PROTRACTED WITHDRAWAL SYMPTOMS FROM BENZODIAZEPINES

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Protracted withdrawal symptoms from benzodiazepines have been discussed previously(1,2). The present chapter updates these articles and adds some more recent research findings.

For some chronic benzodiazepine users, withdrawal can be a long, drawn-out process. A sizeable minority, perhaps 10 to 15%(3) develop a "post-withdrawal syndrome"(4), which may linger for months or even years. This syndrome is clearly not a disease entity; it probably represents an amalgam of pharmacological and psychological factors directly and indirectly related to benzodiazepine use. The syndrome includes (1) pharmacological withdrawal symptoms involving the slow reversal of receptor changes directly induced in the brain by benzodiazepines(1,5-7), and (2) psychological symptoms resulting indirectly from long-term benzodiazepine use, including exposure of poor stress -coping abilities and other personal difficulties. These symptoms merge into a complex clinical picture that may be further complicated by (3) the reappearance of underlying anxiety or depression and (4) possibly also by ill-understood long-term neurological effects of benzodiazepines(1).

Thus, the totality of the benzodiazepine withdrawal syndrome is as difficult to define or demarcate as a bout of influenza, which may include overlapping pathologies of acute viral toxaemia, secondary bacterial infection, prolonged post-viral depression and somatic damage such as cardiomyopathy. Nevertheless, an awareness that symptoms may be protracted is important for clinicians supervising benzodiazepine withdrawal; proper management of the initial withdrawal can decrease the incidence, severity and duration of protracted symptoms and improve the prospects for eventual recovery.

I. ACUTE WITHDRAWAL PHASE

The acute "pharmacological" benzodiazepine withdrawal syndrome is classically described as lasting 5 to 28 days, with a peak in severity around 2 weeks post-withdrawal. after which most symptoms return to pre-withdrawal levels(8-14). The symptom constellation includes symptoms common to all anxiety states, but some features are unusual and considered to be relatively specific to benzodiazepine withdrawal (Table 1).

Table 1. Some common acute benzodiazepine withdrawal symptoms

Symptoms common to all anxiety states	Symptoms less common in anxiety states: relatively specific to benzodiazepine withdrawal
Anxiety, panic attacks, agoraphobia	Perceptual disturbances, sense of movement
Insomnia, nightmares	Depersonalisation, derealisation
Depression, dysphoria	Hallucinations (visual, auditory), misperceptions
Excitability, jumpiness, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light-headedness	Formication
Weakness, "jelly legs"	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasiculation
Muscle pain, stiffness (limbs, back, neck, jaw, head)	Tinnitus
Sweating, night sweats	*Confusion, delirium
Palpitations	*Fits
	*Psychotic symptoms

*Usually confined to rapid withdrawal from high doses of benzodiazepines

However, the duration of this acute phase has probably been underestimated. First, most clinical studies terminate 4 to 8 weeks after withdrawal, and the progress of remaining symptoms is not monitored. Second, most reports do not include the later experience of dropouts, although the reason for dropout is often the continuation of symptoms. Indeed, persistence of high anxiety levels beyond 28 days post-withdrawal is usually interpreted not as a withdrawal effect, but as re-emergence of an underlying anxiety state previously controlled by the benzodiazepine(14,15) and often results in reinstatement of benzodiazepine treatment. Third, it has been assumed that return to pre-withdrawal symptom levels in those who complete withdrawal represents the end of the withdrawal syndrome.

