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The treatment of benzodiazepine dependence

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Abstract

Withdrawal of benzodiazepines is currently advised for long-term benzodiazepine users because of doubts about continued efficacy, risks of adverse effects, including dependence and neuropsychological impairment and socio-economic costs. About half a million people in the UK may need advice on withdrawal. Successful withdrawal strategies should combine gradual dosage reduction and psychological support. The benzodiazepine dosage should be tapered at an individually titrated rate which should usually be under the patient's control. The whole process may take weeks or months. Withdrawal from diazepam is convenient because of available dosage strengths, but can be carried out directly from other benzodiazepines. Adjuvant medication may occasionally be required (antidepressants, propranolol) but no drugs have been proved to be of general utility in alleviating withdrawal-related symptoms. Psychological support should be available both during dosage reduction and for some months after cessation of drug use. Such support should include the provision of information about benzodiazepines, general encouragement, and measures to reduce anxiety and promote the learning of non-pharmacological ways of coping with stress. For many patients the degree of support required is minimal; a minority may need counselling or formal psychological therapy. Unwilling patients should not be forced to withdraw. With these methods, success rates of withdrawal are high and are unaffected by duration of usage, dosage or type of benzodiazepine, rate of withdrawal, symptom severity, psychiatric history or personality disorder. Longer-term outcome is less clear; a considerable proportion of patients may temporarily take benzodiazepines again and some need other psychotropic medication. However, the outcome may be improved by careful pharmacological and psychological handling of withdrawal and post-withdrawal phases.

Introduction

Patients taking benzodiazepines regularly on a long-term basis are currently being advised to withdraw. The reasons for this advice include doubts of long-term efficacy (Committee on Safety of Medicines, 1988), risks of adverse effects (Ashton, 1986), increasing evidence of neuropsychological impairment (Lader, 1987; Schmauss & Krieg, 1987; Bergman *et al.*, 1989) and socio-economic costs (Gabe, 1991).

The estimated population of prescribed long-term benzodiazepine users in the UK is about 1.2 million people (Taylor, 1987; Ashton & Golding, 1989). There is also a growing number (perhaps 100 000) of drug abusers who take high doses of benzodiazepines with other drugs of abuse. It is unknown what proportion of these users are dependent on benzodiazepines, as evidenced by the appearance of withdrawal symptoms on cessation of use. Studies in general practice suggest that only 30–40% of long-term prescribed users have difficulty in withdrawing (Murphy & Tyrer, 1988). This figure may be an underestimate since a high proportion of eligible patients (up to 50%) decline to enter withdrawal programmes (Tyrer, 1983). Indeed, many patients have resisted previous exhortations to withdraw and are only now emerging, often reluctantly (Edwards, Cantopher & Olivieri, 1990), as GPs review their prescription practices.

In patients referred to withdrawal clinics, the incidence of withdrawal symptoms may be 100% (Petursson & Lader, 1981).

Even on the most conservative estimate, present data suggests that a third of the present 1.2 million chronic therapeutic-dose benzodiazepine users in the UK—about 400 000 patients—may have difficulties in withdrawal. The likelihood of dependence appears to increase with increasing dosage, and high-dose abusers have special difficulties in withdrawal, as confirmed by experience in drug addiction centres. Thus perhaps half a million patients in the UK may need help or advice on benzodiazepine withdrawal and the development of effective withdrawal programmes is a matter of importance. The following guidelines are drawn from review of the literature and clinical experience of benzodiazepine withdrawal over a 10-year period.

Benzodiazepine withdrawal strategies

The two essential pillars of a successful benzodiazepine withdrawal strategy are: (1) gradual dosage reduction and (2) anxiety management. Of these, dosage reduction is by far the easiest but psychological support is equally important for successful outcome. The management of withdrawal has been reviewed by Lader & Higgitt (1986), the *Lancet* (1987), Edwards *et al.*, (1990), Livingston (1991), Lader (1991) and many others.

