BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04418.x

Benzodiazepine harm: how can it be reduced?

Malcolm Lader

Institute of Psychiatry, London, UK

Correspondence
Professor Malcolm Lader OBE LLB DSc PhD MD FRC Psych F Med Sci, PO56, Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK.
Tel.: +44 0207 848 0372
Fax: +44 0207 848 0818
E-mail: malcolm.lader@kcl.ac.uk

Keywords
adverse effects, benzodiazepines, reduction of harm

Received
7 May 2012

Accepted
5 August 2012

Accepted Article Published Online
10 August 2012

The benzodiazepines (BZDs) are anxiolytics, hypnotics, anticonvulsants, muscle-relaxants and induce anaesthesia. Adverse effects comprise sedation subjectively and cognitive and psychomotor impairment objectively. Complex skills such as driving can be compromised. Paradoxical excitement can have forensic implications. Long term use beyond the licensed durations is common but both efficacy and adverse effects associated with this have been poorly documented. Withdrawal and dependence have excited particular concern, and even polemic. Perhaps a third of long term (beyond 6 months) users experience symptoms and signs on attempting to withdraw – anxiety, insomnia, muscle spasms and tension and perceptual hypersensitivity. Uncommonly, fits or a psychosis may supervene. The patterns following withdrawal vary widely. The usual method of withdrawal is slow tapering but it may not obviate the problems completely. BZDs are also drugs of abuse either on their own or in conjunction with opioids and stimulants. Claims have been made that the use of BZDs is associated with increased mortality. This is a concern in view of the widespread usage of these drugs, particularly in the elderly. All of these factors impinge on the risk : benefit ratio and the severity of the indications. Harm reduction should focus on choice of alternative treatments both psychological and pharmacological. Guidelines emphasise that BZDs are not drugs of first choice and should only be used short term. Schedules are available to educate about methods of withdrawal in current users, emphasising the slow rate of taper. General principles of harm minimization in the addiction field are appropriate to BZD abuse.

Introduction

The benzodiazepines (BZDs) have anxiolytic, hypnotic, muscle relaxant, anticonvulsant and anaesthesia-inducing indications. Of these, prescribing to reduce anxiety and insomnia are the most common and has caused the greatest problems. The British National Formulary (BNF [1]) follows this division although some drugs such as diazepam, oxazepam and lorazepam are listed under both headings. Internationally, many more benzodiazepines are available and prescription patterns vary widely. Notwithstanding, adverse effects and production of harm are similar across the class. However, the timing and severity of these adverse effects will vary according to the peak concentrations and duration of action of the various BZDs and the short acting hypnotics ('Z-drugs').

This article briefly reviews the adverse effects of BZDs, short term and long term, and their dependence and abuse potential. This section draws heavily on a recent compendious review [2]. However, the overall assessment of the worth of a medication must also involve its efficacy, generally and with respect to subpopulations, the severity of the indications and the availability of alternatives. These are briefly outlined together with the extent of usage which indicates the magnitude of the problem. Finally, the question in the title is addressed although it is difficult to convey the breadth of opinion that prevails and consequent controversies and polemics.

Adverse effects

These have been studied in some detail but far from exhaustively. Gaps still exist, half a century after the introduction of the BZDs [3], particularly with respect to long term usage. Subjectively, sedation with feeling of heaviness and dysphoria is closely dose-related. It usually quickly subsides due to tolerance to the subjective effects.

At higher doses, unsteadiness, slurring of speech and disorientation indicate over-sedation particularly when the BZD is combined with alcohol. Cognitive and psychomotor impairment can be detected even at ostensibly therapeutic doses. This can ensue during the whole day when the BZD is prescribed several times during the day as an anxiolytic, or a long acting BZD the night before as a hypnotic. It will be confined to the morning following a short acting sleeping pill. These objective effects can persist in long term users [4]. Memory appears to be particularly sensitive to BZD action, again augmented by co-administration of alcohol. The more complex the memory task, the greater the impairment following a BZD. These effects persist into the long term [5]. A meta-analysis that combined several rather diverse trials found definite impairments across a range of tests especially with respect to verbal memory [6].

