Postprint Version	1.0
Journal website	http://eurpub.oxfordjournals.org/cgi/content/full/ckm020v1
Pubmed link	http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17412715&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
DOI	10.1093/eurpub/ckm020

This is a NIVEL certified Post Print, more info at http://www.nivel.eu

Prescription of benzodiazepines in general practice in the context of a man-made disaster: a longitudinal study

THIJS FASSAERT[1], TINA DORN[1], PETER M. M. SPREEUWENBERG[1], MARTIEN C. J. M. VAN DONGEN[2], CHRISTEL J. A. W. VAN GOOL[2] AND C. JORIS YZERMANS[1,*]

[1] NIVEL (Netherlands Institute for Health Services Research), Utrecht, The Netherlands
[2] University of Maastricht, Maastricht, The Netherlands
Correspondence: Joris Yzermans, NIVEL (Netherlands Institute for Health Services Research), PO Box 1568, 3500 BN Utrecht, The Netherlands, tel: 0031 (0)30 2729700, fax: 0031 (0)30 2729729, e-mail: j.yzermans@nivel.nl

ABSTRACT

Background: Mental health problems associated with benzodiazepine treatment are often highly prevalent in the aftermath of disasters. Nevertheless, not much is known about benzodiazepine use after disasters. Considering the negative effects associated with prolonged use and the adverse effects of benzodiazepines on recovery of patients with acute stress, the aim of the present study was to explore benzodiazepine use in the context of the Enschede fireworks disaster of 13 May 2000. **Methods:** A longitudinal study using electronic medical records of general practitioners. Subjects were patients aged 16 years and older, registered at one of the practices between 1999 and 2003 (1541 victims and 5370 references). Pre- and post-disaster data were available on benzodiazepine prescriptions, healthcare utilization and sociodemographic characteristics. Benzodiazepine use was defined using different criteria (e.g. any use, daily use, chronic use). Data were analysed using multivariate multilevel logistic regression analyses. **Results:** Compared with patients from a reference group, disaster victims were at increased risk of becoming an incident benzodiazepine user after the disaster. Benzodiazepine use also had a different time course among victims compared with references. However, daily or prolonged use of benzodiazepines was not often observed and did not show dramatic deviations among disaster victims compared with references. **Conclusion:** There is no convincing evidence that general practitioners systematically deviated from clinical guidelines for benzodiazepines, which generally advocate their short time application.

INTRODUCTION

Mental health problems are highly prevalent in the aftermath of disasters.[1,2] Some of these, such as anxiety, stress and sleeping problems, are associated with pharmacologic treatment with benzodiazepines.[3–6]

Benzodiazepines are widely used and relatively safe drugs, but also have negative effects such as sedation, ataxia and cognitive deficits.[7–9] Moreover, their long-term use is associated with physical dependence, marked by tolerance, withdrawal symptoms and relapse anxiety.[10] Concerns about these adverse effects have therefore led to the promulgation of prescription guidelines. Generally, these guidelines state that benzodiazepines should be prescribed conservatively, i.e. intermittently and only for short-term relief.[11,12]

On 13 May 2000, an explosion and subsequent fire in a fireworks depot destroyed a residential area in Enschede, the Netherlands. Twenty-three people were killed outright, almost one thousand were injured and ~1200 residents had to be relocated for many years. Afterwards, a large scale monitoring study was implemented to examine the health problems of victims and their need for aftercare, using data from the electronic medical records of general practitioners (GPs).[13] Results of the Enschede monitoring study showed an excess of psychological problems, like stress, sleeping problems and anxiety immediately after the disaster.[14,15]

Insight in benzodiazepine use after disasters is lacking.[16] Furthermore, studies that have been conducted on benzodiazepine use in the context of disasters and trauma suggest that administration of benzodiazepines soon after trauma is not particularly useful in acute stress disorder.[7] Treatment with benzodiazepines may actually have an adverse effect on recovery by predisposing patients to an increased risk of developing Post-Traumatic Stress Disorder (PTSD), thus stressing the importance of monitoring benzodiazepine use in the aftermath of a disaster.[17–20] The aim of the present study is therefore to explore benzodiazepine use in Enschede and to find possible associations between benzodiazepine use and the fireworks disaster. More specifically, we formulated two study questions:

Are patients, who are a disaster victim and who have no history of pre-disaster benzodiazepine use, more at risk of becoming a (new) benzodiazepine user after the disaster than patients from a reference group?

