Medical Research on Benzodiazepine Injury

Compiled by Colin Downes-Grainger
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Action on Addiction to Tranquillisers.
Lancet 1985; i: 1521.

"MIND, the National Association for Mental Health, is calling for Government action to help people addicted to minor tranquillisers. MINDs director, Mr Christopher Heginbotham, has written to Mr Kenneth Clarke, Minister of Health, declaring that enormous profits have been made by the pharmaceutical industry as a result of overprescription of minor tranquillisers and urging the Government to tap this source for money to finance adequate withdrawal support services.

Ashton H.
Adverse Effects of Prolonged Benzodiazepine Use.
Adverse Drug Reaction Bulletin 1986; 118: 440-443.

"Chronic benzodiazepine usage can cause both depression and "emotional anaesthesia", an apathetic state with dulling of all emotions. In patients with depressive illness, benzodiazepines can aggravate the depression and provoke suicide. On the other hand, some individuals experience euphoria, and benzodiazepines have abuse liability when used intravenously. Occasionally, benzodiazepines produce apparently paradoxical stimulant effects. (---) Patients on low chronic doses of benzodiazepines sometimes commit uncharacteristic antisocial acts such as shoplifting or sexual offences, while higher doses may produce outbursts of rage and violent behaviour, especially in anxious patients. “

Ashton H.
Benzodiazepine Withdrawal: Outcome in 50 Patients.
British Journal of Addiction 1987; 82: 665-671.

"None of these symptoms or behaviours were the original indication for starting on benzodiazepines but developed during chronic use. It is arguable whether the patient would have developed the symptoms over time in the absence of benzodiazepines, but the fact that they were not present before benzodiazepine use, were not amenable to treatment during benzodiazepine use, yet largely disappeared when the drugs were stopped, suggests that benzodiazepines may actually cause or aggravate a variety of psychological and psychosomatic symptoms. " [p. 670]

Ashton H.
Anything for a Quiet Life ?
New Scientist 1989; 6: 34-37.

"Valium, Librium and Mogadon once seemed to provide the perfect answer to stress. We now know how this group of drugs alters the chemistry of the brain; no wonder they create more problems than they solve. " [SUMMARY p. 52]

“Taking benzodiazepines over the long term can cause both depression and "emotional anaesthesia", an apathetic state in which people are unable to feel pleasure or pain. The drugs can aggravate depressive illness and provoke suicide. On the other hand, benzodiazepines sometimes produce apparently paradoxical stimulant effects. Patients may commit uncharacteristic antisocial acts such as shoplifting or sexual offences, or becoming aggressive with outbursts of rage and violence. Some researchers have suggested that chronic use of

benzodiazepines may contribute to "baby-battering", "wife-beating" or "grandma-bashing." [p. 54]

Ashton H.
Protracted Withdrawal Syndromes from Benzodiazepines.
Journal of Substance Abuse Treatment 1991; 8: 19-28.

"Even with long-acting benzodiazepines such as diazepam, there is usually a history in long-term users of steadily increasing anxiety, with the development over the years of new symptoms such as agoraphobia, often with perceptual distortions and depersonalisation, despite continued usage of these supposedly anxiolytic drugs. " [p. 22]
Ban TA, Da Silva T, Gagnon MA, Lamont CT, Lehmann HE, Lowy FH, Ruedy J,Sellers EM.
Therapeutic Monograph on Anxiolytic-Sedative Drugs.
Canadian Medical Association Journal 1981; 124: 1439-1446.

"Various unusual responses have been documented, including nightmares, paradoxical delirium and confusion, depression, aggression and hostile behaviour. Some patients experience a dry mouth, a metallic taste or headaches.
Awareness of the sometimes bizarre effects of these drugs is important. " [p. 1443]

Bergman H, Borg S, Engelbrektson K, Vikander B.
Dependence on Sedative-Hypnotics: Neuropsychological Impairment, Field Dependence and Clinical Course in a 5-Year Follow- Up Study.
British Journal of Addiction 1989; 84: 547-553.

" Despite some neuropsychological improvement in a group of 30 patients who had been hospitalised for primary abuse of sedatives or hypnotics 4-6 years earlier, the prevalence of intellectual impairment was still increased and about as high as before.

Blennow G, Romelsö A, Leifman H, Leifman A, Karlsson G.
Sedatives and Hypnotics in Stockholm: Social Factors and Kinds of Use.
American Journal of Public Health 1994; 84: 242-246.

"It is reasonable to believe that being unemployed or on a disability pension may be associated with number of psychological problems caused by, for instance, social isolation. However, drug use in itself may be the reason for unemployment or a disability pension. [p. 245]

Borg S.
Dependence on Hypnotic/Sedative Drugs.
In: Pharmacological Treatment of Anxiety. National Board of Health and Welfare, Drug Information Committee, Sweden 1988; 1: 135-143.

"In spite of good socio-economic conditions the long-term prognosis for patients with hypnotic/sedative dependence seems to be similar to that encountered in e.g. alcohol abuse. " [p.137]

Byrd JC.
Alprazolam-Induced Rage Reaction.
Journal of Clinical Psychopharmacology 1985; 5: 186-188.

"... this case lends support to the observation that alprazolam shares with other benzodiazepines the capacity to produce rage reactions at therapeutic drug levels. " [p. 187]

"... it seems that alprazolam should be used at least as cautiously as other benzodiazepines in patients who experience anxiety in the context of suppressed rage at hostile or conflict-ridden environments. " [p. 188]

Byrne A.
Benzodiazepines: The End of a Dream.
Australian Family Physician 1994; 23: 1584-1585.

"Benzodiazepine tranquillisers were introduced in 1960 after brief clinical tests at the University of Texas in 1959. Controlled trials were not required for evaluation and "efficacy" was demonstrated by anectdotes and testimonials. If introduced today they would probably only be approved for limited indications." [p. 1584]

"Some critical authors have suggested that the medical profession and drug companies have been guilty of knowingly ignoring the dangers of tranquillisers. " [p. 1584)

“Side-effects, including instability and falls in the elderly, memory disturbance, abnormal sleep patterns, sexual disturbance, depression, fatigue and habituation are all well documented. " [p. 1584]

"Use of these drugs for minor complaints, or as first line of management is no longer justified. " [p. 1584]

"Some patients can withdraw from these drugs rapidly without great trouble. For others, it is a long, harrowing experience. " [p. 1585]

"The dream of the perfect sedative has not come true. For some, it has become a recurrent nightmare. Chloral, bromides, barbiturates, meprobamate and even heroin were all touted in their turn as the ideal, non addictive calming agents. There is still no perfect drug for primary insomnia or anxiety. Benzodiazepines are a limited tool in the pharmacopoeia, but not the panacea once thought. " [p. 1585]

Carney MWP, Ellis PF.
A Policy on Benzodiazepines.
Lancet 1987; ii: 1406.

"We agree with Professor Cohen that there is no place for benzodiazepines in the treatment of anxiety. There may be a place for them in anaesthesia, the management of epilepsy, or parenterally in states of acute psychiatric disturbance - but that is all. What is to replace them in anxiety management ? We suggest a personalised non-drug programme of anxiety management,

Clare AW.
Diazepam, Alcohol, and Barbiturate Abuse.
BMJ 1971; 4: 340.

"It has been recognised for some time that dependence is a potential hazard of benzodiazepine use. This report is of a case of diazepam abuse in a woman who originally sought treatment for disturbed sleep and who over a period of six years became severely dependent on diazepam, alcohol, and barbiturates. " [p. 340]

"It is suggested that the sanguine view held by many members of the medical profession towards the minor tranquillisers has been transmitted to the lay public and militates against

attempts to remove patients from unnecessary and potentially harmful treatment with these drugs. "

Cochran PW.
Drugs for Anxiety.
JAMA 1974; 229: 521.

"Your editorial, "Drugs for Anxiety" (228: 875, 1974) prompts an uneasy feeling that has been growing on me for some time. Diazepam is cited as a safe drug not particularly subject to abuse when prescribed on an as-needed basis with a cover statement that some psychic distress should not be alarming. This is floridly at variance with my uncollated experience; in fact, so much so that I regard it as virtually a "once on, never off" preparation.

