Addictive medication
in relation to
drug treatment and overdose death

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I.   Benzodiazepine prescription for patients in treatment for drug use disorders, a nationwide cohort study in Denmark, 2000-2010.
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II.   Misuse of prescription drugs and overdose deaths.
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Abstract

Background

The involvement of the addictive medications, benzodiazepines (BZDs) and prescription opioids, including opioid maintenance treatment (OMT) medications, have increasingly contributed to the high overdose death rates in Denmark and Norway during the past decades. Investigating prescription patterns and patient behavior in relation to drug treatment and overdose deaths is important to increase our knowledge on how these addictive medications are used, misused, and how they may contribute to overdose deaths.

Study aims

The overall aim of the thesis was to acquire new knowledge of the involvement of addictive medications in the treatment of populations with drug use disorders (DUDs) and also in overdose deaths to improve treatment approaches and reduce detrimental outcomes in a vulnerable group of individuals. More specifically the aim was to investigate prescription patterns and use of addictive medication in relation to drug treatment and overdose deaths among populations in Denmark and Norway. Furthermore, to compare overdose cases with and without detection of legally prescribed addictive medications and investigate factors associated with having detection of non-prescribed addictive medication.

Materials and methods

This thesis was based on three different cohorts/samples from two countries: A Danish nationwide cohort including individuals admitted for treatment for DUDs in 2000-2010 (n=33,203); a Norwegian sample including overdose deaths in the capital city, Oslo, in 2006-2008 (n=167), and; a Danish sample including overdose deaths in Copenhagen, Aarhus, and Odense Municipality in 2008-2011 (n=130). The cohorts/samples were linked with data from population registries, local based registries, and journal reviews by using a unique identification number assigned to all Danish and Norwegian citizens.

Results

Overall, in the period after entering treatment and in the period prior to overdose death, addictive medication was often prescribed to individuals with DUD. In both periods, inappropriate prescription patterns were identified. During the first year after admission to DUD treatment, about one-quarter of the individuals (26.2%) were prescribed BZDs. Of these, about one-third (35.5%) were prescribed BZDs at dose levels that might indicate inappropriate use, and about one-third (34.6%) were prescribed more than one type of BZDs. Particularly individuals with opioid use (43.2%) were commonly prescribed BZDs. Admitting to treatment for a DUD did not increase the specialized psychiatric treatment coverage of this patient group, disregarding use of prescribed BZDs. Among overdose deaths in Denmark and Norway, the prescribed doses of the addictive medications among the deceased were in general higher than recommended. Further, the control/monitoring measures were insufficient and allowing use of multiple prescribing physicians (Norway), low levels of supervised intake of OMT medication (Denmark), and use of multiple prescribed addictive medications (Denmark).

We investigated the deceased with detection of prescribed vs. non-prescribed addictive medication. In the Norwegian sample, we found that a lower proportion of the deceased (with detection of the target medications) had been prescribed BZDs (28.1%), strong analgesics (33.3%), or BZDs plus strong analgesics (50.0%) four weeks prior to death. However, in Denmark the majority of deceased with methadone-related overdose deaths (63.1%) were prescribed methadone as part of OMT at the time of death.

In the Norwegian sample, detection of non-prescribed BZDs and/or strong analgesics was associated with younger age (a-OR=4.9; 95% CI, 1.4-18.0) and to have a permanent place of residence outside Oslo (a-OR=2.9; 1.1-8.1). In the Danish sample, detection of non-prescribed methadone was associated with younger age of 30 years or below (a-OR=9.5; 1.8-50.5), concomitant detection of 6-MAM/heroin (a-OR=3.1; 1.2-7.8), and non-prescribed BZDs (a-OR=4.0; 1.3-12.3).

Discussion and conclusion

The prescription rates of BZDs among individuals with DUDs were much higher than among the general population, and BZDs were prescribed in a fashion that in many cases indicated inappropriate prescribing to this group more than treatment for psychiatric disorders. Also prescription practices towards the deceased prior to overdose deaths involving addiction medication seemed less than optimal with prescription of addictive medication in doses that were higher than recommended, co-prescription of more than one type of addictive medication, and use of multiple prescribers. Inappropriate prescribing of addictive medications may also increase the risk of diversion to individuals outside treatment, and such non-prescribed medication were identified as a contributing factor to many of the overdose dose deaths included in our studies.

Our findings indicate a relationship between the high availability and inappropriate prescription practices of addictive medications through legitimate channels and the diversion, use, and misuse contributing to the high and increasing overdose death rates involving these medications. As this reflects the nature of both the health care and psychosocial treatment of individuals who are prescribed addictive medication as well as drug use practices among individuals with DUD, initiatives to improve care and prevent overdose deaths should involve all treatment providers. Increased knowledge of the risk factors associated with prescription and use of addictive medications among individuals with DUD should be facilitated.

Danish summary

Baggrund

Gennem de seneste årtier har de afhængighedsskabende lægemidler, benzodiazepiner (BZDer) og receptpligtige opioider, inklusiv substitutionsmedicin, i tiltagende grad været involveret i den observerede høje overdosisdødelighed i Danmark og Norge. En undersøgelse af tendenser i ordinationspraksis, og patientadfærd i forbindelse med misbrugsbehandling og overdosisdødsfald, kan styrke vores viden om, hvordan disse lægemidler bliver brugt og misbrugt, og hvordan de kan føre til overdosisdødsfald.

Formål

Det overordnede formål med afhandlingen har været at frembringe ny viden vedrørende involvering af afhængighedsskabende lægemidler i behandlingen af personer med stofmisbrug, og blandt overdosisdødsfald. Med denne viden sigtedes der mod at forbedre behandlingsstrategier, samt at forebygge skadelige virkninger hos en udsat gruppe af personer. Mere specifikt har formålet været at undersøge tendenser i ordination og brug af afhængighedsskabende lægemidler i relation til stofmisbrugsbehandling og overdosisdødsfald i Denmark og Norge. Endvidere ville vi sammenligne overdosisdødsfald med og uden retsmedicinske fund af legalt ordinerede afhængigheds-skabende lægemidler, samt at identificere faktorer associeret med fund af ikke-ordinerede lægemidler.

Materiale og metode

Denne afhandling er baseret på tre forskellige kohorter fra to forskellige lande: En dansk landsdækkende kohorte med inklusion af personer indskrevet i stofmisbrugsbehandling i 2000-2010 (n=33,203); en norsk kohorte med inklusion af overdosisdødsfald i hovedstaden, Oslo, i 2006-2008 (n=167), og; en dansk kohorte med inklusion af overdosisdødsfald i Københavns, Aarhus og Odense Kommune i 2008-2011 (n=130). Disse kohorter er via brug af personnumre blevet koblet med data fra befolkningsregistre, lokale registre og journalgennemgang.

Resultater

Overordnet set blev der i perioden efter indskrivning i misbrugsbehandling og i perioden op til overdosis-dødsfald ofte ordineret afhængighedsskabende lægemidler til personer med stofmisbrug. I begge perioder blev der identificeret en uhensigtsmæssig ordinationspraksis. Omkring en fjerdedel af personerne (26.2%) blev ordineret BZDer i det første år efter indskrivning i misbrugsbehandling. Af disse personer blev omkring en tredjedel (35.5%) ordineret BZDer i dosisniveauer, der kan indikere et uhensigtsmæssigt brug. Omkring en tredjedel (34.6%) blev ordineret mere end én type BZDer. Især personer med misbrug af opioider (43.2%) blev hyppigt ordineret BZDer. At blive indskrevet i misbrugsbehandling medførte ikke at flere personer kom i specialiseret psykiatrisk behandling, uanset brugen af BZDer. Blandt overdosis-dødsfaldene i Danmark og Norge var den ordinerede dosis af afhængighedsskabende lægemidler til disse personer generelt set højere end anbefalet. Niveauet af kontrol og overvågning var utilstrækkeligt og tillod, at der blev benyttet flere forskellige ordinerende læger (Norge), en lav grad af overvåget indtag af substitutionsmedicin (Danmark), og samtidig ordination af flere forskellige afhængighedsskabende lægemidler (Danmark).

Blandt de afdøde personer blev det undersøgt, om de fundne afhængighedsskabende lægemidler var ordinerede eller ikke-ordinerede. I den norske kohorte fandt vi en mindre andel af afdøde personer (med fund af det angivne lægemiddel), der var blevet ordineret BZDer (28.1%), stærke smertestillende lægemidler (33.3%), eller BZDer plus stærke smertestillende lægemidler (50.0%) i op til fire uger før død. I Danmark var hovedparten af personer med metadon-relaterede overdosisdødsfald (63.1%) blevet ordineret metadon som led i substitutionsbehandling på dødstidspunktet.

I den norske kohorte var fund af ikke-ordinerede BZDer og/eller stærke smertestillende lægemidler associeret med yngre alder (a-OR=4.9; 95% CI, 1.4-18.0), samt at have bopæl uden for Oslo (a-OR=2.9; 1.1-8.1). I den danske kohorte var fund af ikke-ordineret metadon associeret med yngre alder på 30 år eller

derunder (a-OR=9.5; 1.8-50.5), samtidigt fund af 6-MAM/heroin (a-OR=3.1; 1.2-7.8), samt ikke-ordinerede BZDer (a-OR=4.0; 1.3-12.3).

Diskussion og konklusion

Sammenlignet med den generelle population blev personer med stofmisbrug i betydeligt højere grad ordineret BZDer. Praksis, forbundet med ordination af BZDer til denne gruppe personer, indikerede en uhensigtsmæssig ordination af dette lægemiddel, snarere end behandling for en psykiatrisk lidelse. Også blandt personer med overdosisdødsfald syntes ordinationspraksis ikke optimal. Dette inkluderede ordination af afhængighedsskabende lægemidler i doser, der var højere end anbefalet, samtidig ordination af flere typer afhængighedsskabende lægemidler, samt at der blev benyttet flere forskellige ordinerende læger. En uhensigtsmæssig ordination af afhængighedsskabende lægemidler kan også øge risikoen for videregivelse/salg af lægemidlet til personer uden for behandling til et ikke-ordineret brug, og sådanne ikke-ordinerede lægemidler blev identificeret som værende medvirkende faktor til mange af overdosisdødsfaldene i undersøgelsen.

Vores fund indikerer, at høj tilgængelighed og uhensigtsmæssig ordinationspraksis af afhængigheds-skabende lægemidler har en sammenhæng med videregivelse, brug og misbrug af disse lægemidler. Denne sammenhæng bidrager endvidere til den høje og stigende overdosisdødelighed med involvering af afhængighedsskabende lægemidler. Resultaterne af afhandlingen afspejler både den psykosociale og sundhedsfaglige behandling af personer, der er blevet ordineret afhængighedsskabende lægemidler, men også tendenser i stofbruget hos personer med misbrug. Derfor bør tiltag såsom forbedret undervisning ikke kun inddrage den sundhedsfaglige behandling men også andre områder af behandlingen for at opnå den ønskede effekt på overdosisdødeligheden. Slutteligt anbefales der fokus på øget viden omkring de risikofaktorer, der er forbundet med ordination og brug af afhængighedsskabende lægemidler til personer med stofmisbrug.

Abbreviations

a-OR: Adjusted Odds Ratio

ATC: Anatomical Therapeutic Chemical

BZD: Benzodiazepine

CI: Confidence Interval

DDD: Defined Daily Dose

DNPR: Danish National Prescription Register

DSATR: Danish Substance Abuse Treatment Register

DUD: Drug Use Disorder

EMCDDA: European Monitoring Centre for Drug and Drug Addiction

IDU: Injection Drug User

MDMA: 3,4-methylenedioxymethamphetamine

MMT: Methadone Maintenance Treatment

NCDR: Norwegian National Cause of Death Registry

NorPD: Norwegian Prescription Database

NPR: Danish National Patient Register

OMT: Opioid Maintenance Treatment

PCRR: Danish Psychiatric Central Research Register

RCT: Randomized Clinical Trial

SD: Standard Deviation

SSRI: Selective Serotonin Reuptake Inhibitor

6-MAM: 6-monoacetylmorphine

1.0 Introduction

Brief overview of the thesis

In the past several years, an overall trend of increasing deaths involving addictive medications and decreasing deaths from illicit drug use has been observed (1, 2). In Denmark and Norway, the involvement of particularly the addictive medications, benzodiazepines (BZDs) and prescription opioids, including opioid maintenance treatment (OMT) medications, have increasingly contributed to the high overdose death rates (3, 4). Investigating prescription patterns and patient behavior in relation to drug treatment and overdose deaths is therefore important to increase our knowledge on how the addictive medications are used and misused and whether they contribute to overdose death (5). This thesis aims to investigate prescription patterns and use of addictive medication in relation to drug treatment and overdose death among populations in Denmark and Norway. The methodological approach has been to investigate cohorts/samples of individuals admitted to treatment for drug use disorders (DUDs) and also overdose deaths, and the application of population registries, local based registries, and journal reviews. The main findings are that opioids, including OMT medications, and BZDs are prescribed in high rates to individuals with DUDs, and these medications are also involved in significant numbers of overdose deaths. The findings add to the understanding on how these addictive medications are used and misused and contribute to intoxication. Awareness of the risks associated with prescription medications to DUD populations needs to be raised among clinicians, pharmacists, and regulators, to help prevent future misuse and overdose deaths.

1.1 Extent of drug use and consequences

It is estimated that a total of 246 million individuals aged 15–64 used an illicit substance in 2013. This corresponds to 5.2 per cent of the adult population (6). Of those, about 27 million individuals had a DUD (6). The number of individuals with DUD has remained stable in recent years. However, the types of drugs used have changed. The prevalence of cannabis and opioids use has gone up, while the prevalence of use of

cocaine, amphetamine-type stimulants and "ecstasy"-group substances (central stimulants) appears to have followed a declining trend. Also non-medical use of prescription drugs and particularly opioids has increased (6, 7).

