

Co-Consumption of Benzodiazepines in Heroin Users, Methadone-Substituted and Codeine-Substituted Patients

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ABSTRACT. Concomitant consumption of benzodiazepines (BZDs) and opioids is a major problem in patients with opioid dependence. It may have substantial impact on morbidity, mortality and clinical course. The current retrospective study aims to determine whether there are differences in the additional use of BZDs among addicts regularly taking

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The authors would like to thank the staff from the detoxification unit 'Villa' for their help with data collection and entry.

This study was supported by 'Modellprogramm Kompakttherapie im Verbund der Drogenhilfe 1990-1995' from the Department of Health from the Federal Republic of Germany.

Journal of Addictive Diseases, Vol. 24(4) 2005
Available online at <http://www.haworthpress.com/web/JAD>
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doi:10.1300/J069v24n04_02

methadone or codeine medications in treatment and untreated addicts injecting heroin. The records of 1,685 patients admitted for detoxification were analyzed using bivariate analysis and multiple logistic regression analysis. Demographic and drug related variables were considered, both as possible confounders and predictors of concomitant BZD use. Daily intake of BZDs was reported in 44.4% of the patients. Patients treated with methadone or codeine medications report daily intake of BZDs significantly more often than the heroin-dependent patients ($p < 0.01$). Using multiple regression analyses, the results were confirmed as independent from the assessed possible confounders. Further we found that daily use of alcohol or barbiturates, early onset of opioid use ($p < 0.01$), unemployment, having a substance dependent family member with, and a history of imprisonment (for all $p < 0.05$) were associated with concomitant daily consumption of BZDs in opioid dependent subjects. These findings underline the need to further explore the causes, interactions and consequences of concomitant BZD and opiate use. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2005 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Co-consumption, benzodiazepine dependence, methadone, codeine, heroin

INTRODUCTION

Benzodiazepine (BZD) use is common in patients with opioid dependence.^{1,2} Basic sciences indicate a close relationship between the opioid system and the GABA systems.³⁻¹⁰ Evidence indicates that concomitant consumption of additional psychotropic substances in opioid dependent patients may have a substantial impact on morbidity, mortality and clinical course. Co-consumption of BZD, alcohol or barbiturates, which are all respiratory-depressants, will increase the risk of complications. Data indicate that an estimated 62-72% of the patients, who had been treated for overdosing, had consumed more than one class of substances.^{11,12} In cases of fatal overdosing, use of multiple substances was reported in 71-92% of patients.¹³⁻¹⁶ In 26-72% of these deaths, BZD was identified.^{12,15,16}

Studies conducted in Munich—the area from which our study population has been recruited—indicate that co-abuse of BZDs is frequent in drug related deaths (72%). This proportion is higher in patients treated

with methadone (82%) and highest in patients treated with codeine medications (88%).¹⁷ BZD use in opioid dependent patients has been found to be correlated with a history of more severe drug abuse,^{18,19} a high level of psychological distress,^{17,20} more HIV risk-taking behaviors,²⁰ and a higher prevalence of hepatitis C virus (HCV) infection.²⁰⁻²²

One of the major goals of substitution therapy is the reduction of use of illegal substances. A number of studies have confirmed that the consumption of illegal drugs such as heroin and cocaine are reduced by methadone treatment programs²³⁻²⁶ as well as in codeine maintenance programs.²⁷ Use of legal substances has received less attention. Current data seem to indicate that substitution therapy do not reduce use of alcohol.²⁸ We wanted to know whether substitution treatment can reduce the consumption of BZDs. And if substitution therapy can do so it would be of interest which substitution substance does reduce the co-consumption more effectively. During the observation period in the years 1991-1996 methadone and codeine were used for substitution treatment. We were in a position to compare patients with no previous addiction treatment (injection heroin users), and patients from a methadone-substitution program (the most intense treatment), with an "intermediate group" of codeine-substituted patients, (regular contact to a physician but no additional supervision, e.g., no psychotherapy and no drug-use control).