Cohen SI.
Alcohol and Benzodiazepines Generate Anxiety, Panic and Phobias.
Journal of the Royal Society of Medicine 1995; 88: 73-77.

“In almost half the patients seeking advice for anxiety, panic and phobias the cause was alcohol or benzodiazepines.” [SUMMARY p. 73]

Cormack MA, Owens RG, Dewey ME.
The Effect of Minimal Interventions by General Practitioners on Long-Term Benzodiazepine Use.
Journal of the Royal College of General Practitioners 1989; 39: 408-411.

"Given the evidence of cross-tolerance of some benzodiazepines with alcohol it might have been expected that subjects would have sought alcoholic alternatives when deprived of their usual drug. However, this was not the case according to the interview data and only one patient reported an increase in cigarette consumption. This parallels Ashton's finding that none of her subjects replaced benzodiazepines with other drugs or alcohol. "

"The evidence of the detrimental effects of benzodiazepines on cognitive and psychomotor performance following long-term use suggest that people may perform better in a number of ways without the drugs... Attempts to tackle the causes of the symptoms may not be initiated or may fail through decreased problem solving skills... Anecdotal evidence from patients seen by one of the authors... and other workers in the field supports the view that people feel that their capacities have been dulled by the drugs and that a new, or forgotten, self emerges when the drugs are discontinued. " [p. 410]

Crawford RJM.
Benzodiazepine Dependency and Abuse.
New Zealand Medical Journal 1981; 94: 195.

"The earlier drugs with longer half lives of several days have now been adequately researched, and two facts emerge:

(1) The longer a person takes them, the harder it is to stop, i.e. withdrawal symptoms (headaches; muscle cramps; light-headedness; vertigo; muscular in-co-ordination; paranoid reactions; epileptic fits, and malaise) occur which the patient learns can be stopped by another pill.

(2) These effects can occur in people who have had doses in the normal recommended clinical range. “

"I particularly wish to draw to your attention that the newer, shorter acting tranquillisers such as oxazepam (Serepax), and lorazepam (Ativan) are associated with quicker development of the addictive state and more severe withdrawal problems, at least in the alcoholic population. Triazolam (Halcion) is being marketed as a very short half life hypnotic. I predict it will have the highest abuse potential of all the benzodiazepines yet marketed. "

Dimascio A, Shader RI, Harmatz J.
Psychotropic Drugs and Induced Hostility.
Psychosomatics 1969; 10: 46-47.

"We generally call it a "paradoxical reaction" of the drug when a patient responds in a manner inconsistent with - or opposite to - our conception of how he or she should respond to a psychotropic agent. But it is only our lack of knowledge - or our limited conception of what these drugs do and in whom the do what that necessitates the label "paradoxical". With knowledge, these actions should not remain "paradoxical" but become "predictable drug effects. " [p. 46]

"These drugs are also supposed to calm and quiet agitated and irritable individuals. Indeed, if you remember, when chlordiazepoxide was first introduced, it was publicised as being able to tame even the wildest and most ferocious of animals, without reducing their ability to move about. The initial expectation, therefore, was that it would do the same in man. However, even from the beginning of the use of the drug, it was noted that in some patients a state of increased anger, irritability and overt aggression was induced or unmasked. Because it was not expected, the phenomenon was labelled as "paradoxical". [p. 46]

"We have seen a number of previously quiet patients become assaultive and break up furniture in an office, shortly after being placed on chlordiazepoxide or another benzodiazepine, diazepam (Valium). In fact, even acts of violence such as murder have been attributed to the rage reaction induced by these drugs (Georgia vs. Robinson 1962 and Ohio vs. Page 1967). " [p. 46]

"When prescribing for patients with anxiety states the potential action of these drugs on hostility and aggression has to also be considered. " [p. 47]

Editorial.
Some Problems with Benzodiazepines.
Drug and Therapeutics Bulletin 1985; 23: 21-23.

"Short-term administration of benzodiazepines impairs psychomotor function and can produce anterograde amnesia. Chronic benzodiazepine users takers have lower scores on some psychological tests than controls matched for age and sex. Such test performances were more impaired than simpler tests of psychomotor function. Whether these findings indicate that long-term use impairs intelligence is unknown, as pre-benzodiazepine tests were not available; there may well be other reasons for a difference between benzodiazepine users and non users." [p. 22]

Edwards JG.
Adverse Effects of Antianxiety Drugs.
Drugs 1981; 22: 495-514.

"The behaviour of patients in whom one suspects benzodiazepine dependence is also noteworthy. In practice we see patients who claim that benzodiazepines have cured their anxiety, while at the same time they continue to demand drugs. Many refuse a trial period without medication. Patients who have been successfully treated with antidepressants or

antipsychotic drugs, although experiencing relief from equally distressing symptoms (including anxiety secondary to the underlying disorder), generally seem not so reluctant to have their treatment stopped. The situation with benzodiazepines is reminiscent of that encountered with other drugs of dependence.

Physicians who carried out ratings on the severity of addiction, blind to the type of drug, changed their opinions when it was revealed that the drug in question was diazepam (Maletzky and Klotter, 1976). This showed a reluctance to accept that benzodiazepines are drugs of addiction.

It is perhaps humiliating for us to realise that we have learnt little from history. Is it possible that having previously contributed to barbiturate and other addiction we are now reluctant to accept that we may have also contributed to benzodiazepine addiction?"

Fava GA.
Anxiety Sensitivity.
American Journal of Psychiatry 1996; 153: 1109.

"We should not be blind to the possibility that benzodiazepines may increase chronicity in panic disorder and that they simply should be avoided whenever possible. " [p. 1109]

Feldman PE.
An Analysis of the Efficacy of Diazepam.
Journal of Neuropsychiatry 1962; 3 (suppl 1): 62-67.
"Instead of prompting the appearance of delusions and/or hallucinations, many of the patients receiving Valium displayed a progressive development of dislikes and hates. The patients themselves deliberately used the term "hate".

Floyd JB, Murphy CM.
Hallucinations Following Withdrawal of Valium.
Journal of Kentucky Medical Association 1976; 74: 549-550.

"Five responses to the withdrawal of Valium in patients is reported. A study of the background of these patients revealed that all demonstrated previous chronic use of Valium.
The magnitude of this problem can be realised by the 1972 pharmaceutical report of 144,000,000 prescriptions for sedatives, one-third of these being for Valium. " [p. 550]

Foy A, Drinkwater V, March S, Mearrick P.
Confusion after Admission to Hospital in Elderly Patients Using Benzodiazepines.
BMJ 1986; 293: 1072.

"In this prospective study of 103 patients aged 65 years or more half were found to be using benzodiazepine drugs, and these patients had an increased risk of developing a confusional state in hospital. The risk appeared to be particularly high in those whose drugs were stopped abruptly.

"... we think that withdrawal was the major cause of confusion as the patients who developed confusion had nothing else in common, and in six patients the reaction resolved promptly when benzodiazepine treatment was restarted. "

Gene-Badia J, Blay-Pueyo C, Soler-Vila M.
Risk-Factors in the Use of Benzodiazepines.
Family Practice 1988; 5: 283-288.

"... general practitioners, who are the principal prescribers of drugs, are causing over-medication in the population. " [p. 283]

"It is also important to note that in our sample, a great number of patients suffering from depression were taking benzodiazepines. A possible interpretation for this is that the physician detecting the existence of a psychopathological disorder is either unable to categorise it or to use a psychopharmacological agent other than benzodiazepine. (- - -) This fact, together with an unjustified fear of non-benzodiazepine psychopharmacological agents, explains why the anxiolytics are prescribed to patients who could otherwise benefit from specific treatment with antidepressants. This therapeutic pitfall tends to mask the symptoms and contributes to a chronic evolution of the depression which is later aggravated by the addictive effects of benzodiazepines.
" [p. 287]

Gillberg C.
"Floppy Infant Syndrome" and Maternal Diazepam.
Lancet 1977; ii: 244.

"In the neonatal care ward of this hospital high concentrations of diazepam and desmethyldiazepam have been found in the sera of children with abnormal neonatal behaviour and whose mothers had taken diazepam towards the end of pregnancy. Diazepam has been indicted responsible, at least in part, for the children's symptoms (hypotonia, sucking difficulties, hypothermia, and attacks of cyanosis). "

Golombok S, Moodley P, Lader M.
Cognitive Impairment in Long-Term Benzodiazepine Users.
Psychological Medicine 1988; 18: 365-374.

