

Patient treatment insistence and medication craving in long-term low-dosage benzodiazepine prescriptions

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ABSTRACT

Background. Long-term low-dosage dependence on benzodiazepines is traditionally explained by withdrawal symptoms. Previous research has not given much attention to reports that suggest that many patients oppose stopping benzodiazepines long before withdrawal symptoms have developed. This study investigates the scope of and factors associated with this pre-withdrawal treatment insistence.

Methods. Patients receiving long-term low-dosage benzodiazepines in primary care were asked to take a drug-holiday of at least 3 weeks. Sociodemographic, medication, morbidity and attitudinal variables were assessed in addition to the GPs' perceptions of their patients.

Results. Two-thirds of the patients rejected the drug-holiday proposal. Patients who refused a drug-holiday were less educated and were using a higher percentage of long-acting benzodiazepines than patients who accepted the drug-holiday proposal. Those who refused were seen by their GPs as being more complaining, harder to satisfy and less co-operative.

Conclusions. These results provide evidence for drug-seeking or craving behaviour of patients who receive low-dosage benzodiazepine prescriptions. A major problem in benzodiazepine withdrawal occurs before the withdrawal programme has even begun. These data show that benzodiazepine low-dosage dependence should be considered a real form of dependence.

INTRODUCTION

Benzodiazepines (BZs) are still frequently prescribed psychotropic drugs (Lohse & Müller-Oerlinghausen, 1995; WHO-programme on Substance Abuse, 1996). Community surveys suggest that BZ prescription practice differs from prescription recommendations as given by textbooks, official guidelines and most authorities in the field, who suggest prescription for a limited time only (Linden, 1989; Ashton, 1994; Lader, 1994). Instead, a considerable number of patients take BZs on a long-term basis (Lyndon & Russell, 1988; Geiselmann *et al.* 1989; Magrini *et al.* 1996; Simon *et al.* 1996). We still lack valid data about reasons for long-term BZ use in the community (Romach *et al.* 1991; Simon *et al.* 1996). A possible explanation is the concept of

'low-dosage dependence', which first emerged following the appearance of withdrawal symptoms in a substantial number of patients after the discontinuation of long-term therapeutic use of BZs (Tyrer *et al.* 1983; Busto *et al.* 1986). However, 'low-dosage dependence' is a disputable term, because neuroadaptive changes under treatment and concomitant withdrawal symptoms are neither necessary nor sufficient criteria for drug dependence (Ballenger *et al.* 1993; Sellers *et al.* 1993). Other criteria for dependence as listed in DSM-IV or ICD-10, such as neglect of important social, recreational or occupational activities in order to obtain the substance, or difficulties in controlling substance-taking, are not characteristic for the majority of long-term therapeutic users of BZs (Sellers *et al.* 1993; Tyrer, 1993).

However, there is evidence by reports or letters from practising physicians (Farnsworth, 1990; Baum, 1991) that patients on long-term

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BZ treatment refuse to stop taking the drug. Few studies on BZ withdrawal focus on this phenomenon, even though about 50% of the initial study sample were reported to oppose a withdrawal proposal (Tyrer *et al.* 1981; Wright *et al.* 1994). These 'refusers' were reported to use higher dosages (Tyrer *et al.* 1981) and to be older (Wright *et al.* 1994) than those patients who took part in a withdrawal programme. However, systematic research on the scope and meaning of this treatment insistence or first-line refusal to terminate BZ long-term treatment is missing.

Unanswered questions include: (a) what is the percentage of patients under long-term BZ treatment who do not even start a withdrawal programme; and (b) what are the characteristics of these patients as compared to those who cooperate at least initially? Such information can help to clarify the concept of 'low-dosage dependence'.

This phenomenon can be observed best, if not exclusively, under routine treatment conditions. Therefore, in this study patients were investigated under long-term therapeutic treatment with BZs in primary-care practice. They were asked to participate in a drug-holiday of a few weeks, and their reactions were monitored. A comparison was made between patients agreeing and those refusing to stop the on-going BZ treatment. Variables, which in the literature have been related to problems with stopping BZs, were included in this study. These are: (a) sociodemographic variables such as older age (Rickels *et al.* 1991; Holton *et al.* 1992), female gender for short-term outcome (Rickels *et al.* 1988), male gender for long-term outcome (Golombok *et al.* 1987) and lower education (Rickels *et al.* 1990); (b) treatment variables such as longer duration of BZ treatment, higher dosage, short BZ elimination half-life (Tyrer, 1993; Woods *et al.* 1995) or high BZ potency (Wolf & Griffiths, 1991); (c) illness characteristics such as less emotional stability or more global psychiatric morbidity (Rickels *et al.* 1988, 1990; Schweizer *et al.* 1990; Holton *et al.* 1992; Nicholas & Hammond, 1992), or the type of psychiatric morbidity, especially depressive (Rickels *et al.* 1990; Joughin *et al.* 1991), dependent or obsessional personalities (Holm *et al.* 1982; Murphy & Tyrer, 1991; Nicholas & Hammond, 1992); furthermore, (d) attitudes,

