Benzodiazepines: Risks and Benefits. A Reconsideration

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Abstract: Over the last decade there have been further developments in our knowledge of the risks and benefits of benzodiazepines, and of the risks and benefits of alternatives to benzodiazepines. Representatives drawn from the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists and the British Association for Psychopharmacology together examined these developments, and have provided this joint statement with recommendations for clinical practice. The working group was mindful of widespread concerns about benzodiazepines and related anxiolytic and hypnotic drugs. The group believes that whenever benzodiazepines are prescribed, the potential for dependence or other harmful effects must be considered. However, the group also believes that the risks of dependence associated with long-term use should be balanced against the benefits that in many cases follow from the short or intermittent use of benzodiazepines and the risk of the underlying conditions for which treatment is being provided.

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The Royal College of Psychiatrists has previously provided guidance on the risks and benefits of benzodiazepines, in March 1988 and January 1997. Over the last decade there have been further developments in our knowledge of the risks and benefits of benzodiazepines, and of the risks and benefits of alternatives to benzodiazepines. In addition, the licensing of some selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors for treatment of a broad range of anxiety disorders (and the licensing of pregabalin for generalized anxiety disorder) has increased choice among potential pharmacological and psychological interventions. Representatives drawn from both the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists and the British Association for Psychopharmacology together examined these developments, and have provided this joint statement with its recommendations for clinical practice.

The working group was mindful of widespread concerns about benzodiazepines and related anxiolytic and hypnotic drugs. The group believes that whenever benzodiazepines are prescribed, the potential for dependence or other harmful effects must be considered. However, the group also believes that the risks of dependence associated with long-term use should be balanced against the benefits that in many cases follow from the short or intermittent use of benzodiazepines and the risk of the underlying conditions for which treatment is being provided. The balance of risks and benefits with benzodiazepines or alternative interventions in an individual patient can be hard to assess, and is ultimately a matter of clinical judgment. The group contends that benzodiazepine prescribing, like other aspects of clinical practice, should be based on thoughtful consideration of the likely risks and benefits of benzodiazepines, and of the risks and benefits of alternative interventions. This consideration should be made in conjunction with the patient, and their carers, where appropriate.

Pharmacological properties of benzodiazepines

Benzodiazepines are 'allosteric modulators' of $GABA_A$ receptors (GABA is the widely distributed inhibitory neurotransmitter gamma-aminobutyric acid). A $GABA_A$ receptor comprises five transmembrane glycoprotein subunits arranged around a central chloride channel. Benzodiazepines bind to a specific site on the $GABA_A$ receptor membrane complex, which is distinct from the GABA binding site. The $GABA_A$ receptor has multiple additional binding sites, including those for benzodiazepines, barbiturates and neurosteroids. It is controversial

whether alcohol interacts directly or only indirectly with the receptor. Different $GABA_A$ subunits are combined together to produce a variety of receptor subtypes, which have distinct distributions within the central nervous system as well as specific pharmacological properties. Binding of a benzodiazepine to its site on the receptor increases the affinity of the receptor for GABA, which in turn leads to a greater likelihood of the receptor 'opening' to allow the passage of chloride ions through the membrane. This normally results in neuronal hyper-polarization and reduced excitability of the target cell. Unlike barbiturates at high doses, benzodiazepines do not mimic the effects of GABA and do not activate chloride channels directly.

The benzodiazepines can be divided into different groups based on their chemical structure and pharmacokinetic properties, although all share a common mechanism of action and produce a range of similar clinical effects. There are other compounds of unrelated structure that also bind to the benzodiazepine site on the $GABA_A$ receptor and share some, but not all, of the pharmacological properties of benzodiazepines. Currently these are the 'Z-drugs' (zaleplon, zolpidem and zopiclone), which are used as hypnotics only. They show subtle differences in pharmacology from the benzodiazepines as well as having an improved kinetic profile for sleep induction with reduced 'hangover'. The general principles that apply to benzodiazepine prescribing also apply to the Z-drugs.

The benzodiazepines differ in their potency, time to effect and duration of action, with some needing repeated daily dosing and others once-daily dosing to achieve their desired clinical effects. Many benzodiazepines (for example, diazepam) have longer-lasting active metabolites, which can accumulate with repeated dosing, especially in elderly patients and those with physical health problems, or those with genetic variants leading to low or absent activity of relevant cytochrome P450 enzymes.