Corresponding to the fact that alcohol consumption is higher in substituted patients than in injection heroin users we present our hypothesis that those patients treated with methadone or codeine use more BZD than the untreated patients injecting illegal heroin.

We further investigated whether there are predictors or risk factors for BZD co-consumption in heroin users and patients treated with codeine or methadone.

SUBJECTS AND METHODS

Subjects

The study population consists of all patients voluntarily admitted to an inpatient detoxification treatment in Munich between April 1991 and December 1996 fulfilling DSM-III-R and ICD-9 criteria for current opioid dependence. Contact with the patients was established by a telephone hotline. Patients could come by self-referral. No previous contact with a counselor or physician was necessary. Order of intake was deter-

mined by perceived severity of drug-associated problems, and by a waiting list.

During the observation period 1,656 admissions were recorded with patients voluntarily admitted to the detoxification inpatient treatment. A total of 35% were females and 65% males. Five hundred thirty-seven of the patients were readmitted within the given time frame. Of these patients only the first admission was included in the analyses. Forty-nine patients were excluded because we were not able to group them due to alternating opioid use. Twenty-one patients were not included since their data collection was incomplete.

Treatment Setting

The detoxification unit is a physically separated ward within a general hospital. It is the former director's mansion—thus colloquially called the 'Villa'—within the hospital compound. A total of 15 beds in seven bedrooms are available for opioid detoxification. The treatment concept called "qualified detoxification" consists of medication-supported detoxification (almost exclusively methadone), diagnosis and treatment of medical consequences of drug addiction, e.g., AIDS, chronic hepatitis B and C, pneumonia, endocarditis, etc.), daily group and individual psychotherapy and social therapy with the goal of facilitating the transition to abstinence-treatment following detoxification. The treatment concept is based on a Minnesota Model-like approach. Individual, dynamically oriented brief psychotherapeutic interventions were added. The Villa is conceptualized as a 'low threshold' treatment. Patients were admitted as soon as there was an opening.²

Methods

On the day of admission, the daily intake of psychotropic substances over the preceding 6 months was established. The patients were questioned for a range of topics including their intake of opioids and other psychotropic substances such as amphetamines/amphetamine derivatives, barbiturates, cocaine, cannabis and benzodiazepines. These declarations were verified by an immunoassay urine test (Triage[®]) and a KIMS (kinetic interaction of micro particles in a solution). Additionally, the patients were asked about their consumption of alcohol and nicotine.

For analysis the patients were divided into 3 groups according to the primarily used opioid during a time period of six months or longer. Those who received daily doses of methadone or levomethadone (sum-

marized as methadone) were included in group 1, those who received dihydrocodeine in group 2, and those with a daily consumption of heroin in group 3. If two opioids were taken every day and no obvious grouping could be established, priority was given to heroin over methadone over dihydrocodeine. If none of the opioids were taken daily, but rather several of them alternatively, then these patients were not grouped at all and excluded from the analyses. Data included in analysis consist of daily intake of other psychotropic substances during the past six months, gender, age, duration of dependence, age at first opioid use, marital status, education, employment, regular counseling (at least once a month), living with a significant other with or without substance dependence, family member with or without substance dependence, history of imprisonment, history of emergency treatment (at any time), suicide attempts (at any time), seropositivity of hepatitis B, hepatitis C and HIV. Co-use of benzodiazepines was defined as daily consumption of benzodiazepines. The use was considered to be “high dose consumption” if the daily dose was equivalent to 60 mg of diazepam a day or more. Two variables of interest were investigated as end points: concomitant use of benzodiazepines and high dose use of benzodiazepines. Consumption of BZD was assumed only if patients reported daily use and provided a positive urine sample.

Statistics

After cross-tabulation and bivariate analyses, logistic regression modeling was applied. Of all the patients enrolled in the treatment program, analyses were restricted to the first detoxification within this time-period. Because preliminary analyses indicated non-linear associations involving age, duration of opioid use, age at first opioid use, these variables were transformed from ordinal to categorical variables. Results are summarized by reporting a ‘full model’ that includes all investigated variables regardless of their statistical significance.