illness concepts or attribution styles of patients (Başoğlu *et al.* 1994); and (e) the patient-physician relationship (Lilja & Larsson, 1994) have been reported to influence BZ discontinuation. Most of these results are not consistent and refer to withdrawal, but not treatment insistence.

METHOD

Sample selection

Thirty-nine family physicians (27 general practitioners and 12 internists), collaborating with the Outpatient Research Group of the Department of Psychiatry at the Free University of Berlin, were asked to present to a research psychiatrist (B.G.) all patients who were: (a) taking BZs continuously for at least 6 months; and (b) not showing any medical contraindication, to participate in a BZ-holiday of at least 3 weeks.

A total of 214 patients was seen by the research psychiatrist. For the purpose of this study, patients were excluded if they had been treated with BZs for less than 6 months ($N = 6$), taking BZs less than four times a week ($N = 28$), or taking BZs in a fixed combination with other psychotropics ($N = 7$). To make sure that only so-called 'low-dosage-dependent' subjects were included, patients were also excluded if they were diagnosed as being current or past alcohol abusers ($N = 16$) or current or past substance abusers ($N = 15$). Also, patients were excluded who showed any symptoms of addictive behaviour (such as taking doses higher than 20 mg diazepam-equivalent ($N = 5$), taking more than one BZ ($N = 14$) or additionally taking other hypnotics or tranquillizers ($N = 7$). Others had to be excluded because they were living in a nursing home ($N = 2$), because data were missing ($N = 3$) and because of non-compliance ($N = 8$). Furthermore, patients were excluded with the diagnosis of an organic brain syndrome ($N = 2$). Twenty-one patients met at least two of these criteria. A total sample of 122 patients remained, they represent a population of 'pure' long-term low-dosage BZ users.

In order to obtain an estimation of possible selection bias in comparison to all BZ treated patients in the practices under investigation, a systematic survey was performed in eight of the 39 practices. Patients under long-term BZ

treatment represent an estimated percentage of about 5% of all practice-patients. Sixty-one per cent of all patients who fulfilled the inclusion criteria had been contacted by the GP and 63.8% of these agreed to participate in the study. A comparison of patients who were and were not contacted did not show any significant differences (for details, see Geiselmann & Linden, 1991).

All patients were asked to take a drug-holiday, i.e. a drug-free period of at least 3 weeks, in order to evaluate whether the on-going BZ prescription was still needed. After this, a decision would be made regarding the continuation or final discontinuation of the medication. They were informed about benefits but also possible withdrawal symptoms, and were offered any necessary medical and psychological assistance. It was recommended that the BZ should gradually be tapered off during a period of 3 or 4 weeks, but patients could also choose to discontinue the drug abruptly if they preferred to do so. The drug-holiday proposal was strongly supported by their GPs.

Measures

Sociodemographic and history data were collected. Patients were asked why they were using the BZ. Psychiatric morbidity was assessed by use of the General Health Questionnaire (GHQ-28, Goldberg & Hiller, 1979) and the Clinical Interview Schedule (CIS, Goldberg & Blackwell, 1970), resulting in global psychiatric morbidity estimates and CIS-syndrome diagnoses. In the next step, psychiatric diagnoses were classified according to DSM-III-R criteria.

Patients' attitudes towards the BZ intake were assessed by self-ratings on bipolar visual-analogue scales. Patients were asked to rate: (a) whether they experienced a strong or only a small effect from the BZ; (b) whether they thought they needed it a lot or only a little; (c) whether the BZ was needed for psychological or somatic problems; and (d) whether or not they thought that their BZ medication carried many risks and side effects (see Table 2). Patients were also asked on a five-point Likert scale if they felt able to withstand the drug-holiday. In order to assess the GPs' perceptions of their patients, they were asked to fill in a brief questionnaire about the patient's personality, illness behaviour and patient-GP relationship (see Table 3). These

questions had to be answered on a three-point Likert scale (yes: a little: no). The physicians were blind to the outcome of the study when filling in the questionnaires.

