

The benzodiazepine withdrawal syndrome and its management

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SUMMARY. *The literature on benzodiazepine dependence and withdrawal is reviewed with an emphasis on social and psychological considerations. The problems of when to prescribe, identifying withdrawal symptoms, effective communication with the patient, the structure of withdrawal programmes, and the use of drugs, psychological approaches and other services are discussed.*

Introduction

THE problems of benzodiazepine dependence and withdrawal have recently assumed a higher profile. There has been a renewal of interest in the popular press with advice to patients which can be interpreted as encouragement to sue their doctors for prescribing benzodiazepines. Recently a timely editorial in the *Journal* outlined a rational approach to benzodiazepine withdrawal.¹ This review highlights the complex nature of the withdrawal syndrome and offers further guidelines on withdrawal to the general practitioner, with particular emphasis on social and psychological issues.

Identifying benzodiazepine withdrawal symptoms

Several reviews conclude that a significant proportion of, but by no means all, patients receiving therapeutic doses of benzodiazepines develop symptoms when withdrawing that indicate physical dependence.²⁻⁴ Many studies have used selected samples of patients who have had previous difficulty withdrawing. Ashton, for example, lists perceptual distortions, paresthesia and difficulty walking as occurring in all her subjects. Other reported symptoms include feelings of unreality or depersonalization, pain, visual disturbances, depression, paranoid thoughts and feelings of persecution, gastrointestinal symptoms and increased sensitivity to light, noise, taste and smell.⁵ A double-blind placebo controlled study, also using a selected sample, found all subjects experienced anxiety, tension, agitation, restlessness and sleep disturbance.⁶

However, studies with less selected samples yielded a similar constellation of symptoms. For example, Tyrer and colleagues found insomnia to be the most commonly experienced withdrawal symptom (57.5% of sample), along with extreme dysphoria, impaired perception of movement, muscle pain and headache.⁷ Onyett and Turpin found sleep disturbance and headache were most frequently reported.⁸ More exceptionally, fits, confusional states and psychosis have occurred following sudden withdrawal.⁹

Although the existence of the withdrawal syndrome is difficult to dispute, its definition and explanation are not simple. Smith and Wesson separate three categories of symptomatology: a 'sedative-hypnotic' constellation which is found with high dosage and has a fairly rapid onset after withdrawal; a 'low dose' constellation beginning soon after withdrawal and improving after weeks or months; and 'symptom re-emergence' entailing a

resurgence of the anxiety symptoms which continue unabated over time.¹⁰ The picture is further complicated by reports of 'rebound anxiety' in which the original symptoms of anxiety return, but temporarily and with greater intensity.¹¹ However, the syndrome involves more than a return to a previous level of anxiety, as shown by withdrawal symptoms that are untypical of anxiety,^{5,6,11,12} the occurrence of the syndrome being unrelated to the patient's psychiatric history,^{5,13,14} and the patient returning to pre-withdrawal levels of anxiety a short time after withdrawal is complete.^{6,11,12}

Although dependence on benzodiazepines has been demonstrated, there is little experimental evidence of craving or drug-seeking behaviour. However, other evidence of tolerance has been shown¹⁵ and the Committee on the Review of Medicines found little evidence of a therapeutic effect for benzodiazepines after four months of continuous use.¹⁶ It has been suggested that beyond this period benzodiazepines may prevent withdrawal symptoms occurring and that, although this may last for a long time, some patients may progress to a 'problem phase' when withdrawal symptoms occur even though medication is still being taken. The most common symptoms of this phase are listed as disturbed sleep, anxiety (with panic attacks occurring when the next dose is due) and agoraphobia.¹⁷ Few clinicians would suppose that the remedy for these symptoms could lie in drug withdrawal rather than prescription. However, of Ashton's 12 patients, 11 had developed agoraphobia while on benzodiazepines. For four of these it resolved with no treatment other than withdrawal.⁵

Another important category of complaint described by Smith and Wesson was 'symptom over-interpretation' resulting from an expectation of unpleasant withdrawal symptomatology.¹⁰ Evidence of such 'pseudo-withdrawal' when patients falsely assumed their drugs were being withdrawn has been found. It was characterized by reported sadness, inability to feel and hostile feelings, while the genuine syndrome involved reduced sleep, depersonalization and derealization.¹²

