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Prevalence of Benzodiazepine Abuse and Dependence in Psychiatric In-Patients with Different Nosology

An Assessment of Hospital-Based Drug Surveillance Data

L. G. SCHMIDT, R. GROHMANN, B. MÜLLER-OERLINGHAUSEN, M. OTTO, E. RÜTHER and B. WOLF

Frequencies of abuse and dependence assessed continuously within a drug surveillance system were analysed as a contribution to risk–benefit evaluations of benzodiazepines (BZDs). In 4.7% of 15 296 patients admitted to psychiatric hospitals between 1980 and 1985, BZDs had been involved in some kind of abuse or dependence. Primary BZD dependence, defined as physical dependence on BZDs in patients who had not been dependent before, was observed in about 1% of admitted patients. Linking these data with psychiatric diagnoses revealed a high risk of primary BZD dependence for in-patients (11.8%) with anxiety neurosis (ICD–9, 300.0), and a lower risk for neurotic (300.4) and for endogenous depressives (296.1) (risk 3.7% and 2.7% respectively). Older age was also related to primary BZD dependence. For depressive in-patients, the risk was twice as high in females as in males. Anecdotal observations advocate more systematic investigation of the emotional effects of long-term therapy with BZDs.

The widespread use of benzodiazepines (BZDs) has created concern about their benefit:risk ratio. In West Germany, prescription rates of BZDs declined between 1981 and 1984 (Müller-Oerlinghausen, 1986), probably as a response to extensive information within the medical profession on the long-term risk during recent years. However, a sound benefit:risk evaluation still remains difficult, since morbidity data are not included in conventional drug utilisation studies; retrospective surveys on clinical populations are burdened with unavoidable methodological drawbacks (Fleischhacker *et al*, 1986; Laux & König, 1987). Therefore, prevalence data on BZD abuse and dependence, which have been assessed continuously in all newly admitted psychiatric in-patients within an ongoing drug surveillance project, are presented. Abuse was evaluated according to the definition of the World Health Organization (WHO, 1965), and dependence was assessed in accordance with DSM–III (American Psychiatric Association, 1980). Special attention was given to the existence of low-dose BZD dependence (Petursson & Lader, 1981; Tyrer *et al*, 1981; Lader, 1983).

Method

With the support of the Federal Health Office (Berlin), a drug surveillance system has been established by AMÜP (Arzneimittel-Überwachung in der Psychiatrie) in several psychiatric hospitals in West Germany since 1979 in order to investigate adverse drug reactions due to psychotropic drugs (Grohmann *et al*, 1984; Schmidt *et al*, 1986*a*). Special emphasis has been laid on monitoring of drug abuse and dependence in hospital in-patients since 1980 (Wolf & Rüther, 1984). This was done by means of a special questionnaire including all necessary information (e.g. all substances currently and previously abused, doses, duration of intake, withdrawal symptoms, psychiatric diagnosis) filled in by specially trained psychiatrists. They acted as drug monitors by contacting the wards of collaborative hospitals at weekly intervals, and questioned all treating physicians about drug abuse and dependence in all newly admitted patients. A comparison of biographical data with urine checks revealed no relevant covert intake of BZD in a subsample of patients.

A BZD withdrawal syndrome was recorded when at least two new symptoms emerged (Tyrer *et al*, 1981) that were specific for BZD withdrawal (Lader, 1983), or when pre-existing symptoms intensified after discontinuation or tapering of dosage and returned to the pre-withdrawal level within some days or weeks. (Withdrawal and rebound symptoms were not differentiated in this study, as both are conceived as manifestations of a common dependence mechanism (Lader & File, 1987).) All cases that were recorded within the first years of the surveillance period were re-assessed by the same procedure. Discrimination of side-effects of the initial psychopharmacological treatment was done by analysing the time course of drug effects.

BZD abuse was diagnosed according to WHO (1965) criteria in the case of drug intake without any clear indication or in higher than recommended doses. BZD dependence was diagnosed in accordance with DSM–III if the patient had shown withdrawal symptoms or tolerance. Primary BZD dependence was diagnosed when BZD had been the first drug in a patient leading to dependence; secondary BZD dependence was supposed if the patient had been dependent on other substances (e.g. alcohol, barbiturates) before he had developed BZD dependence. If BZDs had been the only class of drug leading to abuse or dependence, pure BZD abuse or dependence was recorded. If BZD had been taken with heavy ingestion of alcohol,

or with other medical or illegal drugs, multiple substance abuse was diagnosed. To increase the reliability of diagnoses of abuse and dependence, case conferences headed by an experienced psychopharmacologist were held regularly for final assessments. This procedure had been proven sufficiently reliable in evaluating adverse drug reactions and was shown to be slightly superior to rigid algorithm strategies (Schmidt *et al*, 1986*b*).

