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Prospective cohort study into post-disaster benzodiazepine use demonstrated only short-term increase

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ABSTRACT

Objectives: Benzodiazepines are typically prescribed for anxiety and insomnia, two complaints often reported after disasters. Benzodiazepines can cause mental or physical dependence, especially when taken for a long time. This study aims at evaluating benzodiazepine use in a disaster-stricken community with the help of computer-based records.

Study Design and Setting: This prospective cohort study covers a period of 4 years. For every patient, pre-disaster baseline data are available. Multilevel regression is applied to study differences in benzodiazepine use in 496 patients whose children were involved in the Volendam café fire on January 1, 2001 compared with 1,709 community controls, and 4,530 patients from an unaffected cohort.

Results: In community controls and patients from the unaffected cohort, benzodiazepine use remained stable in the course of the years. In the first year post-fire, parents of disaster victims were more likely to use benzodiazepines than community controls (OR 1.58; 95% confidence interval 1.13–2.23). With regard to long-term use, differences between community controls and parents were statistically nonsignificant.

Conclusions: In the studied community, benzodiazepines were predominantly prescribed as a short-term intervention. Clinical guidelines that advocate a conservative prescription policy were well adhered to.

BACKGROUND

The data in computer-based patient records are increasingly used to evaluate the provision of care [1] and [2]. In pharmacoepidemiological research, the source of data, whether it be pharmacy, physician, or billing records, will affect the quality and content of data [3]. Although pharmacy records provide

detailed and well-structured information on the drugs themselves, data on the consumers often are very limited. The latter is not the case when patients purchase prescription drugs at only one designated pharmacy, as is the case in the Netherlands [4]. In addition, at times, the pharmacies are electronically linked to the registration systems of general practitioners—a favorable situation in drug research [5].

The current study provides an example of how longitudinal data captured in computerized registries can be used to evaluate the provision of care. It aims at quantifying benzodiazepine use in a disaster-stricken community and is centered around the question whether clinical guidelines for benzodiazepines prescribing have been adhered to.

Benzodiazepines are effective antianxiety and sleep-inducing medications [6]. Because anxiety and insomnia are problems which are often presented to health care practitioners after disasters [7], [8], [9] and [10], it is possible that in times of crisis a proportion of the patients is exposed to benzodiazepines for the first time [11]. Although benzodiazepines have several favorable aspects, they are also known to cause physical and psychological dependence when taken for longer periods of time [12] and [13]. Clinical guidelines, therefore, recommend benzodiazepines only for short-time relief [14] and [15].

The disaster described here is considered to be one of the worst mass burn incidents that has happened in the Netherlands in recent years [16], [17] and [18]. The fire broke out in an overcrowded café where about 350 adolescents were celebrating New Year's Eve. Fourteen adolescents lost their lives and a large number suffered burn injuries. The youngest victim was 13 years old, with the others all aged under 25.

Our study concentrates on the parents of these victims. The parents of fire victims were exposed to high levels of postdisaster stress [19], [20], [21] and [22]. Previous research has demonstrated that these parents were more at risk for developing hypertension after the fire than controls from the same community whose children had not been directly affected [23]. Moreover, the parents of the affected children contacted their general practitioners more often for mental health issues when compared to community controls [24].

It is therefore hypothesized that the parents of fire victims are more likely to receive prescriptions for benzodiazepines. We also investigate whether those who lost a child and those whose children suffered burns are more likely to use benzodiazepines than parents of children who have survived the fire without suffering burns [25] and [26]. Finally, we expect affected mothers to use benzodiazepines more often than affected fathers [27], [28] and [29].

2. METHOD

2.1. Setting

The Dutch health care system is organized on an insurance basis. When the study was carried out, two types of health insurance existed, public and private insurance. Patients with an annual income below a specific level were insured through public insurance; above this level, patients were privately insured. Insurance type can thus be used as an indicator for the socioeconomic status of the patient. In the Netherlands, general practitioners (GPs) act as gatekeepers to specialist services. Dutch GPs have fixed patient lists and patients are enrolled with one GP only, which is ideal for population-based research. Usually, complete families are registered with the same practice [30]. Volendam, a former fishing town located 20 miles north of Amsterdam with about 20,000 inhabitants, is served by four general practices. In Volendam, the GP registrations can be linked to the registrations of the local pharmacies due to shared patient identification numbers. These pharmacy records contain virtually complete information on all drugs dispensed to outpatients (either prescribed by the GPs or, on an extramural basis, by specialists). If a prescribed drug is not picked up by a patient (less than 1% of all prescriptions), the prescription is removed from the record. It is thus assumed that the number of prescribed drugs very closely approximates the number of dispensed drugs. The terms “prescribed” and “dispensed” are therefore used interchangeably in this article.

