Mortality Trends in a Cohort of Opiate Addicts, Catalonia, Spain

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Background. Opiate addiction affects young adults whose life expectancy is reduced as a consequence of their habit. In the midst of the AIDS epidemic, the present study objective was to analyse recent overall and cause-specific mortality trends among opiate addicts in Catalonia (Spain).  

Method. Mortality was assessed retrospectively in an opiate addict cohort assembled from admissions to hospital emergency wards and drug treatment centres during the period 1985-1991. The cohort included 15 711 opiate addicts (12 045 men and 3666 women) aged 15-44 years. Overall and cause-specific mortality trends were analysed using age as the time scale and Cox regression with staggered entry determined by the age at entry in the study. Annual trends were adjusted by sex and source of entry, and were stratified by length of opiate use.  

Results. Mortality rates increased throughout the entire period from 13.8 to 34.8 deaths per 1000 person-years, with a statistically significant increase in 1987-1988 and 1988-1989. In a model including age, gender, source of entry and length of drug use, risk increased significantly in men and for longer length of use, but not with age and for source of entry into the study cohort. The causes of death associated with high mortality rates were AIDS and the causes directly related to addiction.  

Conclusions. A threefold increase in mortality rates was observed during the period, mainly accounted for by AIDS and direct addiction-related causes. Length of opiate use was an important determinant of mortality.  

Keywords: mortality, opiate dependence, survival analysis, AIDS

Drug addiction is an important cause of death among those aged 15-45. In Spain it has recently been described as one of the five leading causes of death in this age group. However Spanish follow-up studies of opiate addicts in the early 1980s showed mortality rates in the range reported in other countries at that time, where addicts' global mortality rates fluctuated between 8 and 19 per 1000 person-years. The main causes of mortality in that period were violence, overdose, infections and alcoholism.  

In recent years mortality rates among drug addicts have increased in some areas, but not in others, these differences may be due to the different impact of the human immunodeficiency virus (HIV) epidemic in the population of drug users. Differences in mortality rates between studies could be due to other reasons, such as recruitment sources and differences in health care management. In addition, comparisons of different studies need to consider that the population base may differ not only in treatment resources, but also in addiction history. In this respect, addiction time prior to inclusion into the cohort (usually corresponding to admission to treatment) might be expected to be an important survival factor although no conclusive results had been obtained in previous studies.

Few mortality studies have been done recently in the Mediterranean area, where opiate addiction is associated with a very high prevalence of HIV infection. By the end of 1994, in Spain, 29 520 acquired immunodeficiency syndrome (AIDS) cases had been reported, 64% of whom were intravenous drug addicts. Overdose deaths increased until 1992 in several cities where they are being monitored by the Spanish information system for drug abuse (SEIT).  

The purpose of the present study is to analyse mortality trends in a cohort of opiate addicts drawn from
several health services sources in Catalonia, Spain during the period 1985–1991 in the midst of the AIDS epidemic.

MATERIAL AND METHODS

Data Sources and Study Population
In order to recruit the study cohort, opiate addicts were gathered from two medical data bases or sources of entry: emergency rooms (ER) and treatment centres (TC). Patients who were detected as opiate addicts in the Hospital de Mar ER during the period 1 January 1985 to 31 December 1991, or at three other main Barcelona Hospitals ER during 1989 were included if they were residents of Catalonia and aged 15–44 years. Patients were identified through standardized review of all ER clinical records at monitored hospitals located in the city of Barcelona (1.7 million inhabitants). In 1989 the four hospitals included covered 83% of all opiate ER episodes in the city (Hospital de Mar ER alone covered around 43% of them). Emergency rooms in other parts of Catalonia were not included.

In Catalonia, drug users who visit public treatment centres are notified to a register of treatment admissions. The register is part of SEIT and has been collecting data since 1987 on all individuals who start, or restart, outpatient treatment for drug dependence. From this registry we selected the opiate addicts who fulfilled the same eligibility criteria (i.e., Catalonia residents aged 15–44 years). The register covers all public treatment centres in Catalonia, but it is not known whether the first episode registered between 1987 and 1991 was the first treatment demand for a given patient. Catalanop patients assembled in a cohort through a random sample of treatment patients in 1985 were also included.

