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Pharmacological Agents as Adjuncts in the Management of Benzodiazepine Withdrawal

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ABSTRACT

The Benzodiazepines (BZDs) are widely-prescribed medications used to ameliorate anxiety, tension, insomnia and some forms of epilepsy. They are generally effective but are prone to induce numerous unwanted effects including misuse and sedation. It has become apparent that about a third of long-term (more that 3 months) users develop a state of normal-dose dependence associated with a characteristic withdrawal syndrome on attempted withdrawal. This condition can be severe and occasionally protracted. Little is known about the optimum strategies to facilitate withdrawal except that the tapering of dosage should be gradual within a program of psychological support. Adjuncts to withdrawal include the substitution of cross-tolerant agents such as other BZDs and other anxiolytics and hypnotics. Symptomatic treatments such as antidepressants may be useful. The only putative specific therapy is the BZD antagonist, flumazenil. No authoritative recommendations can be given in the present inchoate state of the literature. The research priority is to assess flumazenil systematically.

INTRODUCTION

Literature search

This descriptive review concentrates on the dependence-inducing potential of the widely-used drugs, the benzodiazepines (hereafter abbreviated to BZD). It excludes other major unwanted effects such as abuse, overdose and interaction with alcohol. A search of the literature was carried out in the Medline, Embase and Cochrane Collaboration databases, using the code word "benzodiazepine(s)", alone, and in conjunction with various terms such as "dependence", and "pharmacological adjuncts". Further hand searches were made based on the reference lists of key papers. As over 1,000 references were found, this review is not exhaustive. Some selection then took place to exclude studies with small numbers and individual case reports. Throughout, I set the literature against my clinical experience extending to about 50 years. In essence, I attempt to answer the question: "Would a practising clinician find this useful in his everyday practice?"

HISTORICAL NOTE

The problems which we have encountered since the introduction and extensive use of the BZDs can be best understood in a historical context. Alcohol has long been known for its sedative and hypnotic properties. A range of substances, including bromides, chloral and paraldehyde, were used in the 19th century as sedatives and hypnotics. They were supplanted by a large range of barbiturates in the 20th century [1]. Their

undoubted efficacy was offset by a range of unwanted effects including over- sedation, headaches, paradoxical excitement, cognitive and psychomotor impairment, and confusion, particularly in the elderly. They were particularly dangerous in over-dosage. Long term use was associated with dependence with severe withdrawal reactions; recreational use and abuse were common. In turn, the barbiturates were replaced, first by meprobamate [2]. However, this was also found to induce similar unwanted effects. In turn, meprobamate was superseded by the BZDs.

The most popular BZD was diazepam, introduced in 1963. Many other compounds became available as sedatives, sleeping tablets and anticonvulsants. Several thousand BZDs have been synthesised [3]. Between 1969 and 1982, diazepam was the most prescribed drug in America, with over 2.3 billion tablets sold in 1978. Indeed, the world-wide use of BZDs has continued to increase until recently, as these drugs have come off patent and become cheaper [4].

More recently, the so–called z-drugs were introduced, comprising the non-benzodiazepine hypnotics: zolpidem, zopiclone, and eszopiclone. They differ in no basic respects from the BZDs [5].

DEPENDENCE AND WITHDRAWAL

Dependence is defined by the World Health Organisation as a strong desire or sense of compulsion to take a substance, a 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.

People who develop misuse of, or become dependent on, BZDs or z-drugs are typically those seeking medical help during increased anxiety or sleeplessness, but unduly increase their prescription to above-normal doses, or prolong the treatment. 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 but this lies outside the scope of this review.

The mildest form of withdrawal is rebound. Rebound comprises the original symptoms recurring transiently at a greater intensity. Withdrawal involves the onset of new symptoms not previously experienced by the patient. Protracted withdrawal has been described but the etiology of these symptoms has been disputed. As tolerance may develop 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 [6]. 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.

Table 1: Common withdrawal symptoms.

