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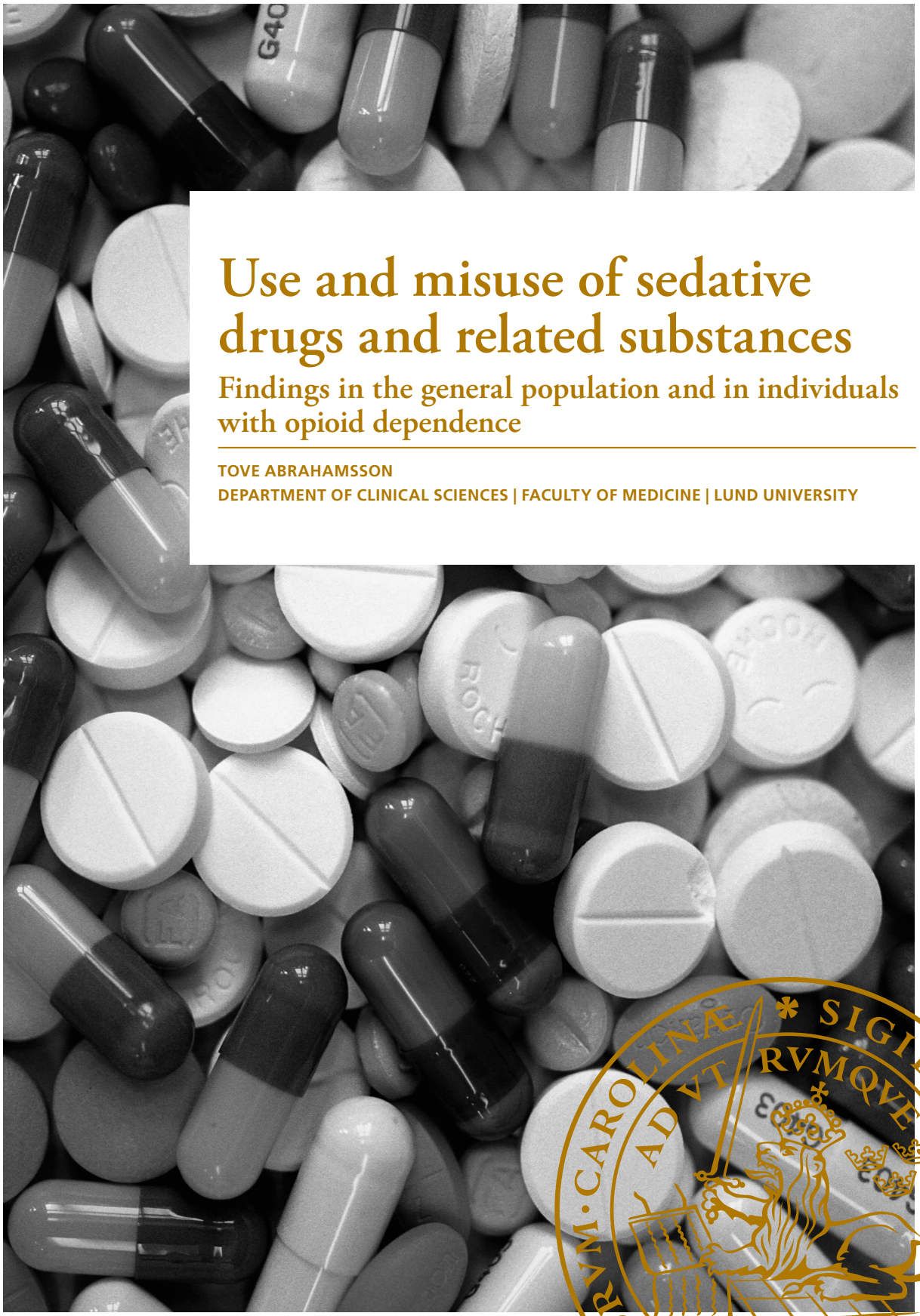

Use and misuse of sedative drugs and related substances

Findings in the general population and in individuals with opioid dependence

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Findings in the general population and in individuals with opioid dependence

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UNIVERSITY

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Title and subtitle: Use and misuse of sedative drugs and related substances: Findings in the general population and in individuals with opioid dependence

Abstract

Background: Prescription sedatives are efficient in the treatment of anxiety and sleeping disorders, but are associated with a risk of misuse and dependence, as well as an increased risk of accidents, injuries and overdoses, both in the general population and especially in individuals with other substance misuse. The present thesis aims to investigate prescription sedative use and misuse in two kinds of samples - in the general population, with focus on its association with subjective health and quality life, and in the subpopulation of individuals with opioid dependence, with focus on treatment outcome in opioid maintenance treatment and mortality.

Materials and Methods: Prescription sedative misuse was studied in three Swedish datasets: 1) a general population survey (n =22,095), 2) a clinical pilot study for the treatment of opioid dependence (n =44 and 36, for the original study and the follow-up study, respectively), and 3) a national register-based study of individuals in opioid maintenance treatment (n= 4,501).

Results: In the general population, sedative misuse was found to be associated with poor self-assessed mental health and poor quality of life. In individuals with opioid dependence, benzodiazepine misuse was found to be negatively associated with retention in opioid maintenance treatment. Prescription of sedatives was associated with mortality in individuals with opioid dependence, including associations between prescriptions of 'z-drug' hypnotics and pregabalin and overdose death.

Conclusions: It is important to be aware of the associations with mental health problems and quality of life in individuals with sedative misuse. In individuals with opioid dependence, clinicians also need to be aware of the increased risk of overdose and non-overdose death, as well as possible negative effects on treatment outcome, that come with sedative use and misuse.

Key words: Substance use; Sedatives; Anxiolytics, Hypnotics, Prescription drug miuse; Benzodiazepines; Z-drugs; Pregabalin; Self-assessed health; Quality of life; Opioid dependence, Opiate maintenance treatment, Mortality

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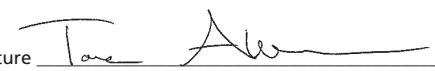
Signature  Date 2016-01-14

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To my husband, my parents, and my grandfather (morfar)

Table of contents

List of papers

The thesis is based on the following papers:

I. Abrahamsson T, Hakansson A. Nonmedical Prescription Drug Use (NMPDU) in the Swedish General Population - Correlates of Analgesic and Sedative Use. Subst Use Misuse. 2015 Jan;50(2):148-55.

II. Abrahamsson T, Berglund M, Hakansson A. Non-Medical Prescription Drug Use (NMPDU) and Poor Quality of Life in the Swedish General Population. Am J Addict. 2015 Apr;24(3):271-7.

III. Abrahamsson T, Widinghoff C, Lilliebladh A, Gedeon C, Nilvall K, Hakansson A. Interim Buprenorphine Treatment in Opiate Dependence – a Pilot Effectiveness Study. Subst Abus. 2015 Jul 15:0.

IV. Hakansson A, Widinghoff C, Abrahamsson T, Gedeon C. Correlates of 9-month retention following interim buprenorphine-naloxone treatment in opioid dependence – a pilot study. J Addict. Accepted for publication.

V. Abrahamsson T, Berge J, Öjehagen A, Håkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment – a nation-wide register-based open cohort study. Manuscript.

Abbreviations

AHR	adjusted hazard ratio
AOR	adjusted odds ratio
APA	the American Psychiatric Association
ATC	anatomical therapeutic chemical
AUDIT	the Alcohol Use Disorders Identification Test
CBT	cognitive behavioural therapy
CI	confidence interval
CDR	the Swedish Cause of Death Register
DAST	the Drug Abuse Screening Test
DDD	defined daily dose
DSM-5	the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUDIT	the Drug Use Disorders Identification Test
HR	hazard ratio
ICD-10	the International Statistical Classification of Diseases and Related Health Problems, 10th revision
IPR	the Swedish National Inpatient Register
K6	Kessler Scale-6
MANSA	the Manchester Short Assessment of Quality of Life
NBHW	the Swedish National Board of Health and Welfare
NIPH	the Swedish National Institute of Public Health
OMT	opioid maintenance treatment
OR	odds ratio
PDR	the Swedish Prescribed Drug Register
SPSS	Statistical Package for the Social Sciences
TPR	the Swedish Total Population Register
WHO	the World Health Organization

Introduction

Prescription sedatives are used in the treatment of anxiety and sleeping disorders and can often be of great benefit for the treated patient.[1-3] However, many prescription sedatives have a potential for misuse and dependence.[4-8] In addition to the risk of dependence, misuse of sedative drugs is associated with an increased risk of accidents, injuries[2], and overdoses. Furthermore, prolonged misuse of certain sedatives might lead to severe withdrawal effects, including seizures, after cessation.[2, 9-11]

Individuals with other substance use disorders are particularly sensitive to the addictive effects of prescription sedatives.[2, 12, 13] The combination of prescription sedatives and other substances with sedative effects, such as alcohol and opioids, is particularly harmful, with a high risk of fatal and non-fatal overdoses.

This thesis investigates use and misuse of prescription sedatives in the Swedish general population, as well as in individuals with opioid dependence, a subpopulation where sedative misuse is prevalent and associated with great health risks.[13-16] In the general population, the focus is on the association between prescription sedative misuse and subjective health and quality of life measures and in individuals with opioid dependence, the focus is on possible consequences of prescription sedative use and misuse on mortality and on treatment outcome in opioid maintenance treatment (OMT).

Definitions of sedative use and misuse

In this thesis, I have chosen to use the term sedatives as an umbrella term for drugs with sedating, hypnotic, and anxiolytic effects. The term sedatives, when used in this thesis, should thus be understood to include both actual sedatives (i.e. drugs with mainly sedating effects, caused by a decrease in agitation and arousal),[2, 17] hypnotics (i.e. drugs that induce drowsiness or sleep),[2, 17] and anxiolytics (i.e. drugs that decrease anxiety and tension, without affecting clarity of consciousness).[2, 17] The distinction between sedatives, hypnotics and anxiolytics is not always precise[18] and a specific drug, or class of drugs, can often have characteristics that belong to two, or even all three, of these groups. For examples,

most benzodiazepines have mainly anxiolytic effects when taken in low doses and more sedative effects when taken in higher doses,[17] whereas some benzodiazepines have mainly hypnotic effects.[2]

Sedative dependence and *harmful sedative use* can be defined in the same way as for other substances. In clinical practice the criteria of the World Health Organization's (WHO) International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10),[19] or the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[20] are usually used to define substance-related diagnoses. In the DSM-5, the term substance use disorder is instead used. This novel diagnosis was created from the collapsing of most of the DSM-IV criteria for substance dependence and abuse, respectively, which are similar to the combined criteria of dependence and harmful use in the ICD-10.

While the ICD-10 and the DSM-5 can thus be used to diagnose sedative dependence and sedative use that is harmful to the individual, the definitions used in these manuals do not encompass riskful or *problematic use* that has not yet led to dependence or obvious harm to the individual.

Defining such problematic use of prescription drugs, including prescription sedatives, is less straightforward than defining problematic use of, for example, illicit drugs or alcohol. With illicit drugs, all use can be considered problematic, because the illicit status itself of these drugs put users at risk of legal problems. Furthermore, because the production and distribution of these drugs is uncontrolled, users can never be certain of the actual content or dose of the drug they are consuming. When it comes to alcohol, there are several well-known and validated definitions of problematic use. For example, the Alcohol Use Disorders Identification Test (AUDIT) is a validated 10-item screening instrument for hazardous and harmful alcohol use, as well as possible dependence.[21] Other screening instruments, such as the Drug Use Disorders Identification Test (DUDIT)[22] and the Drug Abuse Screening Test (DAST)[23] have been developed for problematic drug use, but these instruments do not differentiate between different kinds of illicit and prescription drugs. There are thus no well-known specific screening instruments for problematic use of prescription drugs, and there is no consensus in the scientific literature as to how it should be defined.[24] While all use of prescription drugs that have been obtained illicitly can be considered problematic in the same way as other illicit drug use, there is more of a grey area when it comes to other behaviours, such as using a drug with a prescription, but in higher doses than prescribed, or for a different purpose (i.e. to 'get high'), or using a prescription drug that was obtained from a friend or a relative.

Several different terms are used in the scientific literature to describe problematic prescription drug use, including *abuse*, *misuse*, *recreational use*, and *non-medical*

use, with varying and often overlapping definitions.[18, 24] The term *misuse* is used throughout this thesis, defined as any use without a prescription, or use with a prescription but more frequently, in larger doses, for a longer duration, or for a different reason, than prescribed. The term misuse will also be used when referring to previous studies, but the definitions may vary between studies. In papers I and II of the present thesis, the term *non-medical use* was used, and defined as use without a prescription, or more frequently, or in larger doses, than prescribed by a doctor.