"The finding that patients taking high doses of benzodiazepines for long periods of time perform poorly on tasks involving visual-spatial ability and sustained attention, implies that these patients are not functioning well in everyday life. Furthermore, the lack of relationship between benzodiazepine intake and the cognitive Failures Questionnaire, a subjective measure of impairment, suggests that they are not aware of their reduced ability. This is in line with clinical evidence that patients who withdraw from their medication often report improved concentration and increased sensory appreciation, and that only after withdrawal do they realise that they have been functioning below par. " [p. 373]

"The cognitive effects of long-term administration of benzodiazepines may not only be debilitating but may also be dangerous. Although benzodiazepines have not been directly implicated in road traffic accidents, Hindmarch (1986) estimated that up to 10% of drivers involved in car accidents had been taking psychoactive drugs, and that psychoactive drugs are responsible for the loss of 200 000 lives world-wide on the roads each year. " [p. 373]

“It appears... that not only are long-term benzodiazepine users at risk of dependence, but that cognitive impairment also represents a very real hazard. " [p. 373]

Grant I, Adams KM, Carlin AS, Rennick PM, Judd LL, Schooff K, Reed R. Organic Impairment in Polydrug Users: Risk Factors.
American Journal of Psychiatry 1978; 135: 178-184.

"If our findings are confirmed by others, several implications might be considered. First, sedatives and opiates might produce more long-term toxicity than has previously been suspected. If this is so, we need to rethink practices that have led to exceedingly widespread use of sedatives and minor tranquillisers." [p. 183]

Hall RCW, Joffe JR.
Aberrant Response to Diazepam: A New Syndrome.
American Journal of Psychiatry 1972; 129: 738-742.

"Six patients with a demonstrated aberrant response to diazepam showed a cluster of symptoms consisting of tremulousness, apprehension, insomnia, and depression, followed by ego-alien suicidal ideation. In this series, the syndrome was abrupt in onset and marked in severity and appeared in individuals who had been previously emotionally stable. All of the patients had been taking greater than maximally recommended doses of diazepam (i.e., greater than 40 mg. every day), primarily for medical conditions.

The significance of this syndrome lies in the quality of the suicidal ideation, which negates the usual indicators of suicidal intent. The appearance of any of the preliminary symptoms of this syndrome is therefore an immediate indication for the withdrawal of diazepam and the protection of the patient against suicidal impulses. Furthermore, it is strongly suggested that physicians adhere to the maximum recommended dosages and be aware of the possibility that peripheral vascular disease and age may be a factor in the appearance of cumulative toxic effects."[p. 741]

Haskell D.
Withdrawal of Diazepam.
JAMA 1975; 233: 135.

"The manufacturer's literature warns of physical addiction to diazepam or other benzodiazepines, mainly with excessive doses. However, I have seen several patients experiencing barbiturate-type withdrawal symptoms after four to six months of diazepam therapy in doses as low as 15 mg/day.

Symptoms such as tremors, agitation, fearfulness, stomach cramps, and sweating made patients extremely uncomfortable, but dangerous reactions, such as convulsions, did not occur. All of these patients had been admitted to a psychiatric hospital for depression. They were generally reluctant to stop using diazepam, but when the symptoms subsided after two to four weeks, they were usually happy to be free of medication.

"Also, the possibility of depression after prolonged diazepam treatment, as reported in another letter (226; 1572:1973), underscores the need for further study and caution with this drug. "

Haskell D, Cole JO, Schniebolk S, Lieberman B.
A Survey of Diazepam Patients.
\-\-Psychopharmacology Bulletin 1986; 22: 434-438.

"The major conclusions that may be drawn from this survey are:

1) that most patients at this clinic on diazepam have been taking it a long time; and
2) that they are generally not asymptomatic. In fact, they may be more symptomatic than patients ordinarily considered for anti-anxiety drug studies. They appear to believe they are obtaining continued benefit from their medication and have difficulty tapering or stopping it. It remains unclear whether this difficulty is caused by chronic anxiety symptoms only partially

relieved by BZs, or results from some degree of physical dependence requiring BZ maintenance to suppress withdrawal symptoms. "[p. 437]

Hawthorne M.
Any Questions
BMJ 1991; 302: 1266.

[regarding treatment of tinnitus]
"Anxiolytics, such as benzodiazepines, were a popular treatment some years ago but as their long term use is detrimental should not be used. "[p. 1266]

Hendler N, Cimini C, Ma T, Long D.
Comparison of Cognitive Impairment Due to Benzodiazepines and to Narcotics.
American Journal of Psychiatry 1980; 137: 828-830.

"However, the most significant problem that benzodiazepines create seems to be cognitive impairment with associated EEG changes (---). Acute, single dose administration of diazepam does seem to produce impairment in learning, memory, and psychomotor functioning. " [p. 828]

".. the evaluating psychiatrist noted that a great deal of cognitive impairment seemed to occur more often in patients using benzodiazepines than in patients using only narcotics. " [p. 828]

"...one could conclusively state that benzodiazepines were far more likely to produce cognitive impairment, with concomitant EEG changes, than were narcotics. " [p. 830]

Herxheimer A.
Driving under the Influence of Oxazepam: Guilt without Responsibility ?
Lancet 1982; ii: 223.

"Benzodiazepines can blunt perception, confuse thought, and cause amnesia. The defendant described feeling "fuddled and muddled" and driving less sharply than usual. This state of mind, if it was induced by the drug, would aggravate the difficulty of understanding that something was wrong, and of taking appropriate action, let alone suspecting a connection between the state of mind and taking the drug. "

"The case underlines the importance of warning patients about the possible effects of drugs on driving and other potentially dangerous activities. A doctor who fails to warn his patient at least shares the responsibility for any accident that occurs as a result; in such a case the patient would seem to be entitled to recover damages from the doctor. " [p. 223]

Heyndrickx B.
Fatal Intoxication Due to Flunitrazepam.
Journal of Analytical Toxicology 1987; 11: 278.
"Flunitrazepam is used in many hospitals and prescribed by physicians for use in daily life. (- -) These pharmaceutical compounds are very dangerous and one should take care when prescribing them to elderly people. " [p. 278]

Higgitt AC, Lader MH, Fonagy P.
Clinical Management of Benzodiazepine Dependence.
BMJ 1985; 291: 688-690.

"Withdrawal symptoms have been reported after treatment for as little as four to six weeks. The withdrawal symptoms observed are wide ranging, and, while they include some related to

anxiety, they are clearly distinguishable from a simple re-emergence of pre-existing anxiety. Particularly frequently reported are instances of increased sensory perception such as hyperacusis, photofobia, paraesthesia, hyperosmia, and hypersensitivity to touch and pain, but gastrointestinal disturbances, headaches, muscle spasms, vertigo, and sleep disturbances are also frequent.

The proportion of long term users of benzodiazepines in whom withdrawal symptoms may be expected to emerge has been variably estimated to be between 15% and 44%. The symptoms typically emerge in the first week after stopping the drug but may develop after a reduction in dosage. Until recently the withdrawal syndrome was reported as lasting for up to three months, but we are now seeing more patients whose symptoms have persisted for more than six months - in some cases for a year or more." [p.688]

Higgitt A, Fonagy P, Toone B, Shine P.
The Prolonged Benzodiazepine Withdrawal Syndrome: Anxiety or Hysteria ?
Acta Psychiatrica Scandinavica 1990; 82: 165-168.

"... the results offer no support for either the continued-anxiety or the conversion-disorder accounts of PWS [i.e. Prolonged Withdrawal Symptoms] suggested in the introduction. No evidence was found that psychophysiological indicators of anxiety were marked in this group. (---) The observation that this group is psychophysiologically hard to distinguish from normal controls suggests that PWS is unlikely to be an affective disturbance and lends support to the view that it represents a genuine iatrogenic condition that may be best treated as a complication of benzodiazepine treatment. (---)

"It is fortunate that patients who continue to manifest symptoms long-term following withdrawal are relatively small in number (although they may amount to 30% of a benzodiazepine dependent sample..." [p. 167]

Ingram IM, Timbury GC.
Side-Effects of Librium.
Lancet 1960; ii: 766.