RESULTS

For the 1049 patients included in the analyses, the median age was 28.2 years (16.9-54.6 years), and the median duration of opioid use was 10 years. A total of 135 patients (35.6% females and 64.4% males) had received methadone on a daily base. They are included in group 1 (Methadone group). A total of 646 patients, (33.9% female and 66.1%

male) had taken codeine medication on a daily base. They form group 2 (codeine group). A total of 268 patients, 37.3% female and 62.7% male, reported daily consumption of heroin. They formed group 3 (Heroin group). The size of group 2 (codeine group) has to do with availability at the time of recruitment.²

Among those 1049 patients, a total of 466 (44.4%) consumed BZDs on a daily base (co-use of BZDs). Among BZDs consuming patients a total of 218 (20.8% of the total population analyzed) consumed 60 mg or more diazepam equivalent per day (high dose consumption). Bivariate analyses indicated that patients who were in a methadone or codeine maintenance treatment program significantly more often reported daily consumption of BZDs than the heroin-dependent patients ($p < 0.01$). Prevalence of daily co-consumption of BZDs was lowest in heroin users (25.4%). In patients who were treated with methadone (36.3%), it was lower than those treated with codeine (54.0%; the difference was significant at $p < 0.01$). High dose consumption was reported significantly more often in group 1 (methadone) and 2 (codeine) than in group 3 (heroin; the difference was significant at $p < 0.01$). Table 1 presents bivariate analyses on the key variable and possible confounding variables associated with co-consumption of BZDs, both for daily use overall and for the high dose users.

Table 2 shows the independent variables found as a result of the multiple logistic regression analyses. The key finding is that consumers of heroin took daily BZDs less often compared to substituted patients. This result persisted even when all other variables were included in the model. "Additional consumption of barbiturates" and "additional consumption of alcohol" were significant for co-consumption of BZDs. These variables were significant for the overall and the high dose dependency group.

"Age at first opioid use under 19 years," "counseling" and "history of suicide attempts," "married or living with a partner" and "male" were significantly associated only for the high dose dependency group, whereas "unemployment," "history of imprisonment" and "family member with substance dependence" showed a significance only in the overall group.

DISCUSSION

The primary aim of this study was to investigate differences of BZD consumption within three groups of opioid dependent patients: those treated with methadone, those treated with codeine and those injecting

TABLE 1. Cross tabulation for risk factors associated with co-consumption of benzodiazepines and high-dose dependence. The variables age, education, living with another substance dependent person, family member with substance dependence, daily consumption of THC, infection with hepatitis B, C or HIV are not listed as they were not significant ($p > 0.05$).

Variable	n	Co-consumption of benzodiazepines			High-dose dependence				
		%	O.R.	95% C.I.	p	%	O.R.	95% C.I.	p
Type of opioid dependence									
Methadone	135	36.3	1.68	1.07-2.62	0.000	21.5	2.55	1.43-4.53	0.000
Dihydrocodeine	646	54.0	3.46	1.14-2.01	0.023	25.2	3.14	2.02-4.89	0.000
Heroin	268	25.4	1		0.000	9.7	1		0.000
Sex									
Female	367	43.1	0.92	0.71-1.19	0.512	16.6	0.67	0.48-0.93	0.015
Male	682	45.2	1			23.0	1		
Duration of opioid use									
< 1 year	76	31.6	0.53	0.30-0.93	0.028	7.9	0.29	0.12-0.72	0.068
2-5 years	384	42.4	0.85	0.60-1.21	0.363	20.1	0.85	0.56-1.31	0.007
6-10 years	246	43.5	0.89	0.60-1.30	0.537	22.4	0.98	0.62-1.55	0.467
11-15 years	158	54.4	1.38	0.90-2.11	0.143	24.1	1.08	0.65-1.78	0.932
> 15 years	185	44.4	1			22.7	1		0.769
Age at first opioid use									
1-13.99 years	80	50.0	2.08	1.21-3.57	0.000	23.7	2.31	1.63-4.58	0.000
14-18.99 years	425	53.1	2.35	1.64-3.36	0.000	30.0	3.18	1.96-5.17	0.017
19-22.99 years	342	40.9	1.44	0.99-2.08	0.057	15.9	1.40	0.83-2.37	0.000
>23 years	202	32.5	1			11.9	1		0.210
Marital status									
Single	694	43.4	0.97	0.52-1.80	0.600	18.4	1.16	0.51-2.67	0.010
Married, living with a partner	312	46.8	1.11	0.59-2.11	0.917	26.6	1.86	0.80-4.35	0.722
Divorced, widowed	43	44.2	1		0.748	16.3	1		0.150

