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Benzodiazepines and newer hypnotics

SUMMARY

Despite published guidance on the appropriate use of benzodiazepines as anxiolytics or hypnotics, and the appropriate use of the Z drugs (zopiclone, zolpidem and zaleplon) for the short-term management of insomnia, inappropriate prescribing of these drugs is still a concern. This *Bulletin* describes this issue and the current trends in prescribing. It also summarises the current guidance and considers what action can be taken to rationalise the use of these drugs. The management of insomnia and anxiety is beyond its scope.

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Introduction

Guidance for the appropriate use of benzodiazepines as anxiolytics or hypnotics was published in 1988 by the Committee on Safety of Medicines (CSM) (see **Panel 1**).[1] Since then, three 'Z drugs' have been introduced: zopiclone, zolpidem and zaleplon. These are non-benzodiazepine hypnotics, but act at the benzodiazepine receptor.[2] The Z drugs were developed with the aim of overcoming some of the disadvantages of benzodiazepines (e.g. next day sedation, dependence, withdrawal), but available evidence has not clearly shown these benefits. The National Institute for Health and Clinical Excellence (NICE) has recently advised on their appropriate use (see **Panel 1**).[3]

The effects of specific benzodiazepines are dependent upon the dose administered and the pharmacokinetic profile.[3] Chlordiazepoxide, and shorter-acting oxazepam are licensed for use in anxiety. Nitrazepam (which has a prolonged action and may give rise to residual effects on the following day), loprazolam, lormetazepam and temazepam, are licensed for use in insomnia. Diazepam (longer-acting) and lorazepam (shorter-acting) are licensed for both indications.[2] The Z drugs are only licensed for insomnia.[4–6] Zolpidem and zopiclone are short-acting, and zaleplon is described as very short-acting.[2]

What are the key concerns?

Many people may develop tolerance to the effects of benzodiazepines, gain little therapeutic benefit from chronic consumption, become dependent on them, and suffer a withdrawal syndrome when they stop taking them. The syndrome may include anxiety, depression, nausea and perceptual changes.[3] Concerns over dependence led to the CSM advice issued in 1988 (see **Panel 1**).[1] Factors potentially associated with an increased risk of developing dependency include long-term use, short duration of action, high dose, high

Panel 1: Summary of guidance for prescribing benzodiazepines and Z drugs[1,3]

1988 CSM advice on benzodiazepines[1]

As anxiolytics

- Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
- The use of benzodiazepines to treat short-term "mild" anxiety is inappropriate and unsuitable.

As hypnotics

- Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

NICE guidance on the use of Z drugs[3]

- When, after due consideration of the use of non-pharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications.
- It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics (temazepam, loprazolam and lormetazepam), the drug with the lowest purchase cost should be prescribed.
- It is recommended that switching from one of these hypnotics to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent.
- Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

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potency, alcohol or other drug dependency, personality disorders, and use without medical supervision.[3]

MeReC Briefing Issue No. 17 discussed if there is an association between benzodiazepine use and falls and hip fracture.[7] Several observational studies have suggested that benzodiazepines increase the risk of falls in the elderly. The *Medicines and Older People* section of the *National Service Framework (NSF) for Older People*[8] states that patients taking hypnotics are more liable to fall during the night, and this has been shown for short-acting as well as long-acting drugs. Evidence of an increased risk of hip fracture with the use of hypnotics is conflicting and incomplete.[3,7] However, these potential risks need to be considered when prescribing for older people, especially those vulnerable to hip fracture.[7]

Potential risks of falls need to be considered when prescribing hypnotics for older people

Benzodiazepines may impair judgement and increase reaction time, and so affect ability to drive or operate machinery.[2] Hangover effects of a night dose may impair driving the following day. They also increase the effects of alcohol.[2] Following a *Current Problems in Pharmacovigilance* publication in 1999, product information for all benzodiazepines was updated to include clearer warnings that the ability to drive may be affected, particularly if alcohol is consumed.[9] This was prompted by a study in Scotland of 19,386 drivers involved in road traffic accidents (RTAs) that found benzodiazepine use was associated with an increased risk of a RTA (odds ratio 1.62; 95% CI 1.24 to 2.12).[10] Risk was increased for longer-acting benzodiazepines, those used as anxiolytics and the hypnotic zopiclone.

What are the current prescribing trends?

Although benzodiazepine prescribing has declined substantially since the 1988 CSM advice,[11] large numbers of prescription items are still being issued, often for quantities suggestive of long-term treatment. Furthermore, the use of Z drugs is increasing (see **Panel 2**).[12]

Z drugs and benzodiazepine hypnotics — how do they compare for insomnia?