Dosage reduction

It is generally agreed that dosage should be tapered gradually in long-term benzodiazepine users. Abrupt withdrawal, especially from high doses, can precipitate convulsions, acute psychotic or confusional states and panic reactions. Even with slow withdrawal from smaller doses, psychiatric symptoms sometimes appear and anxiety can be severe. The rate of withdrawal should be tailored to the patient's individual needs and should take into account such factors as lifestyle, personality, environmental stresses, reasons for taking benzodiazepines and amount of support available. Various authors suggest optimal times of between 6–8 weeks to a few months for the duration of withdrawal, but some patients may take a year or more. It has been suggested that very slow rates of withdrawal merely prolong the agony, and that although symptoms may be more severe with more rapid withdrawal, they do not last so long. However, this is an individual matter and in general, the best results are achieved if the patient is in control of the rate of withdrawal and proceeds at whatever rate he/she finds tolerable. Occasionally, however, a therapist-controlled withdrawal rate with patient consent is more appropriate.

The size of each dosage reduction depends on the starting dose. Patients on higher doses can usually tolerate larger dosage decrements than those on lower doses. The majority of patients on therapeutic doses are taking less than 20 mg diazepam (or equivalent) daily. In these cases, dosage reductions of 1 mg diazepam (or equivalent) every 1–2 weeks are generally tolerated, although some patients prefer to reduce by only 1 mg per month. Initial dosage reductions of 2 mg every 1–2 weeks may be more appropriate for patients taking up to 40 mg diazepam daily. When daily dosage has declined to 4–5 mg diazepam, decrements of 0.5 mg at a time may be preferred. Stopping the last few milligrams is often seen by patients as particularly difficult, mainly because of fears about how they will cope without any drug at all. However, the final parting is often surprisingly easy, and patients are encouraged by their new sense of freedom.

It is helpful to provide a written withdrawal schedule rather than only verbal instructions. Patients usually like to record their progress by ticking off dosages or weeks, and a chart also provides an incentive to continue to the final goal. Such schedules may require readjustments from time to time: if symptoms are minimal patients may prefer to increase the rate of withdrawal; if problems arise, either in the form of severe symptoms or major environmental stresses, it may be necessary to stabilize the dosage for a few weeks or to reduce the rate of withdrawal.

For most patients on therapeutic doses of benzodiazepines withdrawal is best carried out as an outpatient. It is quite easy to "detoxicate" patients safely in hospital; such an approach allows for relatively rapid withdrawal over a few weeks, presents few pharmacological problems and removes the responsibility of withdrawal from the patient. However, with this method psychological setbacks on returning home are common, largely because the patient has had no opportunity to build up alternative living skills. Slow withdrawal in the patient's own environment

Table 1. *Approximate equivalent doses for anxiolytic/hypnotic effects and available oral preparations of various benzodiazepines*

Benzodiazepine	Approximately equivalent dosage* (mg)	Oral preparations (BNF)	
		Tablets/capsules (mg)	Oral solution (mg/ml)
Chlordiazepoxide	25	5, 10, 25	
Diazepam	10	2, 5, 10	2/5, 5/5
Loprazolam	1	1	
Lorazepam	1	1, 2.5	
Lormetazepam	1	0.5, 1	
Nitrazepam	10	5	2.5/5
Oxazepam	20	10, 20, 30	
Temazepam	20	10, 15, 20, 30	10/5

*Clinical potency for hypnotic or anxiolytic effects of different benzodiazepines may vary between individuals.

allows time for both pharmacological and psychological adjustments to withdrawal, permits the patient to continue with his normal life and to build up alternative coping strategies.

Individual benzodiazepines. Because of the available dosage forms (scored 10 mg, 5 mg and 2 mg tablets), it is usually most convenient to withdraw from diazepam. Many patients on benzodiazepines with less flexible dosage strengths can be changed over to diazepam, provided equivalent potencies are kept in mind (Table 1). It is worth noting that diazepam has a rapid onset of action and is as efficacious as temazepam or nitrazepam as a hypnotic, while also providing daytime anxiolytic cover by virtue of its slow elimination. Diazepam, temazepam and nitrazepam are also available as oral solutions. These are sometimes helpful for slow reduction, especially in the final stages of withdrawal.