SPSS, Version 5.02 (SPSS, 1992) was used for statistical analysis. Patients who refused to participate were compared with patients who agreed to participate. Chi-squared measures were used for contingency tables, *t* tests were performed for metric data. A logistic regression was performed to evaluate the impact of essential variables in context.

RESULTS

Sample characteristics

The average age of patients was 67.2 years, 78.7% were female. Seventy-six per cent of patients had an education that did not exceed secondary school (9 years of schooling, see Table 1). With regard to marital status: 42.6% of patients were widowed; 33.6% were married; and the rest were either divorced or single.

According to DSM-III-R criteria 63.9% were suffering from at least one psychiatric disorder, i.e. 23.8% from anxiety disorders, 25.4% from depressive disorders, 9.0% from organic mental disorders and 8.2% from somatoform disorders. The patients reported using BZs because of: sleep disturbances (73.8%); anxiety (12.3%); stress, depression or mood disturbances (10.7%); and for other reasons (3.2%).

The most frequently prescribed BZs were bromazepam (29.5%), oxazepam (28.7%) and diazepam (11.5%). Others were lorazepam (8.2%), lormetazepam (8.2%), flunitrazepam (4.1%), clorazepate (3.3%), temazepam and chlordiazepoxide (1.6%), alprazolam, clobazepam, prazepam and triazolam (0.8%). The mean daily dosage was 7.1 mg diazepam equivalent (calculations based on Poser & Poser, 1986). A fixed intake schedule was recorded for 77.9% of all patients, 22.1% took the medication 'as needed'. Previous attempts to discontinue the BZ medication (see Table 1) were reported by 50.8% of all patients ($N = 62$).

Rejection of drug-holiday

Eighty-four patients (68.8%) who were asked to stop BZ treatment for a short period of 3 weeks in order to see whether the medication was still needed, rejected this idea and were not prepared

Table 1. Comparison between refusers and accepters

| | Descriptive statistics | | | | | | | | | | |
|---|------------------------|----------|-------------------|----------|--------------------|----------|-----------------------|-----|---------------------|------------|----|
| | All (N = 122) | | Refusers (N = 84) | | Accepters (N = 38) | | Univariate comparison | | Logistic regression | | |
| | Mean/N | (s.d./%) | Mean/N | (s.d./%) | Mean/N | (s.d./%) | t/ χ^2 | P | OR | 95% CI | P |
| Sociodemographic data | | | | | | | | | | | |
| Age (years) | 67.2 | (13.0) | 67.9 | (12.6) | 65.5 | (13.9) | 0.9 | NS | 1.01 | 0.97, 1.05 | NS |
| Male sex | 26 | (21.3) | 15 | (17.9) | 11 | (28.9) | 1.9 | NS | 1.10 | 0.61, 1.98 | NS |
| > 9 years of schooling† | 29 | (24.2) | 14 | (17.1) | 15 | (39.5) | 7.1 | ** | 0.47 | 0.25, 0.86 | * |
| Treatment variables | | | | | | | | | | | |
| Dosage (mg diazepam-equivalent) | 7.1 | (5.1) | 8.0 | (5.6) | 5.2 | (3.2) | 3.4 | ** | 1.02 | 0.90, 1.16 | NS |
| Duration of BZ intake (years)† | 6.9 | (6.2) | 7.3 | (6.7) | 6.1 | (4.9) | 1.0 | NS | 1.01 | 0.93, 1.11 | NS |
| Daily intake schedule† | 95 | (77.9) | 68 | (81.0) | 27 | (71.1) | 1.5 | NS | 1.02 | 0.55, 1.89 | NS |
| Long BZ half-life | 27 | (22.1) | 23 | (27.4) | 4 | (10.5) | 4.3 | * | 2.30 | 1.05, 5.05 | * |
| High BZ potency | 27 | (22.1) | 21 | (25.0) | 6 | (15.8) | 1.3 | NS | 1.40 | 0.71, 2.76 | NS |
| Illness characteristics | | | | | | | | | | | |
| GHQ-28 score† | 2.3 | (4.2) | 2.6 | (4.7) | 1.5 | (2.7) | 1.6 | NS | | | |
| CIS score**† | 17.8 | (10.2) | 18.3 | (10.3) | 16.8 | (9.9) | 0.8 | NS | 1.55 | 0.77, 3.14 | NS |
| Depressive disorder | 31 | (25.4) | 26 | (31.0) | 5 | (13.2) | 4.4 | * | 0.69 | 0.34, 1.41 | NS |
| Attitudes | | | | | | | | | | | |
| Previous attempts to stop treatment | 62 | (50.8) | 38 | (45.2) | 24 | (63.2) | 3.4 | NS | 0.69 | 0.39, 1.20 | NS |
| Perceived ability to stand drug-holiday†† | 4.2 | (1.0) | 4.3 | (0.9) | 3.8 | (1.0) | 2.6 | ** | 1.68 | 0.99, 2.86 | NS |
| GP-questionnaire Score§ | 17.2 | (4.2) | 18.2 | (3.9) | 15.0 | (4.0) | 4.1 | *** | 2.68 | 1.36, 5.21 | ** |