TABLE 1 (continued)

Variable	n	Co-consumption of benzodiazepines			High-dose dependence		
		%	O.R.	95% C.I.	%	O.R.	95% C.I.
Working status							
Unemployment	759	47.2	1.50	1.14-1.99	22.7	1.55	1.09-2.22
Employment	290	37.2	1		15.9	1	0.016
Counselling							
No	551	41.2	0.76	0.60-0.97	17.1	0.62	0.46-0.86
Yes	498	48.0	1		24.9	1	0.002
History of imprisonment							
Never	611	40.1	0.67	0.48-0.94	18.7	0.60	0.41-0.89
1	268	50.7	1.03	0.70-1.51	21.3	0.71	0.45-1.10
> 1	170	50.0	1		27.6	1	0.127
History of emergency treatment							
No	685	40.6	0.64	0.50-0.83	17.5	0.58	0.43-0.78
Yes	364	51.6	1		26.9	1	0.000
Suicide attempts							
No	839	42.6	0.69	0.51-0.93	19.3	0.66	0.46-0.93
Yes	210	51.9	1		26.7	1	0.019
Daily consumption of cocaine							
No	1015	44.9	1.96	0.93-4.13	21.3	4.32	1.03-18.17
Yes	34	29.4	1		5.9	1	0.046
Daily consumption of barbiturates							
No	976	42.0	0.22	0.13-0.38	19.4	0.36	0.22-0.53
Yes	73	76.7	1		39.7	1	0.000
Daily consumption of alcohol							
No	754	38.9	0.45	0.34-0.59	18.2	0.59	0.43-0.80
Yes	295	58.6	1		27.5	1	0.001

TABLE 2. Multiple logistic regression for risk factors associated with co-consumption of benzodiazepines and high dose dependency. All variables of Table 1 were included, but only significant variables ($p < 0.05$) are shown in this table.

Variable	Co-consumption of benzodiazepines			High-dose dependence		
	O.R.	95% C.I.	p	O.R.	95% C.I.	p
Type of opioid dependency			0.000			0.001
Methadone	1.37	0.82-2.28	0.232	1.88	0.99-3.56	0.053
Dihydrocodeine	2.97	2.08-4.22	0.000	2.50	1.55-4.05	0.000
Heroin	1			1		
Sex						
Female	0.94	0.69-1.28	0.674	0.60	0.41-0.88	0.008
Male	1			1		
Age at first opioid use			0.086			0.001
1-13.99 years	1.90	0.74-4.85	0.180	2.36	0.75-7.40	0.140
14-18.99 years	2.17	1.13-4.17	0.020	3.15	1.38-7.16	0.006
19-22.99 years	1.42	0.84-2.42	0.192	1.18	0.59-2.36	0.640
> 23 years	1			1		
Marital status			0.955			0.016
Single	1.02	0.50-2.10	0.952	1.16	0.46-2.93	0.752
Married, living with a partner	1.07	0.51-2.25	0.855	1.98	0.77-5.07	0.155
Divorced, widowed	1			1		
Employment						
No	1.41	1.03-1.94	0.034	1.35	0.91-2.00	0.141
Yes	1			1		
Counselling						
No	0.76	0.58-1.01	0.059	0.65	0.46-0.90	0.010
Yes	1			1		
Family member with substance dependency						
No	1.49	1.06-2.11	0.022	1.05	0.70-1.57	0.815
Yes	1			1		
History of imprisonment			0.016			0.090
Never	0.64	0.42-0.98	0.040	0.61	0.38-0.98	0.039
1	1.01	0.65-1.57	0.959	0.61	0.37-1.01	0.056
> 1	1			1		
Suicide attempts						
No	0.71	0.49-1.01	0.054	0.61	0.41-0.92	0.018
Yes	1			1		
Daily consumption of barbiturates						
No	0.27	0.14-0.50	0.000	0.50	0.29-0.89	0.018
Yes	1			1		
Daily consumption of alcohol						
No	0.51	0.37-0.70	0.000	0.67	0.47-0.96	0.029
Yes	1			1		

