Benzodiazepines Revisited

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Abstract
Up to 1 million people in the UK are currently long-term prescribed benzodiazepine users. Surveys of general practices show that there are over 180 long-term prescribed users per general practice. Despite repeated recommendations to limit benzodiazepines to short-term use (2–4 weeks), doctors in the UK and worldwide are still prescribing them for months or years. Dependence upon prescribed benzodiazepines is now recognised as a major clinical problem and the National Performance Assessment Framework for the NHS makes it a national priority to reduce this within each health board area. Junior doctors who have recently graduated from medical school are commonly placed in rotations where they have to manage patients on benzodiazepine prescriptions. It is necessary for doctors in general to be aware of the essentials of benzodiazepines not only for the adequate management of patients on chronic benzodiazepine prescriptions, but also for responsible prescription of this drug when it is appropriate.

History of benzodiazepines

The advent of benzodiazepines in the late fifties was met with great excitement by the practicing physicians around the world. Their range of actions – sedative/hypnotic, anxiolytic, anticonvulsant and muscle relaxant – combined with low toxicity and alleged lack of dependence potential seemed to make them ideal medications for many common conditions. The drugs were prescribed long term, often for many years, for complaints such as anxiety, depression, insomnia and ordinary life stressors. They began to replace barbiturates; drugs known to be dangerous in overdose, which tended to cause addiction and were associated with troublesome side-effects. Previous compounds including opium, alcohol, chloral and bromides were similarly burdened.

The first benzodiazepine, chlordiazepoxide (Librium), was synthesized in 1955 by Leo Sternbach while working at Hoffmann–La Roche on the development of tranquilizers. The compound showed very strong sedative, anticonvulsant and muscle relaxant effects when submitted for a standard battery of animal tests. These impressive clinical findings led to its speedy introduction throughout the world in 1960 under the brand name Librium. Following chlordiazepoxide, diazepam was marketed by Hoffmann–La Roche under the brand name Valium in 1963.

The benefits of benzodiazepines and the apparent lack of discouraging factors led an alarming rise of benzodiazepine prescriptions. In the late 1970s benzodiazepines became the most commonly prescribed of all drugs in the world. In 1980, Tyrer reported that each day about 40 billion doses of benzodiazepine drugs are consumed throughout the world. This figure is staggering by any standards. However, towards the end of the 1970s, awareness begin to grow that benzodiazepines were being unnecessarily over-prescribed and it was noticed that certain patients might become dependent on benzodiazepines after chronic use. In particular, patients found it difficult to stop taking benzodiazepines because of withdrawal reactions and many complained that they had become ‘addicted’. Several investigations showed quite unequivocally that benzodiazepines could produce pharmacological dependence in therapeutic dosage.

In 1988, the Committee of Safety of Medicines reacted to the concerns by spelling out emphatic guidelines about the use of benzodiazepines drugs. For anxiety and insomnia, benzodiazepines are indicated for short term relief (two to four weeks) only if the condition is severe, disabling and subjecting the individual to extreme distress.

Tolerance and dependence

Tolerance is a phenomenon that develops with many chronically used drugs. The body responds to the continued presence of the drug with a series of adjustments that tend to overcome the drug effects. In the case of benzodiazepines, compensatory changes occur in the GABA and benzodiazepine receptors which become less responsive, so that the inhibitory actions of the GABA and benzodiazepines are decreased. As a result, the original dose of the drug has progressively less effect and a higher dose is required to obtain the original effect.

Dependence is understood to be the inability to control intake of a substance to which one is addicted. It encompasses a range of features initially described in connection with alcohol abuse, now recognised as a syndrome (see box 1) associated with a range of substances.

Dependence has two components: psychological dependence, which is the subjective feeling of loss of control, cravings and preoccupation with obtaining the substance; and physiological dependence, which is the physical consequences of withdrawal and is specific to each drug. For some drugs (e.g. alcohol) both...
psychological and physiological dependence occur; for others (e.g. LSD) there are no marked features of physiological dependence.

### Box 1: Dependence Syndrome

Three or more of the following manifestations should have occurred together for at least one month or if persisting for periods of less than one month then they have occurred together repeatedly within a twelve month period.