Do victims and patients from a reference group show different patterns of benzodiazepine use in time (i.e. is there a difference between victims and references with respect to the moment at which they receive benzodiazepine prescriptions)?

METHODS

Design

In the Dutch healthcare system, every citizen is obliged to be registered at the list of one single GP who acts as a gatekeeper to secondary care. Longitudinal monitoring of health problems was therefore done using electronic medical records (EMRs) of GPs. Initially, all GPs (N = 60) in Enschede were approached and asked to participate in the monitoring study, of whom 16 refused. Among refusing GPs, there were nine who had no victims registered at their practice, five who expected an unwanted increase in workload and two who worked without an EMR. Eighty-nine percent of all disaster victims appeared to be registered with the remaining participating GPs.[13,14]

Because EMRs were implemented already before the disaster and updated continuously, irrespective of the disaster, the study is a longitudinal study. Data were used from 16-months pre-disaster until 32 months post-disaster (1999–2003). Exposure to benzodiazepines was assessed retrospectively after the disaster through examining the patients' EMRs.

Through EMRs, information was available on sociodemographic characteristics, health problems, corresponding diagnoses and subsequent treatment and prescriptions. Symptoms and diagnoses were documented and coded using the International Classification of Primary Care (ICPC), which is compatible with the 10th Revision of the International Classification of Diseases (ICD-10).[21] Prescriptions for medication were coded according to the ATC/DDD (Anatomical Therapeutic Code/Defined Daily Dose) system.[22] One DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. Benzodiazepines were defined as ATC-groups N05BA, N05CD, N05CF and N03AE. Clonazepam (N03AE) was included because, like other benzodiazepines, it should be effective in the treatment of anxiety disorders, especially panic disorder.[23–25] Because of shared (side-)effects of all benzodiazepines and because some anxiolytics are used clinically as sedatives/hypnotics or vice versa, no distinction was made between sedatives/hypnotics and anxiolytics.[26]

Subjects

All subjects were patients, aged 16 years and older at the time of the disaster, registered at general practices

that participated in the Enschede monitoring study.[14] Patient information used for this study included victim status, age at the time of the disaster, gender and type of health insurance (public or private). The latter was used as a proxy measure for socioeconomic status, because until 2006 a high income in the Netherlands was associated with private health care insurance. Pre-disaster health status was indicated by four proxy variables, indicating whether or not a patient had consulted the GP for a selection of problems. These variables were thought to reflect (ill) health of subjects, the same way hospitalization rates may be used to reflect presence or severity of illness.[27] A selection was made of medically unexplained physical symptoms (MUPS), psychological, musculoskeletal and chronic health problems, because these might be associated with prescription of benzodiazepines.

For the first question, all victims and reference patients from the Enschede cohort study without a history of benzodiazepine use were selected (N = 6911). Victims of the fireworks disaster were marked by the GP in the EMR when patients lived in the disaster area at the time of the disaster, or when the disaster was discussed during consultation. Second, victims were identified from the Information and Advice Centre (IAC) of the municipal authorities, where everybody affected by the disaster could register themselves. For this study, patients were defined as victims if identified as such by both their GP and the IAC. In contrast, the reference group consisted of patients from the same general practices in Enschede, who were marked as a victim neither by their GP nor by the IAC.

For the second question, subjects were selected if they received at least one prescription for benzodiazepines between 1999 and 2003 (N = 2142). Since there are many reasons for prescribing benzodiazepines, this could result in differences between victims and references. To make groups comparable, differences were accounted for by covariates (e.g. age, gender) and by modelling the within-individual correlation between measurements (see 'Statistical method'). Any remaining differences between victims and references were thought to be related to the disaster.

Among patients without a history of pre-disaster benzodiazepine use were 1541 victims and 5370 patients from the reference group (table 1). Victims were less often female and consulted the GP for MUPS less often 1-year pre-disaster. Victims did not differ from references on the other variables. The sample of benzodiazepine users consisted of 660 victims and 1482 reference patients. Users from the victim group were more likely to be male (χ^2 = 6.01, 1 df.). Additionally, users from the victim group were significantly younger than users from the reference group: at the time of the disaster the mean age of victims was 48.6 (SD 17.3) whereas references were on the average 50.7 years old (SD 18.2). Finally, compared with references, victims consulted the GP less often for psychological problems and more often for chronic health problems.

