

Benzodiazepine use in a methadone maintenance programme: patient characteristics and the physician's dilemma

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Summary

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Benzodiazepines (BZD) are among the most prescribed and used psychotropic medications in western countries. In populations of illegal drug abusers benzodiazepine use and abuse is even more widespread. In methadone maintenance treatment (MMT) programmes the physician is confronted daily with the demand for prescribing benzodiazepine. There is a lack of evidence-based data on indications and duration of benzodiazepine prescription to patients in a methadone maintenance treatment. Benzodiazepine abuse in MMT patients is associated with poorer outcome concerning illegal drug abstinence and psycho-social rehabilitation.

The aim of this cross-sectional study was to determine the prevalence of regular benzodiazepine consumption in 101 patients treated in a public methadone maintenance programme in Geneva and evaluate the clinical practice of benzodiazepine prescription. We also assessed the characteristics of the regular benzodiazepine users and compared them with the non-users'. Demographic, medical, psychiatric and social variables from medical charts, Addiction Severity Indexes and auto-questionnaires on benzodiazepine use were compared.

We found a prevalence of 51.5% regular benzodiazepine users in our population. Regular benzodiazepine users showed significantly more psychiatric comorbidity, significantly more abuse of other psychoactive substances and received higher daily doses of methadone. A very large majority of the regular benzodiazepine users received a controlled and regularly evaluated prescription. The prescriptions concerned essentially benzodiazepines with a long half-life, slow absorption and low value on the local black market. A majority of patients were able to diminish their benzodiazepine consumption during treatment. Our study showed that long-term prescription of benzodiazepine was frequent, although evidence-based guidelines in this domain are lacking. In the presence of regular, often anarchic, benzodiazepine consumption at the beginning of a methadone maintenance treatment, it can be extremely difficult to impose a complete and immediate abstinence. Concerning benzodiazepine prescription, physicians prescribing methadone maintenance treatment often find themselves in a dilemma: not prescribing risks denying the high prevalence of current benzodiazepine abuse and dependence and inducing premature dropout from the methadone maintenance treatment; prescribing risks maintaining benzodiazepine dependency and can be considered a medical act without evidence-based justification.

We suggest that before prescribing benzodiazepines, alternative treatment options should be considered and benzodiazepine treatment conditions be specified in a therapeutic contract that is frequently re-evaluated with the patient. Also, treatment-compliance issues should be considered and progressive withdrawal should be regularly proposed.

Keywords: methadone maintenance treatment; substance abuse; benzodiazepines; comorbidity; epidemiology

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Introduction

Methadone maintenance treatment (MMT) is a recognised treatment for opioid addiction. Different studies suggest that methadone maintenance treatment efficiently improves retention in health care, decreases opioid consumption and lowers the risk of mortality and legal contraventions [1–3]. Long-term outcome depends on treatment characteristics such as methadone dose, treatment duration and psychosocial services as well as on patient characteristics such as psychiatric and physical comorbidity, use and/or abuse of other psychoactive substances and the psychosocial context [4, 5]. Polydrug use is frequent in MMT patients [6] and must be taken into account in order to optimise therapeutic practices.

Benzodiazepine use in western countries is estimated to be very frequent, although it is difficult to obtain valid epidemiological data due to divergent definitions and scientific criteria. A nationwide survey in Switzerland in 1998 showed a daily use of hypnotics in the last 7 days for 3.2% of the general population and of tranquillisers for 2.1% [7].

Among illegal drug abusers benzodiazepine consumption is even more frequent. French and British studies found current regular use in more than 50% of this population [8, 9]. A number of studies evaluated the prevalence of current benzodiazepine use in MMT populations [10–12]. The prevalence of current benzodiazepine use varied between 24.9 and 50.6%. Seivewright et al. [12] suggested that the prevalence of current benzodiazepine use in a population of non-prescribed opiate abusers was only half as high than in a population of patients who received prescribed opiates (12 vs 24.9%); 89.6% of the latter received prescribed benzodiazepines. Shaffer and Lasalvia [13] found an increase in benzodiazepine use during the first year of methadone maintenance treatment, whereas the authors of a recent study in Israel [14] described a decrease of benzodiazepine abuse during the same period of methadone maintenance treatment. Consumption of certain benzodiazepines, particularly those with a rapid absorption, play an important role of positive reinforcement of addictive conducts [15]. Benzodiazepine abuse in MMT patients is associated with poorer outcome concerning illegal drug abstinence and psycho-social rehabilitation [11, 16, 17]. Very few data exist on the efficacy of benzodiazepine maintenance treatment. A recent study from Weizman et al. suggests that a maintenance treatment with clonazepam might be successful for reducing abusive benzodiazepine use during methadone maintenance treatment [18].

