Guidelines for the Rational Use of Benzodiazepines
When and What to Use

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Summary

The main actions of benzodiazepines (hypnotic, anxiolytic, anticonvulsant, myorelaxant and amnesic) confer a therapeutic value in a wide range of conditions. Rational use requires consideration of the large differences in potency and elimination rates between different benzodiazepines, as well as the requirements of individual patients.

As hypnotics, benzodiazepines are mainly indicated for transient or short term insomnia, for which prescriptions should if possible be limited to a few days, occasional or intermittent use, or courses not exceeding 2 weeks. Temazepam, loprazolam and lormetazepam, which have a medium duration of action are suitable. Diazepam is also effective in single or intermittent dosage. Potent, short-acting benzodiazepines such as triazolam appear to carry greater risks of adverse effects.

As anxiolytics, benzodiazepines should generally be used in conjunction with other measures (psychological treatments, antidepressants, other drugs) although such measures have a slower onset of action. Indications for benzodiazepines include acute stress reactions, episodic anxiety, fluctuations in generalised anxiety and as initial treatment for severe panic and agoraphobia. Diazepam is usually the drug of choice, given in single doses, very short (1 to 7 days) or short (2 to 4 weeks) courses, and only rarely for longer term treatment. Alprazolam has been widely used, particularly in the US, but is not recommended in the UK, especially for long term use.

Benzodiazepines also have uses in epilepsy (diazepam, clonazepam, clobazam), anaesthesia (midazolam), some motor disorders and occasionally in acute psychoses.

The major clinical advantages of benzodiazepines are high efficacy, rapid onset of action and low toxicity. Adverse effects include psychomotor impairment, especially in the elderly, and occasionally paradoxical excitement. With long term use, tolerance, dependence and withdrawal effects can become major disadvantages. Unwanted effects can largely be prevented by keeping dosages minimal and courses short (ideally 4 weeks maximum, and by careful patient selection. Long term prescription is occasionally required for certain patients.

All benzodiazepines exert, in slightly varying degrees, 5 major actions: hypnotic, anxiolytic, anticonvulsant, muscular relaxant and amnesic. Their main advantages are their high efficacy, rapid onset of action and low toxicity. Few, if any, other drugs can compete with them in all these respects.
In short term use, benzodiazepines can be valuable, and sometimes lifesaving, across a wide range of clinical conditions. Nearly all the disadvantages of benzodiazepines result from long term use, and it is such use, involving some millions of people worldwide, which has earned them a poor reputation, particularly as drugs of dependence. This article suggests how benzodiazepines can best be used rationally, to maximise their advantages and minimise their disadvantages. As with all therapies, the balance between benefits and risks may vary between individual patients.

1. Differences Between Benzodiazepines

Some properties of benzodiazepines are shown in Table I. There are large differences in potency between different benzodiazepines, so that equivalent doses vary as much as 20-fold. This factor must be taken into account when changing a patient from one benzodiazepine to another, and special care must be taken in prescribing minimal effective doses of potent benzodiazepines such as alprazolam, triazolam and lorazepam.

There are slight differences in the potency of separate effects, possibly due to differences in affinity for various receptor subtypes. Thus, some benzodiazepines are more effective than others as anticonvulsants and some may differ in the ratio between anxiolytic and hypnotic actions, although the marketing of different benzodiazepines as hypnotics or anxiolytics is governed more by commercial than by pharmacological factors. Rates of penetration into the brain also differ: oxazepam penetrates relatively slowly and therefore has a slower onset of action than, for example, diazepam. Oxazepam is, thus, less suitable as an hypnotic, but also has a lower abuse potential.

Benzodiazepines also differ markedly in their rates of elimination (elimination half-lives vary from 2 to 100 hours) and some have pharmacologically active metabolites. The possibility of residual effects after single doses and cumulative effects with multiple-dose administration must be kept in mind, especially in elderly patients. Potent benzodiazepines with relatively short elimination half-lives (triazolam, alprazolam, lorazepam) appear to carry the highest risk of causing problems with dependence.[1]

Indications for benzodiazepines and the optimal choice of different benzodiazepines are discussed below in order of the conditions for which they are most commonly prescribed.

2. Rational Use of Benzodiazepines for Insomnia

The UK Committee on Safety of Medicines[2] and the Royal College of Psychiatrists[3] both recommended that benzodiazepines be prescribed for insomnia 'only when it is severe, disabling, or subjecting the individual to extreme distress'. The Drug and Therapeutics Bulletin[4] was scarcely less stringent in its view that they 'should only be used when sleep disturbance markedly affects the life of an individual or his family, and when other approaches have failed'. Yet nearly 14 million prescriptions for benzodiazepine hypnotics are dispensed annually in the UK. Prescribing levels have remained steady despite a decline in the prescription of benzodiazepine anxiolytics.[5]

<table>
<thead>
<tr>
<th>Drug</th>
<th>t1/2 (h) [metabolite] (c)</th>
<th>Approximately equivalent oral dosages (mg)</th>
</tr>
</thead>
</table>

TABLE I. Indications and characteristics of benzodiazepines
### Hypnotics

<table>
<thead>
<tr>
<th>Medicine</th>
<th>t1/2 (h)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loprazolam</td>
<td>6-12</td>
<td>1</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>10-12</td>
<td>1</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>15-38</td>
<td>10</td>
</tr>
<tr>
<td>Temazepam</td>
<td>8-15</td>
<td>20</td>
</tr>
<tr>
<td>Triazolam [a]</td>
<td>2-5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Anxiolytics