"Side-effects were seen in over half the patients. 2 felt drowsy on the smaller dose, 5 on the larger. 2 felt fatigued and apathetic, and dizziness and constipation were reported. 1 patient felt more energetic and 2 complained of severe irritability. After taking the drug for a week a schoolteacher struck his wife for the first time of the twenty years of their marriage. (---). Although the number treated is small and the findings uncontrolled, the results are disappointing enough and the side-effects sufficiently troublesome to deserve attention. Other side-effects reported in trials in the United States have included dissociative reactions, hyperactivity, and ataxia. We feel justified in suggesting that the drug should be used with circumspection and scepticism until the results of controlled trials are available. "

Javed MA.
Misuse of Benzodiazepine.
Journal of Pakistan Medical Association 1995; 45: 289-290.

"The persistence of the withdrawal syndrome furthermore complcates the matter. Surveys have shown that about 15-30% of the patients continue to report significant symptoms from 10 months to 3.5 years following the withdrawal of these drugs. This certainly requires increasingly energetic attempts to help patients to give up benzodiazepines."

Jeffrey DI, Whitfield MF.
Lorazepam Poisoning.
BMJ 1974; 4: 719.

[regarding the overdosage of lorazepam in a 6-year-old boy]
"Hallucinations are a recognised complication of ovedosage with diazepam, a more widely used member of the benzodiazepine group." [p. 719]

Karkos J.
[Neurotoxicity of Benzodiazepines.]
Fortschr Neurol Psychiat 1991; 59: 498-520.

"The experimental data obtained after prenatal application indicate that BDZs can cause malformations, functional deficits and long-lasting behavioural anomalies. (---) The consequences of prenatal exposition to BDZs in m an, particularly their behavioural aspects, have not been sufficiently investigated as yet. Postnatal BDZs application can bring about behavioural disturbances and neurological deficits in animals and man. " [p. 498]

Katz RL.
Sedatives and Tranquilizers.
New England Journal of Medicine 1972; 286: 757-760.

" What can be recommended is that every time a physician reaches for his prescription pad, he ask himself if he is prescribing a sedative or tranquilizer because he has a roomful of patients waiting and is in a hurry to get on to the next patient... or whether he has carefully considered all the evidence, has found that sympathy, understanding, suggestion and reassurance are not sufficient, and has decided to prescribe a sedative or tranquilizer for positive reasons rather than as an easy way out." [p. 670]

Kellett JM.
The Benzodiazepine Bonzanza.
Lancet 1974; ii: 964.

"Dr Tyrer is certainly right to draw attention to the multiplicity of benzodiazepines (---). Not only are there to many, but one suspects that they are too often prescribed in ways which cause harm to the patient."

Kellman AM.
Benzodiazepine Withdrawal.
American Journal of Medicine 1988; 85: 755.

"Unfortunately the widespread use of these medications in the general medical community has not been accompanied by concomitant knowledge of their potential adverse effects. All too often, biased information from pharmaceutical representatives is used to guide therapy with benzodiazepines. In my own experience, I have encountered far more problems with patients who have become inadvertently dependent on benzodiazepines than with patients who refuse to take these medications due to concerns about possible addiction. In particular, I have seen a number of very severe withdrawal reactions from alprazolam, including on death as a result of subdural hematomas incurred during a withdrawal seizure."

Khan A, Joyce P, Jones AV.
Benzodiazepine Withdrawal Syndromes.
New Zealand Medical Journal 1980; 92: 94-96.

"We report eight cases of benzodiazepine withdrawal syndromes seen in a general psychiatric hospital. These consisted of acute organic brain syndrome, grand mal convulsions and abstinence syndromes. All of the cases were using benzodiazepines in prescribed therapeutic doses. These problems appear to be more common than are generally acknowledged. " [SUMMARY p. 94]

All of the reported cases were using benzodiazepines in therapeutic doses and were documented within a short period of time in a relatively small population, alarming us regarding the true incidence of these problems. (- - -)

Amongst the group who manifested the abstinence syndrome certain common features were discerned. These were women who had been prescribed a benzodiazepine in therapeutic doses over a minimum of three years for persisting anxiety and/or depression. On withdrawal they uniformly suffered from insomnia, panic attacks, agitation, depersonalisation and an increase in depression. Their suffering was obvious and they all described it as being the worst experience of their lives. "[p. 96]

King SA, Strain JJ.
Benzodiazepines and Chronic Pain.
Pain 1990; 41: 3-4.

"... their [i.e. the benzodiazepines] frequent prescription is disturbing for several reasons. The benzodiazepines are not innocuous drugs. They are addicting and their sudden discontinuation can result in serious withdrawal reactions. They can produce a variety of side effects, most notably sedation, impairments in cognition, and depression ..." [p. 3]

Krakowski AJ, Langlais LM.
Acute Psychiatric Emergencies in a Geriatric Hospital.
Psychosomatics 1974; 15: 72-75.

The polypharmacy may, however, be responsible for the reciprocal potentiation of untoward effects and be motivated less by the need of the patient than the need of the prescribing physician."[p. 73]

Kripke DF, Garfinkel L.
Excess Nocturnal Deaths Related to Sleeping Pill and Tranquilliser Use.
Lancet 1984; i: 99.

"The group 1 subjects (who took no sleeping pills or tranquillisers) showed disproportionately fewer deaths during the usual hours of sleep, but group 2 subjects showed an excess of deaths during the same hours. The two groups differed significantly in the temporal distribution of deaths." [p. 99]

"These results are consistent with the hypothesis that barbiturate sleeping pills and tranquillisers, in normal use, cause extra deaths during sleep. " [p. 99]

Lader M.
Benzos and Memory Loss: More Than Just "Old Age".
Prescriber 1992; 3: 13.

"Amnesic effects were recognised early on by anaesthetists who, indeed, welcomed a premedicant drug that resulted in the patient forgetting unpleasant diagnostic or operative procedures such as gastroscopy. In this usage, fairly large doses of benzodiazepines are given

intravenously. However, many reports have accrued over the years of patients taking oral doses of a benzodiazepine and then suffering from an amnesic episode, a lapse of memory or "black-out.

The patient behaves quite purposefully, e.g. changes planes at an airport, but has no recollection of events subsequently. Such reports have involved all the benzodiazepine but lorazepam and triazolam seem particularly implicated. The amnesic episodes usually follow the sporadic use of a high dose of benzodiazepine, and are particularly likely if alcohol is taken as well. In some rare instances antisocial behaviour, even involving homicide, seems to have occurred during such an episode.

Reports have also accrued of more persistent memory impairments in patients taking a benzodiazepine on a regular basis. The elderly taking a hypnotic seem particularly at risk: about 15 per cent of the over-65s take hypnotic drugs, and of those 75 per cent have used them regularly for over a year, 25 per cent (i.e. about 4 per cent of the total) for over 10 years. As these chronic users age, they become more sensitive to the benzodiazepine and have lapses of memory, ending up in a chronically confused state. "

Lader M.
History of Benzodiazepine Dependence.
Journal of Substance Abuse Treatment 1991; 8: 53-59.

"The widespread usage of the benzodiazepines has inevitably led to thousands of people becoming dependent, perhaps 500,000 in the UK and twice that number in the USA where long-term use is less common. Patients who have become dependent and have either been unable to withdraw or have only done so with great symptomatic distress justifiably feel aggrieved against their doctors and the benzodiazepine manufacturers for not warning them about the risk. "[p. 58]

Lader M.
Benzodiazepine Problems.
British Journal of Addiction 1991; 86: 823-828.

"Most withdrawal symptoms have subsided by 3 months after final discontinuation. In a few unfortunate patients symptoms may persist and include feelings of unsteadiness, neck tension, a "bursting" head, perceptual distortions and muscle spasm. The strange nature of these symptoms distresses the patient, perplexes the doctor and may lead to the patient being regarded as a hopeless neurotic or even a malingerer. We believe this to be a genuine part of a protracted withdrawal syndrome as the symptoms are identical with those seen earlier in withdrawal. " [p.828]

Lader M.
Anxiety or Depression During Withdrawal of Hypnotic Treatments.
Journal of Psychosomatic Research 1994; 38 (suppl 1): 113-123.

