Mortality among clients seeking treatment for buprenorphine abuse in Finland

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ABSTRACT

Background: It is unclear whether buprenorphine abuse is associated with a similar risk of death to other substance abuse. This study examined all-cause mortality rates and causes of deaths among clients seeking treatment for buprenorphine abuse.
Methods: Structured clinical interviews were conducted with 4685 clients between January 1998 and August 2008. Records of deaths that occurred among these clients were extracted from the Official Causes of Death Register in Finland. Standardized mortality ratios (SMRs) with 95% confidence intervals (CI) were computed using national mortality rates over a 13-year follow-up to examine excess mortality. Kaplan–Meier survival analysis was used to compare survival between buprenorphine and other clients.
Results: Sixty-one of 780 (7.8%) clients who sought treatment for buprenorphine abuse and 408 of 3905 (10.4%) other clients died during the 13-year follow-up period. The most common cause of death was drug-related in buprenorphine ($n = 25$, 41.0%) and other clients ($n = 142$, 34.8%). Survival rates were similar among buprenorphine and other clients (log-rank $\chi^2_{[df=1]} = 0.215$, $p = 0.643$). The SMR was 3.0 (95% CI 2.3–3.8) and 3.1 (95% CI 2.8–3.4) for buprenorphine and other clients, respectively. Excess mortality was highest among women aged 20–29 years, and more pronounced in buprenorphine clients (SMR 27.9 [95% CI 12.6–49.0]) compared to other clients (SMR 14.0 [95% CI 9.3–19.6]).
Conclusions: Clients seeking treatment for buprenorphine abuse had a three times higher mortality rate than the national average, with the excess risk highest among female clients. Overall mortality rates were similar among clients seeking treatment for buprenorphine and other substance abuse.

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1. Introduction

People with substance use disorders have between three to 50-fold increased risk of death compared to the general population (Bargagli et al., 2001, 2006; Stenbacka et al., 2010; Nyhlen et al., 2011; Merrall et al., 2012). Drug-related deaths constitute about 60% of all deaths (Nyhlen et al., 2011; Merrall et al., 2012), with deaths due to violent causes, accidents, suicides and infectious diseases also common (Ødegård et al., 2007; Nyhlen et al., 2011; Merrall et al., 2012). Drug-related or drug-induced deaths refer to those directly associated with drug use, overdoses or poisonings (Nyhlen et al., 2011; European Monitoring Centre for Drugs and Drug Addiction, 2011). Deaths among people with substance use disorders are most commonly related to opioid use (Degenhardt et al., 2005; Ødegård et al., 2007), especially heroin (European Monitoring Centre for Drugs and Drug Addiction, 2011).

Prescription opioid abuse has become a global public health problem (Compton and Volkow, 2006; Degenhardt et al., 2008; Hernandez and Nelson, 2010). Prescription opioid induced overdose deaths increased sevenfold in New York City from 1990 to 2006 (Cerdá et al., 2013). In the United States (U.S.), data from surveys and national databases suggest diversion and abuse

of buprenorphine/naloxone have increased from 2005 to 2009 (Johanson et al., 2012). Buprenorphine is a partial μ opioid agonist with a ceiling effect on the respiratory depression and, therefore, it should be a safe opioid (Walsh et al., 1994). In France, the introduction of high-dose buprenorphine coincided with a 79% decline in opioid overdose deaths from 1995 to 1999 (Gueye et al., 2002; Auriacombe et al., 2004). In addition, buprenorphine appears to be safer than methadone when used in opioid substitution treatment programs (Auriacombe et al., 2001; Bell et al., 2009a). However, reports of buprenorphine related deaths have been published (e.g. Kintz, 2001; Pelissier-Alicot et al., 2010; Simonsen et al., 2011). Megarbane et al. (2010) suggested that buprenorphine overdose can cause an opioid syndrome similar to heroin and methadone.

In Finland, buprenorphine was first used in opioid substitution treatment programs in 1997. Thereafter, abuse of buprenorphine has been increasing. The percentage of clients seeking treatment for buprenorphine abuse at the Helsinki Deaconess Institute increased from 3% in 1998 to 38% in 2008 (Uosukainen et al., 2013). Buprenorphine constituted 25% of all lethal intoxications among people who abused drugs in Finland in 2007 (Simonsen et al., 2011). Lethal buprenorphine intoxications are usually associated with concurrent use of benzodiazepines and alcohol (82% and 58% of buprenorphine poisonings in Finland from 2000 to 2008, respectively; Häkkinen et al., 2012). This is worrying because concurrent use of benzodiazepines is common among buprenorphine users (range 46–82% of buprenorphine users; Winslow et al., 2006; Nielsen et al., 2007; Otiashvili et al., 2010). The number of buprenorphine intoxications has increased in other Nordic countries as well (Simonsen et al., 2011) and buprenorphine-related mortality tripled in the United Kingdom (U.K.) from 1995–1998 to 1999–2002 (Schifano et al., 2005). However, the increase in buprenorphine-related mortality may reflect an increase in the number of clients receiving opioid substitution treatment and, therefore, the increased availability of the drug (Romelsjö et al., 2010).