2.2. Data collection

Three population-based cohorts were tracked throughout 1 year before and 3 years after the fire: (1) parents of the fire victims, (2) community controls, and (3) patients from 14 unaffected Dutch

communities. The last sample consisted of a cohort of patients who are monitored within the Netherlands Information Network of General Practice (LINH), a representative network of computerized general practitioners [31]. For this cohort, only GP-based registrations of benzodiazepine prescriptions were available. These registrations are less comprehensive than pharmacy registrations for three reasons. First, they do not contain prescriptions issued by specialists (as it is the case in pharmacy records). Second, repeat prescriptions are not fully captured in these records. Third, because they are not used for billing (as pharmacy records), they are generally more prone to underregistration. As a consequence, estimates based on GP records are generally lower than estimates based on pharmacy records [32]. Nevertheless, the LINH data were used here because they were available at the patient level and therefore allow for in-depth statistical comparisons of patients who belong to the Volendam community (parents of fire victims and community controls) with patients who do not belong to this community (LINH). Although the LINH data provide an underestimation of true rates, there is no reason to assume that these data were systematically distorted by other factors. On the one hand, the LINH data allow for an assessment of time trends in benzodiazepine use in a population outside Volendam. On the other hand, they are not suitable for the assessment of absolute differences between groups. To compensate for this, we also report estimates of the percentage of benzodiazepine users in the same age group on the national level. These figures were provided by the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kerngetallen, SFK). Because these data were not available at the patient level, the number of patients with more than 90 daily-defined doses (DDDs) per year or 3 year or more months of use cannot be provided in this case. Nevertheless, the figures give a general idea of the level of benzodiazepine use in Volendam in relation to the national level (Table 2).

2.3. Sampling of cohorts

2.3.1. Parents of fire victims and community controls

As a first step, it was necessary to identify the fire victims. According to official estimates, about 300–350 people were in the building at the time of the fire. The four GP practices were able to identify a total of 335 in their registrations (14 deceased adolescents and 321 survivors, with and without physical injuries). Thirty-five of the surviving victims were excluded from the study because they belonged to a practice that was not yet fully computerized. None of the deceased adolescents belonged to this practice. The characteristics of victims enrolled in the nonparticipating practice ($n = 35$) were compared with those of victims enrolled with the participating practices ($n = 286$). Victims included in the final study sample did not significantly differ from nonparticipants with respect to burn size, number of days in hospital, gender, age, or insurance status. Victims with burn injuries had a mean total burned surface area of 14.9% (SD = 17.1) and spent, on average, 34.2 days in hospital during the first 12 months after the disaster (SD = 59.3). As a second step, we identified all parents of deceased and/or surviving victims with the help of the electronic patient registration ($n = 499$). Twenty-seven of these parents lost a child to death and 277 live with a child who is suffering from burn injuries. As a third step, from the three participating GP practices, we selected all patients with children aged 14–20, who had not been trapped in the fire ($n = 1,756$). These patients are referred to as “community controls.”

[TABLE 1]

2.3.2. Sampling of an unaffected control group outside Volendam (LINH-cohort)

According to the same procedure as the community controls, we sampled a cohort of 4,851 patients from the LINH-database. These patients belong to 14 different communities spread throughout the Netherlands.

2.3.3. Inclusion criterion

Patients were included in the analyses when they were enrolled during the full 4-year period. This results in a final sample of 496 parents, 1,709 community controls, and 4,530 patients from the LINH-database.

