Controlled comparison of the characteristics of long-term benzodiazepine users in general practice

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SUMMARY. From three general practices, served by 11 principals, 205 long-term benzodiazepine users were identified and matched for age and sex with controls. Benzodiazepine users had significantly higher rates of previous physical illness, consultation and non-psychotropic drug consumption than controls. The characteristics of those receiving prescriptions for benzodiazepine hypnotics alone, anxiolytics alone and anxiolytics plus hypnotics were also investigated. Significant differences emerged between these three groups. Patients receiving hypnotics only were older, had a history of more physical illness and had received more non-psychotropic medication than patients receiving anxiolytics only. The anxiolytic plus hypnotic group had previously received more hypnotics and were currently receiving more medication than the group receiving anxiolytics alone. The results are discussed in relation to current concerns about benzodiazepine dependence and withdrawal.

Introduction

THE popularity of benzodiazepines,[1,2] and subsequent problems of dependency and withdrawal[3-5] has led to growing concern about the number of patients on long-term benzodiazepine maintenance.[6-10] Long-term use of these drugs is no longer recommended.[11] Although many articles have been published about the characteristics of heterogeneous groups of psychotropic drug users,[12-15] few have been concerned with benzodiazepine users in particular. Of two recently published papers about the characteristics of long-term benzodiazepine users,[16,17] only one[16] incorporated a matched age and sex control group. Both studies were carried out in single general practices and each had a sample size of around 70 subjects. As the authors acknowledge, these factors restrict the generalization of results and support the need for replication. In one of these studies, patients receiving benzodiazepine anxiolytics or hypnotics were apparently included,[17] while in the other study patients on an anxiolytic alone, or an anxiolytic plus hypnotic were included.[16] However, neither study assessed the similarities or differences between anxiolytic and/or hypnotic users. Studies of hypnotic users have often been limited to the elderly[18] or to those in hospital or residential care settings,[19] or have included non-benzodiazepine hypnotic drugs.[20]

In this paper the characteristics of a large group of long-term benzodiazepine anxiolytic and hypnotic users from three general practices are reported, together with a comparison with age and sex matched controls. Although the boundary between a benzodiazepine anxiolytic and hypnotic is not absolute in pharmacological terms[11] or with regard to how the drug is administered, the characteristics of those receiving prescriptions for hypnotics alone, anxiolytics alone and anxiolytics plus hypnotics, were also investigated as this has not previously been addressed in the literature.

Method

The study was conducted with the consent of the 11 principal general practitioners in three practices in the Forth Valley general practitioner research group between December 1987 and February 1988. The three practices had approximately 17 000 patients attending three main and two branch surgeries, all in suburban and rural environments in the Stirling area. All the practices used the Scottish G-Pass computerized repeat prescription system which provided an accurate and readily available list of all patients receiving benzodiazepines on repeat prescription.

Patients in the three practices who were currently prescribed benzodiazepines and who had received three or more consecutive prescriptions of one or more benzodiazepine were identified. The 445 patients were listed alphabetically and a random sub-sample of 205 patients was established by selecting every second patient. This was done separately for men and women benzodiazepine users to ensure that the sex ratio of the sub-sample was the same as the total group. An age and sex matched control sample of 205 patients who were not currently prescribed benzodiazepines were also selected.

Two non-medical research assistants conducted an initial review of the patients' case notes. The characteristics noted for the benzodiazepine group included age and sex, number of years on benzodiazepines, age at first prescription and current benzodiazepine medication. Information was also collected for both benzodiazepine users and matched controls on the frequency of consultations over the past five years and all prescribed medication over the past 10 years.

In addition, an analysis of illnesses by body system was carried out for study and control groups. First, all diagnoses listed over the past 25 years in the medical summary sheet, in hospital letters to or from general practitioners, or in continuation sheets were recorded by the two research assistants. Secondly, the illnesses were divided into major or minor episodes (excluding trivial illness) by a principal in general practice who was blind to users and controls and who did not work in any of the study practices. Allocation to major or minor episode was based on the need for hospital referral, inpatient treatment, investigation, long-term medication, or permanent disability as well as the effect of the illness on the life of the patient. However, some conditions were listed as minor despite referral to hospital. Thirdly, the consistency of the allocation as a major or minor illness was checked by a research assistant. Finally, all the lists

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of major and minor illness were checked against the original patient records to ensure that there were no omissions. Psychiatric illness was excluded from this analysis and is the subject of a separate study.