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	I Increased sensitivity to sound (hyperacusis)
Tinnitus	Objects moving
Metallic taste in mouth	Taste and smell disturbances
Increased sensitivity to light	Photophobia
Derealisation (Feelings of unreality)	Depersonalization

The withdrawal syndrome 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 (Table 1). Withdrawal symptoms include psychological reactions such as anxiety and/or insomnia, nightmares which may disturb the patient, impaired memory and concentration; depressive symptoms may appear. Physical symptoms may ensue such as muscle tension

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and spasm, or weakness, pins and needles, and flu-like symptoms. Almost pathognomonic are the perceptual symptoms affecting most sensory systems with hypersensitivity to light, sound, and touch. Derealisation and depersonalisation are common. Psychological distress and adaptational problems are frequently encountered [7]. More serious or life-threatening symptoms such as fits or psychosis may occasionally occur (Table 2).

Table 2: Severe withdrawal symptoms that may accompany abrupt discontinuation of BZDs.

Delirium tremens	Delusions
Convulsions, status epilepticus which may end in death	
Catatonia, which may result in death	
Depression	
Self-harm	Suicide
Suicidal ideation	Attempted suicide
Homicidal thoughts	Violence
Organic brain syndrome	Psychosis
Confusion	Mania

A prospective study revealed 4 patterns of withdrawal symptoms over time [8]:

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;

4) No change over the 50-week time period.

The withdrawal symptoms may resemble the symptoms of anxiety or insomnia for which the BZD was originally prescribed [6]. Misdiagnoses are common among inexperienced prescribers and the dosage may be increased unnecessarily, perpetuating a vicious cycle.

STRATEGIES OF WITHDRAWAL

An important general principle here is that before instituting BZD dosage tapering, the patient must be assessed for the presence of symptoms which might be lessened by the continuing BZD medication. It is a fine clinical judgement as to whether anxiety or insomnia is a result of persisting symptoms, partial withdrawal, or both. The optimum strategy is to utilise a comprehensive patient education program incorporating information about BZD withdrawal and essentially other ways of dealing with symptoms. In particular, some patients develop depressive symptoms on withdrawal [9] and these must be combated as they materially worsen the prognosis. A careful appraisal of an elderly sufferer may conclude that long-term maintenance rather than an agonising withdrawal is the lesser of the two evils, but the patient must be monitored to prevent accumulation with cognitive impairment. The most efficacious rate of taper is not based on good empirical evidence although elaborate schedules exist (e.g. 10). An established observation is that the early stages of withdrawal are easier to tolerate than the later and last stages. Therefore, a steady progressive 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 fully withdrawn. Stopping in the middle of a withdrawal schedule is counter-productive.

Several withdrawal schedules have been promulgated, the most popular of which is set out in the Ashton Manual [10]. It is important to bear constantly in mind that each patient differs in the likelihood of undergoing a withdrawal reaction, its severity, and their fortitude in coping with the withdrawal symptoms. Some reactions can be severe and persistent. It is essential to retain a high degree of flexibility and not to insist on a rigid schedule to be maintained at all times. It is also important not to prolong the withdrawal schedules to excessive lengths, so as to avoid the schedule becoming a morbid focus. I have encountered some patients whose timetable would extend to a decade or more. Patients should be warned that some symptoms may be unavoidable but that support will be made freely available including a 24/7 emergency contact. Thus, the withdrawal schedule must be individually tailored and modified as necessary.

A stepped care approach to BZD discontinuation [11] began with a minimal intervention with advice from the GP, and moved on to a 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. These minimal interventions in primary care are often helpful [12]. Our 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.

Nevertheless, we recommended that withdrawal in primary care be conducted over an 8 – 12-week schedule for most patients and completed in less than 6 months.

One stratagem which my team has found useful is to instigate an ongoing form of group therapy in which the group members nearing the end of their withdrawal can give support and encouragement to the newcomers. Remember that the withdrawal is from an iatrogenic mismanagement of therapy so the sufferers have typically lost confidence and blame their prescribers. They are much more willing to take advice from fellow-sufferers.

OUTCOME VARIABLES

There are numerous and differing approaches to helping patients withdraw from BZDs and z-drugs, but they are not clearly categorised. Nor are the efficacies, outcome measures clearly categorised and agreed. The most practical outcome is complete and permanent cessation of BZD use. This is a stringent criterion and not easily attained. A less onerous outcome is reduction in usage, particularly to levels below the standard therapeutic dosage. Longer-term follow-up is necessary to confirm that stopping or reducing BZD intake has really been accomplished.

Another outcome variable comprises reduction of symptomatic distress during withdrawal to tolerable levels thus facilitating successful withdrawal.