In our context, we have observed a radical change of treatment philosophy regarding the prescription of benzodiazepine since the opening of public methadone maintenance treatment programmes in Geneva in 1991. During the first 3 years a zero-tolerance policy was practised with regard to the use of benzodiazepine. Patients were required to withdraw from benzodiazepines before beginning a methadone maintenance treatment and benzodiazepines were never prescribed. It soon became obvious that this attitude made accessibility to the programme difficult and resulted in a high dropout rate. For a majority of patients it seemed too difficult to achieve immediate, total benzodiazepine abstinence after a long period of uncontrolled use, often on high doses of different benzodiazepines. For that reason, from 1994 onwards, we started to prescribe long-acting benzodiazepines for these patients and to propose, in principle, progressive withdrawal once they were stabilised in the methadone maintenance treatment programme.

The aim of this study was to assess the prevalence of regular benzodiazepine use and benzodiazepine prescription among patients treated in a comprehensive public methadone maintenance treatment programme and to assess characteristics, especially psychiatric comorbidity and use of other psychotropic drugs, among the regular benzodiazepine users.

Methods

Study setting and subjects

It is estimated that there are 2500 to 3000 illegal drug addicts living in the canton of Geneva (population of 400 000); about half of them are in methadone maintenance treatment. Approximately 20% of the 1400 MMT patients in Geneva are treated in public programmes; the others are in private care. Patients are free to choose the treatment provider and all options are covered by mandatory health assurance. Threshold for admission to a public methadone maintenance treatment programme is low in order to assure maximal accessibility. Patients in the public methadone maintenance treatment programmes are younger, have shorter drug careers, shorter duration of methadone maintenance treatment and more frequent parallel use of opioids and cocaine than those in private methadone maintenance treatment programmes [19]. Patients in our public methadone maintenance treatment programme benefit from medical and psychosocial treatment procured by a multidisci-

plinary team (psychiatrists, general practitioners, psychologists, social workers and nurses). They come to the centre every weekday to take methadone under supervision and receive take-home doses for the weekend. Urine analysis is performed regularly during treatment. Individualised objectives of methadone maintenance treatment are specified in a contract signed by the patient and staff and evaluated at regular intervals. For patients with concurrent benzodiazepine and/or alcohol dependence, benzodiazepine prescription is among the treatment options; only molecules with a long half-life, a slow absorption and a low value on the local black market are prescribed. Benzodiazepines are provided when patients come to take their methadone, benzodiazepine intake is not supervised.

All patients in treatment August 15, 1997 were eligible to participate in the study. Written informed consent was obtained from every participant. There was no financial compensation and patients could leave the study at any moment without consequence for their treatment. The study protocol was approved by the ethical committee on human research of the Geneva University Hospital.

Procedure

This is a cross-sectional descriptive study of all patients in treatment at the given time-point. Data collection was performed between August 1997 and January 1998. Patients were contacted in the waiting room of the treatment centre by one of the two clinical psychologists. If they agreed to participate in the study, an appointment was made for the interview with one of the clinical psychologists. Socio-demographic data, duration of methadone treatment, methadone dosage, benzodiazepine prescription, results of the urine analysis and the results of serological testing for HIV, hepatitis B and C were taken from the medical charts of the patients.

