

Toxicity, Cognitive Impairment, Long-Term Damage & The Post Withdrawal Syndrome

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Abstract

There is a great deal of misinformation, mythology and ignorance surrounding the benzodiazepines, their uses and problems. The attitude of denial by many has a severe impact on patients trying to get help from doctors, treatment for dependency, DLA and other benefits, and help for legal actions.

This paper is an attempt to bring together apparently diverse aspects in a format that hopefully will be informative and a source of further information for those seeking help and compensation for the destruction of their lives.

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1. Introduction

Any drug acting upon the central nervous system (CNS) whether it is an analgesic, stimulant or depressant has a potential for causing toxic side effects, cognitive impairment, neurological disorders and dependence.

The benzodiazepines are depressants of the CNS and have five major therapeutic actions, anxiolytic, hypnotic, muscle relaxant, antiepileptic and amnesic i.e. they are very non-specific drugs. Recipients of these drugs will be subject to all of these actions, whether required or not, and to adverse reactions associated with each therapeutic action. Over 500 different adverse reactions to the benzodiazepines have been reported to the MCA (UK) and the FDA (USA) and not surprisingly many are directly linked with the therapeutic actions e.g. rebound anxiety, rebound insomnia, musculoskeletal problems, epileptic fits and severe memory problems. Because of the wide range of therapeutic actions, and the fat-soluble nature of the benzodiazepines few parts of the body and brain are exempt from adverse reactions. Some patients have dozens of these adverse reactions occurring at the same time or over a given period. No wonder many are mis-diagnosed as having schizophrenia, dementia, chronic fatigue syndrome, or muscular dystrophy. It seems that they will enhance any psychological or physical problem existing prior to ingestion of these drugs, in addition to the many new problems they create.

2. Elimination Half-life and Accumulation

Accumulation of the benzodiazepines in the body and brain is a severe problem with long-term use of many of the benzodiazepines e.g. diazepam, chlordiazepam, chlordiazepoxide, flunitrazepam and flurazepam. This is a result of long elimination half-lives of up to 250 hours and of the formation of active metabolites giving levels for diazepam about six times the daily dose in two weeks and eight times in four weeks. For a given drug the half-life can vary by up to a factor of three between individuals. Metabolic changes in the elderly with kidney or liver problems cause much slower elimination rates e.g. for diazepam half-lives of 400 hours have been measured leading to very high accumulation levels (x20). The benzodiazepines without active metabolites can also produce significant accumulation levels e.g. nitrazepam and lorazepam with half-lives of 18 to 57 hours and 12 to 34 hours respectively producing levels of about 4 and 3 times the daily dose respectively with an ingestion period of one week.

A severe consequence of the accumulation and toxicity of benzodiazepines is the effect on babies born to mothers who have ingested these drugs. They readily cross the placenta and allowing for the measured levels in the umbilical cord, the increased bioavailability, and the weight of the foetus, the level of exposure per unit weight of the foetus is many hundred times that of the daily dose level of the mother. It is not surprising that many babies are born addicted to these drugs, suffering from floppy infant syndrome and other problems. There is sufficient evidence to postulate a causal link between benzodiazepines (and some other drugs) and the Sudden Infant Death Syndrome although the authorities are very quick and keen to deny such a possibility.

3. Individual Variability and Dependence

There is a wide variability in the patterns of response to benzodiazepines among individuals, in both therapeutic and adverse reactions, both wanted and unwanted. Individual variability is determined largely by genetic programming of drug metabolism and responsiveness. A clear-cut example of these phenomena is the 30-fold variation in plasma concentration in patients given the same oral dose of diazepam. This variability is dependent on both genetic and environmental factors such as race, sex, age, smoking, disease and concomitant drug treatment. Wide inter-individual response to these drugs was frequently recorded in research studies and clinical trials in the 1960s, but has seldom been commented upon in recent decades.

There is one area where this variability has a strong impact i.e. the probability of an individual becoming dependent on these drugs. It can readily explain why some become dependent in a few weeks (shortest recorded case - seven days) and others on similar doses may take more than a year or more. This pattern is no different than that for dependence to other drugs acting on the CNS, but the speed of onset for benzodiazepines appears to be quicker than most, especially alcohol (5 mg diazepam = 2 units of alcohol).