<table>
<thead>
<tr>
<th>Medicine</th>
<th>t1/2 (h)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>6-12</td>
<td>0.5</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>5-30 [36-200]</td>
<td>25</td>
</tr>
<tr>
<td>Diazepam [b]</td>
<td>20-100 [36-200]</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10-18</td>
<td>1</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>4-15</td>
<td>10</td>
</tr>
</tbody>
</table>

### Anticonvulsants

<table>
<thead>
<tr>
<th>Medicine</th>
<th>t1/2 (h)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobazam</td>
<td>12-60</td>
<td>20</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>24-48</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Premedication, anaesthesia induction; sedation in intensive care

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam[d]</td>
<td>2</td>
<td>Not available for oral administration. Usual dosage range IV or IM 2-7.5mg</td>
</tr>
</tbody>
</table>

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a Withdrawn from the UK market in 1991.
b Although classed as an anxiolytic, diazepam is a useful hypnotic in single or intermittent dosage and is used im as an anticonvulsant (see table IV).
c Half-life of pharmacologically active metabolite.
d Oral dosage not available.
Abbreviations: IM = intramuscular; IV = intravenous; t1/2 = elimination half-life.

Such widespread prescribing may be considered casual,[6] but there is no doubt that in short term use benzodiazepines are effective sleep inducers and sleep promotors. Their use before an individual has reached a state of 'extreme distress' may sometimes be appropriate. Although the drugs provide only symptomatic relief and do not affect the underlying cause, they can, if prescribed judiciously, improve the quality of life for many patients with insomnia.

**2.1 Prevalence of Insomnia**
Insomnia is common, particularly in the elderly and especially in women. Thus, up to 40% of individuals over 65 years of age complain of disturbed sleep[7] and 'the five million British women over 65 probably consume around 40% of all benzodiazepine hypnotics supplied by the FPS'[5] (FPS = Family Practitioner Service, i.e. general practitioners). However, insomnia is by no means confined to the elderly[6] and rational use of benzodiazepines or other hypnotics for this symptom requires consideration of the causes and types of insomnia, the pharmacological effects of the drugs, and the needs of the individual patient.

2.2 Causes and Types of Insomnia

The many causes of insomnia can be broadly categorised as physical, physiological, psychological, psychiatric and pharmacological - the '5P's'.[8] The sleep disturbance itself may consist mainly of difficulty in falling asleep, frequent nocturnal arousals, early morning wakening or a general dissatisfaction with the quality of sleep that is perceived as unrefreshing. The insomnia may be transient, short term or chronic. Pharmacological treatment is not always, or perhaps rarely, indicated. Explanation of sleep requirements, instruction in sleep hygiene, reduction in alcohol (ethanol) and [7,9] need to be considered before the decision is made to prescribe hypnotics.

2.3 General Indications for Drug Treatment of Insomnia

An international conference (National Institute of Mental Health Consensus Conference) on drugs and insomnia[10] made reasonable general recommendations for appropriate use of hypnotic drugs, based on the cause and duration of insomnia. For transient insomnia caused by disruption of circadian rhythms such as in overnight travel, rapid transit over time zones, alteration of shift work or temporary admission to hospital, an hypnotic drug with a short or moderate duration of action and few residual effects would be appropriate to use on 1 or 2 occasions. For short term insomnia resulting from temporary environmental stress, hypnotics may occasionally be indicated, but should be prescribed in low dosages for 1 or 2 weeks only, or intermittently. Chronic insomnia, which is usually secondary to other conditions (physical, psychiatric or psychological), presents a much greater problem. In selected cases an hypnotic may be helpful, but it should be used in minimal effective dosage, intermittently, or in short courses.

2.4 Effects of Benzodiazepines on Sleep

Benzodiazepines and related drugs are probably the best (as well as the most widely used) hypnotics at present available. However, in prescribing them it is necessary to bear in mind that the sleep they induce differs from natural sleep.

Benzodiazepines in general hasten sleep onset, decrease nocturnal awakenings, increase total sleeping time and often impart a sense of deep, refreshing sleep. However, they alter the normal sleep pattern: Stage 2 (light sleep) is prolonged and mainly accounts for the increased sleeping time, while the duration of slow wave sleep (SWS) and rapid eye movement sleep (REMS) may be considerably reduced. The onset of the first REMS episode is delayed and dreaming is diminished. These effects of benzodiazepines have been well studied.[11-13] The abnormal sleep profile probably results from unselective depression of both arousal and sleep mechanisms in the brainstem. The suppression of REMS may initially be helpful in decreasing nightmares, but may also be an important factor in determining rebound insomnia in drug withdrawal (see section 2.5.2).