In general, withdrawal symptoms occur three to seven days after a reduction in treatment depending on the action of the drug. Although originally thought only to last a few months, symptoms lasting as long as a year or more after withdrawal have been reported but cannot be regarded as withdrawal symptoms in the pharmacological sense.⁵

Incidence and prediction of withdrawal difficulties

It has been found that between 27% and 45% of patients prescribed diazepam or lorazepam for an average of 3.5 years suffered withdrawal symptoms, depending on the criteria for a withdrawal reaction.⁷ Although studies have found withdrawal symptomatology to occur after a period of treatment with therapeutic doses of diazepam of only six weeks^{18,19} it must be stressed that among unselected benzodiazepine users, more than half may be able to withdraw with no ill effects.³

The length of action of the drug is a major predictor of withdrawal symptoms. Higher drop-out rates from withdrawal programmes when patients are on benzodiazepines with few or no active metabolites (for example lorazepam), and the association of symptom levels with percentage falls in serum levels of desmethyldiazepam, the major metabolite of diazepam, suggest that the occurrence of withdrawal symptomatology may be

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related to the rate at which circulating benzodiazepines and their active metabolites are metabolized and excreted.⁷ Therefore, it should be noted that the shorter acting drugs which are so commonly used with elderly patients to avoid problems of accumulation may have greater addictive potential.

Passive and dependent personality traits have been shown to be predictive of withdrawal problems, as have high dosage and chronicity of benzodiazepine use.^{3,12} However, the latter has been contradicted by more recent findings with large samples and it now appears that doctors should not be discouraged from attempting withdrawal with patients who have been taking high dosages for long periods or who have failed to withdraw before because of severe symptoms. Positive outcome in these studies was predicted by younger age, female sex,¹³ good housing and, interestingly, the absence of an intimate relationship.¹⁴

A recent study of psychotropic drugs in general practice found that patients over 55 years of age were more likely to become long-term users than younger patients, particularly if they had a lower level of education.²⁰ One analysis of benzodiazepine use examined the extent to which the drugs were viewed by the patient as a resource enabling the performance of everyday roles. This was found to be particularly the case among long-term users and was mitigated by the availability of other resources such as paid work, leisure opportunities and supportive families.²¹

To prescribe or not to prescribe?

Decisions about whether benzodiazepines are an appropriate therapy require consideration of their costs and benefits. A review of the place of benzodiazepines in psychiatric practice describes problems attending every application.²² Overall, it seems that prescriptions for less than two weeks may be useful in circumstances of major stress although even here benzodiazepines may interfere with psychological adjustment.²² Indeed, it has been suggested that benzodiazepines should be specifically avoided in situations of acute stress, such as bereavement or divorce.²³ The short-term use of benzodiazepines in general practice for the treatment of low levels of anxiety has been brought into question by a recent review²⁴ and one study in primary care found that benzodiazepines had no advantage over placebo.²⁵

The side effects of benzodiazepines include drowsiness, unwanted sedation, blurring of vision, unsteadiness and ataxia¹⁶ and for elderly patients there is the risk of accumulation leading to confusion and apathy which may be mistakenly attributed to dementia.²⁶ Some evidence for psychological impairment and neuroradiological changes as a result of long-term use has been found^{27,28} and there are reports of withdrawal symptoms in neonates who have been exposed to benzodiazepines *in utero*.^{29,30} However, the evidence for irreversible damage from long-term benzodiazepine use is weak.

Despite these problems, many patients report finding benzodiazepines helpful and are likely to be unconcerned as to whether this is for pharmacological or psychological reasons. Where a patient is suspected of being dependent but shows little motivation to stop taking these drugs, enforced withdrawal may be a disservice, pushing the patient in the direction of alcohol or other drugs and causing a sense of guilt about being on benzodiazepines. However, such patients should be regularly reviewed and offered the opportunity to withdraw should their feelings or circumstances change.

