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# Benzodiazepines revisited—will we ever learn?

**Malcolm Lader**

Addiction Research Centre, Institute of Psychiatry, King's College London, London, UK

## ABSTRACT

**Aims** To re-examine various aspects of the benzodiazepines (BZDs), widely prescribed for 50 years, mainly to treat anxiety and insomnia. It is a descriptive review based on the Okey Lecture delivered at the Institute of Psychiatry, King's College London, in November 2010. **Methods** A search of the literature was carried out in the Medline, Embase and Cochrane Collaboration databases, using the codeword 'benzodiazepine(s)', alone and in conjunction with various terms such as 'dependence', 'abuse', etc. Further hand-searches were made based on the reference lists of key papers. As 60 000 references were found, this review is not exhaustive. It concentrates on the adverse effects, dependence and abuse. **Results** Almost from their introduction the BZDs have been controversial, with polarized opinions, advocates pointing out their efficacy, tolerability and patient acceptability, opponents deprecating their adverse effects, dependence and abuse liability. More recently, the advent of alternative and usually safer medications has opened up the debate. The review noted a series of adverse effects that continued to cause concern, such as cognitive and psychomotor impairment. In addition, dependence and abuse remain as serious problems. Despite warnings and guidelines, usage of these drugs remains at a high level. The limitations in their use both as choice of therapy and with respect to conservative dosage and duration of use are highlighted. The distinction between low-dose 'iatrogenic' dependence and high-dose abuse/misuse is emphasized. **Conclusions** The practical problems with the benzodiazepines have persisted for 50 years, but have been ignored by many practitioners and almost all official bodies. The risk–benefit ratio of the benzodiazepines remains positive in most patients in the short term (2–4 weeks) but is unestablished beyond that time, due mainly to the difficulty in preventing short-term use from extending indefinitely with the risk of dependence. Other research issues include the possibility of long-term brain changes and evaluating the role of the benzodiazepine antagonist, flumazenil, in aiding withdrawal.

**Keywords** Abuse liability, adverse effects, benzodiazepines, dependence, efficacy, extent of use.

*Correspondence to:* Malcolm Lader, P 056, Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK. E-mail: malcolm.lader@kcl.ac.uk
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## LITERATURE SEARCH

This descriptive review is based on the Okey Lecture that I delivered at the Institute of Psychiatry, King's College London in 2010. It concentrates on the dependence-inducing and abuse potential of the widely used drugs, the benzodiazepines (hereafter abbreviated to BZD). A search of the literature was carried out in the Medline, Embase and Cochrane Collaboration databases, using the codeword 'benzodiazepine(s)', alone and in conjunction with various terms such as 'dependence', 'abuse', etc. Further hand-searches were made based on the reference lists of key papers. As 60 000 references were found, this review is not exhaustive.

## DEFINITION OF SEDATIVES, ANXIOLYTICS AND HYPNOTICS

Originally the term 'sedative' meant allaying anxiety but it now has the connotation of causing unwanted drowsiness. Instead the terms 'anxiolytic' or (minor) 'tranquillizer' have been used to describe drugs that lessen anxiety. The term 'hypnotic' is used for medications taken in the late evening to induce sleep.

## HISTORICAL NOTE

Alcohol has long been known for its sedative properties. A range of substances, including bromides, chloral and

paraldehyde, were introduced in the 19th century as sedatives and hypnotics. They were supplanted by a large range of barbiturates in the 20th century. These were effective, but unwanted effects included sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment and confusion in elderly people. They were dangerous in overdosage, especially with alcohol, and were likely to be abused. They could induce liver microsomal enzymes. Long-term use induced dependence with severe withdrawal reactions. Recreational use and abuse were common. In turn the barbiturates were replaced, first by meprobamate. However, this was also found to produce unwanted effects including sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment and confusion in elderly people. Again, long-term use can induce dependence with severe withdrawal reactions. Recreational use and abuse were common: it is a scheduled substance. Thus, in turn, the immensely popular but ephemeral meprobamate was ousted by the BZDs.

**Discovery**

The BZDs were discovered by Dr Leo Sternbach. In 1908, he received his doctoral degree in organic chemistry at the University of Krakow [1–3]. In 1941, he was working for Hoffmann-La Roche in Basel but, as a Jew, he had to flee to the United States to escape the Nazis. He worked on the BZD class of drugs in New Jersey. Wallace Pharmaceuticals had already developed a γ-aminobutyric acid A ($GABA_A$) receptor binding compound, meprobamate (Miltown), which proved to have powerful tranquillizing/sedative effects, but also adverse effects, including dependence and abuse potential. Dr Sternbach was asked to develop something similar but safer. He decided to turn to his previous student research at Krakow into a class of compounds eventually called BZDs, suspecting that they might act on the central nervous system (CNS). He tested approximately 40 compounds over 2 years which proved to be pharmacologically inert. Despite these setbacks, in 1956 Dr Sternbach decided to combine one of his compounds with methylamine: he created a white crystalline powder that he called 'Ro 5–0690' When he tested the agent on mice and other laboratory animals, a definite tranquillizing effect was detected with no apparent side effects. This compound was named methaminodiazepoxide and then changed to chlordiazepoxide (Librium). It was approved for use in 1960. In 1963 its congener, diazepam (Valium), was released and became increasingly popular. In the following years, Sternbach developed many other compounds including diazepam, flurazepam, flunitrazepam and clonazepam. More than 1000 BZDs have been synthesized [4]. Between 1969 and 1982, diazepam was the most prescribed drug in America, with more than 2.3 billion tablets sold in 1978.

More recently, the so-called z-drugs were introduced, comprising four non-benzodiazepine hypnotics: zaleplon, zolpidem, zopiclone and the s-enantiomer of zopiclone, eszopiclone. They differ with respect to their elimination half-lives, zopiclone and eszopiclone acting for longer than zolpidem, whereas zaleplon is very short-acting with an elimination half-life of just 1 hour. These compounds are appropriate to treat initial insomnia, but their effects wane during the night. They were dismissed by the National Institute for Health and Clinical Excellence (NICE) [5] as having no worthwhile advantages over the BZDs.

Although, in the last decade, the BZDs have been partly replaced by the SSRIs for anxiety and to some extent by melatonin agonists for insomnia, they remain among the most widely prescribed drugs. Is this popularity justified, or are we making a profound mistake by underestimating their adverse effects, including dependence and abuse, in parallel with over-estimating their efficacy?

## PHARMACODYNAMICS

Anxiety is the expression of a range of brain functions [6] with complex circuitry in the brain [7]. This provides a basis for an extensive series of remedies, with contrasting modes of action. Sleep mechanisms are also complex.

The BZD class of drugs is characterized by an ability to bind to specific benzodiazepine-type receptors on the GABA chloride ion channel complex and potentiate the inhibitory neurotransmitter GABA [8,9]. This then reduces the turnover of several neurotransmitters, including those involved in emotional expression such as noradrenalin (norepinephrine) and serotonin. The main sites of action of the BZDs are in the spinal cord, where they mediate muscle relaxation, the brain stem and the cerebellum, causing ataxia, and the limbic and cortical areas involved in emotional experience and behaviour. Dependence is accompanied by neuropharmacological changes, involving dopamine mechanisms as well [10].

The BZDs vary in their therapeutic spectrum and activity: for example, clonazepam has more anticonvulsant properties than most of the others. The so-called 'z-drug' hypnotics should be included in the class. Although these compounds differ chemically from the BZDs, they have the same pharmacological properties, being agonists at the GABA–chloride receptor complex, thereby increasing GABA-mediated neuronal inhibition [11].

A range of agonists and antagonists is available. The BZD antagonist, flumazenil, binds to BZD receptors and blocks the actions of BZDs: it can be used to reverse BZD

overdosage. BZD inverse agonists have been described; these have the opposite effects to BZDs, being proconvulsant and anxiogenic.

## PHARMACOKINETICS

BZDs are usually well absorbed by mouth. After being injected intramuscularly, they vary in their rate of absorption; diazepam in particular is absorbed erratically by this modality. Intravenous preparations are available but can result in local irritation. A special formulation, diazemuls, is better tolerated than simple solutions.

BZDs can have a pronounced redistribution alpha phase, diazepam being an example. It is therefore quite an effective hypnotic although it will accumulate over time.

A wide range of BZDs are available, mainly as anxiolytics (Table 1) and hypnotics (Table 2). They have very similar actions, differences being related to duration of action, depending on the metabolic half-life and the presence or not of psychotropically active metabolites. Even long-acting BZDs are prescribed as hypnotic medications (e.g. nitrazepam and flurazepam), despite definite residual effects the next day.