Some clinical reports do not support these assumptions. Observations of patients followed up for longer periods suggest that, at least in some individuals, typical benzodiazepine withdrawal symptoms, including paraesthesiae, sensory hypersensitivity, muscle spasms, and tinnitus as well as less specific symptoms such as anxiety, insomnia, and depression, can take 6 to 12 months to subside completely(8,16-23). A further problem is the interpretation of "baseline" symptoms. Patients presenting for withdrawal often have many "typical" benzodiazepine withdrawal symptoms, as well as high levels of anxiety, even while still taking the drugs(1,21). Although these symptoms may return to pre-withdrawal levels in a matter of weeks following an acute withdrawal peak, follow-up observations show that such symptoms may continue to improve over subsequent months. Even without specific treatment, they may decline to levels well below "baseline", sometimes enabling patients to resume their normal lives after years of incapacity(1,19,21).

II. PROTRACTED WITHDRAWAL PHASE

The acute withdrawal phase may merge imperceptibly into a more protracted phase in which symptoms gradually decline but may be punctuated by wave-like recurrences(16,21) interspersed with windows of normality that gradually extend in frequency and duration toward eventual, but occasionally incomplete, recovery. From current evidence, symptoms that are most likely to be long-lasting are anxiety and insomnia, cognitive impairment, depression, various sensory and motor phenomena, and gastrointestinal disturbances (Table 2).

Table 2. Some protracted benzodiazepine withdrawal symptoms

Symptoms	Usual course
Anxiety	Gradually diminishing over a year
Insomnia	Gradually diminishing over 6 to 12 months
Depression	A few months: responds to antidepressants
Cognitive impairment	Gradually improving but may last a year or more and occasionally incomplete
Perceptual symptoms tinnitus paraesthesiae - tingling, numbness, pain usually in limbs, extremities	Gradually receding, but may last at least a year and occasionally persist indefinitely
Motor symptoms muscle pain, weakness, tension, painful tremor, shaking attacks, jerks, blepharospasm	Gradually receding, but may last at least a year and occasionally persist indefinitely
Gastrointestinal symptoms	Gradually receding, but may last at least a year and occasionally persist indefinitely

A. Anxiety

Anxiety persisting after the acute phase of withdrawal may be partly due to the uncovering of a learning defect caused by the benzodiazepines. These drugs cause cognitive deficits(23,24) and specifically impair coping strategies. For example, Gray(25) and others showed that behaviour treatments for anxiety, including those for agoraphobia, are generally ineffective while patients are still taking benzodiazepines, but become more effective when the drugs are stopped. There may be an extended period after benzodiazepine cessation when patients have a decreased ability to cope with stressful situations; full recovery may require the learning of new strategies to replace the years of coping by pharmacological means.

In addition, drug withdrawal may uncover problems in the patient's life that have never been fully addressed. Tyrer(26) points out, for example, that the amnesic effects of benzodiazepines may prevent the resolution of personal stresses such as bereavement. Such buried or half-forgotten stresses may have to be faced after withdrawal and may prolong both anxiety and depression. In contrast, anxiety may be increased by memories of a previous failed and traumatic withdrawal experience, leading to symptoms akin to post-traumatic stress disorder (nightmares and flashbacks).

Hence, persistence or worsening of anxiety after withdrawal does not necessarily imply the re-emergence of an anxiety state existing before withdrawal. Indeed, some patients experience major panic attacks and agoraphobia for the first time after withdrawal and may, for a time, develop a more severe degree of anxiety than was present when the drugs were first prescribed. Nevertheless, these symptoms tend gradually to subside over several months even without formal treatment, although the process may be hastened by appropriate psychological support.

B. Insomnia

Benzodiazepines disrupt normal sleep patterns, suppressing slow wave sleep, rapid eye movement sleep, and dreaming. Cessation of benzodiazepines commonly leads to rebound insomnia(27) and sometimes to nightmares and other sleep disturbances, including "restless legs", nocturnal myoclonus, and hypnagogic hallucinations. Sleep disturbance may persist as part of a protracted anxiety state, but occasionally as an isolated symptom. Several months may elapse before a normal sleep profile is re-established.

