

Benzodiazepines in Addition to Antidepressants in the Treatment of Severely Depressed Inpatients – How Often Does it Lead to Long-Term Intake?

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Abstract

Objective: The study evaluates the risk of inducing long-term treatment with benzodiazepines (BZDs), when severely depressed patients are treated with BZDs in addition to antidepressants to bridge the delayed efficacy of antidepressants.

Method: Medical charts of 880 depressed inpatients were analysed regarding medication and psychopathology. If medication at dismissal included BZDs, patients were followed up and their physicians were asked about the current medication 12-15 months later.

Results: 486 patients (55%) received BZDs during hospitalisation. In comparison to BZD-free patients, these patients suffered significantly more often from severe recurrent depression than from dysthymia or adjustment disorder. They were also older and predominantly female. At discharge, 45% of these patients still received BZDs. At one-year follow-up, 39% of patients treated with BZDs at discharge still took BZDs. However, 67% of these patients had received BZDs already before inpatient treatment.

Conclusion: Psychiatrists should be concerned about the frequent BZDs use. BZDs should be withdrawn before discharge, because there is a high risk of dependency. However, most of these long-intake patients took BZDs already prior to inpatient treatment. During inpatient treatment patients have to be informed with regard to the consequences of long-term intake of BZDs (German J Psychiatry 2008; 11: 134-140).

Keywords: depression, benzodiazepines, long-term treatment, addiction

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Introduction

The administration of benzodiazepines (BZDs) in suicidal, anxious or agitated patients with depression is common international practice (Barak et al., 2006; Furukawa et al., 2001; Morishita et al., 2007; Nelson et al., 1999; Rihmer et al., 2006; Smith et al., 2002). Furukawa et al. (2001) analysed nine studies with a total of 679 patients to determine whether adding BZDs to antidepressants in patients with major depression is associated with benefit in terms of symptomatic recovery or side effects. The intent-to-

treat analysis (with drop-outs assigned the least favourable outcome) showed that patients allocated to the combination therapy were less likely to drop out of study and were more likely to show improvement of depression.

Nevertheless, the prescription of BZDs is recommended to be limited to a period of two to four weeks (Pélissolo et al., 2007; Poser et al., 2007), significant because cognitive impairment (Golombok et al., 1988; Hendler et al., 1980; Tata et al., 1994), tolerance (review Micheline et al., 1996), increased anxiety (Lemoine et al., 1997) and dependency (Hollister et al., 1961; Lader, 1994) were found to be associated with long-term BZDs use.

Table 1: Sample Characteristics

	Total n=880	no BZDs n=394	BZDs n=486	Statistics
Male/female (%)	32 / 38	36 / 64	29 / 71	F=4.894, df 1, p=.027
Age	50 ± 16	45 ± 15	54 ± 15	F=76.626, df 1, p<0.001
Marital status (%)				
Single	21	27	17	
Married	53	46	59	
Divorced	10	13	7	F=3.832, df 1, p=.05
Separated	2	4	1	
Widowed	13	10	16	
Diagnosis - ICD 10 (%)				
bipolar (F31)	13	10	15	
recurrent (F33)	51	34	64	F=73.163, df 1, p<0.001
dysthymia (F34)	6	11	3	
adjustment disorder (F43)	30	45	18	
Duration of illness (years)	8 ± 10	7 ± 9	9 ± 11	F=14.458, df 1, p <0.001
Hospitalisations	2.5 ± 2.6	2.1 ± 2.2	2.8 ± 2.8	F=19.093, df 1, p<0.001
Suicide attempts	.5 ± .8	.5 ± .9	.4 ± .8	F=9.726, df 1, p=.002
BZDs before admission	11%	8%	14%	F=8.513, df 1, p=.004
History of abuse or dependency	25%	30%	20%	F=11.368, df 1, p=.001
AMDP depression*	13 ± 8	9 ± 7	16 ± 8	F=129.218, df 1, p<0.001
AMDP total*	28 ± 16	23 ± 15	32 ± 15	F=95.162, df 1, p<0.001
GFS*	49 ± 12	50 ± 12	47 ± 11	F=6.399, df 1, p=.012