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, not significant.

† Reduced number of cases due to missing data.

‡ 5-point Likert item (1 = without problems, 5 = unable to withstand the drug-holiday).

§ High score = high percentage of items answered with 'yes'.

to give it a chance. A tapering programme was started with patients who agreed to participate. Eighteen (47.4% of these patients) interrupted withdrawal early and took BZs again as before. Eight patients did not fully withdraw but continued on a reduced dosage level. Only 12 patients (9.8% of the original sample) were actually able to stop the BZ medication as intended.

Comparison between patients who accepted/refused drug-holiday

Sociodemographic data

A significantly higher proportion of patients with more than 9 years of school education accepted the drug-holiday proposal. Age, gender (see Table 1) and marital status ($\chi^2 = 1.92$, $P = 0.38$) did not differ significantly between patients who refused and those who participated.

Treatment characteristics

Patients who took part in the drug-holiday used significantly lower dosages than those who refused to participate. Furthermore, patients using long-half-life BZs were less willing to stop their intake even for a short period. All other treatment characteristics, such as BZ potency, duration of prescription or intake schedule, were not related to the patients' decision to take part in the drug-holiday.

Illness characteristics

The global assessment of psychiatric morbidity according to the GHQ-28 and the CIS did not show significant differences between accepters and refusers. Depressive patients were less likely to participate in the drug-holiday (see Table 1). All other psychiatric diagnoses, as well as target complaints, had no effect on the patients' decision to try to discontinue the drug.

Patients' attitudes towards BZ usage

Only 6.9% of all patients considered themselves to be able to take a drug-holiday with only minor problems or no problems at all (item score 1 and 2 on the five-point Likert item at the beginning of the study). This is also evident by virtue of the mean score of this item (see Table 1). Patients who accepted the drug-holiday proposal had significantly less doubt about their ability to stop the medication. However, 67.5%

of them still had severe concern or considered themselves not to be able to take the drug-holiday (item scores 4 and 5). Previous attempts to stop the medication did not significantly influence the decision to take part in the drug-holiday.

All patients reported the drug to be only moderately efficient and as having a moderate effect on psychological complaints and little effect on somatic complaints. On the other hand, they saw themselves as being strongly in need of regular and continuous intake and as expecting to continue BZ intake for a long time to come. They did not expect any relevant side effects. These attitudes were similarly seen in both refusers and accepters (see Table 2).

Physicians' perceptions of patients' personality

GPs reported that in their view patients who refused to begin a drug-holiday had a greater variety of complaints, were less cooperative, harder to satisfy and generally relied more on medications than the patients who accepted. No differences were seen with respect to the item 'patient demands tranquillizers'. However, it should be noted that 81.1% of all patients were judged as demanding tranquillizers from their physicians (see Table 3).

The items of this questionnaire were positively correlated (Cronbach $\alpha = 0.71$) even though they seem at first sight to refer to different topics and problems. Therefore, a patient who is reported to 'have a greater variety of complaints' than other patients is also more likely to be judged as 'much in favour of self-determination' or to be 'harder to satisfy' than other patients. In view of these findings, the common theme of all items could be strain on or the quality of the GP-patient relationship, given that questions answered with 'yes' are an indication of a difficult GP-patient interaction. This is emphasized by the fact that the total score of this questionnaire (high values yielding a high percentage of items answered with 'yes') also differentiated significantly between accepters and refusers (see Table 1).