2.4. Assessment of benzodiazepine use

Information on the benzodiazepine use of parents of fire victims and community controls was extracted from the electronic pharmacy records, information on the use of the LINH-cohort was based on the electronic registrations of GPs. Both registries code prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system [33]. In the current study, a patient was considered a benzodiazepine user if he or she had received at least one prescription for a benzodiazepine (ATC codes: N05BA, N05CD, and N05CF). The proportion of benzodiazepine users was calculated on a yearly basis. Likewise, long-term benzodiazepine use was defined on a yearly basis. It was considered present if

(1) the amount of benzodiazepine prescriptions was more than 90 DDDs. Given that the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, this amount would be sufficient for more than 90 days.

(2) prescriptions for benzodiazepines covered a period of 3 months or more (at least one benzodiazepine prescription per month in at least 3 consecutive months).

These definitions for long-term use were derived from clinical guidelines for benzodiazepine use [6], [14] and [34].

2.5. Analysis

Patient characteristics were compared by *t*-tests (continuous variables) or chi-square tests (categorical variables). Logistic regression analysis was used to model the number of patients using benzodiazepines/using more than 90 DDDs/using benzodiazepines during 3 or more consecutive months. The independent variables were group membership, year, age, gender, and insurance status [27], [35] and [36]. All regressions were carried out within a multilevel framework because it accounts for the dependency of observations in our study [35], [37] and [38]. We specified the following levels—level 1: measurement occasion, level 2: patient, level 3: family, and level 4: practice. In analyses involving only three practices (the comparison of parents of fire victims and community controls), level 4 was eliminated and practice was introduced into the model as an additional independent variable. The variable year was dummy-coded to model the repeated measurements. The omitted category was the year 2000 which functions as a baseline. Next to the main effects, interaction terms were introduced, indicating whether the risk for using benzodiazepines/using more than 90 DDDs/using benzodiazepines during 3 or more consecutive months was higher in these patients than in patients belonging to the reference group during the year in question, holding all other variables in the equation constant. Coefficients are presented as odds ratios (OR) with 95% confidence intervals (CIs). For the analyses, we used the MLWiN (version 1.1) and SPSS (version 11.5) software packages.

3. RESULTS

Table 1 presents patient characteristics at baseline. Parents of victims ($n = 496$) and community controls ($n = 1,709$) did not differ in respect to the proportion of women or patients with private health insurance, neither did community controls nor the LINH-cohort. Although small in size, the age difference between the parents and community controls, and between community controls and the LINH-cohort was statistically significant ($P = 0.013$ and $P = 0.027$). Twenty-seven parents had lost a child due to the fire (5.4%) and 275 parents had a child who suffered from burn injuries as a consequence of the fire (55.4%).

[TABLE 2]

[TABLE 3]

Table 2 presents, on an annual basis, the proportion of users, the proportion of patients who use more than 90 DDDs, and the proportion of patients who use benzodiazepines in at least 3 consecutive months. The proportions in patients belonging to the LINH-cohort were much lower than in parents or community controls, which can be ascribed to the different types of registration systems (LINH: GP-based registrations, community controls and parents: pharmacy-based registrations). At baseline, during the year preceding the fire, parents and community controls did not differ from each other (Table 2). In the parent group, during the first year after the fire, there was a greater increase of the number of users, the number of patients with more than 90 DDDs, and the number of patients with more than 3 months of use when compared to the community controls. In the other 2 years postfire (2002 and 2003), the proportions in the parent group were lower than in 2001, but still higher than in 2000. In the LINH- and SFK-cohorts, the proportions showed a slight increase throughout the years.

3.1. Comparison of parents, community controls, and the LINH-cohort

In a next step, these figures were submitted to statistical testing (Table 3). Models 1–3 compare parents and community controls, and models 4–6 deal with the comparison of community controls and the LINH-cohort. According to model 1 (Table 3), when compared to the year pre-fire, the increase seen in parents during the first year post-fire, was 1.58 times the increase seen in controls (95% CI 1.13–2.23). In 2002 and 2003, differences between the two groups were not statistically significant. The two indicators for long-term use (more than 90 DDDs per year or 3 or more months of use) were nonsignificant for every year postfire, indicating that community controls and parents did not differ in any of the years with respect to long-term use.