[TABLE 1]

Dependent variables

Prescriptions for benzodiazepines were used as a proxy variable for intake. First, a distinction was made between any and daily use. Any use was defined as (i) at least one DDD in a particular month, (ii) more than 30 DDDs in the preceding month or (iii) more than 60 DDDs in the month before the preceding month. The latter two conditions were added to take intermittent and prolonged use into account. Daily use was defined as (i) at least 30 DDDs in a certain month, (ii) at least 60 DDDs in the preceding month or (iii) at least 90 DDDs in the month before the preceding month. Both definitions are explained by some examples.

According to the definition of 'any use', a patient receiving 75 DDDs in January was a user that month. Because one DDD is the assumed average maintenance dose per day, the patient was expected to have ~45 DDDs left in February and 15 in March. Thus, the patient was counted as 'any user' for 3 months. For the definition on daily use, a patient with 75 DDDs in January was a user only until March, because 15 DDDs was not sufficient to last the whole month of March too. However, if a patient received 90 DDDs in January, that patient was expected to have ~30 DDDs left for March and was thus counted as 'daily user' for 3 months.

A second distinction was made between long-term and chronic use. Long-term use was defined as meeting the definition for a user (i.e. either 'any use' or 'daily use', not both) for 3 or more consecutive months. Chronic use was defined as use for 6 or more consecutive months.

Statistical method

The first question was addressed by calculating crude odds ratios as well as odds ratios adjusted for the hierarchical structure of the data and confounding. The hierarchical structure is a consequence of the fact that measurements from patients registered at the same practice tend to be correlated, leading to a violation of the general assumption of independency of observations in ordinary regression analysis.[28,29] Patient characteristics associated with more benzodiazepine use and therefore controlled for as possible confounders were increasing age, female gender, lower socioeconomic status and poor health status.[30–33]

For the second question, multivariate multilevel logistic regression analyses for repeated measures were performed, with benzodiazepine use in a specific period as the outcome measure. Correction for confounding was done by including the same covariates from the first analysis. Apart from the hierarchically structured data, multilevel analysis was done because of the longitudinal data. Measurements nested within subjects tend to be correlated, and measurements that are closer in time are more likely to be correlated than measurements that are more distant. This was taken into account by modelling a full unspecified variance/covariance matrix between measurement occasions within patients, at the practice level. At this level, only the intercept was allowed to vary between practices.[34]

Time trends in prescriptions for benzodiazepines were taken into account by including two time variables, one linear and one quadratic, which discriminated between subsequent observations in the monitoring period. The 4-year monitoring period was divided in 3-month units. In the analyses, the period of the disaster was defined as time period 0. Consequently, time periods –6 and 10 consisted of 1 month (January 1999) and 2 months (November and December 2002), respectively. By contrasting intercepts and/or time trend variables, differences between victims and references were statistically tested using χ^2-tests. Differences between victims and references concerned (i) the number of patients with prescriptions for benzodiazepines at the time of the disaster (i.e. contrasting intercepts), (ii) the development of the number of users in time (i.e. contrasting both time variables) and (iii) the overall difference for the entire monitoring period (contrasting intercepts and time variables). The analyses were performed using multilevel for Windows (MlwiN)[35]

RESULTS

Incidence of benzodiazepine use

Incidence of any benzodiazepine use between May 2000 and January 2004 was nearly twice as high among victims compared with patients from the reference group (table 2). With respect to subtypes of benzodiazepine use, the incidence of long-term and chronic use was much lower, but ~2.5 times and 3.5 times higher, respectively, among victims compared with references. Incidence of daily benzodiazepine use was nearly three times higher among victims compared with patients from the reference group. With respect to subtypes of benzodiazepine use, the incidence of long-term and chronic use was ~2.5 times and 4.5 times higher, respectively, among victims compared with references. Generally, differences between both groups increased if odds ratios were corrected for confounding.

[TABLE 2]

Course of benzodiazepine use

Among any users

The course of any use, irrespective of duration, significantly differed among victims when compared with users from the reference group, which is shown in figure 1. For each 3-month period, the figure indicates which percentage of victims and references, who used benzodiazepines at some time between 1999 and 2003, were a user in each period. The raw data show that the number of users among victims dramatically peaks at the time of the disaster. When tested for differences, the regression lines indicate that the number of users rises faster in the group of victims, reaches a higher peak and drops faster afterwards (χ^2 = 4.13, 1 df.). Also, the number of users in the victim group is larger at the time of the disaster (χ^2 = 4.14, 1 df.). Finally, the overall difference between both groups during the analysed period was statistically significant (χ^2 = 5.03, 1 df.). Differences between victims and references with respect to long-term and chronic use were not statistically significant and are therefore not shown in the figure.

