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# Withdrawing Benzodiazepines in Primary Care

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## Contents



## Abstract

The use of benzodiazepine anxiolytics and hypnotics continues to excite controversy. Views differ from expert to expert and from country to country as to the extent of the problem, or even whether long-term benzodiazepine use actually constitutes a problem. The adverse effects of these drugs have been extensively documented and their effectiveness is being increasingly questioned. Discontinuation is usually beneficial as it is followed by improved psychomotor and cognitive functioning, particularly in the elderly. The potential for dependence and addiction have also become more apparent. The licensing of SSRIs for anxiety disorders has widened the prescribers' therapeutic choices (although this group of medications also have their own adverse effects). Melatonin agonists show promise in some forms of insomnia. Accordingly, it is now even more imperative that long-term benzodiazepine users be reviewed with respect to possible discontinuation. Strategies for discontinuation start with primary-care practitioners, who are still the main prescribers.

This review sets out the stratagems that have been evaluated, concentrating on those of a pharmacological nature. Simple interventions include basic monitoring of repeat prescriptions and assessment by the doctor. Even a letter from the primary-care practitioner pointing out the continuing usage of benzodiazepines and questioning their need can result in reduction or cessation of use. Pharmacists also have a role to play in monitoring the use of benzodiazepines, although

mobilizing their assistance is not yet routine. Such stratagems can avoid the use of specialist back-up services such as psychiatrists, home care, and addiction and alcohol misuse treatment facilities.

Pharmacological interventions for benzodiazepine dependence have been reviewed in detail in a recent Cochrane review, but only eight studies proved adequate for analysis. Carbamazepine was the only drug that appeared to have any useful adjunctive properties for assisting in the discontinuation of benzodiazepines but the available data are insufficient for recommendations to be made regarding its use. Antidepressants can help if the patient is depressed before withdrawal or develops a depressive syndrome during withdrawal. The clearest strategy was to taper the medication; abrupt cessation can only be justified if a very serious adverse effect supervenes during treatment. No clear evidence suggests the optimum rate of tapering, and schedules vary from 4 weeks to several years. Our recommendation is to aim for withdrawal in <6 months, otherwise the withdrawal process can become the morbid focus of the patient's existence. Substitution of diazepam for another benzodiazepine can be helpful, at least logistically, as diazepam is available in a liquid formulation.

Psychological interventions range from simple support through counselling to expert cognitive-behavioural therapy (CBT). Group therapy may be helpful as it at least provides support from other patients. The value of counselling is not established and it can be quite time consuming. CBT needs to be administered by fully trained and experienced personnel but seems effective, particularly in obviating relapse.

The outcome of successful withdrawal is gratifying, both in terms of improved functioning and abstinence from the benzodiazepine usage. Economic benefits also ensue.

Some of the principles of withdrawing benzodiazepines are listed. Antidepressants may be helpful, as may some symptomatic remedies. Care must be taken not to substitute one drug dependence problem for the original one.

For several decades, particularly in the UK, the question of the correct use of benzodiazepine anxiolytics and hypnotics by general practitioners (GPs) has been hotly debated. A 1980 report of the Committee on the Review of Medicines[1] recommended that, in the absence of both long-term efficacy and safety data for benzodiazepines, their use should be limited to 3 months. In 1988, the Royal College of Psychiatrists advised that the maximum period of treatment should be 1 month.[2]

Notwithstanding this apparent consensus, such opinions did not represent the views of most clinicians in countries other than the UK, particularly the US. It was noted that much of the concern expressed about these medicines related not to their effectiveness, but to the risks of abuse and dependence; this could be counterproductive and could prevent some patients from receiving potentially effective treatment.[3] In 1994, a small community-based study found evidence of tolerance in only 8% of patients taking benzodiazepines.[4] The authors expressed concern that a combination of media alarmism and medical conservatism could be denying some patients appropriate treatment. The orthodoxy was further challenged the following year by a review that stated that most clinical benzodiazepine use was appropriate.[5]

Despite all these reassurances, the risks of benzodiazepine use, both short and long term, and particularly as hypnotics in the elderly, have been well

documented.[6] Amongst these risks is daytime drowsiness, higher risks of accidents and falls, and cognitive impairment.[7-11] The incidence of hip fractures is increased.[12] With long-term hypnotic use, it has been asserted that the risk of mortality is increased.[13]

Much of the flurry of concern that sprang up in the late 1980s and 1990s has seemed to subside. Nevertheless, it has become generally acknowledged that benzodiazepines are undoubtedly drugs that can be associated with problems when reduction in dosage or withdrawal is attempted. The discontinuation syndrome can be severe and in some cases may preclude the long-term user from ever stopping the medication.

The fact that discontinuation is a desirable goal has been shown by several studies. For example, Rickels and associates[14] followed up patients who took part in a programme of tapering off benzodiazepines. Of those who had successfully withdrawn, 73% were still managing without anxiolytics 3 years later, compared with only 39% who had reduced but not stopped their benzodiazepines. Of those who refused to participate, only 14% had succeeded in stopping 3 years later. Those who had managed without medication had significantly lower levels of anxiety and depression than those who had continued. Salzman and colleagues[15] reported that a group of elderly nursing home residents improved on measures of memory and cognitive functioning when tapered off benzodiazepine medication compared with those who continued.