For patients taking lorazepam as an anxiolytic several times daily, conversion to diazepam is sometimes more difficult. Substitution is best carried out in stages, one dose at a time over course of 1–3 weeks, beginning with the evening dose. Occasionally, changing from lorazepam to an equivalent dose of diazepam can cause excessive sedation while not fully controlling anxiety. Direct withdrawal from lorazepam by progressive dosage reductions is feasible, although it may be more problematic than withdrawing from other benzodiazepines (Murphy & Tyrer, 1991). It is regrettable that the minimum tablet strength available in the UK is 1 mg (approximately equivalent to 10 mg diazepam) although 0.5 mg lorazepam tablets are available in the US and Canada. Some patients become expert at shaving small fragments off lorazepam tablets. Alternatively, oral suspensions of lorazepam can be prepared and slow reductions in dosage can be accomplished either by decreasing the volume of each dose, using a graduated syringe, or by dilution of the mixture, which most high street chemists will undertake.

Adjuvant drugs. Several drugs have been tested for their ability to alleviate benzodiazepine withdrawal symptoms; none have been shown to be generally effective. Clinical experience suggests that antidepressants are the most important since depressive symptoms, sometimes amounting to major depression, are common after withdrawal (Olajide & Lader, 1984; Ashton, 1987). Suicides have occurred in several studies. Antidepressants are clearly indicated when depression occurs, but there is as yet no clear evidence from placebo-controlled trials for their routine use in withdrawal (Tyrer, 1985; Rickels *et al.*, 1989). Most authors recommend sedative tricyclic antidepressants, many of which are also effective in relatively low doses for anxiety and insomnia. To date there is little experience with specific serotonin reuptake inhibitors (SSRIs) in withdrawal, but in personal observations these drugs have precipitated acute anxiety in some cases. Because of the limited dose preparations of most SSRIs, it is difficult to initiate treatment with small doses, a measure which might obviate such

reactions. (Fluoxetine is available as a liquid preparation 20 mg/5 ml.)

Beta-blockers such as propranolol attenuate palpitations, tremor and muscle twitches but have little effect on subjective states and do not reduce the overall incidence of withdrawal symptoms or dropout rate in controlled trials of withdrawal (Tyrer, Rutherford & Huggett, 1981; Abernethy, Greenblatt & Shader, 1981; Lader & Higgitt, 1986; Ashton 1984, 1987; Cantopher *et al.*, 1990). Some patients experience exacerbations of anxiety, insomnia or physical symptoms on withdrawing from antidepressants or beta-blockers, and these drugs should be tapered slowly after benzodiazepine withdrawal is complete.

Carbamazepine appeared to be promising in several small open studies of benzodiazepine withdrawal and is still used by some psychiatrists. However, in a randomized, placebo-controlled trial in which carbamazepine was administered for 2–4 weeks before benzodiazepine tapering over 4 weeks to 40 patients who had previous difficulties in withdrawing from therapeutic dose benzodiazepines, there were no significant differences from placebo in severity of withdrawal symptoms or outcome at 12 weeks' post-withdrawal (Schweizer *et al.*, 1991). Patients taking more than 20 mg diazepam equivalent appeared to derive benefit, and the authors suggested that carbamazepine may have some utility in patients withdrawing from high-dose benzodiazepines. It may also offer anticonvulsant cover for those with a history of epilepsy (Lader, 1991). Abrupt withdrawal of carbamazepine (up to 600 mg/day) for 8 weeks did not increase symptoms of anxiety or depression. Some authors still recommend barbiturate substitution for high-dose benzodiazepine users or those with mixed benzodiazepine/alcohol dependence (American Task Force, 1990; DuPont & Saylor, 1991).

Buspirone (Olajide & Lader, 1987; Ashton, Rawlins & Tyrer, 1990), clonidine (Joyce *et al.*, 1990; Goodman *et al.*, 1986), nifedipine and alpidem in the doses tested have been shown to confer no benefit, and sometimes to aggravate, withdrawal reactions. Flumazenil appears to alleviate protracted symptoms after withdrawal, but may precipitate withdrawal reactions in dependent patients still taking benzodiazepines (Lader & Morton, 1992). Further investigations of orally administered partial benzodiazepine antagonists are awaited. Sedative antihistamines are occasionally useful for specific symptoms (insomnia and flu-like symptoms). Other hypnotics (e.g. chloral derivatives, zopiclone) are sometimes prescribed but should only be used for a few days or intermittently. Antipsychotics are not recommended. The majority of patients withdraw successfully from benzodiazepines whether taking placebo in clinical trials or without additional drugs in clinical practice.