Differences between benzodiazepine users and controls were calculated by means of two-tailed t-tests. Differences between groups of patients receiving a benzodiazepine hypnotic alone, an anxiolytic alone and an anxiolytic plus hypnotic were calculated by means of one-way analysis of variance. Where significant one-way analyses of variance were obtained, *post hoc* Scheffe comparisons, at the $P<0.05$ level, were applied to determine where specific between-group differences existed.

Results

The prevalence of three or more repeat prescriptions for benzodiazepines among patients in the three study practices was 26 per 1000 patients.

Characteristics of benzodiazepine users

The benzodiazepine group comprised 48 men (23%) and 157 women (77%). The mean age of these patients was 64 years (standard deviation 14 years, range 27–90 years). The mean age of the men was 59 years (SD 15 years, range 29–90 years) and of the women 65 years (SD 13 years, range 27–88 years). Figure 1 shows the age distribution of the practice population aged over 20 years and that of the benzodiazepine users. Only a minority of benzodiazepine users (approximately 18%) were aged 49 years or below. Figure 2 shows that the majority of the benzodiazepine users (66%) first received a benzodiazepine prescription while aged between 40 and 69 years. The mean age at which patients received their first benzodiazepine prescription was 47 years.

The mean length of time patients had been receiving repeat prescriptions for benzodiazepines was approximately eight years (SD six years, range one month–23 years). Among the 201 benzodiazepine users for whom the length of time they had been receiving repeat prescriptions could be ascertained, over half (58%) had been receiving benzodiazepines for six years or more (Figure 3).

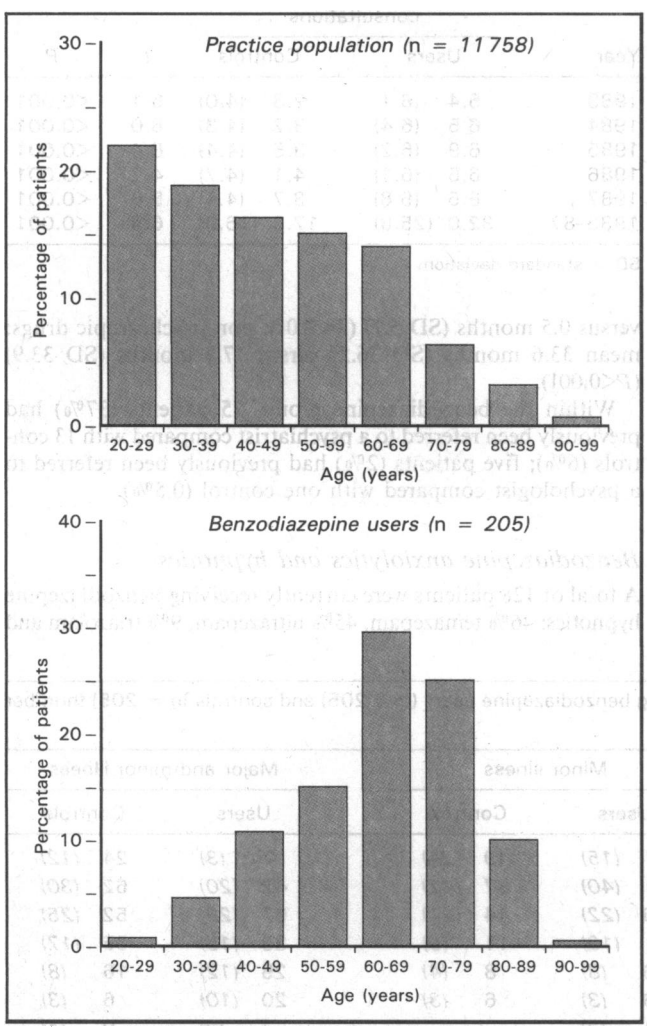

Figure 1. *Percentage age distribution of practice population aged over 20 years and of benzodiazepine users.*