Many useful data should accrue by measuring various functions before, during and after the administration of a BZD anxiolytic or hypnotic preferably with random allocation to drug or placebo and under double-blind conditions. Such studies are the exception, with usually only two out of the three time phases. The above meta-analysis of neuropsychological tests revealed improvement in several cognitive functions, up to 6 months after BZD discontinuation, but ex-users of BZDs still performed poorly [6]. Older adults are at particular risk [7]. Overall, steady withdrawal usually culminates in improvement, if not immediately. All in all the literature remains inconsistent.

As well as these laboratory-based investigations more complex skills, such as driving, have been assessed for the practical safety implications [8]. Epidemiological studies also show an association between BZD use and road traffic accidents [9]. Increased age and alcohol use are contributing factors, and a meta-analysis estimated the risk of accidents to be increased by over 50% [10–12].

Other accounts and injuries are also more common in people using BZDs. Falls and hip fractures have excited most attention. In the elderly the incidence of hip fractures may be increased by 50% or more, particularly when other medication such as antihypertensives and antidepressants are co-prescribed [13].

A note of caution should be introduced. Disorders such as anxiety and insomnia can themselves impair a range of functions. Treatment with a sedative drug may improve the deficits with associated improvement in performance but counteracted to some extent by the direct drug-induced impairment –'confounding by indication'. Very few studies on psychotropic drugs have adequately addressed this issue (see [10], page 152).

Paradoxical excitement is an unwanted effect which also has possible legal implications. 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 and criminal acts such as assault and rape have been recorded [14].

The hazards of long term use have been touched on earlier. Some adverse effects such as cognitive and psychomotor impairments can persist into the long term, although sensitive techniques may be needed to detect them. Others such as sedation wane probably reflecting tolerance. A confounding issue is that patients taking psychotropic medication may lose sight of their original level of feeling and functioning as time elapses. Only when the medication is discontinued does the person realize that their feelings and performance have been sub-optimal. Comparisons with non-users can be problematic because allocation to treatment was never in a rigorous random way [15].

As long term BZD users grow older, they became more sensitive to their medications. This is probably because of reduction in neuronal numbers and receptors and hence a greater receptor occupancy for a constant dose. Increasing impairment can lead to a mistaken diagnosis of dementia, so-called 'pseudo-dementia' [16].

Long term hypnotic use, even at a low dosage level, has been reported to be associated with increased mortality hazards (see below), but subjective effects also alter [17], and many users want to stop.

Withdrawal and dependence

The WHO define dependence as including a strong desire or sense of compulsion to take a substance, difficulty in controlling its use, tolerance and the presence of a withdrawal state. Withdrawal comprises a set of symptoms which supervene on cessation or reduction in dosage of a psychoactive substance taken repeatedly, particularly in high dose. Of all the issues surrounding the BZDs these have occasioned the greatest continuing concern. Opinions have become increasingly polarized with some vociferous professional and lay people condemning the BZDs as instigating major iatrogenic addiction, others defending them as important and worthwhile drugs with a low incidence of dependence. The debate or rather, acrimony, is sadly not based on a firm evidence base.

Discontinuation of many medications may be accompanied by problems. With respect to BZDs, the most common phenomenon is rebound with hypnotics and this can be quantified with polysomnography [18]. After stopping the sleeping tablet, the insomnia can return in an exaggerated form, time to sleep onset is prolonged, sleep is more disturbed and it is shorter in duration. Rebound is generally short lived lasting a night or two, but can panic the patient into resuming the medication.

Withdrawal is a more serious phenomenon, constituting a characteristic grouping of signs and symptoms that ensues on discontinuing or reducing the dose of the anxiolytic or hypnotic. The antecedents of BZD withdrawal syndromes are varied. Many people are started on a BZD but find it insufficiently effective and ask for the prescriber to

increase the dose, often at a time of stress. Usually the patient settles on to that dose and remains there for months, years or even decades. A minority escalate the dose and become high dose users. Attempts to withdraw are accompanied by a BZD withdrawal syndrome which is in the same class as barbiturate or alcohol withdrawal [19, 20]. The patient is regarded as being dependent on the BZD and this group constitutes around 20% of the original users – the remainder can discontinue their medication without difficulty [21]. High dosage, the use of high potency compounds and prolonged continuous use is associated with evidence of dependence.