"In a few unfortunate individuals, the withdrawal symptoms either return or more commonly persist. The existence of this so-called "Persistent Withdrawal Syndrome" is unestablished but many experienced practitioners are convinced of its reality. The syndrome is dominated by anxiety, either generalised or phobic or sometimes both, phobic behavioural disorder, and panic attacks. Many of the litigants involved in the large UK court case have suffered from prolonged disabilities of this type. " [p. 116S]

Lader M.
Clinical Pharmacology of Anxiolytic Drugs: Past, Present and Future.
Advances in Biochemical Psychopharmacology 1995; 48: 135-152.
"A converse, paradoxical psychological effect is the release of anxiety or hostility by therapeutic doses of a benzodiazepine. Reactions include uncontrollable weeping or uncharacteristic antisocial acts like sexual improprieties, impulsive thefts and unprovoked aggression. The feelings and impulses may puzzle the patient who fails to connect them to his medication. Opinions differ as to the frequency of such paradoxical reactions, some regarding them as rare, others as fairly common. " [p. 137]

Lennane KJ.
Treatment of Benzodiazepine Dependence.
Medical Journal of Australia 1986; 144: 594-597.

"A high proportion of long-term normal-dose users are physically dependent, and will suffer significant symptoms if the drug is withdrawn. Two studies by Tyrer et al. suggest that the frequency of significant dependence is between 27% and 45%. " [p. 594]

"... dependence can occur in less than three months. Occasional patients - particularly those who have been dependent on other drugs - give anecdotal reports of almost instantaneous dependence on benzodiazepine drugs, and many such patients develop obvious dependence in five to 10 days. Withdrawal symptoms have been noted in patients who have received benzodiazepine agents for three weeks. " [p. 594]

"Therefore, it seems that the occurrence of withdrawal symptoms if patients try to decrease or stop benzodiazepine agents is keeping up to half the patients taking the tablets. " [p. 595]

"Anxiety, insomnia, irritability, tremulousness, gastrointestinal disturbances and dysphoria occur much as in the withdrawal of any tranquilliser or sedative drug. Other symptoms appear to be more specific. Perceptual distortions occur in all modalities. Sounds may be unduly loud and patients may hear non-existent thumps or tunes. Sights are distorted and may be misinterpreted, with occasional brief visual hallucinations. The most common complaint is of feelings of unreality and depersonalisation, and of seeing "through a veil". Paraesthesia is common, as are distortions of smell and taste. Paranoid thoughts and feelings occur frequently. Pain and stiffness in various parts of the body, especially the face, are common, with muscular spasms which may appear as myoclonic jerks, or as local tremors and fasciculation. (---) Ashton also reports a flu-like illness in 10 of her 12 patients that was reminiscent of narcotic withdrawal, and also menorrhagia and breast pain. Marked weight loss is common. " [p. 595]

"What makes withdrawal so bad, apart from the perceptual disturbances which make patients feel they are going mad, is that it goes on for so long. (---) Benzodiazepine withdrawal symptoms typically last at least four weeks. Ashtons study suggests that many symptoms, though improved by four weeks, may continue intermittently for months. " [p. 595]

"It is clear that patients who are dependent and want to withdraw may face a very unpleasant illness - in most cases, very much worse than the condition for which they were prescribed benzodiazepine drugs in the first place. " [p. 595]

"One [difficulty] is the risk of accumulation in elderly patients, who may develop apathy and confusion, that are attributed erroneously to dementia. Another is the risk that withdrawal symptoms may develop inconveniently and dangerously after admission to hospital for other reasons (for example, surgery). Yet a third is the risk of permanent brain damage, analogous to alcohol-related damage, which it seems may occur with long-term usage. " [p. 595]

"There is a period of a few days to a few months during which the benzodiazepine drug has an active effect. A period of months to years then occurs when there is no longer any active effect, but the drug in normal dosage prevents the occurrence of withdrawal symptoms. Some patients then progress to the "problem" phase. when withdrawal symptoms start to occur although they are still taking the medication. The great majority of such patients do not attempt to compensate for this tolerance by increasing their dosage, and this phase may continue for months or years - until someone realises that the benzodiazepine drug is actually making the patient ill. " [p. 595]

"Patients who keep on taking the tablets must be carefully monitored for the appearance of such "neurotic" symptoms, and the doctor must be aware, if they appear, that the answer is not more medication, but benzodiazepine withdrawal. [p. 595]

"... the patients with the clearest psychological indications for benzodiazepine therapy are those who are most likely to get into trouble with them. " [p. 596]

"It is my personal opinion that it would be helpful if the profession as a whole could accept the evidence and alter their prescribing habits. " [p. 596]

"Primum non nocere is an excellent precept, and is often the best we can do. It is unfortunate that we sometimes fail to achieve even that. " [p. 596]

Levander S.
Psychophysiology and Anxiety - Current Issue and Trends.
In: Pharmacological Treatment of Anxiety. National Board of Health and Welfare, Drug Information Committee, Sweden 1988; 1: 43-51.

"However, it cannot be excluded that treatment with benzodiazepines may have negative therapeutic long-time effects, and may induce neuropsychological impairment, which in the worst case can be permanent. " [p. 49]

Lobo BL, Miwa LJ.
Midazolam Disinhibition Reaction.
DICP 1988; 22: 725.
"Some studies suggest that benzodiazepines have an inherent potential to cause aggression. In a double-blind, placebo-controlled, cross-over study, Gardner and Cowdry showed that alprazolam produced a significant increase in behavioural loss of control in patients with a borderline personality disorder. Wilkinson demonstrated an aggression-enhancing effect with diazepam, especially in the low-anxiety group. Other studies have demonstrated that chlordiazepoxide and diazepam may decrease anxiety but increase affective hostility. " [p. 725]

Mac DS, Kumar R, Goodwin DW.
Anterograde Amnesia with Oral Lorazepam.
Journal of Clinical Psychiatry 1985; 46: 137-138.

"These results support findings by other investigators that lorazepam has a deleterious effect on short-term recall of verbal material. This has implications for students and other preparing for tests or doing mental work while taking therapeutic doses of lorazepam. " [p. 137]

Maletzky BM, Klotter J.
Addiction to Diazepam.
International Journal of the Addictions 1976; 11: 95-115.

"Indeed, the "Warnings" section of the Valium package insert admitting to the occurrence of withdrawal symptoms leads one to believe that addiction can only occur should the usual doses be exceeded or the user be an alcoholic, drug addict, or "addiction-prone", a state further undefined. " [p. 96]

"Diazepam may be vulnerable to self-manipulation because of its capacity to produce immediate positive effects, a trait it shares with addicting substances, such as alcohol or amphetamines, as opposed to non-addicting psychotropic drugs, such as chlorpromazine and imipramine. " [p. 109]

"When asked, 14 of these 25 replied they increased their dose because the prescribed amount was not as helpful as before. " [p. 109]

" ... several subjects complained of extreme anxiety upon abstinence, yet had been free of anxiety when the drug was initially prescribed. in addition, symptoms such as tremor, diaphoresis, and even insomnia, which had been rare prior to taking diazepam, emerged when the drug was stopped. " [p. 110]
"... neither age, sex, psychiatric history, nor the presence of current psychiatric problems have the slightest relationship to drug use and abuse variables. It is disappointing to find no individual characteristics predictive of potential danger with diazepam. " [p. 110]

"In addition, many subjects not thought to be "addiction-prone" developed what appeared to be both tolerance and withdrawal. These subjects, given the drug for medical reasons and without a psychiatric history, were just as likely as psychiatric patients to develop tolerance and withdrawal." [p. 111]

"... age, sex, and the presence or absence of a history of psychiatric, alcoholic, or drug-related problems had no bearing on development of tolerance or withdrawal, thus raising the question about the validity of the "addiction-prone" concept. " [p. 112]

Mendelson G.
Withdrawal Reactions after Oxazepam.
Lancet 1978; i: 565.

"Major withdrawal reactions, including psychotic episodes and grand-mal seizures, have been described in patients who abruptly stopped taking diazepam or chlordiazepoxide in "therapeutic" doses. The effects of such withdrawal may not appear for several days and may take up to 14 days to become apparent."