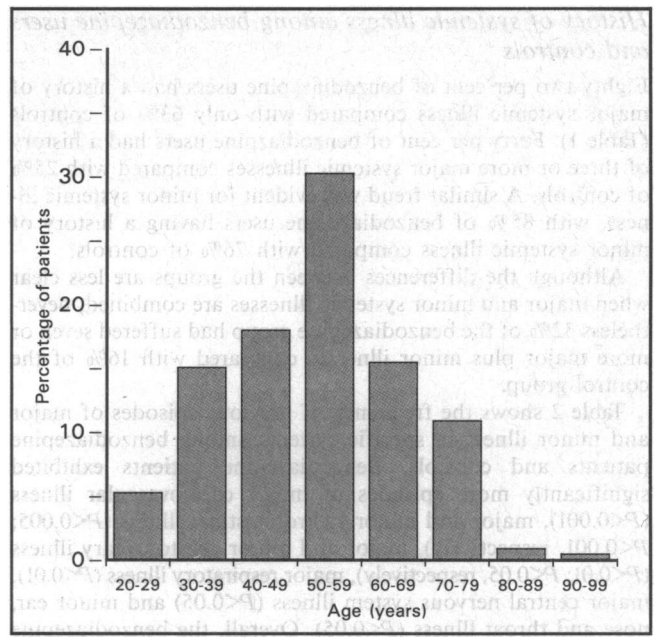

Figure 2. *Percentage distribution of age at which patients first received a benzodiazepine prescription (n = 205).*

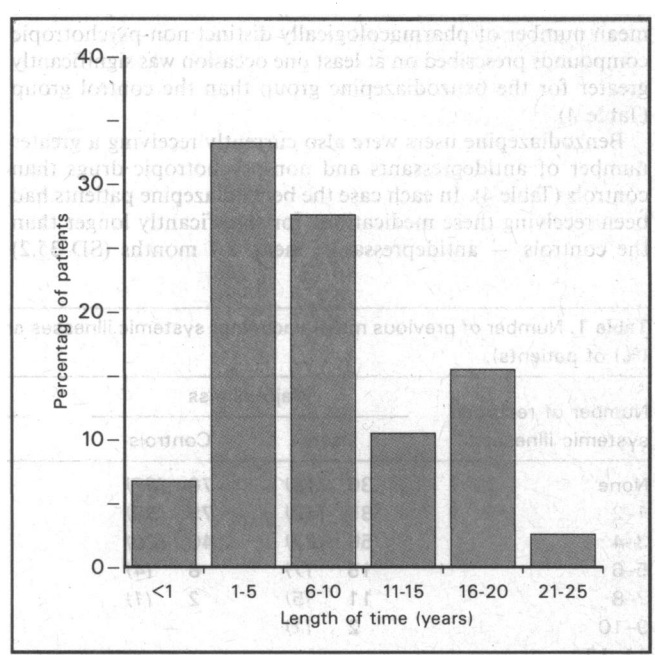

Figure 3. *Percentage distribution of the length of time patients had been receiving repeat prescriptions for benzodiazepines (n = 201).*

History of systemic illness among benzodiazepine users and controls

Eighty two per cent of benzodiazepine users had a history of major systemic illness compared with only 63% of controls (Table 1). Forty per cent of benzodiazpine users had a history of three or more major systemic illnesses compared with 25% of controls. A similar trend was evident for minor systemic illness, with 85% of benzodiazepine users having a history of minor systemic illness compared with 76% of controls.

Although the differences between the groups are less clear when major and minor systemic illnesses are combined, nevertheless 32% of the benzodiazepine group had suffered seven or more major plus minor illnesses compared with 16% of the control group.

Table 2 shows the frequency of previous episodes of major and minor illness in specific systems among benzodiazepine patients and controls. Benzodiazepine patients exhibited significantly more episodes of major cardiovascular illness ($P<0.001$), major and minor gastrointestinal illness ($P<0.005$; $P<0.001$, respectively), major and minor genitourinary illness ($P<0.01$; $P<0.05$, respectively), major respiratory illness ($P<0.01$), major central nervous system illness ($P<0.05$) and minor ear, nose and throat illness ($P<0.05$). Overall, the benzodiazepine group had experienced significantly more episodes of major and minor systemic illness than the control group ($P<0.001$; $P<0.01$, respectively).

Table 2. Nature of previous episodes of major and minor systemic illnesses among benzodiazepine users (n = 205) and controls (n = 205) (number (%) of episodes).