Both sources of entry to the cohort were episode-based registries. To obtain a cohort with unique individual data, both registries were linked using probabilistic record linkage. Confidential identification data including date of birth, gender and two (in TC) or three (in ER) initials from both surnames provided the means to identify unique individuals. An adaptation of the Newcombe record linkage, previously validated for this study population, was used. Addicts were categorized in three groups according to the source of entry with which they were registered (ER, TC or both). They were also classified according to the length of use, a variable only directly calculable for those addicts with an episode in a TC but which was estimated for those entering through ER as explained below.

Follow-up started at the age of the first registered admission, either in a recorded ER or TC, during the study period (1985–1991), if the person was older than 15 years; otherwise at age 15. Follow-up finished at the minimum age of: 45 years, age on 31 December 1991 and age at death.

We excluded 945 people with incomplete identification data, 79 who were resident in Catalonia, 135 that were outside the age range and 475 admitted to treatment centres, but for whom the date of initial drug use could not be determined. They represented 9% of all registered individuals.

Mortality Data
Mortality was ascertained through probabilistic record linkage of cohort individuals with the Catalonia Mortality Registry (CMR), which only covers deaths in the region. Probabilistic record linkage criteria were applied following criteria specified elsewhere. People not detected as dead in the CMR were considered alive at the end of the study period (31 December 1991). Only confidential identification data including three initials of surnames, date of birth and gender were available for the linkage process. Doubtful cases were resolved by checking of available identification data. The protocol was approved by the ethical committees of the two institutions involved in the study.

Mortality in the CMR was coded, during the study years, using the ICD, 9th Revision. Specific mortality was categorized in five groups, according to previous information on causes of death accepted as being related to opiate use or AIDS. Groups were as follows: 1) directly drug-related mortality (overdose, dependence), 2) indirectly drug-related mortality (non-AIDS drug-related infections: endocarditis, hepatitis), 3) violence, 4) AIDS including associated causes according to the 1993 revision of the European AIDS surveillance case definition, and 5) other diseases (other infections, tumours, etc.). The ICD-9 codes included in each group may be requested from the authors.

Statistical Methods
To calculate length of use at inclusion in the cohort, year of first opiate use ('first use') was needed. However this variable was only available for those addicts who had been admitted to a TC. Treatment centre data for those addicts seen at both an ER and a TC allowed us to estimate how long after first use the opiate addicts were admitted to ER, thus allowing estimation of first use for those patients only seen at ER. Addicts gathered by both sources of entry, whose first contact was through an ER, supplied the means to fit three linear regression models to identify predictors of the time since first use at the first ER visit. More variability of year of first use was explained when three regressions were done, one
for each reason for attendance. When the first ER admission was due to withdrawal syndrome or a request for information (N = 862), 81% of the variability in the time since first use was explained by gender, age at first ER admission and time between first and last admission to ER. When reason for attendance was an organic problem (N = 733), gender, age at first ER admission and number of ER admissions explained 83% of time since first use variability. If first ER admission was due to an overdose (N = 187), the only informative variable was age at first ER admission which explained 45% of time since first use variability. Imputation of time since first use was done for people only recruited through ER, according to reason for attendance at their first admission. In order to reduce collinearity with age in the analysis, inclusion of first use was done by categorizing it in three groups corresponding approximately to tertiles (since month of first use was not available, we could not split years) of the length of use: 1) 'long-term'—addicts who had started opiate use between 1960 and 1980, before the AIDS epidemic, 2) 'intermediate'—addicts who started between 1981 and 1984, and 3) 'recent users'—those who started between 1985 and 1991; the study period.

Crude fatality rates were calculated as the ratio of the number of deaths observed to the number of person-years contributed by participants in a given category defined by gender, source of entry and calendar year. In order to tightly control for age we used it as the time scale for the estimation and comparison of hazard rates. Obviously, different individuals entered at different ages so we used the extension of the Kaplan-Meier estimator for handling data with staggered entry or truncation. Software to perform this analysis is widely available (e.g. EGRET) including graphical depictions of the smoothed hazard functions corresponding to the truncated Kaplan-Meier estimator, and thus directly provides age-adjusted mortality rates. Due to the extensive computations required by the truncated Kaplan-Meier estimator and its corresponding smoothed hazard, we used a 33% random subsample for estimation purposes. However, the full cohort was used to make comparisons and to compute confidence intervals.