[FIGURE 1]

Among daily users

The data in figure 2 show that daily use among references is relatively constant, whereas among victims a slight increase can be observed. When tested, the regression lines only revealed differences with respect to development in time ($\chi^2 > 6.09, 1df$). Thus, there were no significant differences in daily use at the time of the disaster, nor for the total monitoring period. As for long-term and chronic daily use, no significant differences were found between victims and references either.

[FIGURE 2]

DISCUSSION

Current international and evidence-based standards advise against prolonged prescription of benzodiazepines. Nevertheless, previous studies have pointed out that benzodiazepines are among the most frequently prescribed medicines, and that prolonged prescription is not uncommon. This study addressed the issue of (prolonged) prescription of benzodiazepines in general practice in the context of a man-made disaster in Enschede, the Netherlands. It offered insight into differences between victims of the disaster and unaffected patients concerning use of benzodiazepines in relation to disaster-related health problems among victims, and therefore contributes to our knowledge of disaster-related health problems. We answered the question whether prolonged prescription of benzodiazepines was more prevalent among victimized users as compared with users from a reference group in two ways. First, (incident) use of benzodiazepines was found to be elevated among victims of the disaster. Incidence of long-term or chronic (daily) use was also twice to five times higher than among controls. Second, the results showed that benzodiazepine use dramatically peaked among victims at the time of the disaster. Additionally, the number of daily users appeared to increase faster among victims, although the overall difference between victims and references was not statistically significant when studying daily use of benzodiazepines.

So far, these findings are explainable and in agreement with our expectations, considering the high incidence of psychological problems after the disaster.[14,15] However, incidence of prolonged benzodiazepine use, although higher among victims compared with references, was not often observed in the period after the disaster. Here, the question rises whether statistically significant differences are also clinically significant. Furthermore, differences among users of benzodiazepines were only present when prescriptions were studied irrespective of duration. In other words, neither long-term use, defined as prescriptions for at least 3 consecutive months, nor chronic use (for at least 6 consecutive months) differed between both groups of users in the second analysis. The results, therefore, do not provide convincing evidence that users of benzodiazepines faced problematic use of benzodiazepines more often as a result of the disaster. This is in agreement with results from a recent study in another disaster setting, where benzodiazepines were found to be prescribed predominantly as a short-term intervention after the disaster and that clinical guidelines were therefore well adhered.[16]

This study has some limitations that need to be considered. For example, it focuses on prescriptions, and not on actual consumption of benzodiazepines. As patients do not always adhere to prescribed medication, we may have overestimated the number of actual users.[36] At the same time, data from EMRs gave no insight into the number of prescriptions for hospitalized patients, which may have resulted in an underestimation of benzodiazepine use, especially in the group of victims. If any underestimation of benzodiazepine intake occurred, however, it should be small. For example, in the Netherlands benzodiazepines are mainly prescribed in general practice.[37] Also, prescriptions of hospital specialists are sometimes registered in EMRs when they are repeated by the GP.[38]

The study also has several major strengths. First, it was part of a large scale monitoring study, which included high quality pre-disaster data from GPs' electronic medical records. Because research in the immediate aftermath of a disaster often lacks priority, the availability of this type of information is of high value. For example, utilization of medical records most likely reduced the risk of recall and selection bias, that otherwise could have been the result of relying only on (self-report) data.[14,39] Another strength of this study concerned the comprehensive definition of benzodiazepine use, often studied in various ways.[40,41] In

this way, the opportunity was created to monitor benzodiazepine use while taking into account that (problematic) use in practice may take multiple forms. Finally, inter-practitioner or practice variation was taken into account using multilevel analysis, which otherwise most likely would have confounded the results. Prescribing behaviour, also with respect to benzodiazepines, is known to vary between practitioners.[42] Additionally, patients from the same practice often share characteristics, like socioeconomic status, and some practices in Enschede were located more closely to the disaster area than others.