In essence, chronic dependence is the repeated taking of the drug to alleviate the adverse reactions caused by that drug. In everyday terms it is taking "the hair of the dog that bit you". Those who are more sensitive to unwanted adverse reactions will become more quickly dependent on these drugs especially if the link between the drug and adverse reaction is not recognised by the patient and the doctor (as happens very frequently). There are ["101" reasons](#) why individuals start taking drugs and continue to take them prior to chronic addiction, but only one to explain how dependence occurs with drugs having widely different and

sometimes opposite therapeutic actions. *In other words - pharmaceutical actions cause adverse reactions - therapeutic actions alleviate adverse reactions.*

Resort to half baked ideas like personality traits and characteristics is not necessary or appropriate. Such an explanation will be less than satisfying to the members of the medical profession and the drugs industry whose thinking is rooted in the 19th century, and revolves around mental and moral issues. It is however far more acceptable to the 13,000 BMA members dependent on alcohol, prescribed drugs and hard drugs (BMA conference, Birmingham 1998).

4. Toxicity

The toxicity of drugs can be related to total dosage i.e. the larger the dose the greater the toxic effects e.g. overdose and death. Most drugs can produce toxic reactions in the normal or therapeutic range, especially those that accumulate in the body with repeated doses. Toxic effects due to overdose are generally a harmful extension of the drugs normal pharmacological reaction and are largely predictable and preventable. Toxic reactions that occur with normal doses are often unrelated to known pharmacology and are responsible for most of the adverse reactions reported for the benzodiazepines.

Toxicity resulting from a drug may be divided into four types (Spilker B., 1992):

Type 1. Toxicity results from an excess of an undesired pharmacological effect. Many of the benzodiazepines adverse reactions are in this category because in general they are presented for only one of the main therapeutic actions e.g. if diazepam is prescribed as a muscle relaxant then the dependence, withdrawal, memory problems, fits, anxiety, etc. are of this type.

Type 2. Toxicity results from an excess of a desired beneficial pharmacological effect for which the drug is used e.g. hangover effect for hypnotics.

Type 3. Toxicity results from effects not observed at therapeutic doses. These are generally predictable and observed in overdose e.g. coma. The safety index of a drug is defined as the ratio between the minimum toxic dose and the maximum effective dose, the larger the ratio the greater the safety. The barbiturates generally have a higher value than the benzodiazepines (but not as high as the blown up estimates of the drug industry) but the individual variability of the benzodiazepines has caused deaths at a few times the therapeutic dose.

Type 4. Toxicity is unexpected (paradoxical reactions). These are idiosyncratic events and often may be the opposite of the intended and anticipated response. For some drugs these occur at low rates but for the benzodiazepines they occur relatively frequently e.g. rebound anxiety, rebound insomnia, muscular tension, aggression and hostility. These occur so frequently that they can no longer be described as unexpected.

Adverse Reactions and Events

Adverse reactions include any undesirable effects that occur e.g.

- i. Physical symptoms
- ii. Psychological symptoms
- iii. Physical signs
- iv. Laboratory values from tests and biological samples

- v. Laboratory values from tests on the patient's EEG etc.
- vi. Other factors relating directly to deterioration of the quality of life and social interactions

The frequency of toxic adverse reactions is not given in data sheets or literature in the UK. Their frequencies are given in some international data sheets e.g. the Spanish data sheets (data supplied by the drug companies) give a wide range of adverse reactions for many benzodiazepines. These reactions include:

- Greater than 25%: drowsiness, confusion and ataxia.
- From 10 - 25%: sedation, depression, disorientation, dysphagia, dysarthria, poor concentration, trembling, changes in libido, incontinence, nausea, vomiting, diarrhoea and hyper salivation.
- From 1 - 9%: hepatitis, dermatitis, urticaria, puritis, leucopenia, anterograde amnesia, paradoxical excitation, changes in vision, diplopia, nystagmus, hearing changes and eosinophilia.
- Less than 1 %: respiratory depression, hypertension, hypotension, bradycardia, tachycardia and palpitations.