Withdrawal symptoms can include anxiety, insomnia, nightmares, memory and concentration impairments, and muscle spasms. Perceptual hypersensitivity such as photophobia and hyperacusis are common; the patient feels ill and loses weight. The symptoms generally subside in 2–4 weeks but can be prolonged. More serious but rare reactions include fits and psychosis. Most cases are anecdotal and few case series exist [22].

A recent prospective study of tapered withdrawal identified four symptom patterns – gradual decrease in severity, initial worsening followed by a decrease after discontinuation, a later increase in severity, and no change [23]. High prevalences have been reported [24]. Numerous protocols for withdrawal exist (e.g. [25]), but minimal interventions often suffice in primary care. Psychological treatments are usually helpful.

About two-thirds of patients stop completely with a slow tapering schedule. Most of the rest achieve some dose reduction. Repeated failure, however, becomes demoralizing, and support on a low dose may be the optimal outcome. Comorbid depression, alcohol use and older age are poor prognostic factors.

BZD abuse

A clear distinction should be maintained between dependence and withdrawal from therapeutic or somewhat higher doses within the medical context and abuse of BZDs in the context of recreational and illicit use. BZDs are widely misused [26], although patterns vary from country to country and from region to region. One type takes the form of binges, say at weekends, another regular sustained high dose usage. Some misusers keep to oral use whereas others inject intravenously or sniff intranasally like with cocaine use. A range of BZDs are abused depending on formulation such as liquid-filled capsules, availability and pharmacokinetics. Temazepam and flunitrazepam have the reputation for being readily misused. Furthermore, the misuser may confine him or herself to BZDs or misuse them as part of polydrug abuse, to potentiate the euphoriant effects of opioids, lessen the offset of cocaine, or interact in a complex way with amphetamines or other drugs of abuse. Some addicts will turn to BZDs if other misused drugs become scarce and expensive. The dangers are well known and mostly associated with intravenous use such as viral infection or local tissue necrosis. Overdose is a hazard, particularly in combination. Another danger is potentiation by the BZD of the depressant effects of alcohol, with criminal acts, often accompanied by amnesia.

Whatever the pattern of misuse, the BZDs are undoubtedly hazardous, and such misuse must be added to the potential harm associated with these compounds.

Mortality

Many of these short-term and long-term adverse effects are unpleasant rather than severe, and most are reversible. However, recent data purported to show that even low usage of hypnotics was associated with excess mortality [27]. The increased hazards were so substantial as to excite public alarm, especially as the results were published in a prestigious journal. The setting was a population served by a large integrated health system in Pennsylvania. The electronic medical records were accessed and 10 529 people who received hypnotic agents were matched by gender, age, smoking status, and time of prescription with 23 676 controls with no hypnotic prescriptions. On average, the samples were monitored for 2.5 years. For patients prescribed 0.4–18, 18–132 and >132 doses per year, the hazard ratios were 3.60 (95% CI 2.92, 4.44), 4.43 (3.67, 5.36) and 5.32 (4.50, 6.30) respectively. Thus, even occasional hypnotic users had over three times the background risk of dying in 2.5 years. Selective prescription of hypnotics for ailing patients was ruled out as the main explanation. However, co-morbidity with physical diseases of various types revealed significant excesses in the patients receiving hypnotics but this accounted for only a small proportion of the excess risk. The results are alarming but as these studies involve data already on file they can easily be replicated using other similar databases. All of the populations in the studies had attended as outpatients and may be unrepresentative of the background population.

A meta-analysis of six cohort and three registry studies suggested that regular users and illicit drug use were associated with increased risk of mortality [28].

