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THE ASHTON MANUAL SUPPLEMENT

A Supplement to *Benzodiazepines: How They Work & How to Withdraw* (2002)

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April, 7 2011
(additions 2012 & 2013)

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Overview

There has been little clinical progress in the benzodiazepine world since 2002 when the last edition of "Benzodiazepines: How they work and how to withdraw" appeared on www.benzo.org.uk. Benzodiazepines are still over-prescribed globally, often in excessive doses and frequently for too long. Prescriptions for benzodiazepines and the similar 'Z-drugs' are actually increasing in many countries. There is a tendency to prescribe the more potent agents such as clonazepam (Klonopin) and, in the U.S. particularly, alprazolam (Xanax) and zolpidem (Ambien), while lorazepam (Ativan) is still the most commonly prescribed drug for anxiety. The availability of benzodiazepines on the internet has increased their use as 'self-medication' in the general public who are often unaware of their adverse effects and dependence potential. This availability has also added to benzodiazepine use in multidrug abusers.

Many doctors have little knowledge of, or expertise in, the management of benzodiazepine withdrawal in long-term users, and skilled psychological support is hard to obtain due to a shortage of clinical psychologists. Good advice on withdrawal is available for doctors in the UK (for example from Clinical Knowledge Summaries or the British Medical Formulary) and in the US from the Maine Benzodiazepine Study Group (MBSG) but few make use of this information. Detoxification centres which also deal with alcohol and illegal drugs are not appropriate for prescribed benzodiazepine users. Such clinics tend to withdraw patients too rapidly, apply rigid rules and 'contract' methods, and provide inadequate support or follow-up. There are no longer any dedicated hospital withdrawal clinics in the U.K. although there are a few NHS-supported charities and support groups devoted to benzodiazepine problems (see contacts list below).

Clinical research on optimal benzodiazepine withdrawal methods is limited. The results from meta-analyses of clinical trials are difficult to interpret because different trials use different rates of withdrawal, different methods of psychological support, often use different adjuvant drugs, many of which have not been tested in controlled studies of withdrawal, and allow only for short-term follow-up. There are no studies examining long-term effects of benzodiazepines such as protracted symptoms or possibly permanent effects. The question of whether benzodiazepines can cause permanent damage to the brain or other systems, as many ex-users claim, remains unanswered by science. Basic research into the molecular mechanisms underlying tolerance, withdrawal symptoms and anxiety, and on the interactions of benzodiazepines with various neurotransmitter systems, has yielded some interesting results but these are not readily translated into clinical practice, although they may lead to future clinical advances.

The advice given to prescribed benzodiazepine users (and their doctors) in the 'Ashton Manual' remains relevant today and requires little updating. This supplement adds further information in response to questions that have frequently been asked by benzodiazepine users during and after withdrawal. Such questions are difficult to answer because, like most benzodiazepine problems, they depend on many individual factors. Such factors

include personality and genetic make-up, reasons for benzodiazepine prescription, dose, duration and type of benzodiazepine use, present symptoms, environmental stresses and others. Individuals seeking answers from the general information provided in this supplement need to work out which factors apply to them personally.

The questions I have most frequently been asked about benzodiazepines are:

1. Does long-term benzodiazepine use cause permanent brain damage?

2. Why do apparent recurrences of benzodiazepine withdrawal symptoms occur, (often a long time after) successful withdrawal?

3. Should benzodiazepine treatment be reinstated if withdrawal symptoms persist after withdrawal?

I have attempted to answer these, and some related, questions in this supplement to the Manual.

Permanent brain damage?

Structural damage. Many long-term benzodiazepine users who have stopped taking the drugs complain of a variety of seemingly irreversible psychological and/or physical symptoms which they attribute to permanent brain damage caused by the drugs. However, the question of whether benzodiazepines cause brain damage is still unsolved. In 1982 Professor Malcolm Lader and colleagues reported the results of a small study using CAT (computerised axial tomography) brain scans in 14 long-term benzodiazepines users compared with control subjects. Two of the benzodiazepine users had definite cortical brain atrophy and there was a borderline abnormality in five others; the rest were normal. In a 1984 study by Professor Lader involving 20 patients, the results were again suggestive but there was no relationship between CAT scan appearances and the duration of benzodiazepine therapy. The study concluded "The clinical significance of the findings is unclear." Subsequent CAT scan studies in 1987, 1993, and 2000 failed to find any consistent abnormalities in long-term benzodiazepine users, and concluded that benzodiazepines do not cause structural brain damage, e.g death of neurones, brain shrinkage or atrophy etc. A later more accurate development in brain scanning, MRI (magnetic resonance imaging), does not appear to have been systematically studied in benzodiazepine users. However MRI, like CAT, only shows structural changes and it is unlikely that the use of this technique would clarify the picture; many still symptomatic long-term ex-benzodiazepine users have had normal MRIs.