Compared to other regions of the world, the treatment coverage is high in Europe among individuals with DUD, totaling around 1.6 million individuals in treatment (4, 6). Of those, opioid users represent the largest group (4). Opioid maintenance treatment, typically combined with psychosocial interventions, is the most common treatment for opioid use disorder. Specialized treatment including OMT reduces risk of morbidity and mortality for individuals with DUD (8, 9). Without treatment, the mortality rates among individuals with DUD are high, and this particularly applies to individuals with opioid use disorders where mortality rates have been reported to be between six and 30 times higher than those of age- and gender-matched general populations (10-12). In recent years, misuse of addictive medications, primarily prescription opioids and BZDs, have increasingly contributed to these high mortality rates (2, 5, 13).

1.2 Addictive medication – benzodiazepines and prescription opioids

Benzodiazepines

Benzodiazepines were discovered in the 1950s by Dr. Leo Sternbach (14). In 1960, the first BZD compound, chlordiazepoxide (Librium), was approved for use (14). Its congener, diazepam (Valium), was released in 1963 and became increasingly popular (15). In the following years, Sternbach developed many other types of BZDs including flurazepam, flunitrazepam, and clonazepam (16). In total, more than 1000 types of BZDs have been synthesized (17). From 1969, diazepam was the most prescribed drug in America, and in the late 1970s BZDs became the most commonly prescribed of all drugs in the world (15, 18). Although, in the last decade, the BZDs have been partly replaced by the SSRIs for anxiety and to some extent by melatonin agonists for insomnia, they globally remain among the most widely prescribed drugs (15, 19, 20).

BZDs were introduced in Norway and Denmark in the 1960s, and the use of BZDs peaked in both countries in the 1980s (21, 22). During the last decades, the health authorities in Norway and Denmark have strived to reduce the use of BZDs, which has led to a reduction in the use of BZDs in the general populations in Norway and particularly Denmark (21-24).

The BZD class of drugs is characterized by an ability to bind to specific BZD-type receptors on the GABA chloride ion channel complex and potentiate the inhibitory neurotransmitter GABA (25). This then reduces the turnover of several neurotransmitters, including those involved in emotional expression such as noradrenalin and serotonin. Dependence is accompanied by neuropharmacological changes, involving dopamine mechanisms as well (26, 27). The pharmacodynamic abilities enables the use of BZDs in treatment of a wide range of conditions including some psychiatric disorders, insomnia, acute alcohol withdrawal, and epilepsy (28).

Prescription opioids

Opium has been used for the relief of pain and suffering for thousands of years (29). Many prescription opioids are still derived from opium (30). In the 20th century, prescription opioids have been used in treatment for acute and chronic pain and dependency. The use of prescription opioids in treatment for opioid dependency started in the 1960´s by Dr. Vincent P. Doyle and Dr. Marie E. Nyswander at the Rockefeller University Hospital (31-34). They found that patients in treatment with methadone, a long-acting synthetic opioid, showed less drug-seeking behavior and increased motivation for rehabilitation (35). These experiences formed the basis for OMT as we know today (36). The use of methadone, and later buprenorphine, has grown to play an important part of the treatment of opioid use disorder on a worldwide scale (37). Concurrently, prescription opioids have been an accepted part of treatment for acute pain, pain due to cancer, and pain caused by a terminal disease (29). However in recent years increased

use, coupled with prolonged use in patients with chronic noncancer pain, have led to concerns on the part of policy makers, health professionals, and the general public (38-40).

The prevalence of opioid use for pain treatment has been stable and high in Norway and Denmark during the last decades (19, 21). The widespread prescription of opioids to particularly patients with chronic pain has raised concerns in both countries (41, 42). Particularly in Denmark, an extensive and liberal use of opioids among the chronic noncancer pain population has been reported (41).

The opioid class of drugs includes natural opiates (e.g., morphine, codeine), semi-synthetic opioids (e.g., heroin, oxycodone), and synthetic opioids (e.g., methadone, buprenorphine) (43). Opioids have multiple actions: they alter body temperature, cause sedation, depress respiration, induce eating, decrease gastrointestinal transit, affect urinary output, and produce either euphoria or dysphoria (44). These effects are primarily produced through actions at the three opioid receptor subtypes: μ, κ, and, δ (45). It is the agonist actions of opioids upon μ-receptors that are thought to underlie their ability to relieve pain, suppress coughing, and alleviate diarrhea. Unfortunately, μ-receptors may also mediate the misuse potential of many prescription opioids (46).

1.3 Dependence and misuse of addictive medication

Tolerance to the effects of both BZDs and prescription opioids develops rapidly, within a few days to a few months of regular use (20, 47-49). Therefore, a considerable proportion of users are gradually prescribed increasing dosages, sometimes to above recommended levels (47, 50, 51). Escalation of dosage and long-term use of BZDs and prescription opioids can cause adverse effects including excessive sedation leading to falls, fractures, and other accidents, and dependence and misuse of BZDs and opioids, including heroin (52-62). The pattern of misuse ranges from occasional binges at weekends to continuing high-dose use, with large doses being taken on a regular basis and often in combination with other drugs (43, 63, 64).

Significant parts of these legally prescribed drugs are therefore included as an integral part of a drug use and risk behavior for overdose, and is also diverted to drug-using populations (53, 63, 65-67).

Benzodiazepines have the ability to prolong the effect of street drugs and to delay and soften abstinence, while prescription opioids can be used as a substitute when street drugs such as heroin are not available (68). They are also commonly co-misused, and the combination may potentiate the euphoric effect (69-71). Particularly the addition of BZDs to methadone seems attractive to drug users as it may induce a more potent opioid effect often described as "heroin-like" (43, 72).

The misuse of prescription drugs is now considered a worldwide concern and constitutes a growing public health problem, and the prevalence of prescription drug misuse among adolescents and young adults is increasing (64, 73). Two of the most widely misused types of prescription drugs are BZDs and opioids (69, 74).

1.4 Addictive medication and patients with drug use disorders

There are a variety of approaches to treating DUDs (75). Drug treatment can include behavioral therapy, medications, or their combination (76). The specific type of treatment combinations will vary depending on the patient's individual needs and, often, on the types of drugs they use (77). As they work on different aspects of addiction, combinations of behavioral therapies and medications generally appear to be more effective than either approach used alone (78). Treatments for misuse of addictive medication tend to be similar to those for illicit drugs that affect the same brain systems. For example, methadone, used to treat heroin addiction, can also be used to treat addiction to opioid pain medications (79). Addiction to prescription stimulants, which affect the same brain systems as illicit stimulants like cocaine, can be treated with behavioral therapies and medical treatment of symptoms connected with dependence (i.e. abstinence symptoms) (75). There are not yet any medications for treating the actual dependence to non-opioids drugs

(80). In recent years outpatient treatment of DUD has largely replaced previous traditions of inpatient treatment (81).

Patients with DUD use BZDs more frequently than the general population (82, 83). In addition, this patient group both has a higher prevalence of psychiatric disorders and an increased risk of developing a misuse when using BZDs (84-87). Particularly long-term use among patients with DUD is of increasing concern as it can result in difficulty in discontinuing treatment, and also dependence and misuse of BZDs itself or as part of polydrug misuse in which BZDs are included (52-54). Further, the risk of adverse events such as dependence and misuse of BZDs differs within the different types of BZDs, where some specific types are preferred among drug using populations and often in combination with other drugs (53).

There is an estimated 33,000 drug users in Denmark (latest numbers from 2009), and the treatment coverage has been relatively stable with around 40% in the last decades (81). Since 2003, patients admitting treatment for DUD have been guaranteed provision of social treatment within 14 days of initial contact (88). Following local government reform in 2007 municipalities became responsible for organizing both the social and medical treatment of patients with DUD (89). According to Danish guidelines, BZDs should not be prescribed to patients with DUD as a general rule (90). Once admitted to treatment, guidelines state that DUD treatment provided by physicians should also address the patient's continued use of BZDs, and other physicians should not prescribe BZDs to patients with DUD without coordinating with the overall treatment plan for DUD (90).

1.5 Addictive medication and opioid maintenance treatment

Opioid use disorder is a major public health problem (6). The illicit use of opioids, such as heroin and prescription opioids, contributes to the global burden of disease and can result in premature disability and death (91). OMT decreases illicit opioid use and reduces morbidity and mortality among individuals with

opioid use disorder (8, 92-94). OMT, combined with integrated health and social care interventions, is found to be the most effective in treating opioid use disorder (95). In most cases, treatment will be required on a long-term basis or even throughout life (96). Such long-term treatment should not be considered a treatment failure but rather a way of prolonging life and improving quality of life (95, 97). The effectiveness of OMT has been demonstrated by a number of randomized trials (RCTs) and observational studies (8, 9, 98-102).

For individuals with opioid use disorder, the OMT medications, methadone, buprenorphine, and buprenorphine-naloxone combinations, are available (103). Of these, methadone is the most commonly prescribed globally (37). Compared to buprenorphine, methadone may be more effective in retaining people in treatment, particularly when compared in lower dosage regiments (99). However, buprenorphine, and particularly the buprenorphine-naloxone combination, has been reported to possess a better safety profile as compared to methadone regarding misuse potential, drug-drug interactions with antiretroviral medications, risk of fatal overdose, and risk of sudden death (associated with QTc-prolongation) (104-107). The long elimination half-life of methadone and also buprenorphine allows dispensing of one single daily oral ration, which makes it easier for the patient to follow the treatment and easier for the professionals at the drug treatment facility to supervise the medication intake (79). Heroin-assisted treatment is now also available in some countries (108-110).

Both methadone and buprenorphine can also be misused and are distributed on the illicit drug market in varying rates (111). Misuse and diversion of OST medication negatively impact treatment outcomes and the community as a whole (112). Diversion of particularly methadone has been implicated as a key contributing factor in fatal and nonfatal methadone-related overdoses (74, 113). Further, individuals using non-prescribed methadone are reported having injected the medication, thereby putting themselves at risk of being infected with blood-borne viruses (e.g., HIV, hepatitis B, and hepatitis C) (114-116). The extent of

misuse and diversion varies in different settings (112, 116). In Denmark and Norway, there are a lack of documented evidence of the quantitative impact and extent of such misuse and diversion (112). Seizures of illicit substances by the police can provide an indication of the extent of misuse. However, the Danish police does not register the seizures of methadone. In Norway, seizures of illicit methadone accounted for 7% of medical narcotics seized in 2006 (117).

To reduce diversion and misuse of OMT medication, control measures in varying degrees have become an integrated part of OMT programs (118, 119). These control measures include supervised intake of OMT medication and a limited number of take-home doses. Introduction of such control measures have been found to reduce diversion and misuse of OMT medication leading to overdose deaths (120, 121). Further, the WHO recommends that methadone doses should be within the limits of 60-120mg daily (95). Doses of methadone within these limits are more effective than lower doses in terms of treatment outcomes, such as illicit opioid use and retention in treatment (122, 123). Doses above the upper limit have not shown better treatment retention than doses within recommended limits, and higher doses of methadone are associated with an increased risk of overdose death and sudden death (104, 123, 124).

Optimization of the strategies to reduce misuse and diversion and improve outcomes in OMT is an ongoing discussion (112, 125). A too strict control policy and prescription of too low doses of methadone can be an important motive for individuals with opioid use disorder to avoid accessing treatment and to terminate treatment (118). On the other hand, a "liberal" treatment approach meaning a minimum of supervised intake, a high number of take-home doses, and prescription of methadone doses above recommended limits, may increase the risk of diversion and misuse of OMT medication leading to overdose deaths (120, 121, 126).

Currently, OMT is the most widespread treatment approach for opioid use disorder. In the European Union and Norway, the European Monitoring Centre for Drug and Drug Addiction (EMCDDA) estimated that about 700,000 individuals received OMT during 2013 which included approximately half of the population with opioid use disorder (4). In Norway, OMT opioids were introduced in 1998 (127). By 2013, a total of 7055 patients were receiving OMT (127). Of these, the majority (56%) were prescribed buprenorphine whilst the remaining 44% were prescribed methadone (127).

In Denmark, OMT is part of the provided drug treatment service and encompasses all systematic forms of maintenance treatment. Methadone as OMT medication has been available in Denmark since 1970, and buprenorphine has been available since 2009 (89). Since the introduction of methadone as OMT medication, Denmark focused on achieving a high treatment coverage among individuals with opioid use disorder by leading a prescription strategy that was less restrictive than other European countries (89, 128). This resulted in a high number of individuals with opioid use disorder entering OMT and also one of the highest prescription rates of methadone in Europe (128). In the 90s and 00s, the strategy progressed with introduction of less restrictive control measures as they were regarded as potential barriers to entering treatment (129, 130). From 1985 to 2011 (latest numbers), the number of individuals in Denmark receiving methadone maintenance treatment (MMT) increased almost fivefold (from 1387 to 6200) and in 2011 comprised 82% of all OMT patients (89, 131). However, concurrently as control measures were regarded as potential barriers to easy access, supervised intake of OMT medication, urine tests, and other control measures which used to be an integrated part of treatment were minimized or abolished (129, 130). Patients receiving OMT got a much higher degree of influence on their prescribed methadone dose (129). Further, strong drug user organizations promoted drug users' dislike of buprenorphine and of being switched from methadone to buprenorphine (129). Overall, the progress in the OMT delivery strategy in Denmark has resulted in liberal treatment approach with a minimum of supervised intake, a high number

of take-home doses, and prescription of methadone doses outside recommended limits (60-120mg) (95, 129, 132).

1.6 Addictive medication and overdose death

Mortality rates among individuals with DUD are higher than of the general population (133). Particularly individuals with opioid use disorder suffer from increased mortality risks that are six to 20 times higher than their age- and gender-matched peers (10, 93, 134). A substantial part of this increased mortality risk is due to overdoses (134, 135). The type of drug used, concurrent use of other drugs, and route of drug administration have a powerful impact on the overdose risk (12, 136, 137). Opioids together with BZDs are a combination of drugs that is often detected in the post-mortem toxicology findings in overdose deaths (3, 126, 138).

Respiratory depression is the primary mechanism of opioid overdose fatality (139). Like other opioid agonists, prescription opioids have the potential to induce lethal respiratory suppression when given in doses that exceed an individual's tolerance (79). Concurrent use of other central nervous system depressants such as BZDs elevates the risk of overdose and can lead to a life threatening situation even at therapeutic levels of each medication alone (3, 140).