The extension of Cox regression to incorporate staggered entry was used to test for differences of the fatality rates according to calendar year, source of entry and length of use. Since duration of drug use was considered the important exposure, we stratified our analysis in three categories according to length of use. Given the formal equivalence of the log-rank test (i.e. the score test of the Cox regression) with the Mantel-Haenzel test for a sequence of 2 x 2 tables, we simplified the computation for this analysis constructing a table for each year of age.

**RESULTS**

The cohort included 15 711 opiate addicts aged 15–44 years and it is described with respect to gender and source of entry in Table 1. Men were mostly recruited through TC, as were women but to a lesser extent. Fatality rates were highest among patients with ER as the only source of entry, with the lowest fatality rates observed among those who entered the study only through the TC. For the three groups of source of entry, women had lower overall fatality rates and were
younger than men. Length of use was similar between men and women but differed by source of entry; patients whose source of entry was a TC were more recent users, whereas users seen at both places had longer periods of use.

Figure 1 shows the smoothed hazard functions (mortality) by gender using age as the time scale (the hazard function of women older than 35 years was excluded from the graph as it dropped down due to the small numbers). Overall, mortality in men was slightly higher than in women. When using log-rank test, the estimated relative mortality of men to women was 1.31 (95% confidence interval [CI] : 1.14-1.51).

Figure 2 shows the estimated hazard functions (mortality) by source of entry. Those who entered through ER had higher mortality rates than the other two groups. Using TC as the reference group, relative mortality was 1.63 (95% CI : 1.43-1.80) for ER and 1.44 (95% CI : 1.24-1.67) for both sources.

Overall, annual fatality rates changed from 13.8 deaths per 1000 person-years in 1985 to 34.8 in 1991. Annual rates per 1000 person-years by calendar year, stratified by gender and source of entry are shown in Table 2. Fatality rates were higher in more recent years for both genders and all sources of entry. The 1989 ER increase in mortality remains even after excluding patients recruited through ER other than at Hospital del Mar. Women had lower fatality rates in all years, except 1987.

When annual mortality was analysed using a Cox regression model to adjust for age, gender and source of entry and stratified by length of use, we observed a mortality risk with a monotonic increase between 1985 and 1991, with a statistically significant slope increase observed in 1988 and 1989, for long-term and intermediate length of use. For recent users an important increase was only observed in 1990 (Table 3).

The principal causes of mortality in our cohort were directly related to addiction (overdose, dependence) (10.9 deaths per 1000 person-years), AIDS (10.8 deaths per 1000 person-years) and violence (3.7 per 1000 person-years). All these causes showed increasing rates during the period, but AIDS had a greater slope, being the most important cause since 1989.

Specific relative hazard trends, adjusted by age, sex and source of entry, differed according to length of use. Considering 1988 as the reference year, AIDS and causes indirectly related to addiction increased most among long-term and intermediate users (Figures 3a and 3b). For recent users, AIDS paralleled the increase in causes directly related to addiction while causes indirectly related to addiction decreased their risk (Figure 3c). Violent death was more frequent among recent users. The hazard ratio of 'other causes' only
increased in the group of addicts with a longer period of use.

DISCUSSION
Between 1985 and 1991, fatality rates in the population of drug users studied increased from 13.8 to 34.8 deaths per 1000 person-years. This increase is similar to the one observed some years earlier in New York City\textsuperscript{13,32} and probably also occurred in Rome,\textsuperscript{33} although in the study by Perucci \textit{et al.} yearly rates were not given. It is important to note that in these three sites, positive HIV prevalence rates among opiate addicts are higher than 50%.\textsuperscript{34-36} In the present study AIDS-related causes accounted for the highest number of deaths by 1989 and kept that ranking in subsequent years for the whole group. Thus, most of the overall mortality increase in the study population could be attributed to the emergence of the AIDS epidemic among Catalan addicts. Only four AIDS cases had been identified before 1984 in Catalonia before annual diagnosed cases started to rise exponentially.\textsuperscript{37}