* at admission

There is only one study examining prospectively the risk of long-term treatment and abuse of BZDs in 71 patients with major depression, published more than twenty years ago (Garvey et al., 1986). Eight months after initial treatment with BZDs, follow-up showed that 39 patients (55%) continued to take BZDs, an abuse (DSM III criteria) was diagnosed in 5 patients (7%). Balestrieri et al. (2005) investigated 1156 BZDs users with regard to reason and source of first prescription. A depressive disorder was present in 36.5%, 13.7% started BDZ treatment during hospitalisation. Schmidt et al. (1989) revealed a lower risk of BZDs dependency in unipolar depressed patients compared to patients suffering from anxiety disorders. In general, older women with a diagnosis of mood or anxiety disorder, socially isolated and somatically ill patients were found to be at risk for BZDs dependency or long-term intake (Ashton et al., 1989; Geiselmann et al., 1989).

The principal aims of this naturalistic study with a high number of subjects were to identify characteristics of patients treated with BZDs during hospitalisation and to identify risk factors for a subsequent long-term intake.

Material and Methods

Participants

Within a period of three years, medical charts were analysed of all inpatients with ICD-10 diagnosis of bipolar affective disorder (F31; n=116), depressive episode and recurrent depressive disorder (F32 and F33; n=444), dysthymia (F34.1; n=54) and adjustment disorders (F43.2; n=266), treated for

48±47 days at the department of psychiatry of the University of Munich.

The AMDP System (Angst et al., 1969) was used for measurement of psychopathology. The AMDP score was rated by the trained ward physician (AMDP rater training every two weeks) at admission and discharge. According to the naturalistic study design, physicians decided to prescribe BZDs according to clinical judgement. Usual criteria were severity of depression, agitation, suicidality or sleep disturbance.

If medication at discharge included BZDs, patients received 12-15 months later a questionnaire addressing present psychopathological state and medication. Moreover, the patients were asked to give their informed consent for contacting the current physician (general practitioner and/or psychiatrist). The physicians were asked for further information on drug therapy since discharge from inpatient treatment and for any evidence that the patient might receive BZDs (also) by another physician. BZDs equivalent were calculated as usual (exact values see Holzbach, 2006). The investigation only concerned the risk of long-term treatment with BZDs. The question of misuse or dependency according to ICD 10 or DSM-IV criteria was not evaluated.

The study design was approved by the local ethics committee.

Statistical analysis

The statistical analysis was realized with SPSS, Version 13. The analysis of variance was performed with a general linear model (univariate analysis of variance, UNIANOVA). A discriminant analysis was used to predict the outcome "BZDs use at follow-up" (DISCRIMINANT, unstandard-

ised). The nominal level of significance was $\alpha=0.05$. In case of multiple testing, alpha adjustment according to Bonferroni procedure was performed to keep the type I error to 0.05.

Results

Demographic data

The total sample of 880 depressed inpatients consisted primarily of women (68%). 53% were married, the average age was 50 ± 16 years. The duration of illness was 8 ± 10 years and they had 2.5 ± 2.6 hospitalisations before the index episode (Table 1).

Incidence of BZDs medication

486 of 880 inpatients received BZDs treatment (55%). In 267 patients, BZDs were discontinued prior to discharge (55% of BZDs-treated patients or 30% of all). Of the remaining 219 patients, who still received BZDs at discharge, 14 were deceased at follow-up (5 by suicide), 29 could not be traced (see figure 1). Thus, 176 patients received the questionnaire, 170 responded (97%) (Figure 1). Two patients did not consent to contact their physician and 9 patients did not mention the use of BZDs, documented by their physicians. The question regarding BZDs prescription by other physicians was answered with „no“ (n=149), „maybe“ (n=4) or „yes“ (n=3).