Common sedatives used in clinical practice

Benzodiazepines

Benzodiazepines are a group of drugs that potentiate the effects of the inhibitory neurotransmitter GABA.[2, 25] Several different types of benzodiazepines have been developed, with varying degrees of sedative, anxiolytic and hypnotic effects.[2, 25] The benzodiazepines were introduced in the 1960s as a safer alternative to barbiturates, and were initially believed to have a low dependence potential.[8] It has since then become clear that these drugs also have euphoric effects[25] and that they in fact have a high potential for misuse and dependence,[2, 4, 5] especially in individuals with other substance use disorders.[2, 12]

Z-drugs

The so-called z-drugs (e.g. zopiclone, zolpidem, zaleplone, and eszopiclone) are newer hypnotic drugs with agonist activity on GABA-receptors similar to benzodiazepines, but more selective hypnotic effects.[7, 25, 26] Initially introduced as safer alternatives to benzodiazepines, with a low dependence potential,[7] z-drugs have become the most commonly prescribed hypnotics in the world.[26] Z-drugs do however have a potential for both abuse and dependence, especially in individuals with substance use disorders.[7]

Other sedatives

Several non-scheduled prescription drugs are used in the treatment of anxiety and insomnia. The anticonvulsant drug pregabalin has been found to be effective in the treatment of general anxiety disorder[27] and has become one of the top ten most

prescribed drugs in the US.[28] While pregabalin is generally believed to have a low dependence potential,[29, 30] recent reports have described misuse of this drug. [31-33]

Some antihistamines, such as hydroxyzine[34] and promethazine[35] are used in the treatment of anxiety and sleeping disorders. Recently, misuse of promethazine has been reported in individuals with opioid dependence[36] as well as in other populations.[37]

Sedative use and misuse in the general population

Prevalence and sociodemographic characteristics

Sedatives are among the most commonly used classes of prescription drugs in many countries.[2] For example, in the United States, 6.1% of the adult population reported use of prescription sedatives in the past 30 days in 2011-2012. This was an increase from 4.2% in 1999-2000.[38]

In another survey, 2.3% of the US population aged 12 or older reported past-year sedative misuse in 2002-2004.[39] In this survey, sedative misuse was defined as use of a prescription sedative that 'was not prescribed for you or that you took only for the experience or feeling it caused'. The prevalence of sedative misuse in countries other than the United States has been insufficiently described.

In Sweden, sedatives are among the ten most prescribed drug classes,[40] and in 2014, 7.2% of the population were prescribed an anxiolytic drug (ATC-code N05B), and 10.4% of the population were prescribed a sedative-hypnotic (ATC-code N05C).[41] To the author's best knowledge, no previous survey has investigated sedative misuse in the Swedish general population before the 'Drug use in Sweden' study,[42] which papers I and II are based on.

Several previous studies from other countries[39, 43-46] have investigated the associations between sedative misuse and sociodemographic variables, such as age, sex, educational level, income and marriage status, but results have not been consistent between studies.

Motives for sedative misuse

Misuse of prescription drugs might be perceived as more attractive than misuse of illicit drugs, because it is perceived as safer and more socially acceptable.[18] Furthermore, prescription drugs are often easier to obtain than illicit drugs. In a US general population study,[47] more than half of individuals reporting non-medical

prescription drug use had received their drugs for free from a friend or a relative, and the second most common source was prescription from a doctor. Only 4.3% had obtained their drugs from a drug dealer or other stranger.

Two main types of motives for prescription drug misuse have been suggested in the scientific literature: recreational use and self-medication.[24, 48, 49] Of these, the self-medication motive seems to be more common.[24, 48, 49]

Prescription drug misuse as a method for self-medication is motivated by a desire to alleviate symptoms of health problems, often, but not always, in accordance with the medical indications of the specific drug.[18, 24]

Self-medication with prescription sedatives might consist of use in therapeutic doses of medications obtained from a friend or a relative. The problem with this type of misuse is that the treatment is not properly supervised and the individual is not getting proper evaluation of and treatment for his or her health problems, and might not get correct or sufficient information about possible contraindications or precautions for use of the drug. This might lead to a greater risk of harms, such as the development of dependence. The potential risks of this type of misuse are even higher if the individual does not have sufficient knowledge about appropriate dosing or interactions with other drugs.

Recreational use is motivated by a desire to achieve intoxicating effects,[24] i.e. to 'get high'. This type of prescription drug misuse is often associated with intake of other substances (e.g. alcohol and illicit drugs)[24, 48] and might also be associated with manipulation of the drug, for administration through other routes than intended, e.g. through snorting, inhalation, or injection.[24] For these reasons, recreational use might be associated with more health risks, including the risk of overdose, than prescription drug misuse motivated by self-medication.[24]

Sedative misuse and subjective health

In accordance with the self-medication theory described above, and as prescription sedatives are efficient for alleviating anxiety and sleeping problems,[2, 3] misuse of prescription sedatives might to a large part be explained by self-medication for underlying mental health problems. However, since some sedatives are also used in the treatment of pain and other physical health problems,[29] it is possible that some patients might also misuse prescription sedatives to self-medicate for physical health problems.

Previous general population studies have consistently found sedative misuse to be associated with psychiatric disorders,[39, 44, 45]as well as with other substance use, including alcohol use and alcohol use disorders,[39, 43-46] tobacco use,[39, 43] and illicit drug use.[39, 46] Two previous studies have also reported an association between

sedative misuse and poor self-assessed general health,[43, 46] whereas one study[39] found no such association. To the author's best knowledge, no previous studies have specifically reported on the association between sedative misuse and self-assessed mental and physical health.

Sedative misuse and quality of life

Quality of life is defined by the WHO as 'an individual's perception of their position in life in the context of culture and value systems in which they live and in relations to their goals, expectations, standards and concerns'.[50]

Measuring quality of life has been suggested to be of particular value in the field of substance use, because problematic substance use can have a negative effect on several life domains, including work, relationships, personal safety, and physical and mental health.[51]

Most studies on quality of life in the field of substance use have been focused on health-related quality of life.[51] While these studies have thus investigated the effects of health status on the individual's subjective perception of his or her physical, psychological and social functioning and well-being, health-related quality of life does not measure satisfaction with other life domains, such as work, relationships and economy. The present thesis is instead focused on overall quality of life, which is a measure of an individual's overall subjective well-being, including satisfaction with several domains of life in addition to physical and mental health.[50, 51]

Previous studies have investigated overall quality of life in individuals with alcohol dependence,[52] tobacco smoking,[53] and illicit drug use,[54-57] and have consistently reported an association between these different types of substance use and poor quality of life. To the author's best knowledge, no previous studies have investigated the specific association between sedative misuse and overall quality of life. However, combined use of benzodiazepines and alcohol has been found to be associated with poor overall quality of life,[57] and benzodiazepine dependence has been found to be associated with poor health-related quality of life.[58]

Sedative use and misuse in individuals with opioid dependence

An overview of opioid dependence and opioid maintenance treatment

Opioids are a class of drugs that bind to opioid receptors and can cause analgesia, euphoria, sedation and respiratory depression.[59] The term opiates refers to opioids that can be naturally extracted from the opium poppy, e.g. morphine and codeine (i.e. not synthetic opioids).[59] Sometimes, semisynthetic opioids, such as heroin and oxycodone, are also included in the term opiates.[60] In Swedish OMT regulations, however, the term opiates has come to be used for the three substances heroin opium and morphine.[61] In the present thesis, the term opiates will only be used when referring to Swedish OMT regulations and when referring to urine drug screens. As heroin is metabolized in the human body to morphine and thus not excreted in urine, morphine is instead the substance analysed in urine tests. When referring to urine drug screens, opiates thus include morphine, and drugs that are metabolized to morphine in the human body.[62, 63] This includes heroin, but not methadone or buprenorphine.[63]

Heroin and other opioids have a high potential for abuse and dependence.[64] Opioid dependence has been described as a chronic, relapsing disease[60, 64] and is associated with high rates of mortality, often caused by overdoses.[65, 66]

OMT is a medical treatment for opioid dependence, given with the full opioid receptor agonist methadone, the partial opioid receptor agonist buprenorphine, or the combination product buprenorphine-naloxone.[67] Buprenorphine-naloxone has been developed in order to decrease the risk of intravenous misuse of buprenorphine.[68] If the buprenorphine-naloxone tablet is crushed and injected, the opioid antagonist naloxone blocks the effects of buprenorphine, causing a withdrawal reaction.[68] OMT has been shown to reduce heroin use, as well as the risk of overdoses, criminality and mortality in individuals with opioid dependence.[67, 69-73]

OMT programs often include psychosocial interventions[74] and are usually offered within specialized units for the treatment of addictive disorders.[75] In many places, access to these programs is limited, resulting in long waiting times to enter treatment.[75-77] Interim treatment, i.e. a temporary phase of medication-only treatment before entering the full-scale OMT program, is one possible strategy aiming to reduce the time on waiting lists for OMT.

Opioid maintenance treatment in Sweden

In Sweden, OMT is highly regulated and may only be prescribed by licensed psychiatrists working in specialized psychiatric clinics.[61] To be eligible for OMT, patients must have a documented opiate dependence (defined as dependence on heroin, morphine or opium) of at least one year, be at least 20 years old (OMT may under special circumstances also be offered to patients aged 18-20), and must not have another ongoing dependence that constitutes an evident medical risk.[61] Patients are to be discharged from treatment if they are absent for more than seven consecutive days, repeatedly misuse narcotic drugs, use alcohol in a way that constitutes a medical risk, repeatedly manipulate urine samples, or are convicted of a drug-related crime.[61] Also, according to the regulations controlling Swedish OMT over the past decade, patients that are discharged from treatment are not allowed to enter another OMT program in Sweden for three months.[61] Despite these strict regulations, retention in Swedish OMT programs is high, at around 80% or more after one year.[78]

Prevalence

Polydrug use is seen in the vast majority of individuals with opioid dependence, and, aside from opioids, benzodiazepines are often reported as the most commonly misused drugs.[14, 15, 79, 80] In patients in OMT, prevalence rates of 46-71% have been reported for ongoing benzodiazepine use.[14, 15] Studies have reported that individuals with opioid dependence show a preference for certain benzodiazepines, notably flunitrazepam, diazepam, and alprazolam.[14] These drugs all have a rapid onset, which might give them a higher abuse liability.[15] Among individuals with opioid dependence, benzodiazepines are often used in extra-therapeutical doses[14] and manipulation of tablets for intravenous or nasal ingestion is common.[15]

Studies have also reported misuse of other prescription sedatives among individuals with opioid dependence. In an Irish study, zopiclone misuse was reported in 23% of patients in an OMT program.[81] Misuse of pregabalin has also been reported in 3-12% of individuals with opioid dependence.[13, 30, 32, 82] A recent study also reported misuse of the antihistamine promethazine in at least 11% of individuals in an OMT program.[36]

Motives for sedative misuse in individuals with opioid dependence

In addition to the self-medication and recreational use motives described above, sedatives are also misused by individuals with opioid dependence to enhance or complement the effects of opioids[15, 24] and to alleviate symptoms of opioid or other substance withdrawal.[15]

Sedative misuse and treatment outcome in opioid maintenance treatment

Previous studies have found that OMT patients who use or misuse benzodiazepines during treatment are more likely to also continue using opioids.[14, 15, 83-86] and other illicit drugs, [14, 15] report higher levels of mental health problems,[15] to have experienced overdoses,[14] and to be involved in criminal activities.[14] Despite this, most previous studies have found no association between benzodiazepine use and retention in OMT programs.[14, 15]

Sedative prescription and mortality in individuals with opioid dependence

Benzodiazepines potentiate the sedative and respiratory depressive effects of opioids, and can furthermore eliminate the ceiling effect of buprenorphine.[14] Benzodiazepine use is a known risk factor for overdose death in individuals with opioid dependence[14, 87, 88] and benzodiazepines have been identified in up to 80% or more of methadone- and buprenorphine-related deaths.[14, 15]

Despite the known increased risk of overdose with combined use of opioids and benzodiazepines, prescription of benzodiazepines seems to be common in individuals with opioid dependence. A Norwegian study reported that 40% of individuals in OMT had been prescribed benzodiazepines during the past year.[83] Benzodiazepine prescriptions were in this cohort eight times more common than in the general age-matched population. In an Australian study, 30% of a cohort of individuals with heroin dependence had been prescribed benzodiazepines in the past month.[89]

A few previous studies have investigated the relationship between benzodiazepine prescriptions and mortality. In a Canadian study, benzodiazepine prescription was associated with an increased risk of opioid-related death,[90] and in two Scottish studies, benzodiazepine prescription was associated with an increased risk of drug-related death.

Other sedative use might also increase the risk of mortality in individuals with opioid dependence. Z-drugs have central nervous depressant effects similar to benzodiazepines,[91] and might thus also potentiate the sedative and respiratory depressive effects of opioids. There is also some evidence that pregabalin might decrease respiration,[92] thus possibly also potentiating or adding to the respiratory depressive effects of opioids. To the author's best knowledge, neither the extent of z-drug and pregabalin prescriptions, nor the association between prescription of these drugs and mortality, has previously been reported in individuals with opioid dependence.

Aims

General aim of the thesis

In the present thesis, I aimed to investigate prescription sedative use and misuse in the Swedish general population and in individuals with opioid dependence. In the general population studies (papers I and II) the focus was on associations with subjective measures of health and quality of life, and in the studies on individuals with opioid dependence (papers III-V) the focus was on associations with treatment outcome in OMT and with mortality.