When looking at cause-specific mortality, causes directly related to abuse (among which overdose accounted for 96% of deaths) had a similar trend to AIDS, but began to rise one year earlier, being

\begin{table}
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\begin{tabular}{lcccccc}
\hline
Calendar year & \multicolumn{3}{c}{Men} & \multicolumn{3}{c}{Women} \\
& Emergency Room & Treatment centre & Both & Emergency Room & Treatment centre & Both \\
\hline
1985 & 27.5 (254) & 0 (2) & 0 (172) & 10.4 (96) & 0 (0) & 0 (58) \\
1986 & 25.0 (680) & 0 (3) & 0 (402) & 7.6 (263) & 0 (1) & 0 (167) \\
1987 & 20.4 (983) & 21.0 (286) & 3.0 (664) & 22.6 (399) & 25.5 (78) & 3.6 (281) \\
1988 & 26.3 (1369) & 32.4 (1357) & 11.5 (1045) & 38.3 (574) & 24.2 (372) & 9.1 (441) \\
1989 & 45.2 (2124) & 26.4 (2874) & 37.2 (1479) & 38.9 (847) & 8.7 (686) & 27.6 (615) \\
1990 & 43.0 (2719) & 26.3 (4263) & 43.8 (1691) & 28.8 (1042) & 17.5 (1028) & 29.0 (723) \\
1991 & 35.6 (2828) & 34.1 (5661) & 52.5 (1714) & 28.2 (1098) & 13.2 (1365) & 44.6 (739) \\
\hline
\end{tabular}
\caption{Annual mortality rate per 1000 person-years (and person-years of follow-up) by gender and source of entry into follow-up}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{smoothed_hazard_functions}
\caption{Smoothed hazard functions of age-specific mortality rates by source of entry. Cohort data: 1985–1991}
\end{figure}
Table 3 Relative hazards for calendar year using 1988 as the reference (95% confidence interval) by length of use and adjusting by age, gender and source of entry into follow-up

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<tr>
<td><strong>Calendar year</strong></td>
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<tr>
<td>1985</td>
<td>0.38 (0.17–0.84)</td>
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<tr>
<td>1986</td>
<td>0.51 (0.27–0.94)</td>
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<tr>
<td>1987</td>
<td>0.47 (0.28–0.80)</td>
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<td>1988</td>
<td>1.00&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1989</td>
<td>1.94 (1.39–2.70)</td>
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<tr>
<td>1990</td>
<td>2.23 (1.61–3.08)</td>
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<tr>
<td>1991</td>
<td>2.73 (1.98–3.76)</td>
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<td><strong>Gender</strong></td>
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<tr>
<td>Women</td>
<td>1.00</td>
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<tr>
<td>Men</td>
<td>1.50 (1.20–1.87)</td>
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<tr>
<td><strong>Source of entry</strong></td>
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<tr>
<td>Treatment</td>
<td>1.00</td>
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<tr>
<td>Both</td>
<td>0.89 (0.72–1.11)</td>
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<tr>
<td>Emergency</td>
<td>1.07 (0.86–1.33)</td>
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<tr>
<td>Age (per year)</td>
<td>0.99 (0.98–1.02)</td>
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<sup>a</sup> Basal mortality rates for 1960–1980 = 25.8.<br>
<sup>b</sup> Basal mortality rates for 1981–1984 = 22.8.<br>
<sup>c</sup> Basal mortality rates for 1985–1991 = 20.6

**Table notes:**

Responsible for 45% of deaths in 1988. Two hypotheses have been suggested to explain increased mortality from heroin overdose: a) increased heroin availability and b) changes in drug purity. Such possibilities are unlikely in the present study given that increased mortality was observed over a long period of time. Other factors, such as an increase in polydrug abuse and poorer living conditions for addicts, which could be important determinants of their increased mortality, are difficult to evaluate. The 1988 and 1989 fatality rate increases in this cohort coincide with a period when overdose deaths in Spain started to rise. Since overdose deaths have been considered an indirect indicator of prevalence such an increase in overdose mortality was thought to reflect an increase in prevalence.

The concurrent increase in both AIDS and overdose mortality observed in our cohort may suggest a direct link between the two phenomena. A similar temporal pattern has been reported by Rezza in Italy. However, in a cohort study in New York City the increased mortality in recent years was restricted to AIDS and related infectious causes; no changes being observed in overdose and other causes like cirrhosis or traumas. Overdose mortality rates in Spanish cities are highly correlated (r = 0.81) to HIV positive seroprevalence in opiate addicts. Other authors have pointed out that overdose fatality might be causally related to HIV infection either through suicide or due to unknown mechanisms. Other factors, like accessibility to health care, which vary in different countries may produce impact on specific morbidity and mortality and may explain the lack of consistency between our results and those reported in New York.