1. A strong desire or sense of compulsion to take the substance.
2. Impaired capacity to control substance-taking behaviour in terms of onset, termination or level of use, as evidenced by: the substance being often taken in larger amounts or over a longer period than intended, or any unsuccessful effort or persistent desire to cut down or control substance use.
3. A physiological withdrawal state (see F1x.3 and F1x.4) when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms.
4. Evidence of tolerance to the effects of the substance, such that there is a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or that there is a markedly diminished effect with continued use of the same amount of the substance.
5. Preoccupation with substance use, as manifested by: important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time being spent in activities necessary to obtain the substance, take the substance, or recover from its effects.
6. Persisting with substance use despite clear evidence of harmful consequences, as evidenced by continued use when the person was actually aware of, or could be expected to have been aware of the nature and extent of harm.

* ICD 10 Classification of Mental and Behaviour disorder, online version 2007.

### Withdrawal syndrome and discontinuation syndrome

Any drug consumed regularly and heavily can be associated with withdrawal phenomenon on stopping. Clinically significant withdrawal phenomena occur in dependence to alcohol, benzodiazepines, opiates and are occasionally seen in cannabis, cocaine and amphetamine use. In general, drugs with a short half-life will give rise to more rapid but more transient withdrawal.

Discontinuation syndrome is a common phenomenon and occurs with all classes of antidepressants. It is only experienced when one tries to discontinue its use. The most common symptoms are dizziness, vertigo, gait instability, nausea, fatigue, headaches, anxiety and insomnia. Less commonly shock-like sensations, paraesthesia, visual disturbances, diarrhoea and flu-like symptoms have been reported. Symptoms usually begin 2-5 days after SSRI discontinuation or dose reduction. The duration is variable (one to several weeks) and ranges from mild to moderate intensity in most patients, to extremely distressing in a small number. Tapering antidepressants at the end of treatment, rather than abrupt stoppage, is recommended as standard practice by several authorities and treatment guidelines11-13.

The terms ‘antidepressant withdrawal syndrome’ and ‘antidepressant discontinuation syndrome’ are used interchangeably in the literature. ‘Discontinuation’ is preferred as it does not imply that antidepressants are addictive or cause a dependence syndrome. The occurrence of withdrawal symptoms does not in itself indicate that a drug causes dependence as defined in ICD 10 (World Health Organisation 1992)14 and DSM –IV (American Psychiatric Association, 1994)15.

### Understanding how benzodiazepines work and their effects

For the first 15 years after the introduction of benzodiazepines, no clear picture emerged as to how these drugs might exert their psychotropic effects. The great breakthrough in our understanding in the mechanism of action of benzodiazepines came in the mid 1970s when biologists at Hoffman-La Roche demonstrated that benzodiazepines exert their psychotropic effects by potentiating GABA neurotransmission.16

GABA, Gamma-Amino butyric acid, is the most important inhibitory neurotransmitter in the mammalian brain representing about 30% of all synapses in the whole brain. GABAergic neurones mediate pre-synaptic inhibition by depressing the release of neurotransmitter at excitatory input synapse, and post-synaptic inhibition by depressing synaptic excitation of the principal neuron. When benzodiazepines react at their receptor site, which is actually situated on the GABA receptor, the combination acts as a booster to the actions of GABA making the neuron more resistant to excitation. Several studies showed that benzodiazepines were able to facilitate both types of inhibition, indicating that the effects of the benzodiazepines were in fact due to an interaction with the GABAergic transmission process17-19.

Various subtypes of benzodiazepine receptors have slightly different actions. Alpha 1 is responsible for sedative effects. Alpha 2 exerts anxiolytics effects. Alpha 1, Alpha 2 and Alpha 5 are responsible for anticonvulsant effects. As a consequence of the enhancement of GABA’s inhibitory activity caused by benzodiazepines, the brain’s output of excitatory neurotransmitters including norepinephrine, serotonin, dopamine and acetylcholine is reduced.
The studies on the receptor binding of benzodiazepines and the subsequent changes that occur in the central nervous system have provided us with an adequate explanation for some or all of the actions of benzodiazepines, which are listed in Box 2.

**Box 2: Four principle biological properties of benzodiazepines**

1. Anxiolytic and behavioural inhibition – The anxiolytic effect is seen in animals as an increase of those behavioural responses that are suppressed experimentally by punishment or which are absent because of innate aversion.

2. Anticonvulsant – Benzodiazepines are most potent against chemically induced epileptiform activities. At higher doses they accumulate raised plasma levels of the drug. For these reasons, benzodiazepines also prevent seizures induced by electric shock.