Structuring the withdrawal programme

Hospital admission for withdrawal is normally only considered for patients who have experienced severe withdrawal reactions before, such as psychosis or seizures, or who have been taking very high doses for long periods of time.³¹

As withdrawal reactions include a physiological, homeostatic response to the cessation of circulating benzodiazepine metabolites, transfer to a drug with a longer elimination half life and gradual reductions in dosage reduce the incidence of withdrawal problems.^{7,11,12}

Patients on short-acting drugs such as lorazepam, triazolam or temazepam may usefully be transferred to longer-acting drugs such as diazepam or nitrazepam. A useful table of equivalents is given by Higgitt and colleagues.²³ Ashton, for example, recommends substituting 10 mg diazepam by 1 mg lorazepam.⁵ For some patients the transfer may be problematic and the drug may have to be substituted in a stepwise manner.

Where daily dosage is variable a ceiling dose can be established which can then be systematically reduced. However, for shorter-acting drugs in particular it may be preferable to stabilize the dosage first since even diurnal variations in circulating benzodiazepine levels may exacerbate symptoms.³²

Where the drug is being taken three or four times daily it will be important to establish which dose to cut first. To reduce the impact of diurnal fluctuations and psychological dependence on the drug during the day, it may be useful to reduce the lunch-time dose first, then the morning dose followed by the evening dose, repeating this format until withdrawal is complete. The evening dose should be cut last as sleep disturbance is often one of the least tolerable symptoms.³²

Most sources recommend 'titrating' reductions, depending on how well the previous reduction was tolerated.^{32,33} The first reduction may be as much as a quarter of the starting dose and successive reductions follow until symptoms are experienced at which point smaller reductions are made. Typical reductions are 0.5–2.5 mg diazepam or its equivalent.

With each reduction the patient is allowed to get over the worst of the symptoms before proceeding. However, in some cases this may give patients too much control over reduction, allowing them to maintain dosage because of reported anxiety, thereby inducing further psychological dependency; the doctor may be interpreted as giving a mixed message in encouraging the patient to withdraw while simultaneously sanctioning drugs to combat anxiety-like symptoms. For patients showing potential addiction, the general practitioner may need to maintain tighter control over the reductions, progressing despite symptoms in the hope that the overall anguish will be minimized. Certainly, a clear idea of the period of withdrawal should be established from the outset. Periods varying from one month to around 16 weeks have been used.³³ Ultimately, with a patient known to be dependent, the decision is often between a short but aversive programme and more prolonged suffering.

During the final stages of a reduction programme, the psychological aspects of dependence are likely to intensify.¹⁵ Tiny reductions, or even taking a dose on alternate days have been recommended.³³ However, this again may run the risk of reinforcing psychological dependence for the reasons outlined above, and this stage should not be prolonged.

After withdrawal, Tyrer recommends, 'intermittent flexible dosage' where the patient is allowed to use drugs in clearly specified situations which are made progressively more rigorous.¹² This may be problematic, both with regard to compliance with the strictures agreed, and the further reinforcement of a 'pills not skills' philosophy. However, the risk of the patient transferring to alcohol or other forms of drug abuse after withdrawal should be borne in mind.

Use of other drugs

Propranolol has been found to have a limited impact on the severity of withdrawal symptoms but does not affect their frequency.⁷ Antidepressant drugs have also been indicated in some

cases.³⁴ For persistent and distressing insomnia as a result of benzodiazepine withdrawal, the use of non-benzodiazepine hypnotics such as promethazine or chlormethiazole has been advocated.¹⁷ Clearly, however, the substitution of one drug for another raises the possibility of further psychological dependence and offers the patient little in terms of alternative coping strategies.

Communication

During withdrawal, the patient should receive weekly face-to-face contact in order that any recrudescence of anxiety may be monitored and support offered.³¹ It may be appropriate for this role to be undertaken by other primary care staff, such as a nurse practitioner, counsellor or clinical psychologist with the general practitioner acting as consultant.