An editorial in the *British Medical Journal* in 1994[16] suggested that GPs should undertake a review of patients taking benzodiazepines long term to see whether they still needed these drugs and, if not, then a slow reduction in dosage should be recommended after warning the patient about a short self-limiting set of symptoms, not to be misconstrued as relapse of prior insomnia or anxiety. The implication was that other psychological methods of combating anxiety and insomnia were desirable. At that time, the success of these techniques, drug and non-drug, had not been assessed systematically using classical controlled trial methods.

Since then, methods for intervention, specifically regimens for discontinuing anxiolytics and hypnotics, by GPs and ancillary staff have been further developed and evaluated. Some methods are quite simple, with gratifyingly useful effectiveness. Others are more elaborate and require the adoption of special skills. A protocol for a stepped-care approach was suggested by Russell and Lader,[17] in which the first two steps involved primary-care practitioners. These comprised a minimal intervention strategy as the first step, followed by systematic discontinuation for patients not responding to the first step. Hospital-based schedules then followed as the procedures became more elaborate and consumed more resources.

Subsequently, a series of studies have accrued under typical conditions of general practice in the UK, the Netherlands and Australia. In particular, a careful meta-analysis of available studies suggested that the early-advised, clinically-based protocol of Russell and Lader[17] was now supported by the results of controlled clinical trials.[18] The authors of the meta-analysis cautiously qualified their conclusions by pointing out the paucity of comparative studies and the lack of knowledge of the optimal tapering schedules.[18] Adjunctive treatments such as cognitive-behavioural therapy (CBT) were used, with limited evidence for their efficacy. The authors concluded that "future research should evaluate more rigorously stepped care programmes and promising augmentation strategies".[18]

The therapeutic landscape has changed in the last few years. The licensing of SSRIs for anxiety disorders and melatonin agonists for insomnia has opened up the therapeutic choices of prescribers. Accordingly, the use of benzodiazepines can be largely avoided, particularly as the newer drugs have clinically significant efficacy established under rigorous clinical trial conditions and are generally better tolerated, without a risk of dependence or abuse.

However, withdrawal of existing benzodiazepine usage can be difficult. Primary-care practitioners need guidance in dealing with patients who have taken benzodiazepines long term, as they can pre-

sent complex management problems. The purpose of this narrative review is to outline the most relevant studies, together with some assessment of both their effectiveness and their feasibility under typical circumstances in primary care. In addition, stratagems from outpatient studies are also evaluated for their relevance to primary care.

## 1. Benzodiazepine Usage

The history of benzodiazepines goes back to their development in the 1950s and their introduction soon after.[19] Most of the numerous members of this class of drugs have been widely used, both therapeutically and sometimes illicitly. Usage increased dramatically during the 1960s, culminating in one benzodiazepine, diazepam, being one of the most widely prescribed drugs of all time. By the late 1970s much concern had developed about the high usage of these drugs. Regulatory agencies such as the UK Committee on the Review of Medicines and the Committee on Safety of Medicines intervened with clear guidelines pointing out that long-term efficacy was not established, yet long-term safety was becoming increasingly questioned.[1] Some GPs curtailed their usage, but numerous prescriptions were still written.

Ashton[20] complained that, despite repeated recommendations to limit benzodiazepines to no more than 2–4 weeks, doctors were still prescribing them for months or even years. This resulted in large populations of long-term users becoming dependent on these drugs. Also, leakage onto the illicit market occurred. The example of the unsuccessful substitution of temazepam gel-type capsules, with even more dangerous injection practices, is significant. The keystones of management of benzodiazepine withdrawal were slow tapering of the dose and psychological support for the patient, when necessary. Withdrawal was followed by improvements in cognitive performance, particularly in the elderly.

Is long-term use synonymous with dependence? A study from the Netherlands looked specifically at long-term users applying both DSM-III-R[21] and ICD-10[22] criteria for dependence.[23] Groups of GP patients (n = 115), psychiatric outpatients (n = 124) and those attending self-help groups (n = 33) were compared. It was reported that the past-year prevalence rate for dependence was 40% in the GP patients, 63% for psychiatric patients and 82% for the self-help group.

The type of drug and the person's age and level of education were predictive of continuing use into the long term. GPs had a significant effect on this process in that they could utilize strategies of initial patient selection and appropriately timed reviews of their treatment.[24] Another study interviewed 15 GPs and 15 GP trainees concerning their management of anxiety problems.[25] Most respondents admitted to prescribing anxiolytics but only for short periods of time in severely distressed patients.