Other treatment programmes, initiated in the immediate aftermath of the disaster and aimed at a reduction of its effects, could help explain the results of this study. In March 2004, a 1-year pilot intervention study was initiated, which aimed at a reduction of the number of chronic users of benzodiazepines in Enschede.[43] Eighteen GPs and six pharmacies from Enschede participated in this intervention. Although this intervention started after our monitoring period finished, the mere fact that it was set up in Enschede indicates that health care professionals were aware of possible problems related to prolonged benzodiazepine use, perhaps already soon after the explosion. This increased awareness among health care professionals, including GPs, may have resulted in better compliance with practice guidelines, explaining why we found no evidence for differences between victims and healthy patients with respect to prolonged use of benzodiazepines before 2004.

ACKNOWLEDGEMENTS

The authors wish to thank Petra ten Veen for the data management and Anja Dirkzwager for her valuable comments on earlier drafts of the manuscripts.

Conflicts of interest: None declared

KEY POINTS

- Disaster victims might be at risk of prolonged benzodiazepine use, but insight in this matter is lacking.
- After the fireworks explosion in Enschede, incidence of (prolonged) benzodiazepine use was higher among disaster victims and use among victims and references also took a different course in time.
- Incidence of prolonged benzodiazepine use only concerned a very small part of the population of Enschede and developments in time concerning problematic benzodiazepine use were similar for victims and references.
- In concordance with clinical guidelines, which generally advise against prolonged benzodiazepine use, the disaster mainly resulted in a rise of short-term benzodiazepine use.
- Longitudinal monitoring of the consequences of a disaster can be useful in determining whether clinical guidelines for the prescription of medication have been adhered to.

TABLES EN FIGURES

Prescription of benzodiazepines in general practice in the context of a man-made disaster: a longitudinal study.
Thijs Fassaert, Tina Dorn, Peter M. M. Spreeuwenberg, Martien C. J. M. van Dongen, Christel J. A. W. van Gool and C. Joris Yzermans
European Journal of Public Health: 2007

Table 1 Characteristics of the study populations

	Patients without history of pre-disaster benzodiazepine use		Benzodiazepine users between 1999 and 2003	
	Victims ($N=1541$)	References ($N=5370$)	Victims ($N=660$)	References ($N=1482$)
Gender				
Female (%)	47.7**	55.5	59.1*	64.6
Age				
Range	16–87	16–100	17–95	16–100
Mean (SD)	42.7 (16.8)	42.2 (17.3)	48.6 (17.3)*	50.7 (18.2)
Insurance type				
Public (%)	71.1	69.1	78.1	75.3
Health status: consultations for[a]				
Psychological problems	4.8	4.5	31.1**	37.7
MUPS	19.9**	24.2	57.7	60.3
Chronic health problems	17.3	18.3	56.7**	43.3
Musculoskeletal problems	9.7	11.5	31.2	32.6
Any benzodiazepines use pre-disaster	n.a.	n.a.	45.8**	54.7

a: 1-year pre-disaster
n.a. = not applicable
*Difference from reference group significant at $P<0.05$
**Difference from reference group significant at $P<0.01$

Table 2 Incident benzodiazepine use after the disaster: percentages and odds ratios

	Victims (%) $N=1541$	References (%) $N=5370$	ORc[a] (95% CI[b])	OR[c] (95% CI[b])
Any use	22.3	12.1	2.09 (1.81–2.42)	2.17 (1.83–2.58)
Long-term	3.0	1.2	2.47 (1.69–3.62)	2.77 (1.81–4.25)
Chronic	1.0	0.3	3.30 (1.67–6.55)	3.47 (1.56–7.71)
Daily use	5.4	2.0	2.80 (2.09–3.75)	2.53 (1.81–3.55)
Long-term	1.2	0.5	2.47 (1.37–4.46)	2.60 (1.32–5.11)
Chronic	0.5	0.1	4.67 (1.62–13.47)	4.94 (1.49–16.40)

a: Crude odds ratio
b: Confidence interval
c: Odds ratio corrected for confounders (gender, age, type of health insurance, pre-disaster health status and clustering on practice level)