Figure 1

BZDs treatment during hospitalisation

Patients treated with BZDs in the hospital received BZDs in an average dose of 13 ± 26 mg diazepam-equivalent over 38 ± 29 days. At discharge, patients with BZDs (n=219) had a dose of 6.7 ± 4.6 mg diazepam-equivalent. Of the 486 patients being prescribed BZDs, 52% received lorazepam (n=255), 29% dikaliumclorazepat (n=139), 12% diazepam (n=60), 11% flurazepam (n=54), 9% lormetazepam (n=43), 5% flunitrazepam (n=22), 3% triazolam (n=15), 2% oxazepam (n=12) and 2% alprazolam (n=8).

Who received BZDs?

The typical patient treated with BZDs was female, older, married and suffered from a recurrent depression (Table 1). In comparison to patients without BZDs treatment, she/he had a longer history of depression and was more often hospitalised. BZDs patients were more severely depressed, however they had less suicide attempts. BZDs treatment before admission occurred more often, history of abuse or dependence however less often.

Who was still taking BZDs at discharge?

39% of patients still continued BZDs treatment after one year. There was no difference in sex, duration of illness, diagnosis, number of suicide attempts, overall psychopathology (AMDP total score), global functioning at admission, BZDs treatment at admission, or history of abuse and addiction between patients with ongoing or discontinued BZDs treatment (Table 2).

Patients with ongoing use of BZDs showed more depressive symptoms at the beginning of hospitalisation. Maximum BZDs dosage during inpatient treatment was significantly higher (22 ± 45 mg vs. 14 ± 23 mg diazepam equivalent; $F 6.359$, $df 1$, $p=.012$) than in patients who discontinued BZDs while hospitalised. Patients who received BZDs at discharge were more frequently prescribed a BZDs with a short half-life time (69% vs. 51%, $F 15.939$, $df 1$, $p<0.001$), the maximal dosage was lower (13 ± 16 mg vs. 23 ± 51 mg diazepam equivalent; $F 8.635$, $df 1$, $p=.003$).

At discharge, 53% received lorazepam (n=116), 13% dikaliumclorazepat (n=28), 5% diazepam (n=11), 7% flurazepam (n=15), 11% lormetazepam (n=23), 3% flunitrazepam (n=7), 3% triazolam (n=7), 3% oxazepam (n=6) and 3% others (n=6).

Who will start (or continue) long-term treatment ?

For the 67 patients still taking BZDs at follow-up, mean BZDs dosage was not significantly different from discharge (6.9 ± 6.2 mg vs. 6.5 ± 5.2 mg). The dosage was not changed for 29 patients (42%), 23 patients (35%) had reduced their dosage to an average of 61% of the dose at discharge and 15 patients (23%) increased the dosage to an average of 210%. The current equivalent diazepam dosage was <5 mg in 36%, 5-9 mg in 36%, 10-19 mg in 12%, 20-30 mg in 6%. 53 patients continued to take the same BZDs they had received at discharge, 13 patients took a different BZDs at follow-up.

There was no difference between patients with ongoing intake of BZDs and those who discontinued with regard to sex, diagnosis, number of hospitalisations, psychopathology and global functioning at admission and dismissal. Patients still on BZDs at follow-up were significantly older (64 ± 11 vs. 54 ± 14 ; $p=.048$) and showed more often a history of abuse or addiction (25% vs. 14%; n.s.) (Table 3).

There was no significant difference in maximum dose and total dose of BZDs during hospitalisation between the groups with ongoing BZDs intake and discontinued BZDs intake after hospitalisation (lower BZDs dosage at follow-up), and no difference in duration of treatment and number of BZDs. Patients with ongoing BZDs treatment received more often BZDs with short half-life time (78% vs. 67%, n.s.) at the end of hospitalisation.