Study-specific aims

Paper I

This paper aimed to investigate socioeconomic, substance use, and subjective health correlates of past-year non-medical prescription sedative use, non-medical prescription analgesic use and combined non-medical prescription sedative and analgesic use. The main focus was on the subjective variables self-assessed physical and mental health. As prescription sedatives are mainly prescribed for psychiatric symptoms, it was hypothesized that non-medical prescription sedative use would be more strongly associated with poor self-assessed mental health than with poor self-assessed physical health.

Paper II

This paper aimed to investigate the association between different patterns of substance use, including non-medical prescription sedative use, and overall quality of life. While no previous studies have investigated the specific association between prescription sedative misuse and overall quality of life in the general population, based on previous research on other patterns of substance use,[52-58] it

was hypothesized that non-medical prescription sedative use would be associated with poor quality of life.

Paper III

The main aim of this pilot study was to evaluate the feasibility of buprenorphine interim treatment, i.e. a temporary medication-only treatment, as a method for facilitated entry into full-scale OMT in a setting with long waiting times to OMT at that time. It also aimed to investigate possible predictors, including benzodiazepine use, of treatment outcome (i.e. successful transfer from interim treatment to full-scale OMT, and opiate-free urine samples during interim treatment). Based on previous studies,[14, 15, 83-86] as well as the strict regulations regarding polydrug use in Swedish OMT programs, which also affected the design of the present study, it was hypothesized that benzodiazepine use would be negatively associated with both successful transfer to full-scale OMT and opiate-free urine samples during treatment.

Paper IV

This was a follow-up study to paper III, aiming to investigate possible predictors, including benzodiazepine use, of 9-month retention in treatment for patients successfully transferred from interim treatment to full-scale OMT. While previous studies have found no association between benzodiazepine use and retention in OMT, again, based on the strict regulations in Sweden regarding polydrug use during OMT, it was hypothesized that benzodiazepine use would be negatively associated with retention.

Paper V

This study aimed to investigate the associations between benzodiazepine, z-drug and pregabalin prescription and overdose and non-overdose mortality in individuals in OMT. Based on previous studies,[90, 93, 94] it was hypothesized that benzodiazepine prescription would be associated with an increased risk of overdose death. Furthermore, while no previous studies have investigated the associations between z-drug and pregabalin prescription and mortality among individuals in OMT, it was hypothesized, based on the assumption that both z-drugs and pregabalin might also potentiate the central nervous depressant effects of opioids,[91, 92, 95] that prescription of these drugs would also be associated with an increased risk of overdose death.

Materials and Methods

This thesis investigates sedative use and misuse in the general population and in individuals with opioid dependence. Papers I and II examine sedative misuse in the Swedish general population, with focus on associations with self-assessed health and quality of life, respectively. Both these studies are based on material from the 'Drug Use in Sweden' study,[42] a large national household survey on substance use. Papers III-V investigate sedative use and misuse in individuals with opioid dependence. Papers III and IV are based on data from the 'Interim Buprenorphine Study Lund' and specifically investigate the influence of sedative misuse on treatment outcome for patients in OMT. Paper V is based on a large register-based cohort study designed to investigate the association between sedative prescriptions and mortality for patients in OMT.

Study design, setting and participants

General population studies

Papers I and II

The 'Drug use in Sweden' study[42] was a collaboration between the Swedish National Institute of Public Health (NIPH) and Clinical Alcohol Research (principal investigator Mats Berglund), Lund University and was part of a larger project, the 'Prevalence Project', which aimed to investigate the epidemiology of illicit drug use in Sweden. The study was carried out through a national household survey that was distributed by mail between November 2008 and February 2009 to a sample of 57,683 individuals aged 15 through 64 randomly selected from the Swedish Total Population Register (TPR). The TPR includes all individuals with permanent residence in Sweden. A stratification process was used, in which sociodemographic groups with an assumed higher probability of illicit drug use (e.g. younger individuals, males, individuals residing in a larger city) were oversampled. Statistics Sweden, the national agency for population statistics, created statistic weights adjusting for the stratification as well as for non-response. Statistics Sweden also processed the returned questionnaires and completed them

with register data. The survey was answered by 22,095 individuals, creating a response rate of 38.3% (n=22,095). The weighted response rate was 52.1%.

Studies on individuals with opioid dependence

Papers III and IV

These papers are based on the pilot study 'Interim Buprenorphine Study Lund'. This was an effectiveness cohort study, with the main aim to evaluate the feasibility of interim treatment with buprenorphine-naloxone as a method to facilitate entry into full-scale OMT. The study also aimed to investigate potential predictors, including benzodiazepine use, of treatment outcome (i.e. successful transfer from the interim condition to full-scale OMT, opiate-free urine samples during treatment, and 9-month retention).

The study was conducted at the out-patient facility for opioid maintenance treatment (the 'methadone clinic') at the Department of Psychiatry, Lund, Skåne Region, Sweden, and started in the spring of 2011. All patients on the waiting list for full-scale OMT at the clinic were offered inclusion in the study. The patients on the waiting list all fulfilled the criteria to receive OMT according to Swedish regulations, i.e. at least 20 years old, with a documented dependence on opiates (defined as heroin, morphine or opium) of at least one year, absence of any other substance dependence that constitutes an obvious medical risk, and not discharged from another OMT program during the past three months.[61] Exclusion criteria were major psychiatric disorder (acute psychotic disorder, active suicidality or imminent risk of self-harm), inability to understand and provide informed consent, inability to adhere to the interim treatment schedule, and pregnancy or lactation. Patients were furthermore not eligible for study participation if the treating physician considered maintenance treatment with methadone to be necessary (e.g. due to primary methadone dependence or previous treatment failures with buprenorphine). In the original pilot study (paper III), 44 patients were included, and in the follow-up study (paper IV), 36 patients were included.

During interim treatment, all patients received out-patient treatment with buprenorphine-naloxone. Dosage was individual, with a maximum dose of 24mg/6mg per day. Doses were administered at the clinic under supervision by a nurse, and were given on a daily basis on weekdays, with triple dosing on Fridays, for the dose to last over the weekend.[96, 97] Patients were not allowed to take home doses. Unannounced urine samples were collected weekly and analysed for amphetamine, cocaine, cannabis, benzodiazepines, opiates, methadone and buprenorphine.

Patients in interim treatment were consecutively offered transfer to the full-scale OMT program as soon as treatment slots became available. To enter the full-scale program, patients had to provide a drug-free urine sample within three weeks of being offered to transfer. Patients who continued to use drugs after being offered to transfer were discharged from the program.

In accordance with Swedish OMT regulations, patients were also discharged if they failed to attend the clinic for more than seven consecutive days, repeatedly manipulated urine samples, or misused alcohol or illicit drugs in a way that presented an evident medical risk.[61]

Paper V

This was a register-based open cohort study designed to investigate the association between benzodiazepine, z-drug, and pregabalin prescriptions and mortality in individuals in OMT. The study utilized data from three Swedish national health registers administered by the Swedish National Board of Health and Welfare (NBHW): 1) The Prescribed Drug Register (PDR), a prescription database that contains information on all personally prescribed drugs dispensed at Swedish pharmacies, starting from July 1, 2005, 2) The Cause of Death Register (CDR), which contains data on date of death and underlying and contributory causes of death (ICD-10 codes) for all known deaths among Swedish residents, 3) The National Inpatient Register (IPR), which contains data on patients treated at Swedish hospitals, including date of admission and discharge, and main and secondary diagnoses (ICD-10 codes). The IPR has an estimated coverage of over 99%.[98] Linkage of data from the different registers was made by the NBHW using the personal identity numbers given to all Swedish residents.

The study population was defined through the PDR and included all Swedish residents who were personally prescribed and dispensed methadone or buprenorphine (including buprenorphine-naloxone) as OMT between July 1, 2005 and December 31, 2012. To exclude individuals who might have been prescribed methadone or buprenorphine for pain or other non-OMT indications, several measures were taken: 1) Only data on methadone and buprenorphine formulations considered by the NBHW to be indicated for OMT were extracted from the PDR. 2) Only prescriptions issued by a psychiatrist working at a psychiatric clinic were included in the analyses. 3) All individuals with at least one prescription with a clear pain indication were excluded. 4) All prescriptions issued through the ApoDos, a multi-dose medication dispensing system, were excluded. 5) Only individuals aged 18 to 50 at the time of first methadone or buprenorphine prescription during the observation time were included. After these exclusions, the final sample included 4,501 individuals.

Measurements

TABLE 1. Summary of outcome measures and independent variables.

	Paper I	Paper II	Paper III	Paper IV	Paper V
Type of study population	General population	General population	Opioid-dependent patients seeking opioid maintenance treatment (OMT)	Opioid-dependent patients referred to OMT through interim buprenorphine treatment	Opioid-dependent patients who are, or have been in, OMT
Outcome measure	Prescription sedative misuse or combined prescription sedative and analgesic misuse	Poor quality of life	Entry into OMT through medication-only interim buprenorphine treatment. Opiate-free urine samples in interim treatment.	9-month treatment retention	Overdose and non-overdose mortality
Independent variables of main interest	Self-assessed mental and physical health	Prescription sedative misuse	Use of benzodiazepines in the 30 days prior to interim treatment entry	Urine samples positive for benzodiazepines in interim treatment and in full-scale OMT	Benzodiazepine, z-drug, and pregabalin, prescriptions
Other independent variables	Age, sex,country of birth, urbanicity, educational level, marital status, social welfare, hazardous alcohol use, habitual smoking, cannabis use, other illicit drug use	Age, sex,country of birth, urbanicity, educational level, marital status, social welfare,, prescription analgesic misuse, hazardous alcohol use, smoking, illicit drug use	Age, sex, marriage status, somatic treatment, psychiatric treatment, overdose history, time on waiting list, AUDIT score, past-30-day substance use prior to treatment entry,	Age, sex,country of birth, overdose history, suicide attempt, time in interim treatment, AUDIT score, past-30-day substance use prior to treatment entry, interim-phase urine analyses, OMT-phase urine analyses	Age, sex, non-fatal overdose, suicide attempt, psychiatric treatment, OMT status.

General population studies

Papers I and II

The outcome variables of paper I were past-year *non-medical prescription sedative use* (without any past-year non-medical prescription opioid use), past-year *non-medical prescription analgesic use* (without any past-year non-medical prescription sedative use), and past-year *combined non-medical prescription*

sedative and analgesic use. These variables were created from an item in the questionnaire asking study participants about whether they had ever used any of a number of listed substances without a doctor's prescription. For prescription sedatives and analgesics, information was given that use without a doctor's prescription also included taking more of the substance, or taking it more often, than prescribed. Prescription sedatives were described as 'prescription sleeping agent or tranquilizing agent' and the brand names 'Rohypnol' (flunitrazepam), 'Stesolid' (diazepam) and 'Stilnoct' (zolpidem) were given as examples. Prescription analgesics were described as 'prescription analgesic agent' and the brand names 'Treo Comp' (acetylsalicylic acid and codeine) and 'Citodon' (paracetamol and codeine) were given as examples. The possible answers for each substance class were: 'No', 'Yes, during the past 30 days', 'Yes, during the past 12 months' and 'Yes, at least once in my life'. The outcome variables were created by categorizing the participants into four groups: individuals who reported past-year non-medical use of prescription sedatives (but not analgesics), individuals who reported past-year non-medical use of prescription analgesics (but not sedatives), individuals who reported past-year non-medical use of both sedatives and analgesics, and individuals who reported no past-year non-medical prescription drug use. The main focus of the thesis is on the two variables describing non-medical prescription sedative use.

In paper I, several independent variables were included in the analyses as potential correlates of non-medical prescription sedative use, non-medical prescription analgesic use and combined non-medical use of both prescription sedatives and analgesics, but the main independent variables of interest were *self-assessed physical and mental health*. These variables were derived from two items asking study participants for how many of the past 30 days their physical and mental health, respectively, had been poor. The variables were created by categorizing the answers into four groups: 0, 1-10, 11-20 and 21-30 days.

In paper II, the outcome variable was *poor quality of life*. This variable was measured using a modified version of the Manchester Short Assessment of Quality of Life (MANSA). The MANSA is an instrument designed to measure overall quality of life, i.e. an individual's subjective perception of his or her well-being and satisfaction with life.[99] The full-version MANSA contains 12 items asking about satisfaction with life as a whole, work, financial situation, friendships, leisure activities, accommodation, personal safety, people that one lives with, sex life, family relationships, and physical and mental health. Respondents are asked to rate their satisfaction on each of these 12 questions on a seven-point scale, where 1 = 'couldn't be worse' and 7 = 'couldn't be better'. In the questionnaire used in present study, the items asking about satisfaction with life as a whole and satisfaction with one's sex life were excluded, and thus, only 10 MANSA items were included. We created a measure of overall quality of life as the mean value of

the ratings on these 10 questions for each individual. As the item non-response was high on three of the items (ranging from 2.6-33.4% for all 10 items) and only 60.9% (n=13,464) of participants answered all 10 items, we included all participants who had answered at least five of the items (89.2%, n=19,706) in the analyses. For individuals with incomplete data, missing values were substituted with the mean score of the available items. *Poor quality of life* was defined as having an overall quality of life score in the lowest quartile of the material, and individuals with poor quality of life were then compared to the individuals in the other quartiles. This resulted in poor quality of life representing mean values below 4.8 on the modified MANSA score.