Overprescription of addictive medication may be a significant driver of availability of addictive medication for non-prescribed use leading to fatal overdose (67, 141, 142). Physician prescribing patterns of opioids and BZDs have likely contributed to the increase in addictive medication availability (143, 144). Risks associated with fatal overdose involving addictive medication include prescription of higher daily doses, the number of dispensed medications, and seeking care from multiple physicians to obtain prescriptions (doctor shopping) (74, 145-147).

Of the prescription opioids, particularly methadone has increasingly contributed to the overdose death rates (2, 148). Methadone carries a higher-risk profile than other opioids with a high incidence of overdose deaths (148). Its rising contribution to the overdose deaths rates has been associated with an increase of the number of methadone prescriptions dispensed for both chronic pain and OMT (143, 149). The number of methadone deaths attributed to OMT medication misuse vs. pain medication misuse is, however, difficult to quantify, as methadone-related overdose deaths can occur among individuals receiving legally prescribed methadone and also among individuals using illicit diverted methadone (149). Of the methadone deaths attributed to MMT medication, it has typically been reported that about one-third of these deaths involved patients receiving MMT, whereas the remainder occurs among individuals outside of MMT (121, 149). The majority of MMT-related methadone overdoses occur within the first 2-4 weeks of therapy due to too rapid dose escalations and multiple drug use (8, 93, 150, 151).

Although heroin or its metabolites are still present in the majority of fatal overdoses reported in Europe, an overall global trend of increasing deaths from prescription opioid use and decreasing deaths from illicit drug use has been observed in the past several years (2, 4). Particular in Northern Europe and the USA, an increase in overdose deaths involving prescription opioids and also BZDs have been observed (3, 152-154). The rate of death from overdoses of prescription opioids in the United States more than quadrupled between 1999 and 2010, far exceeding the combined death toll from cocaine and heroin overdoses (153).

Denmark and Norway are among the countries in Europe with the highest overdose death rates (4). In 2013, the average mortality rate due to overdoses was 70 and 60 deaths per million population in Denmark and Norway, respectively, as compared to 16 deaths per million population in Europe (4). However, the national differences in coding and reporting practices, as well as possible under-reporting, make it difficult to compare countries (4, 137). Although the overall rate of overdose deaths (heroin and prescription opioids combined) has been stable in the past decades, a continuous reduction in heroin-related overdose

deaths has been observed and a rising death rate related to methadone has coincided (81). In Denmark,

methadone is now the presumed main intoxicant in about 60% of all overdose deaths which is among the

highest in the world and almost three times higher than the other Nordic countries combined (3, 81). In

addition to methadone, BZDs are a commonly detected addictive medication among overdose deaths in the

Nordic countries (3). In Denmark and Norway, the proportion of BZD-related deaths has doubled in the last

decades and now constitutes more than two-thirds of all overdose deaths (3).

2.0 Objectives

The overall aim was, based on register data, to investigate prescription patterns and use of addictive medication in relation to drug treatment and overdose death among populations in Denmark and Norway.

The specific aims were:

I.   To investigate prescription of addictive medication and associated prescription patterns (type, doses, very long-term prescription) to patients in connection with admission to treatment for drug use disorders (Paper I).

II.   To examine addictive medication as involved factor in overdose deaths (Paper II and III).

III.   To compare overdose cases with and without legally prescribed addictive medications and investigate factors associated with having detection of non-prescribed addictive medication (Paper II and III).

IV.   To investigate prescribing and dispensing patterns in cases with detection of legally prescribed addictive medications (Paper II and III).

3.0 Material and methods

3.1 Design

This thesis is based on three different cohorts/samples from two countries. A Danish nationwide cohort study including patients admitted for treatment for DUDs in 2000-2010 was used to address aim I (Paper I). A Norwegian study including overdose deaths in the capital city, Oslo, in 2006-2008 was used to address aim II-IV (Paper II). A Danish study including overdose deaths in Copenhagen, Aarhus, and Odense Municipality in 2006-2008 was used to address aim II-IV (Paper III). The cohorts/samples were linked with data from population registries, local based registries, and journal reviews.

3.2 Setting

Copenhagen, Aarhus, and Odense Municipality include most of the capital and two of the largest cities in Denmark which in total hold around 1.1 million of Denmark's population of approximately 5.7 million (155). The three municipalities represent different regions of Denmark, and combined are thought to relatively well reflect particularly the urban parts of a national distribution of the total population. There is an estimated 33,000 drug users in Denmark (latest numbers from 2009), and the number of injecting drug users (IDUs) has been estimated to be between 10,066 and 16,821 (81). The treatment coverage has been relatively stable with around 40% of all drug users in the last decades (81). All treatments in drug treatment facilities are free of charge to the patient, as Denmark provides access to universal health care (including DUD treatments) for all citizens. The overdose mortality rate is approximately 5 deaths per 100,000 inhabitants, and the municipality with the highest numbers of overdose deaths is Copenhagen (3, 81).

The Norwegian capital, Oslo, includes around 600,000 of Norway's population of approximately 5.2 million (156). The number of IDUs in Norway has been estimated to be between 7,200 and 10,100, and heroin is the most commonly injected drug (157). The overdose mortality rate is approximately 6 deaths per 100,000

inhabitants (3). One-third of these overdose deaths occur in Oslo (157-159). This means there is a disproportionately high rate of overdose deaths in the capital compared to other regions.

Drug users are in increased risk of overdose death, and both Denmark and Norway have some of the highest overdose mortality rates in Europe (4). During the past years, the misuse patterns in Denmark and Norway have changed (4, 81). Addictive medication is now more widely misused and is commonly replacing heroin use which is mirrored in the overdose deaths where methadone, often in combination with BZDs, is largely replacing heroin as underlying cause of death (3).

3.3 Sources of data

This thesis is based on data from Denmark and Norway. The data from Denmark was obtained from population registries, local based registries, and journal reviews. The data from Norway was obtained from population registries and journal reviews. An overview of the data sources used to address paper I-III is presented in Table 1. All data sources were linked by use of the personal identification number, a unique identifier assigned to all Danish and Norwegian residents (160).

The Danish Register of Causes of Death

Information about causes of death in Denmark was obtained from the Danish Register of Causes of Death, which is a general mortality register (161). The Danish Register of Causes of Death includes individual-based data of all deaths among Danish residents dying in Denmark. Data from the Danish Register of Causes of Death included underlying cause of death, sex, age, and the type of location of death.

Table 1 Data sources used in paper I-III

Data sources	Paper I	Paper II	Paper III
The Danish Register of Causes of Death			x
The Danish National Prescription Register	x		x
The Danish Departments of Forensic Medicine			x
The Danish National Patient Register			x
The Danish Psychiatric Central Research Register	x		x
The Danish Substance Abuse Treatment Register	x		
The Danish drug treatment facilities			x
The Norwegian National Cause of Death Registry		x	
The Norwegian Prescription Database		x	
The Norwegian Institute of Forensic Medicine at the University of Oslo		x	

The Danish National Prescription Register

Information about dispensed medications in Denmark was obtained from the Danish National Prescription

Register (DNPR) (162). The DNPR contains information about all prescription medications dispensed

through pharmacies in Denmark from 1994 to individuals outside institutions including hospitals and drug

treatment facilities (163). All prescriptions from ambulatory care, whether publicly reimbursed or not, are

stored in the database at DNPR. The data collected for this study were; patient unique identifying number

(encrypted), the date the medication was dispensed, daily dose, and medication information [brand name,

ATC-code, and defined daily dose (DDD)].

The Danish Departments of Forensic Medicine

The Danish toxicological data was obtained from local based registries at the three departments of forensic medicine in Denmark, which are situated in Copenhagen, Aarhus, and Odense.

The Danish National Patient Register

Information about somatic diagnosis was obtained from the Danish National Patient Register (NPR) (164). The NPR contains data on all non-psychiatric hospitalizations in Denmark since 1978 and visits and emergency room contacts since 1995. Discharge/contact diagnoses have been coded according to ICD-10 since 1994.

The Danish Psychiatric Central Research Register

Information about psychiatric diagnosis was obtained from the Danish Psychiatric Central Research Register (PCRR) (165). The PCRR contains data on all psychiatric hospitalizations in Denmark since 1970 and visits and emergency room contacts since 1995. Discharge/contact diagnoses have been coded according to ICD-10 since 1994.

The Danish Substance Abuse Treatment Register

Data about the treatment at drug treatment facilities was obtained from the Danish Substance Abuse Treatment Register (DSATR) (166). The register was established in 1996 and contains information on all patients receiving treatment in publically funded outpatient drug treatment facilities in Denmark. There are very few privately funded drug treatment facilities in Denmark, except for treatment of alcohol use disorders. This means that practically all patients in treatment for DUDs are included. To be registered in the DSATR, patients can have alcohol as a secondary substance use but never as a primary substance use. Date for treatment admission was registered. The patients are registered with one primary illicit drug used,

based on self-report at treatment entry, where patients are asked about "primary drug" in relation to treatment needs.

The Danish drug treatment facilities

Information about OMT was collected locally by journal review at the drug treatment facilities. This included information about place of dispensing of OMT (pharmacy or drug treatment facility), type of OMT (methadone or buprenorphine), doses prescribed, duration of time in OMT, and supervision of intake of OMT. If OMT was dispensed at a pharmacy, information on the date the medication was dispensed, daily dose, and brand name was retrieved from the DNPR.

The Norwegian National Cause of Death Registry

Information about causes of death in Norway was obtained from the Norwegian National Cause of Death Registry (NCDR), which is a general mortality register (167). The NCDR at the Norwegian Public Health Institute (during the study period, the NCDR was managed at Statistics Norway) compiles data on all deaths registered in Norway. Data included information on underlying cause of death.

The Norwegian Prescription Database

Information about dispensed medications in Norway was obtained from the Norwegian Prescription Database (NorPD) (168, 169). The NorPD contains information about all medications dispensed through pharmacies in Norway from 2004 to individuals outside institutions including hospitals, drug treatment facilities and prisons, when individuals have received medications at pharmacies. Information about all prescriptions from ambulatory care, whether publicly reimbursed or not, are stored in NorPD, which covers all individual prescriptions in Norway. The data collected were; patient unique identifying number (encrypted), sex, age, the date the medication was dispensed, prescribing physician ID (encrypted), medication information [brand name, package size, number of packages, ATC-code, and DDD].

The Norwegian Institute of Forensic Medicine at the University of Oslo

The Norwegian toxicological data was obtained from journal review from the Institute of Forensic Medicine, University of Oslo (now Norwegian Institute of Public Health). The data included both the type of location of death and the postal code for the place of death. Data regarding the location of death included the following variables: 'residential address', including shelters providing long-term accommodation; 'outdoors', including parking lots and public toilets; and 'institutions', including hospitals, drug treatment facilities, and prisons. Although, in each case, by definition only one substance was considered to be the main intoxicant by the pathologist, a person could have several other substances in their blood that may have contributed to the death and information on both main intoxicant and other substances were collected.

3.4 Study populations

The study populations in paper I-III are presented in Table 2.

Table 2 The study population in paper I-III

	Paper I	**Paper II**	**Paper III**
Study population	n=33,203	n=167	n=130
Mean age, (SD)	31 (±11)[a]	37.0 (±11)[b]	43.8 (±10)[b]
Female, n (%)	8177 (24.6)	41 (24.6)	31 (23.8)

[a] Age at study entry.
[b] Age at time of death.

Paper I: Patients in treatment for drug use disorders in Denmark

A total of 34,360 patients were consecutively admitted for outpatient treatment for DUDs during the period 2000-2010 in Denmark and registered in the DSATR (126). Those who were younger than 18 years of age at time of admission (n=388) and older than 67 years of age at time of admission (n=38) were excluded from the dataset. Further, we excluded those who did not have a registered birth date (n=308) and those

who died during the first year after admission (n=423). This left 33,203 patients eligible for the study. All patients who were admitted for outpatient treatment in a drug treatment facility with a drug as primary substance use were defined as having a DUD. Study entry was set as the date of first admission into treatment for DUD during the study entry period, 2000-2010. We followed patients during the first year (365 days) after admission with respect to BZD prescriptions.

Paper II: Overdose deaths involving strong analgesics and/or benzodiazepines in Norway

A total of 231 Norwegian residents aged between 15 and 65 years died from a drug-overdose in the period 2006-2008 in Oslo and were registered in the NCDR (158, 159). The 231 deaths represented 30% of all overdose deaths (774 deaths) in Norway in the period. Those who had not undergone autopsy (n=7) and did not have toxicology report (n=1) were excluded from the study. Further, we excluded those with detection exclusively of other medications than BZDs or opioids, nonpharmaceuticals (i.e. illicit drugs such as heroin or central stimulants), and alcohol (n=56). This comprised a study sample of 167.

Overdose deaths were defined according to the classification of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for "drug-induced deaths" (170), which defines these deaths as 'directly due to use of illegal substances, although these often occur in combination with other substances such as alcohol or psychoactive medicines (Table 3). These deaths occur generally shortly after the consumption of the substance' and may be interpreted as overdoses/poisonings (170). They could include accidental poisonings, intentional poisonings (suicides with drugs), poisonings with an undetermined intent, or mental and behavioral disorders due to psychoactive substance use. In the present paper, carisoprodol was also included with opioids in the category of strong analgesics.

Table 3 Applied ICD-10 codes to define an overdose death.

Underlying cause of death	ICD-10 codes
Disorders	Opioids (F11), cannabinoids (F12), cocaine (F14), other stimulants (F15), hallucinogenes (F16), multiple drug use (F19)
Accidental poisoning	X42 [1], X41 [2], X44 [1+2]
Intentional poisoning	X62 [1], X61 [2], X64 [1+2]
Poisoning undetermined intent	Y12 [1], Y11 [2], Y14 [1+2]

[1] In combination with T-codes: T40.0-9 (poisonings by opioids, cocaine, and hallucinogenes).
[2] In combination with T-codes T43.6 (poisonings by psychostimulants with abuse potential).

Paper III: Methadone-related overdose deaths in Denmark

A total of 230 Danish residents aged between 18 and 67 died from a drug-overdose in the period 2006-2008 in Copenhagen, Aarhus, or Odense Municipality and were registered in the Danish Register of Causes of Death (126). The 230 deaths represented 29% of all overdose deaths (805 deaths) in Denmark in the period. Those who had not undergone autopsy (n=48) were excluded from the study. Further, we excluded those with detection exclusively of other medications than methadone, nonpharmaceuticals (i.e. illicit drugs such as heroin or central stimulants), and alcohol (n=52). A total of eight deceased had detection of buprenorphine, of which four deceased had concomitant detection of methadone, and these four were included in the study. This comprised a study sample of 130.

