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Double trouble: Psychiatric comorbidity and opioid addiction—All-cause and cause-specific mortality

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ABSTRACT

Background: Opioid misusers have recognized high mortality but the influence of psychiatric comorbidity in excess cause-specific mortality is unclear.
Methods: Opioid use disorder (OUD) patients were identified in the South London and Maudsley Case Register. Deaths were identified through database linkage to the national mortality dataset. Standard mortality ratios were calculated to compare mortality risk with the general population. Cox and competing risk regression models were used to investigate the effect of psychiatric comorbidity and psychological health on all-cause and cause-specific mortality (respectively) in OUD patients.
Results: Of 4837 OUD patients, 176 had died. Mortality rates were substantially higher than the general population (SMR 4.23; 95%CI 3.63–4.90). Among those with OUD, comorbid personality disorder (PD) and comorbid alcohol use disorder (AUD) was associated with increased all-cause mortality in all models, including the fully adjusted model, controlling for socio-demographic factors, severity of drug use, risk behaviours and physical health (HR2.15, 95%CI 1.17–3.95; HR2.28, 95%CI 1.54–3.36). AUD was associated with increased risk of fatal overdose (HR2.57, 95%CI 1.26–5.26) and hepatic-related deaths (HR7.26, 95%CI 2.79–18.86). Individuals with OUD and comorbid PD had almost four times greater risk of liver related deaths compared to those without PD (HR3.76, 95%CI 1.21–11.74). Comorbid severe mental illness and poor psychological health were not associated with increased mortality.
Conclusions: This study highlights the importance of assessment for PD and AUD in OUD patients in order to identify individuals at substantially elevated mortality risk to enable a more personalized approach to their medical care.

1. Introduction

Opioid dependent individuals are at substantially higher risk of mortality compared to the general population, to those with other drug-use disorders (Harris and Barraclough, 1998; Hayes et al., 2011) and to people with severe mental illnesses (SMI; i.e., psychotic disorders and bipolar affective disorder, Chang et al., 2010; Dickey et al., 2004; Harris and Barraclough, 1998). Previous research has found that individuals with substance use disorders, especially opioid dependence, have more than four times the expected risk of mortality, with life expectancies reduced by more than nine years compared to national norms. This difference was most pronounced in females whose life expectancy was reduced by more than 17 years (Hayes et al., 2011).

Although there is evidence of the link between opioids and elevated mortality risk, factors which may predispose some opiate users to higher or lower mortality risk compared to their peers with the same disorder are not properly understood. Existing literature on such risk factors is mixed, with substantial international (Bargagli et al., 2006; Darke and Ross, 2002), and chorological differences (Ghodse et al., 1985; Shah et al., 2008).

Substance use disorders are strongly associated with other psychiatric disorders in both clinical (Brooner et al., 1997; Weaver et al., 2003) and population samples (Rodriguez-Llera et al., 2006). Lifetime comorbidity with other psychiatric disorders range from 44% to 93% (Brooner et al., 1997; Cacciola et al., 2001; Khantzian and Treece, 1985; King et al., 2000; Krausz et al., 1999; Mason et al., 1998). Psychiatric comorbidity is associated with poor treatment prognosis, greater psychosocial impairment, increased risk of