Currently, prescribing of the 'z'-drug hypnotics, particularly zopiclone, is increasing in the UK, while that of the standard benzodiazepine hypnotics such as temazepam is falling. The aim of one study was to compare the perceptions of primary-care physicians regarding the risk of benzodiazepine and z-drug use, and determine the prescribing behaviour of physicians.[26] To this end, a cross-sectional survey was set up in the West Lincolnshire Primary Care Trust. A self-administered postal questionnaire was sent to all the local GPs. Of the 107 questionnaires sent, 84 analysable responses were received. The general consensus was that z-drugs were more effective than benzodiazepines in terms of patients feeling rested on waking, daytime functioning and total sleep time. The overall perception was that these drugs were thought to be safer in terms of tolerance, addiction, dependence, daytime sleepiness and association with road traffic accidents. In particular, they were thought to be safer for older people. The majority of practitioners attributed greater efficacy and lower adverse effects to the z-drugs. These beliefs are not determined by current evidence or by national guidance such as the NICE report;[27] however, they would certainly account for the increase in z-drug prescribing relative to benzodiazepine prescribing.

A recent study investigated the views of practicing GPs in the North West of England regarding the prescribing of benzodiazepines.[28] The views of

these GPs were discussed in the wider context of psychotropic drug use. It was concluded that the benzodiazepines have been problematic in their use.

Another study compared the characteristics of long- and short-term benzodiazepine users.[29] Data from patients in 32 general practices in the Netherlands were used to compare 164 short-term and 158 long-term benzodiazepine users. The long-term users were older and had a more severe history of mental health problems for which they had received more treatment; these patients used more psychotropic drugs and consulted hospital specialists more frequently. They also had more physical illness and reported a lower perceived general health status.

Short- versus long-term use of benzodiazepines was further evaluated in order to identify patient-related factors predicting long-term use.[30] The same samples as in the previous study[29] were used. The factors associated with long- compared with short-term use included having a DSM-IV[31] disorder and psychiatric co-morbidity, being older, less educated, living alone and using more avoidance coping behaviour.

A study carried out in the late 1990s evaluated prescribing data in 350 practices in North Western England.[32] It was found that the prescribing volume of benzodiazepines was influenced by the level of seniority of the GP. The level of deprivation in the population contributed somewhat to the usage of these drugs.

Admission to hospital has been blamed for introducing many patients to benzodiazepines; however, an audit in Dundee found that admission to hospital had a minor effect on total community prescribing of these drugs.[33] This was mostly for night sedation. Nearly as many patients discontinued benzodiazepines when in hospital as those who started these agents.

## 2. Interventions

### 2.1 Simple Interventions

Using prescribing analysis cost data to quantify the effect of clinical audit, the extent of benzodiazepine prescribing before, during and after the audit was measured in 15 practices encompassing 87 902 patients.[34] The number of defined daily doses dispensed for temazepam, nitrazepam and lorazepam dropped during the audit and there was a significantly greater reduction in the number of items prescribed by those practices who participated in the audit than in those who did not. The investigators concluded that a simple audit of benzodiazepine prescribing can achieve a significant reduction in the volume of drugs dispensed.

A study was undertaken to assess the effectiveness of minimal intervention by GPs in helping long-term users of benzodiazepines to withdraw from their drug and to determine any psychological consequences of such intervention.[35] Patients taking benzodiazepines regularly for at least 1 year were allocated to either a group receiving brief advice during one consultation, supplemented by a self-help booklet, or to a control group who received routine care. Questionnaires regarding general health and benzodiazepine withdrawal were given at the outset of the study, and 3 and 6 months later. Eighteen percent of patients in the intervention group (9 of 50) had a reduction in their prescriptions for benzodiazepines compared with 5% in the control group. Intervention patients had significantly more qualitative but not quantitative withdrawal symptoms at 6 months compared with baseline. It was concluded that some long-term users can successfully reduce their intake of benzodiazepines with simple advice from the GP together with a self-help booklet. This type of intervention does not lead to psychological distress or increased consultation.

The effect of a letter from the GP suggesting a reduction in the use of benzodiazepines was assessed.[36] A second issue was whether the impact of the letter could be increased by the addition of information on how to tackle drug reduction. In general practice, 209 long-term users of benzodiazepines were divided into three groups – two intervention groups and a control group. The first intervention group received a letter from their GP urging gradual reduction and perhaps, in time, cessation of benzodiazepine use. The second intervention group received the same letter plus four information sheets

at monthly intervals, designed to assist drug reduction. The mean age of users was 69 years. After 6 months, both intervention groups had reduced their drug consumption to approximately two-thirds of the original intake of benzodiazepines, which was significantly better than the control group. It was concluded that a simple intervention can have a considerable effect on the use of hypnotic and anxiolytic drugs, even in a sample of elderly users.

A similar study in the Netherlands assessed predictors of short- and long-term discontinuation of benzodiazepines, and relapse and use after minimal intervention with a discontinuation letter followed by an offer of an evaluation consultation.[37] In the family practice population, 1707 long-term benzodiazepine users were sent a discontinuation letter and were followed up at 21 months. Multiple agent use at baseline and the use of antidepressants at 6 months predicted relapse. Shorter duration of use, male sex and the use of a short-acting medication were predictive of complete discontinuation at both 6 and 21 months. It was concluded that the amount of baseline use and duration of use were the main characteristics for successful discontinuation. The discontinuation letter was recommended as a first step within a stepped-care approach to decrease long-term benzodiazepine use.