During the interview with the clinical psychologist two research questionnaires were filled out: the Addiction Severity Index (ASI) and an auto-questionnaire on benzodiazepine use. The ASI is widely used in substance-abuse research for treatment planning and outcome evaluation. It is a semi-structured interview, developed in 1980 by McLellan et al. [20], designed to assess seven potential problem areas in substance-abusing patients: medical status, employment and support, drug use, alcohol use, legal status, family/social status and psychiatric status. The ASI provides two

scores: severity ratings and composite scores. Severity ratings are subjective ratings of the patient's need for treatment as derived by the interviewer, the scale ranging from 0 (no further treatment needed) to 9 (further treatment absolutely necessary, vital indication). Composite scores are measures of problem severity during the prior 30 days and are calculated by a computerised scoring program. The composite scores range from 0 (no severity) to 1 (maximal severity). We used the French translation, validated in 1992 by J. Bergeron, Bordeaux, version October 1996 [21]. The ASI was administered by two trained clinical psychologists. To assess the severity of an eventual psychiatric comorbidity we used the "psychiatric status" section of the ASI. This section investigates the presence of depressive symptoms, anxiety symptoms, hallucinations, cognitive disorder, impulsive or violent behaviour, suicidal thoughts, suicide attempts and if the patients had a prescribed medication for psychological or emotional problems (during the last 30 days and throughout the patient's life-time). Furthermore patients are asked how many days in the last 30 they experienced these psychological or emotional problems, how much they were troubled or bothered by them and it evaluates their subjective need for treatment of these psychological or emotional problems. A severity rating of 6 and more and a composite score higher than 0.5 in the psychiatric status section were considered as indicators of psychiatric comorbidity. The number of interventions of the psychiatric emergency room in the Geneva University Hospital and the number of hospitalisations in the Geneva University Psychiatric Hospital (the only psychiatric inpatient clinic in the canton) during the year before inclusion in the study were used as supplementary indicators of psychiatric comorbidity. The latter data were taken from the administrative data base of the Geneva University Hospitals.

The assessment of parallel use of other psychotropic substances was based on the answers of the "alcohol/drugs" sections of the ASI. For alcohol we took into account regular use, defined as three times a week or more during the last month. For cocaine, heroin and cannabis patients were considered as users if they consumed at least once in the past 30 days.

An auto-questionnaire on benzodiazepine use included the following questions: Have you experienced, in your life, a period when you used benzodiazepines regularly (three times a week or more)? Did you use benzodiazepines regularly during the past 30 days? Do you use prescribed benzodiazepines? Have you changed your habitual

way of use since the start of your methadone maintenance treatment and if so, in what way?

Regular urine analyses were randomly requested for all patients in the methadone maintenance treatment. Urine analyses were performed in the central laboratory of the Geneva University Hospital by an immunological detection test (Test On-line [Roche]). After consumption of a benzodiazepine the test can remain positive for 7 days. The urine testing was carried out with a minimal interval of 7 days. Every patient with 3 positive screenings for benzodiazepines in 4 weeks or 4 positive screenings in 6 weeks was considered as a regular user of benzodiazepines. A certain number of patients had benzodiazepines prescribed at the centre because they presented a dependence of this substance according to ICD-10 criteria and an immediate withdrawal was not indicated at that time. For those patients one urine screening was carried out during the 6-week interval after inclusion. If it was positive, the patient was included in the group of regular benzodiazepine users. Five patients could not be attributed to one of the study groups using the results of the urine screening. These patients were included in the groups of regular users or non-users on the basis of their answers in the auto-questionnaire.

The data from the patient's medical chart and the administrative data base were available for all eligible patients. The results from the ASI and the auto-questionnaire on benzodiazepine use were available only for the patients included in the study.

Statistics

All statistics were done using SPSS PC version 6.1.3. The population was described using frequency analyses. Cross-tabulations between each predictive variable according to user-status were performed and Pearson's Chi Square Statistic was calculated (Fisher's Exact Test if appropriate). The level of significance was set at $p < 0.05$.

Results

Description of the entire population

At study start 151 patients were participating in the methadone maintenance treatment programme at the treatment centre. Three patients were bound to leave the methadone maintenance treatment during the following month. Of the 148 eligible patients 92 (68%) were male. Median age was 30.3 years (range 17–63 years). Median daily

methadone dose was 75 mg (range 7.5–400 mg). The median duration of methadone maintenance treatment was 17 months (range 1–76 months). The prevalence of hepatitis B was 35.8% ($n = 131$), of hepatitis C 57.0% ($n = 135$) and of HIV 16% ($n = 131$).

