BENZODIAZEPINES; RISKS AND BENEFITS. A RECONSIDERATION

Baldwin, Aitchison, Bateson, Curran, Davies, Leonard, Nutt, Stephens and Wilson.

J Psychopharmacol 2013, 27 (11) 967-71

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NOVEMBER 2013

This paper consists of recommendations for clinical practice about prescribing benzodiazepines and managing prescribed benzodiazepine users. It has been compiled by representatives from the Royal College of Psychiatrists and the British Association for Psychopharmacology. Considering that one of the authors and the editor of this journal, Professor David Nutt, has received the 2013 John Maddox Prize for Standing up for Science, it is surprising and disappointing that there is virtually no science in the article.

P 967, col 1 **Introduction**

** " The group contends that benzodiazepine prescribing, like other aspects of clinical practice, should be based on thoughtful consideration of the likely risks and benefits of benzodiazepines,…. and of alternative interventions." "The balance of risks and benefits…. is ultimately a matter of clinical judgment."

This statement is trite and unnecessary since it applies, as stated, to all drug prescriptions and all interventions. It is presumptuous and insulting to doctors to remind them of this ethic which forms the very basis of the medical profession. It is patronising if it is meant to apply especially to benzodiazepine prescriptions. Prescribed benzodiazepine users, the patients themselves, were the first – before the doctors- to recognise that benzodiazepines could be addictive if used long term.

Doctors should be more scientific in their clinical judgments. I have written elsewhere: "How the dependence potential of benzodiazepines was overlooked when it was clear that they could replace barbiturates and similarly acting drugs is a matter for amazement and casts shame on the medical profession which claims to be scientifically based. Cross-tolerance between different drugs, for instance between barbiturates and alcohol, was well understood at the time and clearly implied that if one drug could replace another it must have common characteristics and usually a common mode of action. This similarity between benzodiazepines and barbiturates was ignored and doctors were urged in a campaign by the UK medical profession in the 1970s to prescribe benzodiazepines instead of barbiturates. They complied with such zeal that benzodiazepines, believed to be harmless, were prescribed long term, often for many years, for anxiety, depression, insomnia and ordinary life stresses." (Ashton, 2004)

Thus doctors, acting thoughtlessly and unscientifically, and still today prescribing benzodiazepines long term, are responsible for causing benzodiazepine dependence and all its attendant suffering in millions of people. The victims have received no apology.

P 970, col 1 **Dependence**

**"Withdrawal reactions are generally short-lived, typically lasting less than one month …"

This statement is not scientific; where is the evidence? On how many patients has the withdrawal reaction been measured including, age, drug dose, duration of use, indication for prescription, type of benzodiazepine, length of follow-up, etc.? What is the withdrawal reaction measured from? Is it from the start or the end of dosage tapering? Is it after rapid, sudden or gradual cessation of use? Is it the time after the last molecule of benzodiazepine including active metabolite has left the body? What about patients who already have withdrawal symptoms while still taking the benzodiazepine, because of the development of tolerance? (New symptoms of apparent 'withdrawal' while continuing to take the drugs is common in long term users, and may lead to dosage escalation).

**"There is controversy whether symptoms persisting for many months…..are withdrawal symptoms or simply the features of an underlying disorder, or worsening of that condition triggered by treatment withdrawal."

This statement ignores the large number of patients who have no underlying disorder but who have been prescribed benzodiazepines for sports injuries, after accidents requiring splints (commonly prescribed by orthopaedic surgeons for muscle relaxation after surgery requiring splinting) and those who have been wrongly prescribed benzodiazepines for unrelated conditions such as influenza, menorrhagia, dental treatment, bereavement or other personal tragedies, and many other reasons. These patients may also have persistent withdrawal symptoms after long- term benzodiazepine treatment. The authors have not considered the possibility that benzodiazepines themselves cause the symptoms they suggest as an "underlying disorder". Where is the science in that?

(See also Tolerance, p969, below)

P 969, col 2 **Tolerance**

This section is extremely short. It does not mention the mechanism of tolerance or explain the immense clinical importance of this phenomenon in long term benzodiazepine use and dependence, and its essential contribution to withdrawal effects. I am surprised that Dr Bateson, who reviewed the subject in 2002 (and possibly more recently), let this omission pass, as an author of this paper.

Tolerance to benzodiazepines, probably results as a homeostatic response involving 'down-regulation' of benzodiazepine receptors on GABA-A receptor subunit), which become internalised within neurones during chronic use. Changes in gene transcription (gene expression) occur in the internalised receptors, resulting in a long-term alteration of function. This pathway could operate on different time scales, depending on the receptor subtype and brain region involved, and thus give rise to differing rates of development of tolerance to various benzodiazepine actions. Such tolerance occurs in long-benzodiazepine use in 'therapeutic' dosage, whether taken as anxiolytics or as hypnotics (the latter demonstrated in a study of long-term benzodiazepine hypnotic users by Professor Curran (Curran, 2003).