The typical changes in sleep stages occur with most benzodiazepines in most patients, but individual variations in response are considerable and are influenced by dosage, duration of treatment, type of benzodiazepine, age and clinical state. The increase in total sleeping time appears to be greatest in patients who complain of insomnia and in
those with short baseline sleep duration. However, patients with insomnia tend to overestimate both their baseline degree of sleep disturbance and the efficacy of hypnotic drugs.[14]

2.5 Disadvantages of Benzodiazepine Hypnotics

2.5.1 Tolerance

Benzodiazepines are initially very, efficacious in inducing and prolonging sleep. However, tolerance to the hypnotic effects develops rapidly, sometimes after only a few days of regular use.[15,16] Sleep latency, Stage 2 sleep, SWS, REMS and intrasleep awakenings all tend to return to pretreatment levels after a few weeks.[11,12,16-18] Nevertheless, poor sleepers may report continued efficacy without escalation of dosage[19] and the drugs are often used long term, possibly because of difficulties in withdrawal.

Tolerance to other effects of benzodiazepines does not necessarily develop at the same rate as to the hypnotic actions. Thus, tolerance to the anxiolytic effects appears to develop more slowly (see section 3.4.1), while complete tolerance to some psychomotor and cognitive functions may never develop.[20,21]

2.5.2 Rebound Insomnia

Rebound insomnia, in which sleep is poorer than before drug treatment, is common on withdrawal of benzodiazepines. It is most marked when the drugs have been taken regularly for long periods, but can occur after only 1 week of low dose administration.[16,18,22,23] Sleep latency is prolonged, intrasleep wakenings become more frequent, REMS duration and intensity is increased with vivid dreams or nightmares that may add to frequent awakenings.

Rebound insomnia is conspicuous with moderately rapidly eliminated benzodiazepines (lorazepam, temazepam) and may last for weeks in some patients.[24] With rapidly eliminated benzodiazepines (triazolam), rebound effects may occur in the latter part of the night and cause early morning waking and daytime anxiety.[25] With slowly eliminated benzodiazepines (nitrazepam, diazepam), SWS and REMS may remain depressed for some weeks and then slowly return to baseline, sometimes without a rebound. Rebound effects, when they occur, encourage continued hypnotic usage and contribute to the development of hypnotic dependence.

2.5.3 Hangover Effects

Benzodiazepine hypnotics often give rise to subjective hangover. After most of them, even those that are rapidly eliminated (eg triazolam), psychomotor performance and memory may be impaired the next day.[26] However, there is considerable interindividual variation.[27] The effects also differ between different benzodiazepines, and with dosage and duration of administration.[28]

Residual effects are most likely to occur with slowly eliminated benzodiazepines, especially if used long term, and are most marked in the elderly. Thus, nitrazepam commonly produces a subjective feeling of hangover and impairs performance the next day in single or repeated doses[28,29] although subjective effects may decrease as tolerance develops. Diazepam (5 and 10mg) was shown to produce few residual effects when used in single doses or intermittently,[27] although long term use impairs daytime performance.
It is probably an individual matter whether performance the next morning is likely to be more impaired by lack of sleep or by an hypnotic agent. For transient or short term insomnia, many patients prefer to use an hypnotic rather than to have a sleepless night. Daytime sleepiness resulting from chronic insomnia can itself have adverse effects,[30] but regular hypnotic use does not usually provide a satisfactory long term solution. Treatment is better directed, where possible, towards its underlying cause.

Table II. Rational use of benzodiazepines in insomnia. Recommended drugs include temazepam, lorazepam, loprazolam and diazepam (occasionally in single doses). It is important to warn patients of possible residual effects, risks associated with driving, interactions with alcohol (ethanol) and other depressants, danger of dependence with regular use and possible withdrawal effects.

<table>
<thead>
<tr>
<th>Type of insomnia</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cases</td>
<td></td>
</tr>
<tr>
<td>Transient insomnia (e.g. disruption of circadian rhythm)</td>
<td>1-2 nights only. Minimal dosage (usually not more than diazepam 2.5mg or equivalent)</td>
</tr>
<tr>
<td>Short term insomnia (e.g. temporary environmental stress)</td>
<td>Not for more than 2 weeks. Intermittent if possible (1 night in 2 or 3 nights). Minimal effective dosage (start with small dose; increase if needed, usually not more than diazepam 10mg or equivalent.)</td>
</tr>
<tr>
<td>Chronic insomnia (e.g. secondary to physical, psychological or psychiatric causes)</td>
<td>Treat primary cause first. Intermittent treatment if possible. Not more than 2 weeks (course may be repeated after an interval). Minimal effective dosage (as above).</td>
</tr>
<tr>
<td>Special cases</td>
<td></td>
</tr>
<tr>
<td>Elderly patients[a]</td>
<td>Use half adult doses</td>
</tr>
<tr>
<td>Children</td>
<td>Generally contraindicated, but single dose may be effective.</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td>Avoid regular use in pregnancy, occasional use safe during lactation.</td>
</tr>
<tr>
<td>Disease states</td>
<td>Avoid in chronic respiratory disease. May occasionally be indicated in other disease states if insomnia distressing.</td>
</tr>
<tr>
<td>Benzodiazepine dependent patients[a]</td>
<td>Gradual withdrawal possible and may improve sleep but withdrawal should not be forced.</td>
</tr>
</tbody>
</table>

[a] Continued long term use may sometimes be necessary.

2.5.4 Dependence

Dependence on benzodiazepine hypnotics can develop if the drugs are taken regularly for several weeks.[4] Many long term users are reluctant to withdraw the drugs because of rebound insomnia. Withdrawal from benzodiazepine hypnotics in dependent users may also give rise to anxiety and other typical withdrawal symptoms.[31-35]

2.5.5 Respiratory Depression
Benzodiazepines can cause respiratory depression and decrease the ventilatory response to hypercapnia[34] and increase hypopnoeic episodes during; sleep.[35] Like other drugs which depress respiration they should be avoided in patients with severe chronic obstructive airways disease.