5. Toxic Poisoning

It is interesting to note that the most frequently reported adverse reactions in Canada (about 50% of adverse reactions for single benzodiazepine ingestion) is encephalopathy i.e. organic brain disease. One of the manifestations of this illness is toxic psychosis or toxico mania which the World Health Organisation has defined as a chronic state of intoxication produced by repeated consumption of a drug harmful to the individual or to society.

The characteristics are:

- a. Uncontrollable desire or necessity to continue consuming the drug and try to get it by all means.
- b. Tendency to increase the dose.
- c. Physical and psychic dependence as a result.

Many long-term therapeutic addicts will readily identify with toxico mania, especially those addicted to long half-life benzodiazepines. This aspect of the benzodiazepine problem which put simply is toxic poisoning produces an altered state of consciousness with an altered state of perception of self, others and one's environment and relationships* In many ways this syndrome is similar to that produced by chemical poisoning e.g. organo-phosphates. The lack of self-awareness can take many years to change, often requiring much information, knowledge and counselling to achieve it. **nb after discontinuation of drugs many have an enduring personality change.*

6. Medical Literature

The medical literature contains thousands of papers on toxic effects and resulting adverse reactions and effects. Listed below are some of the topics in the VOT archives with the number of papers in brackets:

1. Dependence and withdrawal (500)
2. Adverse reactions, side-effects and paradoxical reactions (220)
3. Cognitive impairment, memory and brain problems (140)
4. Pregnancy, neonates, infants (120)

5. Toxicity, poisoning, suicides, deaths (100)
6. Driving problems, accidents, injuries (80)
7. Elderly (60)

Many of these papers were published in the 1960s and 1970s and they contain most of the information on benzodiazepine problems that has only recently been accepted and included in data sheets and patient information leaflets. Some problems are still not included. On the other hand most information was published in overseas adverts, journals and data sheets.

Sections A and B contain a selection of extracts from representative and key papers on cognitive impairment, long-term damage and the post withdrawal syndrome.

Section A

Cognitive Impairment and Long-Term Damage

The many papers published in the 1960s and early to mid 1970s on this subject were largely single dose therapeutic dose studies or low-dose studies for periods of a few weeks. They showed a range of deficits in cognitive function, psychomotor performance and short-term memory problems with no development of tolerance. It was not until the late 1970s and early 1980s (when therapeutic dose dependency was belatedly accepted), that cognitive function and other tests on long-term benzodiazepine users (up to 10 years) were studied both during use and in acute withdrawals. From the mid 1980s to mid 1990s there was an increasing number of studies looking at damage after long-term use and at follow-up periods after discontinuation of up to six years. Several of these studies involve CT scans of the brain looking for structural changes.

Summary

1. Benzodiazepines produce impairment of cognitive functioning and psychomotor performance e.g. reaction time, vigilance, arousal, judgement, reasoning, speed and accuracy of information processing, visual spatial ability, co-ordination, short-term and post drug long-term memory, 'blackouts' and learned tasks.
2. These effects are independent of abuse, dependency, non-dependency, normal, healthy, young or old subjects. Impairment increases with chronic use. Development of tolerance to these effects is very slow.
3. CT brain scans show a difference in ventricular cerebral spinal fluid space dimensions between benzodiazepine users and non-users, and also between high and low benzodiazepine users.
4. The functional brain damage causes increased morbidity, increased mortality and social deterioration.
5. Subjects are generally not aware of their reduced capacity or the fact that they are not functioning well in every day life.
6. In general much of the impairment is slowly reversible. Some aspects show improvement after six years, some are semi-permanent or permanent.

Key papers: 1, 4, 10,12, 17, 20, 21, 24, 25, 28, 29, 37, 38, 40.

