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# Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—A nation-wide register-based open cohort study

Tove Abrahamsson [1], Jonas Berge [1], Agneta Öjehagen, Anders Håkansson *

*Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Psychiatry, Lund, Sweden*

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ABSTRACT

*Background:* Use of sedatives may increase risk of death in opioid users. The aim of the study was to assess whether prescription of sedatives may be associated with mortality in patients in opioid maintenance treatment.

*Methods:* This retrospective register-based open cohort study included nation-wide register data including all individuals who were dispensed methadone or buprenorphine as opioid maintenance treatment for opioid dependence between July, 2005 and December, 2012 (N = 4501). Outcome variables were overdose mortality and non-overdose mortality, respectively. Extended Cox regression analyses examined associations between type of sedative prescriptions and death, controlling for sex, age, previous overdoses and suicide attempts, psychiatric in-patient treatment and opioid maintenance treatment status. Opioid maintenance was assumed to last for 90 days (or 30 days in a sensitivity analysis) after the last methadone or buprenorphine prescription.

*Results:* Benzodiazepine prescriptions were associated with non-overdose death (HR: 2.02, 95% CI: 1.29–3.18) but not significantly associated with overdose death (1.49, 0.97–2.29). Z-drug (1.60, 1.07–2.39) and pregabalin prescriptions (2.82, 1.79–4.43) were associated with overdose death. In the sensitivity analysis, all categories of sedatives, including benzodiazepines, were significantly associated with overdose death.

*Conclusions:* Caution is advised when prescribing sedative drugs, including benzodiazepines, z-drugs and pregabalin, to patients in opioid maintenance treatment.



## 1. Introduction

Opioid dependence is associated with a high risk of premature death (Darke and Zador, 1996; Degenhardt et al., 2011), with opioid overdose being a common cause of death (Darke and Zador, 1996; Degenhardt et al., 2011; Clausen et al., 2009; Warner-Smith et al., 2001). Opioid maintenance treatment (OMT) with methadone or buprenorphine is associated with lower rates of overdose death and all-cause mortality (Degenhardt et al., 2011; Clausen et al., 2009), but mortality remains increased compared to the general population (Cornish et al., 2010; Davoli et al., 2007; Grönbladh et al., 1990).

Benzodiazepines are commonly misused by individuals with opioid dependence, with prevalence rates of 46–71% for patients in OMT (Jones et al., 2012; Lintzeris and Nielsen, 2010), and concomitant benzodiazepine use is a known risk factor for fatal and non-fatal opioid overdose (Darke and Zador, 1996; Warner-Smith et al., 2001; Jones et al., 2012). Benzodiazepines have been identified in 40–80% of heroin- and methadone-related deaths, and in 80% or more of buprenorphine-related deaths (Jones et al., 2012). Despite risks for misuse and overdose, prescription of benzodiazepines to OMT patients seems to be common (Cousins et al., 2011; Leece et al., 2015; McCowan et al., 2009; Schuman-Olivier et al., 2013). For example, in a Norwegian study, 40% of patients in OMT had been prescribed benzodiazepines during the past year (Bramness and Kornor, 2007). Few studies have investigated associations between benzodiazepine prescriptions and mortality among OMT patients, but demonstrated that benzodiazepine prescription may be associated with drug-related death in OMT patients (Leece et al., 2015; McCowan et al., 2009). In a later study (Cousins et al.,

* Corresponding author at: Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Psychiatry, Malmö Addiction Center, Södra Förstadsgatan 35, S – 205 02, Malmö, Sweden.
*E-mail address:* anders_c.hakansson@med.lu.se (A. Håkansson).
[1] Shared first author position (contributed equally as first authors).

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2011), the association between benzodiazepine prescription and drug-related mortality remained for patients off treatment, but not for patients in active OMT.

However, other sedative/anxiolytic drugs also may add to the polydrug use pattern and overdose risk in opioid dependence. Z-drugs (hypnotics such as zopiclone and zolpidem) have a potential for misuse and dependence (Hajak et al., 2003), and an Irish study reported zopiclone misuse in 23% of methadone maintenance patients (Bannan et al., 2007). Likewise, pregabalin, an anticonvulsant with anxiolytic effects[17], has been reported to be misused by 3–12% (Schifano, 2014; Wilens et al., 2015; Grosshans et al., 2013) of individuals with opioid dependence. Z-drugs have central nervous depressant effects (Sanger, 2004), but the potential role of z-drugs in overdose among individuals with opioid dependence has been sparsely studied. Pregabalin is associated with CNS adverse effects such as somnolence and confusion (Zaccara et al., 2011), and might cause decreased respiratory rate (Zacny et al., 2012). The combined use of opioids and pregabalin might increase overdose risk (Garassino et al., 2013), and in one study, opioids were found in 91% of pregabalin-associated deaths in individuals with pregabalin abuse (Häkkinen et al., 2014). More research is needed about the potential role of pregabalin and z-drugs in opioid dependence.