Once tolerance has developed, withdrawal of benzodiazepines exposes the recipient to the drug-induced alterations in benzodiazepine receptors, resulting in under-activity in the many domains of function normally modulated by

GABA-ergic mechanisms, accounting for the multiple and diverse nature of benzodiazepine withdrawal reactions. The various changes in GABA /benzodiazepine receptors induced by tolerance, including changes in gene expression, may be slow to reverse after drug withdrawal and may do so at different rates, possibly accounting for the variable time of emergence and duration of individual withdrawal symptoms and the prolonged, and sometimes protracted, nature of the benzodiazepine withdrawal reaction. (See dependence, p970 above).

It is a pity that this whole aspect of benzodiazepine effects, one of the few areas of benzodiazepine actions that has been studied scientifically, is neglected in this article. Where is the science here?

Long-term benzodiazepine use

P 968, col 1

** " …. usually in acute treatment for the reduction of anxiety symptoms, but sometimes in longer-term treatment, designed to prevent a relapse…"

P 968, col 2

** "…. Longer term treatment….might be considered desirable…… in conditions such as chronic treatment-resistant anxiety disorders or in patients who have established dependence and have not been able to stop treatment successfully".

P 969, col 1

** ". …there is little evidence that longer term use [of benzodiazepine hypnotics] is more hazardous than short term use."

There is plenty of evidence that long term use is hazardous, especially in the elderly, because of cognitive impairment (Curran), night wandering, falls and fractures and much else reported in the clinical literature including controlled trials.

P 970, col 1

** " In some patients pharmacological and psychological interventions will be only of limited benefit, so certain individuals will be unable to stop benzodiazepines."

This advice about long-term benzodiazepine use is negative and dangerous. It will tend to perpetuate, prolong and possibly increase long-term benzodiazepine prescribing. It is not a scientific way to solve the problem.

The emphasis on the difficulty of withdrawal in some patients will deter some doctors from even trying. Yet, given information and time, experience has shown that most people can withdraw successfully from their iatrogenic addiction. At present effective withdrawal is mostly carried out by voluntary support groups, largely financed by charities. Some of these have excellent results

(e.g. Bristol and District Tranquilliser project). Patients should be informed of available support groups.

Successful withdrawal may require more time and help than GPs are able to give to individual patients, but doctors should campaign for more support from their grant-giving bodies for practice nurses , counsellors, pharmacists and others who could work within their practice and give advice on withdrawal schedules. In very many cases, patients have been able to withdraw by their own efforts, given information and very little intervention, and have regained better physical and psychological health than patients who remained on long-term benzodiazepines (Heather et al, 2004).

Long-term benzodiazepine treatment, prescribed for whatever reason, inevitably condemns the patient both to dependence and to cognitive impairment and psychomotor slowing, to which complete tolerance does not develop, as many studies of long-term users have shown. Because of the impairment, patients are not always able to recognise their dependence or to make rational decisions about continuance or withdrawal

The effects on the brain of long-term benzodiazepine use have never been adequately researched despite the reports of many patients of enduring, perhaps irreversible, adverse effects. Some preliminary CAT studies of long term users by Professor Malcolm Lader were suggestive of brain damage but have never been followed up with modern techniques such as MRI and fMRI. An influential multi-authored paper of this kind should surely make a plea for further research in this area.

One does not solve problems or advance science by trying to make the best of the status quo - which is what the advice in the present superficial and unscientific paper does. The medical profession deserves better than that of nine distinguished authors.

P 969, col 2 **Risks**

Use of benzodiazepines in pregnancy. Mention should be made that benzodiazepines cross the placenta and affect the foetus. Risks to the neonate (benzodiazepine dependence; floppy infant syndrome) are well known and should be mentioned. There are also as potential risks to the developing foetal brain. Animal studies have shown that maternally administered psychotropic drugs can adversely affect the foetal development of transmitter systems. This is another area which requires research - for example, recording the use of benzodiazepines during pregnancy in mothers of children with ADHD and other pervasive developmental disorders.

P 969, col 1 **Z-drugs**

** “However, the Z-drugs may have some limited advantages… in terms of dependence and withdrawal, and should be considered as an alternative, particularly if there seems to be a potential need for longer-term treatment or in patients presumed to be at increased risk of dependence.”

Superiority of Z-drugs over benzodiazepines in terms of risks of dependence or misuse has never been adequately shown. Z-drugs are addictive in animal studies and there are many reports of misuse/abuse in humans. There are not infrequent cases of the

relatively short- acting zopiclone or zolpidem being taken is excessive doses, and/or up to seven times or more a day, though initially prescribed as a single nightly hypnotic dose. They also have anxiolytic properties and can substitute for benzodiazepines. They have not been shown to be suitable for long-term use.

P 970, col 2 and 971, col 1 **Withdrawing benzodiazepines; Recommendations**

The guidance and recommendations are extremely vague and of no help to doctors inexperienced in prescription or withdrawal of benzodiazepines. These sections should be more detailed, explicit and comprehensive or should give reference(s) to approved sources of advice (e.g. NICE, BNF, Clinical Knowledge Summaries). The recommendations given here may be well-meaning but are unhelpful. They are highly unlikely to lead to any improvement in benzodiazepine prescribing or withdrawal, and are not scientific.

Unfortunately, the paper illustrates how little clinical medicine is influenced by scientific observations. Sixty years after the introduction of benzodiazepines there has been little improvement in clinical benzodiazepine problems. This contribution is certainly not a shining example of 'Standing up for Science'.

References

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