In paper II, *past-year non-medical prescription sedative use* (including non-medical sedative use with and without non-medical analgesic use) was one of the main independent variables included as potential correlates of poor quality of life, as was *past-year non-medical prescription analgesic use* (including non-medical analgesic use with and without non-medical sedative use). These variables were created in a similar manner as in paper I. The main focus will be on the variable *past-year non-medical prescription sedative use*.

In both paper I and II, four other types of substance use were assessed as possible correlates of non-medical prescription drug use and poor quality of life, respectively: *hazardous alcohol use*, *habitual smoking*, *cannabis use*, and *other illicit drug use*. *Hazardous alcohol use* was measured with the AUDIT, which was included in the questionnaire. We used a cut-off score of six or more for women and eight or more for men to define hazardous alcohol use.[100] *Habitual smoking* was derived from an item in the questionnaire asking participants whether they smoked daily or not, and thus, it was defined as current daily smoking. *Cannabis use* and *other illicit drug use* were derived from the item described above assessing participants' drug use. In addition to prescription sedatives, and prescription analgesics, the included substances were cannabis (hashish, marijuana or cannabis oil), amphetamine (including methamphetamine and phenmetrazine), cocaine (crack, powder or coca leaves), opiates (heroin, opium or morphine), ecstasy (MDMA, MDA or MDE) and hallucinogens (LSD, mescaline, peyote, PCP, hallucinogenic mushrooms and DMT). *Cannabis use* was defined as any past-year use of this substance, and *other illicit drug use* described any past-year use of amphetamine, cocaine, opiates, ecstasy or hallucinogens.

The main analyses of both paper I and II also included all variables used in the stratification process. These were: *age* (categorized into three age groups: 15-29, 30-44 and 45 years and above), *sex*, *country of birth* (being born in a Nordic country versus not), *urbanicity* (living in any of Sweden's three largest cities, i.e. Stockholm, Gothenburg, or Malmo, versus not), *educational level* (above high school level versus not), *marital status* (categorized into three groups: married,

unmarried but living with one's partner, and not married or living with one's partner), and *social welfare status* (being a social welfare recipient versus not). The variables *age*, *sex*, *urbanicity*, and *social welfare status* were based on register data, while the variables *country of birth*, *educational level* and *marital status* were based on items in the questionnaire.

In paper II, additional independent variables assumed to influence quality of life were included in the analyses as potential confounders: *income level* (above median vs not), *employment status* (receiving unemployment funding versus not), and *disability status* (receiving disability pension versus not). These variables were based on register data.

Studies on individuals with opioid dependence

Papers III and IV

The outcome variables of paper III were *successful transfer* from the interim condition to full-scale OMT and *opiate-free urine samples* throughout the interim phase. In paper IV, which was a follow-up study, the outcome measure was *9-month retention* in OMT (including both time in the interim condition and in the full-scale OMT program).

In both these papers, several variables, including benzodiazepine use, were assessed as potential predictors of successful transfer to full-scale OMT, opiate-free urine samples during treatment, and 9-month retention. *Benzodiazepine use before treatment* was assessed as a potential predictor in both papers. This variable was measured as the self-reported number of days with benzodiazepine use in the 30 days prior to inclusion.

Additionally, in paper IV, *benzodiazepine use during the interim phase* and *benzodiazepine use during full-scale OMT*, both assessed through urine samples, were analysed as potential predictors of nine-month retention in OMT.

Paper V

The main outcome event of this study was *overdose death* and secondary outcome events were *non-overdose death,* and *all-cause mortality*. These outcome events were defined by the ICD-10 codes registered as the underlying cause of death in the CDR. *Overdose death* was defined as all deaths with ICD-10 codes X40-49 (accidental overdoses) or Y10-19 (overdoses with undetermined intent) registered as the underlying cause of death.[101-103] *Non-overdose death* was defined as all other deaths, including deaths with ICD-10 codes X60-69 (intentional overdoses) registered as the underlying cause of death. *All-cause mortality* included all deaths, i.e. both overdose and non-overdose cases.

The main predictors were *benzodiazepine, z-drug, and pregabalin prescriptions*, defined by ATC-codes[104] in the PDR. Prescriptions of all benzodiazepines registered for use in Sweden were included, i.e. diazepam, oxazepam, lorazepam, alprazolam, nitrazepam, flunitrazepam, triazolam, midazolam, and clonazepam. Likewise, all z-drugs registered for use in Sweden were included, i.e. zopiclone, zolpidem, and zaleplone. *Benzodiazepine, z-drug, and pregabalin prescriptions* were treated as time-dependent variables in the analyses. In contrast to time-independent variables, where values remain unchanged throughout the observation time, the values of time-dependent variables may change once or several times during the observation time for each study participant.[105] The main predictors of the present study could switch between the two states *in treatment* and *not in treatment* several times during the observation time. We used the defined daily dose (DDD, i.e. the assumed average maintenance dose per day for a drug for its main indication in adults)[106] of each drug to define the treatment periods. The total amount of the drug administered at each prescription dispensation was divided by the DDD, yielding the number of days that the prescription was assumed to last.

Several potential confounders were included in the analyses: *sex*, *age*, *previous non-fatal overdose*, *previous psychiatric in-patient treatment*, *previous suicide attempt*, and *OMT status*.

Sex and *age* were obtained from the PDR. Age was treated as a time-independent, continuous variable and was measured at the time of first methadone or buprenorphine prescription during the study period.

The variables *previous non-fatal overdose*, *previous psychiatric in-patient treatment* and *previous suicide attempt* were constructed using data from the IPR. Previous non-fatal overdose was defined as any in-patient treatment during the study period with accidental overdose (ICD-10 codes X40-49) or overdose with undetermined intent (ICD codes Y10-19) as the main diagnosis. Previous psychiatric in-patient treatment was defined as any in-patient treatment during the study period with a non-organic psychiatric diagnosis other than a substance use disorder as the main diagnosis (ICD codes F20-99). Previous suicide attempt was defined as any in-patient treatment during the study period with intentional self-harm, including intentional non-fatal overdoses (ICD codes X60-84), as the main diagnosis. These three variables were treated as time-dependent, but the value could change only once (if an event occurred).

OMT status was treated as a time-dependent variable, in the same way as the main predictor variables. The treatment periods for OMT were defined as lasting for 90 days following dispensation of a methadone or buprenorphine prescription. If a new prescription was dispensed within 90 days from the last, the period of treatment continued for another 90 days from the new dispensation.

Statistical analyses

General population studies

Papers I and II

In paper I, the aim was to identify independent correlates of non-medical prescription drug use, and several potential correlates were analysed in the same models. In paper II, the aim was to investigate the relationship between non-medical prescription sedative use, as well as other types of substance use, and quality of life, while controlling for several potential confounders. In both these studies, we therefore used multivariate statistics for the main analyses. Specifically, we used logistic regression analyses, because the dependent variables (i.e. the outcome variables) were categorical. The logistic regression analyses were performed with unweighted data, with all the stratification variables included as independent variables. In both papers, hierarchical logistic regression models were created, where the independent variables (i.e. the potential correlates) were entered in steps. In paper I, only sociodemographic variables were entered in the first logistic regression model, and in the second model, the substance use and self-assessed health variables were added. In paper II, the substance use variables were entered in the first model, and in the second model, the potential confounders were added. In both papers, individuals with missing data on any of the variables included in each model were excluded from the analyses.

The item non-response was low for all of the independent variables, ranging from 0% to 3.6%.

P-values of <0.05 were considered statistically significant, corresponding to 95% confidence intervals (CIs) for the odds ratios (ORs). All analyses were performed in IBM Statistical Package for the Social Sciences (SPSS), version 20 (paper I) and version 21 (paper II).[107]

Studies on individuals with opioid dependence

Papers III and IV

The associations between the benzodiazepine variables and treatment outcome were in these papers only assessed in bivariate analyses. The continuous variable *benzodiazepine use before treatment* was assessed in both papers. In paper III, the mean number of days of benzodiazepine use within the past 30 days was analysed, using the Student's t-test. In paper IV, the total percentage of individuals who had used benzodiazepines in the 30 days prior to inclusion was instead analysed, using

the Chi-square test. When groups were too small for the chi-square test (n<5), Fisher's exact test was instead used. *Benzodiazepine use during the interim phase* and *during full-scale OMT* were analysed as the median percent of positive samples, using the Mann-Whitney U-test.

P-values of <0.05 were considered statistically significant and p-values between 0.05 and 0.10 were considered to indicate a statistical trend. All analyses were performed in IBM SPSS for Mac, version 20 (paper III) and version 22 (paper IV).[107]

Paper V

This paper aimed to investigate the effect of benzodiazepine, z-drug, and pregabalin prescription on mortality among individuals in OMT, while controlling for several potential confounders. For the main analyses, Cox regression models were used. These analyses are similar to logistic regression analyses, but are used to analyse survival, or time-to-event, including a time variable defining the time to the event or until data are censored.[105] In the main analyses, we examined the associations between benzodiazepine, z-drug, and pregabalin prescriptions, and overdose death, non-overdose death and all-cause mortality. We performed both unadjusted (i.e. including only one independent variable at the time) and adjusted (i.e. including all predictors and confounders) analyses. Individuals with missing data on date of death in the CDR were excluded from all analyses.

In a set of secondary analyses we restricted the data to periods in which patients were currently in OMT. The OMT variable was naturally excluded from these analyses.

We also performed sensitivity analyses, where the treatment period for OMT was defined as lasting 30 days from the last prescription dispensation (as compared to 90 days in the main analyses).

P-values of <0.05 were considered statistically significant, corresponding to 95% confidence intervals (CIs) for the hazard ratios (HRs). All analyses were performed in R version 3.1.3.[108, 109]

Ethical considerations

All studies were approved by the Regional Ethics Committee of Lund, Sweden (file number 2008/221 for papers I-II, file number 2010/596 for papers III-IV, and file number 2013/324 for paper V).

General population studies

Papers I and II

In the 'Drug use in Sweden' study, participants were given written information that the survey was voluntary and anonymous. As answering questions on substance use might awaken concern about one's lifestyle habits and health, participants were also provided information on where to turn for information about and treatment for substance use problems. Informed consent to collection of register data was acquired. The questionnaires were de-identified by Statistics Sweden before data processing. Because all data was de-identified, the risk of harm for the study persons is assumed to be very low.

Studies on individuals with opioid dependence

Papers III and IV

All patients included in the 'Interim Buprenorphine Study Lund' were given oral and written information about the study, including information that the study was voluntary and anonymous, and gave written informed consent to study participation. The collection of data is not considered to infringe on the integrity of the patients to a greater extent than a normal clinical pre-treatment investigation. The advantages of participation for patients (i.e. prompt access to evidence-based medical treatment instead of long waiting times to full-scale OMT) must be considered to outweigh the risks of harm (i.e. the infringement on patients' integrity).

Because of the high rates of mortality and other severe medical complications in out-of-treatment illicit opioid users,[66, 110, 111] an effectiveness design was used, rather than a controlled design with an untreated group. Discharge from treatment, while also potentially ethically problematic given the high risk for mortality and other complications for untreated individuals, was handled in accordance with Swedish regulations for OMT.

Paper V

This was a register-based study and all data were de-identified by the NBHW before delivery to the research group. The use of de-identified register data makes the risk of harm for the study persons very low.

Results

General population studies

The weighted prevalence of past-year non-medical prescription sedative use in the Swedish general population aged 15 through 64 was 2.2%. This translates into approximately 133,500 individuals.

Paper I

In the final logistic regression model, non-medical prescription sedative use was associated with female sex, living in a larger city, being a social welfare recipient, hazardous alcohol use, habitual smoking, cannabis use, other illicit drug use, and poor self-assessed mental health. (Table 2) The strongest correlates of non-medical prescription sedative use were other illicit drug use (AOR: 6.16, 95% CI: 4.50-8.42) and poor self-assessed mental health (AOR: 6.31, 95% CI: 4.42-8.99, for 21-30 days compared to 0 days of poor mental health during the past 30 days). There was a pattern of increasing AORs for each step of more days with poor self-assessed mental health.

Combined non-medical prescription sedative and analgesic use was in the final logistic regression model significantly associated with older age, female sex, being a social welfare recipient, hazardous alcohol use, habitual smoking, cannabis use, other illicit drug use, and poor self-assessed physical as well as mental health. Other illicit drug use had by far the strongest association (AOR: 14.28, 95% CI: 10.33-19.73). For both self-assessed physical and mental health, a pattern of increasing AORs with each step of more reported days with poor health was seen.

TABLE 2. Factors associated with past-year non-medical prescription sedative use and past-year combined non-medical prescription sedative and analgesic use.