The aim of the present study was to assess whether prescriptions of benzodiazepines, z-drugs and pregabalin are associated with increased mortality, including overdose and non-overdose deaths, in patients in OMT. Based on previous studies, we hypothesized that benzodiazepine prescription would be associated with overdose death, but not necessarily with non-overdose death. We also hypothesized, based on the pharmacological profiles of these drugs, that z-drugs and pregabalin prescription might also be associated with overdose death.

## 2. Methods

### 2.1. Study design

This was an open cohort study that utilized data from Swedish national registers administered by the Swedish National Board of Health and Welfare (NBHW): The Prescribed Drug Register (PDR), the Cause of Death Register (CDR), and the National Inpatient Register (IPR). Linkage of data from different registers was made by the NBHW, using the personal identity number given to all Swedish residents, which was then replaced by an arbitrary serial number before data delivery.

The study was approved by the Regional Ethics Committee, Lund, Sweden.

### 2.2. Setting

In Sweden, OMT is, by law, offered only to patients dependent on opiates, defined as heroin, opium or morphine (The National Board of Health and Welfare, 2009), and in clinical practice; this means that almost all Swedish OMT patients are heroin-dependent (Richert and Johnson, 2015). Only licensed psychiatrists in NBHW-approved OMT clinics are allowed to prescribe methadone and buprenorphine as OMT. Patients above 18 years of age, with a documented opiate dependence of at least one year, are eligible for OMT (The National Board of Health and Welfare, 2009; Richert and Johnson, 2015). Patients are discharged from treatment if they fail to comply with treatment regulations, and cannot enter another OMT program for the next three months (The National Board of Health and Welfare, 2009).

### 2.3. Study population and data sources

The study population consisted of all Swedish residents who were prescribed and dispensed methadone or buprenorphine formulations considered by the NBHW to be indicated for OMT between July 1, 2005 and December 31, 2012. Prescription data was retrieved from the PDR, a prescription database containing information on all prescribed drugs dispensed at Swedish pharmacies starting from July 1, 2005. Available data includes product and generic name, ATC code, strength, defined daily dose (DDD), package size and number of packages, as well as information about the patient (e.g., personal identity number, age, sex) and the prescriber (e.g., occupation, specialist code for physicians, workplace code).

In order to eliminate patients prescribed methadone or buprenorphine for pain, several measures were taken: 1) Only prescriptions issued by a psychiatrist working at a psychiatric clinic were included in the analyses. 2) Individuals with at least one prescription with a clear pain indication were excluded. 3) Prescriptions issued through the ApoDos (a multi-dose dispensing system, where patients receive machine-packed, labelled plastic bags of medications) were excluded, as OMT is unlikely to be prescribed through this system. 4) Analyses were restricted to individuals aged 18–50 at the time of first methadone or buprenorphine prescription during the observation time. In previous studies conducted by our research team, only 6–9% of patients in OMT have been aged 50 years or older (data not published).

Swedish OMT clinics may acquire OMT medication from an affiliated hospital and dispense it to patients without a personal prescription. This practice has become increasingly common in Sweden and approximately 25% of all patients receiving OMT in 2011 were estimated to obtain their medication without a personal prescription (The National Board of Health and Welfare, 2012). Drugs dispensed to patients in this way are not recorded in the PDR and thus the present study does not include all Swedish patients in OMT.

For the study population, prescription data for benzodiazepines, z-drugs, and pregabalin during the study period were also retrieved from the PDR.

Data linkage was made to the CDR, which includes data on date of death and underlying and contributory causes of death (ICD-10 codes) for all known deaths among Swedish residents, and the IPR, which contains data on patients discharged from all Swedish hospitals, including date of admission and discharge, and main and secondary diagnoses (ICD-10 codes). The IPR and the CDR have estimated coverage rates of more than 99% (Johansson and Westerling, 2000).

### 2.4. Study variables

The main outcome was overdose death, and secondary outcomes were non-overdose death and all-cause mortality (including both overdose and non-overdose death). *Overdose death* included all deaths with ICD-10 codes X40-49 (accidental overdoses) or Y10-19 (overdoses with undetermined intent) registered as the underlying cause of death in the CDR. *Non-overdose death* included all other causes of death.

Main predictor variables were prescription of benzodiazepines, z-drugs, and pregabalin, identified by ATC codes in the PDR. All benzodiazepines (diazepam, oxazepam, lorazepam, alprazolam, nitrazepam, flunitrazepam, triazolam, midazolam, clonazepam) and z-drugs (zopiclone, zolpidem, zaleplon) registered in Sweden were included. These variables were treated as time-dependent variables in the Cox regression analyses, and an individual could switch between the states *in treatment* and *not in treatment* several times during follow-up. The start of each treatment period was