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Management of benzodiazepine misuse and dependence

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SUMMARY

There are well-recognised harms from long-term use of benzodiazepines. These include dependency, cognitive decline and falls.

It is important to prevent and recognise benzodiazepine dependence. A thorough risk assessment guides optimal management and the necessity for referral.

The management of dependence involves either gradual benzodiazepine withdrawal or maintenance treatment. Prescribing interventions, substitution, psychotherapies and pharmacotherapies can all contribute.

Unless the patient is elderly, it is helpful to switch to a long-acting benzodiazepine in both withdrawal and maintenance therapy. The dose should be gradually reduced over weeks to lower the risk of seizures.

Harms from drugs such as zopiclone and zolpidem are less well characterised. Dependence is managed in the same manner as benzodiazepine dependence.

Introduction

Despite a modest decrease in the annual number of benzodiazepine prescriptions dispensed, the current level of prescribing probably represents significant overuse. Over the last 20 years the quantity of benzodiazepines on each prescription has increased. Alprazolam became the second most popular drug, increasing more than eightfold.[1] Of particular concern are the patients who have been using benzodiazepines for more than six months. There are few indications for long-term therapy and they are generally controversial.[2]

Benzodiazepine-related problems include diversion, misuse, dependency, driving impairment, and morbidity and mortality related to overdose and withdrawal. In older patients they have been associated with cognitive decline, dementia[3] and falls.[4,5] There is evidence of increased mortality with long-term use.[6]

In February 2014, in response to increasing illicit use, alprazolam was rescheduled to Schedule 8. It has greater toxicity in overdose,[7] and associated mortality[8] relative to other benzodiazepines. The public health impact of this rescheduling is yet to be determined. This barrier to prescribing has placed renewed focus on benzodiazepine dependence. However, there is a paucity of research on the optimal management of benzodiazepine dependence, so practice has to be guided by general principles.

Prevention

Any patient who has taken a benzodiazepine for longer than 3–4 weeks is likely to have withdrawal symptoms if the drug is ceased abruptly. The risk of inducing dependence can be reduced by issuing prescriptions limited to 1–2 weeks supply.

Benzodiazepines are often prescribed for insomnia and anxiety. In general, the optimal treatment of these conditions in primary care is non-pharmacological, particularly psychological and behavioural, therapies. Because of tolerance and withdrawal symptoms, long-term use of benzodiazepines can lead to dose escalation and worsening of the underlying condition.

Recognition and assessment

The benzodiazepine-dependent population is heterogeneous and this influences management. A frail 70 year old with falls prescribed flunitrazepam as a sedative hypnotic for 20 years requires a different management approach from a 25-year-old intravenous drug user buying street alprazolam. The principles of management of dependence with 'z-drugs' such as zolpidem and zopiclone are the same as the management of benzodiazepine dependence.

Benzodiazepine substance use disorder can be diagnosed using DSM-5 criteria,[9] but the Severity Dependence Scale is a simple screening tool validated for use in the community.[10] Some patients prescribed benzodiazepines may have aberrant drug-related behaviours, ranging from double dosing to selling medicines illicitly or injecting them. Systems limitations in prescription monitoring in Australia reduce our ability to identify 'doctor shopping' so the

presence of any aberrant drug-related behaviours should prompt further assessment and treatment.

The assessment determines the severity of misuse and informs the risk of relapse and of harm. It should include the indication for prescribing, dose, duration of use, age and any history of psychiatric or medical comorbidity as well as any other past or current substance misuse. Assess for benzodiazepine substance use disorder and the severity of aberrant drug-related behaviours. Supportive social networks and stable housing are positive prognostic indicators. Assessing the patient's readiness to change guides the initial management.

Management

Patient engagement in management is essential as without this any attempts to address harmful use may be hindered by non-adherence or even doctor shopping. If the patient is not ready to change, or is just considering change, then motivational interviewing techniques are recommended. If the patient is ready for change, there are two approaches to the management of dependence:

- benzodiazepine withdrawal with the aim of abstinence
- benzodiazepine maintenance therapy.

The choice of approach depends on an assessment of the risk of harm and relapse. Low-risk patients can be managed in general practice and may benefit most from attempting withdrawal. High-risk patients are best managed with initial stabilisation and maintenance therapy in specialist residential or outpatient addiction services. There are general principles that apply to both groups.