**Table 1** Some benzodiazepine anxiolytics—1959 onwards.

| *Drug* | *Trade name in United Kingdom* | *Half-life (hours)* |
|---|---|---|
| Alprazolam | Xanax | 12–15 |
| Chlordiazepoxide | None—used to be Librium | 6–30 |
| Diazepam | None—used to be Valium | 25–100 |
| Lorazepam | None—used to be Ativan | 12–16 |
| Oxazepam | None—used to be Serenid | 7–20 |

**Table 2** Benzodiazepine and related drugs used as hypnotics.

| *Official name* | *Trade name in United Kingdom* | *Half-life (hours)* |
|---|---|---|
| Flurazepam | (not available in United Kingdom) | 25–100 |
| Flunitrazepam | Rohypnol | 18–26 |
| Loprazolam | None | 12–16 |
| Lormetazepam | None | 8–12 |
| Nitrazepam | Mogadon | 18–24 |
| Temazepam | None | 7–11 |
| Triazolam | (not available in United Kingdom) | 2–4 |
| Zaleplon | Sonata | 1–2 |
| Zolpidem | Stilnoct | 2–4 |
| Zopiclone | Zimovane | 4–8 |
| Eszopiclone | (not available in European Union) | 4–8 |

## CLINICAL INDICATIONS

The British National Formulary (BNF) divides BZDs into anxiolytics which 'can be effective in alleviating anxiety states' and hypnotics, used in some cases for the short-term treatment of insomnia. The BNF lists nitrazepam, flunitrazepam, flurazepam, loprazolam, lormetazepam and temazepam as hypnotics; flunitrazepam and flurazepam are not available in the National Health Service (NHS). Another three BZDs, diazepam, oxazepam and lorazepam, are licensed for both insomnia and anxiety. Alprazolam and chlordiazepoxide are also listed under BZDs in the anxiolytic section and also as an adjunct in acute alcohol withdrawal [12]. The z-drugs zopiclone, zolpidem and zaleplon are listed as hypnotics. Eszopiclone has not been licensed in the European Union (EU). Some of the BZDs have useful anticonvulsant effects [13].

The properties of all these drugs as approved by the Licensing Authority are detailed in each Summary of Product Characteristics ([14], e.g. diazepam).

Many new compounds are being evaluated as anxiolytics and hypnotics [15,16]. Of these, some selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenalin re-uptake inhibitors (SNRIs) are licensed as treatments for generalized anxiety disorder (GAD) and are usually the first choice mentioned in guidelines. Pregabalin acts on calcium channels in the brain, reducing the release of excitatory neurotransmitters. It is also licensed for this indication. Buspirone, an azapirone acting on the serotonin system, is available to treat GAD and is effective, but largely in patients who have not previously had experience of a BZD [17]. Hydroxyzine, an anticholinergic antihistamine, has only modest effects [18]. Propranolol is licensed for symptomatic relief. Increasing interest is being seen in the atypical antipsychotics [19,20]; randomized controlled trials (RCTs) show promising results, but poor tolerability may limit their use. Melatonin agonists have been introduced for the treatment of insomnia.

BZDs are not licensed as antidepressants. However, it is generally believed that coprescription of a BZD improves first-month adherence and response to antidepressant treatment. One large-scale study showed that the adjusted probability of receiving an antidepressant treatment of adequate duration was 42.4% for patients who received a BZD combined with their initial antidepressant, compared with 39.3% for patients treated initially with an antidepressant alone ($P < 0.001$) [21]. Among patients who received combined treatment, 14.1% subsequently used BZDs for at least 1 year, and 0.7% were diagnosed with anxiolytic abuse or dependence. One might argue that the slightly enhanced adherence was outweighed by the risk of long-term use.

A series of Cochrane Reviews have found little or no evidence for efficacy in schizophrenia, delirium, catatonia, aggression and agitation, tardive dyskinesia or akathisia, or breathlessness in cancer or chronic obstructive pulmonary disease (COPD) [22].

## SHORT- AND LONG-TERM EFFECTS ON BRAIN AND BEHAVIOUR

### Subjective sedation

Sedation is the most common subjective effect of the BZDs. In healthy volunteers increased sedation can be detected after each dose, even after a week of treatment [23]. Tolerance appears to develop after a few weeks' treatment, but some residual effects may remain, as increased alertness is reported by patients on stopping treatment with BZDs [24]. High doses of BZDs combined with alcohol are commonly abused by polydrug users to deliberately increase sedation.

### Objective impairment and psychomotor effects

Barbiturates in high doses produce a characteristic syndrome of over sedation with unsteadiness, poor coordination, slurred speech and disorientation. BZDs do not produce as much sedation as this, but nevertheless effects such as poor coordination are related to dose, compound and individual sensitivity. BZDs and other sedative drugs have consistent effects on psychomotor performance, both in acute and repeated doses [25]. They impair the ability to perform simple repetitive tasks both when these are performed on their own and as a component of more complex tasks. The effect is related to speed of execution, participants slowing down to maintain accuracy of performance. They also impair simple tasks of attention. Many years ago, a positive relationship was found between size of effect and dose level [26].

Despite tolerance developing to some measures of sedation and psychomotor performance [27,28], impaired performance on simple repetitive tasks has been shown to persist for up to 1 year [29] and on tests of attention after several years of treatment [30] in long-term BZD users compared to control groups.

### Cognitive effects

Acute and short-term administration of BZDs clearly impairs higher brain functions such as learning and memory [31,32]. These effects are magnified by combination with alcohol [33]. Memory for information acquired pre-drug administration (retrograde memory) is not impaired, but acquisition of new material post-drug (anterograde memory) is consistently impaired by BZDs. The more demands that are made on memory, e.g. increased task complexity and delay in recall, the greater the effect [34]. There are also differences between benzodiazepine compounds. The majority of compounds do not affect implicit memory or priming, but lorazepam has also been found to impair these aspects of memory [35]. Even after months or years of treatment, the characteristic effects of BZDs on episodic memory were still found [35], and were not reversed by flumazenil [36].

A meta-analysis found that BZD users performed worse on the majority of cognitive tasks used, in particular verbal memory, compared to controls or test norms [37]. These studies were very diverse with respect to variables such as length of use, dosage and diagnosis.

### Cognitive decline

Sedative drugs can produce major cognitive disorders such as delirium: this is often associated with different drug combinations. In a meta-analysis of 12 studies, Barker *et al.* [37] noted improvement in all areas of cognitive function up to 6 months after withdrawal, but ex-users of BZDs performed worse on the majority of cognitive tasks used, in particular verbal memory, compared to controls or test norms. Verdoux *et al.* [38] investigated this issue further by reviewing six prospective studies that had been conducted in older adults. Of these, two studies reported a lower risk of cognitive decline in former users, two found no association and three found an increased risk of cognitive decline in users. Nevertheless, withdrawal of the medication generally leads to steady, but not immediate, resolution of the effects. Improvement on both psychomotor tasks and tests of working and episodic memory has been found in two studies comparing patients who have discontinued compared to those who have continued with BZD medication [24,39]. It is likely that effects are related to dose and task complexity, those on higher doses taking longer to recover on more complex functions, so that testing should be carried out at longer follow-up times. Impairment did not resolve in a relatively short time (6 months) after withdrawal of high doses of a BZD (diazepam, mean dose 48 mg) [40], but a follow-up study of patients showing impairment of episodic memory while being treated with alprazolam [35] showed no impairment 3.5 years later [41].

### Accidents and injuries

Sedative drugs increase the likelihood of accidents, injuries and cognitive failures (problems of memory, attention or action). In a questionnaire survey of 8000 people in two districts of Wales, BZD use was associated with injuries outside work and cognitive failures [42]. The association between accidents and sedative drug use is more apparent in elderly people [43–45], who are even more likely to experience falls and hip fractures while

taking BZDs and tricyclic antidepressants in conjunction [46,47]. The risk of hip fractures in older adults can be increased by as much as 50% [48]. However, polypharmacy is common among this population, and side effects of other drugs, e.g. postural hypotension, may also increase the risk of falls and accidents.

### Complex skills and driving

Increased sedation and impaired psychomotor skills impair complex skills such as driving or operating machinery [49–51]. Both simulated driving performance and actual driving ability can be impaired, and accidents are more likely [52]. Epidemiological studies have confirmed that road traffic accidents involving injury or death are associated with sedative drug use [53–55]. This is related to dose, and the risk is increased by the concomitant use of alcohol and increased age [56,57]. A meta-analysis of studies from 1966 to 2000 concluded that BZDs increased the risk of accidents by 60–80% [58]. Driving impairment was generally related to plasma half-lives of hypnotics, but with some exceptions. Daytime anxiolytics impaired driving independently of their half-lives. Additive effects with alcohol are noticeable [59].