High dose abuses. Patients on very large doses of benzodiazepines, either on prescription or illicitly, may need to begin withdrawal in hospital. Such patients may be taking the equivalent of 0.5–1 g diazepam daily. Fairly rapid partial reduction at the rate of approximately 10 mg diazepam daily may be undertaken safely over 2–3 weeks, with appropriate surveillance and psychological support, followed by a period of stabilization. Several spaced admissions may be necessary to reduce dosage to manageable levels, when withdrawal can continue as for therapeutic dose users. Many high-dose users take temazepam, which is preferred among abusers in the UK. Stepwise conversion to diazepam is advisable; alternatively temazepam tablets (which have identical bioavailability to capsules but lower street value) or an oral solution can be used.

Anxiety management

However careful the dosage reduction, patients dependent on benzodiazepines may develop numerous symptoms. Most of these, whether "true" or "pseudo-withdrawal" symptoms (Tyrer, Owen & Dawling, 1983), are manifestations of anxiety. Furthermore, many patients are already anxious before they begin withdrawal (Ashton, 1991). Thus, a withdrawal plan should include provision for some form of psychological support; effective anxiety management can be crucial to success in withdrawal and prevention of relapse.

The degree of support required varies individually, ranging from simple encouragement (in most cases) to formal cognitive, behavioural or other therapies (in a minority). Polydrug and high dose benzodiazepine abusers may need special treatment for drug addiction problems, but anxiety symptoms associated with benzodiazepine withdrawal are similar to those of thera-

peutic dose users. Support should be available not only during dosage reduction but for a prolonged period afterwards, since distress related to withdrawal may last for many months after drug cessation (Du Pont & Saylor, 1991; Tyrer, 1991; Ashton, 1991; Lader, 1991). Frequent contact, even weekly for some patients in the initial stages, may be necessary (Lader & Higgitt, 1986). During these contacts individual causes of anxiety can be explored and dealt with appropriately.

Providing information. Many patients fear the process of withdrawal itself because of misconceptions derived from lurid accounts of others' experiences. It is helpful to provide, at the first consultation, clear information about benzodiazepine withdrawal and to emphasize that slow and individually titrated dosage reduction rarely causes intolerable distress. Other patients become frightened by particular symptoms which are overinterpreted as signs of physical or mental illness. Information may need to be repeated in these cases; in practice the realization that a symptom is a "withdrawal symptom" is temporary, and is not a sign of disease, is immensely reassuring to some patients. Books written for patients are available (Trickett, 1986; Tyrer, 1986), and often the provision of correct information combined with a sympathetic attitude is the only intervention necessary.

Dealing with specific symptoms

Insomnia. Many patients have difficulty in sleeping. Simple reassurance, attention to sleep hygiene measures, including the use of tea, coffee and alcohol, and practical advice such as the use of relaxation tapes and anxiety management techniques (see below) may be sufficient to allay this symptom. Taking the total dose of the benzodiazepine at night during the reduction period may also be helpful. Occasionally adjuvant drugs (see above) are temporarily indicated.

Panic attacks. Panic attacks may appear for the first time during or after withdrawal, although some patients have long experience with this distressing symptom. Explanation of the mental and physical mechanisms of panic and written information (books and pamphlets are available) is valuable, and keeping a diary may help to pinpoint precipitating factors. Whether the panics are "true" withdrawal symptoms or not, it is important to emphasize that the patient can learn to exercise control over them. Various approaches, including instruction in relaxation techniques, breathing exercises (many patients hyperventilate), training in anxiety management skills, cognitive therapy, simple counselling, physical exercise, massage, yoga and others suit individual patients. It is worth stressing that learning to control panic symptoms is a skill which improves with practice and patients should be encouraged to work on relaxation at home, perhaps with the aid of a relaxation cassette. The discovery that a panic attack can be controlled without resorting to a tablet is a great boost to self-confidence, and the development of new stress-coping strategies is often the key to success in benzodiazepine withdrawal.