To our knowledge, no long-term follow-up studies have examined mortality rates in clients seeking treatment for buprenorphine abuse. Previous studies on mortality have been descriptive and small-scale (Kintz, 2002; Lai et al., 2006; Pelissier-Alicot et al., 2010), examined fatal intoxications in medico-legal autopsies (Simonsen et al., 2011), or concentrated on clients receiving opioid substitution treatment and examined the effect of treatment and/or selected drug (methadone or buprenorphine) on mortality (Gibson et al., 2008; Bell et al., 2009a, 2009b; Degenhardt et al., 2009; Cornish et al., 2010; Soyka et al., 2011). The objective of this study was to examine all-cause mortality rates and causes of deaths among clients seeking treatment for buprenorphine abuse.

2. Methods

2.1. Study design

This was a cohort study of clients seeking treatment from the Helsinki Deaconess Institute in Finland between January 1, 1998 and August 31, 2008. Data collected from these clients were linked to the national mortality data from the Official Causes of Death Register and followed-up to December 31, 2010.

2.2. Study population

The study context and data collection have been previously described (Uosukainen et al., 2013). In brief, data were collected from all clients seeking treatment from the Helsinki Deaconess Institute (HDI) between January 31, 1997 and August 31, 2008 (n = 4817). The HDI is a large public utility foundation that provides inpatient and outpatient treatment services for persons with alcohol and other substance abuse disorders among the 1.3 million residents in the greater Helsinki metropolitan area, including Espoo, Vantaa and eight other nearby municipalities in southern Finland.

Data were collected using a structured questionnaire at each client's initial visit. The questionnaire was completed during a clinical interview conducted by specialist physicians and nurses, and it included questions regarding each client's demographics and alcohol and other substance abuse. Clients who reported that buprenorphine was their primary drug of abuse were regarded as buprenorphine clients (n = 780). All other clients seeking treatment from the HDI were regarded as other clients (n = 3905). A subgroup of clients who reported heroin as their primary drug of abuse (n = 582) was separated in order to enable the comparison between buprenorphine clients and other opioid clients. The primary drug of abuse was defined as the substance causing the client the most problems, as defined by the clients themselves or by diagnoses based on International Classification of Diseases, 10th Revision (ICD-10). There were no buprenorphine clients in year 1997 and therefore, all clients seeking treatment in 1997 were excluded from the analyses. Each client was included in the analyses only once even if they made repeated visits to the HDI.

Ethics approval was obtained from the Research Ethics Committee of the North-Savo Hospital District and the Ethics Committee of the Helsinki Deaconess Institute. The Finnish Data Protection Ombudsman also approved the study protocol.

2.3. Mortality data

The mortality data were obtained from Statistics Finland (research permission number TK-53-1065-10). Data on persons seeking treatment from HDI were linked with the Official Causes of Death Register. Both all and cause-specific (drug-related, disease, accident, suicide) deaths were examined. Data on underlying causes of death were based on ICD-10 codes recorded on death certificates. The underlying cause of death was defined according to the World Health Organization (WHO) definition as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" (World Health Organization, 2010). Drug-related death was defined according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) definition as "a death happening shortly after consumption of one or more illicit psychoactive drugs, and directly related to this consumption" (EMCDDA, 2009). This definition was applied to all drugs that were abused by clients seeking treatment. Clients were followed from the date of an individual's first attendance at HDI after 1 January 1998 until the date of death or 31 December 2010, whichever occurred first. The coverage of Finnish Mortality Register has been shown to be close to 100% (Official Statistics of Finland, 2011). There was no loss to follow-up in this study.

The following ICD-10 codes were used to classify cause-specific mortality:
Drug-related deaths were coded according to EMCDDA recommendation (EMCDDA, 2009).

- F11-F12, F14-F16, and F19
- X42, X62, Y12 with the T-codes T40.0-9
- X41, X61, Y11 with the T-code T43.6

Disease, accidental and suicide deaths were coded according to Statistics Finland's standard 54-category list of causes of death (Official Statistics of Finland, 2012).
Disease death

- A00-R99

Subclasses of cardiovascular death (I00-I425, I427-I99), infectious disease death (A00-B99, J65) and cancer death (C00-C97) were examined.
Accidental death

- V01-X44
- X46-X59
- Y10-Y15
- Y85-Y86

Suicide death

- X60-X84
- Y87.0

2.4. Statistical analyses

Percentages, means and medians were used to describe the data. Fischer's exact tests were used to compare categorical variables between client groups.

Time-at risk was calculated as person–years from the date of individual's first visit to HDI after 1 January 1998 until the date of death or the end of follow-up, 31 December 2010, whichever occurred first. Observed numbers of deaths and person–years were calculated separately by gender and age group (less than 20 years, 20–29 years, 30–39 years, and 40+ years old). Standardized mortality ratios (SMRs) were calculated by comparing the observed to expected numbers of deaths. The expected numbers of deaths were calculated by multiplying the cumulative person–years at-risk for each gender and age group by the corresponding average-age national mortality rate during the period of 1998–2010. The method described by Vandenbroucke (1982) was used to calculate 95% confidence intervals (CI) for