C. Depression

Although depression is common in long-term benzodiazepine users and may be aggravated by the drugs(23) it is also a consistent feature of the withdrawal syndrome (8-21). Depressive symptoms may appear for the first time after withdrawal, often some weeks later, and may be severe and protracted for some months. Suicide has been reported in some studies. For example, in a series of 50 consecutive patients undergoing benzodiazepine withdrawal(21) one patient committed suicide, three developed major depressive disorder, and 17 had depression severe enough to require antidepressant medication. It is not clear whether post-withdrawal depression results from a direct pharmacological action of benzodiazepines, such as central serotonin depletion(20), but it responds to antidepressant drugs and usually remits within a few months. There have been no studies to establish whether or not it recurs in later years.

D. Cognitive impairment

Benzodiazepines, even in therapeutic doses used for anxiety and insomnia, have long been known to cause cognitive impairment, particularly of memory processes. Acquisition of new information is deficient, an effect that may be partly due to the sedative actions. However, some specific amnesic effects appear to be separate from sedation(24). Episodic memory (remembering of recent events) is particularly impaired while somatic memory (memory for words), immediate memory and retrieval of memory from long-term stores are relatively unaffected. These effects have been demonstrated with benzodiazepines administered to normal subjects and anxious patients and in long-term benzodiazepine users. Specific defects in visuospatial ability and sustained attention have also been described in long-term therapeutic dose benzodiazepine users(28).

Unlike the tolerance that develops rapidly to the sedative effects and more slowly to be anxiolytic effects of benzodiazepines, complete tolerance to the amnesic effects and other cognitive impairments does not appear to develop even after years of chronic use. Many studies of long-term benzodiazepine users have shown deficits in learning, memory, attention and visuospatial ability (24,29-34). These effects are most marked in the elderly(35) and in heavy alcohol drinkers(36).

Recovery of cognitive functions occurs to some extent after benzodiazepine withdrawal but it may be slow and perhaps incomplete and may persist as a protracted withdrawal symptom. Improvement in cognitive function after benzodiazepine withdrawal was noted in elderly nursing home residents(37) and in elderly patients withdrawn from long-term hypnotics(38). However, several authors have reported that impairments in cognitive functioning persisted in anxious patients several weeks beyond withdrawal(39) although they were no longer evident 3.5 years later(40). Gorenstein et al.(33) reported incomplete recovery of memory functions and psychomotor performance 10 months after benzodiazepine withdrawal and Tata et al.(32) found little improvement in episodic memory functions 6 months after withdrawal of diazepam in chronic users. Bergman et al.(41) and Borg(42) noted incomplete recovery of neuropsychological impairments in high dose benzodiazepine-dependent patients (who had not abused alcohol) 1-6 years after withdrawal. Curran et al.(38) suggest the possibility that benzodiazepine use may add to age-related cognitive decline, and they could conceivably also add to alcohol-related brain changes(36).

E. Perceptual and Motor Symptoms

A variety of perceptual and motor symptoms are characteristic of benzodiazepine withdrawal (Table 1). These usually subside during the acute withdrawal phase, but may sometimes be prolonged.

1. Tinnitus. Tinnitus may initially result from generalised sensory hypersensitivity seen in early withdrawal, but may persist after the symptoms have disappeared. Busto et al.(43) describe two cases of tinnitus persisting for 6 and 12 months after benzodiazepine withdrawal, and they mention a third patient who was unable to withdraw because of severe tinnitus at each attempt. Ashton(1) reported four cases of intractable unilateral or bilateral tinnitus first appearing during benzodiazepine withdrawal and persisting over several years. Three of these patients had symmetrical bilateral hearing defects, which may have been a causative or aggravating factor. Other case reports have appeared sporadically in the literature. Tinnitus, which is often experienced as being precisely localised, can reach almost intolerable levels. One patient described her tinnitus as "a needle of sound" piercing somewhere deep inside her head.