A second set of regression analyses dealt with the comparison of community controls and the LINH-cohort (models 4–6, Table 3). This analysis provided insight into the development over the course of time. The main effect of “group” was significant for every outcome measure (being a user: OR 1.91, 95% CI 1.64–2.22; using more than 90 DDDs: OR 3.39, 95% CI 2.55–4.51; using 3 or more months: OR 3.06, 95% CI 2.29–4.09), indicating that community controls and the LINH-cohort generally differed with respect to these measures. Because none of the interaction terms reached statistical significance, we can conclude that this effect was independent of the year under study. Community controls thus followed the same development over time as patients from the LINH-cohort for any of the three outcome measures.

3.2. Determinants specific to parents of victims

In a separate analysis, we studied determinants specific to parents of victims (Table 4). We aimed at answering the question (1) whether parents of survivors with burns do differ from parents of survivors without burns, (2) whether bereaved parents do differ from nonbereaved parents, and (3) whether affected mothers are more likely to use benzodiazepines than affected fathers. Because the number of patients who were using benzodiazepines for more than 3 months or using more than 90 DDDs was low and significant effects were hard to detect under these circumstances, the analysis was only carried out for the outcome “being a user.” As model 1 (Table 4) indicates, parents of survivors with burns were more likely to use benzodiazepines than parents of survivors without burns (OR 2.16, 95% CI 1.32–3.52), the likelihood was not significantly associated with the year of the study, however (no significant interaction terms). According to model 2 (Table 4), bereaved parents were more likely to use benzodiazepines during the first (OR 3.99, 95% CI 1.13–14.12) and second years postdisaster (OR 3.78, 95% CI 1.09–13.09), but not during the third year postdisaster. It must be noted that the estimates were unstable due to the small cell sizes, which is reflected in the large CIs. Finally, mothers of survivors were generally more likely to use benzodiazepines than fathers (OR 2.03, 95% CI 1.41–2.94), but this was independent of the year of study and thus not related to the fire (interaction terms not significant).

[TABLE 4].

4. DISCUSSION

Our analyses demonstrate that, during the first year after the fire, parents of fire victims demonstrated a significantly larger increase in benzodiazepine use when compared to community controls, taking

into account the pre-fire baseline. In the following years, the *proportion of users* was still higher in parents than in community controls, but these differences did not reach statistical significance. With regard to long-term use, no significant differences between parents and community controls were found. Our results thus show that benzodiazepines were predominantly prescribed as a short-term intervention. We therefore conclude that clinical guidelines that advocate a conservative prescription policy were generally well adhered to.

Because it could not be ruled out that the fire had effects on community controls as well, we also examined the benzodiazepine use of a cohort of patients outside Volendam. The a priori differences between the two groups were large, which very likely was due to the different kind of registration systems that had been used to collect the data. Community controls and patients from the LINH-cohort follow the same trend over time. This indicates that the benzodiazepine use of community controls was not influenced by the disaster in significant ways. In addition, our findings indicate that both before and after the fire, the percentage of benzodiazepine users in the unaffected families in Volendam was comparable to the percentage found elsewhere in the Netherlands.

Finally, we studied determinants which are specific to parents of fire victims. More precisely, we expected parents of burn victims, mothers, and bereaved parents to be more likely to use benzodiazepines. Our results showed that parents of victims with burns did not significantly differ from parents of physically uninjured victims in respect to benzodiazepine use. Already before the fire, the share of benzodiazepine users was higher among parents of burn victims. The same applied for women. The last finding is consistent with other studies on benzodiazepine use which generally indicate that women are more likely to use benzodiazepines than men [27], [28], [35] and [36]. Furthermore, as expected, our study demonstrated that parents who had lost a child due to the fire were more likely to use benzodiazepines during the first and the second years after the fire when compared to parents of surviving victims.

In this context, some limitations of our study should be noted. First, the number of bereaved parents in our study was small ($n = 27$) and the power of the analyses was therefore low. This is reflected in relatively large CIs. The same was the case when indicators of long-term use were examined. With small sample sizes, significant effects are hard to detect. Second, the fact that having a child with burn injuries did not significantly predict benzodiazepine use in our study could be due to the circumstance that parents of seriously burned victims had been seen in specialized burn centers, especially during the first months after the fire. It cannot be ruled out that some of the parents had received benzodiazepines there. Because these clinics are located outside of Volendam [17] and [39], we were not able to capture benzodiazepine use in these cases. It should be noted that, although not statistically significant, our results pointed into the expected direction.