Overdose deaths were defined according to the classification of the EMCDDA for "drug-induced deaths" (Table 3; See further description at "Paper II: Overdose deaths involving strong analgesics and/or benzodiazepines in Norway") (170).

3.5 Subgroups of patients

In paper I, we defined two groups according to amount BZDs prescribed during the first year after admission: (i) yearly dose <584 DDD (moderate-high dose) and (ii) yearly dose ≥584 DDD (very high dose) (See "3.6 Measurements"). This amount of DDD was selected as patients in the upper quartile received a yearly BZD dose of ≥584 DDD. Further, we performed analyses in two different strata. In the first strata, we included patients with at least one prescription of BZDs in the year prior to admission (previous users). In the second strata, we included patients without prescription of BZDs in the year prior to admission (new users). To assess very long-term prescription of BZDs, only patients who had been prescribed BZDs in 2000-2007 were included in the analyses. For this subgroup analysis, patients were consecutively excluded if they had died during the year of assessment.

In paper II, we defined three groups according to the post-mortem toxicological findings: (i) only BZDs present; (ii) only strong analgesics present; and (iii) both BZDs and strong analgesics present. This was done in order to separate mono- from combined use.

In paper III, we defined two groups depending on if methadone had been prescribed and dispensed six weeks prior to methadone-related overdose deaths: (i) prescribed methadone and (ii) non-prescribed methadone. Further, of the deceased with detection of prescribed methadone, we defined two groups according to the prescribed daily dose of methadone: (i) methadone dose within recommended limits (60-120mg) and (ii) methadone dose outside recommended limits (<60mg; >120mg) (95).

3.6 Measurements

Type and amount of medication

The medications are classified according to the Anatomical Therapeutic Chemical (ATC) classification (171). The study used prescription data about opioids and BZDs from the DNPR, and prescription data about

opioids, carisoprodol, and BZDs from the NorPD. For each prescription, the numbers of DDD dispensed were recorded. A DDD is defined as the assumed average maintenance dose per day for a medication used on its main indication in adults. ATC code and DDD's for the different opioids, BZDs, and carisoprodol are presented in Table 4.

Methadone and buprenorphine are used for both OMT and pain treatment in Norway and Denmark. In the Danish study (Paper III), we included prescriptions of methadone and buprenorphine when these medications were prescribed for either indication. However, none of the persons in this study group had dispensed methadone and buprenorphine with pain as indication. In the Norwegian study (Paper II), we only included prescriptions of methadone and buprenorphine when these medications were prescribed for the treatment of pain. Carisoprodol was used in Norway until it was withdrawn from the market in May 2008, and has been shown to have a large potential for misuse as well as being a contributing factor in fatal overdoses (172, 173). Heroin-assisted treatment has been available in Denmark since 2009 (174). However, none of the included deceased with overdose deaths in Denmark had been prescribed heroin-assisted treatment prior to death (paper III).

All opioids, BZDs, and carisoprodol require prescriptions in Denmark and Norway. Data for BZDs and opioids were analyzed for the periods of four weeks, six weeks, eight weeks, and one year prior to death. In paper I, we used prescription of BZDs 1 year after treatment admission in (i) moderate-high doses and in (ii) very high doses as measurements (See "3.5 Subgroups of patients" for definitions). These measurements were investigated in both strata.

Table 4 ATC code and defined daily dose (DDD) of benzodiazepines, prescribed opioids, and carisoprodol (171, 173, 175-177)

	ATC code	DDD (oral administration)
Benzodiazepines		
Antiepileptic		
Clonazepam	N03AE01	8 mg
Anxiolytics		
Diazepam	N05BA01	10 mg
Chlordiazepoxide	N05BA02	30 mg
Oxazepam	N05BA04	50 mg
Lorazepam	N05BA06	2.5 mg
Bromazepam	N05BA08	10 mg
Clobazam	N05BA09	20 mg
Alprazolam	N05BA12	1 mg
Hypnotics		
Flurazepam	N05CD01	30 mg
Nitrazepam	N05CD02	5 mg
Flunitrazepam	N05CD03	1 mg
Estazolam	N05CD04	3 mg
Triazolam	N05CD05	0.25 mg
Midazolam	N05CD08	15 mg
Prescription opioids		
Morphine	N02AA01	100 mg
Hydromorphone	N02AA03	20 mg
Oxycodone	N02AA05	30 mg
Dihydrocodeine	N02AA08	150 mg
Codeine	N02AA59	[a]
Ketobemidone	N02AB01	50 mg[b]
Pethidine	N02AB02	400 mg
Fentanyl	N02AB03	0.6 mg[c]
Methadone	N02AC52/N07BC02	100 mg
Dextropropoxyphene	N02AC54	140 mg
Buprenorphine	N02AE01/N07BC01/ N07BC51	1.2 mg[d]
Morphine with scopolamine	N02AG01	10mg[e]
Tramadol	N02AX02	300 mg
Carisoprodol	M03BA02	1400 mg

[a] All codeine products are fixed combinations with acetaminophen. For the products that contain 400mg paracetamol, one DDD will represent 1600mg paracetamol and 120mg codeine. For the products that contain 500mg paracetamol, one DDD will represent 1500mg paracetamol and 90mg codeine.

[b] Parenteral and rectal administration only.

[c] Sublingual, rectal, and transdermal administration only.

[d] Parenteral, sublingual, and transdermal administration only.

[e] Parenteral administration only.

Exploratory variables

The exploratory variables used in paper I-III are listed in Table 5.

Table 5 Exploratory variables in paper I-III

Exploratory variables	Paper I	Paper II	Paper III
Gender	- Female* - Male	- Female* - Male	- Female - Male
Age groups (years)	At treatment admission date;* - 18 – 27 - 28 – 37 - 38 – 47 - 48 – 67	At date of death;* - <26 - 26-35 - 36-45 - >45	At date of death;* - ≤ 30 - 31-45 - >45
Permanent place of residency	NM	- Residency in Oslo* - Residency outside Oslo	- Copenhagen Municipality - Aarhus Municipality - Odense Municipality
Place of death	NA	- Residential address - Outside residential address	- Residential address - Outdoors - Public buildings - Institutions
Primary drug use at treatment admission	- Cannabis* - Methadone/ Buprenorphine - Heroin - Other opioids - Benzodiazepines -Central stimulating drugs[d] - Other illicit drugs/unknown	NA	NM
Psychiatric	Treatment received in 1 year prior to treatment admission;* - Yes - No	NA	Diagnosis;* - Yes - No
6-MAM/heroin[a,b]	NA	- Yes* - No	- Yes* - No

Methadone or buprenorphine[a]	NA	- Yes - No	NM
Non-prescribed strong analgesics[a]	NA	NM	- Yes - No
Non-prescribed benzodiazepines[a,c]	NA	NM	- Yes* - No

NA: not available.

NM: not measured.

* Variables included in the adjusted analysis. The variables included in the adjusted analysis were based on the statistical significance in univariate analysis which was set to p<0.05. Excluded variables from the adjusted analysis were added in turn to the multivariate model and multinomial model to test if the overall model fit (i.e. the residual variance) improved after their inclusion.

[a] In post-mortem toxicological findings.

[b] 6-MAM (6-monoacetylmorphine) is a unique metabolite of heroin: when detected in bodily fluids, its presence confirms the use of heroin.

[c] Nitrazepam, oxazepam, temazepam, bromazepam, lorazepam, chlordiazepoxid, clonazepam, nordazepam, flunitrazepam, alprazolam, diazepam.

[d] Amphetamine, cocaine, MDMA.

Cause of death

Underlying cause of death and additional diagnoses are registered according to ICD-10. The underlying cause of death, as well as other contributing causes, are registered based primarily on data from death certificates and, when available, results of a forensic autopsy. In the Danish and Norwegian studies, 79% and 97%, respectively, of all overdose deaths had undergone a post-mortem toxicological examination (126, 158).

Detection of substances in the post-mortem toxicological examination

The Danish and Norwegian toxicological evaluations of the detected substance concentrations were performed according to the experience and established procedures at the participating institutes and in line with reports from the literature (3, 178-180). In the Danish sample, the forensic institutes decided not to determine a main intoxicant as this judgment often is connected with uncertainties. In the Norwegian sample, deaths caused by overdose were recorded according to the drug that forensic pathologists in Oslo judged to be the main intoxicant.

Heroin is rapidly metabolized to 6-monoacetylmorphine (6-MAM) and further to morphine. Consequently, if 6-MAM was not detected, it was impossible to determine on the basis of the analysis whether heroin or morphine was used. However, heroin intake was often indicated in police reports. In the studies included in this thesis, fatal intoxication by heroin/morphine was verified by the presence of morphine in the blood and, in many cases, also by the presence of 6-MAM in a biological specimen (usually blood or urine).

Prescribed vs. non-prescribed medication

Detection of BZDs and strong analgesics was defined as non-prescribed if the medications had not been dispensed to the deceased during the four weeks prior to death. However in the Danish study (Paper III), detection of methadone as OMT medication was defined as non-prescribed if the medication had not been dispensed from the pharmacy or a drug treatment facility to the deceased during the six weeks prior to death. This was done as methadone as OMT in Denmark is usually dispensed once a week but in some cases dispensed up to once in six weeks, as according to clinical guidelines.

3.7 Data analysis

In paper I-III all analyses were conducted using SPSS version 19.0 for Windows [26].

Chi-square test, Fischer´s exact test, Students t-test, and ANOVA were performed, whenever appropriate, to compare characteristics in the analyses in paper I-III (Table 6). Chi-square test was performed to investigate whether distributions of categorical variables differ from one another, when n≥20 observations in each variable. When n<20 observations in one or more categorical variables, Fischer´s exact test was performed. Students t-test was performed to investigate whether the means of continuous variables were different in the two groups. When the means of continuous variables in three or more groups were compared, ANOVA was performed. The level of significance was set to $P<0.05$

Table 6 Statistical analyses used for paper I, II, and III

Statistical analysis	Paper I	Paper II	Paper III
Chi-square test	x	x	x
Fischer´s exact test		x	x
Students t-test			x
ANOVA	x		
Multivariate logistic regression		x	x
Multinomial logistic regression	x		

In paper I, we assessed the proportion of different types of BZDs in the moderate-high and the very high dose categories in both previous and new users. A subgroup analysis was performed on previous and new users of BZDs in 2000-2007 regarding the proportion with very long-term prescription of BZDs. As the outcome variable has more than two values while the exploratory variables were both continuous and categorical, we used multinomial logistic regression (95% CI) in both strata to determine the associations of the exploratory variables on relative risk for having prescription of BZDs in (i) moderate-high doses and in (ii) very high doses. We assessed the proportion (%) with 95 % confidence intervals (CI) of different categories of psychiatric diagnoses that was given to patients without and with prescription of BZD in moderate-high and very high doses in the year after admission.

In paper II, descriptive statistics on the three groups regarding mean, median, and range were presented in relation to amount dispensed, measured as DDD, and number of prescriptions dispensed of the medications in the periods of 4 weeks and 1 year prior to death. As the outcome variable was binary (yes/no) while the exploratory variables were both continuous and categorical, we used multivariate

logistic regression (95% CI) to determine the associations of the exploratory variables and outcome by estimating odds ratio for having detection of non-prescribed BZDs and/or strong analgesics.

In paper III, groups with different prescribed daily doses of methadone were compared regarding socio-demographic characteristics, somatic diagnosis, psychiatric diagnosis, and toxicological findings at the time of death. Differences in detection of non-prescribed BZDs were investigated among deceased with detection of prescribed (dispensed at a pharmacy or at a drug treatment facility) or non-prescribed methadone. As the outcome variable was binary (yes/no) while the exploratory variables were both continuous and categorical, we used multivariate logistic regression (95% CI) to determine the associations of the exploratory variables and outcome by estimating odds ratio for having detection of non-prescribed methadone.

3.8 Ethics

Paper I and III

The studies were approved by The Danish Data Protection Agency, who approved all procedures in relation to data collection from all used databases, and also storage of the data. Use of information from medical records and medicinal administration records was approved by the Danish Health and Medicines Authority. The National Committee on Health Research Ethics in Denmark was informed about the study and determined that the study did not need to be reported to the Committee. All linkages were performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.

Paper II

Permission was given by the Higher Prosecuting Authority in Norway to access autopsy reports. The record linkage was approved by the Norwegian Data Inspectorate and endorsed by the Regional Committee for Medical Research Ethics.

4.0 Results

4.1 Aim I: Prescription of addictive medication in connection with treatment

A total of 33,203 patients were admitted for outpatient treatment for all types of DUDs during an 11 year period in Denmark (paper I). During the first year after admission to treatment, approximately one-quarter of the patients (N=8705, 26.2%) were prescribed BZDs (BZD users). Of these patients, 29.5% (N=2566) had not been prescribed BZDs in the year prior to treatment (new users).

Indicators of inappropriate prescribing of addictive medication

We investigated likely indicators of inappropriate prescribing of BZDs to patients admitting for treatment for DUDs. These indicators included; long-term prescription, high doses, less than optimal types of BZDs, and co-prescription of opioids.

Long-term prescription was investigated among previous and new BZD users. We found that a high proportion of patients with previous prescription of BZDs continued into very long-term use of prescribed BZDs after admission (4 years after admission: 62.6%) (Figure 1). Of the new users, approximately one-quarter (27.5%) continued into very long-term use of BZDs during the study period. The doses prescribed were investigated among all BZD users, of which more than one-third (35.5%) were prescribed BZDs in dose levels that might indicate inappropriate prescription (>365 DDD per year (as an example, the DDD per day for diazepam is 10 mg, equivalent to 3650 mg per year)). The prescribed mean yearly dose was 438.1 DDD. Diazepam was the most commonly prescribed type, and approximately one-third (34.6%) were prescribed more than one type of BZDs. Among patients with opioid use, 43.2% were prescribed BZDs which was three times higher than for patients with cannabis (12.2%) or central stimulating drugs (13.8%) as primary drug use.