Prescribing interventions

Staged dispensing is effective in both withdrawal and maintenance. This can be done by regular dispensing of small quantities at a local pharmacy with clinical review, for example daily dispensing with fortnightly clinical review. Liaison with a community pharmacist is a useful strategy.

Benzodiazepine substitution

Some benzodiazepines, notably alprazolam, appear to have a greater propensity for misuse and are more dangerous in overdose. The reasons for this are multifactorial, including perception of intoxication, potency relative to formulation (e.g. a single 2 mg alprazolam tablet is equivalent to four 5 mg diazepam tablets), shorter half-life and risk of withdrawal phenomena. A common approach is substituting these shorter half-life drugs, such as alprazolam, with longer half-life drugs, such as diazepam.[11] Conversion tables are available to guide conversion to diazepam equivalents (Table). When tapering benzodiazepines, fewer patients taking longer half-life drugs drop out, however there is a lack of robust evidence supporting substitution. Studies in older patients have found gradual withdrawal without substitution can be successful.[12,13]

Monitoring

When treatment is offered, ensure the patient is not doctor shopping to obtain more prescriptions. Doctors can register with Medicare's Prescription Shopping Information Service which provides a limited telephone report. However, this relies on doctors calling the program rather than being alerted automatically. With written patient consent, authority can be gained to release information on Pharmaceutical Benefits Scheme prescriptions over a given time period.[14]

Urine drug screening is complicated by the presence of benzodiazepine metabolites. Care should be taken in interpreting the results as some metabolites are themselves parent compounds. For example, temazepam and oxazepam are metabolites of diazepam, which may lead the practitioner to conclude that the patient had been taking other benzodiazepines during diazepam treatment. Urine drug screening should be used as a tool to engage the patient rather than as a punitive measure.

Table **Benzodiazepine and z-drugs half-life and conversion table**

Drug	Approximate half-life (hours)	Dose of oral benzodiazepine approximately equivalent to diazepam 5 mg
Short- to intermediate-acting benzodiazepines		
Triazolam	1–3	0.25 mg
Oxazepam	4–15	15 mg
Temazepam	5–15	10 mg
Lorazepam	12–16	1 mg
Bromazepam	20	3 mg
Alprazolam	6–25	0.5 mg
Flunitrazepam	20–30	0.5 mg
Nitrazepam	16–48	5 mg
Clobazam	17–49	10 mg
Long-acting benzodiazepines (includes effects of active metabolites)		
Clonazepam	22–54	0.5 mg
Diazepam	20–80	5 mg
Z-drugs		
Zolpidem	2.4	10 mg
Zopiclone	5.2	7.5 mg

Discontinuation with the aim of abstinence

Long-term abstinence rates following discontinuation vary greatly. These range from 25% at 12 months for those with complicated dependence[15] to 80% for older adults in general practice.[16] Abrupt cessation of benzodiazepines after a period of 1–6 months of use can cause life-threatening seizures so the dose should be gradually reduced.

The duration of weaning depends on tolerability and the starting dose. While not specifying a withdrawal period, most studies in primary care have found that gradual withdrawal over at least 10 weeks is successful in achieving long-term abstinence.[12]

Box **Benzodiazepine withdrawal syndrome – clinical features**

General

Headache

Palpitations

Sweating

Musculoskeletal

Tremor, fasciculations

Muscle pain, stiffness and aches (limbs, back, neck, jaw)

Neurological

Dizziness, light-headedness

Paraesthesia, shooting pains in neck and spine

Visual disturbances (blurred vision, diplopia, photophobia, vision lags behind eye movements)

Tinnitus

Faintness and dizziness, sense of unsteadiness

Confusion, disorientation (may be intermittent) – a common cause of confusion in older patients

Delirium (in the absence of autonomic hyperactivity) – particularly in older patients

Delusions, paranoia

Hallucinations (visual, auditory)

Grand mal seizures 1–12 days after discontinuing benzodiazepines

Gastrointestinal

Nausea

Anorexia

Diarrhoea (may resemble irritable bowel syndrome)

Psychological

Rebound insomnia, nightmares

Anxiety, panic attacks

Irritability, restlessness, agitation

Poor memory and concentration

Perceptual distortions – sensory hypersensitivity (light, sound, touch, taste), abnormal sensations (e.g. 'cotton wool' sensations)