Usage

The literature suggests heavy use of BZDs in many countries, although the pattern varies greatly [29]. Because different methods were used in the various usage studies, the data are too heterogeneous to sustain a meta-analysis. The prevalence figures from one UK study show that anxiolytics were used in the 15–44 year age group by 0.4% of the population, in the 45–64 year age group by 0.8% and in the over 65-year-olds by 1.9%. Corresponding figures for hypnotic usage are 0.3, 1.4 and 5.2%. BZD anxiolytic usage has

stayed largely the same over the past two decades [30].Use of hypnotic BZDs has reduced sharply but has been largely replaced by the Z-drug hypnotics.

According to one Dutch study, correlates of 'inappropriate' use include mentally or physically vulnerable subjects, particularly the elderly [31].

The literature suggests that the elderly, women, poor perceived health status and poor actual physical health are associated with long term use, especially with hypnotics. Long term users at particular risk of becoming dependent include those with depression and those with previous alcohol problems.

Efficacy

BZDs and the Z-drugs cover a range of pharmacological properties, both wanted and unwanted. Also their pharmacokinetic properties vary substantially from ultra-short acting to very long acting. As a consequence their efficacy is dependent on numerous considerations. On important factor with respect to long term use is whether tolerance is a major complicating factor.

The most relevant assessment is of the risk : benefit ratio. The adverse effects, at least in the short term, have been documented. What of the benefits?

A recent meta-analysis systematically reviewed 27 randomized controlled trials of drug treatments for generalized anxiety disorder (GAD) [32]. The only benzodiazepine included was lorazepam, presumably reflecting the advent of BZDs antedating the establishment of GAD as a diagnostic category. Fluoxetine was ranked first for response and remission and pregabalin for tolerability. Lorazepam showed up poorly but data for it were limited and the authors did not comment further.

With respect to hypnotics, numerous studies have compared a long list of benzodiazepines and Z-drugs with placebo and with each other [33, 34]. Another meta-analysis identified 24 studies in the elderly where the bulk of the prescribing is concentrated [35]. Sleep quality was found to have improved, total sleep time increased, and the number of night time awakenings decreased with hypnotic use as compared with placebo. However, adverse effects were nearly five times as common. The authors concluded that improvements in sleep did occur but the size of the effects was 'small'. Their use in the over 60-year-olds was attended by increased risk which might not be justified.

Choice of treatment

Numerous guidelines are extant for the management of anxiety disorders and insomnia. The most quoted are those issued by the National Institute for Health and Clinical Excellence (NICE) [36]. With respect to anxiolytic use, selective serotonin re-uptake inhibitors (SSRIs) are favoured as drugs of first choice, pregabalin is regarded as a stand-by for patients who cannot tolerate SSRI or serotonin-norepinephrine re-uptake inhibitor (SNRI) antidepressants. BZDs are relegated for the treatment of GAD in primary and secondary care for use only as a short term measure during crises. The advice in the BNF has been the given wisdom for many years:

Benzodiazepines are indicated for the short term relief (2 to 4 weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness.
The use of benzodiazepines to treat short term 'mild' anxiety is inappropriate and unsuitable.

The NICE advice does not suggest alternatives but dismisses the Z-drugs as indistinguishable pharmacologically and therapeutically from BZDs [37]. Again the BNF urges great caution with respect to BZD treatment of insomnia:

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

Reduction of harm: a personal view

Instituting treatment

The overview above has assessed the harm associated with BZD use, the efficacy and effectiveness in practice, the extent of usage and guidelines concerning alternatives. Each of these issues is open to debate. The listed hazards, major and minor, are dismissed by the enthusiasts as actually reflecting the safety of these drugs which have been available for half a century. At the other end of the spectrum, some regard the harm in absolute terms as precluding their prescription. Similarly, a range of opinion exists concerning the severity of the indications – anxiety and insomnia – for which they are prescribed. The BNF implies that severe anxiety equating to the licensed indication for SSRIs and SNRIs, namely GAD, does justify the occasional short term prescription of these drugs. NICE concurs, regarding BZDs as short term expedients in crisis situations.