The discriminant analysis with age, sex, marital status, depression-score admission (AMDP) and half-life time of

BZDs at discharge showed a canonical correlation of .389

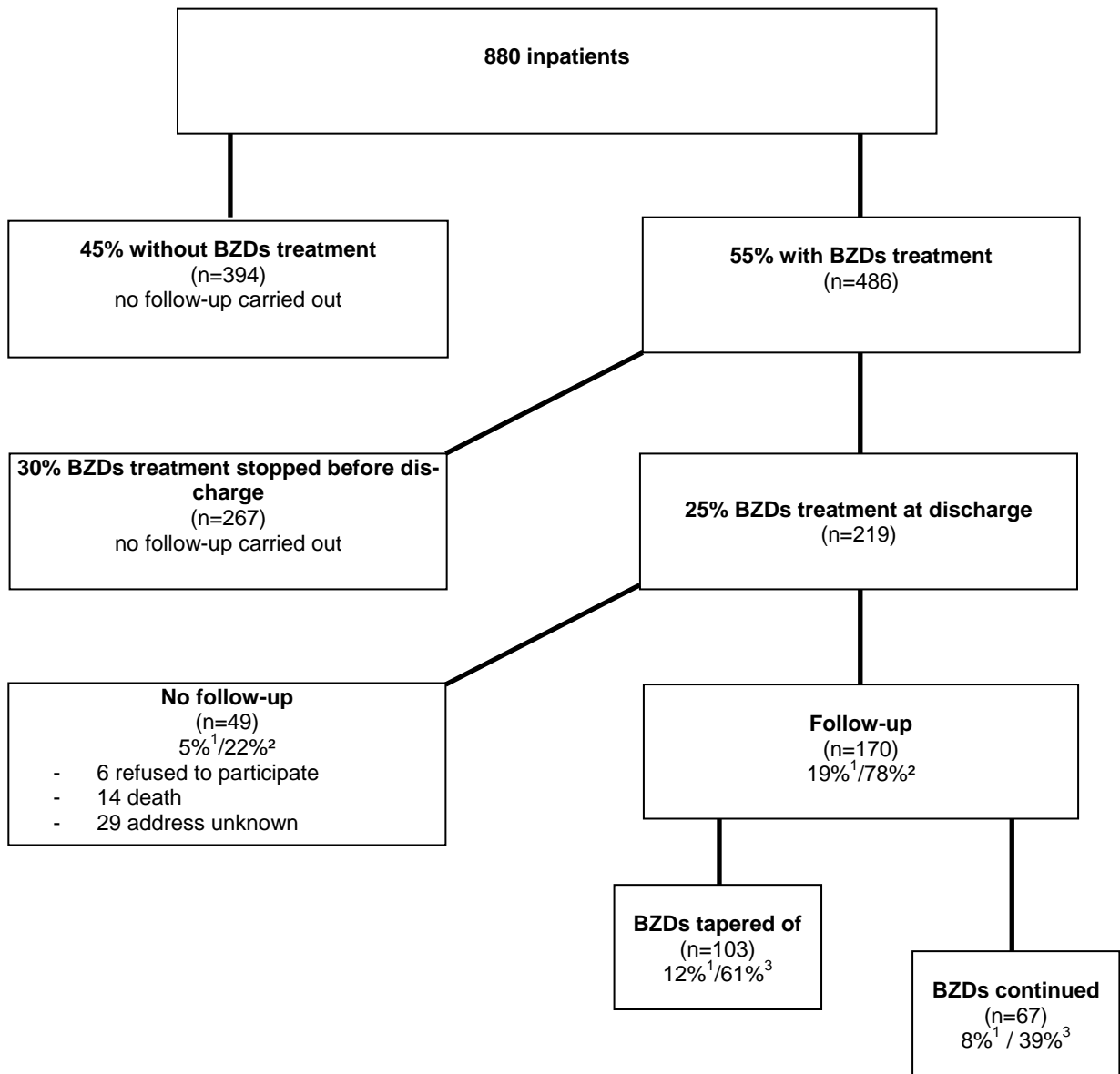


Figure 1. BZDs prescription during inpatient treatment (7±7 weeks) and at follow-up (12-15 months later)

¹ of 880 patients (total group)

² of 219 patients (patients with BZDs at discharge)

³ of 170 patients (patients with follow-up)

and Wilks' Lambda with .849 ($p < 0.001$). Patients with ongoing BZDs intake at follow-up were more depressive at discharge, older, predominantly female, widowed and treated with a short-half-life-time BZDs.