Generally, our findings probably provided a slight underestimation of benzodiazepine users because the pharmacy records used here supplied information on benzodiazepine prescriptions issued on an extramural basis. Inpatient benzodiazepine use thus could not be monitored here. The underestimation should be very small, however, because in the Netherlands more than 95% of benzodiazepines are prescribed in general practice [27]. Another issue concerns the calculation of the rate of long-term benzodiazepine users. In the first year of the study, this rate may have been underestimated. More specifically, some patients may have met the definition of long-term use if their use in the months before the chosen time window was known. Because this underestimation applies to all examined groups, it will not affect the conclusions of the study, however.

Finally, it should be noted that drug prescribing does not necessarily equal drug intake. Although the term benzodiazepine use was applied in this article, the present study primarily provided evidence on prescriber behavior and not on the actual use of benzodiazepines.

Despite these limitations, the study has several strengths. First of all, its design was strong with the presence of baseline data, the use of two control groups (LINH-cohort and community controls) and the long follow-up period. Furthermore, nonresponse bias and recall bias, which can be a problem in survey data, could be ruled out because the study was based on existing electronic registrations [40], [41] and [42]. Finally, because we were able to link the pharmacy record to information stemming from the patients' GP records, additional information on the consumers of the drugs was available and a population-based approach was possible—a circumstance which is rather the exception than the rule in drug epidemiology research [43].

On one hand, the current study demonstrated that health care providers indeed prescribed benzodiazepines more often to patients who suffered from disaster-related distress. On the other hand, they seemed to prescribe in a way that minimized the risk of abuse and dependence. Possibly, this was the result of the continuous efforts to promote a rational use of benzodiazepines in the past [44].

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[TABLES]

Table 1

Background characteristics of parents of victims, community controls, and noncommunity controls (LINH)

	Parents of victims (n = 496)	Community controls (n = 1,709)	LINH (n = 4,530)	Parents vs. community controls	Community controls vs. LINH
Men (%)	237 (47.8)	819 (47.9)	2,153 (47.5)	ns [#]	ns [#]
Women (%)	259 (52.2)	890 (52.1)	2,377 (52.5)		
Mean age (SD)	46.1 (4.6)	46.7 (4.8)	46.4 (5.1)	*	*
Insurance					
Public (%)	302 (60.9)	963 (56.3)	2,526 (55.8)	ns [#]	ns [#]
Private (%)	194 (39.1)	746 (43.7)	2,004 (44.2)		
Lost a child due to the fire (%)	27 (5.4)	—	—	—	—
Child has burn injuries (%)	275 (55.4)	—	—	—	—

**P* < 0.05, [#]not significant.

Table 2

Number of users, number of patients with >90 DDDs, patients with 3 or more months of use; comparison of parents (P), community controls (C), noncommunity controls (LINH), and national estimates (SFK),^a 1 year prefire and 3 years postfire

Outcome measure	2000 (prefire)	2001 (postfire)	2002 (postfire)	2003 (postfire)
Users (%)				
P	101 (20.4)	153 (30.8)	113 (22.8)	120 (24.2)
C	328 (19.2)	360 (21.1)	334 (19.5)	347 (20.3)
LINH	503 (11.1)	504 (11.1)	478 (10.6)	501 (11.1)
SFK	455,925 (19.6)	454,569 (20.0)	453,148 (20.3)	446,651 (20.4)
Patients with >90 DDDs (%)				
P	33 (6.7)	50 (10.1)	43 (8.7)	44 (8.9)
C	109 (6.4)	114 (6.7)	118 (6.9)	126 (7.4)
LINH	88 (1.9)	93 (2.1)	92 (2.0)	101 (2.2)
Patients with 3 or more months of use (%)				
P	29 (5.8)	43 (8.7)	33 (6.7)	40 (8.1)
C	98 (5.7)	99 (5.8)	100 (5.9)	103 (6.0)
LINH	87 (1.9)	99 (2.2)	99 (2.2)	112 (2.5)

^a Adjusted for age and gender (n = 2,324,265).

