressive behaviour both towards the self and others.⁷

Psychomotor impairment

Higher doses of benzodiazepines may cause psychomotor impairment which could affect activities such as driving and operating machinery. Therefore, when starting benzodiazepines a low dose should be given initially. Furthermore there is a particular problem with the elderly, who are more sensitive to benzodiazepine effects and who metabolize long-acting benzodiazepines slowly. There is a build-up of drug over time and this may result in chronic intoxication and falls resulting in fractures.⁷

Sleep

Studies have shown that patients who have taken benzodiazepines for period in excess of 4-6 months have become, inadvertently, dependent and experience withdrawal insomnia.⁸ Psychiatric disorders such as anxiety, depression and abuse of drugs and alcohol are common causes of chronic insomnia. Chronic insomnia is rarely benefited by hypnotics such as benzodiazepines. Instead the underlying psychiatric complaint should be treated.¹² Therefore, the Committee on Safety of Medicines (CSM) suggests that benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.¹²

Recommendations

Studies still show a continued high prevalence of benzodiazepine use despite the well known adverse effects

Table 2: Withdrawal guideline for patients on benzodiazepines¹²

1. Transfer patient to equivalent daily dose of diazepam preferably taken at night
2. Reduce diazepam dose every 2-3 weeks in steps of 2 or 2.5mg; if withdrawal symptoms occur, maintain this dose until symptoms improve
3. Reduce dose further, if necessary in smaller steps (diazepam 500 micrograms to 2.5mg)
4. Stop completely; time needed for withdrawal can vary between patients

Practice Points

- When a patient complains of insomnia one should first consider non-pharmacological measures, such as avoiding caffeine-containing products late at night, exercise during the day, identify and avoid, if possible, the cause of the insomnia.
- Benzodiazepines should only be prescribed for insomnia for short-term use in accordance with their licensed indications.
- If insomnia continues to be a problem, one may opt to prescribe a short-term non-benzodiazepine hypnotic, for a maximum of 2 weeks' duration.
- Whilst withdrawing benzodiazepines, the patient will need other supportive measures such as counseling and relaxation techniques.
- If a patient is benzodiazepine and opioid dependent, both drugs would not normally be withdrawn simultaneously. The opioid dose is kept stable until full withdrawal from the benzodiazepine has been attained.

of benzodiazepines discussed above and the availability of safer and effective alternatives. From these studies it was shown that primary care physicians are averse to addressing the public health problem of benzodiazepine overuse in the elderly.¹³ Researchers found contraindications, including falls and depression, in 75 per cent of those given benzodiazepines.^{14,15} Therefore, repeat prescriptions could be a cause of benzodiazepine overuse.¹⁶ Doctors' attitudes generally conflict with practice guidelines and they complain of a lack of training in constructive strategies to address this problem.¹³ Hence, the following recommendations are being made:

- Benzodiazepines should not be prescribed in the absence of a clear indication.
- Benzodiazepines should be prescribed in as low a dose as possible to afford symptomatic relief⁷ and patients should be advised of the risk of dependence associated with long-term use.⁸ Patients should also be advised to obtain their prescriptions for benzodiazepines from the same doctor, wherever possible, so that risk of dependence may be monitored.⁸ In addition patients should be advised on possible adverse effects such as drowsiness, which may have an effect on driving or operating machinery.⁹
- When prescribing benzodiazepines long-term patients should be reviewed. This should include a review of the indication for continued use of the benzodiazepine,

the dosage regime and any possible side-effects.

- Benzodiazepine reduction and cessation should be with the patient's consent and co-operation.
- Even after the short-term use of benzodiazepines, it is advised that a tapering-off regime (i.e. at least 2 weeks at reduced dosage) should be used to minimize rebound phenomena. After longer use this reduction period may have to be extended, sometimes to several months in extreme cases.⁷
- Benzodiazepine tapering-off may be facilitated by changing patients to long half-life medications, such as diazepam, and then slowly reducing the dose. A suggested withdrawal guideline for patients who have difficulty in stopping benzodiazepines is shown in Table 2.

Conclusion

Benzodiazepines may be prescribed safely and effectively for the short-term treatment of anxiety and insomnia and can also be used for some forms of epilepsy and spasticity. Dependence is now recognized as a significant risk in patients receiving treatment for longer than one month and is often extremely difficult to treat. Therefore, doctors have to examine the benefit:risk ratio of continued prescription in each individual early in treatment, so that if dependence occurs, it is anticipated by doctor and patient alike.²

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