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Research paper

Effect of ageing and time since first heroin and cocaine use on mortality from external and natural causes in a Spanish cohort of drug users

Gemma Molist[a,b], M. Teresa Brugal[c,d], Gregorio Barrio[e,*], Beatriz Mesías[f], Marina Bosque-Prous[c,d], Oleguer Parés-Badell[c,d], Luis de la Fuente[b,g], Spanish Working Group for the Study of Mortality among Drug Users[1]

[a] Área de Recerca i Innovació, Hospital General de Granollers, Barcelona, Spain, Spain
[b] Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP), Madrid, Spain
[c] Public Health Agency of Barcelona, Barcelona, Spain
[d] Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Barcelona, Spain
[e] National School of Public Health, Carlos III Health Institute, Madrid, Spain
[f] Addiction Institute, Madrid, Spain
[g] National Epidemiology Center, Carlos III Health Institute, Madrid, Spain

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ABSTRACT

Background: We aimed to assess the effect of ageing and time since first heroin/cocaine use on cause-specific mortality risk and age disparities in excess mortality among heroin (HUs) and cocaine users (CUs) in Spain.

Methods: A cohort of 15,305 HUs and 11,905 CUs aged 15–49 starting drug treatment during 1997–2007 in Madrid and Barcelona was followed until December 2008. Effects of ageing and time since first heroin/cocaine use were estimated using a competing risk Cox model and the relative and absolute excess mortality compared to the general population through directly age-sex standardized rate ratios (SRRs) and differences (SRDs), respectively.

Results: Mortality risk from natural causes increased with time since first heroin use, whereas that from overdose declined after having peaked in the first quinquennium. Significant effects of time since first cocaine use were not identified, although fatal overdose risk seemed higher in CUs after five years. Mortality risk from natural causes (HUs and CUs), injuries (HUs), and overdoses (CUs) increased with age, the latter without reaching statistical significance. Crude mortality rates from overdoses and injuries remained very high at age 40–59 among both HUs (595 and 217 deaths/100,000 person-years, respectively) and CUs (191 and 88 deaths/100,000 person-years). SRDs from all and natural causes were much higher at age 40–59 than 15–29 in both HUs (2134 vs. 834 deaths/100,000 person-years) and CUs (927 vs. 221 deaths/100,000 person-years), while the opposite occurred with SRRs.

Conclusion: The high mortality risk among HUs and CUs at all ages from both external and natural causes, and increased SRDs with ageing, suggest that high-level healthcare and harm reduction services should be established early and maintained throughout the lifetime of these populations.

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1 Introduction

Heroin and cocaine use disorders are chronic and relapsing diseases, which can seriously affect drug users' health for many years. In a recent *meta*-analysis the pooled mortality risk compared to the general population (GP) was 15 and 4–8 times higher among heroin users and cocaine users, respectively (Degenhardt, Bucello et al., 2011; Degenhardt, Singleton et al., 2011). However, the mortality risk also depends greatly on other cohort characteristics, especially drug-injecting prevalence or time in opioid substitution treatment (OST). Thus, among heroin users one meta-analysis

* Corresponding author at: Escuela Nacional de Sanidad. Instituto de Salud Carlos III. Pabellón 7. Monforte de Lemos 5. 28029 Madrid, Spain.
E-mail addresses: g.molist@gmail.com (G. Molist), tbrugal@aspb.cat (M. T. Brugal), gbarrio@isciii.es (G. Barrio), mesiaspb@madrid.es (B. Mesías), mbosque@aspb.cat (M. Bosque-Prous), opares@aspb.cat (O. Parés-Badell), lfuente@isciii.es (L. de la Fuente).

[1] The Working Group for this study includes the following people: Beatriz Arranz, Montserrat Bartroli, Cristina Cabeza de Vaca, Carmen Puerta, Teresa Hernández, Nieves Herrero, Mercedes Rodriguez, Ester Teixidó-Compañó, Albert Espelt, José Pulido, and Sara Santos.

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found that mortality risk in cohorts with drug-injecting prevalence >85% was double that of those with lower prevalence (Degenhardt, Bucello et al., 2011), while another found it was triple during the period outside OST than when they were in OST (Sordo et al., 2017). Among heroin users such excess mortality is largely due to overdoses, although injuries (unintentional injuries, suicide and homicide) also contribute substantially (Degenhardt, Bucello et al., 2011; Degenhardt, Larney, Randall, Burns, & Hall, 2014; Pierce, Bird, Hickman, & Millar, 2015). In cocaine users, overdose, injuries and circulatory diseases may make an important contribution to excess mortality, although the evidence is scarce (Degenhardt, Singleton et al., 2011). Finally, in some cohorts with high drug-injecting prevalence, infectious diseases (mainly HIV) are a major cause of death (Degenhardt, Bucello et al., 2011; Degenhardt, Singleton et al., 2011).