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relapse and higher rates of HIV risk behaviour (Arendt et al., 2007; Brooner et al., 1997; Darke and Ross, 1997; Disney et al., 2006; Landheim et al., 2006; Rounsaville et al., 1982, 1986). Comorbid alcohol problems are highly prevalent in this patient population (25%) (Gossop et al., 2001) and are reportedly associated with an increased risk of fatal overdose (Darke and Ross, 1997). Mood and anxiety problems (41%), personality disorders (PD) (40%) and psychotic disorders (12%) are found to be the common comorbid diagnosis not only in opioid users (Rodriguez-Llera et al., 2006) but also in other drug users (Weaver et al., 2003). Antisocial personality disorder is a rare diagnosis in the general community (4%) (Robins and Regier, 1991), but occurs at rates of up to 65% in heroin-using samples (Bargagli et al., 2006; Darke et al., 1994). In addition, people with a diagnosis of PD have a four-fold higher mortality, with substantially reduced life expectancy (Fok et al., 2012). Similarly, substantially higher mortality rates are found in people with SMI and depressive disorders when compared to the general population (Chang et al., 2010). In spite of this, the impact of psychiatric comorbidity on mortality risk in substance use disorders has received only moderate attention, with existing investigations reporting mixed results (Arendt et al., 2011; Davoli et al., 1993; Gossop et al., 2002; Mattisson et al., 2011).

Given the high prevalence of comorbid alcohol, mood problems, PD and SMI among opioid users, and particularly high hazard ratios for mortality risk in individuals with these diagnoses, it is plausible that these psychiatric problems may contribute to the elevated mortality risk observed in this patient group, with regard to both natural and unnatural causes of death. Investigating the impact of comorbid psychiatric problems in opioid users and looking beyond unnatural causes of mortality may help improve our understanding of the pathways to premature mortality among opioid users as well as identifying subgroups at substantially elevated mortality risk. We used a large and well-established South London and Maudsley (SLaM) case register (Stewart et al., 2009) to explore these relationships more fully. The study described here investigates the associations between subjective ratings of psychological health, such as feelings of depression and anxiety, comorbid diagnosis of PD, SMI and AUD, in relation to all-cause as well as cause-specific mortality in a large cohort of opioid-dependent patients receiving secondary mental healthcare.

2. Method

2.1. Study setting

SLaM is one of the largest specialist mental healthcare services in Europe, which provides, within the framework of the British National Health Service (NHS), comprehensive mental healthcare and addiction services to a catchment population of approximately 1.2 million residents across seven multicultural, ethnically diverse, highly dense boroughs of London. Within the framework of NHS in the United Kingdom, mental health trusts have close to 100% monopoly for service provision to its geographic catchment. Electronic health records (EHRs) have been used comprehensively across most SLaM services since 2006 and across addiction services since April 2008. In 2008 the CRIS system, linked with mortality tracing at a national level, was developed at the SLaM NIHR Biomedical Research Centre for Mental Health, which enables researchers to search and retrieve EHRs in a de-identified form, with more than 250,000 cases currently represented on the system. The protocol for the SLaM case register has been described in detail elsewhere (Stewart et al., 2009). CRIS is approved as a dataset for secondary analysis by Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5).

2.2. Inclusion criteria

Diagnoses in CRIS are coded according to the 10th edition of the World Health Organization International Classification of Diseases (ICD-10; WHO, 1993). In this analysis, the sample comprised a cohort of 4837 SLaM patients who were diagnosed with an ICD-F11 opioid use disorder within the period between 1st April, 2008 and 31st December, 2012 (inclusive) and who had been assessed by a clinician using the National Drug Treatment Monitoring System (NDTMS) and the Treatment Outcome Profile (TOP; Marsden et al., 2008) at least once during the observation period. All drug treatment agencies must provide a basic level of information to the National Drug Treatment Monitoring System (NDTMS) on their activities each month. The TOP is a reliable and valid 20-item instrument for monitoring substance misuse treatment outcomes and is designed to capture pertinent features such as substance use, health risk behaviour, offending, health and social functioning; and both NDTMS and TOP are now firmly embedded in the routine in-treatment monitoring of outcomes across the UK. In the SLaM case register, OUD is the second most frequently diagnosed substance use disorder after AUD (Hayes et al., 2011) and approximately 96% of SLaM patients with an OUD, within the observation period, appeared on the NDTMS and 89% had the TOP completed on at least one occasion.