The use of reminder cards in medical records was expected to enhance the effectiveness of an audit by providing feedback to improve the care of patients taking long-term benzodiazepine drugs. Eighteen general practices in Leicestershire were divided into groups; in the first group of practices feedback was given, and in the second group there was feedback plus reminder cards.[38] Various outcome measures were used, such as compliance with care, assessment for suitability for withdrawal, being told about dependency, and a consultation with a GP in the past year. Data were collected before and after feedback or feedback plus reminders. Of a total population of 125 846 people, 2409 (1.9%) had been taking benzodiazepines for 4 weeks or longer. Of these, three-quarters were women with a mean age of 68.7 years. Some had been taking benzodiazepines for over 5 years. The interventions were effective but the reminder cards did not add to the usefulness of feedback to the patients.

In a prescribing intervention study, 369 patients aged ≤70 years with a repeat prescription for benzodiazepines were assessed.[39] The intervention policy was set up by a pharmacist who called to monitor prescriptions. A letter was sent to patients inviting them to an appointment with a GP to discuss their drug usage. Ninety-six patients had their prescriptions inactivated because they had not been requested for 3 months and 206 patients were invited for a review, of which 151 attended and collected information about how to reduce their benzodiazepine usage. At the end of the project only one-quarter of patients remained on a repeat prescription. The number of benzodiazepine tablets prescribed was reduced by 64%. It was concluded that this methodology provided a quick and effective method of assisting GPs in reducing their prescribing. It seemed to be a successful and worthwhile investment in time and resources. Thus, enlistment of community pharmacists in this role would be a useful stratagem.

In an Australian study, a 'multi-strategic partnership' approach for reducing benzodiazepine use in the management of insomnia was instituted, as recommended in Australia's national policy on the quality use of medicine.[40] A population of over 20 000 in a rural region of South Australia were involved. The intervention was multi-dimensional, including the provision of treatment guidelines, provision of consumer information, a local media campaign, and education and training of health professionals. The quantitative evaluation after 2 years follow-up used pharmacy-based dispensing data for benzodiazepines. It was found that there was a 19% reduction in benzodiazepine dispensing compared with a 6% reduction nationally. It was thought that this approach was reasonably successful.

Interest in simple interventions continues, particularly in Scandinavia. For example, new regulations were introduced in Denmark for the prescription of benzodiazepines and cyclopyrrolones (zopiclone).[41] The regulations included restricting prescriptions to only 1 month at a time, and only

following a consultation. Renewal of prescriptions by telephone was not allowed. The GPs were asked to discuss with their patients their future medicatio requirements and possible tapering. The outcome variable was the rate of prescriptions. After 15 months, the use of zopiclone was reduced by one-half and the use of benzodiazepines was reduced by almost as much. During the first 3 months, only 4.3 additional consultations per week per 1000 patients were needed to implement this policy, and even this fell in subsequent months. Specialist back-up facilities, such as psychiatrist consultations, home care, attendance at addiction units and hospital referrals proved essentially unnecessary. No serious adverse effects supervened. What is clear is that the practitioners and their ancillary staff who took part were carefully and extensively educated regarding the need to reduce anxiolytic and hypnotic use, and were enthusiastic about the programme. Publicity was provided in the local newspaper.

### 2.2 Pharmacological Interventions

A Cochrane Review was published in 2006 that covered studies on pharmacological and other interventions for benzodiazepine monodependence in outpatient settings.[42] A standard Cochrane literature search and analysis was carried out and a total of 753 studies were originally identified on the topic of pharmacological interventions. However, these were then whittled down, first to 35 studies and then to only 8 studies. Five were UK studies, two were conducted in the US, and one in France.[43-50] Many other studies were excluded for a variety of reasons, including inappropriate outcome measures, setting and selection of participants.[51-73] Several of these studies will be discussed in due course.

The eight selected studies comprised a total of 458 participants. No pooling of studies or meta-analyses was possible because of the heterogeneity of interventions. The advice to taper benzodiazepines over several weeks rather than abrupt withdrawal was supported by the data on dropout rates. Short half-life compounds were associated with higher dropout rates, but withdrawal symptoms were no more severe than with longer half-life benzodiazepines. Thus, switching from short- to long-acting benzodiazepines before gradual taper was not supported. The use of adjunctive agents (propranolol, dothiepin, buspirone, progesterone and hydroxyzine) was not helpful. The only compound worth considering was carbamazepine (200–800 mg/day), which, in patients receiving diazepam 20 mg/day or its equivalent, was associated with reductions in withdrawal severity[48] (see also Ries et al.[74]). The authors acknowledged the paucity of data and the consequent need for larger studies, particularly exploring the use of antidepressants.

It should be pointed out that some of the substitution studies were not carried out primarily as therapeutic studies but were designed to establish whether the introduction of another drug, such as a partial agonist, could suppress the withdrawal syndrome until it was itself withdrawn. In other words, the question of cross-tolerance was the focus of the study. If the introduction of the other drug (e.g. buspirone[45] or alpidem[56]) failed to suppress withdrawal, then this drug was unlikely to be associated with benzodiazepine-type dependence. If the introduced drug did suppress withdrawal, only for the symptoms to occur when it was in turn withdrawn, the drug showed cross-tolerance and was likely to be similar to the benzodiazepines in its dependence potential.