Sixty-seven (49%) patients were attributed to the group of regular current users of benzodiazepines, 68 (51%) in the group of non-users.

Comparison of included vs not included patients

Of the 148 eligible patients, 101 (68%) accepted to participate in the study; of the 47 patients (32%) who could not be included 19 refused to participate and 28 never showed up for the proposed appointments. There were no significant differences between those who participated and those who did not with regard to sex, age, duration of the current methadone maintenance treatment, daily methadone dosage, medical prescription of benzodiazepines, hepatitis B and C status and number of psychiatric hospitalisations during the past year. The patients included in the study had significantly more interventions of the public psychiatric emergency services than those not included ($p = 0.002$). On the other hand, those not included in the study were significantly more frequent HIV positive ($p = 0.02$).

Comparison of regular users of benzodiazepines vs non-users

Of the 101 patients included in the study 52 (51.5%) were regular users of benzodiazepines according to our criteria. Forty-eight of those regular users (92.3%) received their benzodiazepines by medical prescription.

Regular users of benzodiazepines received more frequently daily methadone dosages over 75 mg ($p < 0.0005$). They also used alcohol more frequently in the preceding month ($p = 0.001$). Heroin and cocaine abuse were more frequent in the group of benzodiazepine users but this difference was not statistically significant ($p = 0.05$ for heroin and 0.06 for cocaine).

Regular benzodiazepine users showed more psychiatric problems: their composite scores and severity ratings in the psychiatric status section of the ASI were significantly higher ($p = 0.04$ for composite scores and 0.005 for severity ratings). They were more often hospitalised at the psychiatric inpatient clinic during the past year ($p = 0.001$), received prescription for medication for

psychological or emotional problems more often ($p < 0.0005$), suffered more from severe anxiety or tension ($p < 0.0005$) and felt more subjective need for treatment of psychological or emotional problems ($p = 0.005$) than the non-users.

Except for the psychiatric status, composite scores and severity ratings of the other sections showed no significant differences between the two groups. We found no significant differences concerning the other psychopathology items of the ASI between the two groups. The results of the comparison between regular users and non-users are summarised in table 1.

Results from the auto-questionnaire on benzodiazepine consumption

Of all patients ($n = 98$) 78.5% reported having consumed benzodiazepines regularly (three times a week or more) during their lifetime. Almost 2/3 of those who were current non-users had experienced a period of regular benzodiazepine consumption in the past. Concerning the regular users of benzodiazepines during the preceding month, the answers of the auto-questionnaire showed a significant correlation to the results of the urine testing ($p < 0.0005$). Only 4 of the 51 regular benzodiaz-

Table 1 Comparison of regular users and non-users of benzodiazepine.