Beneficial effects of benzodiazepines

The beneficial effects of benzodiazepines include the reduction of anxiety, the induction and maintenance of sleep, muscle relaxation, and the treatment and prevention of epileptic seizures. These properties are shared by most currently approved benzodiazepines but to varying degrees, depending on their potency and pharmacokinetic properties.

Treatment of anxiety disorders

Randomized controlled trials have provided evidence for the efficacy of some benzodiazepines in certain anxiety disorders, usually in acute treatment for the reduction of anxiety symptoms, but sometimes in longer-term treatment, designed to prevent a relapse of symptoms in someone who has made a good response to acute treatment. There is good evidence for efficacy in acute treatment of generalized anxiety disorder, social anxiety disorder and panic disorder, but limited evidence for efficacy in obsessive-compulsive disorder. Benzodiazepines have not been found to be efficacious in randomized controlled trials in post-traumatic stress disorder, and may indeed be unhelpful in preventing the emergence of post-traumatic symptoms after traumatic events.

There have not been many direct comparisons of the efficacy of benzodiazepines with alternative pharmacological treatments such as selective serotonin reuptake inhibitors. Alternative pharmacological approaches are generally somewhat better tolerated, and for these reasons recent guidance from the National Institute for Health and Care Excellence (NICE), the British Association for Psychopharmacology and other bodies suggests that other approaches should be used in preference to benzodiazepines, which are generally reserved for patients who do not respond to other treatments. Benzodiazepines do not have an antidepressant effect when used alone, which is a disadvantage in patients with anxiety disorders who are also depressed, but they may sometimes be used to cover the period of illness before antidepressants become effective (typically a few weeks) and to reduce possible exacerbations of anxiety during this period.

Benzodiazepine anxiolytics should be prescribed primarily either for the short-term relief of severe anxiety symptoms, or where anxiety disorders are disabling and severe and causing both significant personal distress and substantial impairment of daily activities. Where the rationale for treating anxiety symptoms does not meet either of these criteria, psychological or pharmacological treatments with an evidence base for long-term use are more suitable.

To reduce the risk of dependence on benzodiazepines they should generally not be prescribed as a regularly administered medication for longer than four weeks. Ideally they should be given on an 'as required' basis and intermittently every few days during this period. Benzodiazepines may exert beneficial effects within a few days of starting treatment, and may offer the prospect of symptom relief while other treatments such as cognitive–behavioural therapy have yet to be started or before antidepressant drugs have had time to act.

There are clinical circumstances in which longer-term prescription of benzodiazepines might be considered desirable because the alternatives are probably worse than the continued use of benzodiazepines.

This may be the case in conditions such as chronic treatment-resistant anxiety disorders or in patients who have established dependence and who have not been able to stop treatment successfully. In rare instances longer-term prescriptions of benzodiazepines may be seen as a form of harm reduction in patients who would otherwise consume illicit benzodiazepines or abuse alcohol to 'cope' with anxiety: again, efforts should be made to reduce the dosage over time, wherever possible. There are other situations where anxiety is complicated by other medical conditions, or where the risk of dependence with benzodiazepine use may be considered acceptable because of the severity of illness and potential hazards associated with other treatment approaches, such as may occur in some patients with schizophrenia.

INDUCTION OF SLEEP

Adequate treatment of insomnia is often difficult, and depends on many factors such as age, presence of physical illness, pain, use of concomitant medication, and history of drug or alcohol misuse. The adoption of 'sleep hygiene' techniques forms the initial part of management. The benzodiazepines and Z-drugs are the most effective drugs for the short-term treatment of insomnia that is severe, disabling and causing distress. They can reduce the time taken to fall asleep, increase the duration and efficiency of sleep, and reduce periods of wakefulness after the onset of sleep. Drugs with a relatively short half-life can facilitate falling asleep with a lower risk of residual daytime drowsiness ("hangover") than is seen with drugs that have longer half-lives.