Prevalence rates of BZD abuse and dependence, and of multiple substance abuse (including BZDs), were calculated by means of the diagnostic data on all patients admitted to the psychiatric hospitals of the Free University of Berlin (FU-B) and of the Ludwig Maximilian University of Munich (LMU-M) between 1980 and 1985. In both hospitals, diagnoses had been made according to ICD-9 (WHO, 1978). The drug utilisation data of our hospitals are described elsewhere (Schmidt *et al*, 1988). However, it should be stressed in this context that initially patients are often treated drug-free to ensure diagnostic security.

Results

Drug dependence and abuse were diagnosed in 6.6% of all patients admitted to the collaborating hospitals, with BZDs being involved in 4.7% (i.e. 726) of all patients. In 35.4% of these 726 patients, pure BZD abuse/dependence was diagnosed, and in 64.6% BZDs had been taken in combination with other substances (multiple substance abuse). BZDs were the drugs by far the most commonly involved in abuse and dependence (Table I).

The prevalence rates of BZD abuse and dependence and multiple substance abuse (including BZDs) in diagnostic subgroups are presented in Tables II and III. Excluded

TABLE I

Frequency of drug abuse and dependence in in-patients of the psychiatric hospitals of the Free University of Berlin (FU-B) and the Ludwig Maximilian University of Munich (LMU-M) between 1980 and 1985

	FU-B	*LMU-M*	*Total*
Number of in-patients	4008	11 288	15 296
Patients with drug abuse or dependence:			
number	256	753	1 009
%	6.4	6.7	6.6
Medication involved in patients with abuse or dependence[1]			
Benzodiazepines: %	67.2	73.6	72.0
Non-narcotic analgesics:[2] %	28.1	24.3	25.7
Barbiturates:[3] %	10.5	12.1	11.7
Psychostimulants/ anorexigenics: %	11.3	8.1	8.9
Other hypnotics:[4] %	3.5	5.4	4.9
Narcotic analgesics: %	3.9	4.9	4.7
Clomethiazole: %	0.8	5.3	4.2
Anti-Parkinsonian drugs: %	3.5	2.0	2.4
Laxatives: %	1.2	0.7	0.8

1. In the case of multiple substance abuse, the patients were counted for each category.
2. Including barbiturates.
3. Barbiturates excluding combinations with analgesics.
4. e.g. diphenhydramine, bromoureide, methaqualone.

TABLE II

Prevalence of pure BZD abuse and dependence and multiple substance abuse in psychotic patients

	Organic psychosis	*Schizophrenia*	*Affective psychosis*		*Total*
			Mania	*Uni- and bipolar depression*	
	ICD-9 290-4	*ICD-9 295, 7-9*	*ICD-9 296.0, 2*	*ICD-9 296.1, 3-9*	
	(n = 1274)	*(n = 6029)*	*(n = 737)*	*(n = 3411)*	*(n = 11451)*
Pure BDZ abuse/dependence					
Total: %[1]	1.6	0.4	0.3	2.0	1.0
Abuse: %	0.3	0.2	-	0.6	0.3
Primary dependence: %	0.7	0.2	0.3	1.3	0.6
Secondary dependence: %	0.6	-	-	0.1	0.1
Multiple substance abuse					
Total: %	4.5	0.3	0.1	0.8	0.9
BZD + alcohol: %	0.9	-	0.1	0.2	0.2
BZD + other medical drugs: %	2.1	0.2	-	0.5	0.5
BZD + alcohol + other medical drugs: %	1.3	0.1	-	0.1	0.2
BZD + alcohol + other medical drugs + illegal drugs: %	0.2	-	-	-	-

1. Percentages are in terms of the total number of patients in the relevant diagnostic subgroup.

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TABLE III
Prevalence of pure BZD abuse and dependence and multiple substance abuse in non-psychotic patients