Table 3

Logistic regression analysis with group membership predicting being a user, using more than 90 DDDs, using benzodiazepines during 3 or more months; comparison of parents (P), community controls (C), and noncommunity controls (LINH): 1 year prefire and 3 years postfire

	P vs. C ^a			C vs. LINH ^b		
	Model 1			Model 4		
	OR	95% CI		OR	95% CI	
User^c						
Group	1.10	0.85	1.42	1.91	1.64	2.22
2001 ^d	1.13	0.95	1.34	1.00	0.88	1.14
2002 ^d	1.02	0.86	1.22	0.94	0.83	1.08
2003 ^d	1.08	0.91	1.28	1.00	0.87	1.14
Group × 2001	1.58	1.13	2.23	1.12	0.91	1.39
Group × 2002	1.13	0.80	1.61	1.08	0.87	1.35
Group × 2003	1.17	0.83	1.66	1.08	0.87	1.34
More than 90 DDDs^e						
Group	1.08	0.72	1.63	3.39	2.55	4.51
2001 ^d	1.05	0.80	1.38	1.06	0.79	1.42
2002 ^d	1.09	0.83	1.43	1.05	0.78	1.40
2003 ^d	1.17	0.90	1.53	1.15	0.87	1.53
Group × 2001	1.51	0.89	2.59	0.99	0.67	1.48
Group × 2002	1.23	0.71	2.12	1.04	0.70	1.55
Group × 2003	1.17	0.68	2.02	1.02	0.69	1.50
Three or more months^f						
Group	1.01	0.76	1.35	3.06	2.29	4.09
2001 ^d	1.02	0.77	1.36	1.14	0.86	1.52
2002 ^d	1.06	0.79	1.40	1.14	0.86	1.52
2003 ^d	1.53	0.87	2.69	1.30	0.98	1.71
Group × 2001	1.13	0.63	2.03	0.89	0.59	1.33
Group × 2002	1.35	0.76	2.39	0.90	0.60	1.34
Group × 2003	1.01	0.76	1.35	0.81	0.55	1.21

^a Dummy variable; reference category is community controls.

^b Dummy variable; reference category is LINH-cohort.

^c Coefficients adjusted for gender, age, and insurance status; dependent variable is coded as user (1), nonuser (0).

^d Dummy variable; reference category is year 2000 (prefire).

^e Coefficients adjusted for gender, age, and insurance status; dependent variable is coded as receiving more than 90 DDDs (1), 0–90 DDDs (0).

^f Coefficients adjusted for gender, age, and insurance status; dependent variable is coded as receiving a prescription in at least 3 or more consecutive months (1), not receiving a prescription/receiving a prescription in less than 3 consecutive months (0).

Table 4

Logistic regression analysis with being the parent of a child with burns, being a bereaved parent, being a mother, predicting being a user—1 year prefire and 3 years postfire

	Model 1		
	OR	95% CI	
User ^a			
Bereaved ^c	5.17	3.34	7.98
Burn ^d	2.16	1.32	3.52
2001 ^b	1.82	1.33	2.49
2002 ^b	1.19	0.86	1.64
2003 ^b	1.31	0.95	1.80
Burn × 2001	1.27	0.67	2.41
Burn × 2002	0.82	0.43	1.59
Burn × 2003	0.52	0.27	0.99
	Model 2		
	OR	95% CI	
User ^a			
Burn ^d	1.86	1.47	2.36
Bereaved ^c	1.89	0.74	4.80
2001 ^b	1.80	1.33	2.45
2002 ^b	1.14	0.83	1.56
2003 ^b	1.24	0.91	1.70
Bereaved × 2001	3.99	1.13	14.12
Bereaved × 2002	3.78	1.09	13.09
Bereaved × 2003	3.44	0.99	11.90
	Model 3		
	OR	95% CI	
User ^c			
Gender	2.03	1.41	2.94
2001 ^b	1.53	1.21	1.92
2002 ^b	1.06	0.82	1.36
2003 ^b	1.15	0.89	1.47
Gender × 2001	0.96	0.60	1.52
Gender × 2002	1.34	0.80	2.25
Gender × 2003	1.22	0.74	2.02

^a Coefficients adjusted for sex, age, and insurance status; dependent variable is coded as user (1), nonuser (0).

^b Dummy variable; reference category is year 2000 (prefire).

^c Coefficients adjusted for age and insurance status; dependent variable is coded as user (1), nonuser (0).

^d Dummy variable; reference category is parents of survivor without burns.

^e Dummy variable; reference category is nonbereaved parents of survivors.

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