The use of benzodiazepines as hypnotic agents should be only one aspect of general management. As in the treatment of patients with anxiety disorders, the use of benzodiazepines should generally be limited to a maximum of four weeks, though there is little evidence that longer-term use is more hazardous than short-term use. In the United Kingdom, though not in the the United States and some other countries, all hypnotics are licensed for short term use only. Prescriptions should preferably be at the lowest effective dose and given intermittently. Care should be taken to exclude or manage associated conditions such as mood disorders or substance misuse. Some conditions such as sleep apnoea may be aggravated by the use of benzodiazepines. In patients with chronic insomnia, benzodiazepines should be used only in the short term while more appropriate longer-term treatments are started. Elderly individuals are more vulnerable to the adverse effects of prescribed medication, but consume the majority of sleeping tablets. They often have co-existing physical disease, and a pragmatic approach to treatment may need to be adopted, whilst paying attention to issues such as drug–drug interactions.

Alternatives to benzodiazepines such as zopiclone, zolpidem and zaleplon are now available for managing insomnia. They have pharmacological similarities to benzodiazepines and produce similar side-effects, but have relatively shorter half-lives and in some cases are more selective for specific $GABA_A$ receptor subtypes. Like benzodiazepines, these drugs are licensed for short-term use only. Where the effects are selective on certain $GABA_A$ receptor subtypes, the anxiolytic effects are few. However, the Z-drugs may have some limited advantages over traditional benzodiazepines in terms of dependence and withdrawal, and should be considered as an alternative, particularly if there seems to be a potential need for longer-term treatment or in patients presumed to be at increased risk of dependence.

OTHER BENEFICIAL EFFECTS

Benzodiazepines have anticonvulsant and muscle relaxant effects that are considered to be independent of their anxiolytic actions. These effects can be valuable in the emergency treatment of seizures or in the management of spasticity or muscle spasms, or movement disorders associated with the use of antipsychotic drugs. Tolerance may develop with long-term use, particularly to their anticonvulsant effects, and they are therefore not generally recommended for prophylactic use in epilepsy, other than in some rare childhood syndromes. They are sometimes used as part of induction procedures prior to anaesthesia.

Although the evidence for potential benefit is rather mixed, some patients with excitement, agitation or severe psychotic symptoms may be prescribed short-term benzodiazepines as part of acute 'rapid tranquillization', or as an adjunct to the use of antipsychotic drugs. In these situations, the dose and duration of treatment needs to be monitored closely. Certain benzodiazepines such as clonazepam can be used in the treatment of patients with acute mania. When these compounds are no longer required, patients should be withdrawn from them, in a tapered manner.

Benzodiazepines – notably diazepam and chlordiazepoxide – are useful in managing withdrawal from alcohol in patients with alcohol dependence, especially in the prevention of epileptic seizures and delirium tremens. There is only limited evidence to suggest that benzodiazepines may be useful in the management of patients with acute confusional or delirious states, and their use in these conditions is not recommended. There is little evidence that previously alcohol-dependent patients may derive benefit from benzodiazepines in helping to facilitate continuing abstinence from alcohol.

Risks of benzodiazepines

Benzodiazepines have a range of untoward adverse effects that may outweigh the benefits in certain patient populations, which therefore limits their use in clinical practice.

Cognitive effects

Controlled studies and systematic reviews have shown that benzodiazepine administration can result in sedation and drowsiness, mental slowing and anterograde amnesia (difficulty in forming new memories). These effects are all dose-dependent. Some but not all of these adverse cognitive effects reduce with continued administration – for example, sedation and drowsiness become less prominent with continued use, but memory problems are likely to continue. Withdrawal from benzodiazepines may be associated with some improvement in cognitive performance after abstinence.

It has been argued that these untoward effects can reduce the likelihood of responding to psychological interventions, although the evidence of this is limited. Similar concerns have been expressed about impairment in the ability to adjust to psychological traumas such as bereavement; despite this, it remains common (although not necessarily best) practice to provide a benzodiazepine to the recently bereaved. However, this may defer the emergence of a bereavement reaction until the benzodiazepine is stopped.

Psychomotor effects

Benzodiazepine administration can result in an impairment of performance whilst driving similar to that seen with blood alcohol levels below the current UK legal limit, the magnitude of effects being influenced by the drug, dosage and other factors. There is also an interaction with alcohol that potentiates the degree of impairment seen with either drug alone. Pharmacoepidemiological studies suggest that benzodiazepine use is associated with an increased risk of road traffic accidents, over and above that seen with untreated mental disorders. Patients should be advised to contact the Driver and Vehicle Licensing Agency (DVLA) when they are taking medications that may impair driving performance, and to avoid drinking alcohol. Due to drug accumulation, use of drugs with longer half-lives may be more hazardous than use of drugs that have a shorter half-life. Elderly patients are more vulnerable to the cognitive and psychomotor effects of benzodiazepines and eliminate long-acting drugs more slowly than younger patients, and an increased risk of falls should be considered when contemplating possible benzodiazepine prescription to such patients.