Metallic taste

Distortions of body image

Feelings of unreality, depersonalisation, derealisation

Depression, dysphoria

Patients with a lower risk of relapse are those taking a daily dose of 10 mg diazepam equivalent or less at the start of tapering, and those who have made a substantial dose reduction themselves before the start of tapering. Other low-risk characteristics are less severe benzodiazepine dependence (measured on a dependence scale), no previous withdrawal attempts, high life satisfaction and no use of alcohol.[15,17] Patients without unstable psychiatric or medical comorbidity, no history of seizures and no concurrent drug abuse or dependence are also at a lower risk of harm from benzodiazepine withdrawal.

Patients may find that the symptoms of withdrawal (see Box) are typical of their previous problems such as insomnia or anxiety. This should be discussed with them, and psychotherapy or appropriate pharmacotherapy offered.

There are no standard tapering regimens and the rate of tapering depends on the starting dose, duration of therapy, risk of relapse and how well tapering is tolerated by the patient. In general, at higher doses (e.g. greater than 10 mg diazepam equivalents per day) the dose may be tapered more rapidly. Once the patient achieves 10 mg the dose should be tapered more slowly (e.g. 5 mg twice daily for two weeks, then once daily for two weeks, and then 2 mg daily for two weeks and then cease).

Pharmacotherapy

Anticonvulsants have some efficacy in benzodiazepine withdrawal if the patient is not dependent on other drugs. Carbamazepine has a modest benefit[12] and pregabalin can be effective.[18] Antidepressants and beta blockers have no proven benefit.

Flumazenil, a $GABA_A$ receptor antagonist, has been used as a low-dose intravenous or subcutaneous infusion over four days to help patients rapidly withdraw from benzodiazepines to a lower dose or to abstinence without significant withdrawal symptoms. A proposed mechanism is reversal of receptor desensitisation and down regulation. There are some data showing effectiveness, albeit in small groups of patients.[19] Although relatively uncommon, seizures can occur with low-dose flumazenil infusion and so it should only be considered in a specialised unit.[20]

Psychotherapy

A meta-analysis of treatment for benzodiazepine discontinuation found that gradual dose reduction combined with psychological treatment was superior to gradual dose reduction alone.[21] A recent Cochrane review assessed randomised controlled trials of many different psychosocial interventions. It found only moderate evidence that adding cognitive behavioural therapy during taper was more effective than just

tapering the dose. There was insufficient evidence to make any conclusions regarding motivational interviewing. Interventions that could reduce benzodiazepine use include a tailored letter from the patient's GP advising reducing or quitting the drug, standardised interviews and relaxation techniques.[22]

Stabilisation and maintenance therapy

Some patients are reluctant to consider ceasing their benzodiazepine and are at high risk of relapse or harm. A harm reduction strategy may be more appropriate for this group. This involves using a long half-life substitute to prevent intoxication and withdrawal phenomena, and allowing the patient to engage in holistic treatment of their dependence, before slowly reducing the dose.

Patients who may need maintenance therapy are those who are on a high diazepam equivalent dose, have a range of aberrant drug-related behaviours (especially doctor shopping) and have a chaotic social setting or unstable psychiatric diagnoses. Patients who are alcohol or drug dependent may also benefit from this approach.[23] These people are often difficult to manage and should be referred to a specialist addiction service. To support management in rural and remote settings, health professionals in all states and territories have access to 24-hour phone support services.[24]

Patients on maintenance therapy may eventually reach a period of stability in which withdrawal to a lower dose or abstinence may be considered. High-risk patients or those with unstable medical conditions or a significant seizure history may benefit from admission to an inpatient service for stabilisation or withdrawal.

Conclusion

There is significant concern regarding overprescribing of benzodiazepines and the resultant harms. People who are benzodiazepine dependent or at risk because of misuse should be identified and appropriately assessed to determine their risk of harm. Depending on patient characteristics, benzodiazepines can be withdrawn or the patient stabilised on a maintenance program.

Prescribing interventions, substitution, psychotherapies and pharmacotherapies all contribute to the management of benzodiazepine dependence. However, some of these interventions have limited supporting evidence. There is therefore a need to develop a better evidence base and treatment paradigm for these patients.

Conflict of interest: none declared

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