Benzodiazepines - Section A

Cognitive Impairment/Long-Term Damage

References and extracts

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2. Kleinknecht R. (1975) Review of Effects of Diazepam on Cognitive and Psychomotor Performance. J. Nerv. Mental Dis. 161, 399-411. 23 studies (1970-75) Mainly young healthy volunteers after a few days ingestion showed impairment in 6 areas of cognitive function.
3. Liljequist R. et al. 1978 Effects of Diazepam and Chlorpromazine on Memory Functions in Man. Europe J. Clin. Pharmacol. 13, 339-343. Single doses, 2 weeks treatment. Impairment of acquisition, reaction time, co-ordination and memory. Impaired transfer from short to long term memory.
4. Grant I. (1978) Organic Impairment in Poly Drug Users, Risk Factors. Amer. J. Psychiatry, 135, 2, 178-184. Extensive use (up to 10 years) of CNS depressants (incl. Benzodiazepines) causes neuropsychological impairment detectable 3 months after cessation of drug taking and may be long lasting.
5. Lucki I. et al. (1980) Chronic use of Benzodiazepines and Psychomotor and Cognitive Test Performance. Psychopharmacology, 88, 426-433. Behavioural and cognitive tests on chronic users (5yrs) gave results that are similar or worse than a control group with diagnosed anxiety disorders (no pills). [*So much for the effectiveness of benzodiazepines - RFP*]
6. Hendler N. et al. (1980) Comparison of Cognitive Impairment due to Benzodiazepines and Narcotics. Amer. J. Psychiatry, 137, 828-830. Cognitive impairment due to benzodiazepines is marked, no effect due to narcotics at clinical doses.
7. Bergman H. et al. (1980) Neuropsychological Impairment and Exclusive Abuse of Sedatives or Hypnotics. Amer. J. Psychiatry, 137, 2, 215-17. Chronic use for 5 to 10 or more years. Tests 3 to 10 months after withdrawal showed significant decrease in neuropsychological performance and intellectual impairment compared with a control group.
8. Scharf M. (1982) Lorazepam, Efficacy, Side Effects and Rebound Phenomena. Clin. Pharmacol. Ther., 31, 2, 175-179. Lorazepam (4mg) used in 18-night sleep study with insomniacs. Rebound insomnia, rebound anxiety, severe hangover and impaired functioning, including anterograde amnesia.
9. Petursson H. et al. (1983) Psychometric Performance during Withdrawal from Long-Term Benzodiazepine Treatment. Psychopharmacology, 81, 345-349. Chronic use of benzodiazepines results in selective and chronic psychological deficits including fine motor control and co-ordination. Rebound effects measured during withdrawal. Likelihood of cerebellar damage.
10. Block R.I. et al. (1984) Alprazolam and Lorazepam Effects on Memory Acquisition and Retrieval Processes. Pharmacol. Biochem. and Behaviour, 20, 233-241. Both benzodiazepines produced marked memory impairment of acquisition and retrieval for long term memory (pre drug). [*This study supports the anecdotal reports of hundreds who claim that their retrograde memory was impaired for many years after stopping the benzodiazepines - RFP*]
11. Romney D.M. et al. (1984) A Brief Review of the Effects of Diazepam on Memory. Psychopharmacol. Bull., 20, 313-315. Review of about 30

papers. Supports memory loss is due to a consolidation process of impairment i.e. short- to long-term memory transfer. Queries use of psychotherapy whilst patient is on diazepam.

12. [Lader M.](#) et al. (1984) Computerised Axial Brain Tomography in Long-Term Benzodiazepine Users. *Psychological Med.*, 14, 203-206. Benzodiazepine users have larger ventricular brain ratio than control group.
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14. Mac D.S. et al. (1985) Anterograde Amnesia with Oral Lorazepam. *J. Clin. Psychiatry*, 46,137-138. Young healthy volunteers, 2mg Lorazepam, single dose. Deleterious effect on short-term recall of verbal information.
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16. Pomara M. et al. (1985) Increased Sensitivity of the Elderly to the Central Depressant Effects of Diazepam. *J. Clin. Psychiatry*, 46, 5,185-187. Groups of old and young healthy volunteers. Single 2.5 mg dose. Impaired immediate and delayed recall memory and psychomotor performance for elderly is much greater than for the young.
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19. Brosan L. et al. (1986) Performance Effects of Diazepam During and After Prolonged Administration. *Psycholog. Med.*, 16, 561-571. Repeated doses for 3 weeks. Reduced performance while on drug and for 3 weeks afterwards e.g. reduced reaction time and reasoning.
20. Borg S. (1986) Dependence and other Long-Term Effects Associated with Benzodiazepines. *Lakartidningen*, 83; 321-326. Withdrawal symptoms occur after 1-2 weeks of benzodiazepine ingestion, 15% become dependent with short term use (weeks). Benzodiazepines cause functional brain damage similar to that seen with alcohol abuse. Increased mortality and marked social deterioration. Whether brain damage is permanent requires further research.
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22. Smiley A. (1987) Effects of Minor Tranquillisers and Antidepressants on Psychomotor Performance. *J. Clin. Psychiatry*, 48, Suppl.12, 22-28. Review of studies of the effects of benzodiazepines on tracking, reaction time, vigilance and divided attention. Diazepam clearly impairs

performance for several hours after dosing. No evidence of tolerance for up to 3 weeks. Effects are the same for groups of anxious and normal subjects.