Selected characteristics	Sedatives only (n = 426) AOR (95% CI)	Combined use (n = 360) AOR (95% CI)
Age in years		
15-29 vs 45 or older	0.76 (0.39-1.47)	**0.41 (0.23-0.71)***
30-44 vs 45 or older	1.39 (0.72-2.67)	0.66 (0.38-1.15)
Sex		
Male vs female	**0.56 (0.45-0.71)***	**0.55 (0.42-0.72)***
Country of birth		
Nordic country vs other	1.22 (0.83-1.80)	1.14 (0.74-1.78)
Urbanicity		
Larger city vs other	**1.27 (1.03-1.57)***	0.99 (0.78-1.25)
Educational level		
Above high school vs not	0.95 (0.76-1.18)	0.87 (0.67-1.13)
Social welfare status		
Social welfare recipient vs not	**1.81 (1.40-2.33)***	**1.69 (1.28-2.24)***
Marital status		
Married vs other	0.88 (0.31-2.46)	1.00 (0.33-2.99)
Living with partner vs other	1.00 (0.81-1.25)	0.94 (0.72-1.21)
Hazardous alcohol use		
Yes vs no	**1.72 (1.38-2.14)***	**1.80 (1.39-2.33)***
Habitual smoking		
Yes vs no	**1.41 (1.11-1.79)***	**1.87 (1.45-2.42)***
Cannabis use		
Yes vs no	**2.64 (1.97-3.55)***	**3.13 (2.26-4.34)***
Other illicit substance use		
Yes vs no	**6.16 (4.50-8.42)***	**14.28 (10.33-19.73)***
Days with poor physical health		
1-10 vs 0	1.24 (0.99-1.56)	**1.43 (1.07-1.91)***
11-20 vs 0	1.34 (0.88-2.03)	**2.98 (1.93-4.60)***
21-30 vs 0	1.27 (0.85-1.89)	**3.74 (2.53-5.52)***
Days with poor mental health		
1-10 vs 0	**2.27 (1.70-3.03)***	**1.54 (1.09-2.17)***
11-20 vs 0	**3.89 (2.71-5.60)***	**3.01 (1.99-4.58)***
21-30 vs 0	**6.31 (4.42-8.99)***	**5.17 (3.48-7.66)***

Clients included in analysis: 19,436

* p= <0.05

Abrahamsson T, Hakansson A. Nonmedical Prescription Drug Use (NMPDU) in the Swedish General Population - Correlates of Analgesic and Sedative Use. Subst Use Misuse. 2015 Jan;50(2):148-55.

Paper II

In the first logistic regression model, where only substance use variables were entered, there was a significant association between non-medical prescription sedative use and poor quality of life (OR: 2.97, 95% CI: 2.51-3.52), and this association was significantly stronger than for any of the other substance use predictors (non-medical prescription analgesic use, cannabis use, other illicit drug

use, hazardous alcohol use, and habitual smoking). (Table 3) In the second logistic regression model, where sociodemographic variables were also included, non-medical prescription sedative use was still significantly associated with poor quality of life, and although this association was somewhat weakened, non-medical prescription sedative use remained the strongest substance use predictor of poor quality of life (AOR: 2.11, 95% CI: 1.76-2.54).

TABLE 3. Substance use and sociodemographic factors associated with poor quality of life (MANSA lowest quartile).

Selected characteristics	**Model 1** AOR (95% CI)	**Model 2** AOR (95% CI)
Non-medical prescription analgesic use		
Yes vs no	**1.49 (1.28-1.74)***	**1.39 (1.18-1.64)***
Non-medical prescription sedative use		
Yes vs no	**2.97 (2.51-3.52)***	**2.11 (1.76-2.54)***
Cannabis use		
Yes vs no	1.03 (0.89-1.19)	1.11 (0.95-1.30)
Other illicit drug use		
Yes vs no	0.98 (0.80-1.19)	0.93 (0.76-2.54)
Hazardous alcohol use		
Yes vs no	**1.23 (1.14-1.33)***	**1.45 (1.33-1.57)***
Habitual smoking (vs not)		
Yes vs no	**2.21 (2.01-2.43)***	**1.45 (1.31-1.61)***
Age in years		
15-29 vs 45 or older		0.81 (0.65-1.02)
30-44 vs 45 or older		**1.29 (1.04-1.61)***
Sex		
Female vs male		**1.71 (1.58-1.56)***
Country of birth		
Nordic country vs other		**0.67 (0.60-0.75)***
Urbanicity		
Larger city vs other		1.01 (0.94-1.09)
Educational level		
Above high school vs not		**0.87 (0.80-0.94)***
Marital status		
Married vs other		**0.34 (0.24-0.49)***
Living with partner vs other		**0.56 (0.51-0.61)***
Income level		
Above median vs not		**0.58 (0.52-0.64)***
Employment status		
Receiving unemployment funding vs not		**1.38 (1.21-1.58)***
Disability status		
Receiving disability pension vs not		**2.92 (2.43-3.51)***
Social welfare status		
Receiving social welfare vs not		**2.36 (2.11-2.63)***
Cases included in the analysis	18,343	18,034

* p= <0.05

Abrahamsson T, Berglund M, Hakansson A. Non-Medical Prescription Drug Use (NMPDU) and Poor Quality of Life in the Swedish General Population. Am J Addict. 2015 Apr;24(3):271-7.

Studies on individuals with opioid dependence

Paper III

Of the 44 patients included in the study, 11% (n=5) were women. The mean age was 35 years (range 20-55 years).

Aside from opiates, benzodiazepines were the most commonly used drugs, both before and during interim treatment. Benzodiazepine use in the 30 days prior to treatment start was reported by 77% (n=34) of patients (including patients with prescriptions for benzodiazepines), with a mean of 10.8 days of use (for all patients) during this time period. During the interim treatment period, 75% (n=33) of patients had at least one urine sample positive for benzodiazepines (excluding four patients who had a prescription for a benzodiazepine during the treatment period).

Of the 44 patients included in the study, 57% (n=25) were successfully transferred from interim treatment to full-scale OMT. Benzodiazepine use before treatment start was neither associated with successful transfer to full-scale OMT (Table 4), nor with opiate-free urine samples during interim treatment. (Table 5) In conclusion, benzodiazepine use was common in this study, both before and during interim treatment, but there were no significant associations between benzodiazepine use before treatment start and treatment outcome.

TABLE 4. Baseline variables potentially associated with successful transfer to full-scale OMT.

	Successful transfer (n=25)	Drop-outs (n=19)
Age (years, mean)	34.5	36.1
Male sex (%)	84	95
Married/living with partner (%)	8	21
Somatic in-patient treatment, past three months (%)	12	11
Psychiatric in-patient treatment, ever (%)	20	32
Overdose, ever (%)	60	68
Time on waiting list (days, mean)	186	219
AUDIT score (mean)	4.4	12.6***
Illicit substance use, past 30 days		
Heroin (days, mean)	7.2	9.9*
Methadone (days, mean)	3.7	3.0
Buprenorphine (days, mean)	12.3	8.6
Buprenorphine-naloxone (days, mean)	1.3	2.2
Amphetamine (days, mean)	1.0	0.6
Cocaine (days, mean)	0.2	0.2
Cannabis (days, mean)	5.2	10.4*
Benzodiazepines (days, mean)	11.4	9.9

*p<0.10,

***p<0.001

Abrahamsson T, Widinghoff C, Lilliebladh A, Gedeon C, Nilvall K, Hakansson A. Interim Buprenorphine Treatment in Opiate Dependence – a Pilot Effectiveness Study. Subst Abus. 2015 Jul 15:0.

TABLE 5. Baseline variables potentially associated with opiate-free urinalyses in interim treatment.

	Opiate-free (n=19)	Opiate positive (n=25)
Age (years, mean)	34.9	35.4
Male sex (%)	84	92
Married/living with partner (%)	21	8
Somatic in-patient treatment, past three months (%)	16	8
Psychiatric in-patient treatment, ever (%)	37	16
Overdose, ever (%)	79	52*
Time on waiting list (days, mean)	170	223
AUDIT score (mean)	10.8	5.8
Illicit substance use, past 30 days		
Heroin (days, mean)	4.5	11.3**
Methadone (days, mean)	4.5	2.6
Buprenorphine (days, mean)	14.2	8.0*
Buprenorphine-naloxone (days, mean)	1.8	1.6
Amphetamine (days, mean)	1.2	0.6
Cocaine (days, mean)	0.1	0.3
Cannabis (days, mean)	5.9	8.6
Benzodiazepines (days, mean)	9.6	11.6

*p<0.10

**p<0.05

Abrahamsson T, Widinghoff C, Lilliebladh A, Gedeon C, Nilvall K, Hakansson A. Interim Buprenorphine Treatment in Opiate Dependence – a Pilot Effectiveness Study. Subst Abus. 2015 Jul 15:0.

Paper IV

Of the 36 patients included in the study, 11% (n=4) were women. The median age was 33 years (range 20-52 years).

In this study, benzodiazepine use during the 30 days prior to interim treatment was reported by 69% (n=25) of patients, with a median of 4 days of use. The median of urine tests positive for benzodiazepines during the interim period was 33%, (including two patients with a prescription for a benzodiazepine during treatment), and the median of tests positive for benzodiazepines during full-scale OMT was 6%.

The nine-month retention rate was high, at 83% (n=30). Of the variables assessed as potential predictors of treatment retention, the only significant result was for benzodiazepine use during full-scale OMT, which negatively predicted retention. Benzodiazepine use during the interim phase also tended to negatively predict retention in OMT. Benzodiazepine use during the 30 days prior to inclusion did not predict retention. (Table 6)

TABLE 6. Characteristics of subjects with and without 9-month retention in OMT after transition from buprenorphine interim phase.

	Total	Retention > 9 months	Retention < 9 months	p
No. of patients	36	30	6	
Age, median (IQR)	33 (29-42)	32 (29-42)	35 (30-50)	0.419
Male sex, % (n)	89 % (32)	90 % (27)	83 % (5)	0.635
Born in Sweden, % (n)	86 % (31)	83 % (25)	100 % (6)	0.281
Previous overdose, % (n)	69 % (24)	66 % (19)	83 % (5)	0.392
Previous suicide attempt, % (n)	31 % (11)	31 % (9)	33 % (2)	0.912
Days spent in the interim phase, median (IQR)	35 (24-50)	35 (25-50)	31 (20-55)	0.756
AUDIT score, median (IQR)	5 (1-10)	5 (1-11)	4 (1-14)	0.881
Substance use in the past 30 days, % (n)				
Heroin	72 % (26)	70 % (21)	83 % (5)	0.506
Methadone	53 % (19)	50 % (15)	67 % (4)	0.455
Buprenorphine	75 % (27)	77 % (23)	67 % (4)	0.606
Buprenorphine-naloxone	25 % (9)	27 % (8)	17 % (1)	0.606
Benzodiazepines	69 % (25)	67 % (20)	83 % (5)	0.418
Cannabis	53 % (19)	53 % (16)	50 % (3)	0.881
Amphetamine	36 % (13)	27 % (11)	33 % (2)	0.877
Cocaine	6 % (2)	7 % (2)	0 % (0)	0.515
Percent positive urine samples in IT, median (IQR)				
Opiates	0 (0-23)	0 (0-17)	13 (0-57)	0.393
Benzodiazepines	33 (0-59)	27 (0-56)	60 (19-93)	0.087
Cannabis	6 (0-69)	18 (0-70)	0 (0-37)	0.297
Amphetamine	0 (0-6)	0 (0-9)	0 (0-4)	0.577
Cocaine	0 (0-0)	0 (0-0)	-	0.239
Percent positive urine samples in full-scale OMT, median (IQR)				
Opiates	1 (0-4)	1 (0-4)	2 (0-10)	0.930
Benzodiazepines	6 (2-20)	4 (2-16)	23 (13-43)	0.006
Cannabis	4 (0-20)	4 (0-16)	11 (0-28)	0.965
Amphetamine	1 (0-5)	1 (0-5)	1 (0-13)	0.894
Cocaine	0 (0-1)	0 (0-0)	1 (0-4)	0.105

Hakansson A, Widinghoff C, Abrahamsson T, Gedeon C. Correlates of 9-month retention following interim buprenorphine-naloxone treatment in opioid dependence – a pilot study. J Addict. Accepted for publication.

Paper V

The final sample included 4,501 individuals who had been prescribed methadone or buprenorphine as OMT between July 1, 2005 and December 31, 2012. The median age was 34.4 years and 26.2% were female. Prescription of sedative drugs was common in this patient population: 32.4% had received at least one prescription for a benzodiazepine during the study period, 40.8% had received at least one prescription for a z-drug, and 22.2% had received at least one prescription for pregabalin.