2.6 Choice of Benzodiazepine Hypnotic

For an hypnotic drug, a rapid onset combined with a medium duration of action is usually desirable. Temazepam, loprazolam and lormetazepam meet these criteria (Table II). Temazepam tablets act as rapidly as when the drug is administered in soft gelatine capsules. The tablets also have less abuse potential and can be cut in half to minimise dosage.

Rapidly eliminated benzodiazepines, such as triazolam, can impair memory the next day,[26,28] give rise to daytime anxiety,[25] and probably carry a greater dependence risk.[1] Oxazepam is not recommended as it has a relatively slow onset of action. Nitrazepam is only slowly eliminated. Diazepam acts rapidly and, although slowly eliminated, does not have a prolonged action when used in single doses.

Doses should be minimised to avoid residual effects (especially important for drivers, airline pilots, and machinery operators) and the patient should be warned about additive effects with alcohol and other depressants. Recommended dosage schedules are shown in Table II.

2.6.1 The Elderly

The elderly are especially vulnerable to adverse effects of hypnotic drugs. Rates of metabolism of benzodiazepines that are oxidised (diazepam, nitrazepam) decline with age.[35,36] Elderly patients are also more susceptible to CNS depression and may develop confusional states and ataxia, leading to falls and fractures.[37] They are sensitive to respiratory depression and prone to sleep apnoea and other sleep disorders.[38]

However, insomnia is particularly common in this age group and regular hypnotics may sometimes be indicated if sleep disturbance is distressing. Temazepam, lormetazepam and loprazolam (which do not have pharmacologically active metabolites) remain suitable choices. but dosage should be adjusted, usually to half the recommended adult dose.

2.6.2 The Young

Hypnotics are generally contraindicated for children. Sedative antihistamines are commonly used if sedation is required, but a single dose of a benzodiazepine, with suitable dosage reduction, may be more effective.

2.6.3 Pregnancy and Lactation

Regular use of hypnotics in pregnancy is contraindicated as the drugs readily traverse the placenta. Intermittent doses of relatively rapidly eliminated benzodiazepines have been shown to be safe during breastfeeding.

2.6.4 Disease States

Benzodiazepines are rarely helpful in insomnia due to organic disease and may depress respiration in chronic pulmonary disease. However, in terminal conditions, the possibility
of drug dependence becomes less important and regular use of hypnotics should not be denied if they provide symptomatic relief.

2.6.5 Withdrawal of Benzodiazepine Hypnotics

Many patients who have taken benzodiazepine hypnotics nightly for years can have the drugs withdrawn successfully (see section 3.5.2). Often there is surprisingly little sleep disturbance if withdrawal is carried out sufficiently slowly. Many patients find they actually sleep better without the drugs. The use of liquid preparations of temazepam, nitrazepam or diazepam facilitates small dosage reductions. However, unmotivated patients (often elderly patients who have taken hypnotics for years) should not be forced to withdraw these agents against their will simply because they are dependent. Long term prescriptions (in minimal dosage) are sometimes necessary.

2.6.6 Alternatives to Benzodiazepines

Benzodiazepines compare favourably with other hypnotics in efficacy and safety. They have fewer adverse effects than chlormethiazole and chloral derivatives and are more efficacious than sedative antihistamines.[4] Zopiclone, which has a similar mechanism of action, is expensive and is not free of dependence liability and other adverse effects.[39,40] Although antidepressants and antipsychotics may improve sleep in patients with depression or psychosis, they are more toxic than benzodiazepines and should not be used as general hypnotics, but reserved for patients with disorders for which these drugs are specifically indicated.

3. Rational Use of Benzodiazepines for Anxiety

Official recommendations on the use of benzodiazepines in anxiety are similar to those for insomnia. The UK Committee on Safety of Medicines[2] advised that they 'are indicated for the short term relief (2-4 weeks only) of anxiety that is severe, disabling or causing unacceptable distress'. To a considerable extent this advice appears to have been heeded and yearly prescriptions for benzodiazepine anxiolytics have decreased in the UK from a peak of 18 million in 1978 to less than 10 million at present. There is no doubt that benzodiazepines can be highly efficacious in anxiety. The indications for their rational use in different types of anxiety disorders have become clearer in recent years.[41,42]

3.1 Prevalence of Anxiety

Anxiety symptoms are common in the general population. Uhlenuth et al.[43] estimated the prevalence of generalised anxiety disorder among US adults to be 6.4%, while another 3.5% experienced panic, agoraphobia and other phobias. Prevalence (often elderly patients who have taken hypnotics for years) should not be forced to withdraw these agents against their will simply because they are dependent. Long term prescriptions (in minimal dosage) are sometimes necessary.