Hypnotics are dealt with in a similar fashion, with insomnia being only occasionally severe or disabling.

A difference exists between anxiolytic and hypnotic use of the BZDs and Z-drugs in insomnia. Proven reasonably effective drugs such as SSRIs, SNRIs and pregabalin are available and appropriately licensed as treatments for GAD. The only alternative to hypnotic BZDs is the melatonin prolonged release formulation (Circadin) [38], and then only for insomniacs aged over 55 years. Off-label

alternatives include sedative antidepressants such as mirtazapine [39], and sedative antihistamines. This paucity of choice may alter soon as non-BZD hypnotics become increasingly available, such as orexin antagonists.

The extent of usage of BZDs in both indications is such that even a minor problem or miscalculation could result in a major clinical problem. Recently, availability of BZDs is increasing due to easy internet access [40]. Regulation of the internet is notoriously ineffective.

In my opinion the advisability of initiating a BZD prescription hinges on the problem of preventing short term use (less than 4 weeks for anxiolytic use and 2 weeks for hypnotic use) from being prolonged insidiously into long term use. The advice to limit such a prescription to the severely anxious and insomniac may even compound this difficulty as the more severely may obtain greater relief and not wish to discontinue. Informing the patient about the dangers that might occur on longer-term use is essential but patients may be reluctant to follow that. No clear indicators exist of who will reduce and cease their BZD use, or switch to other medication, and who will become chronic users. Even switching to another class of medication may carry some risks such as long term dependence on SSRI/SNRIs.

These problems have led to calls for prescribers to avoid BZDs entirely. That these calls are falling on deaf ears is evidenced by BZD prescribing figures in which no significant reduction has occurred over the past 20 years [30].

In many of these debates, the epicentre is the use of medications. For many years the use of psychosocial treatments has been an alternative measure. Dynamic psychotherapy may help some but the evidence base for its efficacy is lacking. Cognitive behavioural therapy (CBT) has a proven track record in depression and more recently in GAD. Use in treating insomnia is only now developing and its effectiveness is still unestablished. In the UK, the problem is the lack of qualified therapists, resulting in dauntingly protracted waiting lists. Combining drug and psychological treatments is possibly the way forward for the more seriously ill patients/clients but few studies have accrued.

Current users

What of the hundreds of thousands of patients already taking BZDs, especially with hypnotic use in the elderly? Guidelines with respect to tapering withdrawal are already widely promulgated [25, 41]. However, this advice stems from first pharmacological principles. Empirical evidence for the optimal approach to withdrawal regimens is scanty and confusing [42]. Even so gradual tapering of the medication is regarded as not particularly effective and combination with cognitive-behavioural therapy seems superior [43]. Another strategy is to substitute another medication as an aid to withdrawal; many have been tried, usually in small scale studies. No firm conclusions can be drawn [44]. Pregabalin has shown recent promise [45] as has prolonged release melatonin [46].

The glaring deficiency on the part of the NHS is the lack of clinics dealing with BZD dependence separately from Addiction Units. Middle-aged anxious housewives and elderly insomniacs dread being referred to an Addiction Unit and encountering 'junkies'. Calls for the establishment of a network of such BZD dedicated agencies have been ignored. The success rate in terms of reducing or ceasing BZD use can be quite high with simple measures, such as advice from the GP [47]. Only the failures need specialist referral. Some long term users have taken their BZDs for decades. Withdrawal attempts may be fruitless, but monitoring of symptoms and functioning must be instituted and maintained. Flumazenil has been investigated as an aid to withdrawal, success has been claimed, but few clinics anywhere offer this service.

The rate of tapering has become a contentious issue. Some long term users require protracted withdrawal regimens over months or years, but it is difficult to predict the duration in any one case. Indeed, some chronic users can discontinue with surprisingly little upset. It is probably a better clinical strategy to aim to withdraw over 2–3 months but to slow down if the symptoms become too severe.