A potential stratagem of particular pharmacological interest is the possible use of the benzodiazepine antagonist, flumazenil.[75] Although initially regarded as a ‘pure’ antagonist, subsequent work in both animals and humans has suggested that flumazenil is a mixed agonist/antagonist, depending partly on dose.[76] An animal study suggested that it might reverse some features of benzodiazepine withdrawal and might prove useful in clinical withdrawal.[77] A pilot study of flumazenil suggested that this drug might usefully lessen anxiety and other withdrawal symptoms when administered as a single intravenous dose to patients who had distressing long-term symptoms following withdrawal.[78] Another study focused on precipitating withdrawal by giving repeated intravenous doses; withdrawal symptoms su-

pervened in the placebo group of benzodiazepine-treated patients but not in those administered flumazenil.[79] Further studies have confirmed that flumazenil can reduce or even obviate withdrawal symptoms in long-term benzodiazepine users (for example see Saxon et al.[80] and Gerra et al.[81]). However, other studies have clearly shown that the administration of this drug can result in the provocation of panic attacks in patients with panic disorder,[82] withdrawal symptoms in long-term users,[83] and stressful reactions and panic attacks in long-term benzodiazepine users.[84] Thus, the possible use of flumazenil in facilitating withdrawal from long-term benzodiazepine usage has not been satisfactorily resolved. Because of the possibility of precipitating severe reactions, including fits, this stratagem is not one that is recommended to primary-care practitioners.

Most of the compounds deemed to be beneficial in managing benzodiazepine withdrawal are antidepressants or mood stabilizers, such as carbamazepine, imipramine, valproate and trazodone.[85] This reflects the finding that co-morbidity with depression is a common problem. This can be present before benzodiazepine treatment, during the ingestion of the benzodiazepine, and can emerge as a new symptom after withdrawal of the drug.[86] A large-scale Dutch study examined the efficacy of paroxetine as an addition to gradual discontinuation in long-term benzodiazepine users in general practice who also met the criteria for major depressive disorder.[87] Of those identified as eligible for the study, only one-half were willing to participate. The first step was transfer to and stabilization on diazepam. Next, patients were randomized to receive paroxetine 20 mg/day or placebo. In those patients whose depression resolved, a gradual taper of the benzodiazepine was instituted. Three-quarters of the paroxetine group, compared with 61% of the placebo group, attained remission (Hamilton Depression Rating Scale [HAM-D] score of ≤7) for their depression ($p = 0.067$; trend only). However, those treated with paroxetine had no greater success rate for withdrawal (67%) than those receiving placebo (64%). At long-term follow-up (2–3 years), only 13% of patients were still drug free (26% of those who had successfully tapered off benzodiazepines versus 6% of the total group). It was concluded that the SSRI played only a minor role in the short term. No data were presented for those patients whose depression did not remit.

Withdrawing from temazepam was the focus of a study in a single general practice.[88] This audit was motivated by general concern over the addiction potential of this drug. Two strategies were compared – substituting another benzodiazepine, or using an alternative class of agent such as chloral hydrate or an antihistamine. These interventions were successful but antihistamines were not recommended because of persisting daytime sedation.

### 2.3 Psychological Interventions

The range of psychological strategies for discontinuing benzodiazepine treatment has been reviewed.[89] These techniques have three goals. First, these interventions must facilitate the withdrawal itself and help with withdrawal symptoms as well as any anxiety or insomnia that eventuates following relapse of the underlying condition. Second, the intervention should maintain abstinence over time, i.e. act as a relapse-prevention strategy. Third, the intervention should treat any underlying disorder. Cognitive aspects are important as the patient may feel threatened by possible withdrawal symptoms, and may feel ill-equipped to deal with any symptoms and attendant problems. The authors advocate the adoption of techniques found to be effective in dealing with panic disorders. The steps involve educating the patient about dependence and withdrawal, instituting a tapered withdrawal schedule, coping with increases in symptoms and providing disorder-specific CBT as an alternative to despairing resumption of pharmacological treatment. It is emphasized that the course of drug therapy should be completed before psychological treatment is concluded.

A controlled study that evaluated psychological functioning within a randomized controlled trial compared a taper regimen plus group CBT with tapering off alone, and with usual care.[73] Tapering led to a significantly higher rate of successful dis-

continuations than usual care (62% vs 21%); however, CBT did not alter the success rate of discontinuation.

An open-label study in elderly patients with chronic insomnia randomly assigned 65 long-term hypnotic users to gradual tapering or tapering plus CBT over 8 weeks.[90] Immediately after the completion of the course of treatment, a significantly higher proportion of patients had withdrawn in the combined treatment group than the tapering alone group (77% vs 38%). The beneficial effects of therapy were sustained for up to 1 year.

Group CBT was assessed in a controlled study.[73] 180 patients were randomly allocated to tapering plus group CBT, tapering alone or usual care. Tapering comprised a 25% reduction in dose every week. Sixty-two percent of those in the two tapering groups succeeded in stopping drug use, compared with only 21% of patients who discontinued with usual care. However, the addition of CBT made no difference to the discontinuation rate (58% vs 62%). The participation rate was low – 180 of 1036 patients who were deemed suitable; therefore, biases in the acceptance process may have skewed the results. The authors commented that the tapering was feasible and effective in general practice.