3. Sedative/hypnotic – These effects of benzodiazepines are most easily observed as a decrease of spontaneous locomotor activity in rodents placed in an observation chamber. Benzodiazepines will shorten sleep latency (amount of time taken to fall asleep after the lights have been switched off) which can be demonstrated by electroencephalogram.

4. Muscle relaxant - Common tests on rodents show that benzodiazepines impair performance at motor performance tasks for example the rodent’s ability to balance on a rotating drum. The cat shows marked ataxia at after relatively low doses.

What are benzodiazepines used for?

**Sleep disorders**

The benzodiazepines are used widely in the treatment of sleep disorders and many have been developed and licensed for this purpose. They are mainly known as hypnotic drugs (sleeping pills) because insomnia is the main target use. Certain factors are important in determining the choice of the hypnotic drug. Ideally, the hypnotic should be effective at inducing sleep in the individual, and should enhance objective and subjective elements of sleep. It should have a fast onset with minimal side effects and the absence of withdrawal symptoms.

The early benzodiazepine hypnotics were drugs such as nitrazepam and flurazepam. After their introduction, it was found that they had half-lives of more than a day, and individuals suffered undesirable effects such as sedation, ataxia or amnesia during the day. This was problematic especially for those individuals who needed to drive or operate machinery. Another consequence was of falls with subsequent hip fractures in the elderly population because, due to slower metabolism, they accumulated raised plasma levels of the drug. For these reasons, benzodiazepines with shorter half lives were developed so that plasma levels fall below the functional threshold concentration by the next morning.

The first of the shorter half-life benzodiazepine hypnotics to be introduced were temazepam and triazolam. Temazepam has a half-life of 5 hours and is commonly used in primary, secondary and tertiary settings for insomnia. A possible drawback of very short half-life hypnotics is rebound insomnia. This is a state of worsening sleep which commonly follows discontinuation of a regularly used hypnotic.

An important point to note is that although the subjective efficacies of benzodiazepines are widely reported, the use of polysomnography (a sleep study that involves recording a variety of physiological measures including electroencephalograph, electro-oculogram and electromyogram) has shown that sleep architecture in individuals with insomnia is not normalised by benzodiazepines. The increase in sleep duration can be accounted for by an increase in the time spent in stage 2 of sleep, while the amount of time spent in slow-wave sleep (deep) and REM (rapid eye movement) is actually decreased.

**Anxiety disorders**

It can be argued that the benzodiazepines are probably the most efficacious and best tolerated pharmacological treatments of anxiety. Numerous studies, many of them conducted under stringent double-blind conditions, have consistently shown that benzodiazepines produce significantly more improvement than placebo in both somatic and emotional manifestations of anxiety.

Before the introduction of benzodiazepines, anxiety disorders were treated either with the barbiturates or related drugs such as meprobamate and glutethimide. These agents were highly likely to be abused and led to a great deal of dependence. Moreover, they were toxic in overdose and fatalities were high in populations using them. The improved efficacy and safety profile of benzodiazepines, aided by intense campaigns to restrict use of barbiturate-type drugs, meant they rapidly became the first choice drugs for anxiety within a few years of them being introduced.

Much clinical practice and opinion suggests that benzodiazepine can be used as first-line treatment for acute anxiety episodes as long as CSM guidelines are adhered to. For more intractable conditions such as established social phobia, generalised anxiety disorder and panic disorder, they should probably be reserved for adjunctive or second-line agents.

In contrast to the treatment of sleep disorders, it is important to achieve a constant level of receptor occupation to maintain anxiolysis throughout the day. So for anxiety, compounds with longer elimination half-lives are preferred, whereas for sleep induction, short half-life drugs are favoured. The principal benzodiazepines used as anxiolytics include diazepam, chlordiazepoxide, clonazepam, lorazepam, alprazolam and oxazepam.
The use of benzodiazepines as first-line agents for anxiety has been on the decline since the 1990s. There are changing cultural and medical attitudes to the prescription of drugs for the treatment of anxiety disorders as a result of growing evidence that psychological approaches are also effective. The risks of dependence and withdrawal difficulties are problematic in a significant number of patients. Another issue is the abuse of benzodiazepines by drug addicts and diversion of legitimate supplies to the black market. There is competition from other agents (buspirone, tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) which have a different side-effect profile and are free from dependence/withdrawal problems.