Michelini S, Cassano GB, Frare F, Perugi G.
Long-Term Use of Benzodiazepines: Tolerance, Dependence and Clinical Problems in Anxiety and Mood Disorders.
Pharmacopsychiatry 1996; 29: 127-134.

"Long-term use of BZ seems to induce chronic dysphoric mood, with persistence of anxiety, irritability, difficulty in concentration and memory impairment." [p. 130]

"...anterograde amnesia, irritability, anger, hostility, depression and the impulse dyscontrol with high suicidal risk are clinically relevant findings in a well-defined number of long-term users with mood and anxiety disorders. In spite of this, these symptons are often interpreted as an exacerbation or as a natural evolution of previous disorders and the chronic use of sedatives is overlooked." [p. 131]

Murray D, O'Leary D.
Recommendations for Data Sheets on Benzodiazepines Ignored.
BMJ 1984; 288: 717.

"The Committee on Review of Medicines, in its guidelines for data sheets on 10 named benzodiazepines, "considered that an appropriate warning regarding long-term efficacy be included... particularly in view of the high proportion of patients receiving prescriptions for extended periods of time." In conjunction with a survey on prescribing patterns we examined the Association of the British Pharmaceutical Industry's Data Sheet Compendium 1983-1984. We found the 10 named compounds represented by 17 proprietary preparations. Although 16 warn that "prolonged" or "excessive" use may lead to dependence, only one carries a caution regarding long term efficacy. **If the pharmaceutical industry is allowed such latitude in the data sheets we can hardly expect higher standards in their advertising literature."**

O'Brian CP, McLellan AT.
Myths about the Treatment of Addiction.
Lancet 1996; 347: 237-240.

"... addictions are similar to other chronic disorders such as arthritis, hypertension, asthma and diabetes. Addicting drugs produce changes in brain pathways that endure long after the person stops taking them. Further, the associated medical, social, and occupational difficulties that usually develop during the course of addiction do not disappear when the patient is detoxified. These protracted brain changes and the associated personal and social difficulties put the former addict at great risk of relapse. Treatment for addiction, therefore, should be regarded as being long term... " [p. 237]

Olajide D, Lader M.
Depression Following Withdrawal from Long-Term Benzodiazepine Use: A Report of Four Cases.
Psychological Medicine 1984; 14: 937-940.

Depression following withdrawal from long- or short-term use of benzodiazepines is not uncommon, yet it is underreported in the benzodiazepine withdrawal literature. Four cases of depressive illness supervening during benzodiazepine withdrawal are reported. Depression may, it is suggested, be an integral part of the benzodiazepine withdrawal syndrome. [SUMMARY p.937]

Olson KR, Yin L, Osterloh J, Tani A.
Coma Caused by Trivial Triazolam Overdose.
American Journal of Emergency Medicine 1985; 3: 210-211.

Physicians should be aware that unlike older, longer-acting benzodiazepines, the new hypnotic triazolam may cause serious central nervous system depression following relatively small overdosage. Patients receiving triazolam should be carefully instructed not to exceed usual recommended doses. [SUMMARY p. 211]

Oster G, Huse DM, Adams SF, Imbimbo J, Russell MW.
Benzodiazepine Tranquilizers and the Risk of Accidental Injury.
American Journal of Public Health 1990; 80: 1467-1470.

"We found accident-related care was more likely among persons who had been prescribed benzodiazepines; among these persons, the probability of an accident-related medical encounter was higher during the months in which a prescription for a benzodiazepine had recently been filled compared to other months. " [p. 1467]

**Pomara N, Stanley B, Block R, Guido J, Stanley M, Greenblatt DJ, Newton RE, Gershon S.
Increased Sensitivity of the Elderly to the Central Depressant Effects of Diazepam.
Journal of Clinical Psychiatry 1985; 46: 185-187.**

"The most striking finding in the present study is that a low diazepam dose, 2.5 mg, produced significant impairment in the elderly on the four performance tasks sensitive to diazepam effects, while our comparison group of normal young subjects showed no significant diazepam effects in these tasks. These findings support the hypothesis that elderly people may show greater adverse diazepam effects on memory and psychomotor performance. " [p.186-187]

**Poser W, Poser S.
[Abuse of and Dependence on Benzodiazepines.]
Internist 1986; 27: 738-745.**

"The withdrawal syndrome does not abate rapidly in all patients, occasionally it may be protracted for months after ingestion of the last dose. The authors know of certain patients, who are complaining of perceptual disturbances for years afterwards, although no anxiety disorder was known prior to the benzodiazepine dependence. "[p. 744]

**Power KG, Jerrom DWA, Simpson RJ, Mitchell M.
Controlled Study of Withdrawal Symptoms and Rebound Anxiety after Six Weeks Course of Diazepam for Generalised Anxiety.
BMJ 1985; 290: 1246-1248.**

"Our results suggest that withdrawal from diazepam by substitution with single blind placebo leads to an increase in both rebound and withdrawal symptoms after a short period of treatment."

"Our finding that withdrawal symptoms can occur, albeit without graded withdrawal, after a relatively short period of treatment has important implications for management. The present trend has been the advocacy of reduced duration of treatment. The minimum length of regular treatment before dependence can occur is regarded by some as three months. Our study suggests that withdrawal symptoms occur at normal therapeutic doses and when diazepam is used for what has hitherto been regarded as a safe length of treatment. " [p. 1248]

**Prescott LF.
Safety of the Benzodiazepines . In: Costa E, ed. The Benzodiazepines. From Molecular Biology to Clinical Practice. New York: Raven Press, 1983; 253-265.**

"The most common and most important adverse effects of the benzodiazepines are those affecting the central nervous system. These effects usually represent exaggerated pharmacological actions and include drowsiness, lethargy, retardation, depression, dysarthria, ataxia, confusion, disorientation, and, in the elderly, dementia. These drugs also have subtle effects on mood, mentation, and behaviour, reducing activity, drive, and initiative to the extent that patients may fail to react appropriately to adverse or dangerous situations and be unable to face and cope with their problems. In addition they may blunt discretion and precipitate the taking of an overdose. The elderly are particularly susceptible to the central effects of benzodiazepines, and they are also least able to compensate for cerebral functional impairment. " [p. 254]

"The benzodiazepines are often prescribed as a panacea for the pressures and problems of life in people who are disappointed, unhappy, or frustrated. Al though some undoubtedly obtain

benefit, there is evidence that others are made worse and have more difficulty in coping with adverse circumstances. More worrisome is the possibility that these drugs might cause or aggravate depression and predispose to self-poisoning. Certainly, in my experience, many patients admitted to hospital with self-poisoning admit that the benzodiazepines prescribed previously for their personal problems actually made them worse, making them feel more "depressed" and less able to cope. " [p. 255]

"The adverse effects of drugs on psychomotor function may be subtle and unrecognised by the patient. The risks again are likely to be greatest with the cumulative long-acting benzodiazepines since effects may persist for many hours or days after the last dose. The patient who takes nitrazepam at night will still have about 85% of the dose in his body as he drives his car to work the following morning. " [p. 256]

"It is the prescribing doctor's clear responsibility to warn patients accordingly. Unfortunately many patients who had been prescribed these drugs do not seem to have been warned of the possible risks by their doctors. I have encountered drivers of double-decker buses, heavy goods vehicles, and even the operator of a very large dockside crane who stated they had been prescribed benzodiazepines without any warnings or restrictions. " [p. 256]

Priest RG, Montgomery SA.
Benzodiazepines and Dependence: A College Statement.
Bulletin of the Royal College of Psychiatrists 1988; 12: 107-109.

Amnesia is frequently a real side effect of the use of benzodiazepines and not just a figment of the individual's imagination or a coincident symptom of emotional disorder.
It is often inadvisable to prescribe benzodiazepines to a patient in an acute crisis as the amnestic property of these compounds may not allow patients to make an optimum response to the situation which they are facing. In cases of loss or bereavement, the psychological adjustment to this trauma may be severely inhibited by benzodiazepines and any tendency to denial could be reinforced. " [p. 107]

Rickels K, Case WG, Schweizer EE, Swenson C, Fridman RB.
Low-Dose Dependence in Chronic Benzodiazepine Users: A Preliminary Report on 119 Patients.
Psychopharmacology Bulletin 1986; 22: 407-415.