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25. [Lader M.](#) (1987) Long-Term Benzodiazepine Use and Psychological Functioning. *The Benzodiazepines in Current Clinical Practice*. *Roy. Soc. Med.*, 1987, 55-59. Patients perform poorly on tasks involving visual spatial ability and sustained attention. They are not aware of their reduced ability. Only after they have withdrawn do they realise that they have been functioning below par.
26. Larson E. et al. (1987) Adverse Drug Reaction Associated with Global Cognitive Impairment in Elderly Persons. *Ann. of Inst. Med.*, 107, 169-173. Patients on long-term/long half-life benzodiazepines diagnosed with dementia. After discontinuation 30% re-diagnosed i.e. no dementia after 1 year follow up.
27. Lavender S. (1988) Psychophysiology and Anxiety: Current Issues and Trends. *Pharmacological Treatment of Anxiety*,145-51. Benzodiazepine induced neurophysiological impairment, in worst cases permanent.
28. Golombok S. et al. (1988) 'Impairment in Long Term Benzodiazepine Users' *Psychological Med.*,18, 365-374 Patients on benzodiazepines not functioning well in everyday life and not aware of reduced ability. Recognition of below par functioning after withdrawal. Cognitive impairment greater with chronic medication.
29. Bergman H. et al. (1989) Dependence on Sedative Hypnotics, Neuro-Psychological Impairment, Field Dependence and Clinical Course in a 5 yr Follow Up Study. *Br. J. Addiction*, 84, 547-553. Cerebral disorders present 4-6 years after drug discontinuation - permanent? CT scans show dilation of ventricular system in brain.
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31. Penetar D.M. et al. (1989) Triazolam Impairs Learning and Fails to Improve Sleep in a Long-Range Aerial Deployment. *Aviation, Space and Envir. Med.*, June, 594-597. Ability to recall recent verbal information impaired 8 hrs after ingestion of triazolam.
32. Curran H.V. (1991) Benzodiazepines, Memory and Mood: A Review. *Psychopharmacol.*, 105,1-8. Effect of benzodiazepines on anxiety, cognitive function and arousal. Detailed discussion on memory processes affected by benzodiazepines. Slow tolerance to memory impairment, i.e. tolerance not fully developed.
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35. Bowen J.D. (1993) Drug Induced Cognitive Impairment. *Drugs and Ageing* 3 (4), 349-357. Benzodiazepines have a high risk of cognitive impairment. A common cause of delirious and a confounding factor in dementia.
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37. Moodley P. et al. (1993) Computed Axial Brain Tomograms in Long Term Benzodiazepine Users. *Psychiatric Research*, 48,135-144. Differences in the density of some areas of the brain between benzodiazepine and non-benzodiazepine users.
38. Tata P.R. et al. (1994) Lack of Cognitive Recovery Following Withdrawal from Long-Term Benzodiazepine Use. *Psycholog. Med.*, 24, 202-213. Modest recovery of cognitive deficits after 6 months cessation of benzodiazepines compared with pre and post withdrawal and a follow up.
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40. Patten S.B. et al. (1994) Neuropsychiatric Adverse Drug Reactions. From Canadian Adverse Data Base (65-94) *Intl. J. Psychiatry in Med.*, 24 (24), 45- 62. Over half of all reports (for single benzodiazepines) were for encephalopathy (organic brain disorder).
41. Tonne U. et al. (1995) Neuropsychological Changes During Steady State Drug Use. *Acta Psychiatr. Scand.*, 91, 299-304. Neuropsychological deficits only partly reversible on discontinuation at 1 yr follow up.
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Section B

Long-Term Damage and The Post Withdrawal Syndrome (PWS)

The existence of the post withdrawal syndrome is recognised and accepted for other drugs like the barbiturates, opiates and alcohol. (See references 3, 20, 26). Its occurrence is routine enough for it seldom to be commented upon. Although many alcoholics and hard drug addicts receive primary treatment for four to ten weeks, a minority need and receive residential treatment and rehabilitation for up to 12 months. It would be appropriate if similar opportunities were available to benzodiazepine therapeutic addicts. There is a desperate need for them.