	Neurosis			*Personality disorder*	*Alcoholism*	*Depressive reaction*	*Others*	*Total*
	Anxiety	*Depressive*	*Hypo-chondriac*					
	ICD-9 300.0 (n = 136)	*ICD-9 300.4 (n = 649)*	*ICD-9 300.7 (n = 175)*	*ICD-9 301 (n = 460)*	*ICD-9 305, 5.0 (n = 1408)*	*ICD-9 309.0, 1 (n = 792)*	*(n = 225)*	*(n = 3845)*
Pure BDZ abuse/ dependence								
Total	17.7	6.9	4.0	4.5	-	0.5	6.2	3.7
Abuse: %	4.4	2.0	0.0	1.3	-	0.4	1.8	1.0
Primary dependence: %	11.8	3.7	2.9	1.9	-	0.1	2.2	2.0
Secondary dependence: %	2.2	1.2	0.5	1.3	-	-	2.2	0.7
Multiple substance abuse								
Total	9.5	10.8	6.9	12.1	19.2	0.8	11.3	9.3
BZD + alcohol: %	4.4	4.5	-	4.5	9.9	-	4.5	3.4
BZD + other medical drugs: %	2.2	2.6	6.9	2.4	-	0.8	3.6	2.7
BZD + alcohol + other medical drugs: %	2.9	3.5	-	3.7	8.2	-	3.0	2.7
BZD + alcohol + other medical drugs + illegal drugs: %	-	0.2	-	1.5	1.1	-	0.2	0.5

from these tables are patients with drug abuse and dependence but no other psychiatric diagnosis. These comprise three patients with drug abuse (ICD 305) and 61 patients with drug dependence (ICD 304), among whom are eight patients with primary and four patients with secondary BZD dependence.

Prevalence rates of pure BZD abuse/dependence were higher in non-psychotic than in psychotic admissions (3.7% and 1.0% respectively). For multiple substance abuse (including BZDs) the difference was even more pronounced (9.3% for non-psychotic and 0.9% for psychotic). Primary BZD dependence was observed most frequently in anxiety neuroses (11.8%) and was diagnosed rather rarely in types of neurosis (in 3.7% of depressive neurotics, and 2.9% of hypochondriac neurotics). For all endogenous depressives, the rate was 1.3%, which was doubled (2.7%) in the subgroup of patients of unipolar type (ICD 296.1). Abuse of BZD in combination with alcohol was observed most frequently in alcoholics (9.9%), and BZD in combination with medical drugs was abused most frequently by hypochondriac neurotics (6.9%). BZD abuse patterns (including alcohol and other medical drugs) were highest in alcoholics (8.0%). Multiple substance abuse including illegal drugs occurred most frequently in patients with personality disorders (1.5%).

Characteristics of patients with primary BZD dependence compared with non-dependent patients are shown in Table IV. In all diagnostic subgroups, patients with BZD dependence were generally older than non-dependent patients; on average, the age difference was 9.5 years in depressive neurotics, 9.8 years in anxiety neurotics, and 5.8 years in endogenous depressives. In endogenous (unipolar type) and neurotic depression, the risk for BZD dependence was twice as high for females as for males (3.3% v. 1.6%, $P<0.001$; 4.6% v. 2.3%, $P<0.001$).

To obtain the frequency of subtypes of primary BZD dependence, the doses the patients had taken before admission were converted to diazepam equivalents (Poser & Poser, 1986). Dependence on low doses (i.e. ≤ 30 mg diazepam equivalent per day) was observed in 44.3% of patients, on intermediate doses (i.e. >30, <80 mg per day) in 40.7%, and on high doses (i.e. ≥ 80 mg per day) in 4.3%; in 10.7% of patients information regarding dose was insufficient. Of 86 patients with endogenous (unipolar type) or neurotic depression, 34 (50%) reported intake of low doses; of 16 patients with anxiety neuroses, 11 (68.7%) had increased their doses to an intermediate level; and of 8 BZD-dependent patients without any other diagnoses, 6 (62.5%) had taken high doses of BZD. Lorazepam and Bromazepam were mentioned most frequently in all patient groups with primary BZD dependence (21.8% and 18.0% respectively of all BZD counts).

Of the patients with primary BZD dependence, 19.3% reported having taken BZD continuously less than one year, 33.6% had taken BZDs between one and four years, 25.0% between four and ten years, and 8.6% more than ten years; in 8.6% of patients, no information

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TABLE IV
Comparison of patients with primary BZD dependence and non-dependent patients in diagnostic subgroups

	Endogenous depression unipolar		*Neurotic depression*		*Anxiety neurosis*		*Hypo-chondriacal neurosis*		*Others*		*Total*	
	ICD-9 296.1		*ICD-9 300.4*		*ICD-9 300.0*		*ICD-9 300.7*					
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
All patients	575	1054	257	392	37	99	109	66	5705	7001	6684	8612
% of patients with dependence	1.6	3.3	2.3	4.6	10.8	12.1	2.8	3.0	0.1	0.7	0.4	1.3
Mean age of patients without dependence: years	51.0	56.5	36.4	40.1	30.6	30.4	39.7	44.7	35.1	42.2	26.7	43.9
Mean age of patients with dependence: years	53.3	61.8	49.8	47.6	35.5	41.8	47.6	50.0	50.4	50.5	48.7	51.8

was available regarding the length of time for which drugs had been taken.