Tolerance

Tolerance to the effects of benzodiazepines can occur; this is more pronounced for the anticonvulsant and sedative effects. Tolerance to the hypnotic and anxiolytic effects can also develop, but probably less often and more slowly. It is unusual for patients to steadily increase their dosage, but this can occur in some patients, particularly those with a history of alcohol dependence or other substance misuse. Should tolerance occur, possible reasons for this need to be explored, and the possibility of misuse considered.

Dependence

Probable dependence on benzodiazepines is usually manifest by the emergence of withdrawal symptoms on either stopping or too rapidly reducing treatment. Withdrawal symptoms can be physical (such as flu-like complaints and muscle cramps) or psychological (such as irritability, insomnia, nightmares, perceptual changes, and depersonalization or derealization). Symptoms can be prolonged and are sometimes hard to distinguish from those of underlying anxiety disorders, although perceptual disturbances are relatively infrequent in untreated patients with anxiety disorders. Withdrawal reactions are generally short-lived, typically lasting less than one month, although duration is influenced by individual pharmacokinetic factors. There is controversy about whether symptoms persisting for many months (reported by approximately one-quarter of patients) are withdrawal reactions, or simply the features of an underlying disorder, or worsening of that condition triggered by treatment withdrawal.

Established benzodiazepine dependence is preferably treated by advice, pharmacological optimization or substitution, gradual withdrawal and psychological support. In some patients, pharmacological and psychological interventions will be of only limited benefit, so certain individuals will be unable to stop benzodiazepines. Risk factors for continuation include a history of substance misuse, comorbid depression, dependent personality disorder and physical ill-health. In patients with persistent symptoms, a joint decision should be made about whether they are generally better off with or without treatment.

Patients with affective disorders

Benzodiazepines may reduce early adverse drug effects in the treatment of depression and bipolar affective disorder. However, they may sometimes

appear to worsen depressive symptoms, perhaps by reducing prominent anxiety symptoms and thereby 'revealing' underlying depression. They have minimal effects in reducing the severity of mild depressive symptoms and in some patients may reduce the likelihood of responding to antidepressant treatment. Stopping benzodiazepines can also be associated with the emergence of depressive symptoms. Benzodiazepines are no substitute for effective continuation treatment with antidepressant drugs in patients with recurrent unipolar depression.

PATIENTS WITH PSYCHOSIS

Lorazepam (either orally or intramuscularly) is commonly prescribed in inpatient settings for the management of patients with psychosis and prominent behavioural disturbance. If regular benzodiazepine prescription is required, clonazepam may be preferable, as its long half-life makes it suitable for once-daily dosage.

ABUSE OF BENZODIAZEPINES

Some individuals abuse benzodiazepines (especially temazepam, flunitrazepam and diazepam) and/or related drugs, as part of a wider drug (e.g. heroin, crack cocaine) and/or alcohol problem. Intravenous injection of temazepam can result in emboli and gangrene. Altering the formulations of certain drugs has made them less easy to inject, and restricting the previously most widely abused drug (temazepam) has probably limited its use by this route. Some 'benzodiazepines' sourced through the Internet are of uncertain nature and strength, and may contain hazardous contaminants. Clinicians should be aware of the increased risks in overdose when benzodiazepines are mixed with other respiratory depressants.

Benzodiazepines are often used as an alternative when supplies of other drugs of abuse are scarce. Benzodiazepines are also sometimes used by young people to 'come down' after taking stimulant 'party drugs'. Prescriptions of benzodiazepines should be subject to regular review. Doctors should be aware that the medication they prescribe may be diverted into the wrong hands and enter the 'black market', and so should be wary of prescribing to certain individuals, such as those with a history of multiple drug abuse. Prescription of benzodiazepines in conjunction with methadone is no longer regarded as good clinical practice.