Just as there was (and is) a strong resistance from the medical profession and the drug companies to recognising and accepting therapeutic dose dependence there was (and is) a similar reaction to the benzodiazepine post withdrawal syndrome. There is a strong knee-jerk reaction geared to diverting the blame from the drugs and prescribing practices onto the patients. A range of speculative reasons is offered e.g. the symptoms are a return of the original complaint, latent mental problems exposed by the drugs and the old chestnut, personality disorders.

Contrary to these myths are the following:

- i. Few if any studies have actually checked the original records for prescribing diagnosis, most information is anecdotal. The best evidence there is suggest that at least 85% of prescriptions are given for non psychiatric disorders.
- ii. There is no evidence that personality traits or characteristics predispose anyone to dependence (Royal College of Psychiatrists, 1987). The few before, during and after dependency studies show no correlation.
- iii. All aspects of drug dependency can be fully explained by biochemical factors (World Health Organisation 1993).
- iv. The claim that drugs expose latent problems is unprovable, unsustainable and unscientific. What is provable is that psychoactive drugs cause psychiatric disorders and marked changes in personality.

From the mid-1980s to the mid-1990s there was an increasing number of papers studying this syndrome up to five years after discontinuation of drug taking. These studies were sometimes in parallel with investigations of the nature of long-term damage and conclude that it is an iatrogenic condition. In addition, there is a significant overlap between the syndrome, acute withdrawals and long-term ingestion of benzodiazepines, clearly establishing a link between the post withdrawal syndrome and adverse reactions caused by these drugs.

Summary

1. There is a very wide range of physical and psychological symptoms for example: paranoia, delusions, shaking and trembling, paraesthesiae, depression, behavioural disorders, unstable mood, headache, irritability, insomnia, anxiety, malaise, poor concentration, gastrointestinal problems, abdominal discomfort, depersonalisation, derealisation, emotional instability, sensory disturbances, perceptual changes, auditory changes, tinnitus, vulnerability to stress, unsteadiness, neck tension, neuro-muscular problems, "bursting head", phobias, panic, obsessive features and palpitations.
2. The post withdrawal syndrome is largely responsible for relapse - from 30 to 70% in different studies, up to five years after discontinuation.
3. The studies have established that the PWS is:
 - Linked with biological abnormalities - up to 3.5 years
 - Is reversed for short periods by flumazenil, an antagonist, up to five years.
 - Associated with a non-reversal of tolerance up to 3.5 years.
 - Linked with permanent changes to the central nervous system.
4. Patients with a history of benzodiazepine dependence are unlikely to respond normally to these drugs after discontinuation.
5. There is a 1:1 correspondence between long-term damage and the post withdrawal syndrome.
6. Careful management of the PWS is required and should include help from doctors, family, friends, support groups, stress management, cognitive behavioural therapy, knowledge and information - to help the patient come to term with the patients changed life situation.
7. At least 30% of benzodiazepine dependent patients experience the PWS rising to nearly 100% for long-term chronically dependent patients.

Key papers: 4, 5, 6, 7, 10, 18, 24, 25, 27, 28.

Little has changed

"Physicians pour drugs of which they know little to cure diseases of which they know less, into humans of whom they know nothing." Voltaire (1694-1778)