### Forensic and behavioural problems

Paradoxical excitement is an unwanted effect which also has possible legal implications [60]. This disinhibitory effect of the BZDs can produce increased anxiety, acute excitement and hyperactivity. Aggressive impulses may be released with the emergence of hostility and rage; criminal acts such as assault and rape have been recorded. Estimates of incidence range from less than 1% to at least 20% of those taking BZDs; the variation depends on the patient sample. High-risk patients include those with borderline personality disorders, impulse control disorder and persistent alcohol problems. The combination of a BZD and alcohol is particularly likely to lead to paradoxical reactions. The patient may have complete or partial amnesia for the event, such as an episode of 'air-rage' in an aeroplane. Disinhibitory reactions to sedative drugs are related to type of BZD, dose and mode of administration [61]. Thus, pre-operative intravenous administration of high doses of high potency BZDs poses a particularly enhanced risk.

## LONG-TERM USE

There have been few studies on the long-term efficacy of the BZDs in GAD [62,63]. This contrasts starkly with the realization that the most insidious adverse effects of the BZDs are related to long-term rather than short-term usage. Long-term effects can differ from short-term effects, first because tolerance may develop to some of the short-term effects; secondly, new effects may supervene as time passes. These can even be detected in normal volunteer subjects [64]. Social and economic costs can be high [65].

Comparisons of users with non-users suggest that users have worse physical and mental health, but interpretation is difficult because the original allocation to BZD medication was not random [66]. With respect to hypnotic use, the long-term effects have not been re-appraised in recent years [67], but those patients who do manage to discontinue report an improvement in health [68], and this is apparent to others [69]. One suggestion is that toxic effects cumulate [70]. Patients who discontinue successfully make less use of medical services [71]. Recovery is slower than following abstinence from alcohol misuse [72].

The cognitive, psychomotor and practical impairments with BZDs have been outlined above and often apply in greater force to long-term users [29,37,73–75]. There is some evidence that discontinuation of long-term BZD use is followed by a slow, rather than a rapid improvement [37,39,41]. One study suggested that subtle, reversible but small effects of long-term BZD use on speed-dependent tasks may ensue in older adults [76]. They were probably of little clinical significance.

One particular concern has been the onset of severe cognitive decline, which may be misdiagnosed as a dementing process [77]. Drug-induced cognitive impairment in older adults can be a confounding factor in dementia, in some cases leading to the apparent worsening of cognitive decline and pseudo-dementia [78–80], or it can constitute a syndrome in its own right. The extent of the problem is disputed [81,82]. One study suggests that both duration and cumulative exposure to a BZD has a small negative effect on the long-term cognitive functioning of elderly people in the community [83]. A detailed and extensive survey in the Bordeaux region of France concluded that former use of BZDs could be a risk factor for dementia [84]. Current thinking is that BZDs should be avoided as much as possible in elderly people and avoided altogether in the very old population.

In insomniac patients treated long-term with BZDs, complex changes in sleep architecture were found, varying from subject to subject. Chronic usage may be associated with poor sleep. Some, but not all, indicators returned towards normal [85]. A survey showed that about half of elderly long-term users of hypnotics wanted to stop, but needed advice and information as to how to accomplish this [86].

Other reported effects of long-term use include impairment of the immune system [87] and blepharospasm [88].

An early controversy which has recently been re-activated with great force concerns the possibility of brain damage of some type in long-term users. This notion stems from the well-known association between alcohol and brain damage [89,90]. Because alcohol and the BZDs have a common pharmacology and because cognitive and psychomotor effects are evident in long-term BZD users, it was essential to investigate the possibility of brain damage in such users. The practical problem concerned the necessity of studying BZD users who did not also abuse alcohol, thereby confusing the aetiology. In the first study carried out by my research group [91], computerized axial tomography (CAT) scans were performed in 20 long-term BZD users. Clear abnormalities were reported by the radiologist in three BZD users, three alcoholics and one control. The mean ventricle–brain ratio was increased in these patients compared with age- and sex-matched normal subjects. A group of alcoholics showed more marked changes. No relationship was found between the brain appearances and duration of BZD use. We concluded that: 'The clinical significance of the findings is unclear'.

In a second study, 25 subjects who had never taken BZDs were compared on their CAT scan appearances with nine short-term users, 30 current users and 17 withdrawn from BZDs [92]. There were no overall differences between the groups. A few brain regions—caudate nuclei, frontal and occipital areas—differed between non-users and heavy users, particularly those taking lorazepam. Again, the clinical implications remained unresolved.

Other investigations addressed the same question. Heavy abusers of BZDs showed enlarged cerebrospinal fluid (CSF) spaces [93]. Uhde & Kellner [94], studying patients with panic disorder, found a significant positive correlation between ventricle–brain ratios (VBRs) and duration of benzodiazepine use, although the mean values of patients' VBRs still fell within the normal range in the literature. A study from Sweden also detected brain damage in heavy users, perhaps irreversible [95]. Electroencephalogram (EEG) abnormalities persisted following withdrawal of BZDs [96]. Conversely, two studies were negative [97,98].

Alarmed by the possible implications of our preliminary findings, I requested the UK Medical Research Council (MRC), my employers, to investigate the matter. Meetings were convened in 1980–1981, chaired by the late Professor Robert Cawley and attended by a small group of experts from various disciplines. A recommendation was made that further research be undertaken. Proposals were submitted by me and later by Professor Heather Ashton, but neither set of proposals was successful; no further action was taken. A parliamentary question by Mr Woolas in 1999 was answered by the Department of Health to the effect that no further research was envisaged because adequate warnings were already in place [99].

For some reason of which I am unaware the transcripts of the original meetings were to be classified until 2014 so were unavailable for perusal. Notwithstanding, the All Party Parliamentary Group on Involuntary Tranquilliser Addiction, under the chairmanship of Jim Dobbin MP raised the matter [100]. (I have had no contacts with this Group.) They alleged discrimination against BZD users because there were no appropriate specialist services, non-recognition of the protracted BZD withdrawal syndrome and lack of rehabilitation schemes. Inevitably, conspiracy theories involving the Medical Research Council (MRC) and the Department of Health developed. The *Independent on Sunday* newspaper published a long article on the issue written by Ms Lakhani [101], but this was not followed-up by any other media. Ms Lakhani interviewed me, but I could throw no further light on the issue. Rumours circulate about a possible class action by BZD users against the MRC and the Department of Health. One hopes that it progresses further than the large class action against the BZD drug manufacturers 20–30 years ago. At the moment of writing no definite claims have been submitted.

However, a communication from the Department of Health states:

> The literature review currently being carried out by the National Addiction Centre (NAC) at King's College London (KCL) will consider the evidence in relation to the long term effects of benzodiazepines. The review includes reference to work kindly provided by Professor Lader, who is emeritus professor at KCL.
>
> This detailed literature review is now available [102].

## EFFECTS IN DRUG ABUSERS

The effects of BZDs and other sedative drugs are increased in combination with alcohol. Little research has examined the effects of BZDs in opioid-dependent individuals, but clear acute effects have been reported in some studies, which parallel the acute effects of BZDs alone described above. In combination with methadone, diazepam, flunitrazepam and triazolam produced increased sedation [103,104], decreased psychomotor performance and attention and impaired episodic memory [105]. In combination with buprenorphine, diazepam produced similar but less significant effects [105,106]. Impairment increased with higher doses, simulating abuse conditions.

These impairments not only increase the risks already listed above but are likely to contribute to specific drug-related harms involved in the preparing and injecting of

drugs, thereby increasing the risk of transmission of blood-borne viruses such as human immunodeficiency virus (HIV) and hepatitis C and of injections missing veins, causing abscesses. Polydrug misuse involving sedatives has also been associated with criminal activity and increased risk of overdose in both heroin users and those on opioid maintenance programmes [107,108].

Data are sparse, but mortality seems to be increased among BZD misusers [109].

## DEPENDENCE AND WITHDRAWAL

Dependence is defined by the World Health Organization as a strong desire or sense of compulsion to take a substance, difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others.

Withdrawal comprises a group of symptoms which occur on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/or in high doses. The syndrome may be accompanied by signs of physiological disturbance. A withdrawal syndrome is one of the indicators of a dependence syndrome.

Stopping BZDs is but part of a much wider topic of how medications are discontinued. This is a neglected subject compared with the choice and initiation of therapy [110].

People who develop misuse of, or become dependent on, BZDs or on z-drugs are typically those seeking medical help during increased anxiety or sleeplessness, but continuing their prescription beyond the recommended time-frame or at doses outside the recommended range. They are maintained on this by their prescriber, so this is sometimes called 'involuntary' or iatrogenic dependence. A second group actively seek the sedative/hypnotic for its intentional abuse because of its psychoactive properties. The latter are more likely to have a comorbid diagnosis of another substance-misuse disorder, and to derive their drugs from varied sources such as prescriber, illicit sales of diverted supplies or internet sites [111].