3.2 Classification of Anxiety

There is still some controversy about how anxiety states should be classified. Anxiety disorders recognised on the DSM-III-R criteria [45] include generalised anxiety disorder, panic disorder, agoraphobic disorder, social phobia, simple phobia and post-traumatic stress disorder. Generalised anxiety is the most common of the disorders, but Tyrer [46,47] stresses the considerable overlap of symptoms between different anxiety disorders, as well as the co-occurrence of depressive symptoms. He argues for a simple descriptive term, the generalised neurotic syndrome, to encompass most categories.
Acute stress reactions and post-traumatic stress disorder, which may persist as adjustment disorders, are clearly precipitated by major life events, but the reasons for anxiety in generalised anxiety disorder, panic and phobias is usually not known.[47] Vulnerability to stress may be linked with genetic factors[48] and environmental influences. Most patients with anxiety symptoms have a long history of high anxiety levels going back to childhood.

Management of anxiety conditions, however classified or caused, usually calls for nondrug measures that may range from simple counselling to specific psychological techniques. The latter may include anxiety management training, behaviour or cognitive therapy. Drug treatment may also be indicated and the range of effective drugs includes benzodiazepines, antidepressants, antipsychotics and β-blockers, each with its own advantages, disadvantages and specific indications.[47] Possible alternatives include buspirone and some newer anxiolytics likely to be introduced soon (alpidem, suriclone and others).[49,50]

3.3 Effects of Benzodiazepines on Anxiety

Benzodiazepines are potent anxiolytic agents and are effective both in otherwise-healthy patients undergoing stress and in anxious patients. Anxiolytic effects are exerted in doses that cause minimal sedation, although the hypnotic, muscular relaxant and perhaps amnesic actions may all contribute to relief of associated tension and insomnia. The relatively selective effect on anxiety is probably related to the fact that benzodiazepines suppress activity in many limbic and other brain areas involved in anxiogenesis, including the septal area, amygdala, hippocampus, hypothalamus, locus coeruleus and raphé nuclei. They also decrease the turnover of acetylcholine, norepinephrine (noradrenaline), serotonin (5-hydroxy-tryptamine, 5-HT) and dopamine in these areas.[51] Suppression of noradrenergic and/or serotonergic pathways appears to be of particular importance in relation to anxiolytic effects.

The major clinical advantage of benzodiazepines as anxiolytics is the rapid onset of action, usually apparent after a single dose. This immediate effect contrasts with the delayed anxiolytic effects of antidepressants, buspirone and psychological treatments. In addition, benzodiazepines are relatively non-toxic and safer than most of the alternative drugs. Their immediate efficacy and safety combine to make benzodiazepines the drugs of first choice for rapid relief of anxiety that is unacceptably distressing, whatever the cause.

As in insomnia, benzodiazepines provide only symptomatic treatment for anxiety; they do not cure the underlying disorder. Nevertheless they can provide valuable short term cover, allowing time for more specific treatments to take effect, and can alleviate exacerbations of anxiety which are often self-limiting.

3.4 Disadvantages of Benzodiazepine Anxiolytics

3.4.1 Tolerance

Tolerance to the anxiolytic effects of benzodiazepines seems to develop more slowly and less completely than to the hypnotic effects. There is, however, little evidence that they retain their effectiveness after 4 months of regular treatment.[52,53] While some studies indicate that anxiolytic effects are maintained for at least 22 weeks in chronic anxiety states,[54] clinical observations of long term recipients of these agents suggest that the prolonged benzodiazepine use over years does little to control and may even aggravate anxiety states.[55]
The question remains controversial.[44,56] but there is general agreement that benzodiazepine use in most anxiety states should be limited where possible to short term (ideally not more than 4 weeks) or intermittent courses.[2,41,42,47]

3.4.2 Psychomotor Impairment

Subjective oversedation is not usually a problem with anxious patients, but the drugs can impair psychomotor performance, increasing the risk of traffic and other accidents, especially when combined with alcohol. Memory lapses may lead to uncharacteristic behaviours such as shoplifting.[57,58] Benzodiazepines, by inhibiting learning, may decrease the effectiveness of psychological therapies.[59] Although judicious short term administration of benzodiazepines can improve psychomotor performance by counteracting the disruptive effects of anxiety, long term users of normal therapeutic dosages show cognitive deficits, especially in visuospatial and learning ability.[21]

3.4.3 Disinhibition, Paradoxical Effects

Occasionally benzodiazepines produce paradoxical stimulation. This effect is most marked in anxious patients[60] and in children. Symptoms may include excitement, increased anxiety, irritability, hostility and outbursts of rage, sometimes leading to violent behaviour. Although this phenomenon appears to be rare,[61] it is not always clinically recognised and its true incidence may be underreported. [62]

3.4.4 Affective Reactions

Long term use of benzodiazepines can cause or aggravate depression, a possible risk in patients with mixed anxiety/depression, and suicidal tendencies may be increased.[60] Some patients complain of 'emotional anaesthesia', while some obtain a degree of euphoria. A minority of anxious patients escalate their dosage to the point of abuse, and benzodiazepines have become popular among illicit drug abusers who take them in addition to their other drugs of abuse.

3.4.5 Dependence

Long term use of benzodiazepines carries an undisputed risk of inducing dependence. Approximately 35% of patients taking benzodiazepines for more than 4 weeks develop dependence as evidenced by the appearance of withdrawal symptoms if dosage is reduced or the drugs are stopped.[63] Factors increasing the risk of dependence include high dosage, regular continuous use, dependent personality characteristics and previous drug dependence. [1,53,64]

3.5 Choice and Use of Benzodiazepines in Anxiety

Despite the drawbacks of long term use, benzodiazepines remain valuable in the short term management of anxiety, especially where immediate action is required. In most cases, diazepam is the drug of choice, since onset of action is rapid, while slow elimination protects against major fluctuations in blood concentration. Potent benzodiazepines such as lorazepam and alprazolam have been widely used for anxiety, but are probably inappropriate. These drugs are relatively quickly eliminated and interdose anxiety frequently occurs.[65] Lack of recognition of the high potency of these drugs relative to diazepam (Table 1) has often led to excessive dosages, increasing the risk of adverse effects, dependence and problems in withdrawal.