'DISINHIBITION'

There is some controversy about whether benzodiazepine use alone can result in disinhibited or impulsive behaviour. Studies in patients with personality disorders suggest that benzodiazepines may increase the risk of suicidal behaviour, especially when combined with alcohol. In theory, use of benzodiazepines by predisposed individuals may 'release' aggressive behaviour towards others, but it is hard to distinguish this possible effect from the features of an underlying disorder.

WITHDRAWING BENZODIAZEPINES

In general, benzodiazepines should be prescribed in as low a dose as possible to afford adequate symptom relief. It is difficult to produce a 'risk table', but compounds with higher potency and shorter half-life are associated with a greater likelihood of developing dependence. Unless there are clear risks of more severe problems if the drug is stopped, patients should be encouraged to withdraw gradually after long-term use. Many patients who were previously treated with benzodiazepines over long periods have already withdrawn successfully, but newly dependent patients are still accruing, as prescriptions for benzodiazepines are not declining. Many of those who remain on benzodiazepine anxiolytics will have trouble stopping unless expertly and sympathetically managed, including being offered psychological and other alternative therapies.

Concerns about the use of benzodiazepines as hypnotics are different from the concerns in patients with anxiety disorders. The sudden withdrawal of a long-established treatment can be extremely distressing and possibly dangerous, for example through inducing epileptic seizures. Dependence is more likely with higher dosages but can also occur with low doses, and formulations of compounds at lower strengths and with longer half-lives may be useful in helping patients reduce from higher doses. Even after short-term use, a tapering-off regime (i.e. at least two weeks at reduced dosage) should be considered to minimize the risk of rebound phenomena, that is, the reappearance of symptoms present prior to treatment. After longer-term use this reduction period should probably be extended, sometimes to several months in patients who have been treated for many years. Where benzodiazepine dependence is diagnosed but a considered decision is made that continued prescription is nonetheless appropriate, they should be prescribed at gradually reducing doses wherever possible.

RECOMMENDATIONS

1. Benzodiazepines have a range of beneficial effects and a range of untoward effects, like all forms of pharmacological and psychological treatment.

2. Benzodiazepines may be prescribed safely in the short term and can be effective treatments in many patients whose quality of life is significantly affected by distressing anxiety symptoms or troublesome insomnia.
3. Some other classes of psychotropic drugs have proven efficacy in anxiety disorders, so it is important to consider alternatives to prescribing benzodiazepines. Consideration of alternatives should include a balanced appraisal of the relative benefits and risks of the range of options, in acute and longer-term treatment. Psychological interventions should always be considered as alternatives or additions to pharmacological treatment.
4. Dependence is recognized as a significant risk in some patients receiving treatment for longer than one month, and health professionals should be conscious of this when considering the relative benefits and risks of treatment. The potential risks of long-term treatment need to be considered prior to starting short-term treatment.
5. As with all interventions, health professionals should examine the likely benefits and risks in each individual case early in treatment, so that if problems occur, they have been anticipated by doctors, patients and their carers.
6. If dependence on benzodiazepines has become established, it is often difficult to treat and can become a longterm and distressing problem.
7. Many health professionals have been dissatisfied with previous guidance that benzodiazepines should be used for short-term treatment only and no longer than four weeks in regular dosage. All patients should be made aware of the risks of dependence if they continue benzodiazepines in regular dosage over a longer period. A clinical judgement has to be made as to whether alternatives may be more suitable, for each patient, and for each proposed medication.
8. Many patients are able to take short courses of benzodiazepines (or to use them on an 'as required' basis) quite safely and to stop them when no longer needed. If treatment courses lasting longer than four weeks are required, this should not necessarily be regarded as a deviation from good clinical practice, although continuing vigilance of potential hazards is needed throughout treatment.
9. If there is no history of drug dependence, and positive indicative 'lifestyle' factors are present, a conscious decision to continue benzodiazepine treatment may be more reasonable than the alternatives, provided the patient periodically attempts to slowly reduce the dosage at regular intervals and tries to stop altogether when or if possible.
10. If the alternative to benzodiazepine treatment is the use of another form of treatment, either psychological or pharmacological, which proves to have little benefit in practice, a patient may return to the prescriber and ask to be put back on a benzodiazepine. This request should not be automatically declined but there should be a sympathetic consideration of whether or not this is appropriate.

Further reading

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Notes