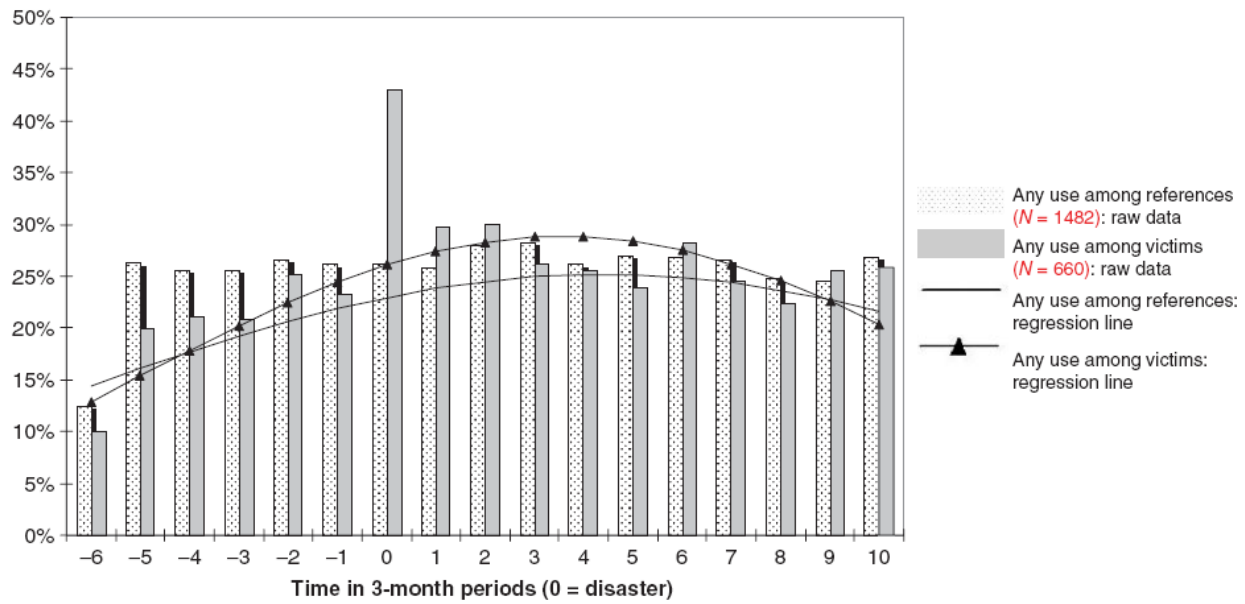

Figure 1 Development in time: proportion users of patients who used benzodiazepines at some time between 1999 and 2003

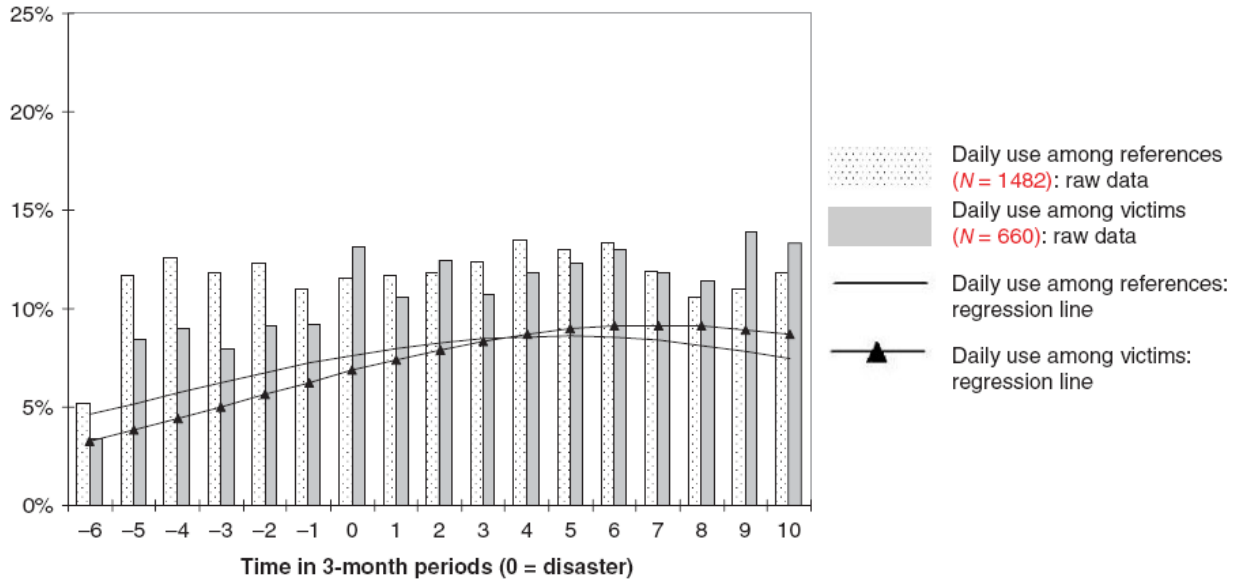

Figure 2 Development in time: proportion daily users of patients who used benzodiazepines at some time between 1999 and 2003