In developed countries, problem heroin and cocaine users are getting older, and long-term users (Arndt, Clayton, & Schultz, 2011; Armstrong, 2007; Barrio et al., 2013; Degenhardt et al., 2014; EMCDDA, 2015; Wu & Blazer, 2011) are accumulating many comorbidities and increased social isolation (Darke et al., 2009; Giraudon, Vicente, Matias, Mounteney, & Griffiths, 2012; Rosen, Smith, & ReynoldsIII, 2008; Larney et al., 2015; Rosen, Hunsaker, Albert, Cornelius, & ReynoldsIII, 2011; Wu and Blazer, 2011). This could partly explain why, despite improved care (i.e., OST), their mortality risk has not declined greatly, except for HIV-related causes (EMCDDA, 2015; Giraudon et al., 2012; Hedegaard, Chen, & Warner, 2015). Quantifying changes in cause-specific mortality by age and time since first heroin/cocaine use is important to target intervention programs more accurately. However, few studies among such drug users have focused on these aspects (Degenhardt, Bucello et al., 2011; Degenhardt et al., 2014; Nambiar et al., 2015; Pierce et al., 2015), and they sometimes show inconsistent results. There is evidence that among heroin users and drug injectors, the main causes of death change with age, with external causes (overdose and injuries) predominating among younger users, and natural causes (i.e., liver disease) among older ones (Clausen, Waal, Thoresen, & Gossop, 2009; Degenhardt et al., 2014; Maxwell et al., 2005; Maxwell, Pullum, & Tannert, 2005). Moreover, it is generally accepted that fatal and non-fatal overdose occur not only among the youngest and most inexperienced opioid users, but also in older users with many years of drug use (Darke & Hall, 2003; UNODC, 2015; Warner-Smith, Darke, Lynskey, & Hall, 2001). Many studies have found that fatal overdose risk does not decrease with age (Bartu, Freeman, Gawthorne, Codde, & Holman, 2004; Bird, Hutchinson, & Goldberg, 2003; Buster, van Brussel, & van den Brink, 2002; Clausen et al., 2009; Merrall, Bird, & Hutchinson, 2012; Odegard, Amundsen, & Kielland, 2007; Pierce et al., 2015) or time since first opioid use (Odegard et al., 2007). Mortality risk from natural causes usually increases with age, especially after age 50 (Brugal et al., 2005; Clausen et al., 2009; EMCDDA, 2015; Larney et al., 2015; Pierce et al., 2015), the same as in the GP, whereas fatal-injury risk shows inconsistent results between studies, with increases (Clausen et al., 2009), stability (Larney et al., 2015; Pierce et al., 2015), and decreases (Copeland, Budd, Robertson, & Elton, 2004; Degenhardt et al., 2014) with age. Among cocaine users, the aforementioned effects have rarely been studied, although considering the morbidity studies (Bernstein et al., 2007; Chen, Scheier, & Kandel, 1996; Kaye & Darke, 2004; Santos et al., 2012) and the increased all-cause mortality with age (Hser et al., 2006; Hser et al., 2012; Pavarin, 2008; de la Fuente et al., 2014), an increase of mortality risk from cocaine overdose (acute intoxication) and natural causes with age and time since first cocaine use can be reasonably expected. The effects of age and time since first drug use on mortality can influence each other given their high correlation (Odegard et al., 2007), thus the age effect in users under 45–50 may sometimes be reduced or disappear after adjusting by time since first drug use (Ortí et al., 1996). Disentangling the two effects is important to prioritize and target interventions more effectively, and to assess changes by age in excess mortality of drug users compared with the GP. However, excess mortality has generally been measured using standardized mortality ratios (SMRs), which presents methodological problems (Brugal et al., 2016). For example, the higher all-cause SMR in younger than older drug users (Degenhardt, Bucello et al., 2011) is largely due to very low mortality among young people in the GP (EMCDDA, 2015). To assess healthcare needs, it is also relevant to use absolute measures of excess mortality, which, however, may often yield results opposite to the SMR. The objective of this study was to assess the effect of ageing and time since first heroin/cocaine use on mortality risk from overdose, injuries and natural causes, as well as to quantify age changes in excess mortality from such causes among heroin and cocaine users admitted to drug treatment in Spain during 1997–2008 compared to the GP.

2 Methods

2.1 Cohort participants

A retrospective cohort was recruited. The main characteristics can be found elsewhere (Brugal et al., 2016; de la Fuente et al., 2014). It included all heroin (HUs) and cocaine users (CUs) aged 15–49 admitted to outpatient drug dependence treatment in publicly funded facilities during 1997–2007 in Madrid and Barcelona, regardless of any previous admission. Double counting was avoided using a personal identifier. All HUs were using heroin when starting treatment, regardless of whether they were also using cocaine, while CUs were using cocaine but not heroin. The criterion for heroin (or cocaine) use was having requested treatment to control the use of such drug or having used it within 30 days prior to admission.

2.2 Baseline assessment

When treatment began, information was collected on recruitment date, personal identifiers (first name, surname, birthdate and sex), socio-demographic variables (age, education attainment, and current employment), and drug use (lifetime drug injection, current frequency of heroin/cocaine use, and calendar-year of first heroin/cocaine use). Frequency of heroin/cocaine use referred to the last 30 days prior to treatment admission. Missing values were less than 4% for all variables. Data were stored in two databases on separate computers, one containing identifiers, and another the study variables, and later linked with a meaningless code.

2.3 Follow-up

The follow-up ended on 31-12-2008. Vital status, date and underlying cause of death were obtained through record linkage with the general mortality register using the personal identifier. Individuals not identified as dead were considered alive at the end of follow-up. It was estimated that during follow-up 0.2% of the GP aged 15–59 emigrated abroad (INE, 2017). The cause of death initially assigned was the underlying cause coded following the International Classification of Diseases –ICD- (ICD-9 for 1997–1998 and ICD-10 for 1999–2008). However, since in Spain coding of external causes in the general register has limitations, especially for overdose (Santos et al., 2010), in Barcelona the forensic-toxicological register was consulted, assigning the cause from this source to discrepant cases. In this consultation, it was observed that 81% of the deaths included in the general register under nonspecific codes such as cardiac arrest (427.5, I46), pulmonary oedema (514, 518.4, J81), respiratory failure (799.1, J96), ill-defined conditions (780–799, R00-R74, R76-R99) and toxic effects of alcohol (980.0) were actually overdoses. Since forensic and toxicological consultation to correct the underlying

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