Nature of systemic illness	Major illness		Minor illness	
	Users	Controls	Users	Controls
Cardiovascular	145 *(29)*	68 *(23)*	55 *(9)*	47 *(10)*
Gastrointestinal	88 *(18)*	46 *(15)*	102 *(17)*	50 *(11)*
Genitourinary	70 *(14)*	41 *(14)*	104 *(17)*	70 *(16)*
Respiratory	30 *(6)*	8 *(3)*	17 *(3)*	13 *(3)*
Skin	10 *(2)*	13 *(4)*	45 *(7)*	46 *(10)*
Central nervous system	16 *(3)*	5 *(2)*	11 *(2)*	12 *(3)*
Haematology	5 *(1)*	5 *(2)*	16 *(3)*	8 *(2)*
Endocrine	30 *(6)*	15 *(5)*	12 *(2)*	10 *(2)*
Locomotor	68 *(14)*	65 *(22)*	139 *(22)*	111 *(25)*
Ear/nose/throat	19 *(4)*	14 *(5)*	61 *(10)*	38 *(8)*
Ophthalmic	12 *(2)*	13 *(4)*	39 *(6)*	30 *(7)*
Other	3 *(1)*	4 *(1)*	15 *(2)*	14 *(3)*
Total	496 *(100)*	297 *(100)*	616 *(100)*	449 *(100)*

Consultation rates

For each of the five years 1983–87 benzodiazepine patients consulted their general practitioner at a significantly higher rate than controls (Table 3).

Table 3. Comparison of mean annual number of consultations for benzodiazepine users (n = 205) and controls (n = 205) (df = 408).

Year	Mean (SD) number of consultations		t	P
	Users	Controls		
1983	5.4 (6.1)	2.8 (4.0)	5.1	<0.001
1984	6.5 (6.4)	3.2 (4.3)	6.0	<0.001
1985	6.9 (6.2)	3.5 (4.4)	6.4	<0.001
1986	6.6 (6.1)	4.1 (4.7)	4.7	<0.001
1987	6.5 (5.8)	3.7 (4.4)	5.6	<0.001
1983–87	32.0 (25.8)	17.3 (16.9)	6.8	<0.001

SD = standard deviation.

Psychotropic and non-psychotropic medication and psychiatric referral

Over the 10 year period 1977–87, benzodiazepine users had received a significantly greater number of antidepressants, major tranquillizers, benzodiazepine anxiolytics and hypnotics, and other psychotropic drugs than controls, although the overall frequencies were relatively low (Table 4). Over the same period the mean number of pharmacologically distinct non-psychotropic compounds prescribed on at least one occasion was significantly greater for the benzodiazepine group than the control group (Table 4).

Benzodiazepine users were also currently receiving a greater number of antidepressants and non-psychotropic drugs than controls (Table 4). In each case the benzodiazepine patients had been receiving these medications for significantly longer than the controls — antidepressants: mean 8.7 months (SD 35.2) versus 0.5 months (SD 5.7) ($P<0.01$); non-psychotropic drugs: mean 33.6 months (SD 36.5) versus 17.3 months (SD 33.9) ($P<0.001$).

Within the benzodiazepine group, 75 patients (37%) had previously been referred to a psychiatrist compared with 13 controls (6%); five patients (2%) had previously been referred to a psychologist compared with one control (0.5%).

Benzodiazepine anxiolytics and hypnotics

A total of 128 patients were currently receiving benzodiazepine hypnotics: 46% temazepam, 45% nitrazepam, 9% triazolam and

Table 1. Number of previous major and minor systemic illnesses among benzodiazepine users (n = 205) and controls (n = 205) (number (%) of patients).

Number of recorded systemic illnesses	Major illness		Minor illness		Major and minor illness	
	Users	Controls	Users	Controls	Users	Controls
None	36 *(18)*	76 *(37)*	31 *(15)*	49 *(24)*	7 *(3)*	24 *(12)*
1–2	85 *(42)*	79 *(39)*	81 *(40)*	87 *(42)*	42 *(20)*	62 *(30)*
3–4	56 *(27)*	40 *(20)*	46 *(22)*	44 *(21)*	57 *(28)*	52 *(25)*
5–6	15 *(7)*	8 *(4)*	21 *(10)*	11 *(5)*	33 *(16)*	35 *(17)*
7–8	11 *(5)*	2 *(1)*	16 *(8)*	8 *(4)*	25 *(12)*	16 *(8)*
9–10	2 *(1)*	–	6 *(3)*	6 *(3)*	20 *(10)*	6 *(3)*
11–12	–	–	4 *(2)*	–	7 *(3)*	9 *(4)*
13+	–	–	–	–	14 *(7)*	1 *(0.5)*

Table 4. Comparison of mean number of drugs prescribed for benzodiazepine users (n = 205) and controls (n = 205) (df = 408).