Harm minimization is a well-known concept in the wider field of addiction [48]. A fundamental change in attitude led to the encouragement of drug using habits, such as availability of sterile water for injection in order to minimize serious adverse events such as the development of local abscesses and the contagion of viral diseases such as HIV and hepatitis. Similar but less extreme measures are appropriate to benzodiazepine abuse.

In conclusion, much BZD prescribing is for unlicensed or unspecified indications ('off-label'), or exceeds the approved duration of use or dosage. It would appear that official recommendations concerning the use of these medicines are widely ignored. In turn, such practice raises legal issues about standard of clinical care. 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. Similar surveys should be feasible in other countries.

Declaration of Competing Interests

I received no financial support for writing this paper. I lecture occasionally for Pfizer Ltd. This review has not been published in full or in part in any other journal.

I the sole author. have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf *(available on request from the corresponding author) and*

declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 British National Formulary. (BNF 63). London: Pharmaceutical Press, 2012.

2 Lader M. Benzodiazepines revisited – will we ever learn? Addiction 2011; 106: 2086–109.

3 Baenninger A, Costa e Silva JA, Hindmarch A, Moeller HJ, Rickels K. Good Chemistry: The Life and Legacy of Valium Inventor Leo Sternbach. New York: McGraw-Hill, 2004.

4 Gorenstein C, Bernik MA, Pompeia S. Differential acute psychomotor and cognitive effects of diazepam on long-term benzodiazepine users. Int Clin Psychopharmacol 1994; 9: 145–53.

5 Curran H. Tranquillising memories: a review of the effects of benzodiazepines on human memory. Biol Psychol 1986; 23: 179–213.

6 Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 2004; 18: 37–48.

7 Verdoux H, Lagnaoui R, Begaud B. Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies. Psychol Med 2005; 35: 307–15.

8 Leung SY. Benzodiazepines, opioids and driving: an overview of the experimental research. Drug Alcohol Rev 2011; 30: 281–6.

9 Skegg DCC, Richards SM, Doll R. Minor tranquillisers and road accidents. BMJ 1979; 1: 917–9.

10 Dassanayake T, Michie P, Carter G, Jones A. Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review and meta-analysis of epidemiological and experimental evidence. Drug Saf 2011; 34: 125–56.

11 Orriols L, Philip P, Moore N, Castot A, Gadegbeku B, Delorme B, Mallaret M, Lagarde E. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clin Pharmacol Ther 2011; 89: 595–601.

12 Maxwell HG, Dubois S, Weaver B, Bédard M. The additive effects of alcohol and benzodiazepines on driving. Can J Public Health 2010; 101: 353–7.

13 Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987; 316: 363–9.

14 Paton C. Benzodiazepines and disinhibition: a review. Psychiatr Bull 2002; 26: 460–2.

15 Authier N, Balayssac D, Sautereau M, Zangarelli A, Courty P, Somogyi AA, Vennat B, Llorca PM. Benzodiazepine dependence: focus on withdrawal syndrome. Ann Pharm Fr 2009; 67: 408–13.

16 Wu CS, Wang SC, Chang IS, Lin KM. The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data. Am J Geriatr Psychiatry 2009; 17: 614–20.

17 Bierman EJ, Comijs HC, Gundy CM, Sonnenberg C, Jonker C, Beekman AT. The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or indifferent? Int J Geriatr Psychiatry 2007; 22: 1194–2000.

18 Dikeos DC, Soldatos CR. The pharmacotherapy of insomnia: efficacy and rebound with hypnotic drugs. Primary Care Companion. J Clin Psychiatry 2002; 4: (Suppl 1): 27–32.

19 Poyares D, Guilleminault C, Ohayon MM, Tufik S. Chronic benzodiazepine usage and withdrawal in insomnia patients. J Psychiatr Res 2004; 38: 327–34.

20 Fontaine R, Beaudry P, Le Morvan P, Beauclair L, Chouinard G. Zopiclone and triazolam in insomnia associated with generalized anxiety disorder: a placebo-controlled evaluation of efficacy and daytime anxiety. Int Clin Psychopharmacol 1990; 5: 173–83.