Figure 1 Proportion of patients (%) with very long-term prescription of benzodiazepines after admission for treatment for drug use disorders (Paper I)
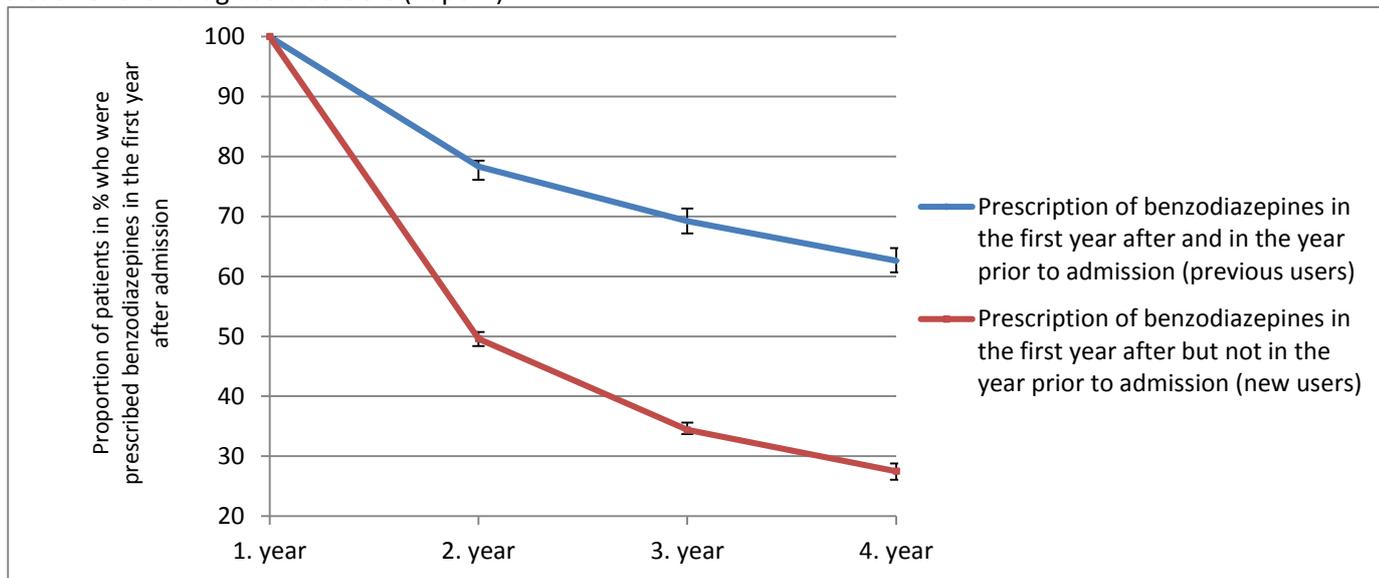
Indicators for an underlying psychiatric disorder

As a likely indicator for an underlying psychiatric disorder, we investigated the initiation of psychiatric treatment for BZD users after admission to DUD treatment. We found that admitting to treatment for DUD did not increase the specialized psychiatric treatment coverage of this patient group, disregarding use of prescribed BZDs.

4.2 Aim II: Addictive medication as involved factor in overdose deaths

We investigated BZDs and/or strong analgesics as involved factor in overdose deaths in Oslo, Norway (Paper II). By using the sample from Denmark, where methadone is widely used, we further investigated specifically methadone as involved factor in overdose deaths (Paper III).

Overdose deaths involving addictive medication

In Oslo, Norway, 167 individuals (72.0% of all overdose deaths) were recorded as having deaths related to the use of BZDs and/or strong analgesics as confirmed by post-mortem toxicological findings during a three year period. The median age at death was 36 years (interquartile range: 27-47 years).

In Copenhagen, Aarhus, and Odense Municipality, Denmark, methadone was detected in 130 overdose deaths (71.4% of all overdose deaths) during a four year period. The median age at death was 45 years (interquartile range: 38-51 years). In the same period, about three-quarters had detection of BZDs and/or strong analgesics (n=142; 78.0%), and BZDs only were detected in two-thirds of all overdose deaths (n=122; 67.0%) (unpublished results).

Detection of addictive medication and illicit non-prescription drugs

We investigated the deceased with detection of prescribed vs. non-prescribed addictive medication. In the Norwegian sample, we found that a lower proportion of the deceased (with detection of the target medications) had been prescribed BZDs (28.1%), strong analgesics (33.3%), or BZDs plus strong analgesics (50.0%) four weeks prior to death. However, in Denmark the majority of deceased with methadone-related overdose deaths (63.1%) were prescribed methadone as part of MMT at the time of death. In a subgroup analyses of the Norwegian sample, we found that particularly among the deceased with a permanent place of residence outside Oslo (30.5% of all deceased), a low proportion of the deceased were prescribed addictive medication (of the target medications) prior to death (11.3%).

We further examined if the deceased had co-detection of illicit non-prescription drugs (heroin, cocaine, amphetamine/methamphetamine, ecstasy, or cannabis). We found that more than two-thirds of the deceased in both the Norwegian sample (77.2%) and the Danish sample (68.5%) had co-detection of at least one illicit non-prescription drug.

4.3 Aim III: Comparison of overdose cases with and without prescribed addictive medications

Comparison of overdose cases with and without prescribed addictive medications

We compared the deceased with and without legally prescribed addictive medications detected in the blood. Overall, we found that deceased with detection of non-prescribed addictive medication had a younger age and co-detection of other non-prescribed addictive medications and illicit non-prescribed drugs (not significant in adjusted analysis in the Norwegian sample).

Further, we investigated the differences in proportion of non-prescribed BZDs detected among deceased with detection of methadone dispensed at a drug treatment facility or pharmacy and compared to deceased with detection of non-prescribed methadone (Figure 2). We found that non-prescribed BZDs were more often co-detected among those with detection of non-prescribed methadone (80.0%) compared to those with methadone dispensed at a pharmacy (25.0%) (P<0.001).

Figure 2 Overdose deaths with prescribed (dispensed at a pharmacy or at a drug treatment facility) or non-prescribed methadone in the post-mortem toxicological findings and co-detection of prescribed and non-prescribed benzodiazepines, N=95
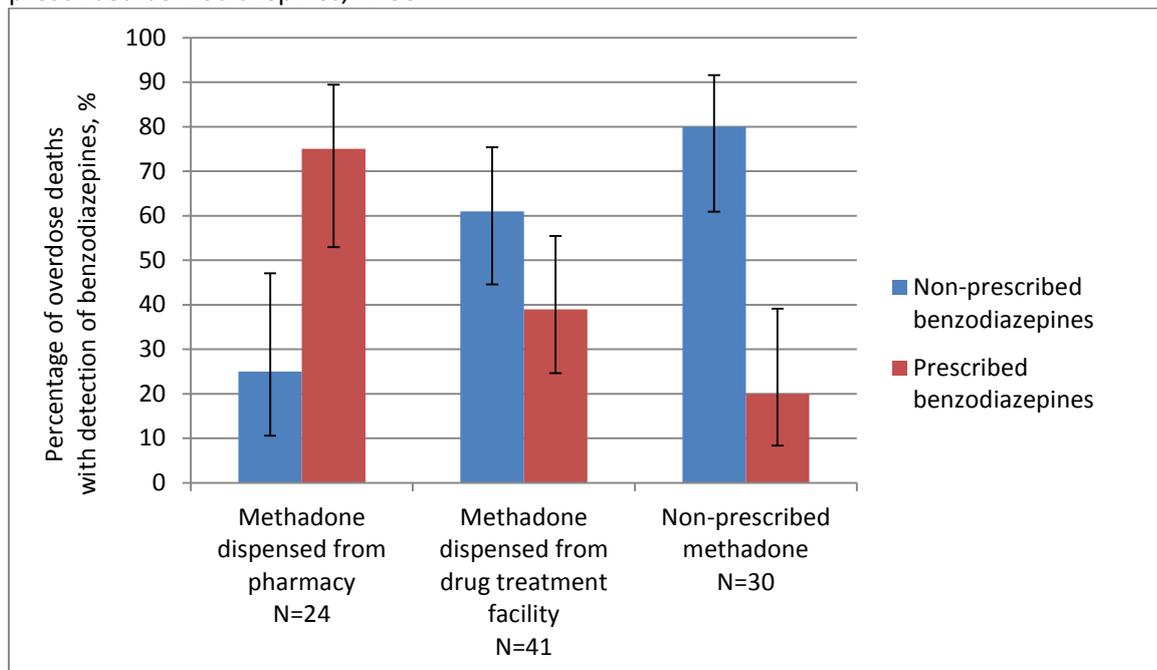
Following types of benzodiazepines were detected in the post-mortem toxicological findings: nitrazepam, oxazepam, temazepam, bromazepam, lorazepam, chlordiazepoxid, clonazepam, nordazepam, flunitrazepam, alprazolam, diazepam.

Factors associated with having detection of non-prescribed addictive medication

In the Norwegian sample, results from multivariate logistic regression showed that the detection of non-prescribed BZDs and/or strong analgesics after adjustment was associated with younger age (a-OR=4.9; 95% CI, 1.4-18.0) and to have a permanent place of residence outside Oslo (a-OR=2.9; 1.1-8.1). In the Danish sample, results from multivariate logistic regression showed that the detection of non-prescribed methadone was associated with younger age of 30 years or below (a-OR=9.5; 1.8-50.5), concomitant detection of 6-MAM/heroin (a-OR=3.1; 1.2-7.8), and non-prescribed BZDs (a-OR=4.0; 1.3-12.3).

4.4 Aim IV: Investigation of prescribing and dispensing patterns

In general, the prescribed doses of the addictive medications among the deceased were higher than recommended. Further, the control/monitoring measures were insufficient and allowing use of multiple prescribing physicians (Norway), no supervised intake of OMT medication (Denmark), and use of multiple prescribed addictive medications (Denmark).

In the Danish sample, almost half (43.8%) were prescribed a higher methadone dose than 120mg daily, and 8.8% were prescribed a lower methadone dose than 60mg daily. We investigated detection of BZDs and supervision of methadone intake in different prescribed dose categories of methadone. We found that deceased who were prescribed a methadone dose outside recommended limits (60-120mg) were more likely to have detection of prescribed BZDs (33.3% and 31.0% vs. 64.3%, P<0.001) and not having supervised intake of methadone, as compared to being prescribed a methadone dose within recommended limits (28.6% and 20.0% vs. 50.0%, P<0.001).

4.5 Brief summary of main findings

In the period after entering treatment and in the period prior to overdose death, addictive medication was often prescribed to individuals with DUD. In both periods, inappropriate prescription patterns were identified.

After entering treatment, addictive medication and particularly BZDs were prescribed with multiple and non-optimal types, high doses, on long-term basis, and with co-use of opioids. Among overdose deaths involving addictive medication, the post-mortem toxicological findings revealed two different groups of deceased with detection of prescribed vs. non-prescribed addictive medication. The deceased with detection of non-prescribed medication constituted the majority. They were in general younger, lived outside a major city, and used illegal sources to obtain multiple types of non-prescribed addictive medications and illicit drugs. The deceased with detection of prescribed medication used more legal sources to supply their drug use. Overall, they were prescribed addictive medication in patterns indicating misuse with doses that were higher than recommended, and with insufficient control/monitoring measures allowing use of multiple prescribing physicians with prescription of additional addictive medications. These insufficient control measures were particularly observed among deceased with detection of methadone, where the majority was enrolled in a liberal MMT program with prescription of higher doses of methadone combined with BZDs and with no supervised intake of OMT medication.

5.0 Methodological considerations

5.1 Type II error

A type II error fails to reject the null hypothesis, although the alternative hypothesis is the true state of nature. It confirms an idea that should have been rejected, claiming that two observances are the same, even though they are different (181).

Research on small patient groups is challenging. Norway and Denmark only have 5 and 6 million inhabitants, respectively, and the number of overdose deaths involving addictive medication is numerically relatively low in research terms, although also represent too high numbers of human suffering. In Denmark it is difficult to conduct nationwide studies including information on prescription practices of OMT medication as most OMT medication dispensed at drug treatment facilities are not registered on an individual level in the national prescription register but kept registered locally at the drug treatment facilities. As the majority of the 98 municipalities in Denmark administer their own drug treatment facility, a large and time consuming study setup would be necessary to collect data from all drug treatment facilities.

Some challenges with small sample sizes are that existing differences are not detected as the sample sizes are too small to show these differences. These concerns apply to two of the three studies (Paper II and III) included in this thesis. Our samples from paper II and III were included from all overdose deaths in Norway and Denmark, respectively. In Norway, we included overdose deaths from the Norwegian capital, Oslo, which in total hold around 600,000 (12%) of Norway's population. In Denmark, we included overdose deaths from three of the largest municipalities which in total hold around 1.1 million (19%) of Denmark's population. In each country around 230 overdose deaths occur each year. Our study criteria allowed inclusion of 167 subjects over a three year period in Norway, and inclusion of 130 subjects over a four year period in Denmark.

In both our studies investigating overdose deaths (Paper II and III), we found that was no association between gender and detection of non-prescribed medication. Our result of no association is supported by another larger study investigating overdose deaths involving addictive medication (74). Moreover, in both our studies we found that younger age was associated with having non-prescribed methadone which is in line with another study (74). In the Danish study investigating overdose deaths (Paper III) we found that concomitant detection of heroin was associated with having detection of non-prescribed methadone. However, in the Norwegian study (Paper II), this association (a-OR=1.2; 95% CI 0.5-2.6)) was not statistically significant. Another study found that concomitant detection of an illicit non-prescription drug (cocaine, heroin, or methamphetamine) was associated with having detection of non-prescribed addictive medication. In the Norwegian study, the lack of association might be due to too low numbers included in the study.

Overall, the sample sizes included in our studies are considered appropriate in order to estimate effects based on a limited number of covariates and can also provide prevalence measures. However, a tendency towards an underestimation of associated variables may be present in the multivariate logistic regression analyses in two of the studies (Paper II and III).

5.2 Selection bias

Biases are systematic errors, can arise in all phases of epidemiological studies, and lead to erroneous estimations of the true association between an exposure variable and the outcome. Selection biases represent common violations of internal validity and stem from the procedure used to select subjects and from factors that influence study participation (182). They are present when the exposure and/or outcome differ between those who participate and those from the source population who do not participate in the study.