ADJUNCTIVE TREATMENTS

Various adjunctive treatments have been suggested but a recent Cochrane Review adduced little clear support for any [13]. It concluded that the quality of the evidence was "very low". The proposed interventions fall into 2 categories. The first comprises the administration of drugs that are cross tolerant with the BZD from which withdrawal can be smoother: but this has not proved to be more successful. The second is symptomatic treatment to ameliorate the withdrawal symptoms.

9.1. Substitution therapy

The simplest strategy is to substitute one BZD for the one being prescribed. Some BZDs seem more difficult to manage in the withdrawal context. A general consensus seems to find lorazepam, flunitrazepam, clonazepam and alprazolam as being more problematic to stop than diazepam, chlordiazepoxide, and oxazepam, but this is essentially a clinical impression. It may well be that these latter compounds have a lower potency in the technical sense than the others, rendering them likely to be associated with less severe withdrawal. A second consideration is pharmacokinetics – compounds with long beta elimination half-lives should ensure a smoother offset of action than short-acting BZDs and z-drugs. A third consideration is the convenience of appropriate formulations; liquid preparations are particularly appropriate, allowing a more incremental decrease of dosage than tablets or capsules.

Caution is needed because the dose of a long-acting BZD that will substitute fully for a shorter-acting agent may be greater than anticipated. A second problem is that complications may ensue during the switch which should be gradual with overlapping dosages. It also prolongs the procedure. The practical advice is to try tapering without substitution, only resorting to using another compound when failure has occurred.

Some clinicians, particularly in the USA, used to favor phenobarbital or another barbiturate as a substitute medication to prevent severe withdrawal reactions such as fits. This is not a useful manoeuvre as the barbiturates carry much greater risks of misuse, dependence and overdose [14].

9.2. Symptomatic treatments

Other drugs which have been substituted or supplement the withdrawal schedule include antidepressants, serotoninergic anxiolytics, anticonvulsants, and beta-blockers; these may help in management without reducing the severity of the withdrawal [15]. The addition of an SSRI to tapering in depressed patients withdrawing from BZDs was of limited value [16]. In general, psychological treatments are helpful but some believe only when tapering has ceased [17]. The addition of cognitive behavioural therapy to a careful tapering schedule was of limited value in one investigation [18], but was successful in another [19]. An intervention study compared a single tailored intervention with multiple tailored interventions and GP care [20]. The interventional procedures were much better than routine care. Another review included 32 articles involving interventions solely focusing on increasing appropriate prescribing and reducing long term use of BZDs [21]. Three major intervention approaches were identified: education, audit and feedback, and alerts. Studies which had used a combined approach reported the largest and most sustained reductions in BZD use.

The non-BZD anxiolytic, buspirone, was largely ineffective. The anxiolytics pregabalin and gabapentin showed some success in pilot studies and were reasonably successful as a substitute anxiolytic [22, 23]. Carbamazepine has some evidence supporting its use [15].

The position of melatonin in this array exemplifies the disappointments encountered in the search for a useful adjunct to BZD withdrawal. Melatonin has hypnotic effects especially in the elderly and is licensed for this indication. Although pilot studies were encouraging, a systematic review and meta-analysis of 6 studies randomising 322 patients found no evidence for efficacy in aiding BZD withdrawal [24]. Even the effect of melatonin on sleep quality was inconsistent.

9.3 Flumazenil

A relatively overlooked approach to aiding BZD withdrawal which actually has a putative rationale is the use of the BZD antagonist, flumazenil. This agent is used routinely in the treatment of BZD overdose, and can constitute a diagnostic test. It is usually considered a BZD antagonist or partial agonist. It can therefore produce effects which resemble BZD withdrawal. A pioneering study to explore the use of flumazenil was that of Lader and Morton [25]. Patients had been complaining of severe, continuing typical withdrawal symptoms despite being BZD-free for 4 weeks to several years. Intravenous infusions of 0.2 – 2 mg of flumazenil were noted to decrease symptoms in a placebo-controlled evaluation. These findings were confirmed [26]. One obvious hazard is precipitating dangerous withdrawal in chronic users, particularly those on high doses, but this does not seem to be a problem in practice.