Seizure Disorders

The anti-convulsant effects of benzodiazepines find their greatest clinical use in the acute control of seizures. Diazepam, clonazepam and lorazepam have all been used in the treatment of status epilepticus.

Status epilepticus is a life-threatening condition in which the brain is in a state of continuous seizure activity which can result in impaired respiration, hypoxic brain damage and brain scarring. It is a medical emergency that requires quick and effective intervention.

Diazepam was reported to be effective for the treatment of status epilepticus in the mid-1960s [30-32] and is still widely considered to be the drug of choice for the initial control of seizures. Given intravenously, diazepam has a rapid onset of clinical activity achieving cessation of the seizure within 5 minutes of injection in 80% of the patients in one study [33]. Where facilities for resuscitation are not immediately available; diazepam can be administered as a rectal solution.

Although intravenous diazepam is effective for status epilepticus, it is associated with a high risk of thrombophlebitis which is why BNF suggests use of intravenous lorazepam. Lorazepam is also highly active [34]. Its onset of action is rapid but because of its slower rate of tissue distribution, its anticonvulsant activity is prolonged compared to diazepam [35,36].

Gestaut et al (1971) showed that clonazepam was an even more potent anti-convulsant than diazepam in the treatment of status epilepticus [37]. It can be administered via the buccal mucosa (an advantage in children) and can also be given as a suppository.

Benzodiazepines are undoubtedly potent anti-convulsants on acute administration but their use in long-term treatment of epilepsy is limited by the development of tolerance to the anti-convulsant effects and by side-effects such as sedation and psychomotor slowing [38,39]. They are usually considered as an adjunct to standard drugs where these have failed to give acceptable control.

### Table 1: Pharmacokinetic profile of common benzodiazepines and their licensed indications

<table>
<thead>
<tr>
<th>Long-acting</th>
<th>TMax (hrs)</th>
<th>T1/2 (hrs)</th>
<th>Licensed indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide [42]</td>
<td>2</td>
<td>7-14</td>
<td>Short-term use in anxiety, adjunct to acute alcohol withdrawal</td>
</tr>
<tr>
<td>Diazepam [42]</td>
<td>0.5-2</td>
<td>32-47</td>
<td>Short term use in adjunct to acute alcohol withdrawal, insomnia, status epilepticus, muscle spasm, peri-operative use</td>
</tr>
<tr>
<td>Clonazepam [33]</td>
<td>2.5</td>
<td>25.5</td>
<td>all forms of epilepsy, myoclonus, status epilepticus</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam [43]</td>
<td>1</td>
<td>5-8</td>
<td>Insomnia; peri-operative use</td>
</tr>
<tr>
<td>Nitrazepam, Flurazepam [44,45]</td>
<td>1-3</td>
<td>16-48</td>
<td>Short-term use for insomnia</td>
</tr>
<tr>
<td>Loprazolam, Lormetazepam [42]</td>
<td>1-3</td>
<td>8-10</td>
<td>Short-term use for insomnia</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam [32]</td>
<td>1-1.5</td>
<td>10-20</td>
<td>Short term use in anxiety or insomnia; status epilepticus; peri-operative use</td>
</tr>
<tr>
<td>Oxazepam [42]</td>
<td>2.2-3</td>
<td>5-15</td>
<td>Short term use in anxiety</td>
</tr>
<tr>
<td>Midazolam [33]</td>
<td>0.6</td>
<td>2.4</td>
<td>Sedation with amnesia, sedation in intensive care, induction of anaesthesia</td>
</tr>
<tr>
<td>Alprazolam [32]</td>
<td>1.2-1.7</td>
<td>10-12</td>
<td>Short term use in Anxiety</td>
</tr>
</tbody>
</table>

Tmax: time to peak plasma concentration
T1/2: half-life

* Nitrazepam and flurazepam have prolonged action and may give rise to residual effects on the following day. Temazepam, Loprazolam and Lormetazepam act for a shorter time and have little or no hangover effect.

a Short-acting compounds preferred in hepatic impairment but carry a greater risk of withdrawal symptoms.