21 Lader M. Long-term anxiolytic therapy: the issue of drug withdrawal. J Clin Psychiatry 1987; 48: (Suppl): 12–6.

22 Ashton H. Benzodiazepine withdrawal: outcome in 50 patients. Br J Addict 1987; 82: 655–71.

23 Vikander B, Koechling UM, Borg S, Tönne U, Hiltunen AJ. Benzodiazepine tapering: a prospective study. Nord J Psychiatry 2010; 64: 273–82.

24 Kan CC, Breteler MHM, Zitmann FG. High prevalence of benzodiazepine dependence in out-patient users, based on the DSM-III-R and ICD-10 criteria. Acta Psychiatr Scand 1997; 96: 85–93.

25 Russell VJ, Lader M. Guidelines for the Prevention and Treatment of Benzodiazepine Dependence. London: Mental Health Foundation, 1993.

26 UK Department of Health and the Devolved Administrations. Drug Misuse and Dependence: UK Guidelines on Clinical Management. London: Department of Health, 2007.

27 Kripke DF, Langer RD, Kline LE. Hypnotic association with mortality or cancer; a matched cohort study. BMJ Open 2012; 2: e000850.

28 Charlson F l, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiol Drug Saf 2009; 18: 93–103.

29 Donoghue J, Lader M. Usage of benzodiazepines; a review. Int J Psychiatry Clin Pract 2010; 14: 78–87.

30 Prescription Services Division of the NHS Business Services Authority. Available at http://www.nhsba.nhs.uk/PrescriptionServices.aspx (last accessed 30 August 2012).

31 Manthey L, Van Veen T, Giltay EJ, Stoop JE, Neven AK, Penninx BW, Zitman FG. Correlates of (inappropriate) benzodiazepine use: the Netherlands Study of Depression and Anxiety (NESDA). Br J Clin Pharmacol 2011; 71: 263–72.

32 Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder; systematic review and meta-analysis. BMJ 2011; 342: d1199.

33 Lader MH. Hypnotics. How effective are they for insomnia? Psychiatr Times 2009; May: 23–5.

34 Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med 2007; 22: 1335–50.

35 Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005; 331: 1169–73.

36 National Institute for Health and Clinical Excellence. Anxiety. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Clinical Guideline 113. March 2011. London: National Institute for Health and Clinical Excellence.

37 National Institute for Health and Clinical Excellence. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. Technology Appraisal 77. April 2004. London: National Institute for Health and Clinical Excellence.

38 Wade AG, Ford I, McConnachie A, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. Curr Med Res Opin 2011; 27: 78–98.

39 Wiegand MH. Antidepressants for the treatment of insomnia; a suitable approach? Drugs 2008; 68: 2411–7.

40 National Center on Addiction and Substance Abuse at Columbia University. You've Got Drugs! Prescription Drug Pushers on the Internet. New York: Columbia University, 2006.

41 Ashton CH. Benzodiazepines: how they work and how to withdraw. (Revised Edition 2011), University of Newcastle, 2002.

42 Parr JM, Kavanagh DJ, Cahill L, Mitchell G, Young RM. Effectiveness of current treatment approaches for benzodiazepine discontinuation; a meta-analysis. Addiction 2008; 104: 13–24.

43 Baillargeon L, Landreville P, Verreault R, Beauchemin J-P, Grégoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering; a randomized trial. Can Med Assoc J 2003; 169: 1015–20.

44 Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database Syst Rev 2006; (3)CD005194.

45 Hadley SJ, Mandel F, Schweitzer E. Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: a double-blind, placebo-controlled trial. J Psychopharmacol 2012; 26: 461–70.

46 Kunz D, Bineau S, Mmaman K, Milea D, Toumi M. Benzodiazepine discontinuation with prolonged-release melatonin: hints from a German longitudinal prescription database. Expert Opin Pharmacother 2012; 13: 9–16.

47 Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. CNS Drugs 2009; 23: 19–34.

48 O'Brien CP. Benzodiazepine use, abuse and dependence. J Clin Psychiatry 2005; 66: (Suppl 2): 28–33.