Guidelines for benzodiazepine use in various types of anxiety are provided by Tyrer,[47] Consensus Conference,[41] and Russell and Lader[42] among others. Single doses may
be appropriate as prophylaxis against acute stress reactions in predictably stressful situations (e.g. air travel, dental appointments in phobic patients), although psychological therapies are preferable in the long run.

Similarly, very short term treatment (1 to 7 days) may be indicated in stress reactions after catastrophic events (natural disasters, accidents), which have a high rate of spontaneous resolution. Benzodiazepines are not usually recommended after bereavement as they may impair the adjustment to grief, but a few days' use may sometimes be justified. The drugs are probably not suitable for adjustment disorders and post-traumatic stress disorders that can persist for many months; psychological treatments are preferable in these cases.

Intermittent treatment in courses of 2 to 4 weeks can be of value in episodic anxiety often associated with fluctuations in chronic generalised anxiety. Similarly a short course (2 to 4 weeks) of benzodiazepines may be indicated for the immediate relief of anxiety in generalised anxiety disorder, but the longer the duration of therapy the less the benefit and the greater the disadvantages. In these cases benzodiazepines are best combined with longer term treatments such as antidepressant drugs and/or psychological therapies.

Long term treatment over months or years has been much used in the past for chronic generalised anxiety disorder. However, Rickels et al.[54] found that most patients with chronic anxiety remained symptom-free for at least several months after a course of diazepam lasting 22 weeks, and in 37% there was no recrudescence of anxiety within a year. Similar sustained improvement was noted after a shorter 6-week course of diazepam. The authors concluded that intermittent rather than long term benzodiazepine therapy is preferable in most cases.

A course of 2 to 4 weeks' medication followed by tapering over 1 to 2 weeks, and temporary reinstatement of treatment only if anxiety symptoms recur, is probably rational. Nondrug therapies should be offered. However, there remains a small core of patients who fail to benefit from psychological and other therapies and, for these patients, prolonged treatment, combined with general support, may be the only practical option.

3.5.1 Panic Disorder and Phobias

There is a divergence of opinion over the use of benzodiazepines in panic disorder, agoraphobia and other phobias. Alprazolam, lorazepam, diazepam and clonazepam have been widely used for these disorders.[66-72] Some of these studies and others reviewed by Marks and O'Sullivan[73] and Tyrer[47] have compared the efficacy of benzodiazepines with that of antidepressants and other treatments.

Most investigations have shown that high doses of benzodiazepines (e.g. as much as 6 to 10mg alprazolam daily) can be effective. They have a rapid onset of action and improvement with benzodiazepines, compared with antidepressants, is greater in the first 4 to 5 weeks of treatment, but is not superior after 5 to 6 weeks. Tyrer [47] concludes from the available evidence that 'monoamine oxidase inhibitors, tricyclic antidepressants, and benzodiazepines are all effective in the treatment of panic with a hierarchy of efficacy headed by MAOIs with benzodiazepines as the least effective'.

Since cessation of pharmacological treatment in panic disorders and agoraphobia is followed by relapse in over 80% of cases, [66] there is a tendency to use the drugs long term. However, long term use of benzodiazepines, especially in high dosages, carries the disadvantages of inducing dependence, tolerance withdrawal reactions if the drugs are stopped,[1] increased anger/hostility,[74] cognitive impairment[21] and other adverse effects mentioned in section 3.4. There is evidence that psychological treatments, such
as exposure therapy (supervised, gradually increasing exposure to the specific anxiety or panic-provoking situations), can decrease relapses and improve the long term outcome, but benzodiazepines appear to interfere with such treatments.[59,73]

For these reasons the consensus of current opinion in much of Europe and Australasia is that antidepressant drugs combined with psychological therapies are in the long run superior to benzodiazepines for panic disorder, agoraphobia and other phobias.[47,53,73,75] In North America, there may be less concern about long term benzodiazepine use for these conditions. Nevertheless, it would seem more logical to reserve benzodiazepines for short term initial cover if panic is severe and disabling, while awaiting the delayed effects of other treatments.

Furthermore, panic and agoraphobia may coexist with generalised anxiety as part of the general neurotic syndrome. In these cases, intermittent use of benzodiazepines may be combined with antidepressants and psychological therapies.[47] The observation that low dose intranasal midazolam taken at the first sign of panic may abort the attack[76] may offer a further use of benzodiazepines in panic disorder, but confirmation of the efficacy and safety of this treatment is needed.

Benzodiazepines are not suitable for obsessive-compulsive disorder and should be avoided where possible in depression, or in the presence of significant depressive symptoms. Alprazolam is claimed to have antidepressant properties[77] and is effective in secondary depression associated with anxiety[78] but carries a high risk of dependence and other adverse effects, especially when used long term.