An overdose death, being an important outcome measure in our studies, was identified according to a defined set of ICD-10 codes as described in the 'Material and methods' section. The validity of our identification of overdose deaths depends largely of the correctness of the statement of the underlying cause of death from the national cause of death registries (161).

Forensic autopsy and toxicological analysis are mandatory in all cases of suspicious deaths including suspected overdose deaths. However in 21% of all cases with overdose deaths as identified from the Danish Register of Causes of Death, a forensic autopsy and toxicological analysis was not performed (126). The majority of these deaths had an F-code as the ICD-10 code for underlying cause of death. Deaths with an F-code as underlying cause are typically deaths of a known drug user where drugs presumably have been involved as a central contributing cause. Nevertheless, these deaths are typically coded without autopsy and toxicology and hence with less confirmed knowledge of the cause of death, and are rather based more on assumptions made by the doctors issuing the deaths certificates. Therefore there is a likely omission of methadone-related overdose deaths included in paper III, in particular among those in the group without autopsy. In comparison, forensic autopsy and toxicological analysis were not performed in 3% of all cases with overdose deaths as identified from the Norwegian National Cause of Death Registry (159). This proportionally decreases the risk of omission of including overdose deaths involving addictive medication in paper II. Previous studies have estimated the impact on mortality statistics by the lack of post-mortem examination in cases of sudden death of adults (183). It was found that the reported cause of death in 30% of the cases had to be changed after an autopsy was performed.

The three different departments of forensic medicine in Denmark use the same methods to measure the concentration of the substances and also use similar thresholds of concentrations to determine when a test is positive for a substance. Of the overdose deaths identified from the Norwegian National Cause of Death

Registry, almost all (94%) were examined at the Institute of Forensic Medicine at the University of Oslo (158). The remaining deaths were examined at a hospital. However, it may have introduced measuring bias if the method or threshold value was changed during the course of the study period.

The cohort including patients admitting for DUD treatment included unselected individuals with a DUD that require care at a drug treatment facility, and encompassed all individuals registered in Denmark (Paper II). For types of DUDs that can also be treated in e.g. general practice, cases included in the study may to some degree represent a selected patient group, with either high severity of the DUD in question (e.g. cannabis use disorder) or a combination of different DUDs leading to a lower threshold for contact or referral to a drug treatment facility compared with patients without a such a combination of DUDs.

The cohort from one study (Paper I) included in the thesis comprised all individuals admitting for outpatient DUD treatment in Denmark and thus can be regarded as a complete national cohort of patients. The samples from two of the studies (Paper II and III) were included from defined regions in Denmark and Norway. As all overdose deaths within these regions were assessed for eligibility, the samples can be considered complete and without selection. Compared to similar studies including overdose deaths involving addictive medication, the sample sizes are reasonable (74, 113, 149, 184-187). In conclusion, substantial selection mechanisms were not likely present in the study material. The cohort/samples may be considered representative for the situation in Oslo and in particularly urban areas in Denmark in the described study periods, and similarly the calculated estimates in the studies are relatively robust.

5.3 Information bias

Information bias has been defined as systematic error that occurs when the information collected from or about study subjects is erroneous or misclassified (188).

Data from the DNPR and the NorPD was used in paper I+III and paper II, respectively. Data on dispensed drugs was registered at pharmacies so it can be assumed that the information retrieved from the registries is accurate and represents prescriptions dispensed. Therefore the risk of information bias is considered low. The ATC and DDDs were used to describe prevalence and amount of the prescription medication used. In 2007, 2% of the prescriptions dispensed in NorPD had invalid personal identifications numbers (169). For the DNPR, the proportion of dispensed prescriptions with invalid personal identifications numbers has recently been estimated to below 2% (189). Prescriptions with invalid personal identification may have contributed to a slightly lower proportion of deceased who had been prescribed addictive medication prior to death. For the same reason, it may be that the amount of the different addictive medications is slightly underestimated.

Each medication detected in the overdose deaths could either be prescribed or non-prescribed according to whether the medication was dispensed to the deceased 4 weeks prior to death or not. Therein lays an underlying assumption that the dispensed medication is consumed by the individual within 4 weeks prior to death. 4 weeks is a relatively conservative limit compared to other studies where the limit was set either 30 days (74), 60 days (185), 1 year (190), or any time prior to death (111, 191). Therefore the specificity of our studies in including medication as prescribed may be higher than other studies, and the specificity of our studies in including medication as non-prescribed may be accordingly lower. Moreover, dispensed medications from pharmacies and drug treatment facilities are not necessarily consumed by the recipients and this study cannot account for individuals who may have given away or sold their prescribed medications. Also, if individuals enrolled in MMT

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used non-prescribed methadone in addition to prescribed methadone at time of death, the study was not able to record the use of non-prescribed methadone.

Data from the NPR and the PCRR was used in paper I and paper III. Private hospitals and clinics are potential sources of underreporting in registries (192). Although it has been mandatory for private health care providers to report all activities since 2003, and the Danish Health and Medicines Authority runs information campaigns to promote registration, registration from private hospitals and clinics remains incomplete (193). Private hospitals offer services paid by taxes due to the rules of "free hospital choice" or as part of an agreement with a region, as well as services paid privately either by insurance companies or private parties. Services paid for by private parties have the highest degree of incomplete registration (193). As a consequence we may have underestimated the proportion of patients/deceased who have received a psychiatric/somatic diagnosis and/or received treatment, although drug using populations in general may be less likely to privately pay for health care services.

Overall, there was a tendency towards underreporting in estimates involving individuals being prescribed medication and being in contact with health care services. The consequence might be that a higher proportion of individuals admitting for DUD treatment were prescribed BZDs than reported in the study, and hence that our current estimates are conservative (Paper I). However, as to the proportional difference in individuals receiving specialized psychiatric care prior to and after admission to DUD treatment, it is likely that our estimates were not influenced, as the potential underreporting was influencing both groups equally. The consequence of underreporting among individuals with overdose deaths might be, that the estimated proportion of individuals with detection of legally prescribed medication and also the associated amounts prescribed was too low (Paper II and III). However, as the proportion of dispensed prescriptions with invalid personal

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identifications numbers is very low, it is likely that the underreporting is limited and the influence on

our estimates equally low.

5.4 Confounding

Confounding has been defined as "the confusion, or, mixing, of effects" (188). This definition suggests that

effects of one or more variables are mixed with the effects of exposure, which leads to a bias (188).

Overall, the studies included in this thesis were limited by the predetermined variables of the

different registries that we used in the studies. This made our results potentially vulnerable to

confounding variables that we could not observe and/or control for. A confounding factor is a

variable that is independently related to both the exploratory variable of interest and the outcome,

without being on the causal pathway in between these, and whose presence may partly or entirely

explain the association between these (188). The distortion caused by a confounding factor can be

large, and it can lead to overestimation or underestimation of an effect depending on the direction

of the association with the confounding factor (194). The effect of confounding may however be

reduced through stratification or adjustment in multivariate analysis, thus stratification and/or

adjusted multivariate analysis were applied in all the papers presented in this thesis.

Of the patients who admitted for DUD treatment, the majority (64.1%) dropped out of treatment

within 1 year after admission (Paper I). Of these patients, one-fifth (21.9%) were prescribed BZDs in

the year after admission. In comparison, of the patients who stayed in drug treatment 1 year after

admission or more, one-third (33.9%) were prescribed BZDs. One explanation for this difference in

proportion of BZD users between the two groups might be that some patients were not offered

substitution for an illicit BZD use and therefore dropped out of treatment. It has previously been

argued that use of long-acting BZD can be helpful in some circumstances, especially to retain people

with cooccurring severe anxiety disorders who are receiving treatment for DUD (195, 196). Another explanation might be that cannabis users in general often drop out of treatment and that the effects of cannabis, as opposed to opioids, are not increased by using BZDs and hence more rarely combined. Our findings support the latter explanation as patients with cannabis use disorder were more likely to drop out of treatment than patients with other types of DUD and at the same time less likely to be prescribed BZDs.

Channeling bias (confounding by indication) was assessed for prescription of BZDs among patients in treatment for DUD (Paper I). Channeling bias is a form of confounding that occurs when a drug is preferentially prescribed to individuals with certain characteristics. For example, patients with DUD often have comorbid psychiatric disorders and particularly anxiety disorders which is an indication for prescription of BZDs. We found that patients with opioid use disorders were more often prescribed BZDs than patients with other types of DUD. This finding may be due to the misuse potential of the BZD and opioid combination use, but may also be due to higher prevalence of anxiety disorders among patients with opioid use disorders. However, we found that the proportion of patients with opioid use disorders receiving psychiatric treatment received in 1 year after admission was not higher compared to patients with other types of DUD. This finding is supported by other studies where patients with different types of DUD, involving opioids, cannabis, or central stimulating drugs, had similar prevalences of anxiety disorders (86).

In two of the studies included in this thesis, we examined overdose deaths involving addictive medication (Paper II+III). However, the blood concentration by the toxicological examination of each substance detected is not registered in the data used for these studies. Some of these medications might have had documented lethal levels at the toxicological examination that lie within concentrations ranges commonly seen when the drugs are misused. Others might have concentrations that can be achieved in drug users

who have built up tolerance to the medication, for example BZDs and methadone. A stratification of prescribed addictive medication in different levels of blood concentration might more clearly reveal the causal role of the addictive medications (leading back to the prescription practices) in the overdose deaths and reduce the effects of a potential confounder. However, after such stratification we would still not be able to surely record if individuals used non-prescribed addictive medication in addition to prescribed addictive medication at time of death. Also, patients receiving MMT may be at risk of a fatal intoxication when combining even prescribed medications and therapeutic concentrations of methadone with other psychoactive substances (140). On the other hand therapeutic concentrations of methadone may be fatal when the drug is misused by sporadic or naïve users. Therefore it is difficult to determine to what extent that methadone contributed to the overdose in the methadone-related deaths, particularly for deceased receiving MMT. However, a patient that is stable in OMT without a concurrent drug misuse should not overdose.

To suggest generalizability of the findings in a study, a high internal validity is a prerequisite. The studies included in this thesis are all based on registries of high quality and involve reasonable sample sizes (160-162, 197). Therefore, our estimates might overall be considered reliable. However, particularly among the prevalence estimates, a tendency towards underreporting is suggested. Moreover, in two of the studies (paper II and III), existing associations may not have been detected due to lack of power.

5.5 External validity

The process of generalization in science involves making assumption about the domain in which the study apply, and is often a question of whether the factors studied distinguish the studied groups from other groups, and somehow modify the results from the study (194). Before generalizing the findings reported in the studies included in this thesis it is important to recognize that there may be differences between the

cohorts studied and the corresponding drug using populations in Denmark, Norway, and other European countries. There are marked variations between countries, both in the cultural context of drug use, and with regard to the legal, administrative, governmental, and medical framework (119). Furthermore, the organization of drug treatment and OMT is more or less unique for each country. During periods under investigation in the Danish studies (Paper I and III), the criteria for admission and re-admission to drug treatment and OMT in Denmark were less strict than other European and particularly Nordic countries. It has been suggested that increased and easy access to treatment could make patients more prone to drop out, which might partially explain the high drop-out rate during the first year after admission (Paper I) (198). In addition, the OMT in Denmark has been described as liberal with prescription of higher doses of methadone and co-prescription of BZDs combined with less strict control measures including unsupervised intake of OMT medication as compared to other countries (132).

Countries in different parts of Europe differ with regard to prescription practices of addictive medication including opioids and BZDs (19). Norway and particularly Denmark has one of the highest per capita opioid consumptions for medical purposes in Europe and the world (19, 41, 199). Regarding BZDs, the prescribing of this medication in Denmark and Norway is high but has been decreasing during the past decade (21, 22). As addictive medication is prescribed in all European countries, also misuse of addictive medication is observed across Europe (7). However, regional trends in medicine misuse indicate heterogeneity across the European countries with respect to misused medication types (7).

Also the preferred drugs among drug users and route of administration differ among European countries. Norway, and particularly Oslo, has experienced challenges related to injecting use of heroin. Comparison of drug use patterns among European countries shows a variance with respect to IDUs. Estimates range from 2.6 (IDUs per 1000 inhabitants) in Germany to 4.8 in Luxembourg. Both Norway and Denmark fall within the high end of this range with an estimated rate of 4.3 (200).

In Denmark, we studied the OMT strategies among methadone-related overdose deaths in municipalities including three of the largest cities in Denmark. First, as we examined the prescription practice of addictive medication prior to overdose deaths, this practice may not necessarily apply to all patients in OMT who are alive or died of other causes. For example, we found that, the mean methadone dose prescribed to the deceased was 146mg daily. In comparison, the mean methadone dose prescribed to all individuals receiving MMT in the same period was lower (125mg daily) (126). Second, as the OMT strategies of the different municipalities differ in Denmark, the OMT strategy described in the study may not apply to the overdose deaths occurring in other municipalities (201). Third, as the overdose deaths primarily occurred in larger cities, it may primarily describe an urban phenomenon. However, the three municipalities included in the study represent different regions of Denmark, and overdose deaths occurred in most Danish municipalities in the same period of time (126). Hence, although our findings primarily cover urban areas in Denmark, it is probable that they may also be considered representative for overdose deaths in Danish municipalities outside the current setting.

However, despite the variations in treatment settings and drug use patterns between different countries and municipalities, the non-medical use of addictive medication and also overdose deaths involving addictive medication are increasing issues of concern across Europe and other regions (3, 7, 39). Previous international studies conducted in a range of different countries have found that less than optimal prescription practices of addictive medication as described in our studies may influence the risk of an overdose death (120, 145, 186). Moreover, high prescription rates of addictive medications, including BZDs, have previously been described in other countries than Denmark investigating drug users in treatment (82, 202, 203). Overall, this suggests that it is possible that our findings can be of relevance to the Nordic countries and other Northern European countries. Particularly, it suggests that our findings can be generalized to urban areas in countries with high rates of injecting drug use and poly drug use patterns. In

conclusion, it is therefore believed that the described patterns of high prescription rates of addictive medication to drug users combined with inappropriate prescription practices of addictive medication prior to overdose deaths can be useful in other settings. However, the exact effect sizes of the patterns are likely to vary across settings.