### Other uses

**Alcohol detoxification**

Benzodiazepines have become the standard pharmacological treatment for alcohol withdrawal. In acute alcohol detoxification, long acting benzodiazepines, such as diazepam or chlordiazepoxide are more appropriate than shorter acting agents like lorazepam or temazepam. The two principal reasons for this are 1) former drugs provide stable plasma concentrations over several hours which is necessary to maintain control over central nervous system excitability, and 2)
There is a higher risk of addiction with short-acting drugs in this patient population.

In alcohol dependent patients with hepatic impairment, oxazepam or lorazepam is more suitable as they are not eliminated by hepatic oxidation through the Cytochrome P450 system. Cytochrome p450 (CYPs) is a collective generic term use to describe a superfamily of membrane bound heme-thiolate proteins of critical importance in the oxidative and reductive metabolism of both endogenous and foreign compounds. CYPs are the major enzymes in drug metabolism accounting for 75% of the total metabolism. Many of the CYPs in humans are found in the liver and the gastrointestinal tract. After the acute detoxification is over, many patients enter rehabilitation programmes aimed at maintaining abstinence in the community. There is no evidence that use of benzodiazepines is useful in reducing alcohol craving or facilitating abstinence.

**Anaesthesia** – The psychotropic effects of benzodiazepines make them appropriate for use as anaesthetic agents or as adjuncts to anaesthesia. Muscle relaxation, sedation and retrograde amnesia are sought after properties in anaesthetic agents. Midazolam is used as a sedative agent in patients undergoing minor invasive practices considered as traumatic, such as dental treatment or endoscopy.

**Muscle relaxants** – The muscle relaxant properties of benzodiazepines are an indication for their use in some neurological disturbances for symptomatic relief of muscle spasms and spasticity.

**Assessment and management of patients with chronic benzodiazepine dependence**

Because of the adverse effects, lack of efficacy and socioeconomic costs of continued benzodiazepine use, long-term users have for many years been advised to withdraw if possible or at least to reduce dosage. Echoing the CSM advice, the Mental Health National Service Framework (NSF), which was published in 1999, recommended that benzodiazepines should be used for no more than two to four weeks for severe and disabling anxiety. The Mental Health NSF called upon health authorities to implement systems for monitoring and reviewing prescribing of benzodiazepines within local clinical audit programmes. Primary Care Trusts (PCTs) should ensure that this recommendation is still being implemented.

In primary care, early detection and intervention are the main principles of assessment. The initial assessment should

- Establish the pattern of benzodiazepine usage: onset, duration, which benzodiazepine/s, dosage history, current regime and any periods of abstinence.
- Check for evidence of benzodiazepine dependence (see box 3).

- If benzodiazepine dependence is present, determine the type of benzodiazepine.
- Detail any history of previous severe withdrawal (including history of seizures).
- Establish the level of motivation to change.

Dependence on benzodiazepines often indicates psychosocial problems in a person. Benzodiazepines are increasingly used in conjunction with other substance of abuse to enhance the effects obtained from opiates, and to alleviate withdrawal symptoms of other drugs of abuse such as cocaine, amphetamines or alcohol. The patient needs to have an individualised and a comprehensive assessment of their physical and mental health needs and any co-morbid use of other drugs and alcohol. Stable psychological health and personal circumstances are desirable features for successful withdrawal from benzodiazepines. 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. Referral to specialist teams may be appropriate for some, e.g. if the patient is also dependent on other drugs or alcohol, if there is co-existing physical or psychiatric morbidity or if there is a history of drug withdrawal seizures. In some circumstances, it may be more appropriate to wait until other problems are resolved or improved.

**Box 3 – Benzodiazepine Withdrawal Symptoms**

**Psychological symptoms** – excitability, sleep disturbances, increased anxiety, panic attacks, agoraphobia, social phobia, perceptual distortions, depersonalisation, derealisation, hallucinations, misperceptions, depression, obsessions, paranoid thoughts, rage, aggression, irritability, poor memory and concentration, intrusive memories and craving (rare).

**Physical symptoms** – Headache, pain, stiffness, tingling, numbness, altered sensation, weakness, fatigue, influenza-like symptoms, muscles twitches, jerks, tics, “electric shocks”, tremor, dizziness, light-headedness, poor balance, visual problems, tinnitus, hypersensitivity to stimuli, gastrointestinal symptoms, appetite change, dry mouth, metallic taste, unusual smell, flushing, sweating, palpitations, over breathing, urinary difficulties, skin rashes, itching, fits (rare).