Relevance of BZDs half-life

BZDs with short elimination time (lorazepam, lormetazepam, triazolam and oxazepam) were discontinued less often (50%) than BZDs with long half-life (dikaliumclorazepat, diazepam, flurazepam and flunitrazepam), which were withdrawn in 70% before discharge ($F 15.939, df 1, p < 0.001$).

Table 2: Who was still taking BZDs at discharge?

	BZDs n=486	BZDs stopped n=267	BZDs at dis- charge n=219	Statistics
Male/female (%)	29 / 71	30 / 70	27 / 73	n.s.
Age	54 ± 15	51 ± 14	57 ± 14	F 22.100, df 1, p<0.001
Marital status (%)				
single	17	21	12	
married	59	58	59	
divorced	7	8	7	F 8.184, df 1, p=.004
separated	1	-	2	
widowed	16	13	20	
Hospitalisations	2.8 ± 2.8	2.5 ± 2.6	3.1 ± 2.9	F 5.843, df 1, p=.016
AMDP total admission	32 ± 15	31 ± 15	33 ± 15	n.s.
AMDP total score dismissal	8 ± 9	7 ± 7	9 ± 10	F 8.053, df 1, p=.005
AMDP total score difference	25 ± 15	25 ± 15	25 ± 16	n.s.
AMDP depression admission	16 ± 8	14 ± 8	17 ± 8	F 17.515, df 1, p<0.001
AMDP depression score di- smisal	3 ± 4	3 ± 4	4 ± 5	F 12.629, df 1, p<0.001
AMDP depression score dif- ference	12 ± 9	11 ± 8	13 ± 9	F 6.601, df 1, p=.010
GFS admission	47 ± 11	45 ± 12	49 ± 9	n.s.
GFS dismissal	66 ± 14	67 ± 15	65 ± 13	n.s.
GFS difference	21 ± 13	24 ± 13	16 ± 11	F 14.433, df 1, p<0.001
Number of BZDs	1.3 ± .6	1.2 ± .5	1.5 ± .7	F 28.686, df 1, p<0.001
Maximum dose*	17 ± 35	14 ± 23	22 ± 45	F 6.359, df 1, p=.012
Total dose of BZDs*	593 ± 1464	360 ± 665	879 ± 2026	F 15.300, df 1, p<0.001
Duration of BZDs treatment (days)	38 ± 30	30 ± 25	48 ± 32	F 49.774, df 1, p<0.001
Half life time short / long (%)	59 / 41	51 / 49	69 / 31	F 15.939 df 1, p<0.001

* in mg diazepam equivalent

At follow-up, a similar difference was found: 94 of 143 (66%) of the BZDs with short half-life were withdrawn and 52 of 66 (79%) with long half-life (not significant).

With regard to long vs. short half-life BZDs prescription, there was no difference for sex, marital status, duration of illness, number of hospitalisations or suicide attempts, duration of symptoms or somatic illness. However, patients with short half-life BZDs were older (55±15 vs 51±14; F 9.752, df 1, p=.002) and had more psychopathological symptoms at admission (AMDP total 34 ± 15 to 30 ± 14; F 10.685, df 1, p=.001; AMDP depression 17 ± 9 to 14 ± 8; F 10.553, df 1, p=.001). During hospitalisations, these patients had a greater benefit from treatment (F 10.531, df 1, p=.001) and, therefore, similar psychopathology at discharge (AMDP total 7.41 ± 9 to 7.63 ± 7; n.s.; AMDP depression 3.28 ± 4 to 3.54 ± 4; n.s.).