5.6 Strengths

The studies include three different cohorts from two Nordic countries. Combined, the studies are thought to present a relatively large set-up aiming to investigate the role of addictive medication and associations with drug treatment and overdose death.

In most countries, the linkage of data are made by an exact match on first name, last name, and birth date to link records. However, data entry errors, e.g. misspelled names, transposed digits, may complicate the task of linking (204, 205). In Denmark and Norway, records are linked by using the unique personal identification number assigned to all residents. An important strength of the studies included in this thesis was hence to have a good match between each included patient/case and the information from the different applied registries, and thereby low rates of missing data. Moreover, appropriate population-based study designs can reduce selection biases in cohort studies for three reasons (193). First, the Danish and Norwegian populations have a relatively stable and homogeneous demography with regard to race and religion. Second, the universal health care system, including drug treatment, prevents selection bias arising from selective inclusion of specific regions or age groups. Third, virtually complete follow-up of all individuals is possible as the Danish and Norwegian civil registration systems record vital status and migrations on a daily updated basis (206). In Denmark, the civil registration system has a prevalence of disappeared individuals on around 0.3 % (206).

In all three studies, we investigated dispensed medication in relation to drug treatment or overdose death. Studying dispensed, rather than prescribed medication has an advantage since some individuals may not comply with treatment and fail to go the pharmacy to hand in the prescription (207). Consequently, the prescribed medication may not be dispensed. Following all individuals to control that they actually ingest the medication is not possible. Therefore, studying medication that is dispensed is probably the closest we can get to accurately describe use of prescribed medication in a population (208). Studies investigating information on prescribed medications recorded in prescription databases, and compared this information with selfreported medication use, have been conducted among other population groups (such as pregnant women, adolescents, and children with asthma) than patients with DUD (209-212). The studies indicated that the prescription data can give valid information on medications used for chronic conditions. However, information on medications used for acute conditions is less valid.

To our knowledge, no previous studies have investigated prescription of addictive medication to patients with other types of DUD than opioid use disorder. We used a complete national cohort of patients admitting for treatment for all types of DUD to investigate addictive medication in relation to drug treatment. This included all patients who subsequently admitted to DUD treatment in the period of 2000-2010.

6.0 Discussion of results

6.1 Aim I: Prescription of addictive medication in connection with treatment

Consistent with previous findings, patients with DUD were frequently prescribed addictive medication and particularly BZDs (82, 202, 213). Compared to the general population in the same age group and same time period in Denmark (one year prevalence 5-6%), the prevalence of being prescribed BZDs was five times higher among patients with all types of DUD, and 8 times higher among patients with opioids as primary drug use (214). Previous studies have speculated whether this excess prescription of BZDs to patients with DUDs reflected a true need for treatment for psychiatric disorders or an inappropriate prescription practice of BZDs in DUD populations (82). Collectively, our findings, as described in the following, point toward an inappropriate prescribing practice of BZDs in many cases more than treatment for psychiatric disorders (Paper I).

Inappropriate prescription of addictive medication

Each type of BZD possess different effects in terms of half-life and speed of onset, and their appeal to drug users as a source of drugs to get high differ accordingly (53). We found that diazepam was the most commonly prescribed type of BZD followed by oxazepam. In comparison, a Norwegian study investigating BZDs prescribed to patients receiving OMT found that oxazepam was the most commonly prescribed BZD followed by diazepam. Use of BZD types with a faster onset, such as diazepam, may provide a more immediate and desirable euphoriant effect (215). In line with its pharmacokinetic abilities, diazepam is one of the most commonly misused and desired type of BZDs among drug users and also often detected in opioid-related deaths (53, 149, 216-218). On the other hand, types of BZDs with a slow onset, such as oxazepam, have a less euphoriant effect and are therefore recommended as medication of choice for this group of patients (82, 215, 219).

Moreover, one-third was prescribed more than one type of BZD which is about twice the proportion as compared to the findings of a study including individuals with depressive and/or anxiety disorders (220). Use of more than one BZD at a time may indicate inappropriate use of BZDs and may also indicate use of multiple prescribers (220).

The amount of BZDs prescribed in this study was measured by use of DDD (Defined Daily Dose). Therapeutic amount of BZD for its main indication is defined as 1 DDD per day, equivalent to 365 DDD per year (171). In our study, one-third (35.5%) was prescribed above 365 DDD per year, which is higher than the findings of studies among general populations (6.1-18.5%) (221-223). Use of BZDs in higher doses than recommended may be due to development of tolerance and associated dose escalation (18, 224). However, as BZD users who misuse their BZDs are more likely to exceed the recommended dose than other BZD users, prescription of higher amounts than 365 DDD per year may also indicate inappropriate use of BZDs (225).

We found that of the patients using BZDs during the first year after admission, about one-quarter of new users and two-thirds of previous users continued to use for the following 4 years. These findings are consistent with previous studies of very long-term use among general populations of Norway, Sweden, and the USA (only 3 three years of follow-up) (226-228). Although long-term use of BZDs is a very common phenomenon, it may also be an indicator of other disorders and conditions (20). Long-term use of BZDs is associated with having a psychiatric disorder and also conditions such as poor health, stress, and pain (229). Moreover, it may indicate inappropriate use of BZDs where BZDs are an integral part of a drug use pattern (220).

In our study, almost all patients, who were prescribed BZDs, did not report BZDs as their primary drug use at treatment admission. This might either reflect that the patients perceived their use of BZDs as treatment

for psychiatric disorder or that they did not consider their BZDs misuse as their main problem. Other studies have found that more than three-quarters of patients with a BZDs misuse did not report BZDs as their primary drug use at admission (230). Hence, patients admitting to treatment for DUD often use other drugs, particularly opioids, in addition to BZDs. Concurrent use of BZDs among long-term opioid users has been reported to independently increase the risk of emergency department visits, visits for alcohol and drug-related medical encounters, overdose, and opioid and non-opioid misuse/dependence (231-234). BZDs are able to enhance the positive subjective effects of opioids, and evidence of the dangers of simultaneous prescription and use of BZDs and opioids continue to build (43, 231).

Prescription of addictive medication as treatment for psychiatric disorders

Prescribing BZDs is mainly approved for short- to intermediate-term treatment in low doses. However, BZDs are not indicated for long-term use, except in the case of severe generalized anxiety disorder (235, 236). Therefore, a higher prevalence of generalized anxiety disorders among patients with DUD could be a possible explanation of our result of high BZD use among this patient group.

Patients with DUD more often have comorbid psychiatric disorders and particularly anxiety disorders compared to patients without DUD (86). The prevalence of anxiety disorders among patients with DUD has been estimated to 30–60% (86, 237). In Denmark, national guidelines recommend that patients in long-term treatment with BZDs are evaluated by the specialized psychiatric care system once a year (90). We found that admitting to treatment for DUD with prescribed BZDs did not seem to increase the specialized psychiatric care involvement in the year after admission. In addition, during the year after admission, only the psychiatric diagnosis "mental and behavioral disorders due to psychoactive substance use" was more common in the groups with prescription of BZDs compared to the group without prescription of BZDs. No difference between these groups was found regarding the psychiatric diagnosis "neurotic, stress-related, and somatoform disorders" which includes anxiety disorders.

Among patients with different types of DUD involving opioids, cannabis, or central stimulating drugs, no difference regarding the prevalence of anxiety disorders have been reported (86). Still, the proportion of BZD users were three times higher among patients treated for opioid use compared to patients treated for use of cannabis or central stimulating drugs. Opioids combined with BZDs are known to induce greater levels of euphoria, as opposed to cannabis and central stimulating drugs (83, 238). Collectively, this investigation does not point towards treatment of comorbid psychiatric disorders and particularly anxiety disorders as a likely explanation of our results. On the contrary, the high doses of BZDs seem to be a part of the addictive syndrome, and needs to be treated as such.

6.2 Aim II: Addictive medication as involved factor in overdose deaths.

The median age at death was 36 years in the study in Norway (2006-2008) and 45 years in the study in Denmark (2008-2011) (Paper II and III). The higher median age in the Danish study might reflect an increasing median age among overdose deaths in general, a lower proportion of deceased with detection of heroin compared to the Norwegian study, and a higher proportion of IDUs in Norway (239, 240). Both use of heroin and injecting drug use are risk factors for early overdose death (5, 10, 136). In addition, only the Norwegian study included deceased with permanent place of residence outside the city, and this group were younger than the group of deceased with permanent place of residence in Oslo (158). The median age at death was similar to the findings of other studies including overdose deaths involving addictive medication (5, 74, 146). Even though the median age of overdose deaths involving addictive mediation has increased, dependence and misuse of addictive mediation is still a notable and rising contributor to global premature mortality (2, 91).

Above two-thirds of all overdose deaths in our studies involved addictive medication (Paper II and III) which is consistent with the findings of other studies (153). An overall trend of increasing deaths from

prescription opioid use and decreasing deaths from illicit drug use in the past several years has been noted across many countries (2). In Denmark, a similar development has been observed, however, almost solely driven by an increase in methadone-related deaths (3, 241). Moreover, in both Denmark and Norway, a substantial increase in BZD-related deaths has co-occurred (3). BZDs are usually almost always detected in combination with other drugs at the toxicology examination, and this was also the case in our study where none of the overdose deaths had BZDs determined as being main intoxicant (159). However, we found that more than three-quarters of overdose deaths involving addictive medication had co-detection of BZDs which is similar to the findings of other Nordic countries (3). Compared to non-Nordic studies our proportion is substantially higher and may reflect the high prescription rates of BZDs in general during the time periods of the study and also inappropriate prescription practices of BZDs to patients with DUD in particular (Paper I) (3, 19, 153, 242).

The majority of the deceased had at least one contact with the social or health care services in the year prior to death and was therefore already known to the treatment services (Paper III) (158). Almost one-quarter of the deceased had been discharged/released from a psychiatric hospital, somatic hospital, inpatient drug treatment, or prison four weeks prior to death (Denmark). The period immediately after discharge/release is challenging for drug users and associated with increased risk of overdose death, often due to discontinuities of care and loss of opioid tolerance (243, 244). Improving linkage within the current social and health care system may have a beneficial effect on reducing overdose risk if service and treatment providers can collaborate better (243).

Many of the contacts with the health care system in the time prior to death were to due to dispensing of OMT medication (Paper III). OMT medication can be dispensed at drug treatment facilities or pharmacies. The group of deceased who had had their medication dispensed at a pharmacy more often had co-detection of legally prescribed BZDs, an older age, lower proportion with co-detection of heroin, fewer

contacts with the social and health care system, and more often died at their residential address, compared to the deceased with dispensing at the drug treatment facility or with detection of non-prescribed medication. Hence, overall, this group seemed more difficult to reach with the current overdose preventive services at the drug treatment facilities or at street level. Dispensing of OMT medication at a pharmacy has advantages compared to dispensing at a drug treatment facility, as pharmacies often have longer opening hours and are situated in closer proximity to the residence of the patient. However, the continuous clinical assessment of a patient by professionals at the drug treatment facilities may be less performed when the medication is dispensed elsewhere. Our results suggest that the group of deceased with dispensing at pharmacies seemed more isolated from services and might have benefited from closer and more frequent contact with social and health care system such as a drug treatment facility.

Approximately one-third of the deceased with overdose deaths involving addictive medication in Oslo, Norway, and one-fifth of the deceased with overdose deaths in Copenhagen, Aarhus, and Odense Municipality, Denmark, had a permanent place of residence outside a major city or capital (Paper II) (126). Individuals who die from an overdose in a major city or capital, but who do not live in the city, may well have different characteristics and risk factors to those residing in the city (158). In a Norwegian study, non-Oslo residents were more likely to have been found outdoors with detection of heroin in the blood and to not have had contact with the social and health care system within Oslo (158). Our study adds to that notion as we found that non-Oslo deceased were less likely to have detection of prescribed medication and hence did not bring with them prescriptions from local general practitioners in their home region to the capital (Paper II). Individuals travelling to drug scenes in major cities may not have the same access to services within that city, and seem to lack firm affiliation to service providers within their home region. Lack of access to services may include access to general practitioners and thus legal prescriptions. Improved and easier access to social and health care system services for drug users in as well as outside cities with drug scenes should be considered for this group. Targeted preventive measures within the host city should also

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be ensured for individuals travelling to other cities.

6.3 Aim III: Comparison of overdose cases with and without prescribed addictive medications

Addictive medication was detected in the majority of all overdose deaths. In most cases, the addictive medication detected in overdose deaths involving such medication in Norway did overall not stem from legal sources (Paper II). This result is consistent with the findings of other studies (5, 74, 245). However among methadone-related overdoses deaths in Denmark, the majority was receiving MMT at the time of death (Paper III). This result differs from the findings of other studies where the majority of deceased with methadone-related deaths was not receiving MMT (111, 121, 149, 184, 185, 190, 191).

The prescription histories of the deceased revealed that non-prescribed medication use involved different subpopulations of individuals abusing medication, than those primarily relying on prescribed medications (Paper II and III). Those in the group using non-prescribed methadone resemble those traditionally associated with the misuse of street drugs in that having detection of non-prescribed addictive medication were associated with having a younger age and co-detection of other non-prescribed addictive medications and illicit non-prescribed drugs (not significant in adjusted analysis in the Norwegian sample) (68). On the other hand, those in the group using prescribed BZDs additionally to prescribed opioids were more likely to have been prescribed higher medication doses and not having supervised intake of methadone (Denmark). This might indicate use of more legal sources to supply their medication/drug use.

Misuse of addictive medication can be perceived by drug users as less stigmatizing, less dangerous, and less subject to legal consequences than misuse of illicit non-prescription drugs (66). However for many, the misuse of addictive medication may also serve as a gateway to the use of illicit non-prescription drugs such as heroin (66). Moreover, addictive medication is often used by drug users as a supplement to using illicit non-prescription drugs. Benzodiazepines have the ability to prolong the effect of illicit non-prescription

drugs and to delay and soften abstinence, while prescription opioids can be used as a substitute when illicit non-prescription drugs such as heroin are not available (68). This correlates with our results where more than three-quarters of the deceased with detection of only BZDs also had detection of heroin, while less than 10% of the deceased with detection of prescription opioids with or without co-detection of BZDs also had detection of heroin.