The specific effectiveness of CBT, combined with tapering, was also evaluated in 61 patients with generalized anxiety disorder (GAD), and was compared with nonspecific therapy.[91] Cessation of anxiolytic intake was achieved in 75% of the experimental group compared with 37% in the control group. Follow-up at 3, 6 and 12 months confirmed the outcomes and differences between the two groups. The number of patients no longer meeting the criteria for GAD was also greater in the CBT group.

Edinger and Wohlgemuth[92] discuss the concept of primary insomnia and provide a rationale for the use of behavioural interventions. Morgan and colleagues[93] made a detailed evaluation of both the clinical and cost impact of setting up a CBT treatment package for insomnia in primary care. Several comparisons were made in patients reporting chronic sleep difficulties. CBT treatment was associated with improvements in sleep quality and quality of life. CBT-treated patients reported decreases in the frequency of hypnotic drug usage, with many stopping hypnotics altogether. Improvements were maintained at 12-month follow-up.

As the main indications for benzodiazepines (anxiety disorders and insomnia) tend to be chronic conditions, patients withdrawing from these drugs are liable to relapse. An essential strategy is to have other treatments available, both drug and nondrug, to help manage any emergent symptoms. Among these therapies, GPs may rely on counselling in one of its forms, but also on CBT, which is at last beginning to become increasingly available. An observational cross-sectional study was undertaken to evaluate the relationship between the provision of various intensities of counselling and the prescription of psychotropic drugs.[94] Ninety percent of the responding GPs referred patients for counselling. The highest rate of prescribing was among GPs who referred patients to counsellors who practiced at the same premises as the GP; the lowest rate of prescribing was in those who sent their patients to counsellors who practiced at different premises. These results seem counter-intuitive, as one might expect GPs with ready access to their referred patients to regulate their prescribing more closely.

In summary, GPs generally agree that counselling can be as effective as anxiolytics but found it demanding of their time.[25] Increased provision of clinical psychology services was seen as the most desirable development to facilitate management of anxious patients. However, the limited data that are available suggest that psychological techniques only seem efficacious when directed at the underlying psychiatric abnormalities,[91] rather than the withdrawal process itself.[73] Whether this could form the basis of a specific recommendation is still too early to conclude.

### 2.4 Meta-Analysis of Various Interventions

As adumbrated in the introduction, as many of these discontinuation studies as possible were entered into a standard meta-analysis.[18] Twenty-nine papers met the strict inclusion criteria; these articles

were rated using the Amsterdam-Maastricht consensus list covering the Chalmers criteria.[95] Two groups of interventions were identified. Minimal intervention comprised simple advice by letter or face-to-face (only three studies met the criteria). Systematic discontinuation involved treatment programmes led by a physician or psychologist (n = 26). Both were more effective than treatment as usual. The addition of imipramine or group CBT for insomnia was superior to systematic discontinuation alone. The authors acknowledged the limitations of the database due to heterogeneous samples. In addition, favourable prognostic factors could not be clearly identified. One particular deficiency is that different tapering schedules have never been compared in a randomized clinical study. Recommendations concerning augmentation strategies, for example with imipramine or carbamazepine, can only be tentative. Despite this, primary-care doctors ask for guidance on how to withdraw benzodiazepines from long-term users, as do the users themselves. A primer for patients has been written;[96] the final section of this review provides a brief equivalent for the treating doctor.

## 3. Outcomes

Outcomes in terms of cessation or reduction in benzodiazepine use were studied in three groups of patients – those attending either a general practice, a hospital clinic or self-help groups (TRANX; Tranquilliser Recovery And New Existence).[97] The hospital patients used higher doses of anxiolytics for anxiety, and had a high rate of psychiatric co-morbidity. The TRANX patients had the best outcome. No conclusions can be drawn as to the choice of management as allocation to treatment setting was not random. An audit of benzodiazepine prescribing and withdrawal was carried out in 87 900 patients in 15 practices.[98] A total of 3234 patients were found to be taking these drugs at the start of the study (37 per 1000 registered patients). Of these, 16% managed to discontinue benzodiazepine use within the next 8 months. Success was not related to initial levels of prescribing. Older patients (>65 years) were less likely to stop than younger patients.

One comprehensive study aimed at determining whether withdrawing from benzodiazepine hypnotics led to changes in elderly patients' cognitive function, quality of life, mood and sleep.[99] 192 long-term users of benzodiazepine hypnotics aged ≥65 years were identified in 25 general practices. Of these, 104 who wished to withdraw from benzodiazepines were randomly allocated to one of two groups under double-blind, placebo-controlled conditions. In the first group, the benzodiazepine dose was tapered from week 1 of the trial. Group 2 were administered their usual dose for 12 weeks, which was then tapered. An additional group of 35 patients who did not wish to withdraw from benzodiazepines participated as controls. All patients were assessed at 0, 12 and 24 weeks, and one-half of these patients were re-assessed at 52 weeks. Sixty percent of the patients had been taking the drug continuously for >10 years, while 27% of the patients had been taking the drug continuously for >20 years. Of all the patients beginning the trial, 80% had withdrawn successfully 6 months later. There was little difference between groups 1 and 2, but both groups differed from the controls in that the performance of the withdrawers on several cognitive and psychomotor tasks showed relative improvements at 24 and 52 weeks. Withdrawers and controls did not differ in sleep or benzodiazepine withdrawal symptoms. These results have clear implications for clinical practice in that withdrawal from benzodiazepines produces some subtle cognitive advantages for elderly people, yet little in the way of withdrawal symptoms or emergent sleep difficulties. The results also suggest that long-term benzodiazepines do not aid sleep.