During the study period, 356 individuals (7.9%) in the study population died. The total unadjusted mortality rate was 16.6 per 1,000 person-years. Mortality rates were higher during periods with benzodiazepine, z-drug and pregabalin prescriptions. Drug overdose was the most common cause of death (54.2%, n=193)

In the unadjusted Cox regression models, benzodiazepine prescription was significantly associated with overdose death, as well as with non-overdose death and all-cause mortality. However, in the final models, adjusting for sex, age, previous non-fatal overdose, previous psychiatric in-patient treatment, previous suicide attempt, and OMT status, the association between benzodiazepine prescription and overdose death was no longer significant, whereas the significant associations with non-overdose death (AHR: 2.02, 95% CI: 1.29-3.18) and all-cause mortality (AHR: 1.75, 95% CI: 1.28-2.39) remained. (Table 7)

For z-drug prescription, there was a significant association with overdose death and all-cause mortality in the unadjusted analyses, whereas in the adjusted analyses only the association with overdose death remained (AHR: 1.60, 95% CI: 1.07-2.39). There was no association between z-drug prescription and non-overdose death.

Pregabalin prescription was significantly associated with overdose death and all-cause mortality in both the unadjusted and the adjusted analyses (AHR: 2.82, 95% CI: 1.79-4.43, and AHR 2.01, 95% CI: 1.38-2.9, respectively), but there was no association between pregabalin prescription and non-overdose death.

In the secondary analyses, including only periods in which patients were in active OMT, periods with benzodiazepine prescriptions were no longer significantly associated with all-cause mortality. For periods with z-drug prescription, there was a significant association with all-cause mortality. Other results for benzodiazepine, z-drug and pregabalin prescriptions were similar to those of the main analyses.

In the sensitivity analyses, where an OMT period was defined as lasting 30 days from the last prescription dispensation (as compared to 90 days in the main and secondary analyses), the association between periods with benzodiazepine prescriptions and overdose death became significant in the analysis including all person-time. Other than this, results for benzodiazepine, z-drug and pregabalin prescriptions were similar to those of the main and secondary analyses.

TABLE 7. Variables associated with overdose death, non-overdose death, and all-cause mortality using an extended Cox regression model.

	Overdose death		Non-overdose death		All-cause mortality	
	HR (95% CI)	AHR (95% CI)	HR (95% CI)	AHR (95% CI)	HR (95% CI)	AHR (95% CI)
Time-independent variables						
Female sex	0.57 (0.39-0.83)*	0.58 (0.40-0.85)*	0.67 (0.46-0.99)*	0.67 (0.46-0.99)*	0.62 (0.47-0.81)*	0.63 (0.48-0.82)*
Age at baseline	0.99 (0.98-1.01)	1.00 (0.98-1.02)	1.08 (1.05-1.10)*	1.08 (1.05-1.11)*	1.03 (1.02-1.05)*	1.04 (1.02-1.05)*
Time-dependent variables						
Non-fatal overdose	2.73 (1.55-4.83)*	1.79 (0.93-3.47)	1.55 (0.76-3.17)	1.09 (0.50-2.34)	2.14 (1.37-3.35)*	1.46 (0.87-2.43)
Psychiatric diagnosis	1.22 (0.66-2.26)	0.77 (0.40-1.49)	2.19 (1.30-3.67)*	1.92 (1.11-3.32)*	1.68 (1.13-2.49)*	1.24 (0.81-1.9)
Suicide attempt	2.48 (1.45-4.22)*	1.53 (0.85-2.76)	2.38 (1.37-4.11)*	2.49 (1.38-4.51)*	2.43 (1.65-3.58)*	1.87 (1.22-2.86)*
OMT	0.33 (0.24-0.44)*	0.34 (0.25-0.46)*	1.04 (0.75-1.45)	0.97 (0.70-1.35)	0.56 (0.45-0.69)*	0.55 (0.44-0.68)*
Benzodiazepine treatment	2.02 (1.36-2.98)*	1.49 (0.97-2.29)	2.44 (1.64-3.62)*	2.02 (1.29-3.18)*	2.21 (1.67-2.92)*	1.75 (1.28-2.39)*
Z-drug treatment	1.98 (1.38-2.84)*	1.60 (1.07-2.39)*	1.42 (0.92-2.20)	0.96 (0.59-1.59)	1.72 (1.3-2.26)*	1.28 (0.93-1.75)
Pregabalin treatment	3.22 (2.13-4.86)*	2.82 (1.79-4.43)*	1.37 (0.74-2.55)	1.16 (0.60-2.25)	2.32 (1.65-3.27)*	2.01 (1.38-2.91)*

HR: Unadjusted hazard ratio

AHR: Adjusted hazard ratio

* p = <0,05

Discussion

Methodological considerations

First of all, as the famous saying goes, correlation does not imply causality, and given the observational nature of all papers included in the thesis, absolute conclusions about causality of the observed associations are difficult to draw. While papers I and II have a strictly cross-sectional design, papers III and IV, and to some degree paper V, have a longitudinal design and thus the temporal relationship between the independent and the dependent variables may appear to be more certain. However, the analyses of the pilot study in papers III and IV were not adjusted for possible confounders and mediators. In paper V, analyses were adjusted for several important confounders, but it is of course still possible that the associations found in this paper are mediated or confounded by other external factors not adjusted for in the analyses. Below, I will discuss possible reasons for the associations found in the papers of this thesis, but it is important to note that these discussions have to be mainly hypothetical.

Papers I and II

These studies were based on data from a general population study on illicit drug use. This was the largest survey on illicit drug use conducted in Sweden in recent years,[42] and, to the author's best knowledge, the first large survey to assess non-medical prescription drug use in the Swedish general population. The strengths of papers I and II thus include the large study sample (n=22,095) that is representative of the Swedish general population.

As the survey included only Swedish residents aged 15 through 64, study results are not generalizable to younger or older individuals and might furthermore not be generalizable to other countries.

The response rate of 38% (52% weighted) is somewhat low compared to other general population surveys on substance use.[47, 112-114] The low response rate might increase the risk of sampling bias. Specifically, there is a risk that individuals with substance use are less likely to respond to the survey, thus leading to an underestimation of substance use in the population. A drop-out analysis was

performed, in which 1,000 randomly selected non-respondents were contacted by telephone and interviewed using a shortened version of the original survey. The drop-out analysis showed no significant differences in substance use between respondents and non-respondents. However, the response rate of the drop-out analysis was also fairly low, at 53%, and sample bias thus cannot be ruled out.

As in all self-report surveys, there is also a risk of respondent bias, i.e. wrongful reporting of certain information by the respondents, for example underreporting of non-medical prescription sedative use. As the surveys were answered privately by the respondents (rather than through an interview) and the respondents were guaranteed anonymity, they might be more likely to answer sensitive questions about substance use more truthfully. However, respondent bias might also result from inability to correctly recall certain events, and this type of bias is more difficult to prevent.

In the question on non-medical prescription sedative use, sedatives were defined as 'prescription sleeping agent or tranquilizing agent', and the brand names 'Rohypnol' (flunitrazepam), 'Stesolid' (diazepam) and 'Stilnoct' (zolpidem) were given as examples of sedatives. However, no further information was given about which specific substances the question referred to. While it is reasonable to assume that respondents might have concluded from the given examples that benzodiazepines and z-drugs were to be included, it was not clear whether the question also referred to unscheduled sedatives such as pregabalin and antihistamines. Among respondents who had only used unscheduled sedatives non-medically, some may thus have answered affirmative and others negative to the question on past-year non-medical prescription sedative use. This is a limitation to the survey that could have been prevented by providing a list of included drugs.

In paper I, the main independent variables of interest were self-assessed physical and mental health. It would have been interesting to also include more objective measures of health in the analyses, such as specific diagnoses or treatment episodes, to see how objective health status is associated with non-medical prescription sedative use, as well as how it affects the associations between self-assessed health and non-medical prescription sedative use. In paper II, a variable describing whether respondents received disability pension or not was included as a possible confounder in the analyses. However, this variable only measures severe physical or mental conditions, and thus the analyses were not fully adjusted for respondents' health status. No other objective measures of health were available for analysis in this study.

In paper II, a modified version of the MANSA was used to measure quality of life. While the MANSA is a validated instrument, the modified version, where two questions were excluded, has not been validated. There was furthermore a high

item non-response (up to 33.4%) on three of the MANSA questions. All respondents who had answered at least five of the ten MANSA questions were included in the analyses, and missing items were substituted with the mean score of the available items for each respondent. While fewer respondents were thus excluded from the analyses, this method still introduces some uncertainty to the results.

Papers III and IV

These papers are based on a small pilot study, with a cohort effectiveness design. A controlled design with an untreated group was considered unethical, given the high risk of mortality and other severe medical complications in individuals with an untreated opioid dependence.

An obvious limitation to both papers is the small sample size. A small sample size decreases the reliability of the findings and increases the risk of type II errors, i.e. failing to find a difference, or an association, that actually does exist. With a small sample size, only differences of a greater magnitude will be detected. Thus, some of the negative findings in papers III and IV might actually have been significant if the sample sizes had been larger. In paper IV, associations with a p-value of more than 0.05, but less than 0.10 were reported as statistical trends, but increasing the significance level in this way instead increases the risk of type I errors, i.e. finding differences that actually do not exist.

A small sample size also makes multivariate analyses more difficult, because it only allows a small number of independent variables. Therefore, in paper III, only independent variables that were significantly associated with, or tended to be associated with, the outcome variables were entered in logistic regression analyses. Benzodiazepine use before treatment was not one of these independent variables. In paper IV, because benzodiazepine use during treatment was the only significant predictor of 9-month retention, no logistic regression analysis was performed. As mentioned above, the association between benzodiazepine use during treatment and 9-month retention in OMT thus is not adjusted for potential confounders.

When it comes to generalizability, the study samples consisted mainly of individuals with heroin dependence, with a high degree of polysubstance use and complications (e.g. overdoses and suicide attempts), comparable to other cohorts of individuals with heroin dependence.[16, 73, 115, 116] However, findings may not generalize to other populations, such as individuals mainly dependent on opioid analgesics. Furthermore, the study samples included few females, and thus findings may not fully generalize to female individuals with opioid dependence. Because the study investigated maintenance treatment with buprenorphine,

findings may not be generalizable to individuals in methadone maintenance treatment. Lastly, OMT in Sweden is highly regulated and only provided in specialized clinics, with a high degree of monitoring and a low tolerance for continued substance use during treatment. Findings may thus not generalize to other settings, with lower degrees of monitoring of patients in OMT.

Considering the study design, the small sample size, and the possible problems with generalizability, a cautious interpretation of the findings of papers III and IV would thus be that, in a Swedish setting of individuals with heroin dependence, there probably are no *strong* associations between benzodiazepine use before treatment and successful transfer from interim treatment to full-scale OMT, opiate-free urine samples during treatment, or retention in OMT, while there might be an association between benzodiazepine use during treatment and treatment retention.

Paper V

This was a large cohort study which aimed to investigate the associations between sedative use and mortality in individuals with opioid dependence. The study was based on high-quality national registers and the observation time was relatively long.

The main analyses were extended survival models, adjusted for several important potential confounders. However, the analyses could have benefitted from inclusion of additional potential confounders. Notably, no socio-economic variables were included in the analyses.

The study population consisted of individuals who had received methadone or buprenorphine as OMT for opioid dependence. Both methadone and buprenorphine can however also be prescribed for pain. As described in the materials and methods section, several measures were taken to exclude individuals receiving methadone or buprenorphine for a pain indication from the analyses, but it is not certain that all those individuals have been successfully removed from the material. Furthermore, some individuals with OMT treatment but with an occasional prescription for methadone or buprenorphine for acute pain might have been mistakenly removed from the material.

The PDR does not include data on individual dosages, and the DDD was therefore instead used to calculate treatment periods for benzodiazepines, z-drugs, and pregabalin. As the DDDs for methadone and buprenorphine are lower than typical doses used in OMT,[106, 117, 118] an assumed treatment period of 90 days per prescription was instead used for these drugs. As this estimation might have been too conservative, sensitivity analyses were performed, in which the treatment period was instead assumed to be 30 days for each prescription. In contrast to the

main analyses, these analyses showed a significant association between benzodiazepine prescription and overdose death. The actual relationship between benzodiazepine prescription and overdose death is thus uncertain. However, for z-drugs and pregabalin, results of the sensitivity analyses remained similar to the main analyses.

Determining whether an overdose death was accidental or intentional can be difficult and this can lead to misclassification.[102] In the present study, both accidental overdoses and overdoses with undetermined intent were classified as overdose deaths, whereas intentional overdoses were classified as non-overdose deaths. This distinction between categories of diagnoses was intended to separate suicides from non-suicidal acts of intoxication. A previous Swedish study, by Björkenstam et al,[102] found that substance use disorders were more common among overdose deaths classified as being of undetermined intent, than among those classified as accidental, and least common among those classified as intentional. Based on this study, as well as a study from our research group,[103] strengthening the findings of Björkenstam et al. of a closer connection between substance use and overdoses with undetermined intent, this category was collapsed into the same category as accidental overdoses.

The PDR only includes personally prescribed prescriptions. In recent years, many OMT clinics in Sweden have moved from personal prescriptions to in-clinic dispensation of methadone and buprenorphine acquired from an affiliated hospital.[77] Patients receiving their OMT medications in this way (approximately 25% of OMT patients in 2011)[77] are not included in the present study. This might affect the validity of the OMT variable, because some OMT patients might have first received their medications through personal prescription, but later during the observation time through in-clinic dispensation. Some of the person-time defined as not in treatment might thus in fact be time in treatment for individuals who have been transitioned to in-clinic dispensation. This is however not expected to cause any substantial bias to the estimates, as in-clinic dispensation involves all patients at a certain clinic. Secondary analyses were performed, in which the OMT variable was omitted, and the results were similar to the main analyses with regards to overdose and non-overdose death.