As with benzodiazepines, Z drugs are only indicated for short-term use in insomnia that is severe, disabling or subjecting the patient to extreme distress. Treatment duration should not exceed four weeks for zolpidem[5] and zopiclone,[6] and two weeks for zaleplon.[4]

A recent meta-analysis of short-term benzodiazepine use in the treatment of insomnia showed an increase in total sleep duration (from sleep records; one to seven day treatment) by an average of 61.8 minutes (95% CI 37.4 to 86.2) compared with placebo.[13] However, sleep latency (time to fall asleep) was decreased (from sleep records; one to seven day treatment) by an average of only 4.2 minutes (95% CI -0.7 to 9.2). More patients reported adverse effects with benzodiazepines than placebo, though dropout rates were similar.

NICE has reviewed the clinical and cost effectiveness of the Z drugs relative to benzodiazepines approved for the treatment of insomnia.[2] The review of clinical effectiveness included 17 short-term randomised controlled trials (RCTs) conducted in patients with insomnia. It was considered that the RCTs available did not reflect current NHS practice. None of the RCTs had appropriately compared the Z drugs with shorter-acting benzodiazepines used at appropriate doses, and the most common comparator used was the longer-acting nitrazepam. Comparison of results from the different studies was difficult due to methodological problems and variations in outcome measures used. There was evidence of selective reporting of significant findings.[3]

Although there were some statistically significant differences found for some of the efficacy outcome measures within individual RCTs, differences were not consistent across the trials. In most cases, the absolute difference was small and the clinical significance difficult to establish.[3] NICE also reviewed nine RCTs conducted in healthy volunteers in whom insomnia had been induced. There were no consistent differences between the drugs. Most of the studies had small sample sizes or were of short duration. Again, none of the RCTs had appropriately compared the Z drugs with shorter-acting benzodiazepines, used at appropriate doses.[3]

NICE concluded that there was no compelling evidence of a clinically useful difference between the Z drugs and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse. Although RCTs to assess the relative clinical and cost effectiveness of the Z drugs and the shorter-acting benzodiazepines could be potentially useful, a more worthwhile use of NHS resources would be to focus on the clinical and cost effectiveness of pharmacological treatments relative to non-pharmacological interventions.[3] As previous trials concentrated

Panel 2: Prescribing trends over the last four years[12]

PPA data for the last four years shows that:

- Each year, approximately 15.5 million prescription items are dispensed for benzodiazepines or Z drugs in England.
- The number of items dispensed each year for *hypnotics* has remained approximately the same at around 10 million items.
- In 2001, approximately 42% of all hypnotic items dispensed were for temazepam and 18% were for nitrazepam.
- In 2004, approximately 35% of all hypnotic items dispensed were for temazepam and 15% were for nitrazepam.
- However, from 2001 to 2004, the proportion of hypnotic items dispensed each year that are Z drugs has increased from approximately 33% to 44%.

on sleep-specific outcome measures, NICE suggests that further research should include the impact of hypnotics on daytime functioning and health-related quality of life.[3]

What action can be taken to reduce the use of benzodiazepines and Z drugs?

Audit

The importance of auditing the prescribing of these drugs has been highlighted in several key national pieces of guidance. However, audit is only a first step and it is essential there is a commitment to change practice, where necessary.

In 1999, the Mental Health NSF reinforced CSM advice recommending that benzodiazepines should be used for no more than two to four weeks for severe and disabling anxiety.[14] It stated that, by 2001, all health authorities should have systems in place to monitor and review prescribing rates of benzodiazepines within the local clinical audit programme. PCT managers should ensure that this recommendation is being implemented.

The Prescribing Toolkit, developed by the Prescribing Support Unit (PSU), includes several prescribing indicators that can be used to monitor prescribing. An indicator relating to benzodiazepines has been developed, although this does not include the Z drugs (ADQs [Average Daily Quantities] per benzodiazepine STAR-PU [Specific Therapeutic Age-sex Related Prescribing Unit]).[15] The toolkit is useful for prescribing advisers to gain an overview of prescribing, however ePACT.net should be used for further analysis, particularly at practice level.

Until 2004/2005, drugs acting on benzodiazepine receptors (benzodiazepines and Z drugs) were the focus of one of the national performance indicators (separate to the prescribing indicators above) used to assess PCTs and inform the annual star ratings. This indicator looked specifically at prescribing rates for drugs acting on benzodiazepine receptors (ADQs per STAR-PU) and used a STAR-PU specific to these drugs.[15,16] This indicator has also been included in the Prescribing Toolkit, to allow comparisons with cluster matched PCTs.[15]

The NICE guidance on the use of Z drugs for the short-term management of insomnia suggests criteria that could be used for audit purposes (see **Panel 3**, page 20). To ensure consistency, these criteria will need local agreement on definitions and documentation.[3]

The recent clinical guideline from NICE for anxiety[17] suggests benzodiazepines as one of the options to be considered (along with support and information, problem solving, sedating antihistamines and self-help) if immediate management of generalised anxiety disorder is necessary. It adds that benzodiazepines should not usually be used beyond two to four weeks, in keeping with all previous guidance (see **Panel 3**).