In the present study mortality was higher in patients with a longer period of use, although previous studies did not give concordant results. Length of drug abuse was an important factor for mortality trends in the Norway study, after controlling for HIV seropositivity. In the present study, length of use was also an important factor and can be considered as a confounding variable in mortality studies of drug addicts. Risk attributed to age was no longer significant when analysis was adjusted by length of use. In spite of the possible errors in the imputation of first use to patients entering the study through ER (probably minimized by categorizing it in three periods), inclusion of time of first opiate use allowed a better approach to the study of mortality in opiate addicts. However, it was not possible to control for HIV status and, as positive HIV seroprevalence increases with length of abuse, it is not possible to exclude HIV infection as a contributing factor for increased mortality in the long-term users.

As in several previous reports, men in our cohort showed a higher mortality than women. Other
studies have shown no significant gender differences in mortality,\textsuperscript{14,15} or an increased risk in women.\textsuperscript{45} In Spain, the male/female ratio of deaths due to overdose is higher (7.0) than in drug-related ER visits (3.9).\textsuperscript{46} It has been suggested that women have a higher morbidity,\textsuperscript{47} and some mortality studies have observed an increase in mortality from infectious diseases in women whereas in men there are more deaths from violence and overdose.\textsuperscript{16} Differences between the genders in reported studies may originate from a sex differential in fatality for different conditions together with a different morbidity case-mix.

Some studies have observed increased mortality immediately after the start of treatment (probably related to reduced drug tolerance).\textsuperscript{14,48} In this cohort we did not know whether the patients' treatment episode that prompted inclusion into the cohort was the first episode ever or a re-admission. Also 29\% of patients were only seen in ER where no detoxification treatment was given and ER patients are not routinely referred to TC. Source of entry has been controlled for in the analysis because some factors that might be related to it could have distorted the results. In fact, higher risk associated with ER at crude analysis was reduced in multivariate analysis. Inclusion in the cohort of addicts gathered from ER widens the range of the opiate population usually studied and our results suggest that cohorts based only on treatment patients could underestimate total mortality. Some patients may be more likely to contact health services when they are already very ill, thus giving a less favourable survival picture for those presenting at ER. Maybe ER patients only monitored during 1989 were more severely ill at inclusion as we did not allow them to appear previously. During the study period emergency care in the city of Barcelona improved,
particularly with respect to ambulances attending overdoses.

The cohort did not cover street addicts. It is difficult to study mortality in the early phases of addiction, or to study street addicts for a long enough period and under comparable procedures, to assess the impact on mortality during the first phases of addiction. Mortality in the group that started use during the study period (hence in an early addiction phase), although lower than for other groups, was high.

Among other problems faced by cohort mortality studies, three need to be highlighted in this cohort of opiate addicts. The inception cohort was assembled throughout the study period with unequal catchment periods and included patients seen at several health services (TC and ER), further, it was not representative of all Catalan opiate consumers. Thus it is not possible directly to apply mortality rates found because consumers not included in the cohort might be different in terms of drug use frequency, risk behaviours and community involvement. Also we do not know if addicts included gave up their habit during the follow-up period.

Since mortality ascertainment has relied on record linkage, deaths could have been missed for two reasons: deaths of addicts in our cohort in other regions of Spain were not available to us, and the record linkage could have missed some cases. We minimized the first one by restricting our cohort to residents in Catalonia, although migration could not be excluded. On the other hand, both the sensitivity and specificity of the linkage procedure used were high. However we cannot exclude some degree of underascertainment.

Validity of assigned cause of death in medical certificates is probably lower in opiate addicts. In our study, overdose deaths and also AIDS-related causes could even be higher than those observed as some causes in the fifth group (other causes) could be hiding stigmatized deaths. Some studies do highlight this problem.

In the present study, 'other causes' included 'lung congestion', a specific code with a considerable number of deaths (n = 20) that showed a time distribution similar to overdose death.

Nevertheless we can assert that Spanish opiate addicts' life expectancy has been considerably reduced by the impact of the AIDS epidemic. The epidemic will probably continue to affect them as adequate measures aimed at reducing their risk of infection only began during the early 1990s.

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