As in papers III and IV, and because of Swedish OMT regulations, the study cohort consists mainly of individuals with heroin dependence. Findings may thus not generalize to other populations of individuals with opioid dependence, and may furthermore not generalize to settings with significantly different practices for OMT, such as settings with very little monitoring of OMT patients. As analyses were limited to patients aged 18 to 50 at the time of the first OMT prescription during the observation time, findings may not generalize to older or younger individuals.

Main findings

Sedative misuse in the general population - self-assessed health and quality of life

In paper I, both non-medical prescription sedative use and combined non-medical prescription sedative and analgesic use were strongly associated with poor self-assessed mental health, and these associations were stronger (i.e. odds ratios were higher) for more reported days with poor mental health. For combined non-medical prescription sedative and analgesic use, there was also a strong association with poor self-assessed physical health, but there was no significant association between isolated non-medical prescription sedative use and poor self-assessed physical health.

In paper II, non-medical prescription sedative use was significantly associated with poor quality of life. Interestingly, this association was stronger than for any of the other substance use variables (i.e. non-medical prescription analgesic use, hazardous alcohol use, habitual smoking, cannabis use, and other illicit drug use).

These associations remained strong even after the analyses were adjusted for sociodemographic variables and other substance use. Non-medical prescription sedative use thus seems to be strongly associated with subjective perceptions of poor mental health and poor quality of life.

As mentioned above, the study design prevents certain conclusions about the causal relationships of the findings of the present papers, i.e. whether non-medical prescription sedative use leads to an increased risk of poor mental health and poor quality of life, or whether poor mental health or poor quality of life can lead to an increased risk of non-medical prescription sedative use. The associations could furthermore be caused by confounders not controlled for in the analyses, such as, for example, a general hereditary vulnerability which increases the risk of both mental health problems and problematic substance use.

The findings of paper I regarding the association between self-assessed mental health and non-medical prescription drug use supports the theory that a large part of non-medical prescription sedative use might be motivated by a desire to self-medicate for mental health problems.[18, 24] Individuals who report mental health problems would of course be more likely to receive prescription drugs, including prescription sedatives, for these problems, and some of these individuals might use more of their medication than prescribed, or use it more often. Some individuals might also buy prescription sedatives illicitly or obtain them from other sources (e.g. from friends or relatives) and use them to self-medicate for mental health

problems.[18] Non-medical prescription sedative use might thus be seen as a form of self-medication for sub-optimally treated mental illness.

Conversely, it is also possible that overuse of prescription sedatives might lead to or increase mental health problems. For example, there is some evidence that long-term use of benzodiazepines might maintain higher levels of anxiety, and that hypnotics might cause problems with rebound insomnia.[119] Furthermore, attempts to discontinue sedatives after long-term use might lead to withdrawal symptoms, including increased anxiety and insomnia.[119]

Underlying mental health problems, leading to an increased risk of non-medical prescription sedatives use, might also partly explain the association with poor quality of life. This hypothesis is supported by studies showing that individuals with mental health problems often report lower scores on quality of life than individuals with somatic disorders.[120, 121] These findings might also help to explain why non-medical prescription sedative use was in the present paper a significantly stronger correlate of poor quality of life than non-medical prescription analgesic use, as prescription analgesics are assumed to be used mainly for pain, i.e. for physical rather than mental health problems. Some mental health problems, for example depression, might also cause affected individuals to have a more pessimistic outlook on life,[19] thus reporting lower scores of quality of life than they might have done if they were healthy.

Another possible explanation for the association with non-medical prescription sedative use is that individuals with poor quality of life might be more likely to use prescription sedatives in a way analogous to the self-medication theory described above, i.e. to "comfort" themselves or to "escape" from their troubles.

The causative relationship between non-medical prescription sedative use and poor quality of life could of course also have the opposite direction, i.e. non-medical prescription sedative use leading to impaired quality of life, for example through relationship or work-related problems.

Findings in relation to previous studies

In the present general population sample, 2.2% of respondents reported past-year non-medical prescription sedative use. This is very similar to a previous US study, where 2.3% reported past-year prescription sedative misuse.[39]

To the author's best knowledge, no previous studies have investigated the relationship between non-medical prescription sedative use and self-assessed mental health in the general population. However, two previous studies have reported an association between non-medical prescription sedative use and poor self-assessed general health.[43, 46] One of these studies also reported an association between non-medical prescription sedative use and self-reported emotional

problems.[43] Furthermore, another study[44] investigated the associations between non-medical prescription sedative use and specific DSM-IV psychiatric diagnoses. In this study non-medical prescription sedative use was associated with all mood, anxiety and personality disorders investigated.

The findings of paper I thus seem to be in accordance with these previous studies. However, one previous study, by Becker et al.,[39] somewhat contradicts the findings of paper I and other previous studies. While non-medical prescription sedative use was in this study associated with psychological distress, as measured with the Kessler Scale 6 (K6) and with symptoms of panic disorder, non-medical prescription sedative use were neither associated with symptoms of other psychiatric disorders, nor with poor self-assessed general health.

To the author's best knowledge, no previous studies have investigated the specific relationship between non-medical prescription sedative use and overall quality of life. One study, by Ventegodt and Merrick,[57] investigated the relationship between quality of life and combined use of alcohol and benzodiazepines in the Danish general population, and found a significant correlation between this pattern of substance use and poor overall quality of life. In another study, benzodiazepine dependence was associated with poor health-related quality of life.[58] Furthermore, several other patterns of substance use, including alcohol dependence,[52] tobacco smoking,[53] and illicit drug use,[54-57] have been shown to be associated with poor overall quality of life. While findings from these studies are not directly comparable to the findings of paper II, problematic substance use generally seems to be associated with decreased quality of life, a finding which we now also see for non-medical prescription sedative use.

Sedative misuse in individuals with opioid dependence - treatment outcome in OMT

In this cohort of individuals entering OMT, benzodiazepine misuse was extensive. In paper III, 77% of patients reported benzodiazepine use before treatment and in paper IV this figure was 69%. Aside from opioids, benzodiazepines were the most commonly misused drugs both before and during treatment.

In accordance with Swedish OMT regulations, extensive polydrug use was in the interim study a reason for exclusion from treatment and furthermore, a drug-free urine sample was required for transfer from the interim condition to full-scale OMT. It was therefore hypothesized that benzodiazepine use, as well as other polysubstance use, would be negatively associated with transfer to full-scale OMT and 9-month retention in treatment. It was also hypothesized, based on findings from previous studies,[14, 15, 83-86] that benzodiazepine use before treatment would be negatively associated with opiate-free urine samples during treatment.

In contrast to these hypotheses, benzodiazepine use before treatment was neither associated with transfer to full-scale OMT, 9-month retention in treatment, nor with opiate-free urine samples during treatment. However, benzodiazepine use during treatment was significantly and negatively associated with 9-month retention.

Interestingly, use of other drugs during treatment was not associated with treatment retention, and benzodiazepine use was in fact the only variable examined in paper IV that was significantly associated with retention. Benzodiazepine misuse might thus be more strongly associated with a difficult treatment course during OMT than misuse of other drugs. Given the high rates of continued benzodiazepine use during OMT, as measured through urine drug screens, it appears that many patients are unable to discontinue their benzodiazepine use. It has been reported that 18-54% of patients seeking treatment for opioid dependence, also have a benzodiazepine dependence.[14] Thus, in order to improve treatment outcome in OMT, more efforts might be needed to treat patients with benzodiazepine dependence.

It is not unreasonable to think that benzodiazepine misuse might be a marker for psychiatric co-morbidity, which is common in individuals with opioid dependence,[15] and which might complicate treatment. In accordance with this theory, studies have shown that individuals in OMT who also have a benzodiazepine dependence are more likely to report poor mental health[122] and symptoms of anxiety and depression than OMT patients with irregular or no use of benzodiazepines.[15] It is however also possible that benzodiazepine use may cause symptoms of anxiety and depression.[2, 15] Studies have also shown that individuals in OMT who use or misuse benzodiazepines are more likely to also use illicit drugs during treatment, to be unemployed, to report criminal activity, and to have a greater overdose history,[15] all of which are factors that might potentially complicate treatment.

Findings in relation to previous studies

Prevalence rates for benzodiazepine misuse in paper III and IV were slightly higher than what has been reported in the previous literature.[14, 15] With reservation for the small sample sizes, it might thus be that benzodiazepine misuse is even more common in Swedish OMT programs compared to other countries.

Most previous studies have found no significant associations between benzodiazepine use before or during OMT and retention in treatment.[14, 15] These findings are in accordance with the findings of papers III and IV when it comes to benzodiazepine use before treatment, but are in contrast with the finding of a negative association between benzodiazepine use during OMT and treatment retention in paper IV. This difference between the present and previous studies

might partly be explained by the strict rules regarding polysubstance use in Swedish OMT programs, which were also applied in the present study.

The lack of an association between benzodiazepine use and opiate-free urine samples during treatment is contrasting to most previous studies.[14, 15, 83-86] This might partly be explained by the small sample size, creating a problem with statistical power. Another possible explanation for the difference between the results of the present and previous studies is that most previous studies have assessed benzodiazepine misuse during treatment as a possible predictor of continued opiate use during treatment, whereas in the present study, benzodiazepine use before treatment was instead assessed.

Sedative prescriptions in individuals with opioid dependence - associations with mortality

It was hypothesized that benzodiazepine, z-drug, and pregabalin prescriptions would be associated with an increased risk of overdose death in individuals who had received OMT for opioid dependence. Surprisingly, for benzodiazepine prescriptions, the main analysis of paper V instead showed a significant association with non-overdose death, but no significant association with overdose death. These results remained in the secondary analysis, but in the sensitivity analysis, there was also a significant association between benzodiazepine prescriptions and overdose death.

While the findings on the relationship between benzodiazepine prescriptions and overdose death are thus inconclusive, all analyses showed a significant association between benzodiazepine prescriptions and non-overdose death. A possible explanation to this finding might be that individuals with terminal illness are more likely to receive prescriptions for benzodiazepines.[123, 124] Furthermore, benzodiazepine use can impair motor and cognitive functioning and is associated with a higher risk of accidental injuries.[2] This might also contribute to the association between benzodiazepine prescriptions and non-overdose death.

For both z-drugs and pregabalin prescriptions, the hypotheses were confirmed, with all analyses showing significant associations with overdose death, but not with non-overdose death. Results remained in the secondary analyses, restricted to periods in which subjects were in active OMT, suggesting that the increased risk of mortality for opioid-dependent individuals receiving prescriptions for benzodiazepines, z-drugs and pregabalin remain while patients are in active treatment, i.e. in a more controlled environment.

These findings suggest that even though benzodiazepine use is a known risk factor for overdose death among patients in OMT,[14, 87, 88] z-drug and pregabalin

prescriptions might actually be stronger risk factors for overdose death than benzodiazepine prescriptions. The analyses were adjusted for sex, age, previous psychiatric in-patient treatment, previous non-fatal overdose, previous suicide attempt, and OMT status. Furthermore, the fact that prescription of both z-drugs and pregabalin were associated only with overdose death, and not with non-overdose death, suggests a possible role of these drugs in overdose mortality. Both z-drugs[125] and pregabalin[126] can, when taken in high doses, cause or contribute to overdose deaths. Furthermore, both drugs may have respiratory depressant effects[91, 92] and might thus add to the respiratory depressant effects of opioids when co-ingested.

There are several possible explanations to why z-drug and pregabalin prescriptions, but not benzodiazepine prescriptions, were associated with overdose death. First of all, both z-drugs and pregabalin have been considered to have a lower potential for abuse and dependence than benzodiazepines.[7, 29, 30] Clinicians might thus be less cautious when prescribing z-drugs and pregabalin to individuals with known opioid dependence, than when prescribing benzodiazepines. Furthermore, because benzodiazepine use, unlike z-drug and pregabalin use, is a well-known risk factor for fatal overdoses in individuals with opioid dependence, clinicians might be less likely to prescribe benzodiazepines to individuals with other risk factors for overdose (e.g. individuals with a high degree of polysubstance use, or individuals who are not in active OMT). Lastly, while benzodiazepine misuse is widespread among individuals with opioid dependence,[14, 15] and often consists of non-prescribed use,[14, 15] misuse of z-drugs[81] and pregabalin[13, 30, 32, 82] is less common. Compared to benzodiazepine misuse, prescribed use might thus constitute a larger part of the total misuse of z-drugs and pregabalin, and thus a larger risk factor for fatal overdoses.

Findings in relation to previous studies

In contrast to the findings of the present study, previous studies have found associations between benzodiazepine prescriptions and opioid-related[90] and drug-related[93, 94] death in individuals with opioid dependence. These definitions differ somewhat from the outcome measure of overdose death used in the present study, and there are also other methodological differences between the present and previous studies, such as the use of different methods for statistical analysis. However, these minor methodological differences between the present and previous studies do not seem enough to explain the contrasting findings.