heroin. Our hypothesis was proved with this study: patients under substitution treatment with methadone or codeine have a higher co-consumption with BZDs than untreated patients injecting illegal heroin.

The study indicates that among the three groups heroin users constitute the group with the lowest proportion of daily consumption of BZDs. Among patients in substitution treatment those taking codeine medication use BZDs more often than those taking methadone (Table 2). This is according to the results for alcohol co-consumption.²⁸ In the current investigation barbiturates and alcohol use turned out to be the strongest predictors for daily BZD consumption. Obviously patients having co-consumption tend to take additionally more than one substance. A possible clinical explanation might be that the substitution substances have less rewarding or hedonic effects compared to heroin. When the “hedonic argument” is used the differences between heroin and substitution substances are generally attributed to differences in pharmacokinetics, e.g., methadone has a much longer elimination half-life. But if elimination half-life would be the determining factor, concomitant use of BZD should be lower in codeine medications users compared to methadone users. This is not the case. Perhaps differences in pharmacodynamics need to be taken more into consideration. Understanding the specific effect of these substances in the living human brain still is far from being complete.

In contrast to the general population, where female gender predicts benzodiazepine use,²⁹ our study indicates male gender to be associated with increased use of high dose use of BZDs, but not for any use. Recently, it was reported that BZDs were more often used by overdosing opiate dependent males than females.³⁰ Another recent study on polysubstance use found increased use of BZD in patients with earlier age of onset,³¹ consistent with our finding. Early onset of use has been used as a marker for increased genetic loading. Early onset might indicate a higher preference for substance use, a faster progression to polydrug use, resulting in a faster progression to treatment settings. It should be noted, that age of onset but not length of use is associated with co-consumption of BDZs.

The association of unemployment with concomitant BZD use may be explained by the reduced ability to fulfill job obligations if BZD and opioids are consumed concomitantly. Concomitant use of opioids and BZDs increases sedation and cognitive deficits.

High dose users are more often receiving counseling. Perhaps polysubstance users are less in control of their dependence. Another possible explanation might be increased anxiety and depression in this group.

This same might also explain why suicide attempts predict use of BZDs. A study in Munich indicated that 72% of overdose deaths were associated with BZD use.¹⁶

We found an association with imprisonment, counseling and suicide attempts. Probably those drug users, who have not been able to maintain their heroin centered life style and have had enough problems to either be arrested and imprisoned, or started treatment, or decided to end their lives, are those who are at increased risk to regularly use sedatives including BZDs.

Results of this study are limited due to three facts: the self selection of the sample, the question of generalizability of results from a single treatment centre and the restrictions in the number of possible confounders assessed in the current study. Further, the inference of causality is restricted by the study being retrospective. Finally, we are not able to answer the question if differences in concomitant BZD use are due to the specific pharmacological profile of the opiate used (heroin, methadone or codeine), or if the differences are due to environmental background (increased risk of those with a history of imprisonment, treatment or counseling) or if the differences are the result of self-selection due to individual differences (early onset of opioid use). But this study indicates that these groups of different opiate users do show significant differences in concomitant BZD use and that these differences are associated with a number of specific factors. These finding underline the need for further exploration of the causes, interactions, and consequences of concomitant BZD and opiate use.

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