2. Paraesthesiae. Tingling or numbness in the extremities, scalp, or face is common in benzodiazepine withdrawal and in anxiety states and may be associated with hyperventilation. It may persist as continuing "pins and needles"(6) or as severe burning pain without demonstrable neurological cause(5). Two such cases were described by Ashton(1).

Other perceptual disturbances, including sensations of movement, inner vibration, and bizarre skin sensations, may persist in the absence of any detectable psychopathology.

3. Motor Symptoms. Increased muscle tension, hyperreflexia, tremor, fasciculation, and muscle jerking are common in early withdrawal. These signs may represent rebound from the myorelaxant effects of benzodiazepines. However, a range of these symptoms may persist for months or years, including tension, weakness, muscle cramps, tremor, shaking attacks, muscle jerks, and blepharospasm(1,6). As with sensory disturbances, long-lasting motor symptoms are not necessarily associated with high levels of anxiety or other mood disorder.

4. Gastrointestinal Symptoms

Gastrointestinal symptoms are common during chronic benzodiazepine use and in withdrawal and usually fit into such categories as "nervous diarrhoea" or "irritable bowel syndrome", which may be aggravated by hyperventilation(44). Such symptoms may disappear after withdrawal, but are prominent in some patients who develop a post-withdrawal syndrome. Common complaints are of gaseous abdominal distension, lower abdominal pain, and alternating diarrhoea and constipation. Symptoms often appear to be exacerbated by certain foods, and patients may be convinced that they have food allergies or intestinal candidiasis despite negative laboratory findings. However, the incidence of food intolerance and pseudo-allergic reactions is reported to be high in chronic hyperventilators, possibly associated with histamine release(44). The cause of these symptoms in withdrawal is not clear but the effect of benzodiazepine withdrawal on gastrointestinal function and on immune responses merits further attention.

III. PHARMACOLOGICAL MECHANISMS OF TOLERANCE AND WITHDRAWAL SYMPTOMS

The pharmacological mechanisms underlying tolerance and withdrawal are still imperfectly understood. The basic mode of action of benzodiazepines is to enhance the activity of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) in the central nervous system by interaction with specific receptor sites on the postsynaptic $GABA_A$ receptor complex. However, the discovery of multiple $GABA_A$ receptor subtypes has added considerable complexity to the possible changes caused by chronic benzodiazepine administration. For example, $GABA_A$ receptor may contain at least 18 subunits (including alpha1-6, beta1-3, gamma1-3 and others)(45). Different receptor

assemblies have different brain distributions and different affinities for agents that act on them(7). At present it appears from gene 'knockout' experiments in mice that alpha2-containing subtypes mediate anxiolytic effects of benzodiazepines; alpha1-containing subtypes mediate sedative and amnesic effects, and alpha1-containing, as well as other subtypes, mediate anticonvulsant effects(45).

A recent review of possible mechanisms of benzodiazepine tolerance(7) proposed that chronic benzodiazepine administration sets in train a chain of events in which uncoupling of the linkage between $GABA_A$ and benzodiazepine receptor sites leads to preferential degradation of certain $GABA_A$ receptor units. These become internalised within the neurone and in turn provide a signal for changes in gene response, resulting in a long-term homeostatic adaptation to the chronic presence of benzodiazepines. This pathway could operate on different time scales depending on the receptor subtype and/or the brain region involved and thus give rise to differing rates of development of tolerance to various benzodiazepine actions.