It might thus be that the association between benzodiazepine prescriptions and overdose death seen in studies from other countries, is not as evident in a Swedish setting. A possible explanation for this might be differing practices for OMT and prescription of benzodiazepines in different countries. Swedish OMT programs are, compared to most other countries, highly regulated, with a high degree of

control and supervision of patients in treatment.[61, 78, 127] It is plausible that this might also lead to a higher degree of control and caution in the prescription of benzodiazepines to these patients, thus decreasing the risk of prescribed benzodiazepines contributing to overdose deaths.

Interestingly, the findings in the present study of no significant association between benzodiazepine prescriptions and overdose death, but instead an association with non-overdose death, mimic the findings of a previous study on the relationship between benzodiazepine prescriptions and emergency department visits.[128] In this study, benzodiazepine prescriptions were significantly associated with accidental injuries, but not with non-fatal overdoses.

The present study is, to the author's best knowledge, the first to report on the association between z-drug and pregabalin prescriptions and mortality among individuals with opioid dependence. The relationship between these drugs and overdose death thus need to be investigated in future studies, to see if the findings of the present study can be replicated.

Conclusions

- In the Swedish general population, non-medical prescription sedative use seems to be associated with higher levels of poor self-assessed mental health, but not with poor self-assessed physical health.
- Non-medical prescription sedative use also seems to, in the Swedish general population, be associated with poor quality of life, to a higher degree than non-medical analgesic use, tobacco use, hazardous alcohol use, cannabis use, and other illicit drug use.
- In individuals entering treatment for opioid dependence, benzodiazepine use before treatment start does not seem to be associated with neither successful entry into full-scale OMT, opiate-free urine samples during treatment, nor retention in treatment. However, benzodiazepine misuse during treatment might, in a Swedish setting, be negatively associated with retention in treatment.
- In individuals who are, or have been, in OMT, benzodiazepine prescription is associated with a higher risk of mortality. In a Swedish setting, prescription of benzodiazepines seems to be associated with an increased risk of non-overdose death, but not overdose death. Conversely, prescription of both z-drugs and pregabalin seems to be associated with an increased risk of overdose death, but not non-overdose death.

Clinical implications

When prescribing sedatives, clinicians need to be aware of the risks of misuse, especially in patients with other problematic substance use. Patients who receive prescriptions for sedatives with a known potential for misuse and dependence should be monitored, and clinicians should ensure that these patients are not receiving prescriptions for sedatives from several prescribers (so-called doctor shopping). In Sweden, this can be monitored through the national register for prescribed drugs provided by the Swedish eHealth Agency (Läkemedelsregistret).

The associations between non-medical prescription sedative use and poor subjective mental health might partly be explained by self-medication for mental health problems. Clinicians should therefore be aware of and investigate symptoms of mental health problems in patients with non-medical prescription sedative use, and try to optimize treatment when needed. It might also be useful to inquire patients with non-medical prescription sedative use about their quality of life, and, if needed, inform them on where to turn for help with specific life domain problems, such as unstable housing, relationship problems or financial problems.

Conversely, clinicians also need to be observant of prescription sedative misuse in patients with poor mental health or poor quality of life. When prescription sedative misuse is discovered or suspected, patients should be offered support to discontinue their misuse. For patients with low-grade misuse, brief interventions, i.e. providing patients with information about the risks of continued excessive sedative use, as well as information about how to decrease or discontinue their use on their own, might be sufficient.[129] When it comes to benzodiazepines and z-drugs, abrupt cessation after a long period of use might cause severe withdrawal, including seizures.[2, 9-11] These drugs therefore need to be tapered slowly.[130] Providing cognitive behavioural therapy (CBT) in addition to structured tapering might increase the chances of successful discontinuation.[131] There is not enough scientific evidence to support any pharmacological treatment of prescription sedative misuse and dependence.[132]

Given the extensive problem of prescription sedative misuse, especially benzodiazepine misuse, in individuals with opioid dependence, and the higher risk of mortality for these patients, as well as the possible negative effects on retention in OMT programs, patients with opioid dependence should be monitored for prescription sedative misuse, for example through urine drug screening, and for doctor shopping. Treatment for benzodiazepine misuse and dependence is especially important in this group. In addition to the treatment strategies described above, a few studies have shown promising results for short-term treatment with flumazenil infusions for the treatment of benzodiazepine withdrawal in patients

with high-dose benzodiazepine misuse.[133] This treatment is however still in an experimental phase.

In patients with opioid dependence, clinicians need to be aware of the higher risk of mortality associated with benzodiazepine use. Prescription of benzodiazepines should preferably be avoided and when considered necessary, patients should be closely monitored. Likewise, until the associations between z-drug and pregabalin prescriptions and overdose death have been further investigated, clinicians should be cautious when prescribing these drugs to patients with opioid dependence.

Implications for future research

Non-medical prescription sedative use in the general population needs to be further studied, especially in countries other than the United States. In the Swedish general population, more detailed investigations of the severity of and motives for non-medical prescription sedative use are needed, as well as investigations of sources of prescription sedatives used in a non-medical way. For a deeper understanding of the associations between non-medical prescription sedative use and poor subjective mental health, it would be useful to investigate non-medical prescription sedative use in both clinical populations of patients with psychiatric disorders and in populations of individuals with no specific psychiatric diagnoses.

While previous studies have found no association between benzodiazepine use and treatment retention for patients in OMT, the finding of a negative association between benzodiazepine use during OMT and treatment retention in a Swedish setting needs to be further explored in larger studies.

The associations between z-drug and pregabalin prescription and overdose death in individuals with opioid dependence also need to be further studied and confirmed in future research. Future studies should investigate the presence of z-drugs and pregabalin in opioid-related deaths. Studies on the specific toxicity of combined use of high-dose opioids and pregabalin are also needed. In a Swedish setting, the inconclusive findings regarding the association between benzodiazepine

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Populärvetenskaplig sammanfattning

Receptbelagda lugnande läkemedel används i behandling av framför allt ångest och sömnbesvär och har i det sammanhanget stor betydelse. Dessvärre kan beroende av dessa läkemedel utvecklas. Det förekommer även så kallad felanvändning av dessa läkemedel, d.v.s. användning utan recept, eller i högre doser, mer ofta, eller för annat syfte, än vad läkare har ordinerat. Sådan felanvändning sker ofta i syfte att självmedicinera mot olika psykiska besvär, t.ex. ångest, oro och sömnbesvär. Ett annat motiv kan vara att uppnå euforiserande effekter, d.v.s. ”bli hög”. Personer som har ett beroende av alkohol eller illegala droger kan även använda dessa mediciner för att lindra de besvär som uppstår vid minskad användning av ”huvuddrogen” (s.k. abstinensbesvär), eller för att få ökad effekt denna huvuddrog. Personer som redan utvecklat ett beroende av t.ex. alkohol eller opiater är särskilt känsliga för de beroendeframkallande effekterna av lugnade läkemedel och löper även risk för s.k. överdosering, vilket kan leda till döden.

Ämnet för denna avhandling är användning och felanvändning av lugnande läkemedel, dels i den allmänna befolkningen, dels i kliniska populationer med svårt narkotikaberoende individer, där felanvändning av dessa preparat medför stora hälsorisker. Avhandlingen består av fem arbeten. Två arbeten rör hur vanligt förekommande felanvändning av receptbelagda lugnade medel är i befolkningen och huruvida sådan felanvändning har samband med upplevd hälsa respektive livskvalitet. Tre av arbetena rör personer med opiatberoende. Två av dessa är baserade på en studie där man försökt behandla individer med opiatberoende med enbart substitutionsläkemedel, s.k. interimbehandling, för att snabbare kunna överföra dem som står i kö till fullskalig läkemedelsassisterad rehabilitering vid opiatberoende (LARO-behandling). Denna behandling har ett tydligt regelverk och innefattar både behandling med substitutionsläkemedel, psykologiskt stöd, och sociala insatser. I dessa arbeten studerades hur användning av receptbelagda lugnande läkemedel påverkar behandlingsförloppet. Det femte arbetet rör uppföljning av dödligheten hos en stor klinisk population av personer som erhållit LARO-behandling, och dess eventuella samband med förskrivning av olika lugnande läkemedel.

Arbete 1 och 2

Både arbete 1 och 2 utgår från en befolkningsundersökning som genomfördes av Lunds universitet i samarbete med dåvarande Folkhälsoinstitutet. Undersökningen syftade till att kartlägga förekomsten av droganvändning i befolkningen och hur olika faktorer hade samband med olika typer av droganvändning. Dessa båda artiklar fokuserar på felanvändning av receptbelagda lugnande läkemedel. Undersökningen besvarades av drygt 22 000 personer och svarsfrekvensen var 38% (52% efter att man tagit hänsyn till att man, som del i studiedesignen, skickat ut enkäten till fler individer i vissa befolkningsgrupper).

Förekomsten av felanvändning av receptbelagda lugnande läkemedel var 2,2 procent under det senaste året i den vuxna befolkningen. I det första arbetet sågs att felanvändning av receptbelagda lugnande läkemedel hade ett starkt samband med narkotikaanvändning, men också med självskattad psykisk ohälsa.

Den andra studien av samma material analyserade alkohol- och drogvanor i befolkningsmaterialet i förhållande till självrapporterad livskvalitet. Både felanvändning av receptbelagda läkemedel, riskkonsumtion av alkohol, och rökning hade samband med låg livskvalitet i detta material. Det starkaste sambandet med låg livskvalitet sågs hos personer som rapporterade felanvändning av lugnande läkemedel.

Arbete 3 och 4.

Arbete 3 och 4 undersökte felanvändning av de lugnande läkemedlen bensodiazepiner bland kliniska patienter med opiatberoende. Dessa arbeten baserades på en pilotstudie med 44 patienter, vars syfte var att undersöka ett nytt sätt att föra över obehandlade personer med opiatberoende (främst personer med heroinberoende) till LARO-behandling, den s.k. interimstudien i Lund. I arbete 3 var hypoteserna att felanvändning av bensodiazepiner skulle ha en negativ inverkan på möjligheten att kunna föras över till fullskalig LARO-behandling, samt öka risken för att patienterna fortsatte använda opiater under behandling. I studien sågs dock inga sådana samband mellan felanvändning av bensodiazepiner och övergång till LARO-behandling, eller fortsatt användning av opiater. Totalt kunde 57% föras över till fullskalig LARO-behandling.

I arbete 4 studerades huruvida felanvändning av bensodiazepiner före behandling, under interimfasen, samt under den fullskaliga LARO-behandlingen påverkade hur länge patienterna stannade kvar i behandling, s.k. retention. Andelen som stannade kvar i behandling var hög, 83%. Felanvändning av bensodiazepiner under

fullskalig behandling var förknippad med en ökad risk för att inte kvarstå i LARO-behandlingen efter 9 månader. Det sågs även en tendens till att felanvändning av bensodiazepiner under interimfasen hade samband med risk att inte kvarstå i behandling efter 9 månader.

Arbete 5

I detta arbete studerades förutom bensodiazepiner även de receptbelagda sömnmedlen zopiklon, zolpidem och zaleplon (s.k. z-droger) och det receptbelagda ångestlindrande läkemedlet pregabalin. I denna studie, där ca 4 500 individer ingick, användes nationella registerdata för att undersöka om dödligheten hos opiatberoende patienter i LARO-behandling har samband med legal förskrivning av dessa lugnande läkemedel. Hypotesen var att samtliga dessa läkemedel skulle vara kopplade till en ökad risk för framför allt död till följd av överdos. Studien visade att förskrivning av bensodiazepiner var kopplat till ökad risk för död av andra orsaker än överdos, men inte till överdosdöd. Däremot var förskrivning av både z-droger och pregabalin kopplat till överdosdöd.

Betydelse

Arbete 1 och 2 ger stöd för att felanvändning av receptbelagda lugnande läkemedel ofta kan vara motiverat av en önskan att självmedicinera mot psykiska besvär eller andra problem i livet. Hos individer där felanvändning av läkemedel upptäcks kan det därför vara viktigt att utreda och behandla eventuell bakomliggande psykisk ohälsa. Det kan även vara av vikt att förhöra sig om hur personen i fråga har det i livet i övrigt, och vid behov ge information om vart man kan vända sig för hjälp med t.ex. relationsproblem, ekonomiska bekymmer, eller bristfällig bostadssituation.

Arbete 3 och 4 ger stöd för att felanvändning av bensodiazepiner förekommer i hög grad hos personer med opiatberoende, och att felanvändning av dessa preparat hos patienter i svensk LARO-behandling tycks påverka behandlingsförloppet negativt.

Arbete 5 visar på en ökad risk för dödliga överdoser bland individer med opiatberoende som erhåller recept på z-droger och pregabalin, samt ökad risk för död av annan orsak bland individer som erhåller recept på bensodiazepiner. Studien tycks ge anledning till stor försiktighet med förskrivning av dessa läkemedel till individer med opiatberoende.

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