The Clinical Governance Research and Development Unit at the University of Leicester recently updated an audit protocol for benzodiazepine prescribing in primary care.[18] It can be used for individual or multi-practice audit and has been divided into 'must do' and 'should do' criteria, so aspects of care can be prioritised. (see **Panel 3**).[18]

Reducing use

The Leicester audit protocol suggests that chronic users (four to eight weeks or longer) should be identified through a structured programme and, where appropriate, encouraged to gradually withdraw;[18] abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens.[2] More detailed information on managing withdrawal is provided in PRODIGY guidance on hypnotic or anxiolytic dependence[19] and the BNF.[2] The BNF includes a suggested withdrawal protocol involving transfer to an equivalent dose of diazepam and slowly reducing the dose.[2] There is little published information regarding withdrawal of Z drugs, although their respective SPCs indicate that similar precautions are necessary.[4–6]

One simple intervention that has shown some benefit in reducing benzodiazepine use in long-term users is the sending of a GP letter to targeted patients. The letter discussed the problems associated with long-term benzodiazepine use and invited patients to try and reduce their use and eventually stop, with an offer of further advice if needed.[20]

Certain patients will be unsuitable for withdrawal, e.g. those patients experiencing a current crisis or having an illness for which the drug is required at the current time.[20] Referral to specialist teams may be appropriate for some, e.g. if the patient is also dependent on other drugs or alcohol, or if there is co-existing physical or psychiatric morbidity.[19]

Some PCTs have identified patients taking long-term benzodiazepines and arranged benzodiazepine review clinics. In some cases, PCTs participating in the Medicines Management Services (MMS) Collaborative, hosted by the National Prescribing Centre, have piloted such reviews as part of their improvement work.[21] In some parts of the country, specialist clinics are available to help people with benzodiazepine dependence.[11]

Opportunities to change practice will also arise on an ad-hoc basis. For example, the *National Service Framework (NSF) for Older People*[8] identified certain groups of older people

There is no compelling evidence of a clinically useful difference between the Z drugs and shorter-acting benzodiazepine hypnotics

The BNF includes a suggested benzodiazepine withdrawal protocol

Panel 3: Potential audit criteria[3,17,18]

Suggested audit criteria from NICE Technology Appraisal No. 77: Guidance on the use of Z drugs for the short-term management of insomnia[3]

- Hypnotic drug therapy is used for the management of severe insomnia interfering with normal daily life only after due consideration of the use of non-pharmacological measures.
- When hypnotic drug therapy is used, the drugs are prescribed for short periods of time only, in strict accordance with the licensed indications.
- When hypnotic drug therapy with shorter-acting benzodiazepine hypnotics, zaleplon, zolpidem or zopiclone, is prescribed, the drug with the lowest purchase cost is chosen.
- A patient is switched from one of these hypnotic drugs to another only if he or she experiences adverse effects considered to be directly related to a specific agent.
- A patient who has not responded to one of these hypnotic drugs is not prescribed any of the others.

Suggested audit criterion from the NICE clinical guideline for anxiety[17]

- A patient with generalised anxiety disorder is not prescribed benzodiazepines for longer than two to four weeks.

'Must do' criteria from the Leicester audit protocol for benzodiazepine prescribing in primary care[18]

These are the minimum criteria that practices need to audit, as there is firm research evidence to justify their inclusion. Every practice must include these criteria in the audit:

- New benzodiazepine prescriptions should only be issued for short-term relief (no longer than four weeks) of severe anxiety or insomnia.
- Records show that a patient receiving a prescription (either new or repeat) for a benzodiazepine has been given advice about non-drug therapies for anxiety or insomnia.
- Records show that the patient has been given appropriate advice about the risks of benzodiazepine use, including the potential for dependence.

Implementation of the CSM advice for benzodiazepines and NICE guidance relating to Z drugs should remain a priority

known to be at higher risk of medicines-related problems. It recommends that all patients over 75 years of age should have their medication reviewed at least annually.[8] These reviews are an opportunity to consider withdrawal of long-term benzodiazepines. Since patients taking hypnotics are more liable to fall during the night, such review can play an important part in falls prevention. Where a patient has fallen, medication review and subsequent prescribing changes have been shown to reduce further falls.[8]

Consistency of approach and improved communication between primary and secondary care and mental health trusts could also help reduce over-prescribing. This could involve the use of shared treatment guidelines that specify duration of therapy and cessation of treatment following hospital discharge.[11] Drug and therapeutic committees may be the most appropriate strategic forum to raise issues such as benzodiazepine prescribing.

Conclusion

The prescribing of benzodiazepines has declined substantially since the release of the CSM advice in 1988.[11] However, hypnotics still account for a large number of prescription items, of which Z drugs are an increasing proportion. Although there is no longer a national performance indicator relating to benzodiazepines and Z drugs, prescribers and PCTs should not be complacent. Implementation of the CSM advice for benzodiazepines and NICE guidance relating to Z drugs should remain a priority.

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