Functional damage. It is more likely that any long-term brain changes caused by benzodiazepines are *functional* rather than *structural*. In order to show such changes it would be necessary to examine abnormalities of brain *activity* in long-term benzodiazepine users. Techniques for such studies are available: fMRI (functional MRI) measures regional blood flow; PET (positron emission tomography) and SPECT (single photon emission tomography) measure neurotransmitter and receptor activity; QEEG (quantitative electroencephalography) and MEG (magnetoencephalography) measure regional electrical activity. None of these techniques has been utilised in controlled studies of long-term benzodiazepine users. Cognitive performance could indicate impairments in certain brain areas, but no studies have extended for more than six months. Finally *post-mortem* studies could show abnormalities in brain receptors, and animal studies could show changes in neuronal gene expression. None of these studies has been undertaken. Nor have there been any studies examining abnormalities in other tissues or organs in long-term benzodiazepine users.

A controlled study of long-term benzodiazepine users using brain function techniques would have to be carefully designed and would involve a large number of age and sex matched subjects, probably over 100 in both control and user groups. In the benzodiazepine group it would have to take into account dose, type of benzodiazepine, duration of use, psychiatric history, symptoms, use of alcohol and other drugs, and a number of other factors. Such a study would be expensive and funding would be difficult to obtain. Drug companies would be unlikely to offer support, and to date 'independent' bodies such as the Medical Research Council, the Wellcome Foundation and the

Department of Health have shown little interest. Thus the question of whether benzodiazepines cause brain or other organ damage remains unanswered.

Long-term effects of benzodiazepines

One mechanism which might be involved in long-term (and possibly permanent) effects of benzodiazepines is an alteration in the activity of benzodiazepine receptors in brain GABA neurones. These receptors down-regulate (become fewer) as tolerance to benzodiazepines develop with chronic use. Such down-regulation is a homeostatic response of the body to the constant presence of the drugs. Since benzodiazepines themselves enhance the actions of GABA, extra benzodiazepine receptors are no longer needed, so many are, in effect, discarded. These down-regulated receptors are absorbed into neurones where, over time, they undergo various changes including alterations in gene expression. When these receptors are slowly reinstated after drug withdrawal, they may return in a slightly altered form. They may not be quite so efficient as before in increasing the actions of GABA, the natural 'calming' neurotransmitter. As a result, the brain may be generally less sensitive to GABA and the individual is left with heightened central nervous system excitability and increased sensitivity to stress. Molecular biologists point out that changes in gene expression can be very slow, or even unable, to reverse. (The action of benzodiazepines at GABA receptors is explained more fully in the Manual).

Some people appear to be naturally more prone to anxiety than others. Brain imaging and pharmacological studies have shown that there is a decreased density (decreased numbers) and subsensitivity of brain GABA/benzodiazepine receptors in patients with generalised anxiety disorder and panic disorder and in patients with tinnitus, even if they have never been treated with benzodiazepines. Perhaps these individuals with genetically fewer GABA/benzodiazepine receptors are those more likely to experience long-term effects of benzodiazepines, protracted symptoms after withdrawal, and apparent recurrence of withdrawal symptoms.

Symptoms of a chronic hyperactive nervous system persisting after withdrawal are listed in the Manual Chapter 3, Table 3.

Benzodiazepine receptors: is there a natural benzodiazepine?

Readers may well ask: Why do we have specific benzodiazepine receptors in our brain? They have clearly not evolved over thousands and millions of years just to sit there and wait until Valium arrived! Most drugs that affect the brain act on receptors that are already there, and all of these drugs have subsequently been found to take the place of natural substances synthesised within the body. For example, the receptors for morphine react with natural endogenous endorphins and enkephalins, the physiological pain-killers; the receptors for cannabis are normally stimulated by natural substances called anandamides (named after the Sanskrit word ananda, which means "bliss"); nicotine in tobacco reacts with nicotine receptors for the natural neurotransmitter acetylcholine; all the psychotropic drugs like antidepressants and antipsychotics affect the receptor for natural neurotransmitters such as serotonin, noradrenaline and dopamine. The conclusion from such discoveries is that there must exist a natural benzodiazepine which normally modulates the activity of GABA at GABA/benzodiazepine receptors, like diazepam, and acts as an inborn, calming, sleep-inducing and anticonvulsant agent.