"In fact, one hard-earned lesson is that long-term BZ users are in need of much more intensive psychiatric and social support than other anxious or depressed patients. " [p. 414]

Roberts K, Vass N.
Schneiderian First-Rank Symptoms Caused by Benzodiazepine Withdrawal.
British Journal of Psychiatry 1986; 148: 593-594.

“Benzodiazepine withdrawal has been found to give rise to numerous physical and psychological symptoms.”

Roche Products Inc. Manati, Puerto Rico.
"The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. " [p.893]
[In advertisement for "Valium", Archives of General Psychiatry 1990; 47: 893.]

" SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache,

incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. "

Romney DM, Angus WR.
A Brief Review of the Effects of Diazepam on Memory.
Psychopharmacology Bulletin 1984; 20: 313-316.

"Moreover, it [i.e. diazepam] appears to produce side effects, previously unnoticed, both on mood, causing depression and rage, and on cognitive and psychomotor functioning. " [p. 313]

Ross M.
Lorazepam-Associated Drug Dependence.
Journal of the Royal College of General Practioners 1986; February: 86.

"I should like to draw attention to what, in my opinion, are the unequivocal risks of lorazepam-associated drug dependence and exaggerated withdrawal symptoms. In my experience, this can occur often with low dosage, short courses and for many months after cessation of therapy.

It is common to find other general practitioners and psychiatrists who share this view and there is also widespread lay awareness of the problem. For the last year and a half I have been communicating with the Committee on Safety of Medicines about the problem. They answer that they have received few yellow card reports on this problem.

My personal view is that this is because doctors do not realise that reporting an expected side-effect of a drug is as useful for epidemiological purposes as is reporting an unexpected side-effect for general scientific purposes. I should like, therefore, to appeal to all the general practitioners who must be seeing this problem, to report any cases to the Committee on Safety of Medicines. "[p. 86]

Rowlatt RJ.
Effects of Maternal Diazepam.
BMJ 1978; 1: 985.

" High doses (30 mg or more) of diazepam administered during labour cause, in the infant, failure to start breathing, shallow, inadequate respirations, periodic cessations of respiration, floppiness, subnormal temperature, and poor sucking. These effects last several days and significant plasma levels of diazepam and of its active metabolites persist for up to eight days. Diazepam accumulates in tissue of the fetus, and is metabolised and excreted slowly by the newborn baby. "

"The depressant effects of pethidine and other drugs given during labour would be made worse by diazepam. "

"Diazepam is excreted in breast milk, which may sedate the baby and cause feeding difficulty. Finally, there is the fear of impairing future intellectual development by exposing the developing brain to the influence of tranquillisers."

"How often must we be reminded of the ancient precept primum non nocere ? "

Scharf MB, Jacoby JA.
Lorazepam - Efficacy, Side Effects, and Rebound Phenomena.
Clinical Pharmacology and Therapeutics 1982; 31: 175-179.

"The spontaneous reports of amnesia by three of our subjects after oral doses of lorazepam strongly suggest that this side effect, thought to occur rarely after oral doses of other benzodiazepines, may be a more frequent side effect of lorazepam." [p. 178]

Schneider-Helmert D.
Why Low-Dose Benzodiazepine-Dependent Insomniacs Can't Escape Their Sleeping Pills.
Acta Psychiatrica Scandinavica 1988; 78: 706-711.

"Comparison with drug-free insomniacs showed that LBD (= low-dose benzodiazepine dependence) leads to a complete loss of hypnotic activity and substantial depression of delta and REM sleep."

"Upon withdrawal, recovery from this suppression, especially in REM sleep, occurred, while insomnia did not increase. The patients, however, reported sleeping longer while taking the drug compared with withdrawal. This misperception seems to be a specific effect of benzodiazepines, and contrasts with the full awareness of insomnia upon withdrawal. It is concluded that these effects play a leading role in the patient's inability to escape their sleeping pills. "

"It has recently been recognised that the widespread use of benzodiazepines bears a considerable risk for patients to develop dependence on therapeutic dosage. One of the major reasons to use these substances on a long-term basis is chronic insomnia. Half of the patients reporting to the Medical Center Mariastein are dependent on benzodiazepines according to clinical criteria. They typically defend their persistent use of sleeping pills with the claim that they experience such poor sleep when stopping medication for only one or two nights and they therefore feel forced to continue drug intake despite fading hypnotic efficacy. In fact, insomnia has been reported to be among the most frequent withdrawal symptoms after somatic dependence has developed with the use of benzodiazepines in therapeutic dosage for months or years. "[p. 706]

Schweizer E, Case WG, Rickels K.
Dr. Schweizer and Associates Reply.
American Journal of Psychiatry 1989; 146: 1242.

"It is our position that most of these patients did not require long-term benzodiazepine therapy - certainly not continuously for many years. In fact, we have unpublished data which demonstrate that many patients, once they have been withdrawn from their maintenance benzodiazepines, show more improvement on clinical measures of anxiety and depression than they did during their chronically medicated state. " [p. 1242]

Short TG, Maling T, Galletly DC.
Ventricular Arrhythmia Precipitated by Flumazenil.
BMJ 1988; 296: 1070-1071.

"The patient was extubated 20 hours after admission by which time her electrocardiogram was normal. Further questioning disclosed that she had a nine year history of physical dependency on benzodiazepines and had developed insomnia, anxiety, and phobias on attempted withdrawal. "[p. 1071]

Smith RJ.
Study Finds Sleeping Pills Overprescribed.
Science 1979; 204: 287-288.

"Sleeping pills, the most prescribed medication in the world, are more dangerous and less useful than either physicians or patients realize, according to a recent report by the Institute of Medicine (IOM) - National Academy of Sciences. " [p. 287] “

"Currently, more than 25 million such prescriptions are written annually in the United States alone, and more than 8 million persons use the pills sometimes during the year.
The panel is particularly concerned that persons are taking the pills for to many consecutive nights, beyond the period of proved effectiveness, and to a point where the hazards may be severe: Physicians should rarely, if ever, prescribe hypnotic drugs for periods beyond 2 to 4 weeks. Clinical trials cited by the panel show that the effectiveness of most pills begins to drop off after 7 nights. Currently, most prescriptions are for 30 tablets or more, however. " [p. 287]

"... the IOM report concludes that, although barbiturates are indeed as hazardous as everyone thinks, the chief alternatives, benzodiazepines, may be just as risky, and in some ways may be even more risky than barbiturates. " [p. 287]

"In addition, the panel reported, Dalmane may not have some of the attributes ascribed to it by its manufacturer, Hoffmann-La Roche Inc. Labelling in the Physician's Desk Reference and in the company's advertising, for example claims, "Sleep laboratory studies have objectively determined that Dalmane is effective f or at least 28 consecutive nights of drug administration." Nowhere, the IOM panel says, "do these advertisements reveal that the claim of effectiveness for 28 nights is based on studies of only ten patients and that hundreds of individuals with sleep complaints had to be screened to select these severe insomniacs for research purposes. " [p. 287]

"... the panel concluded that what was thought to be Dalmane's greatest attribute was, for all practical purposes, unimportant. Unlike barbiturates, Dalmane is not lethal by itself in overdose. But the panel discovered that an increasing proportion of drug-related deaths involve alcohol; because both drugs are lethal in combination with alcohol, Dalmane does not offer any significant advantage in diminishing the overall number of deaths related to sleeping pills. " [pp. 287-288]

"The committee finds information from these sources tends to be incomplete and of questionable value to the physician." One example is the current PDR listing for Dalmane, which claims that Dalmane is effective for a month of consecutive use. This listing is based on only two studies in sleep laboratories with five people each. Asked about this, a company spokesman admits that "perhaps this is not satisfactory." Also, no mention of Dalmane's long-acting metabolite was made until last year, 5 years after the characteristic became known. When the information was added, consequent adverse effects were not mentioned; the company instead brags that the drug is even more effective than known earlier. "[p. 288]

Snaith RP, Hindmarch I.
Psychotropic Drugs and Road Accidents.
BMJ 1977; 2: 263.