REFERENCES

1 Norris FH, Friedman MJ, Watson PJ, et al. (2002) 60 000 disaster victims speak: Part I. An empirical review of the empirical literature, 1981–2001. Psychiatry 65:207–39.[ISI][Medline]
2 Dorn T, Yzermans CJ, Kerssens JJ, et al. (2006) Disaster and subsequent healthcare utilization: a longitudinal study among victims, their family members, and control subjects. Med Care 44:581–9.[CrossRef][ISI][Medline]
3 Rubonis AV and Bickman L. (1991) Psychological impairment in the wake of disaster: the disaster-psychopathology relationship. Psychol Bull 109:384–99.[CrossRef][ISI][Medline]
4 Lavie P. (2001) Sleep disturbances in the wake of traumatic events. N Engl J Med 345:1825–32.[Free Full Text]
5 Herz M. (1993) Benzodiazepine prescribing in a community in crisis. Fam Pract 10317–19.
6 Reijneveld SA, Crone MR, Verhulst FC, Verloove-Vanhorick SP. (2003) The effect of a severe disaster on the mental health of adolescents: a controlled study. Lancet 362:691–6.[CrossRef][ISI][Medline]
7 Stevens JC and Pollack MH. (2005) Benzodiazepines in clinical practice: consideration of their long-term use and alternative agents. J Clin Psychiatry 66:Suppl 2, 21–7.
8 Stewart SA. (2005) The effects of benzodiazepines on cognition. J Clin Psychiatry 66:Suppl 2, 9–13.
9 Rosenbaum JF. (2005) Attitudes toward benzodiazepines over the years. J Clin Psychiatry 66:Suppl 2, 4–8.[ISI][Medline]
10 O'brien CP. (2005) Benzodiazepine use, abuse, and dependence. J Clin Psychiatry 66:Suppl 2, 28–33.[ISI][Medline]
11 Gorgels WJ, Oude Voshaar RC, Mol AJ, et al. (2001) Het langdurig gebruik van benzodiazepinen. [Long-term use of benzodiazepines]. Ned Tijdschr Geneeskd 145:1342–6.[Medline]
12 Ashton H. (2005) The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry 18:249–55.[ISI][Medline]
13 Roorda J, van Stiphout W, Huijsman-Rubingh R. (2004) Post-disaster health effects: strategies for investigation and data collection. Experiences from the Enschede firework disaster. J Epidemiol Community Health 58:982–7.[Abstract/Free Full Text]
14 Yzermans CJ, Donker GA, Kerssens JJ, et al. (2005) Health problems of victims before and after disaster: a longitudinal study in general practice. Int J Epidemiol 34:810–9.[Abstract/Free Full Text]
15 van Kamp I, van der Velden PG, Stellato RK, et al. (2006) Physical and mental health shortly after a disaster: first results from the Enschede firework disaster study. Eur J Public Health 16:252–8.[Abstract/Free Full Text]