Multivariate analysis

Since the previously described variables cannot be expected to be independent from each other, a logistic regression was performed in order to

Table 2. Attitudes towards BZ usage: patients ratings on visual analogue scales

| | All (N = 122) | | Refusers (N = 84) | | Accepters (N = 38) | | Refusers v. Accepters P |
|--|---------------|--------|-------------------|--------|--------------------|--------|-------------------------|
| | Mean | (S.D.) | Mean | (S.D.) | Mean | (S.D.) | |
| 'The tranquillizer is very effective' 1 = very weak; 100 = very strong | 37.1 | (26.9) | 37.4 | (25.1) | 36.3 | (30.7) | 0.84 |
| 'I need the medication regularly' 1 not at all; 100 = absolutely | 80.2 | (27.3) | 79.7 | (28.4) | 81.1 | (25.4) | 0.80 |
| 'The medication has a lot of side-effects' 1 = none; 100 = many | 8.0 | (16.6) | 7.1 | (15.0) | 9.8 | (19.5) | 0.40 |
| 'I will need the medication for a long time' 1 = very long time; 100 = short period | 23.0 | (29.4) | 20.0 | (27.4) | 29.0 | (32.7) | 0.12 |
| 'I think that I am dependent on the medication' 1 = no; 100 = very strongly | 37.3 | (35.3) | 34.4 | (35.0) | 43.2 | (35.8) | 0.21 |
| 'The medication helps with somatic ailments' 1 = not at all; 100 = very good | 27.1 | (36.7) | 26.2 | (36.1) | 28.9 | (38.3) | 0.70 |
| 'The medication helps with psychological ailments' 1 = not at all; 100 = very good | 50.0 | (43.1) | 52.0 | (43.0) | 45.5 | (43.7) | 0.45 |

Table 3. Questionnaire for the consulting GPs: 'yes' answered items

| | All | | Refusers | | Accepters | | Refusers v. Accepters P |
|--|-----|--------|----------|--------|-----------|--------|-------------------------|
| | N | (%) | N | (%) | N | (%) | |
| 'The patient has a greater variety of complaints than the average of my patients' | 48 | (39.3) | 41 | (48.8) | 7 | (18.4) | 0.002 |
| 'The patient is observing himself with greater care than the average of my patients' | 54 | (44.3) | 40 | (47.6) | 14 | (36.8) | 0.27 |
| 'The patient is much in favour of self-determination' | 29 | (23.8) | 24 | (28.6) | 5 | (13.2) | 0.06 |
| 'The patient asks more questions than my patients usually do' | 35 | (28.7) | 24 | (28.6) | 11 | (28.4) | 0.97 |
| 'The patient demands tranquillizers' | 99 | (81.1) | 71 | (84.5) | 28 | (73.3) | 0.16 |
| 'The patient is uncooperative' | 18 | (14.8) | 18 | (21.4) | 0 | (0.0) | 0.002 |
| 'The patient is harder to satisfy than my patients usually are' | 43 | (35.2) | 36 | (42.9) | 7 | (18.4) | 0.009 |
| 'The patient-physician relationship is very intensive' | 40 | (32.8) | 20 | (33.6) | 12 | (31.6) | 0.85 |
| 'The patient generally relies on medications' | 40 | (32.8) | 33 | (39.3) | 7 | (18.4) | 0.02 |

estimate their relative impact on patients' acceptance or refusal of the drug-holiday proposal. All variables listed in Table 1 were entered in the analysis. To avoid too many collinearity problems, the GHQ-28 and CIS-scores were standardized and added to a single score that measured psychiatric morbidity. Odds ratios were calculated to predict patients' refusal to participate in the study. All 13 variables were entered at the same time.

Ten cases were excluded due to list-wise deletion of missing data. Seventy-six per cent of the cases were predicted correctly. As in the univariate analyses, education, BZ half-life, and the GP questionnaire score significantly predicted differences between accepters and re-

fusers. The most significant differences were shown in the questionnaire given to the GPs. Patients' attitudes towards the drug-holiday, depressive disorders and BZ dosage lost their statistical significance. None of the variables that had not shown an impact in univariate analyses became statistically significant after multivariate analysis.