Discussion

Clinical experience, not always based upon scientific evidence (Naber et al., 2003), indicates that BZDs may be combined with AD to produce a faster relief from depressive stupor and mutism, to reduce the risk of suicide and to increase compliance with antidepressant treatment. The risk of

long-term treatment and dependency is usually mentioned, but its frequency is not known.

In this study, 880 patients, hospitalised for 7 weeks on average (SD ±7) because of an affective disorder, were investigated with regard to BZDs treatment and current medication. Patients with a BZDs prescription at discharge were reinvestigated one year later. The high percentage (78%) of patients, who responded to the questionnaires and gave permission to contact their doctors, as well as the high agreement in the statements of patients and their doctors indicate that data on BZDs intake at follow-up are reliable.

They reveal that the administration of BZDs in addition to antidepressants led to long-term BZDs intake in around 39% of patients. BZDs were given mostly to severely depressed patients with a recurrent depressive disorder and less often to patients with dysthymia or adjustment disorders. The study confirmed results of other studies (Ashton et al., 1989; Geiselman et al., 1989; Luijendijk et al., 2007; Merikangas et al., 2008; Pélioso et al., 2007) that older widowed female patients have a higher probability to be treated with BZDs.

Although BZDs were supposed to be applied for a short period only and to be withdrawn before discharge, 45% of the patients with BZDs during inpatient treatment still took BZDs at discharge. In 20% of patients with BZDs treatment during hospitalisation, current BZDs abuse or dependency was already known. For this population, BZDs treatment was most often not withdrawn. It is hard to evaluate whether

Table 3: Who was still taking BZDs at follow-up?

	BZDs at dismissal, reached at follow-up n=170	BZDs stopped n=103	BZDs at follow-up n=67	Statistics
Age	58 ± 14	54 ± 14	64 ± 11	F 26.212, df 1, p<0.001
Marital status (%)				
single	12	12	12	
married	61	67	52	F 5.329, df 1, p=.022
divorced	7	7	8	
separated	2	3	-	
widowed	18	12	29	
History of abuse or addiction	18%	14%	25%	F 4.722, df 1, p=.031.
Duration of illness (years)	10 ± 11	8 ± 11	12 ± 11	F 5.643 df 1, p=.019
AMDP total score dismissal	8 ± 8	7 ± 9	8 ± 8	n.s.
AMDP depression score at dismissal	4 ± 5	4 ± 5	4 ± 5	n.s.
GFS dismissal	67 ± 11	68 ± 11	65 ± 12	n.s.
Maximum dose*	22 ± 49	28 ± 61	14 ± 16	n.s.
Total dose of BZDs*	961 ± 2228	1193 ± 2777	596 ± 677	n.s.
Duration of BZDs treatment (days)	50 ± 32	49 ± 34	52 ± 30	n.s.
Half life time short/long (%)	71 / 29	67 / 33	78 / 22	n.s.

* in mg diazepam equivalent

stronger efforts to withdraw BZDs would have been successful or would have caused serious complications such as non-compliance or suicidal ideation.

Of major relevance but unsolved is the question whether a BZDs with a short half-life is more difficult to be withdrawn (Hollister, 1978). To our knowledge, this is the first study with a high number of patients showing that this might be true. Outcome predictions in terms of age, sex, marital status, diagnosis, depression score at admission (AMDP) and half-life time of BZDs at discharge are limited.

Conclusion

The development of abuse or dependency cannot be differentiated in this study. However, the risk to induce high-dose dependency is markedly limited; only 6% of patients discharged with BZDs increased their dosage to 20-30 mg/day. The only comparable study by Garvey and Tollefson (1986) revealed similar data: 39 of 71 patients (55%) with major depression treated with BZDs still took BZDs after 8 months, an abuse was diagnosed in 5 patients (7%).

Data indicate that for the majority of depressed patients, short-term BZDs treatment is justified and the danger to induce long-term intake or dependency is mostly restricted to patients known to be at risk.

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