A search for the elusive natural benzodiazepine has been going on for about twenty years. Natural benzodiazepines have been found in plants, including potatoes, wheat, corn, rice, valerian and poppy and have also been demonstrated in animal tissues. Diazepam and its metabolite nordiazepam have been found in human blood and brain but these could have been derived from dietary sources. However, some substances which are not chemically related to benzodiazepine drugs but combine with GABA/benzodiazepine receptors have been found in the brain and other tissues of a variety of animals including rats, cattle, frogs, fish and humans and in isolated rat brain slices. These agents, which are small polypeptides, have been termed *endozepines* and are thought to be the body's natural benzodiazepines. They have a number of actions, among which is the ability to react specifically with the benzodiazepine site of the GABA-A receptor and to modulate GABA neurotransmission in the brain. Endozepines probably interact also with other types of GABA receptors which are distributed all over the body and have many functions.

There is still much to discover about endozepines. Some inhibit diazepam binding and may therefore be anxiogenic while others appear to act like diazepam and enhance GABA activity (as explained in the Manual, Chapter 1). It seems likely that the balance between different endozepines acting at the GABA-A receptor may determine an individual's susceptibility to anxiety and response to benzodiazepine drugs by acting as 'fine-tuners' of GABA-A function.

The role of endozepines is still controversial but in my opinion natural benzodiazepines certainly exist, and they may already have been tracked down. Their presence adds to the complexity and sophistication of the brain. We know so little about what goes on in the brain, which makes it difficult to give advice on individual benzodiazepine problems.

Recurrence of symptoms after successful withdrawal

It is not unusual to experience recurrence of apparent benzodiazepine withdrawal symptoms years after a successful withdrawal and a return to normal health. The particular pattern of symptoms is unique to the individual, depending on his physical and psychological makeup, and no doubt on the innate density of his/her benzodiazepine receptors and the balance of his endozepines (see above). The experience of benzodiazepine withdrawal is deeply etched into the mind and memory of those who have been through it, and is actually physically present in the strength and connections of their neural synapses, as all memories are. These recurrent symptoms are all signs of GABA underactivity with its accompanying increased output of excitatory neurotransmitters, resulting in a hyperactive, hypersensitive central nervous system. The mechanism is exactly the same as that of benzodiazepine withdrawal, which is why the symptoms are the same.

In nearly every case of apparent recurrence, the precipitating cause for the return of symptoms turns out, on close inspection, to be an increase in environmental stress. The trigger may be a new stress or worry which may be unrecognised so that the return of symptoms seems to occur out of the blue. Contributing factors can be an infection, surgery, dental problems, work problems, fatigue, bereavement, family problems, loss of sleep, adverse reaction to a drug, change of environment - almost anything. It may also be that with increasing age and long-term worries, the brain simply gets less efficient at coping with stress. In addition, there may still be some lingering old disturbing worries/thoughts/memories that have been buried in the unconscious mind but are resurfacing now because the brain has not been able to deal with them adequately in the past. For those who have experienced a traumatic benzodiazepine withdrawal, an element of post-traumatic-stress disorder (PTSD) may be involved. This is a recurrent condition that can be triggered by small reminders of the past trauma. It is as if any new stress pushes the individual over the limits of his stress-coping abilities. As discussed above, some people who have been on long-term benzodiazepine treatment have a lowered tolerance to stress, even after they have stopped taking the drug, and are therefore more vulnerable to new or recurrent stresses.

It is not clear why many people report experiencing adverse effects from new drugs or drugs they have tolerated before taking benzodiazepines. The drugs involved are so disparate - from skin ointments to eye drops to local anaesthetics to antidepressants, steroids and many others - that it is difficult to attribute these reactions to metabolic effects, allergies or other known effects. Presumably the general hypersensitivity of the nervous system magnifies the reaction to any foreign substances, but no clear explanation has yet emerged. An exception is quinolone antibiotics which displace benzodiazepines from their binding sites and should not be taken by patients on, or recently on, benzodiazepines.

Reinstatement, updosing

A dilemma faced by some people in the process of benzodiazepine withdrawal, or after withdrawal, is what to do if they have intolerable symptoms which do not lessen after many weeks. If they are still taking benzodiazepines, should they increase the dose? If they have already withdrawn, should they reinstate benzodiazepines and start the withdrawal process again? This is a difficult situation which, like all benzodiazepine problems, depends to some degree on the circumstances and the individual, and there are

no hard and fast rules.