References and extracts

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4. [Ashton H.](#) (1986) [Adverse Effects of Prolonged Benzodiazepine Use](#). *Adverse Drug Reaction Bull.*,118, 440-443. Acute withdrawal is followed by a prolonged period (many months) of gradually diminishing, mixed psychological and somatic symptoms. The illness produced by the protracted syndrome may be more severe than that for which the benzodiazepines were originally prescribed.
5. [Ashton H.](#) (1987) [Benzodiazepine Withdrawal: Outcome in 50 Patients](#). *Br. J. Addiction*, 82, 665-71. Patients assessed from 10 - 42 months after withdrawal. 48% had slight symptoms, 22% had moderate symptoms, 16% had severe symptoms interfering with life, 6% were polysymptomatic and on other medication, 8% had relapsed on benzodiazepines.
6. Higgitt A. et al. (1988) *The Natural History of Tolerance to the Benzodiazepines*. *Psychological Med. Monograph Supple.*,13 Cambridge University Press. 'It is no longer debated that tolerance develops over periods of 6 months! Tolerance is still present in patients off benzodiazepines for 5 - 42 months. Low single dose challenge to patients precipitated withdrawal symptoms. It is unlikely that patients with a history of benzodiazepine dependence will respond normally to these drugs'. The presence of permanent changes to the CNS is indicated.
7. Marks J. (1988) Techniques of Benzodiazepine Withdrawal in Clinical Practice. *Med. Toxicology*, 3, 324-333. Post withdrawal syndrome of many months consists of a fluctuating malaise, poor concentration, abdominal discomfort, depersonalisation, derealisation and emotional lability. Management of the PWS requires various forms of help to come to terms with the patients' life situation, e.g. help from doctors, family friends, support groups and stress management.
8. Busto U. et al. (1988) [Protracted Tinnitus after Discontinuation of Long Term Therapeutic Use of Benzodiazepines](#). *J. Clin. Psychopharmacol.*, 8, 359-61. Sensory disturbances of long term duration are among the most distinctive clinical features of benzodiazepine withdrawal syndrome. Tinnitus present 1 year after discontinuation.
9. Montgomery S.A. et al. (1988) Benzodiazepines: Time To Withdraw. *Journal of the Royal College of General Practitioners* 1988; 38: 146-147. After withdrawal patients remain vulnerable to stress for at least 6 months.
10. Higgitt A. et al. (1990) The Prolonged Benzodiazepine Withdrawal Syndrome; Anxiety or Hysteria? *Acta. Psychiatr. Scan.*, 82,165-168. PWS is a genuine iatrogenic condition. 30% of dependent patients get it.

Tests point to biological abnormalities. Patients discontinued and tested after 5 to 42 months.

11. Roche Products Ltd. (ca.1990) [Benzodiazepines and your Patients: A Management Programme](#) (Sent to prescribers on request). The post withdrawal syndrome can manifest itself as fluctuating levels of malaise, lack of concentration, abdominal discomfort, depersonalisation and emotional lability. If post withdrawal symptoms occur good support from the general practitioner over at least the first year reduces the risk of relapse.
12. Holm M. (1990) One Year Follow up of Users in General Practice. Danish Med. Bull., 188-191. First time users more likely to discontinue in one year (55%) than long term users (12%).
13. Holton A. (1990) Five Year Outcome In Patients Withdrawn from Long Term Treatment with Diazepam. BMJ,1241-1242. High level of relapse (75%), taking benzodiazepines for insomnia, anxiety and stress.
14. [Ashton H.](#) (1991) [Protracted Withdrawal Symptoms](#). J. Substance Abuse Treatment, 8,19-28. Persistent symptoms may last for many months and are related to long-term benzodiazepine use. Delayed or slow reversal of tolerance may account for some protracted withdrawal symptoms. The possibility is that benzodiazepines produce slowly reversible functional changes in the CNS and cause structural neuronal damage.
15. [Lader M.](#) (1991) Benzodiazepine Problems. Br. J. Addiction, 86, 823-828. Persisting symptoms - unsteadiness, neck tension, 'bursting' head, perceptual distortion, muscle spasm, anxiety, phobias, panic, obsessive and depressive features.
16. Rickels et al. (1991) Long Term Benzodiazepine Users - 3 Years after Participation in a Discontinuation Program. Am. J. Psychiatry,148, 6., 757-761. Anxiety and/or depression in patients who had discontinued benzodiazepines for 3-5 years was less than that (but still significant) in patients who continued to take benzodiazepines [*benzodiazepines cause depression and anxiety - RFP*].
17. Tyrer P. (1991) The Benzodiazepine Post Withdrawal Syndrome. Stress med., 7,1-2. Feelings of tension, threat, bodily feelings, unsteadiness, shaking, palpitations, gastrointestinal symptoms, agoraphobia. There is a considerable overlap between symptoms of the post withdrawal syndrome and the acute withdrawal syndrome.
18. [Lader M.](#) (1992) Pilot Study of the Effects of Flumazenil on Symptoms Persisting after Benzodiazepine Withdrawal. J. Psychopharmacology, 6. 357- 363. Patients off benzodiazepines for 1 month to 5 years had persisting benzodiazepine withdrawal symptoms significantly lessened. Symptoms include clouded thinking, tiredness, muscular symptoms, neck tension, cramps, shaking, pins and needles, burning skin, pain and sensations of bodily distortion and mood disorder. The benefits lasted several hours to several days.
19. Higgitt A. et al. (1992) Withdrawal from Benzodiazepines and the Persistent Benzodiazepine Withdrawal Syndrome. In Granville Crossman (ed) Recent Advances in Clin. Psychiatry: No. 8, London, Churchill Livingstone,1992, 49-59. 30% of patients experiencing acute withdrawals continue with the persistent withdrawal syndrome. Cognitive processes linked to high risk of PWS. [*Impaired cognitive processes induced by benzodiazepine ingestion - RFP*].
20. Landry M.J. et al. (1992) Benzodiazepine Dependence and Withdrawal, Identification and Management. J. Amer. Board Fam. Pract., 5(2),167-75. A prolonged sub acute low dose benzodiazepine withdrawal syndrome can last for months or even years.