Some non-systematic studies using slow bolus infusions of flumazenil suggested a reduction in the symptoms of withdrawal. A larger-scale study involved flumazenil 1 mg iv twice a day compared with oxazepam tapering (30 mg) and placebo in the control of BZD withdrawal symptoms in three groups of BZD dependent patients [27]. Flumazenil significantly reduced withdrawal symptoms in comparison with oxazepam and placebo on both self-reported and observer-rated withdrawal scales. Patients treated with flumazenil showed significantly lower relapse rates on days 15, 23 and 30 after the detoxification week.

A number of sporadic studies, mainly uncontrolled case-series, have been carried out around the world in patients with persistent symptoms but also in users attempting to withdraw for the first time [28]. Such treatment is available in specialised centres in Italy, Australia, Brazil, and elsewhere. It usually involves costly inpatient treatment and seems likely to be suitable only for a small number of severely dependent patients with a history of prolonged BZD abuse. Nevertheless, is surprising that the procedure is so little used [29], although the advent of cheaper subcutaneous formulations may facilitate matters [30, 31]. Some large-scale case-series have accrued but fully controlled RCTs remain to be carried out. The overall impression is that flumazenil is one of the few possibly useful treatments in the management of primary withdrawal and the management of distressing persistent withdrawal symptoms.

The mechanism of the flumazenil effect is somewhat unclear. It probably causes up-regulation of the receptor site for BZDs by resetting, modifying and normalizing the relationship between the BZD and GABA sites.

PROGNOSIS

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 that fail to discontinue have a poor prognosis and repeated failure may ensue, demoralising the patient. Predictive unfavourable factors include previous failed attempts, lack of family or social support, an unsympathetic general practitioner, a history of alcohol-related problems, older age, co-morbid depression, physical conditions or a personality problem.

Those that achieve a successful total withdrawal should never risk a relapse by taking BZDs again, even for short periods. Alcohol should be avoided as it shares some pharmacological actions with the BZDs, including cross-tolerance.

RECOMMENDATIONS AND CONCLUSION

Can any reliable conclusions be drawn from this welter of studies, mostly uncontrolled, and can any firm recommendations regarding clinical management be made? The efficacies of adjunctive aids are not great and are offset often by appreciable unwanted effects [32]. Nevertheless, there are 2 widely accepted issues. The first is that BZDs should never be stopped abruptly as severe reactions can develop especially

when high doses of short-acting compounds have been administered for some time. Indeed, it is probable that some jurisdictions would condemn such a practice as legally negligent. The tapering schedule should be flexible and tailored to the patient's express wishes as interpreted by the practitioner. Tapering must always be gradual. How gradual is a matter of contention. Too rapid and symptoms may become intolerable; too slow and the withdrawal is unduly protracted and the procedure is in danger of becoming a morbid focus.

Second, it is important to prepare the patient both for the withdrawal but also to try and establish ways of dealing with the symptoms of anxiety, tension and insomnia using alternative methods to the long-term use of a BZD. It is preferable to use non-pharmacological methods of coping with these symptoms especially as the patient's confidence in both the prescriber and the drugs is typically undermined. I have mentioned an ongoing group as useful although systematic data regarding effectiveness is scanty [21].

One form of medication which is often needed before initiating withdrawal is an antidepressant as lowered mood carries a poor prognosis both in the short and long term. This forms one type of symptomatic therapy which may be needed but care must be taken to minimise the risk of substituting another form of dependence as well as therapy. Controversy surrounds the use of antidepressants with some compounds seemingly especially liable to be associated with withdrawal reactions of their own, usually of definite clinical significance. A wide range of other symptomatic therapies are available but there is little to support their use. Withdrawal should be attempted wherever feasible without adding yet more medication.

The other strategy is to substitute a medication known to be cross-tolerant to the BZDs to render the withdrawal more feasible usually because of a more convenient formulation. Liquid preparations may be useful.

The one hiatus in our knowledge is the use of flumazenil to aid withdrawal and to lessen the symptoms of prolonged withdrawal. Claims have been made for its effectiveness but no rigorous studies have been published to support its use and to enable specific recommendations to be made. A few centres advocate its use. In view of the severity of withdrawal, its persistence, and the otherwise poor prognosis, many patients will turn to this therapy in desperation. Some rationale can be adduced but careful observations are needed to record the outcome in each case. If that evaluation was double-blind and placebo-controlled, some progress could at last be made.

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