Drugs prescribed	Mean (SD) number of drugs: Users	Controls	t	P
Prescribed 1977–87				
Antidepressants	0.9 (1.5)	0.3 (0.9)	4.9	<0.001
Major tranquillizers	0.1 (0.5)	0.03 (0.2)	2.5	<0.05
Benzodiazepine anxiolytics	0.9 (1.1)	0.3 (0.7)	6.1	<0.001
Benzodiazepine hypnotics	0.5 (0.7)	0.2 (0.6)	4.0	<0.001
Other psychotropic drugs	0.4 (0.7)	0.2 (0.5)	3.8	<0.001
Non-psychotropic drugs	11.4 (9.6)	7.4 (8.0)	4.7	<0.001
Currently prescribed				
Antidepressants	0.1 (0.4)	0.01 (0.1)	4.8	<0.001
Non-psychotropic drugs	2.4 (2.2)	0.9 (1.5)	8.0	<0.001

1% lormetazepam. Of the 110 patients receiving benzodiazepine anxiolytics 51% were receiving diazepam, 31% oxazepam, 12% lorazepam and 6% chlordiazepoxide. Thirty nine per cent of patients received anxiolytic medication alone, 48% received hypnotic medication alone, and 14% received anxiolytic plus hypnotic medication. In the total sample of 205 patients two were receiving repeat prescriptions concurrently for two different hypnotics, and three were receiving two different anxiolytics.

One-way analysis of variance with *post hoc* Scheffe comparisons was used to establish significant differences between groups. Table 5 summarizes the mean scores for variables that differed significantly between groups and presents the results of the statistical analysis. Patients currently receiving a benzodiazepine hypnotic only were significantly older and had received their first benzodiazepine prescription at a later age than patients currently receiving a benzodiazepine anxiolytic alone, or a benzodiazepine anxiolytic plus hypnotic. Furthermore, patients receiving a benzodiazepine hypnotic alone, when compared with the anxiolytic alone group had suffered a significantly greater number of major plus minor systemic illnesses, especially major, and had also received a significantly greater number of non-psychotropic medications. The anxiolytic plus hypnotic group revealed similar scores to those of the hypnotic alone group on these three variables. Finally, the anxiolytic plus hypnotic group had previously received a significantly greater number of medications than the anxiolytic alone group. This may be due to the dual nature of benzodiazepine prescribing for the anxiolytic plus hypnotic group. However, no such differences emerged between the hypnotic alone and anxiolytic plus hypnotic groups.

Discussion

The data obtained from the three study practices confirm estimates of other researchers of extensive long-term use of benzodiazepines.[6,21] The prevalence of 26 long-term benzodiazepine users per 1000 patients can be extrapolated to provide an estimate of 133 120 patients on long-term benzodiazepine medication in Scotland. While no national rate of benzodiazepine prescribing is available for Scotland, the Common Services Agency (Information and Statistics Division) reported that 1.78 million hypnotic prescriptions and 1.39 million sedative and tranquillizer prescriptions were issued in 1986 to a Scottish population of just over five million people.

The age and sex distribution of the benzodiazepine group is similar to that reported in previous studies,[16,17] and the concentration of users in the older age groups provides a substantial challenge to primary care. However, this controlled study of one of the largest groups of benzodiazepine users studied in the UK reports significantly more specific systemic illness among users than controls. Previous studies have lacked controls or reported general levels of illness in single practices with sample sizes of about 70 subjects.[16,17]

The categories of disease that presented significantly more often in benzodiazepine users in this study may repay more detailed investigation. A possible criticism of the study is that allocation to major or minor illness categories was subject to error or bias. If so, this would have been equally applicable to both user and control groups as the initial allocation to illness categories was done blind. It therefore seems appropriate to conclude that benzodiazepine users exhibit higher rates of cardiovascular, respiratory, central nervous system, gastrointestinal, genitourinary, and ear, nose and throat illnesses than matched controls.

These higher rates of illness could be explained by the parallel treatment of discomfort or anxiety accompanying somatic

Table 5. Means (standard deviations) and summary of differences between groups of patients receiving a benzodiazepine hypnotic alone, anxiolytic alone, and anxiolytic plus hypnotic (df = 2202).