"Sedative drugs, of course, are not detected in the breathalyser and if they were there would be no legal implications. Yet there is good evidence that the sedative drugs commonly prescribed (previously the barbiturates and now the benzodiazepines) do potentiate the effect of alcohol." [p. 263]

"Prescriptions for sedative drugs and hypnotics now run into millions a year. The people to whom they are prescribed are also likely to be using alcohol... yet there is no requirement placed upon the medical profession to issue a warning of this interaction effect when the drugs are prescribed." [p. 263]

"We believe that research in this field has been to long delayed and that it should now be accorded priority... Complaints may be made that issuing such warnings and recommendations will inevitably decrease treatment compliance, but if this is to be set against the potential saving of life then the balance will be favourable, for sedative drugs are frequently prescribed for trivial reasons. " [p. 263]

Surendrakumar D, Dunn M, Roberts CJC.
Hospital Admission and the Start of Benzodiazepine Use.
BMJ 1992; 304: 881.

"The identification of 17 potential new users of benzodiazepines after admission to the general beds in one district in two weeks was higher than expected and is unacceptable. If the study is representative it implies a considerable potential risk for subsequent dependence. (- - -)
Our study suggests that hospital prescribing continues to contribute to benzodiazepine use in the community as half the group had first been prescribed the drugs in hospital.
In addition to the inappropriate supply of drugs at the end of a hospital stay, poor prescribing was evident by the drug's apparently unwarranted use in an elderly demented patient and continuous use in a stroke victim. There was also clear evidence that benzodiazepine hypnotics were being prescribed at the time of admission, before an assessment of the need could have been made. There is no room for complacency in hospitals regarding benzodiazepine prescribing. This study highlights the need for prescribing policies to be formulated and instituted. "

Tata PR, Rollings J, Collins M, Pickering A, Jacobson RR.
Lack of Cognitive Recovery Following Withdrawal from Long-Term Benzodiazepine Use.
Psychological Medicine 1994; 24: 203-213.

“Twenty-one patients with significant long-term therapeutic benzodiazepine (BZ) use, who remained abstinent at 6 months follow-up after successfully completing a standardized inpatient BZ withdrawal regime, and 21 normal controls matched for age and IQ but not for anxiety, were repeatedly tested on a simple battery of routine psychometric tests of cognitive function, pre- and post- withdrawal and at 6 months follow-up. The results demonstrated significant impairment inpatients in verbal learning and memory, psychomotor, visuo-motor and visuo-conceptual abilities,compared with controls, at all three time points. Despite practice effects, no evidence of immediate recovery of cognitive function following BZ withdrawal was found.

Modest recovery of certain deficits emerged at 6 months follow-up in the BZ group, but this remained significantly below the equivalent control performance. The implications of persisting cognitive deficits after withdrawal from long-term BZ use are discussed.” [SUMMARY p. 203]

"The main cognitive functions assessed in this study include working memory, verbal learning and memory, visuo-motor and visuo-conceptual skills. The lack of evidence for clinically significant cognitive recovery raises concern about the severity and reversibility of any underlying BZ-induced organic impairment." [p. 211]

"The adverse effects of acute diazepam administration on memory and arousal in man are well known (Lister & File, 1984; Lister, 1985), and have been linked to the high density of BZ

receptors in the hippocampus and reticular formation (Wolkowitz et al. 1987), although the neurochemical basis of chronic post-withdrawal deficits has yet to be demonstrated. " [p. 212]

"Persisting neuropsychological deficits affecting psychomotor function and new verbal learning have occupational implications. Driving and safety at work with machinery may both be impaired (Skegg et al. 1979, Roy-Byrne & Cowley, 1990).Patients' impairment, following withdrawal from long-term BZ use, is likely to be less than that due to acute drug ingestion or the early withdrawal phase. Yet, one must be cautious in predicting either rapid or comprehensive cognitive recovery for those patients contemplating or undergoing a withdrawal regime, or in estimating the cognitive effects of mood dysfunction, which require further investigation. " [p. 211]

Trickett S.
Withdrawal from Benzodiazepines.
Journal of the Royal College of General Practitioners 1983; 33: 608.

"I have started a support through withdrawal scheme for people coming off benzodiazepines. The enormous amount of suffering I see makes me wonder how much information on the toxic effects of these drugs, and illness caused by their withdrawal, reaches the doctors. The pharmacological manuals grossly understate the dangers of tolerance, dependence and withdrawal that have been demonstrated so clearly after the use of these drugs. This is not only after long-term use at high dosage, but also after very short-term use (two weeks), on a normal therapeutic dose.

We must look urgently for the most effective treatment, since a quarter of benzodiazepine users will become severely physically dependent. Widespread dependence, as much as overprescribing, must be the reason for the enormous use of these drugs.

The withdrawal syndrome has many unique features and needs to be treated as a new disease. In acute withdrawal, psychosis, convulsions and suicides are a great deal more common than the literature would suggest. The physical symptoms, many of which are not typical of anxiety, are the worst aspect of the illness.

Some of the symptoms are belated and are not associated with the drugs by patient or doctor. Rebound insomnia is a persistent symptom. Unfortunately, and so often, doctors prescribe another benzodiazepine for night sedation when the patient complains of this.

Psychological dependence is less of a problem. Many users report craving for the drugs, but at the same time feel revolted by them, and angry that they have to take them to avoid withdrawal symptoms.

Thousands of people could not possibly invent the bizarre symptoms caused by the therapeutic use of benzodiazepines and reactions to their withdrawal. Many users have to cope, not only with a frightening range of symptoms, but also with the disbelief and hostility of their doctors and families. It is not uncommon for patients to be "struck off" if they continue to complain about withdrawal symptoms. Even when doctors are concerned and understanding about the problem, they often have little knowledge of withdrawal procedure, and even less about treatment. The drugs newsletter on benzodiazepines issued in this region will help them. Is anything being done elsewhere?

Banning benzodiazepines would be unrealistic; there is nothing to replace them. But I would urge doctors to seek more information about them, and to listen to what their patients are saying.

Release and self-help groups all over the country have done wonderful work, but why should people need to form groups for an urgent medical problem? This is drug-induced disease, not drug abuse. "

Tyrer P.
The Benzodiazepine Post-Withdrawal Syndrome.
Stress Medicine 1991; 7: 1-2.

"Much more needs to be done to establish the post-withdrawal syndrome as a clinical and pharmacological entity, but it is unlikely to be an artefact or entirely "mediogenic" (created by the media). The subject certainly deserves more attention from research workers in the stress disciplines. " [p. 2]

van der Kroef C.
Reactions to Triazolam.
Lancet 1979; ii: 526.

"During the past nine months I have been confronted in my psychiatric practice with a syndrome which is almost certainly induced by the benzodiazepine triazolam ("Halcion")
Triazolam can produce the following symptoms: severe malaise; depersonalisation and derealisation; paranoid reactions; acute and chronic anxiety; continuous fear of going insane; depression and deterioration of existing depression; hyperaesthesia, especially for sound but also for smell, taste and light; sometimes hypoaesthesia for the same stimuli; nightmares; restlessness; inability to concentrate; verbal and physical aggression; conflicts with entourage; severe suicidal tendencies; hypnagogic hallucinations; impulse actions; amnesia; dysphagia, accompanied by nasty taste, painful tongue and mucous membranes, dry mouth, loathing of food, rigid feeling in the throat and emaciation up to 2½ stone; cervical pains; headaches that are often extremely sensitive to sound; pressure on the ears; numb and cold feeling in fingers and toes, extending to the distal parts of the extremities; tingling feeling, muscular cramps and paralyses, often at the sinistral side; catatonically impaired motor functioning; reading complaints and blurred vision; dysfunctional speaking and writing; sweating.

This syndrome must be classified with the exogenous syndrome of Bonhoeffer. Symptoms ususally disappear within a couple of days after stopping triazolam; sometimes there are withdrawal symptoms, such as rapidly mounting panic and heavy sweating.
These side-effects appear in patients who are taking other drugs and in those who are not and in patients who have never had psychiatric treatment as well as in those with a psychiatric history. Patients with this syndrome may be admitted on suspicion of brain tumour or schizophrenia. They impress the observer as seriously ill and the patients themselves often feel desperate and have to fight an almost irresistible impulse to commit suicide. I know of one patient who did commit suicide..."