On this model, withdrawal of the benzodiazepine once tolerance has developed would expose the recipient to all the drug-induced alterations in GABA receptors, now no longer opposed by the presence of the drug. The result would be underactivity in the many domains of central function normally modulated by GABA-ergic mechanisms. Since GABA is a universal inhibitor of neural activity and decreases the release of many excitatory neurotransmitters (acetylcholine, noradrenaline, dopamine, serotonin, glutamate)(46), there would be a surge of excitatory nervous activity. Increased release of dopamine, noradrenaline and serotonin has been demonstrated in certain areas of the rat brain during benzodiazepine withdrawal after chronic treatment(47,48). Such increases, coupled perhaps with "downstream" increases in sensitivity of excitatory receptors, may account for many benzodiazepine withdrawal symptoms. The various changes in GABA receptors occurring during tolerance may be slow to reverse after drug withdrawal and may do so at different rates(7), possibly accounting for the variable time of emergence and duration of individual withdrawal symptoms(1,18) and for the sometimes protracted nature of benzodiazepine withdrawal syndrome(1,2). For example, the protracted perceptual and muscular disturbances described above raise the possibility that benzodiazepines are capable of inducing long-term hyperexcitability in central sensory and motor neural pathways.

Compelling evidence that GABA/benzodiazepine receptor changes are involved in benzodiazepine tolerance and withdrawal, including protracted symptoms, is provided by experience with the competitive benzodiazepine antagonist flumazenil. Two small placebo-controlled clinical studies have shown that flumazenil can reverse or attenuate persistent symptoms after benzodiazepine withdrawal(6,49). Lader and Morton(6) found that intravenous infusion of flumazenil, but not saline, brought rapid relief of protracted symptoms (including muscle tension, pins and needles, weakness, muscle cramps or jerks, tremor or shaking) that had been present for 5-42 months after benzodiazepine withdrawal. These symptoms were improved by 27-82%. Anxiety, depression and poor concentration were also alleviated but this could have been secondary to somatic improvement. Not surprisingly, flumazenil can precipitate withdrawal reactions in subjects chronically taking benzodiazepines(50-53) but there are also a few reports that it can reduce some symptoms during withdrawal in benzodiazepine-tolerant patients(54-56). Possible mechanisms for these actions such as "resetting" of benzodiazepine receptors are discussed by Nutt(5).

IV. OTHER BRAIN CHANGES

Since tolerance to and recovery from the cognitive changes associated with long-term benzodiazepine use is incomplete and some neurological symptoms appear to persist indefinitely, it is difficult to explain these symptoms only in terms of slowly reversible

receptor adaptations. Perhaps some receptor changes are incompletely reversible but the possibility remains that long-term benzodiazepine use can cause permanent neurological damage. Curran et al.(38) suggest that chronic benzodiazepine use may be implicated in age-related cognitive decline and dementia, conditions associated with neuronal cell loss and cortical shrinkage. There is equivocal evidence in the literature that long-term or high dose benzodiazepine use may cause structural brain damage. Two CT (computerized axial tomography) studies gave contradictory results(57,58). However, Schmauss and Krieg(59) found a significant dose-related cerebral ventricular enlargement in 17 long-term high dose benzodiazepine users who had never abused alcohol compared with control subjects. Another CT study(41) found that some (7 out of 29 females) high dose benzodiazepine abusers showed signs of cerebral atrophy, an incidence significantly greater than in a random sample of 200 women from the general population. Moodley et al.(60) found marginal abnormalities in CT scan appearances (reductions in density in frontal and other brain regions) in long-term lorazepam but not diazepam users. These findings are difficult to interpret but suggest that long-term lorazepam use may induce minor neuroanatomical changes. However, the authors state that at present no anatomical or physiological inferences are justifiable. The most recent CT study(6 1) of 20 long-term benzodiazepine users aged 23-59 years compared with 36 age and sex matched controls found no differences in brain atrophy between the groups and concluded that long-term benzodiazepine therapy does not result in brain abnormalities that can be demonstrated by CT scans. Thus, present evidence suggests that the risk of cortical atrophy, if it occurs, applies mainly to long-term high dose benzodiazepine users and may be compounded by alcohol abuse. Further research with up-to-date imaging techniques is urgently needed to show whether or not benzodiazepines can cause permanent neurological damage.