Although groups of individuals abusing prescribed medication and non-prescribed medication, respectively, in many ways may be distinct, a connection may also exist between the two groups. Many of the former may sell their legally prescribed medication for profit to individuals who use non-prescribed medications, or exchange them for illicit non-prescription drugs (66, 68). Obtaining addictive medication from multiple prescribers, also known as doctor shopping, and in higher doses is a way in which addictive medication may be misused and diverted (74). In our studies, the doses of addictive medication prescribed were overall higher than recommended. Prescription of higher doses of addictive medication to particularly patients with DUD should in general be avoided due to increased risk of misuse and overdose death (145, 147, 185, 233). Furthermore, we found that about one-third of the deceased had obtained addictive medication from five or more different prescribers in the year prior to death, which corresponds to the findings of an American study (74).

6.4 Aim IV: Investigation of prescribing and dispensing patterns

The overdose death rates are high in both Denmark and Norway compared to other European countries (4). However, the substances detected in overdose deaths in the two Nordic countries differ. In 2012, more than two-thirds of all overdose deaths in Denmark had detection of methadone, whereas about one-third of the overdose deaths in Norway had detection of methadone (246). None of the other Nordic countries had detection of methadone in more than one-third of their overdose deaths (246). We found that above 60% of the deceased with methadone-related overdose deaths were receiving MMT at the time of death

(Paper III), which is three times higher than among deceased with methadone-related deaths in Norway of which most were overdose deaths (149).

The mean doses of methadone prescribed to the deceased were about 40% higher in Denmark compared to Norway, and in Denmark almost half of the deceased where prescribed doses above recommended levels (>120mg daily) (Paper III) (149). Also, among all patients receiving MMT in two of the municipalities included in our study (where data was available), the mean methadone dose prescribed was overall above recommended levels (average 125mg daily). In comparison, the mean methadone dose prescribed in Norway has decreased from 103mg daily in 2011 to 95mg daily in 2015 (247). Similar data on methadone doses is not available in Denmark. Guidelines in Denmark state that methadone maintenance dose should normally not exceed 120 mg daily whereas Norwegian guidelines do not state a maximum dose but recommend a maintenance dose of 80mg daily (248, 249). A too high dose of prescribed methadone is associated with increased risk of misuse and overdose death (113, 124, 250).

Also Danish and Norwegian guidelines differ regarding supervised intake of methadone as part of OMT (248, 249). In Denmark, OMT guidelines advise daily supervised intake of methadone in the initial phase of treatment (248). When treatment has been stabilized, medication for self-administration may be dispensed as "take-home-medication" but should not be dispensed for more than one week at a time. In Norway, OMT guidelines state that intake of methadone should be supervised once a week as a minimum to better assess the continued need for the prescribed dose (249). The Norwegian guidelines argue that such regulations are necessary to prevent diversion and reduce risk of overdose (249). Supervision of methadone intake has previously shown a positive effect on methadone-related death rates (113, 120, 121). About two-thirds of the deceased in the Danish study did not have supervised intake of MMT and this particularly applied to deceased who had been prescribed higher doses of methadone (Paper III). The proportion of all OMT-patients who have supervised intake of their medication is not known in either

Denmark or Norway. However, in average each OMT-patient in Norway has supervised intake of the medication 3.7 times per week (247).

The regulatory and clinical differences between Denmark and Norway in approaching OMT may be historically bound. As one of the first countries in Europe, Denmark introduced treatment with OMT opioids in 1970 (89). Since the introduction, Denmark focused on achieving high treatment coverage among individuals with opioid use disorder by leading an OMT medication prescription strategy that was less restrictive than other European countries (89, 128). This resulted in a high number individuals with opioid use disorder entering OMT and also one of the highest prescription rates of methadone in Europe (128). Norway, however, introduced OMT in 1998 along with relatively strict criteria for admission and also a stricter approach to treatment (132). During the 00ies, the number of patients receiving OMT in Norway increased almost threefold (251). This increase continued after the introduction of new OMT guidelines in 2010 which included a less strict approach towards OMT. Today, the treatment coverage among individuals with opioid use disorder in Norway is approximating the treatment coverage in Denmark (132, 239).

The buprenorphine-naloxone combination is first-line recommendation as OMT medication in both Denmark and Norway (248, 249). Still in Denmark only about 18% of the patients in OMT is receiving buprenorphine (and 82% % of the patients in OMT is receiving methadone), whereas 56% of the patients in OMT in Norway is receiving buprenorphine (and 44% is receiving methadone) (81, 252). The move towards an increased prescribing of buprenorphine in Norway occurred during a period of expansion of services in the 00ies. This shift in choice of medication has proven more difficult in Denmark, and even today more than two-thirds of the newly admitted patients in OMT are prescribed methadone (239). One reason for this might be that addictive medicine is not a medical specialty in Denmark resulting in a lack of formal training and knowledge among physicians regarding OMT medication, best practice, and national guidelines. This has also likely contributed to the substantial variation in OMT approach between the

different municipalities in Denmark, and also to a medical practice in the municipalities that in many cases does not follow national guidelines (253). Moreover, the patients receiving OMT in Denmark have gotten a much higher degree of influence on their prescribed OMT medication, and strong drug user organizations have promoted drug users' dislike of buprenorphine and of being switched from methadone to buprenorphine (129).

Overall, the high overdose death rates in Denmark involving methadone are likely driven by a less than optimal health care treatment provided in conjunction with psychosocial treatment as part of OMT. This includes a "methadone culture" which in decades have involved a liberal OMT approach; a clinical field of addictive medicine that lacks mandatory training of particularly physicians and other health care personnel, and; prescription practices of addictive medication that in many cases does not follow national guidelines. The result is a liberal approach to OMT delivery that does not necessarily prevent overdose deaths overall and even may result in an increased risk of overdose for individuals in OMT as well as outside OMT due to diversion.

6.5 Concluding remarks

Our findings coupled with the results of previous studies indicate a relationship between the availability and prescription practices of addictive medications through legitimate channels and the diversion and misuse of these medications leading to overdose death as an associated adverse outcome (21, 41, 149, 199). The high availability and misuse of addictive medication among drug using populations in Denmark and Norway is reflected in the number of overdose deaths involving these medications, which is equally high and increasing (3).

The observed trends in overdose deaths involving addictive medication are likely related to several factors. The prescription rates of BZDs among individuals with DUD were much higher than among the general

population, and BZDs were prescribed in a fashion that in many cases indicated inappropriate prescribing to this group more than treatment for psychiatric disorders. Also prescription practices towards the deceased prior to overdose deaths involving addiction medication seemed less than optimal and may well have contributed to the deaths. These practices included prescription of addictive medication in doses that were higher than recommended, co-prescription of more than one type of addictive medication, and use of multiple prescribers. Moreover, inappropriate prescribing of addictive medications might not only do more harm than good to patients for which the medication was prescribed. It may also increase the risk of diversion to individuals outside treatment, and such non-prescribed medication was identified as a contributing factor to many of the overdose dose deaths included in our studies. Lastly, patients with pain disorder, psychiatric disorder, and DUD, and also those with a propensity for diversion and misuse of medication, all represent the source population for which addictive medications are prescribed. An appropriate treatment for these patient groups should involve other types of treatment than medication, and hence the findings of this thesis reflect the comprehensive psychosocial and health care treatment to patients who are also prescribed addictive medication. This emphasizes the need for further education and training of all providers who are engaged in treatment of this vulnerable group of individuals.

7.0 Implications

The findings of this thesis contribute to the improved understanding of misuse and overdose deaths involving addictive medications in Denmark and Norway, which is an increasing issue of concern. When opioids, including OMT medications, and BZDs are prescribed appropriately as part of a treatment for pain disorders, psychiatric disorders, or DUDs, it can improve health and also prevent DUD and overdose death. The studies included in this thesis identified inappropriate prescription practices of addictive medication in relation to both drug treatment and overdose deaths in significant numbers. Inappropriate prescription practices of addictive medication increase the risk of the medications being consumed in ways other than those medically intended which can result in misuse and overdose death. The present findings improve our knowledge on the complexity of factors leading to misuse, diversion, and overdose death involving addictive medication, which can help further development of preventive measures that need to be diverse. On a system level, prescription drug monitoring programs, with warning systems included to notify prescribers, pharmacies, and regional chief physicians, could be implemented to monitor the distribution and prescription pattern of addictive medication (254, 255). On a physician level, screening tools to assess a potential misuse or diversion of medications should be used when prescribing addictive medications (256, 257). On a user level, education on overdose risk behavior and opioid antagonist distribution among drug users should be prioritized as part of a prevention and treatment program (258).

In Denmark, less than optimal prescription practices were identified among the deceased prior to methadone-related overdose deaths. These practices included prescription of methadone doses outside recommended limits and also without supervision of OMT medication intake, which are both associated with increased risk of overdose and worse functioning in OMT (99, 113, 120, 124, 259). Hence, the current OMT approach in Denmark likely contributes to the high overdose death rates involving methadone. To improve the approach to OMT in Denmark, engagement of both health care and psychosocial personnel is pivotal. Our results point toward, that more formal training of both health care and psychosocial personnel

at drug treatment centers should be introduced. Particularly training of physicians in best practice and national guidelines is needed as addiction medicine is not a specialty in Denmark and no organized training currently exists. Such formal training could promote responsible prescribing and include adoption of more balanced supervision and control procedures in accordance with evidence-based guidelines. These steps toward a more strict prescription practice and OMT approach should occur without impeding treatment engagement or reducing accessibility and attractiveness of drug treatment. National strategies to improve provision of drug treatment, including OMT, and reduce the number of methadone-related overdose deaths have previously successfully been introduced in other countries (113, 120).

In Denmark and particularly Norway, many of the overdose deaths involving addictive medication have occurred in individuals who had not been prescribed these medications. This suggests that diversion of prescription medication is likely a significant problem and may be related to the inappropriate prescription practices identified in our studies. We found that individuals using non-prescribed medication prior to death were characterized by having a younger age, by having a permanent place of residence outside a major city, and by co-using other types of non-prescribed medication and illicit drugs. Coupled with previous findings this indicates that individuals using non-prescribed medication are largely not in contact with the treatment system (126, 158). Hence, besides improving outcome for individuals in treatment, strategies should also aim at reducing misuse of medication in individuals outside treatment. Improved and easier access to health care and social services should be considered for this group. This could include further implementation of low-threshold facilities specifically targeting treatment-naive individuals with DUD. The aim of such initiatives should be to make current treatment services more attractive to individuals with DUD and thereby reduce their time as active drug users.

Compared to the general population, BZDs were highly prescribed to patients admitting to treatment for DUD and particularly to patients with opioid use disorder. Still, admitting to treatment did not increase the

specialized psychiatric treatment coverage of this patient group, disregarding use of prescribed BZDs. Also among the majority of overdose deaths involving addictive medication, BZDs were detected and likely contributed to the death. Increased awareness and identification of misuse patterns, particularly including opioids, is required by physicians in all treatment services to better (re)evaluate the indication for BZD prescription. Patients with misuse patterns of BZDs deserve medical support during tapering off their BZD dependence. If the use of BZDs is continuing, the physician can consider a short term (six weeks to six months) reducing of BZDs on frequent pickup and with prescription of BZD types with a long half-life and slow speed of onset (260). Patients with psychiatric disorders in need for long-term BZD prescription are likely a minority, and management including specialized psychiatric care should be considered part of an appropriate BZD treatment for this patient group. For the remainder of the patients, physicians would likely help their patients better if prescription of BZDs is avoided than prescribed.

8.0 Future research

This thesis included studies that focused on populations in Denmark and Norway, respectively. Studies investigating misuse and overdose deaths involving addictive medication across several Nordic and also other European countries may shed further light on of the role of regulatory measures and regional differences, including differences in risk factors. Studies which take multiple European countries into account are rare, showing that research on misuse and overdose deaths involving addictive medication in the Nordic countries and the EU is at an early stage and that the potential for growth within this field is large (7). Between the Nordic and also other European countries there are many differences on how the societies respond to DUDs and treatment provision. Exploring these differences and their consequences on drug use and prevention could help us further understand which strategies are optimal in preventing harms from drug use in our societies. Furthermore, information exchange and networking between the European countries would strengthen the dissemination of knowledge and resources. This could in turn improve cooperation to gain better insight into medication misuse and overdose deaths across nations, and implement policies that may help prevent misuse and overdose death.

Not only differences between countries were observed regarding prescription practices prior to death. We also identified differences within different regions of a country regarding prescription practices of OMT medication. But as we only investigated prescription patterns prior to an overdose death and we only included deceased from three municipalities, we were not able to make associations to the consequences of different approaches towards OMT in Denmark. A nationwide cohort study including all patients receiving OMT would more precisely be able to investigate which aspects of an OMT approach that contribute to the observed differences among overdose deaths across regions. This could include identification of protective as well as high risk treatment practices associated with diversion and misuse of medication, and also overdose death.

We found that BZDs were highly prescribed to patients admitting for DUD treatment and particularly to patients with opioid use disorder. It has previously been difficult for physicians to estimate the risk of non-medical use of prescribed addictive medication by the patient. Future studies should assess groups of individuals at risk for misuse and overdose death involving addictive medications. Mixed-method studies including individuals who are prescribed addictive medication could investigate factors associated with risk of misuse and overdose death involving these medications. Participation of user organizations may benefit such studies and contribute with new information otherwise difficult to access. If only a quantitative study is possible, prescription-monitoring programs could be used to estimate indicators (such as doctor shopping) for misuse (218).

In Denmark, methadone is the presumed main intoxicant in 60% of all overdose deaths which is among the highest in the world and almost three times higher than the other Nordic countries combined (3, 81). We found that in the period of 2008 to 2011, more than two-thirds of all overdose deaths in Denmark had detection of methadone. Of these methadone-related deaths, almost two-thirds were receiving MMT at time of death. However, to what extent the prescribed and also non-prescribed methadone was a critical factor in the overdose deaths is not known. Such knowledge could in turn help identify factors associated with an increased risk of overdosing when prescribed one or more addictive medications at therapeutic levels. Future studies should thus aim at screening blood samples for substances in all overdose deaths involving addictive medication and include concentration levels of the detected substances.

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