The potential problem with BZD dependence, at least at high doses, was predicted by Hollister and his colleagues in 1961 [112]. They gave 11 patients in prison 300–600 mg/day of chlordiazepoxide (several times the usual dose) for several months. On switching to placebo, within 2–8 days 10 patients developed depression, psychosis, agitation, insomnia, loss of appetite and nausea. Two had seizures.

Hollister and his colleagues were concerned that patients would escalate their dose, but it transpired that fewer than half of users did so in practice. Most of the patients using BZDs who show clear signs of dependence, as evidenced by a characteristic syndrome on attempted withdrawal, are still taking the original prescribed dose. Only a minority escalate their dosage above recommended therapeutic levels. Those who do attain high doses usually have a more severe form of dependence than those patients keeping to the therapeutic dosage range. The high-dose users usually indulge in a form of BZD misuse.

The mildest form of withdrawal is rebound. The distinction is that rebound comprises the original symptoms recurring at a greater intensity for a time. Withdrawal involves the onset of *new* symptoms not experienced previously by the patient. Rebound is likely when stopping hypnotic BZDs, particularly short-acting ones, even after only a few days or nights of use [113–116]. Polysomnography furnishes a sensitive measure of rebound. Daytime withdrawal symptoms may occur and have been described with triazolam and zopiclone [117,118].

The similarities between BZD withdrawal and the syndromes accompanying alcohol and barbiturate withdrawal were recognized early on [119]. Withdrawal can result in severe syndromes [120]. Protracted withdrawal has been described, but the aetiology of these symptoms has been disputed [121]. The occurrence of the withdrawal syndrome is related to high dosage and long-term treatment, but the severity of the withdrawal syndrome is not so closely related [122]. However, severe withdrawal syndromes may still occur despite slow withdrawal over several months or even years [123].

As tolerance may supervene in some patients, withdrawal syndromes may supervene insidiously in patients maintained on a constant dose and puzzle the prescriber.

Withdrawal symptoms from the BZDs can ensue after 4–6 weeks of use, but only in about 15–30% of patients [124]. The reasons why some can withdraw with impunity after even years of continuous use while others undergo agonies remains unclear. Dosage reduction as well as complete withdrawal can result in withdrawal symptoms. The common and less severe ones are listed in Table 3. These include psychological symptoms such as anxiety and/or insomnia, nightmares which may disturb the patient, memory and concentration are impaired, and depressive symptoms may appear. Physical symptoms may ensue, such as muscle tension and spasm or weakness, pins-and-needles and flu-like symptoms. Very characteristic are the perceptual symptoms affecting most sensory systems with hypersensitivity to light, sound and touch. Derealization and depersonalization are common. Occasionally, fits or a paranoid or a confusional psychosis may occur. More serious or life-threatening symptoms may occasionally occur [125] (Table 4). Many of these are reported anecdotally, and few case series exist. Their status remains controversial.

**Table 3** Common withdrawal symptoms [120,125].

| | |
|---|---|
| Psychological symptoms | |
| Anxiety, possible terror and panic attacks | Agitation and restlessness |
| Mood swings | Paranoia |
| Impaired concentration | Impaired memory |
| Indecision | Dysphoria |
| Nightmares | Insomnia |
| Bodily symptoms | |
| Perspiration | Increased urinary frequency |
| Hot and cold flushes | Headache |
| Muscular spasms, twitches cramps | Stiffness |
| Aches and pains | Fatigue and weakness |
| Numbness and tingling | Electric shock sensations |
| Blurred vision | Dizziness |
| Loss of appetite and weight loss | Nausea and vomiting |
| Tachycardia | Postural hypotension |
| Dry mouth | Chest pain |
| Flu like symptoms | Gastrointestinal problems |
| Perceptual symptoms | |
| Increased sensitivity to touch | Increased sensitivity to sound (hyperacusis) |
| Tinnitus | Objects moving |
| Metallic taste in mouth | Taste and smell disturbances |
| Increased sensitivity to light | Photophobia |
| Derealization (feelings of unreality) | Depersonalization |

**Table 4** Severe withdrawal symptoms that may accompany abrupt discontinuation of benzodiazepines (BZDs) but may occur despite slow tapering [120,125].

| | |
|---|---|
| Delirium tremens | Delusions |
| Convulsions, status epilepticus which may end in death | |
| Catatonia, which may result in death | |
| Depression (often severe) [276] possible suicidal ideation | |
| Self-harm | Suicide |
| Suicidal ideation | Attempted suicide |
| Homicidal thoughts | Violence |
| Organic brain syndrome | Psychosis |
| Confusion | Mania |

The symptoms appear within two to three half-lives of the particular BZD, but the duration is unpredictable: generally the symptoms wane within a few weeks or months. High neuroticism, lower educational level and lower quality of life were associated with higher levels of distress during withdrawal [126], and with higher doses and low levels of social support [127]. Often the symptoms fluctuate quite markedly before finally resolving [128–130].

A recent prospective study revealed four patterns of withdrawal symptoms over time [131]:

1. a gradual decrease over the 50-week time-period;
2. an increase in the severity of symptoms at the onset of tapering and a decrease in severity post-tapering;
3. an increase in the severity of symptoms 4 weeks after the cessation of BZD tapering; and
4. no change over the 50-week time-period.

As is evident from Table 3, the withdrawal symptoms may resemble the symptoms of anxiety or insomnia for which the BZD was prescribed originally [123]. Misdiagnoses are common among inexperienced prescribers and the dosage may be increased unnecessarily, perpetuating a vicious cycle.

The prevalence of BZD dependence in out-patient users was estimated to be 40%, but up to 97% in those attending self-help groups [132]. The risk was regarded as high.

Russell & Lader [133] published a stepped-care approach to BZD discontinuation. It began with a minimal intervention with advice from the general practitioner (GP), and moved on to systematic tapering of doses by the GP for patients if the first stratagem was unsuccessful. Hospital-based BZD discontinuation was then considered necessary if these two stages were repeatedly unsuccessful.

Minimal interventions are often helpful [134]. A 10-year follow-up used medical records of patients in the Netherlands who had discontinued BZD use successfully after advice about discontinuation in a letter from their GP. Of these patients, 60% continued abstinent. Those who were not able to maintain their abstinence usually managed on lower or average doses of BZDs [135]. Curtailing prescriptions was effective in a study in Denmark [136].

Withdrawal schedules are promulgated widely and involve tapering, usually after substituting diazepam [137]. However, such substitution has little evidence to support its efficacy [138]. The rate of taper is not based on good empirical evidence but the clinical experience of the prescriber [139]. An important observation is that the early stages of withdrawal are easier to tolerate than the later and final stages. Thus, a person may reduce quite quickly from 15 mg of diazepam a day to 5 mg, and then stall as the symptoms increase thereafter with dosage reduction. Therefore, regular tapering may not be the most appropriate. It is usual to start fairly briskly and then slow down. Patients may not feel better until they have withdrawn fully [139]. Stopping in the middle of a withdrawal schedule is counterproductive.

Substitution of a long-acting BZD such as diazepam or chlordiazepoxide is often used to facilitate withdrawal. It is also useful because the formulations available such as liquid preparations facilitate small

decrements. Caution is needed, because the dose of long-acting BZD that will substitute fully for a shorter-acting agent is greater than anticipated. Some experts, particularly in the United States, used to favour phenobarbitone as the substitute [140], but it has no advantages over diazepam. Other drugs which have been substituted include antidepressants, serotoninergic anxiolytics, anticonvulsants and beta-blockers; these may help in management without reducing the severity of the withdrawal [141]. The addition of an SSRI to tapering in depressed patients withdrawing from BZDs was unhelpful [142]. In general, psychological treatments are helpful but some believe only when tapering has ceased [143]. The addition of cognitive–behavioural therapy (CBT) to a careful tapering schedule was of limited value [144]. However, two other trials showed that CBT facilitated tapering among chronic BZD users [145,146]. Ten Wolde *et al*. [147] showed that chronic users receiving a tailored intervention were twice as likely to quit benzodiazepine use compared to the usual GP letter.

A recently published meta-analysis of 24 intervention studies compared routine care with gradual dose reduction (GDR) and GDR with psychological techniques or pharmacological substitutions [148]. Routine care was less effective than the interventional procedures.

Another review assessed 32 articles involving interventions focusing solely on increasing appropriate prescribing and reducing long-term use of BZDs [149]. Three major intervention approaches were identified: education, audit and feedback and alerts. Studies which had used a multi-faceted approach reported the largest and most sustained reductions in BZD use. The choice of outcome measures, delivery style of educational messages and advice by GPs to stop BDZs, either by letter or face to face, showed no differences on the success rates of the intervention.