3.5.2 Withdrawal of Benzodiazepines

There remains a large population of patients, numbering over a million in the UK[5,79] who have taken benzodiazepines for many months or years. Many of these suffer from symptoms included in the general neurotic syndrome (chronic anxiety, panic attacks, agoraphobia, depression). Slow withdrawal of benzodiazepines is a practical option for motivated patients. Withdrawal symptoms, when they occur, are mainly those of increased anxiety, although some perceptual and motor disturbances may be especially prominent.[1]

The management of benzodiazepine withdrawal consists of gradual dosage reduction combined with appropriate psychological support. The rate of dosage tapering should be tailored to individual needs, and best results are usually obtained in an outpatient setting with the patient in control of the rate of withdrawal and proceeding at whatever pace is found to be tolerable. The process may take 2 to 3 months in some patients or up to a year in others.

Typical dosage reductions for a patient taking 20mg diazepam (or equivalent) daily would be 1mg every 1 to 2 weeks initially, followed by decrements of 0.5mg every 1 to 2 weeks when a dosage of 4 to 5mg has been reached. Initial dosage reductions of 2mg every 1 to 2 weeks may be more appropriate for patients taking over 20mg diazepam equivalent daily. No adjuvant drugs have been found to be generally helpful in alleviating withdrawal symptoms, but antidepressants may be indicated for depression and β-blockers are useful for some patients with prominent somatic symptoms.

The degree of psychological support required is also an individual matter and may range from simple encouragement to formal anxiety management or cognitive and behavioural therapy. Support should be available not only during dosage reduction, but also for a prolonged period afterwards. Frequent contact with the physician or other therapist or counsellor is often desirable throughout withdrawal and post-withdrawal phases.
In the majority of cases, symptoms gradually improve after withdrawal [55,80] although some patients may need further temporary courses of benzodiazepines.[81] For those unwilling to withdraw or who find withdrawal symptoms intolerable, and for those in whom withdrawal is likely to incur more serious problems, such as alcohol dependence,[1] continued prescribing in minimal doses may be necessary.

**Table III.** Rational use of benzodiazepines in anxiety. Recommended agent is diazepam in most cases. Minimal effective dosage may vary from 5 to 30mg daily; usually best given divided twice daily. Start with a small dose and increase if necessary. It is important to warn patients of sedative effects, risks associated with driving, interactions with alcohol and other depressants, danger of dependence with regular use and possible withdrawal effects.

<table>
<thead>
<tr>
<th>Anxiety state</th>
<th>Duration of treatment</th>
<th>Other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild anxiety</td>
<td>Benzo[a]diazepines not recommended</td>
<td>Counselling, psychological treatment</td>
</tr>
<tr>
<td>Acute stress reaction prophylaxis (e.g. dental appointments, aeroplane travel in patients with phobias)</td>
<td>Single dose before event</td>
<td>Psychological treatment</td>
</tr>
<tr>
<td>Acute stress reaction (accidents/disasters)</td>
<td>1-7 days</td>
<td>Counselling</td>
</tr>
<tr>
<td>Acute stress reaction (bereavement)</td>
<td>Single doses or a few days only if distress is severe</td>
<td>General support, counselling, psychological treatment</td>
</tr>
<tr>
<td>Adjustment disorders; post-traumatic stress</td>
<td>Single doses or a few days only initially - not suitable for long term management</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Episodic anxiety</td>
<td>Single or intermittent courses (2-4 weeks followed by 1-2 weeks in tapering doses). Use in conjunction with other treatments</td>
<td>Antidepressants, B-blockers, psychological treatment</td>
</tr>
<tr>
<td>Chronic generalised anxiety[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General neurotic syndrome[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panic disorder[a]</td>
<td>Initial course 2-4 weeks (if symptoms severe) followed by 1-2 weeks tapering. Use in conjunction with other treatments as above (alprazolam not recommended in UK, especially high dose, long term, though widely used in US)</td>
<td>Antidepressants, B-blockers, psychological treatment</td>
</tr>
<tr>
<td>Agoraphobia[a]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other phobias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine-dependent patients[a]</td>
<td>Gradual withdrawal is possible and may improve anxiety symptoms, but should not be forced. Longer term prescriptions may sometimes be necessary</td>
<td>Psychological support, antidepressants</td>
</tr>
</tbody>
</table>

[a] Occasionally, longer term prescriptions are required for patients who do not respond to other measures.

### 3.5.3 Prevention of Benzodiazepine Dependence

Prevention of dependence in new patients depends partly on patient selection, avoiding prescriptions where possible in patients with dependent-avoidant personalities, identified clinically as 'timid worriers'.[64] Minimal effective dosage should be used and courses kept short (4 weeks maximum whenever possible).
The risk of dependence is probably greater with potent, short-acting benzodiazepines such as lorazepam and alprazolam. Monitoring of patients before issuing a repeat prescription is important to ensure that short term treatment does not insidiously become long term. Practitioners should also be aware that prescriptions (especially of temazepam capsules) are sometimes diverted to illicit use.

Recommended schedules for benzodiazepine treatment in anxiety are shown in Table III.

4. Benzodiazepines as Anticonvulsants

4.1 Status Epilepticus

Benzodiazepines are drugs of first choice for status epilepticus and convulsions due to drug poisoning, and are effective in 80% of cases. Diazepam is given intravenously or as a rectal solution. Clonazepam and lorazepam can also be given intravenously.