This list is probably not inclusive. Not all patients get all the symptoms. Different individuals get a different combination of symptoms.

**Management of benzodiazepine withdrawal**

Withdrawal of the benzodiazepine drug can be managed in primary care if the patients in consideration are willing, committed and compliant. Clinicians should seek opportunities to explore the possibilities of benzodiazepine withdrawal with
patients on long-term prescriptions. Interested patients could benefit from a separate appointment to discuss the risks and benefits of short and long term benzodiazepine treatment\(^\text{14}\). Information about benzodiazepines and withdrawal schedules could be offered in printed form. One simple intervention that has been shown to be effective 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\(^\text{46}\). Adequate social support, being able to attend regular reviews and no previous history of complicated drug withdrawal is desirable for successful benzodiazepine withdrawal.

**Switching to diazepam:** This is recommended for some people commencing a withdrawal schedule. Diazepam is preferred because it possesses a long half-life, thus avoiding sharp fluctuations in plasma level. It is also available in variable strengths and formulations. This facilitates stepwise dose substitution from other benzodiazepines and allows for small incremental reductions in dosage. The National Health Service Clinical Knowledge Summaries recommend switching to diazepam for people using short acting benzodiazepines such as alprazolam and lorazepam, for preparations that do not allow for small reductions in dose (that is alprazolam, flurazepam, loprazolam and lormetazepam) and for some complex patients who may experience difficulty withdrawing directly from temazepam and nitrazepam due to a high degree of dependency\(^\text{49}\). See table 2 for approximate dose conversions of benzodiazepines when switching to diazepam.

**Gradual Dosage Reduction:** It is generally recommended that the dosage be tapered gradually in long-term benzodiazepine users such as a 5-10% reduction every 1-2 weeks\(^\text{46}\). Abrupt withdrawal, especially from high doses, can precipitate convulsions, acute psychotic or confusional states and panic reactions. As mentioned earlier, benzodiazepines’ enhancement of GABA’s inhibitory activity reduces the brain’s output of excitatory neurotransmitter such as norepinephrine, serotonin, dopamine and acetylcholine. The abrupt withdrawal of benzodiazepines may be accompanied by uncontrolled release of dopamine, serotonin and other neurotransmitters which are linked to hallucinatory experiences similar to those in psychotic disorders\(^\text{46}\).

The rate of withdrawal should be tailored to the patient’s individual needs and should take into account such factors as lifestyle, personality, environmental stressors, reasons for taking benzodiazepines and the amount of support available. Various authors suggest optimal times of between 6-8 weeks to a few months for the duration of withdrawal, but some patients may take a year or more\(^\text{15,50}\). A personalised approach, empowering the patient by letting them guide their own reduction rate is likely to result in better outcomes.

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Approximate equivalent dosage (mg)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.5</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>25</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>1</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15-30</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>1</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>1</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>10</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>20</td>
</tr>
<tr>
<td>Temazepam</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\) Clinical potency for hypnotic or anxiolytic effects may vary between individuals; equivalent doses are approximate.

Patients may develop numerous symptoms of anxiety despite careful dose reductions. Simple reassurance and encouragement should suffice in most cases however, in a minority who are experiencing significant distress, formal psychological support should be available. Cognitive therapy, behavioural approaches including relaxation techniques and breathing exercises for anxiety management as well as other therapies such as massage and yoga may alleviate difficulties during withdrawal. Psychoeducation around withdrawal symptoms should be offered and a referral to a support organisation or group is helpful.

**Resources**

- The Ashton Manual,  
- NHS Clinical Knowledge Summaries,  
- The Maudsley Prescribing Guidelines

**Summary**

Although prescriptions of benzodiazepines have declined substantially since 1988, there is an ongoing challenge within all sectors of the NHS to prevent benzodiazepine dependence. This can be achieved by adhering to official recommendations to limit prescriptions to 2-4 weeks, or for brief courses or occasional usage. All health authorities should have clinical audit programmes reviewing and monitoring prescribing rates for benzodiazepines. Through this, increased awareness of CSM guidelines amongst all health care professionals should aid in more appropriate prescriptions and subsequent monitoring that is required to prevent unnecessary prescriptions. Patients on long-term prescriptions should be offered the opportunity for controlled withdrawal and the relevant psychological and social support.
Competing Interests
None declared.

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