2.3. Main outcome measures

The main outcome in this study was mortality, within the period 1st April, 2008 to 31st December, 2012 (inclusive), in individuals with primary or secondary OUD. Routine mortality identification is performed on a monthly basis by SLaM through a linkage to the national mortality base using the unique NHS number assigned to all UK citizens. Every death in the UK must be reported to the Office for National Statistics General Records Office, which is then conveyed to the NHS Care Records Service and available to all NHS organizations. This mortality tracing allowed us to establish who had died during the observation period and includes active as well as non-active SLaM cases. The full procedure for identifying and confirming SLaM patient deaths has been described elsewhere (Chang et al., 2010). In addition, a linkage to data specifically derived from death certificates allowed us to establish the recorded underlying cause of each death. Based on death data extracted within our cohort, ICD-10 codes A00-B99 were classified as infectious diseases; codes C220, K703-K769 were classified as alcoholic and other hepatic diseases; codes C349, J13-J449 were grouped as pneumonia and other pulmonary diseases; codes V01-Y98 were classified as unnatural causes, with codes X420-X450, Y120, Y125 sub-classified as overdose deaths. The remainder of ICD-10 cause of death codes within this cohort related to other natural causes of mortality and were classified as such. These groupings were based on the most common causes of mortality in this patient group where groups had sufficient power to allow for multivariate analysis.

2.4. Explanatory variables

The main characteristics of interest in this study were psychological health and psychiatric comorbidity, measured by investigation of four aspects of mental health, including patients' subjective psychological health ratings, and comorbid diagnosis of a SMI, PD and AUD.

Psychological health status data, a subjective 21-point scale rating, was extracted from the TOP. Cohort members were classified as having a comorbid diagnosis of SMI if they had received at least one of the following diagnoses during the observation period: schizophrenia (ICD-F20), schizoaffective disorders (ICD-F25), and bipolar affective disorder (ICD-F31). Similarly, the cohort was classified as having a comorbid diagnosis of PD if they had received either a specific personality disorder (ICD-F60) or mixed and other personality disorder diagnosis (ICD-F61), and a comorbid diagnosis of AUD if they had received an ICD-F11 alcohol use disorder diagnosis. Consequently those with more than one comorbid diagnosis could appear in more than one category.

In addition to the main exposures of interest, an extensive list of other covariates derived from TOP and NDTMS were considered as potential confounders. Date of birth, ethnicity and gender are routinely recorded on SLaM electronic patient records in their designated fields. Age was calculated from the date on which individuals received their ICD-F11 OUD diagnosis within the observation period. Ethnic classifications were condensed into "White British", "Other White background", "African, Caribbean and other black background", and "Mixed, unknown and other". The level of deprivation for the neighbourhoods was established by linking the patient's residential postcode to the UK Census data projected for 2007. The full procedure for measuring level of deprivation is described elsewhere (Hayes et al., 2012). Severity of drug use included 'age at first primary problem drug, frequency of opioid use in the past 28 days' and a 'total number of different drugs used', reported within the observation window. Other variables included risk behaviours (injecting) and physical health rating. Likelihood ratio tests indicated that it was acceptable to include psychological and physical health rating, age at first diagnosis, level of deprivation and the total number of different drugs used as continuous variables.

2.5. Statistical analysis

Standardized mortality ratios (SMRs) using indirect standardization in STATA 12 for the period between 1 April, 2008 and 31 December, 2012 were calculated. The numerator was the number of deaths observed in SLAM records within the observation period and the denominator was the number of deaths we would expect to occur over the observation period based on age and gender specific death rates for the England and Wales population in 2008 (ONS, 2009). SMRs were age-standardized using 5-year age bands and stratified by gender, and are presented in Table 2. Cox regression (Cox, 1972) for survival analysis was used to model the associations of psychological health and psychiatric comorbidity with all-cause mortality. Competing risk regression was performed to model cause-specific mortality in our sample.

Patient's 'at risk' period commenced from the date of their first OUD diagnosis within the observation period between 1 April, 2008 and 31 December, 2012 and