Our recent descriptive review of research on withdrawing BZDs in primary care concluded that there are few objective data on the optimal rate of benzodiazepine withdrawal; that the optimal duration of withdrawal is undetermined, and may vary for each patient [134]. Nevertheless, we recommended that withdrawal be conducted over an 8–12-week schedule for most patients and completed in less than 6 months. Flexible schedules were necessary that allowed for slowing down if the withdrawal symptoms become too disturbing. Group therapy might help, as it draws upon support from other patients, while the value of individual counselling as an adjunct has yet to be established. CBT may be a useful adjunct particularly for preventing relapse, and promising results have been found using the internet [150]. However, another study showed no enhanced efficacy over standard therapy [151].

The prognosis with a slow tapering schedule is usually fairly good, with about two-thirds of patients achieving total cessation. Others achieve a reduction in dosage but this is an inadequate outcome, as there is a high rate of relapse. Those who fail to discontinue have a poor prognosis and repeated failure may ensue, demoralizing the patient. Predictive factors include previous failed attempts, lack of family or social support, an unsympathetic general practitioner and a history of alcohol-related problems, older age, comorbid depression or physical conditions or a personality problem. Patients prescribed medication by their usual GP are more likely to respond positively to brief intervention than those whose medication was prescribed by another medical practitioner [152].

A careful appraisal may conclude that long-term maintenance is the better option, the lesser of the two evils, but the patient must be monitored to prevent accumulation with toxicity such as cognitive impairment and pseudo-dementia.

Those who achieve a successful total withdrawal should never risk a relapse by taking BZDs again, even for short periods [153]. Even alcohol should be avoided because of cross-tolerance and dependence.

Various adjunctive treatments have been advocated [138]. These fall into two categories. The first comprises the administration of drugs that are cross-tolerant with the BZD from which withdrawal is being attempted. This includes other BZDs and barbiturates (see above). The second group are agents which should help to assuage the symptoms of withdrawal if they emerge. These drugs can be given prophylactically or as needed. The best example is antidepressant medication, which is useful if comorbid depression is apparent or if the patient has a history of affective disorders. Gabapentin has also been tried [154]. The antipsychotic, cyamemazine, which has 5-HT blocking effects as well as dopamine-blocking actions, has been reported as effective [155,156].

The non-BZD anxiolytic, buspirone, was largely ineffective [157]. Carbamazepine has also some evidence supporting its use [158]. Pilot studies of pregabalin were reasonably successful [159,160]. Psychological therapies or support groups should be used routinely during the period of withdrawal. Group therapy may instil the patient with confidence that as others can withdraw, so can they.

Withdrawal from high doses of BZDs is conducted in a similar manner, although supervision of doses may be necessary in polydrug abusers, diazepam being administered alongside methadone in specialist drug services, to avoid diversion of the medicine. However, if attempts are unsuccessful in a high-dose dependent patient, it has recently been suggested that maintenance treatment with a slow-onset, long-acting BZD might be a viable

option [161]. The problem of cognitive and memory impairments was recognized as a major limitation. The suggestion was hotly debated; a supporting article pointed out possible advantages [162], but the stratagem was also dismissed as not evidence-based [163].

A different approach using the BZD antagonist and partial agonist, flumazenil, has been tried with some success. One obvious hazard is precipitating dangerous withdrawal in chronic users, particularly those on high doses. This does not seem to be inevitable [164], but normal subjects given repeated doses of lorazepam showed precipitated withdrawal [165].

A controlled study showed that flumazenil can precipitate withdrawal in chronic low-dose BZD users [166], characterized by anxiety and panics. Following a suggestion by an anaesthetist [167], Sally Morton and I used flumazenil with some success in patients plagued with persistent withdrawal symptoms, often severe and debilitating [168]. A series of studies has been carried out around the world on similar patients but also on users attempting to withdraw for the first time [169–172]. Treatment with flumazenil was found to be more effective than tapering or placebo. It reversed BZD effects usually without precipitating severe withdrawal symptoms, and also reduced craving. This procedure involves in-patient treatment and is likely to be suitable only for a small number of severely dependent patients with a history of prolonged BZD abuse. Nevertheless, large-scale RCTs remain to be carried out.

The teratogenic risk with the BZDs is low [173]. However, pregnant women are often withdrawn from their BZD treatment. This should never be abrupt [174]. If BZDs are continued into late pregnancy, neonatal withdrawal syndromes may occur in the baby and can be severe [175].

In summary, most patients show no dose escalation yet physical dependence on the BZDs is apparent, as shown by unpleasant symptoms on discontinuation. This comprises a characteristic withdrawal syndrome ('sedative/alcohol'), with often bizarre symptoms. The withdrawal can be hazardous with fits, psychosis and depression. There have been copious reports of a prolonged syndrome. The outcome is usually favourable with tapered withdrawal, but elderly people have a worse prognosis.

### Official guidelines on benzodiazepine and z-drug withdrawal

Official guidelines have recently been promulgated. The Drug Misuse and Dependence: UK Guidelines on Clinical Management provide information suitable for a long-term BZD and z-drug withdrawal regimen in the community [176]. The guidelines recommend converting the medications into an equivalent dose of diazepam based on clinical experience of withdrawal schedules (Table 5) (135). Diazepam is recommended because it has a relatively long half-life and is available in different-strength tablets and in liquid form. Being long-acting, it can be prescribed as a once-daily dose that can be titrated according to the patient's withdrawal symptoms.

**Table 5** Approximate dosages of common benzodiazepines and z-drugs equivalent to 5 mg of diazepam.

| *Drug* | *Dose* |
|---|---|
| Chlordiazepoxide | 15 mg |
| Diazepam | 5 mg |
| Loprazolam | 500 mg |
| Lorazepam | 500 μg |
| Nitrazepam | 5 μg |
| Oxazepam | 15 mg |
| Temazepam | 10 mg |
| Zaleplon | 10 mg |
| Zoplicone | 7.5 mg |
| Zolpidem | 10 mg |

## ABUSE OF BENZODIAZEPINES

Abuse is defined in the American Psychiatric Association's Diagnostic and Statistical Manual IV as a maladaptive pattern of use indicated by . . . continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by the use [or by] recurrent use in situations in which it is physically hazardous.

BZDs are undoubted drugs of abuse [177–179]. BZD abuse may have different patterns in different countries. The pattern of misuse ranges from occasional binges at weekends to continuing high-dose use, with large doses being taken on a regular basis [180]. They are classified under the Convention of Psychotropic Substances as Schedule IV, except for flunitrazepam and temazepam, which are scheduled as III because of perceptions of greater dangers [181]. In the United Kingdom, particular problems arose with a liquid formulation of temazepam. It was injected readily, so that the intravenous abuse of temazepam liquid-filled capsules, in particular, spread rapidly among opiate users in the United Kingdom. In turn, manufacturers reformulated the filling to a hard gel, but this could still be liquefied and injected and this led to serious physical complications [182]. Currently, temazepam is only available as a tablet formulation in the United Kingdom. Temazepam may be particularly prone to induce abuse problems, perhaps because of its pharmacokinetic profile and ready availability because of its widespread prescription as a hypnotic [183,184]. Abuse

of this substance has become very widespread in many countries, ranging from northern Europe to South East Asia. Some countries such as Sweden have banned it.

The prevalence of sedative misuse has been calculated from data derived from the National Comorbidity Study in the United States [185]. The life-time prevalence of non-prescribed sedative use was found to be 7.1% among adults. Unfortunately, the type of sedative was not specified in this study and other similar surveys suffer from the same drawback. In reality, abuse of BZDs in particular is likely to be higher in countries where they are easily obtainable and there are fewer controls, e.g. parts of Asia and South America. However, much of the literature relates to the US and European nations where misuse often results from diverted prescriptions. In the United States, alprazolam is commonly misused.

Patients who are prescribed licit BZDs for problems with anxiety or sleep do not usually escalate their doses, even over a lengthy period of use [186]. However, high-dose BZD monodependence has been reported [122,187], with doses ranging up to 95 mg/day lorazepam. Laboratory studies of abuse liability show that although BZDs have the potential for abuse, this is at a much lower level than for heroin, cocaine or the barbiturates [188]. Primary iatrogenic BZD abuse is therefore uncommon, but secondary abuse with alcohol or other drugs is much more common. It usually involves high doses as part of a pattern of polydrug abuse [189]. Patients with problems with alcohol abuse or dependence are more likely to use higher doses of BZDs [190]. Initially, patients with drug or alcohol abuse may be prescribed higher than average doses by GPs or other medical specialists for problems with anxiety or insomnia, but they may then exceed the prescribed dose, obtain prescriptions from different doctors or buy them on the illicit market. The main source is diverted supplies often stolen from pharmacists. Prescriptions are commonly forged [191]. Sometimes the BZDs are taken regularly, but they can also be taken in an intermittent binge-type pattern. They are used frequently with alcohol because the combination results in increased feelings of intoxication [33], or with other sedative drugs such as tricyclic antidepressants or opiates [192,193].