21. Edwards R. (1993) Benzodiazepines and Dependence. *Statens Offentliga Utredningar*, 5,135-140. Duration of withdrawal phenomena; recent figures of over 1 year have been proposed. It is well recognised that withdrawal syndromes from barbiturates, narcotics and other psychoactive drugs may also be similarly prolonged.
22. [Lader M.](#) (1994) Anxiety or Depression During Withdrawal of Hypnotic Treatments. *J. Psychosomatic Res.*,18, Suppl. 1,113-123. Hypnotic withdrawal. Persistent withdrawal syndrome dominated by anxiety (generalised, phobic or both), phobic behavioural disorder and panic attacks. Many of the litigants involved in the UK court case suffered from prolonged disabilities of this type.
23. Geller A. (1994) Management of Protracted Withdrawal. *Amer. Soc. of Addiction*, Ch.2,1-6. Persistent symptoms - impaired concentration, derealisation, depersonalisation, headaches, sleep disturbances, tension, irritability and lack of energy.
24. [Ashton H.](#) (1995) [Protracted Withdrawal from Benzodiazepines; The Post Withdrawal Syndrome](#). *Psychiatric Annals*, 25,174-179. A substantial minority of patients have a PWS including perceptual symptoms and gastrointestinal symptoms gradually receding, lasting at least one year and occasionally permanent.
25. [Ashton H.](#) (1995) [Toxicity and Adverse Consequences of Benzodiazepine Use](#). *Psychiatric Annals*, 25,158-165. Some symptoms decline more slowly merging into a period of increased vulnerability to stress lasting many months. Protracted symptoms include prolonged anxiety and depression, gastrointestinal disturbances, tinnitus, neuromuscular abnormalities and paraesthesiae.
26. Okada C. (1995) Treating the Patient with Benzodiazepine Addiction. *Hospital Update* Sept. 396-401. A small proportion of patients report significant withdrawal symptoms up to 3 years following withdrawal.
27. O'Brien C. P. et al.(1996) Myths About the Treatment of Addiction. *Lancet*, 1996, 347, 237-240. Addiction drugs produce changes in brain pathways that endure long after drug taking stops. The associated medical, social and occupational difficulties that develop during addiction do not disappear with detoxification. Protracted brain changes, personal and social difficulties put the former addict at great risk. Treatments for addiction should be regarded as long-term. [*A paper refuting the myths - RFP*].
28. Roche Products Ltd. (ca.1990) [Benzodiazepines and your Patients: A Management Programme](#) (Sent to prescribers on request). The post withdrawal syndrome can manifest itself as fluctuating levels of malaise, lack of concentration, abdominal discomfort, depersonalisation and emotional lability. If post withdrawal symptoms occur good support from the general practitioner over at least the first year reduces the risk of relapse.