The same patients also had their beliefs and attitudes explored.[100] In addition, 83 practice staff were interviewed. Beliefs in the efficacy of hypnotics, as assessed by self-reporting of insomnia, varied according to the willingness of the patient to attempt withdrawal. Most patients reported no warnings from professionals regarding adverse effects of using benzodiazepine hypnotics. One-half of the patients had tried to discontinue drug usage at some time but their attempts had been aborted. Patients

**Table I.** Some principles of primary-care management

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|---|
| Every patient should be taught ways of dealing with as many of the anxiety and insomnia problems as they can.[73] Some have long since recovered from their emotional disturbance and are considered 'cured'. They are left with a dependence on benzodiazepines that withdrawal will correct, without recrudescence of anxiety or insomnia. Others still have anxiety or insomnia, and withdrawal will leave them anxious or insomniac, perhaps even in a worse state than before treatment. They need to be able to manage this anxiety as the effects of the medication wear off, even if the medication has only been partly successful |
| Family and friends can help by instilling confidence and providing encouragement. They can help in practical ways, e.g. by doing the shopping if agoraphobic symptoms become troublesome. However, other members of the family may occasionally attempt to sabotage the withdrawal regimen, either because they are over-helpful or they have their own reasons to perpetuate the patient's 'sick role' |
| Review patients' prescription records, and see those receiving long-term benzodiazepines to discuss the situation |
| Send out letters suggesting methods of tapering off the benzodiazepine. Such a letter is surprisingly effective and is often enough to motivate a patient to withdraw |
| Refer patients to additional agencies, such as a nearby support group. Some of these groups are run independently but others are conducted within the health services, usually under the aegis of the local community and mental health services |
| Only refer to local drug dependence services if the service has shown a specific interest in benzodiazepine dependence or the patient has a drug addiction problem. Similarly, most alcohol services are inappropriate unless the patient is misusing alcohol as well as having benzodiazepine dependence, a combination that is not uncommon |
| Recognize that withdrawing from benzodiazepines can be stressful |
| Advise changes in lifestyle, such as regular exercise. The patient should keep to a regular routine, right throughout the week, including weekends |
| Alcohol must be avoided. It is pointless trying to help a patient come off a benzodiazepine when they are substituting alcohol as a sedative |
| Avoid mild stimulants such as caffeine and theobromine as they can cause anxiety, panic and insomnia. Cigarettes are even more difficult to give up permanently than benzodiazepines. Postpone advice on giving up smoking until after the benzodiazepine has been withdrawn |

and doctors had distinctly different views of the advantages and disadvantages of the risk of stopping benzodiazepine hypnotic use. Increased patient awareness of the problems of long-term benzodiazepine use, together with an evidence-based approach to withdrawal, is needed to reduce the consumption of the medication that appears to have little real benefit.

Measures of baseline psychological distress and anxiety were associated with both discontinuation and the emergence of withdrawal symptoms and distress during the withdrawal period.[101,102] A higher dosage of the benzodiazepine was also a predictive factor of withdrawal distress.

## 4. Practical Issues

Based on the data and analyses available, evidence-based recommendations for management of the withdrawal of benzodiazepines in patients with long-term anxiety and insomnia can only be preliminary, even after decades of concern. Ten general pointers for primary-care management are listed in table I.

Most patients in the UK are maintained on diazepam. If not, a common strategy is to substitute diazepam for the benzodiazepine being taken. Various schedules are extant, but 4 weeks' substitution is usually feasible. Equivalent doses of other benzodiazepines are shown in table II. This equivalence is based on clinical experience of withdrawal schedules, not on equivalent efficacies. Thus, the dose of diazepam (10 mg) seems very high as an equivalent to lorazepam (1 mg). Withdrawal seems smoother on diazepam than with other drugs in its class, presumably reflecting the long half-life of diazepam

**Table II.** Some equivalents to diazepam 10 mg for subsequent tapered withdrawal[a]

| Benzodiazepine | Equivalent dose (mg) |
|---|---|
| Chlordiazepoxide | 30 |
| Loprazolam | 2 |
| Lorazepam | 1 |
| Lormetazepam | 2 |
| Nitrazepam | 10 |
| Oxazepam | 30 |
| Temazepam | 20 |

a Diazepam is usually taken in three or four fractions during the day – morning, afternoon, evening and before going to bed.

and its major metabolite, desmethyldiazepam (nordazepam). In addition, the availability of a liquid preparation is very useful logistically. Some prescribers are of the opinion that a long-acting compound such as diazepam can be stopped abruptly when a low dosage (5–10 mg/day) has been reached.