variable	regular users n = 52	non-users n = 49	OR (IC 95%)	p
male sex	67.3%	63.3%	1.7 (0.5–1.9)	0.67
age <30 years	40.4%	46.9%	0.8 (0.4–1.8)	0.51
MMT duration <18 month	46.2%	51.0%	0.8 (0.4–1.9)	0.62
methadone dose >75 mg	67.3%	30.6%	4.7 (2.0–10.8)	<0.0005
benzodiazepine prescription	92.3%	–	–	–
HBV positive	40.0% (n = 45)	31.9% (n = 47)	1.4 (0.6–3.7)	0.42
HCV positive	60.4% (n = 48)	47.8% (n = 46)	1.7 (0.7–4.1)	0.22
HIV positive	8.3% (n = 48)	13.6% (n = 44)	0.6 (0.1–2.6)	0.41
one or more psychiatric hospitalisation during the last year	46.2%	16.3%	4.4 (1.6–12.5)	0.001
one or more psychiatric emergency intervention during the last year	30.8%	20.4%	1.7 (0.6–4.8)	0.23
alcohol use 3 times a week or more during last 30 days	38.5%	10.2%	5.5 (1.7–18.9)	0.001
heroin use during the last 30 days	50.0%	30.6%	2.3 (1.0–5.1)	0.05
cocaine use during the last 30 days	32.7%	16.3%	2.5 (0.9–7.2)	0.06
cannabis use during the last 30 days	76.9%	65.3%	1.8 (0.7–4.7)	0.20
composite score psychiatric status >0.5	28.6%	12.2%	3.2 (1.04–9.8)	0.04
severity rating psychiatric status 6 or more	36.5%	12.2%	4.1 (1.5–11.5)	0.005
composite score medical status >0.5	48.1%	30.6%	2.1 (0.9–4.7)	0.07
severity rating medical status 6 or more	13.5%	14.3%	0.9 (0.3–2.9)	0.9
severe depression during the last 30 days	27.5%	12.2%	2.7 (0.9–7.8)	0.06
severe anxiety during the last 30 days	84.3%	51.0%	5.2 (2.0–13.2)	<0.0005
suicidal thoughts during the last 30 days	13.7%	2.0%	7.6 (0.9–64.6)	0.06 Fisher's Exact Test
prescribed medication for psychological or emotional problems during the last 30 days	62.7%	26.5%	4.7 (2.0–10.9)	<0.0005
patient's subjective need of treatment for psychological or emotional problems	26.0%	12.0%	3.3 (1.4–7.9)	0.005

epine users declared themselves non-users (sensitivity of the self-declaration 92%). Eleven of the 47 patients attributed by us to the group of the non-users declared that they had consumed benzodiazepines three times or more a week during the last month (specificity of the self-declaration 77%). Of all patients 79.6% said that they had changed their benzodiazepine use since the beginning of their methadone maintenance treatment: 68.6% of the users at the time said that they had diminished their consumption of benzodiazepines, 19.6% of current regular users affirmed that they had increased their consumption of benzodiazepines. Of current non-users 59.6% declared they had stopped regular benzodiazepine use since they had been treated in the methadone maintenance treatment programme.

Discussion

This cross-sectional study showed among our methadone-maintained patients a high current prevalence of regular use of benzodiazepines of 51.5%, which is much higher than in the general population. Of the current non-users, 61.7% declared to have regularly consumed benzodiazepines in the past, meaning a lifetime prevalence of regular benzodiazepine use, and probably dependence, of 79%. When comparing our data with the data of other studies of methadone-maintained patients, our findings of current prevalence are situated in the mean range (20 to 70%) [8, 10, 11]. The results are not easily comparable because of methodological differences. In certain American studies a rather low prevalence of benzodiazepine use is found, but this can partially be explained by the more frequent prescription of barbiturates, which are rarely prescribed in European settings.

Although there is a lack of evidence-based recommendations for benzodiazepine prescription to MMT patients, we were surprised to find that 92.3% of the regular users in our study population received a controlled and regularly evaluated prescription of benzodiazepines. Concerning benzodiazepine prescription, physicians prescribing methadone maintenance treatment often find themselves in a dilemma: not prescribing risks denying the high prevalence of current benzodiazepine abuse and dependence in a patient group often not ready to quit benzodiazepine use for different reasons and inducing premature dropout from the methadone maintenance treatment; prescribing risks maintaining benzodiazepine dependency and can be considered a medical act without evidence-based justification.

The regular benzodiazepine users in our study showed significantly more psychiatric problems which might lead to the hypothesis that some regular users take benzodiazepines to decrease their psychological suffering. If a regular consumption of benzodiazepines is present at the beginning of a methadone maintenance treatment, it can be extremely difficult to impose a complete and immediate abstinence. In order to avoid premature dropout, it seems justified to prescribe benzodiazepines under certain conditions. We suggest prescribing preferably molecules with a long half-life, a slow absorption and a low value on the local black market and specifying benzodiazepine treatment conditions and goals in a therapeutic contract. Such contracts often exist for methadone maintenance treatment, but not for benzodiazepine prescription. This might reflect a certain tendency of caregivers and caretakers to adopt a fatalistic attitude towards benzodiazepine prescription for MMT patients. The risk of maintaining benzodiazepine dependence at long term is then very high. In the daily work with drug abusers, who often insistently request benzodiazepine prescription or continuation of prescription, there exists a risk to use benzodiazepine prescription for other reasons than strictly medical ones, such as creating or strengthening a therapeutic alliance, or cutting short time-consuming negotiations.