Variable	Patient groups: Hypnotic only (n = 98)	Anxiolytic only (n = 79)	Anxiolytic + hypnotic (n = 28)	F	P	Scheffe[a]
Patient age (yrs)	68.9 (12.3)	58.7 (13.2)	60.9 (12.9)	14.4	<0.001	1-2,1-3
Age benzodiazepine first prescribed (yrs)	57.0 (13.1)	47.7 (14.1)	48.0 (12.2)	12.2	<0.001	1-2,1-3
Number of previous major plus minor systemic illnesses	6.0 (4.0)	4.4 (3.1)	6.2 (4.3)	4.7	<0.01	1-2
Number of previous major systemic illnesses	2.8 (2.2)	1.9 (1.8)	2.7 (2.2)	4.8	<0.01	1-2
Number of previously prescribed non-psychotropic medications	12.7 (9.4)	9.1 (9.6)	13.6 (8.7)	4.1	<0.01	1-2
Number of previously prescribed hypnotics	0.5 (0.7)	0.4 (0,7)	0.9 (0.8)	4.7	<0.01	2-3
Number of currently prescribed medications	3.8 (2.4)	3.7 (2.1)	4.8 (2.1)	4.4	<0.01	2-3

[a] *Post hoc* Scheffe treatment group comparisons: 1 = hypnotic; 2 = anxiolytic; 3 = anxiolytic + hypnotic. Groups separated by a hyphen differ significantly from each other.

pathology, or the presence of specific organic system vulnerability or weakness underlying the most commonly expressed symptoms of a given anxiety disorder as suggested by Malmo and Shagass.[22] Another explanation may be that major systemic illness exacerbates the development of anxiety symptoms, thus leading to a subsequent demand for benzodiazepine medication in patients with anxiety prone personalities. Alternatively doctors may experience difficulty helping patients to cope with a chronic physical complaint, and may therefore prescribe benzodiazepines to try to alleviate the anxiety and/or despondency that accompany the complaint. Further detailed study of the precise sequence of physical illness, psychiatric sequelae and subsequent prescription will be needed to determine which of these explanations is correct.

The higher consultation rates in the benzodiazepine group compared with controls may simply reflect attendance for a repeat benzodiazepine prescription, although during the period studied repeat prescriptions could easily be obtained without consultation. Alternatively, more frequent consultation could be related to the higher level of somatic morbidity rather than a lower tolerance of disease. However, the benzodiazepine group also received a greater variety of psychotropic medication, which may reflect a higher incidence of psychiatric morbidity, drug dependency or poor alternative coping resources among patients and doctors.

It is interesting to note that significant differences existed between patients currently receiving a hypnotic alone, an anxiolytic alone, or an anxiolytic plus hypnotic. The hypnotic alone users were older than the other two groups, and had suffered more previous systemic illnesses than those prescribed an anxiolytic alone. These results suggest that benzodiazepine hypnotics may be prescribed if patients' sleep is disrupted by serious illness, the process of ageing, or both.

The characteristics of long-term benzodiazepine users in this study reflect a picture of ill health in a predominantly aged population. It is interesting to note that the mean age at which patients received their first benzodiazepine prescription was 47 years, an age which is arguably higher than the suggested age of onset for anxiety disorders.[23]

It is currently accepted that long-term benzodiazepine use is inappropriate for the treatment of anxiety states or insomnia,[11] and there is growing pressure for patients to be withdrawn from long-term use. However, issues affecting first-time prescription must be distinguished from the approach to current long-term users. This study highlights the confounding influence of major somatic morbidity in a population of long-term users. The need for further investigation of the interrelationship between benzodiazepine prescribing and physical illness is required and may need to be addressed separately from the issues surrounding long-term use in anxiety states. Furthermore, the implementation of graded withdrawal programes for long-term benzodiazepine users must attempt to address such issues, as different management strategies may be necessary for those long-term benzodiazepine users characterized by chronic physical illness, as opposed to those who are in relatively good health. The balance of benefits and risk in steady state moderate long-term use of hypnotics in physically ill older patients also needs to be addressed separately from that of younger users who are free from such somatic problems.

The challenges which long-term use of benzodiazepines presents to the medical profession and patients is considerable. However, the response should be a careful and measured one. Patients should not be stressed by ill-prepared abrupt withdrawal, carried out as a response to media and legal pressure, in the absence of adequate support strategies. Further research into the use of alternative graded withdrawal programmes in primary care settings will be required before clear guidelines can be formulated on the best form of management of these patients.

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