A significant proportion of people with alcohol problems also abuse BZDs. They are used by heroin-dependent individuals [194] and by patients in opioid substitution treatment to prolong and enhance the opiate effects [195]. A common combination is with amphetamines, and these misusers are at particular risk of adverse effects [195,196]. BZDs can also be used when preferred drugs are scarce. They are used by stimulant users to alleviate the increased jitteriness and anxiety after a binge and to induce sleep. They are usually taken orally, but both intranasal [197] and intravenous abuse [197] occurs, the pattern of use varying according to compound, formulation and country [198]. Snorted flunitrazepam has a high abuse liability [199], and this type of abuse was popular in Chile. Other BZDs have been abused intravenously.

The abuse of high doses of BZDs in combination with opiates is implicated in potentially fatal overdoses [107,109]. Intravenous use can result in thrombophlebitis abscesses, cellulitis, deep vein thrombosis and gangrene and may even necessitate amputation. The usual problems of transmission of HIV and hepatitis are present, perhaps to an exaggerated extent, because BZD users have a reputation for being disorganized and confused. They are over-represented in police detainees [200]. Abuse is associated with amnesic episodes, blackouts and fits. Aggression and violence are common, resulting from a combination of the aggression- and disinhibition-inducing properties of the BZDs. BZDs also have great notoriety as drugs to facilitate crime such as rape and robbery. Flunitrazepam is usually regarded as the main culprit. The effects are due to the induction of profound memory impairment, disinhibition and muscle relaxation [201,202]. However, the BZDs are usually administered together with alcohol, and the concentration of alcohol can usually account for the effects on its own.

The National Treatment Agency for Substance Misuse [203] commissioned a detailed report, covering three main aspects:

1 An analysis of relevant National Drug Treatment Monitoring System (NDTMS) data and prescription data to investigate prevalence and trends;
2 Structured interviews with targeted Primary Care Trusts/partnerships to better understand the commissioning, governance (of prescribing and drug treatment provision) and provision of drug treatment services; and
3 Surveys and structured interviews with specialist drug treatment providers and dedicated providers of treatment for prescription-only medicines/over-the-counter medicines (POM/OTC) dependency to determine what is being provided and how local services are configured.

Despite detailed analysis of the treatment and prescription data available at a national level and extensive consultation with the field, it was not possible to establish a definite prevalence of medicines of addiction or dependency in the general population. Nevertheless, an overall decrease was found in the prescribed quantities of hypnotic and anxiolytic medicines from 878.7 million items in 1991 to 550.4 million items in 2009. Within the overall decrease of hypnotic and anxiolytic medicine an increase in the prescribing of z-drugs was seen against a general decrease in the amount of BZDs prescribed. In

2009–10, just 2% (3735) of those in drug treatment services reported that their primary problem was with POM or OTC preparations. A further 14% (28 775) whose primary dependency was illegal drugs reported additional problems with POM/OTC.

As with low-dose dependence, tolerance sets in rapidly and withdrawal syndromes, sometimes severe with fits and psychotic reactions, can supervene on attempted discontinuation. The effects of long-term use of high doses are relatively poorly documented, but worsening of anxiety, phobias and depression may occur [204].

## EXTENT OF USAGE

Anxiety and sleep disorders occur commonly. In the 2007 Adult Psychiatric Morbidity Survey of England, 4.4% of the population met diagnostic criteria for GAD in the week prior to interview, approximately 3.4% of men and 5.4% of women [205]. Sleep disorders are yet more common: chronic insomnia occurs in about 10% of the general population and in about 20% of the over 65-year-olds [206,207].

Primary care is the setting for most management of anxiety. BZDs are not recommended for first-line long-term treatment of GAD. Despite these recommendations, BZD use remains widespread, perhaps reflecting the complexity and refractory nature of GAD, as well as poor tolerability in some patients to SSRIs and SNRIs.

A very extensive and detailed review of the usage of the BZDs and the z-drugs is available in Reed *et al*. [102] and in a shorter review by Donoghue & Lader [208]. However, some criticisms have been levelled at the methodology of many trials [209]. Most studies focused on individual characteristics of respondents, neglecting the potential contribution of health care professionals to psychotropic drug use, especially among elderly people.

With all the known adverse effects and the lack of evidence of long-term effectiveness and repeated official warnings over 30 years, one might expect a decline in the prescription of BZDs. Thus, in 1980, the UK Committee on the Review of Medicines issued a statement that warned about the overuse of BZDs, particularly with respect to duration of treatment [210]. More recently, a comprehensive review of the treatment of GAD stated that although BZDs were effective in the treatment of GAD, as they offered rapid relief of symptoms and adverse effects including sedation and psychomotor impairment were usually mild; nevertheless, their long-term use was not recommended because of concerns over dependence and withdrawal symptoms [211]. Indeed, even short-term *effectiveness* as opposed to *efficacy* in the RCT context has been questioned [212].

A survey in the United Kingdom found that the point prevalence in the general population for chronic BZD use was 0.5% [213]. In a larger study, a sample of almost 5000 non-institutionalized individuals aged 15 years or older was interviewed by telephone [214]. Overall, 3.5% of the sample reported current use of psychotropic medication, with 63% of the medicines prescribed being BZDs. Insomnia was the most common and use by women (4.6%) was twice that of men. Consumption rose significantly from the age of 35 and increased considerably again over the age of 65. The hypnotics used comprised mainly temazepam and nitrazepam, and the anxiolytics, mainly diazepam. The median duration of psychotropic intake was 52 weeks. Among patients taking hypnotics, 60% had used for them for more than 1 year. Of those using a drug to aid sleep, half estimated the quality of their sleep as markedly improved, 18% moderately improved and 30% reported little or no change.

A cross-sectional survey using a self-administered postal questionnaire was completed by 84 GPs [215]. Most attributed greater efficacy and lower side effects to z-drugs compared with BZD hypnotics. In particular, they were thought to be safer for older people. These beliefs were not recognized in national guidance such as the NICE report [5], but could still account for the increase in z-drug prescribing relative to benzodiazepine prescribing in the United Kingdom. A later study reported that GPs were negative in their attitudes towards hypnotics and favoured reducing prescribing for sleep problems [216]. GPs needed to develop better strategies for both the assessment and the non-pharmacological management of patients presenting with insomnia for the first time, as well as for those on long-term hypnotics.

A total of 8580 subjects aged 16–74 years participated in a national survey designed to investigate the comorbidity with and impact of hypnotic use [217]. Any insomnia at all was reported by a third of the sample and was moderate in 12%; it was associated with fatigue in 13%. Symptoms fulfilling diagnostic and severity criteria for primary/secondary insomnia were reported by 5% of the total sample. BZD hypnotics were used in about 1.2% of those with any report of insomnia and 4.4% of those who met diagnostic criteria for insomnia. In those aged 25–34, medication use was 0.7% but rose to 9.7% in the 55–64-year age groups and to 8.5% in those more than 65 years.

The 1946 British birth cohort database was used to describe antidepressant, anxiolytic and hypnotic drug use over a 22-year period [218]. The prevalence of prescribing of all three groups of medication increased significantly from 1977, when it was 30.6 per 1000, to 1999 when it had almost doubled to 59.1 per 1000. Previous use of such drugs was a strong predictor of future use during an episode of mental disorder.

The close relationship between gender, age and BZD use has been shown in studies in Italy [219–221], France

[222] and the Netherlands [223–225]. Another study in the Netherlands examined 1756 cases: GPs diagnosed a mental health problem in 13.2% and treated 86% of these patients themselves, with half receiving a prescription and nearly all those with a sleeping problem being prescribed a hypnotic [226]. Even in those with only psychosocial problems, a fifth received a BZD. A Norwegian study monitoring the use of BZDs in primary care found that two-thirds of prescriptions were for women and just over half were for patients aged 65 and/or older [227]. Eighty two per cent were repeat prescriptions, and this proportion increased with the patients' age.

In France a representative sample of non-institutionalized adults was surveyed by telephone [228]. The point prevalence of benzodiazepine use was 7.5%, almost twice as high among women than men, increasing with age and among the unemployed. The duration of usage was more than 6 months in three-quarters of users and increased with age.

In a longitudinal study in a 20 000-strong Swedish community, nearly 70% of the cohort continued the use of BZDs during the first follow-up year, 56% during the second year and one-third continued using BZDs throughout the 8-year period [229]. Heavy previous use of these drugs and age were the best predictors of future use. A comparison between communities in Sweden and the Netherlands showed very similar patterns of usage [230].