However, we observed that a majority of patients declared to have been able to diminish their consumption during the methadone maintenance treatment, independently of their current user status.

We think that the number of regular benzodiazepine users in our study was not overestimated. Even if, theoretically, a patient with only four single consumptions during six weeks could have been included in the group of regular users due to our inclusion criteria, this pattern of consumption is very rare in persons with addiction problems. Moreover, 48 of the 52 regular users (92.3%) received their benzodiazepine under medical prescription. Underestimation of benzodiazepine prevalence is not excluded, although urine tests were carried out at the treatment centre under visual control and the benzodiazepine screening is believed to be reliable. However, 11 patients (23.4%) who were attributed to the group of non-users according to the urine test results declared themselves regular users in the auto-questionnaire. It should be kept in mind that even if there is a slight underestimation of the number of regular users, this would not compromise the significance of the results as we would expect even more significant results if we corrected for an underestimation.

The regular users of benzodiazepine had significantly higher daily dosages of methadone than non-users. Comparable studies [11, 17] made similar observations. The regular benzodiazepine users in our study also consumed heroin more frequently during the preceding month, which might result in prescription of higher doses of methadone to achieve stabilisation. It is also possible that among non-users there were more stabilised persons who were tapering off their methadone during the end phase of methadone maintenance treatment.

The composite scores and the severity ratings concerning the psychiatric status in the ASI as well as the number of psychiatric hospitalisations in the past year were significantly higher in the group of the regular consumers. These results confirm the hypothesis that benzodiazepine users in an MMT population suffer from more serious psychiatric troubles, as was also shown in the studies of Drake et al. [11] and Bleich et al. [17]. Only 12 patients (12.2%) signalled no psychiatric problems at all (composite score 0) and of these 12 only two were in the group of regular benzodiazepine users.

Concomitant use of other psychotropic substances than methadone and benzodiazepine is a frequent problem in MMT programmes and benzodiazepine users seem especially at risk. Benzodiazepine users had significantly more regular alcohol consumption during the past month, they also showed a clear tendency to consume heroin and cocaine more frequently. Other studies also showed a correlation between benzodiazepine consumption and use of other psychotropic substances. Drake et al. [11] found more frequent cocaine and amphetamine consumption during the past month among benzodiazepine abusers in methadone maintenance treatment. Bleich et al. [17] described a correlation between benzodiazepine abuse and heroin, cocaine and cannabis consumption in an Israeli MMT population. These cross-sectional studies, as ours, do not permit the establishment of a causal link between the two parameters. Regular benzodiazepine consumption in our population of MMT patients was not correlated with the ASI items measuring the quality of family and social relations, professional status, medical status or legal situation. Problems in these four fields are most probably linked to substance abuse in general.

Conclusion

The present results show that regular benzodiazepine use is frequent among patients in methadone maintenance treatment. The regular benzodiazepine users present more severe psychiatric

problems, more frequent consumption of other psychotropic substances, in particular alcohol, and higher daily doses of methadone. In our specific study we found a surprisingly high proportion of regular users who received their benzodiazepines under medical prescription (92.3%). This reflects an "unofficial" but in our unit generally accepted therapeutic tendency to substitute anarchic uncontrolled benzodiazepine use in the beginning of methadone maintenance treatment by benzodiazepines with long half-life and slow absorption under therapeutic doses. It should be kept in mind that medium- or long-term benzodiazepine prescription is not an evidence-based intervention and that formal trials with a sufficient long-term follow-up are needed before we can recommend this attitude.

Alternative treatment options, such as cognitive-behavioural approaches for anxiety disorder or antidepressant medication for depression with symptoms of anxiety, should be considered before prescribing benzodiazepines. As long as there is no scientific evidence for efficiency and benefits of benzodiazepine maintenance treatment, benzodiazepine prescription should be indicated with caution, re-evaluated frequently and progressive withdrawal should be regularly proposed to patients.

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