Benzodiazepines should not be withdrawn abruptly because there is a risk of epileptic fits or of the patient becoming confused or experiencing paranoid psychosis. Nevertheless, abrupt cessation can be justified if a very serious adverse effect supervenes during treatment.

The rate of withdrawal is the most contentious and least researched issue. The early stages of withdrawal are easier to tolerate than the later and last stages. The optimal duration is not clear and may indeed vary from patient to patient. We advocate a fairly rapid schedule but with the flexibility of slowing down if symptoms become too disturbing. In most patients, a brisk schedule is possible (8–12 weeks). A schedule that is too long should be avoided, otherwise the withdrawal becomes the focus of the patient's existence. In patients who have tried but failed to withdraw previously, a 6-month schedule may be necessary (table III).

**Table III.** Recommended tapering schedule

| Week | Dosage (mg/day) |
|---|---|
| 1 | Starting dosage (e.g. diazepam 15 mg/day or equivalent) |
| 2 | 15 down to 11 |
| 4 | 11 down to 8.5 |
| 6 | 8.5 down to 6 |
| 8 | 6 down to 4.75 |
| 10 | 4.75 down to 3.5 |
| 12 | 3.5 down to 2.5 |
| 14 | 2.5 down to 2 |
| 16 | 2 down to 1.5 |
| 18 | 1.5 down to 1 |
| 20 | 1 down to 0.75 |
| 22 | 0.75 down to 0.5 |
| 24 | 0.5 down to 0.25 |
| 26 | 0.25 down to 0 (stop) |

## 5. Other Medications

### 5.1 Antidepressants

As mentioned in section 3, some patients receiving benzodiazepines have an underlying depressive illness. If an antidepressant is needed to treat depression of at least a moderate degree, clinicians should prescribe one with a low withdrawal potential, e.g. fluoxetine or escitalopram, rather than fluvoxamine, venlafaxine or paroxetine. If an SSRI is used, it should be started at a low dose because it can increase anxiety and insomnia during the first week of treatment. The full dose should then be taken and maintained right throughout the benzodiazepine withdrawal process. The SSRI can be subsequently tapered off using a similar tapering schedule.

### 5.2 Symptomatic Treatments

There are few data supporting the use of symptomatic treatments.[42] Care must be taken that the symptomatic treatment does not, in turn, become a problem. For example, regular and prolonged administration of an opioid analgesic for pain may induce opioid dependence.

Insomnia may be upsetting, with the patient wondering if a regular sleep pattern will ever be reestablished; however, administering a benzodiazepine sleeping tablet or one of the 'z-drugs' (zopiclone, zolpidem or zaleplon) will only substitute dependence on one medicine for another. If insomnia persists, a nonbenzodiazepine can be tried cautiously. Some TCAs are also antihistaminic, and may help both the depression and the insomnia. Melatonin and similar compounds have been advocated by some clinicians.

β-adrenoceptor antagonists such as propranolol may give some relief for severe palpitations or gastric upsets.[103] Muscle spasms can be very upsetting. Some people withdrawing from a benzodiazepine are particularly plagued by unpredictable stiffness and spasms in the limbs, neck, jaw and back. Headaches, again a major feature of withdrawal, are due to spasms in the muscles of the scalp. Jaw clenching may occur during sleep. No useful specific remedies exist as muscle relaxants may not work.

Very occasionally, serious reactions, such as epileptic fits, may occur during withdrawal. The treatment for fits is an antiepileptic medication, but reinstitution of the benzodiazepine may be needed, followed by prolonged and carefully monitored withdrawal. Psychoses with confusion, paranoid ideas or visual hallucinations may develop very occasionally, necessitating antipsychotic medication. If alcohol involvement is suspected then an alcohol withdrawal schedule must be used, together with vitamin supplements.

## 6. Conclusions

Almost 50 years after their introduction, benzodiazepines remain controversial and problematical. Despite ongoing debate over the decades, benzodiazepines still remain popular.[104] Views vary widely, with some clinicians regarding them as useful anxiolytics and hypnotics to others dismissing them as having risk/benefit ratios that are too adverse to warrant their use, particularly in the elderly. Many practitioners still prescribe these drugs in the short term. Data would suggest that long-term use is rarely justified, and the elderly are too often left with insufficient long-term supervision. In general, most patients receiving long-term medication show improvement when their medication is withdrawn. Cognitive functioning, memory and balance improve on drug discontinuation, particularly in the frail elderly. Fundamental questions are, first, how to prevent a course of low-dose treatment intended in good faith to be short term (<1 month) continuing beyond that time, and second, how to distinguish long-term use that might be justified because of symptomatic treatment of the underlying disorder from long-term use reflecting chronic dependence.

The method of discontinuation should always include tapering; however, the rate of tapering remains controversial. The best strategy is to remain flexible but to try to avoid prolonging the process beyond 6 months. Adjunctive medication is not firmly established, except that the depressed individual should be treated appropriately, usually with an antidepressant. Only weak evidence supports the use of other medications such as carbamazepine. The use of the benzodiazepine antagonist flumazenil remains unclear.

Nondrug strategies range from simple audit and advice to tapering off, to CBT. Counselling is not promising as a strategy; however, group sessions with other patients may be effective but this has not yet been adequately evaluated.

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