Data from the Norwegian Prescription Database covering all the population showed that the strongest predictors for long-term prescription of a BZD were previous use of anxiolytics, hypnotic rather than anxiolytic use, being male and being prescribed the hypnotic by a psychiatrist [231].

Two large surveys of BZD use across Europe have been conducted. The first interviewed representative samples of the non-institutionalized general populations above the age of 15 years in France, Germany, Italy and the United Kingdom, using a sleep-evaluation knowledge database system [232]. This comprised 18 679 individuals and represented more than 200 million inhabitants. Psychotropic medicines were being taken by 6.4% of the subjects—anxiolytics by 4.3% of the sample, hypnotics by 1.5%, antidepressants by 1% and antipsychotics and others by fewer than 1%. The highest rate of hypnotic users was found in France (2.5%), followed by the United Kingdom (1.6%), with only 0.7% in Germany and Italy. Many subjects said that they were taking an anxiolytic to help them to sleep and only a quarter that it was primarily to reduce anxiety.

The extensive European Study of the Epidemiology of Mental Disorders (ESEMeD) study was designed to assess psychotropic drug utilization in the population of six European countries—Belgium, France, Italy, Germany, the Netherlands and Spain [233]. Individuals were asked about any psychotropic drug use in the past 12 months. Among those with a mental disorder, only one in three was prescribed a psychotropic medicine. For major depression without any comorbidity only one in five received an antidepressant. The study questioned the appropriateness of current pharmacological treatments, particularly for major depression. These findings paralleled those of a similar study in the United States [234].

The Harvard/Brown Anxiety Disorder Research Project (HARP) assessed psychotropic drug usage in the United States using prospective, longitudinal data [235]. Prescribing patterns had remained fairly stable over 12 years; BZDs were the most common medications, being used in half of those diagnosed as suffering from GAD. After 12 years a third of these patients were still taking them. A Canadian population survey reported that 4% used BZDs at any time; they were more likely to be female, elderly, smokers, non-English-speaking and to have completed high school education [236]. However, only previous BZD use predicted long-term use. A comparison of BZD use in Nova Scotia and Australia found that usage in Canada was at least twice that in Australia; longer-acting agents were favoured in Australia [237].

A study in Norway on a sample of the general population addressed z-drug use [238]. Usage for the licensed indication of insomnia was common. The authors note that: 'In general the satisfaction with taking sleep medications was high, indicating that most users experienced at least some relief from their sleep problems'. Most current users reported difficulty stopping the drugs, but the authors comment that: 'This may represent dependence on the drugs or reflect an actual persistence of the sleep problem'.

Paradoxical effects of sedative drugs were detected by Victorri-Vigneau *et al*. [239]. However, the majority of users in the sample reported that the medication induced the expected sedative effects. Tolerance and dependence were reported in both groups, although the authors noted that dependence was reported more often in the first group. The median dose was higher in the first group (300 mg) compared to the second group (200 mg).

BZD prescribing and use were found to be common in a large sample size of the general adult Swiss population [240]; a subgroup was identified being prescribed at higher than recommended doses. In France, a study among normal workers found that 5.4% started psychotropic drug usage in a 5-year period [241].

Many studies have concentrated on BZD usage in elderly people [44,242–248]. The results are remarkably consistent. In country after country the usage of BZDs is greater and more long-term, extending over years and decades, than in younger subjects (see Table 6.) Most investigators comment on the inappropriateness of the

**Table 6** Benzodiazepine usage by age in a primary care survey in the United Kingdom (adapted from [213]).

| *Age (years)* | *Prevalence of anxiolytic usage* | *Prevalence of hypnotic usage* |
|---|---|---|
| 15–44 | 0.4% | 0.3% |
| 45–64 | 0.8% | 1.4% |
| ≥65 | 1.9% | 5.2% |

prescribing and deprecate the lack of adequate clinical care. In-patient usage is a particular concern [249].

Usage data cannot throw light automatically on whether the usage in elderly people is appropriate and evidence-based. An indicator of such usage has been developed [277].

One study concluded that in only a third of elderly medical in-patients in the United Kingdom were the BZDs prescribed appropriately, with an acceptable indication and no contraindications [250]. The More and Romsdal Prescription study found that inappropriate drug prescriptions were common among elderly patients in general practice [227,242]. Previous psychiatric diseases, poor self-perceived life satisfaction and multiple physical illnesses were associated significantly with subsequent BZD use [250]. A recent study from Brazil evaluated patients receiving emergency psychiatric care [251]. BZDs were the drugs used most commonly by psychiatrists on duty, regardless of patient's age. The authors urged caution in prescribing these drugs and suggest alternatives to the treatment of psychiatric disorders in elderly people.

BZDs are not recommended for use in depressed patients. Prescribing data from mental health settings in 129 US Veteran Administration facilities revealed that just over a third of those diagnosed as depressed were given a BZD, and 89% an antidepressant [252].. Factors predicting prescription of a BZD included being older, white or Hispanic, and suffering from a comorbid anxiety disorder.

Because of concern over suicidality with SSRIs, the use of psychotropic medication in children and adolescents has become a topic of increasing interest. The dispensing rates for anxiolytics, hypnotics and antidepressants to children and adolescents aged 3–17 years in a region of southern France were analysed [253]. Overall, 2.7% of the adolescents had received a prescription, increasing with age and in girls. Most were dispensed anxiolytics. Jorm and colleagues [254] found that in both inexperienced and experienced BZD users, the intention to use BZDs was a predictor of length of use. Experienced users were more inclined to consume BZDs when they had less control over drug taking. For inexperienced users, the perceived attitude of the prescribers towards use of the BZD was a strong determinant.

A longitudinal study from 1996 to 2005 was carried out by Donoghue & Lader, although the data have received only a preliminary analysis. The data were obtained from prescriptions written by 520 primary care doctors in 100 practices across the United Kingdom. A total of about 780 000 patients (1.3% of the UK population) were monitored with particular respect to 'new' BZD prescriptions, defined as a BZD being prescribed for the first time or after a BZD-free interval of a year or more. In 2005, 4404 patients received such a prescription, which corresponds to 340 444 nation-wide. Over the years 1996 to 2005 the number of patients decreased by only 1.6% and the number of prescriptions decreased by 7%. Average doses decreased by 25% and the mean length of treatment decreased by 15%. The duration of usage exceeded a year (i.e. chronic usage) in 6% of those aged over 70 compared with 1–2% in those under 50. Comorbidity of anxiety and depressive symptoms doubled the rate of prescription.

In summary, a common finding is that the licit use of long-term BZDs is very common and is usually more prevalent with hypnotics than with anxiolytics. Prevalence rates of BZD use range from 2.2% to 17.6%. Secondly, the factors that predict increased usage include increasing age, with higher rates of prescribing for women than for men, and patients' perceived physical health status with poor physical health being associated with increased use.

The extent of illicit usage has been assessed in several studies. In patients presenting to a Norwegian acute psychiatric university department, illegal use was admitted by 13%, licit use by 39% and no use in the remainder [255].

In a sample of 311 patients prescribed a BZD, only a third of usage was appropriate. Another recent study concluded that mentally or physically vulnerable subjects were most likely to use BZDs and to be at highest risk of inappropriate use [256]. In the absence of firm evidence of the effectiveness of BZDs in long-term use, the authors recommended caution in initiating BZD prescriptions, particularly when patients were chronically ill and elderly.

The prevalence of BZD misuse was reviewed in detail by Reed *et al.* [102] (Fig. 1). Dispensing data showed an overall substantial decrease in dispensing of BZDs in England from 1991 to 2009. This was due mainly to a drop in dispensing of hypnotic BZDs. By contrast, dispensing of anxiolytic BZDs dispensing rose, except for 2004–2006. However, total BZD dispensing decreased by 51.3% from 1980 to 2009. Analyses of General Practice Research Data (GPRD) showed that about half of all BZD prescriptions coincided with an episode of opiate substitution treatment (methadone or buprenorphine) in drug misusers. Almost all prescriptions were repeat. The