DISCUSSION

The first strength of this study is that the patient sample is similar to epidemiological samples of long-term BZ users living in the community (Balter *et al.* 1984; Pariente *et al.* 1992; Del Rio & Alvarez, 1996) reflecting BZ prescription in

general practice routine care, thus complying with requests in the recent literature (Magrini *et al.* 1996; Simon *et al.* 1996). The second strength of this study is that strict selection criteria ensured that only 'low-dosage dependent' patients, i.e. patients continuously treated with BZs in therapeutic dosages for more than 6 months were included in the sample, and any patients suspected of misuse or addictive behaviour were excluded. The third strength of this study is that a multidimensional assessment was made that included clinical, attitudinal or sociodemographic variables.

The first and most important finding of this study is that 68.8% of patients receiving long-term low-dosage treatment cling to their medication. They insisted upon treatment continuation and refused even an attempt to stop the medication. This result reveals that a major problem in BZ withdrawal exists long before withdrawal has even started and before first withdrawal symptoms could have occurred. The number of patients who refused to attempt to stop BZ intake was higher than figures reported in other studies (Tyrer *et al.* 1981; Wright *et al.* 1994), which reported that about 50% opposed stopping to take the drug.

Most variables that are considered to influence successful withdrawal did not show any impact on this pre-withdrawal 'treatment insistence'. In contrast to the findings of Wright *et al.* (1994), the patients who refused to participate in a drug-holiday were not older than those who agreed to participate. Furthermore, no differences were found in gender, psychiatric morbidity, duration or regularity of BZ intake and previous attempts to stop BZ intake.

The only significant difference in socio-demographic variables was found with respect to education. Refusers had less years of education than patients who agreed to participate in the drug-holiday. This conclusion is in line with similar findings by Rickels *et al.* (1990). Furthermore, there were significant relationships between medication variables and patient treatment insistence. In univariate analysis, higher dosages and more BZs with a longer half-life were related to difficulties in stopping the medication. These findings are similarly argued by Tyrer *et al.* (1981). In multivariate analysis, longer half-life probably absorbed the common variation and was revealed as being the most

potent predictor. Since blood BZ concentrations under long-term treatment depend more on pharmacokinetic factors than daily dosage, this result speaks for the fact that receptor drug exposure predicts an independent part of variance of treatment insistence and drug-seeking behaviour, indicating a direct drug-induced dependence potential of long-acting BZs. This should be seen independent of the fact that BZs with longer half-lives are expected to cause fewer withdrawal symptoms. Drug insistence or craving is obviously a different phenomenon that cannot be explained through withdrawal symptoms as such.

Finally, there are also indicators for the importance of psychological variables in the explanation of treatment insistence with BZs. First of all, all patients in long-term treatment programmes showed a very peculiar pattern of treatment-related attitudes that can be called 'definite modest efficacy expectation' (Wilms & Linden, 1992). The amount of help they expect from the drug is rather small, but their conviction that they are in need of the drug is definite. This definite modest treatment attitude seems to characterize long-term treatment. Given this background, refusers even show an additional tendency to believe that they cannot live without the drug.

Patients who refused were seen by their physicians as complaining more, being more difficult to satisfy and generally more reliant on medication. In line with other reports (Rickels *et al.* 1990; Joughin *et al.* 1991; Murphy & Tyrer, 1991; Nicholas & Hammond, 1992), BZ withdrawal problems are associated with depressive or dependent personality characteristics. However, contrary to this assumption is the fact that patients who refused were also seen as more dominant and uncooperative, leading us to conclude that primarily patients with independent and dominant personality may insist upon treatment, i.e. imposing their will on the prescribing physician.

It must be kept in mind that in medical practice treatment decisions are never the result of medical considerations alone but rather the outcome of a negotiation process between physician and patient (Lilja & Larsson, 1994; Linden, 1994). Patients in general exert a great deal of influence on treatment decisions, be it by non-cooperation in the sense of non-compliance,

or by insistence on preferred choices of treatment. This may be a clue to the concept of 'low-dosage dependence' that has been neglected in recent research. It is, therefore, not surprising that the results of the GP questionnaire also indicate considerable strain in the physician-patient relations.

In summary, this study suggests that BZ 'low-dosage dependence' is rightly termed 'dependence', since there are drug effects that act on patients' refusal to stop BZ intake as well as evidence of psychological dependence and drug-seeking behaviour. These factors are clearly manifest in data from GP-rating and self-rating questionnaires as well as the broad scope of refusal to participate in a drug-holiday. Thus, these factors are seen long before any withdrawal symptoms can have emerged.

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