The leading withdrawal symptoms in all patients with primary BZD dependence were tremor/shakiness (54.1% of patients), agitation/restlessnes (53.3%), sweating/perspiration (42.6%), sleep disturbance (32.8%), and anxiety/tension (15.6%). Characteristic perceptual disturbances were observed in 9.8% of patients, delirium in 4.9%, and seizures in 1.6%. It should be noted that due to the naturalistic design of this study, in 34.4% of all BZD-dependent patients, BZDs were gradually discontinued after admission in order to reduce or alleviate withdrawal symptoms; 3.3% of this patient group left hospital against medical advice.

Discussion

Concern about BZDs in regard to general health is indicated, as cross-sectional studies (Mellinger *et al*, 1978; Murray *et al*, 1981; Koenig *et al*, 1987) show that 6–12% of the population in Western countries take BZDs, about 0.5–2% on a long-term basis (exceeding one year). Up to 63% of the patients admitted to psychiatric hospitals in West Germany are prescribed BZDs (Ahrens *et al*, 1986). According to the present study, in 4.7% of admitted patients, BZDs were involved in some kind of abuse or dependence. Compared with prevalence figures of retrospective studies (Fleischhacker *et al*, 1986; Laux & König, 1987) and older large-scale surveys (Greenblatt *et al*, 1975; Marks, 1978), the prevalence of primary BZD dependence is much higher in this survey (1% of the hospital population). This is probably due to the fact that older studies focused mostly on high-dose dependence, which was found to be rare also in the present study (4 per 10 000 admissions). All other cases of primary BZD dependence (134 of 140 cases) involved low or intermediate doses taken by patients with psychiatric disorders.

The rate of risk for primary BZD dependence was highest in the anxiety neuroses. BZDs are known as rather efficacious in this particular patient group and are recommended on a short-term basis or with flexible dosage (Tyrer & Murphy, 1987). However, according to the present findings, BZD dependence existed in about one in eight admitted patients (11.8%). As in-patients with anxiety neuroses seem to be a highly selective patient group with chronic and severe symptomatology (Krieg *et al*, 1987), general conclusions for out-patients cannot be drawn from our data. For in-patients with neurotic or endogenous depression, the risk (3.7%; 2.7%) was much lower than for anxiety neurotics. The finding that among in-patients with depression the risk for females was double that for males may correspond to higher rates of prescription of BZDs to females and to higher exposures of depressed males to alcohol (Mellinger *et al*, 1978; Williams *et al*, 1982; Hasin *et al*, 1985; Koenig *et al*, 1987).

Higher age was also related to BZD dependence – a finding that was true especially for patients with neurotic and endogenous depression and also for anxiety neurotics. This observation is also compatible with the higher prescription rates in older patient groups (Mellinger *et al*, 1978; Koenig *et al*, 1987). In accordance with other longitudinal data (Krieg *et al*, 1987), it can be speculated that patients with anxiety and depression who develop BZD dependence present a more ill subgroup with long-persistent symptomatology.

It should be emphasised that BZD dependence in depressive patients is rather heterogeneous. One group

consisted of patients with endogenous depression who had been misdiagnosed and mistreated with BZDs. These patients showed signs of physical dependence, but later remitted under tricyclics. Another group was formed by patients suffering from major depression with chronic symptomatology who had been treated with BZD, or tricyclics in combination with BZD. These patients showed only partial improvement under clinical treatment (Garvey & Tollefson, 1986). A third group was presented by neurotic depressives often characterised by dependent personality. We would not exclude that BZD medication, possibly justified initially but not terminated early enough, could have contributed to depressive–apathetic syndromes in some patients before leading to BZD dependence (Olajide & Lader, 1984; Lydiard *et al*, 1987). Therefore, systematic studies are urgently needed to investigate the risk:benefit ratio of BZDs on a long-term basis.

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*L. G. Schmidt, MD, Dipl-Psych, *Senior Registrar, Department of Psychiatry, Free University of Berlin*; R. Grohmann, MD, *Senior Registrar, Department of Psychiatry, University of Munich*; B. Müller-Oerlinghausen, MD, *Professor, Chief, Laboratory of Clinical Psychopharmacology*; M. Otto, *Research Assistant, Department of Psychiatry, Free University of Berlin*; B. Wolf, MD, *Research Assistant, Department of Psychiatry, University of Munich*; E. Rüther, MD, *Professor, Head, Department of Psychiatry, University of Göttingen*

*Correspondence: *Eschenallee 3, D-1000 Berlin 19 (West), Germany*