Some education of the patient may be necessary, particularly when explaining why a short-acting drug is being replaced by a long-acting one. Although much of the popular literature on benzodiazepine withdrawal is rather alarming and may incline the patient towards pseudo-withdrawal, more balanced sources are available.³⁵

Perhaps the first issue that the general practitioner will have to address is how to inculcate in the patient an appropriate expectation of withdrawal. Should a full account of all the symptoms that could be encountered be given, thereby incurring the risk of overinterpretation of symptoms and anticipatory anxiety, or should the possibilities be minimized? A middle course lies in telling patients that there is at least a 50-50 chance that they will be able to withdraw with only mild problems. However, patients, particularly those who have experienced withdrawal problems before, should be warned of the possibility of sleeplessness, anxious feelings and perhaps some sensations which will appear rather strange and unfamiliar to them (for example some heightened sensitivity to light and noise, and depersonalization). It can be helpful to describe the reactions as a homeostatic response that will re-establish a natural balance within a short time.

Another issue is whether patients should be encouraged to attribute their symptoms to withdrawal. Since many of the symptoms are likely to be due to anxiety, to do so may create an unrealistic expectation of what it is like to be drug free. However, it has been argued that correcting the mislabelling of withdrawal symptoms as anxiety symptoms and interrupting the cycle of withdrawal symptoms triggering drug taking, are crucial to the prevention of relapse.³⁶ The most helpful course may be to point out that most people are anxious about withdrawal and to describe some of the physical consequences of this while encouraging patients to keep to their schedule for withdrawal.

The dangers of repeated contacts where the patient is implicitly encouraged to focus on physical symptoms have been described.³⁷ Where questions and in some cases the information distributed on benzodiazepine withdrawal incline the patient towards greater sensitivity to symptoms, a vicious cycle can be set up whereby physical states are interpreted more strongly, leading to their interpretation as more abnormal by the patient and doctor, leading the doctor into further investigation and more questioning. A preferable alternative is to focus on the patients' perceived ability to cope with everyday demands rather than investigating symptoms which may be of a transitory nature. Where persistent problems occur, it may be necessary to invoke more sophisticated assessments, such as diary keeping, in order to identify more clearly the possible causes of anxiety symptoms.

Psychological therapy and social support

A review of medically managed withdrawal programmes estimated that although, with gradual reduction, 88-100% of

patients succeed in withdrawing, approximately two thirds of these patients have problems after withdrawal and a high proportion may subsequently relapse.^{14,23} Although one study found that following general practitioner contact only, 63% of the sample were still off benzodiazepines at up to five months follow-up³⁸ the success rate might be improved further with supplementary or alternative approaches.

Since there are similarities between the withdrawal syndrome and clinical anxiety, anxiety management procedures may be useful. Moreover, since benzodiazepines were probably prescribed because of anxiety related problems, anxiety management training may have an important role in stopping relapse by preventing the return of anxiety symptoms and promoting more constructive coping strategies. However, controlled studies examining anxiety management groups have not shown a significant advantage over more minimal interventions although 40-50% of the samples were taking a quarter or less of their original drug dose at follow up.^{8,39} Other studies have found similar success rates using anxiety management techniques in group^{36,40-42} and individual formats.^{36,43}

It seems reasonable to infer that intensive training in psychological skills can be reserved for those patients with intractable withdrawal symptoms or a concurrent anxiety state. Training in progressive muscle relaxation, breathing exercises and behavioural goal setting, and guidelines on coping with sleep disturbance have been rated by patients as particularly valuable.⁸ Attention has also been drawn to the need to include help with problem solving and changing negative thoughts, and to the advantages of involving the patient's partner or confidant during withdrawal.⁴¹ Clearly, attention should also be paid to concurrent sources of stress such as financial pressures, social isolation, or problems with children which may require referral to social services or voluntary agencies.⁴⁴ Local self-help groups, such as Tranx may be available, although these have not yet been the subject of systematic evaluation.

Conclusion

Attempts to treat anxiety with benzodiazepines have found a sharp sting in the tail, with evidence of dependence which has led to considerable public concern. The withdrawal syndrome is both a physiological and a psychological phenomenon, and the general practitioner must consider not only a rational method of structuring withdrawal but also of communicating to the patient a realistic expectation of withdrawal and being free from drugs. Although in most cases withdrawal can be achieved with little disturbance to the patient, for some the process may be more difficult, requiring supplementary effort from other primary care staff or agencies with specific psychological expertise.

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