V. IMPLICATIONS FOR MANAGEMENT OF WITHDRAWAL

"Treatment for benzodiazepine dependence should take account of the post-withdrawal syndrome, and therapeutic contact should not be discontinued too early"(4). Two essential pillars of a successful withdrawal strategy are gradual dosage reduction and psychological support. Careful initial management of benzodiazepine withdrawal is important for a successful outcome and particularly for reducing the incidence and severity of protracted symptoms.

A. Dosage reduction

It is generally agreed that dosage should be tapered gradually in long-term benzodiazepine users. The rate of withdrawal should be individually tailored to the patient's lifestyle, personality, environmental stresses, reasons for taking benzodiazepines, and amount of support available. For most patients on therapeutic doses of benzodiazepines, withdrawal is best completed on an outpatient basis. Such an approach, in the patient's own environment, allows time for both pharmacological and psychological adjustments and permits the patient to continue with his normal life while building up alternative coping strategies.

For high dose benzodiazepine abusers, admission to hospital may be indicated where drug reduction can be initiated under supervision at a faster rate. On reaching more moderate dosage levels, withdrawal in these patients can be continued as for "therapeutic" dose users.

It is usually easier to withdraw from slowly eliminated benzodiazepines such as diazepam, which is available in low dosage strengths, and it is often advisable at some stage to transfer patients taking potent, rapidly eliminated benzodiazepines, such as alprazolam, onto this drug. Detailed advice on withdrawal schedules from different benzodiazepines is given by Ashton(62) and is available on the internet at

http://www.benzo.org.uk/index.htm. Contrary to popular belief, withdrawal symptoms are not inevitable if dose tapering is carried out at a gradual enough pace.

At present there is no conclusive evidence that any adjuvant drugs are generally helpful in preventing or alleviating withdrawal reactions if they occur. In individual cases antidepressants, beta-adrenoceptor antagonists (for palpitations or tremor) or carbamazepine (for withdrawal from high doses of benzodiazepines) may be indicated(63). Buspirone is ineffective(17,20). Flumazenil is impractical for general use since it is short-acting and requires intravenous administration though it has been used successfully in some trials(54-56). Zopiclone, zolpidem and zaleplon are contraindicated since they act like benzodiazepines and cause dependence and are sometimes abused. Gabapentin was reported to be effective in one patient(64) but has not been investigated in controlled trials.

B. Psychological Support

However careful the dosage reduction, some patients dependent on benzodiazepines may develop symptoms (Table 1), and a withdrawal plan should include provision for some form of psychological support. The degree of support required varies individually, ranging from simple encouragement and information to formal cognitive, behavioural, or other therapies. Polydrug and high-dose benzodiazepine abusers may need special treatment for drug addiction problems, but anxiety and other withdrawal symptoms are similar to those of therapeutic dose users. Appropriate support should be available not only during dosage reduction, but also for a prolonged period afterward.

Patients who have the greatest difficulties in withdrawing, and who are most vulnerable to protracted withdrawal symptoms, are those with high anxiety levels before withdrawal, those with personality disorder or difficulty, and those with continuing life stresses, although none of these factors contraindicate withdrawal in motivated patients.

Unfortunately, no treatment has yet proved generally effective for the few patients who develop protracted neurological symptoms, although these tend to lessen in severity over time. For the majority, the outcome of slow benzodiazepine withdrawal coupled with long-term sympathetic support is good. Most patients feel better than when they were taking benzodiazepines and both physical and mental health improves(2,38,65).

SUMMARY AND CONCLUSIONS

In a minority of patients, benzodiazepine withdrawal is followed by a protracted post-withdrawal syndrome lasting many months. Both pharmacological and psychological factors may be involved and the symptoms include anxiety, insomnia, depression, cognitive impairment and a variety of perceptual, motor, and gastrointestinal disturbances. Treatment for benzodiazepine dependence should take into account prolonged symptoms, which may be minimised by gradual dosage reduction and long-term therapeutic contact with appropriate psychological support.

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