Reinstatement after withdrawal? Many benzodiazepine users who find themselves in this position have withdrawn too quickly; some have undergone 'cold turkey'. They think that if they go back on benzodiazepines and start over again on a slower schedule they will be more successful. Unfortunately, things are not so simple. For reasons that are not clear, (but perhaps because the original experience of withdrawal has already sensitised the nervous system and heightened the level of anxiety) the original benzodiazepine dose often does not work the second time round. Some may find that only a higher dose partially alleviates their symptoms, and then they still have to go through a long withdrawal process again, which again may not be symptom-free.

Updosing during withdrawal? Some people hit a "sticky patch" during the course of benzodiazepine withdrawal. In many cases, staying on the same dose for a longer period (not more than a few weeks) before resuming the withdrawal schedule allows them to overcome this obstacle. However, increasing the dose until a longed-for plateau of 'stability' arrives is not a good strategy. The truth is that one never 'stabilises' on a given dose of benzodiazepine. The dose may be stable but withdrawal symptoms are not. It is better to grit one's teeth and continue the withdrawal. True recovery cannot really start until the drug is out of the system.

Pharmacologically, neither reinstating nor updosing is really rational. If withdrawal symptoms are still present, it means that the GABA/benzodiazepine receptors have not fully recovered (see above). Further benzodiazepines cause further down-regulation, strengthen the dependence, prolong withdrawal, delay recovery and may lead to protracted symptoms. In general, the longer the person remains on benzodiazepines the more difficult it is to withdraw. On the whole, anyone who remained benzodiazepine-free, or has remained on the same dose, for a number of weeks or months would be ill-advised to start again or to increase dosage. It would be better to devote the brain to solving individual symptoms and to finding sources of advice and support. Advice about how to deal with individual symptoms is given in the Manual (Chapter 3).

Nutritional supplements (added April 12, 2012)

There is no evidence that nutritional supplements such as vitamins, minerals, amino acids etc. are helpful in benzodiazepine withdrawal. Excessive doses of some can be toxic and others may even contain benzo-like substances that have the same adverse effects as benzodiazepines themselves. Nor is there any evidence that suggests benzodiazepine withdrawal causes vitamin, mineral or other deficiencies. No-one should take supplements without clear evidence of a specific deficiency. Those who advocate multiple supplements should first show evidence of any deficiency and then conduct proper controlled trials. In particular, taking GABA precursors does not increase GABA concentrations in the brain. Benzodiazepines do not decrease GABA concentrations; instead they alter GABA-receptor affinity. This slowly reverses without the need for supplements and there is no evidence that supplements speed the process. People taking or withdrawing from benzodiazepines should eat a normal healthy diet - which, after all, consists of "natural" substances and contains all the ingredients necessary for the body.

Some products which people have tried and found to be at best useless, at worst harmful include: mineral and vitamin supplements, valerian, St. John's Wort, kava-kava, melatonin, Rescue Remedy, BeCalm'd, choline, Noni juice, 5htp, SAMe and GABA. Most recently someone reported adverse effects from a product called Exhilarin (see Terri's Story).

Metabolism of benzodiazepines (added November 21, 2013)

It has long been known that there is a wide variation between individuals in the rate at which they metabolise psychotropic drugs, including benzodiazepines, antidepressants and antipsychotics. People can be poor or slow metabolisers, normal metabolisers, or extensive metabolisers for these drugs, depending on the genetically determined activity of certain drug metabolising enzymes (CYP450 2D6 enzymes). In particular, there appear to be more poor and slow metabolisers among Asian patients than in European populations, according to an important US study. This means that Asian patients respond to lower doses and

experience more serious side-effects on standard doses of benzodiazepines than other ethnic groups.

These days when multi-ethnic populations, including many people of Asian extraction, exist world-wide, doctors and psychiatrists may need to be reminded that in Asian patients, benzodiazepine (and antidepressant or antipsychotic) prescriptions, if considered necessary, should be started at half the standard dose in case they are poor or slow metabolisers.

Conclusion

The advice and explanations given in the Supplement may seem inadequate. They no doubt illustrate how much more we still need to know about benzodiazepines. However, it is important to remember that by far the greatest majority of long-term benzodiazepine users do recover from withdrawal - given time. Even protracted symptoms tend to decrease gradually, sometimes over years. The individual needs to know that the actual drug withdrawal is only the first step towards recovery. It may be followed by a prolonged period of convalescence during which the damage caused to the person's body - and often to his whole life - needs to be repaired as far as possible. But the brain, like the rest of the body, has an enormous capacity for adapting and self-healing. That is how life survives and how ex-benzodiazepine 'addicts' can be optimistic about their future.

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She has for sale all the books published by benzodiazepine users

See also the Support & Contacts page.