4.2 Prophylaxis in Epilepsy

Clonazepam (a 1,4-benzodiazepine) and clobazam (a 1,5-benzodiazepine) are available as oral anticonvulsant drugs. Clonazepam is effective in myoclonic and generalised absence seizures but less effective in generalised tonic-clonic seizures. Clonazepam is also effective in these forms of seizures, but is usually reserved as adjunctive therapy in refractory epilepsy. It can also be valuable when used intermittently in epilepsy related to menstruation or in patients who have regular clusters of generalised tonic-clonic or partial seizures, and as cover during changes of anticonvulsant medication. Most other benzodiazepines have anticonvulsant actions in varying degrees and are useful in individual cases. Diazepam and chlordiazepoxide are used briefly in alcohol detoxification to prevent withdrawal seizures, fits and anxiety symptoms (but care is needed to ensure that alcohol dependence is not followed, after relapse, by alcohol plus benzodiazepine dependence).

4.3 Adverse Effects

Benzodiazepines are not generally suitable for the long term treatment of epilepsy because of the development of tolerance in a high proportion of patients. However, tolerance may be partial and some patients may continue to show a reduction in seizure frequency and/or severity. Both clonazepam and clobazam may cause sedation and psychomotor impairment, although this is less marked with clobazam. These agents may also result in irritability, depression, and behaviour disturbance with aggression and hyperkinesis in children. Exacerbation of seizures may occur on withdrawal which, as with any anticonvulsant, should always be carried out slowly. Indications and dosage schedules are shown in Table IV.

5. Other Uses of Benzodiazepines

5.1 Anaesthesia

Benzodiazepines are valuable in anaesthetic practice for their sedative and amnesic actions. Oral lorazepam and temazepam, or intramuscular midazolam are suitable for premedication and for brief procedures such as cardioversion. Midazolam can be combined with a local anaesthetic for surgical procedures, can be used intravenously for induction of anaesthesia and as an infusion for patients under mechanical ventilation. Patients who have undergone benzodiazepine withdrawal can be reassured that the use of a benzodiazepine for anaesthesia will not re-establish dependence.
5.2 Motor Disorders

The muscular relaxant effects of benzodiazepines can sometimes be used in a variety of motor disorders.[88] These include a range of dystonias and involuntary movements, myoclonus, akinesia, restless legs syndrome and muscle spasm associated with pain. However, tolerance develops with long term use and the drugs are not always effective and may give rise to withdrawal problems. More esoteric uses are to control muscle spasms in tetanus and rabies.

Table IV. Use of benzodiazepines as anticonvulsants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Diazepam</td>
<td>IV 10-20mg (5 mg/min), repeated if necessary</td>
</tr>
<tr>
<td>Convulsions due to poisoning</td>
<td>Diazepam Alternatives:</td>
<td>IV infusion (max 3 mg/kg/day) PR 10mg (adult), IV</td>
</tr>
<tr>
<td>Prolonged or recurrent febrile convulsions</td>
<td>Diazepam</td>
<td>PR 500 μg/kg (repeated if necessary)</td>
</tr>
<tr>
<td>(children)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Seizure prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>Clonazepam (short term or</td>
<td>PO 2-8mg</td>
</tr>
<tr>
<td></td>
<td>as adjunctive therapy)</td>
<td></td>
</tr>
<tr>
<td>Generalised absence seizures</td>
<td>Clonazepam (short term or</td>
<td>PO 2-8mg</td>
</tr>
<tr>
<td></td>
<td>as adjunctive therapy)</td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic seizures</td>
<td>Clonazepam (short term or</td>
<td>PO 2-8mg</td>
</tr>
<tr>
<td></td>
<td>as adjunctive therapy)</td>
<td></td>
</tr>
<tr>
<td>Refractory epilepsy</td>
<td>Clonazepam (short term or</td>
<td>PO 10-40mg</td>
</tr>
<tr>
<td></td>
<td>as adjunctive therapy)</td>
<td></td>
</tr>
<tr>
<td>Cluster or catamenial exacerbations</td>
<td>Clonazepam (short term or</td>
<td>PO 10-40mg</td>
</tr>
<tr>
<td></td>
<td>as adjunctive therapy)</td>
<td></td>
</tr>
<tr>
<td>Detoxification from alcohol (ethanol) and other</td>
<td>Diazepam</td>
<td>PO - not more than 7 days in declining doses</td>
</tr>
<tr>
<td>CNS depressants</td>
<td></td>
<td>(also alleviates anxiety symptoms)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IV = intravenous; PO = oral; PR = rectal.

5.3 Acute Psychoses

In acute psychoses with hyperexcitability and aggressiveness (drug-induced, mania, schizophrenia), benzodiazepines in single doses or as short term therapy may be an effective addition to antipsychotic drugs. Their value as adjunctive treatment in chronic psychosis has not been established.[89]

6. The Future
With rational prescribing, benzodiazepines are likely to remain valuable drugs for many years. Total numbers of prescriptions should continue to decline as the number of long term users decreases and fewer new patients become dependent. The development of partial benzodiazepine agonists/antagonists and of other drugs that act more selectively on different subtypes of benzodiazepine receptors may overcome some of the disadvantages of these agents.[90] However, the degree to which such drugs, if effective, are free of the problems of tolerance and dependence in long term use remains to be established.

References

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