Agoraphobia. Agoraphobia and other phobias (especially social phobia) may also first appear during withdrawal, although agoraphobia is sometimes the initial reason for prescribing benzodiazepines. In long-standing cases behavioural treatment may be required, but such therapy is less effective during benzodiazepine use than after withdrawal, probably because of the adverse effects of benzodiazepines on cognitive function (Gray, 1987). Exposure treatment also becomes more effective after patients have learned to control panic symptoms (see above). In many cases, however, agoraphobia disappears along with other symptoms after drug withdrawal, without the need for any formal therapy (Edwards *et al.*, 1990; Ashton 1987).

Depression. Significant depression may require antidepressant drugs but may also respond to cognitive approaches.

Support organizations. Self-help groups run by ex-benzodiazepine users have undoubtedly helped many patients, but professional organizations using psychologists or trained counsellors, or experienced paramedical workers attached to a practice, are probably more effective if available. Individual treatment, although more time-consuming, is more effective than group therapy for patients withdrawing from benzodiazepines, especially in the early stages. Many patients are low in confidence and self-esteem and fear to expose themselves to others. Many have unresolved personal or social problems which lie at

the root of their anxiety and long-term benzodiazepine use. It is often helpful to involve the spouse or family, who may be able to give additional support. Ideally, a close liaison should be maintained between any available support organization and the medical practitioner.

Motivation. Highly self-motivated patients are usually successful in withdrawal and are compliant with withdrawal regimens. Motivation can be increased in more reluctant patients by pointing out the advantages of withdrawal and by suggesting a trial reduction in dosage, without commitment to total cessation. Patients (including the elderly) are often pleasantly surprised to find that they can make small reductions without adverse consequences, even in the dose of a hypnotic taken for many years and believed to be essential for sleep. Personal observations have shown that even spastic patients, who are often prescribed large doses of benzodiazepines for muscle relaxation, can be withdrawn slowly, resulting in improved mental alertness without increased spasticity. Some such patients may continue to total withdrawal; others may settle for dosage reduction, intermittent courses, or use only in emergencies (some carry benzodiazepines around as an insurance, but rarely take them). Although there are few contraindications to withdrawal of long-term benzodiazepines in patients who wish it, it is unwise and unkind to compel unwilling patients to withdraw: enforced withdrawal is usually unsuccessful and leads to unnecessary distress.

Course and outcome of withdrawal

During benzodiazepine withdrawal, symptoms characteristically wax and wane, varying in severity and type. Some symptoms disappear, but others take their place. Patients need not be discouraged by these wave-like recurrences: typically "windows" of normality, when the patient feels well for hours or days, appear after some weeks, and over time these "windows" enlarge while discomfort slowly regresses. However, patients remain vulnerable to external stresses for some time (Murphy & Tyrer, 1988) and the clinical course after drug cessation can be protracted (Ashton, 1991; Tyrer, 1991).

With slow dosage reduction and sufficient psychological support, the success rate for stopping benzodiazepines is high (approximately 90%). Successful withdrawal is not affected by duration of use, dosage or type of benzodiazepine, rate of withdrawal, severity of symptoms, psychiatric history, or the presence of personality disorder or difficulty (Golombok *et al.*, 1987; Ashton, 1987; Ashton *et al.*, 1990; Murphy & Tyrer, 1991). Long-term outcome is more difficult to assess. Abstinence from benzodiazepines 1–5 years after withdrawal varied in different studies between 54% (Golombok *et al.*, 1987), 66% (Holton & Tyrer, 1990) and 92% (Ashton, 1987). Variable numbers of patients, between 6% and 75%, took benzodiazepines for some time after the initial withdrawal, but most of them stopped again. About 20% of patients took antidepressants or other psychotropic drugs. Overall it appears that over 80% of patients felt better after withdrawal from long-term benzodiazepines than when they were taking the drugs, and there is no evidence of increased alcohol use or psychiatric morbidity (Ashton, 1987; Edwards *et al.*, 1990). As experience in withdrawal methods increases and non-pharmacological methods of anxiety management become more available, it is likely that the long-term outcome will continue to improve.

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