16 Dorn T, Yzermans CJ, van der Zee J. (2007) Prospective cohort study into post-disaster benzodiazepine use demonstrated only short-term increase. J Clin Epidemiol [in press].
17 Gelpin E, Bonne O, Peri T, et al. (1996) Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry 57:390–4.[ISI][Medline]
18 Mellman TA, Bustamante V, David D, Fins AI. (2002) Hypnotic medication in the aftermath of trauma. J Clin Psychiatry 63:1183–4.[ISI][Medline]
19 Davidson JR. (2006) Pharmacologic treatment of acute and chronic stress following trauma: 2006. J Clin Psychiatry 67:Suppl 2, 34–9.[ISI][Medline]
20 Yehuda R. (2002) Post-traumatic stress disorder. N Engl J Med 346:108–14.[Free Full Text]
21 Lamberts H and Wood M. (1987) ICPC. International Classification of Primary Care(Oxford University Press, Oxford).
22 WHO Collaborating Centre for Drug Statistics Methodology. , Norway http://www.whocc.no/atcddd (accessed on 24 May 2005).
23 Huffman JC, Pollack MH, Stern TA. (2002) Panic Disorder and chest pain mechanisms, morbidity, and management. Prim Care Companion J Clin Psychiatry 4:54–62.[Medline]
24 Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ. (2003) Multidisciplinary Guideline Anxiety Disorders. Guideline for the Diagnosis, Treatment and Guidance of Adult Clients with an Anxiety Disorder. [Multidisciplinaire richtlijn Angststoornissen. Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen cliënten met een angststoornis](CBO/Trimbos-instituut, Utrecht).
25 Shelton CI. (2004) Diagnosis and management of anxiety disorders. J Am Osteopath Assoc 104:Suppl 3, S2–5.[Medline]
26 Pathiyal A, Hylan TR, Jones JK, et al. (1997) Prescribing of selective serotonin reuptake inhibitors, anxiolytics, and sedative-hypnotics by general practitioners in the Netherlands: a multivariate analysis. Clin Ther 19:798–810.[CrossRef][ISI][Medline]
27 Rask KJ, Williams MV, McNagny SE, et al. (1998) Ambulatory Health Care Use by Patients in a Public Hospital Emergency Department. J Gen Intern Med 13:614–20.[CrossRef][ISI][Medline]
28 Merlo J, Chaix B, Yang M, et al. (2005) A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. J Epidemiol Community Health 59:1022–8.[Abstract/Free Full Text]
29 Merlo J, Chaix B, Ohlsson H, et al. (2006) A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health 60:290–7.[Abstract/Free Full Text]
30 Isacson D. (1997) Long-term benzodiazepine use: factors of importance and the development of individual use patterns over time – a 13-year follow-up in a Swedish-community. Soc Sci Med 44:1871–80.[CrossRef][ISI][Medline]
31 van de Lisdonk E and Huisman I. (1998) Lage-rugpijn en benzodiazepine: een relatie vol spanning. [Low back pain and benzodiazepines: a tensed relationship]. Huisarts Wet 41:75–9.
32 Zandstra SM, Furer JW, van de Lisdonk EH, et al. (2002) Differences in health status between long-term and short-term benzodiazepine users. Br J Gen Pract 52:805–8.[ISI][Medline]
33 de las Cuevas C, Sanz E, de la Fuente J, et al. (1999) Prescribed daily doses and 'risk factors' associated with the use of benzodiazepines in primary care. Pharmacoepidemiol Drug Saf 8:207–16.[CrossRef][ISI][Medline]
34 Yang M, Goldstein H, Browne W, Woodhouse G. (2002) Multivariate multilevel analyses of examination results. J Roy Stat Soc 165:137–53.[CrossRef]
35 Goldstein H. (2003) Multilevel statistical models(Edward Arnold, London).
36 Safran D, Taira D, Rogers W, et al. (1998) Linking primary care performance to outcomes of care. J Fam Pract 47:213–20.[ISI][Medline]
37 Van der Waals FW, Mohrs J, Foets M. (1993) Sex differences among recipients of benzodiazepines in Dutch general practice. Br Med J 307:363–6.[ISI][Medline]
38 Florentinus SR, van Hulten R, Kramer M, et al. (2006) Linking community pharmacy dispensing data to prescribing data of general practitioners. BMC Med Inform Decis Mak 6:18.[CrossRef][Medline]
39 Noji EK. (2005) Disasters: introduction and state of the art. Epidemiol Rev 27:3–8.[Free Full Text]
40 Zandstra SM, Furer JW, van de Lisdonk EH, et al. (2002) Different study criteria affect the prevalence of benzodiazepine use. Soc Psychiatry Psychiatr Epidemiol 37:139–44.[CrossRef][ISI][Medline]
41 Zitman FG and Couvee JE. (2001) Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off: report on behalf of the Dutch Chronic Benzodiazepine Working Group. Br J Psychiatry 178:317–24.[Abstract/Free Full Text]

42 Davis P, Gribben B, Lay-Yee R, Scott A. (2002) How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. J Health Serv Res Policy 7:202–8.[CrossRef][Medline]
43 DGV (the Dutch Institute for the Proper Use of Medicine). (2004) Annual report 2004. Jaarverslag http://www.medicijngebruik.nl/downloads/jaarverslag_2004_s.pdf (accessed on 11 July 2006).