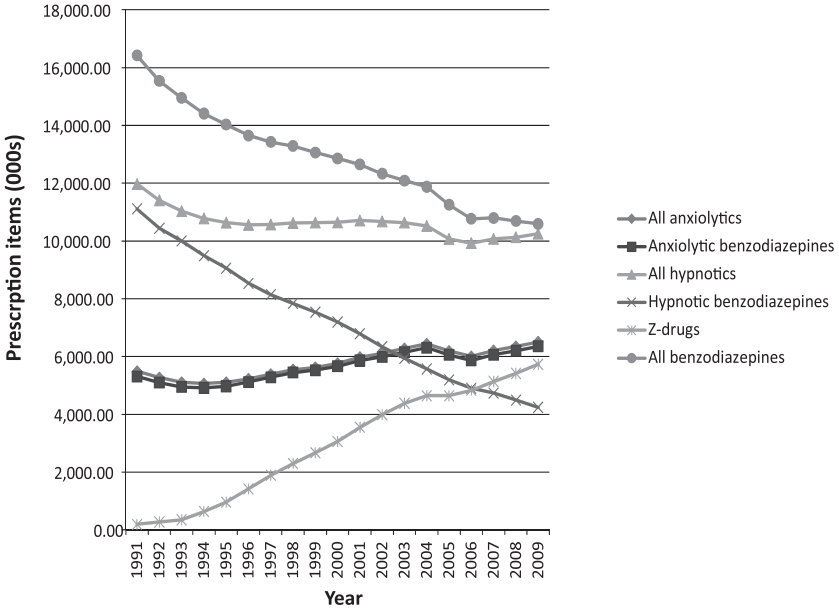


**Figure 1** Prescriptions dispensed in the community in England from 1991 to 2009 (prescription services division of the National Health Service business services authority) [275]

median length of a BZD prescribing episode (series of prescriptions) was 29 days, so only marginally exceeding the maximum time-frame recommended by the NICE guidelines [257]. However, just over a third was prescribed for more than 8 weeks. Dispensing data showed an increase in the dispensing of z-drugs in England from 1991 to 2009, but this increase in z-drug dispensing was less than the decrease in hypnotic BZD dispensing over that time; thus there is a decrease in total hypnotic dispensing. Longer-term hypnotic prescribing, however, of more than 8 weeks, has shown no consistent decrease or increase across the time-period, fluctuating around the 20% mark.

## CONCERNS

Extensive usage was apparent within a few years of the introduction of the BZDs. By 1975 in the United States, total anxiolytic and hypnotic sales comprised 10% of all prescriptions; in the United Kingdom, 15% of all prescriptions, and in France, 20%. Tyrer regarded the extensive use as 'The benzodiazepine bonanza' [258], and I dubbed them the 'Opium of the masses' [259]. Concern then shifted from the extent of usage to the reasons for this. Widespread media attention focused on linking long-term usage to dependence with addiction [260,261]. The BZDs (and fluoxetine) followed similar patterns of initial widespread public endorsement, followed by growing public criticism and recommendations for guidelines for more restrictive usage [262].

The greatest concern was expressed in the United Kingdom and Australia, with less concern in the United States and almost none in France and Belgium. Tightening of prescribing recommendations, warnings and restrictions followed and more recently NICE has issued guidelines [11,257]. The media in the United Kingdom mounted a sustained campaign during the 1980s and 1990s to establish the extent and severity of normal-dose dependence. Following a consumer programme (Esther Rantzen) on this topic on TV, the highest number of letters ever on a health issue was received. Women's magazines were particularly concerned, decrying the trivialization of BZDs as 'mother's little helper'. Numerous websites were set up. For example, Battle Against Tranquillisers pointed out that 1.5 million prescriptions/year were written in the United Kingdom for these drugs, and that they were Class C drugs under the Misuse of Drugs legislation. The campaigners asserted that the insidious effects of BZDs were often misdiagnosed and cited me as saying that they were harder to come off than heroin. They called for a National Treatment Agency, separate from the Addiction Treatment Centres. They quoted Professor Field, the president of the Royal College of General Practitioners, as advising their use for only a few days, but concluded: 'the best thing to do is not to prescribe them in the first place'.

The continuing prescription of BZDs despite official exhortations to limit their use has its apologists [263]. General practitioners in Belgium professed caution in using BZDs, but they felt overwhelmed by the intractable psychosocial problems of their patients and powerless to intervene effectively [264]. They used their prescribing usage to express empathy with the patient by thus indicating that they accepted a medical basis for the symptoms. However, they appeared unaware of the addictive potential of these drugs.

'Judicious' long-term use of BZDs is advocated as a treatment for patients with mood and anxiety disorders

[265]. These authors play down the risks dismissing the dangers of tolerance and dependence on them as having been 'catastrophized'. Similar rationalizations were used to justify BZD prescribing in a specialist psychiatric hospital [266]. Most consultants found official guidance too restrictive and prescribed BZDs for a variety of difficult management problems. The prescribers were concerned about the dependence potential but not the abuse propensities of the BZDs. One survey reported that GPs tended to endorse BZDs as effective treatment for anxiety, citing quick action and strong patient satisfaction. Indeed, the use of BZDs in older adult people was not seen to be problematic because they did not show drug-seeking or escalating dose behaviour suggesting addiction [267,268].

## ENVOI

It is clear that much BZD prescribing is for unlicensed or unspecified indications ('off-label'), or exceeds the licensed duration of use (typically, 4 weeks for an anxiolytic, 2 weeks for a hypnotic). Such practice inevitably raises legal issues about a breach of the duty of care, laying prescribers open to actions for negligence and personal injury. I am encountering increasing numbers of legal actions in which the GP expert regards prescription for unlicensed indications or beyond licensed durations as *prima facie* a breach of duty of care until proven otherwise, perhaps by invoking exceptional circumstances. It may well be that the prescription patterns of BZDs will be changed more by the legal than the medical profession.

However, the various issues relating to the use of BZDs are not as clear-cut as the apparent public consensus about their use suggests. Set against the various problems must be the observation that, more frequently than not, prescribed doses are not considered to be excessive although some studies did not find this not to be the case. In addition, there are several reports to indicate that, despite received wisdom, patients find these medicines helpful without an intolerable burden of adverse effects, and that their efficacy does not diminish over time. They are often reluctant to discontinue them [268]. This is reflected in the concern expressed about these medicines, which relates less to their effectiveness and much more to the risks of abuse and dependence. However, evidence of widespread dependence in population-based studies is limited: one study found evidence of tolerance in only 8% of patients taking BZDs [57], and none of the usage studies I have reviewed provided data to quantify tolerance or dependence.

It is clear that official recommendations concerning the use of these medicines are widely ignored. Does this suggest that other means of meeting patient needs are inadequate, not available or, in a risk-averse climate of clinical practice, has the risk–benefit relationship of these medicines been wrongly estimated—to the detriment of some patients? Concern has been expressed that a combination of media alarmism and risk-averse clinicians may have denied some patients appropriate treatment because of undue fears [269,270]. Is it likely that these medicines have a greater clinical utility than the available evidence suggests? Have clinical guidelines achieved the correct balance in framing their recommendations to meet the needs of both patients and clinicians? In this context, the view expressed by one group, that treatment guidelines that insist that these medicines should be restricted to short-term use, may not be applicable in the 'real world' of clinical practice, may be understandable [221]. Thus, despite current guidelines, many clinicians still regard BZDs as acceptable treatment options, both in the acute and the chronic phases of the treatment of anxiety disorders, partially because of their rapid onset of action and their efficacy with a favourable side effect profile, and also because of the sometimes only partial therapeutic response and side-effect burden of alternative medications [271].

With the increasing availability of prescription medicines over the internet, access to BZD medicines without a prescription is likely to increase across many countries: Levine [111] reports that BZDs are the most frequently offered controlled drug on the internet, with an estimated 89% of internet supply sites not requiring a physician's prescription in order to buy them [272]. It will be a Sisyphean task to control such self-medication. For a long time the question of the continuing use of BZDs in primary care has been raised without resolution of the issues [273]. The issues of abuse and dependence continue to raise concerns [274].

Continual monitoring of the situation is essential. In the United Kingdom this could be achieved by using the GPRD data in an ongoing analysis of the extent of BZD prescribing by GPs. Attention should be focused on elderly people, particularly those using these drugs (and the z-drugs) continuously over long periods. The data could be augmented by a UK survey of community pharmacists to establish patterns of dispensing prescribing these drugs. Similar surveys should be feasible in other countries.

With respect to specific gaps in our knowledge, it is a platitude to complain that further research is needed, but two areas stand out. First, the niggling question of possible long-term anatomical and biochemical changes in the brains of long-term users needs urgent attention to allay mounting concerns in view of the continuing extensive use of BZDs. Secondly, the possible use of flumazenil as an aid to withdrawal would lessen a great deal of symptomatic distress, in people who have developed dependence to drugs prescribed by their doctors.

To conclude, the controversy boils down to the familiar risk–benefit ratio, both short-term and long-term, the significance of the indications, the availability of effective and well-tolerated alternatives and possible misuse. Short-term adverse effects are a definite hazard, but short-term benefits are also present. The problem is the difficulty of preventing short-term use from drifting into long-term use where efficacy is largely unestablished, and the range of unwanted effects including dependence remains a major public concern. Abuse is also a salient issue. The advent of viable alternatives for both anxiety and insomnia should lead to a reappraisal of the BZDs. This review is designed to open up that debate.

## Declarations of interest

None.

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