Mortality during opioid agonist treatment in Norway:

A comprehensive study of the years 2014 and 2015

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Contents

Summary

Background: Although opioid agonist treatment (OAT) substantially reduces morbidity and mortality in individuals with opioid dependence, mortality is still higher than in the general population. To improve treatment and prevent premature mortality, more research is needed.

Objectives: This thesis consists of two studies. Study 1 (Paper 1) aimed to explore crude mortality rates (CMR) and causes of death among patients who died during OAT in the years 2014–2015 in Norway. In study 2, we aimed to document organ pathology (Paper 2) and the substances and their concentrations (Paper 3) in those who died during OAT in 2014–2015 and had an autopsy. In Paper 3, we also aimed to calculate pooled benzodiazepine and opioid concentrations using conversion factors from the Norwegian Road Traffic Act.

Methods: Both studies had a cross-sectional design. We collected data from hospital records, the Norwegian Patient Registry, the Norwegian Cause of Death Registry and autopsy reports.

Results: Two-hundred patients who died during OAT (defined as within five days of the last reported intake of OAT medication) between 1 January 2014 and 31 December 2015 were included. The mean age at the time of death was 48.9 years, and 74% were men. The CMR was 1.4 per 100 person years (PYs), and increased with age. Somatic causes of death (45%) were most common, followed by drug-induced deaths (42%) and traumatic causes of death (12%). Increasing somatic comorbidity as measured by the Charlson comorbidity index was independently associated with reduced odds of drug-induced death compared with other causes of death (adjusted odds ratio [aOR] = 0.72; 95% confidence interval [CI] = 0.61–0.86).

Among the 200 who died, 125 (63 %) had an autopsy, of whom 122 patients had available autopsy reports. The most common organ pathologies detected post-mortem were chronic liver disease (84%), cardiovascular disease (68%) and pulmonary emphysema (41%). Two-thirds (65%) of the decedents had more than two organ system diseases. Older age was

independently associated with cardiovascular pathology (aOR = 1.10; 95% CI = 1.04–1.16) and renal pathology (aOR = 1.06; 95% CI = 1.01–1.12), adjusted for sex and body mass index (BMI).

Among the 122 deceased with available autopsy reports, 107 had post-mortem toxicological analysis from peripheral blood. A median of four substances was detected. In addition to prescribed OAT medications, the most common substances were benzodiazepines (76%), tetrahydrocannabinol (37%), stimulants (29%) and heroin/morphine (28%). The pooled opioid (i.e., morphine-equivalent) concentration was significantly higher in drug-induced deaths compared with other causes of death (362 ng/mL versus 182 ng/mL, $P < 0.001$), in contrast to the pooled benzodiazepine (i.e., diazepam-equivalent) concentration (5466 versus 5701 ng/mL, $P = 0.353$). Only increasing pooled opioid concentration was independently associated with increased odds of drug-induced death (aOR = 1.003; 95% CI = 1.001–1.006), adjusted for age, sex, OAT medication and pooled benzodiazepine concentration.

Conclusions: In Norway, 1.4% of patients receiving OAT died in 2014–2015. Both somatic and drug-induced deaths were common. HCV-related liver disease, cardiovascular disease and emphysema were highly prevalent in those who had an autopsy. The pooled opioid concentration seemed to play the most important role in drug-induced deaths during OAT. However, several substances were detected in a majority of the cases, and the role of prescribed OAT medications in drug-induced deaths remains unclear. Patients receiving OAT require comprehensive treatment and care that considers physical and mental health problems, aging, pharmacological treatment and drug use, living conditions, and wider societal factors. To further reduce mortality related to multimorbidity and/or polydrug use, multidisciplinary and integrated treatment and care in a life course perspective is necessary.

Sammendrag

Bakgrunn: Selv om legemiddelassistert rehabilitering reduserer sykelighet og dødelighet hos personer med opioidavhengighet, er dødeligheten fortsatt høy sammenlignet med befolkningen generelt. Det er behov for mer kunnskap for å kunne gi bedre behandling og redusere dødeligheten.

Hensikt: Avhandlingen består av to studier. Hensikten med studie 1 (artikkel 1) var å undersøke dødelighetsrater og dødsårsaker hos alle pasienter som døde i LAR-behandling i Norge i 2014–2015. I studie 2 ønsket vi å undersøke organpatologi (artikkel 2) og toksikologi (artikkel 3) hos de pasientene som døde disse to årene og som ble obdusert. I artikkel 3 ønsket vi også å beregne totale (summerte) benzodiazepin- og opioid-konsentrasjoner med bruk av omregningsfaktorer fra Vegtrafikkloven.

Metode: Avhandlingen består av to tverrsnittsstudier. Vi samlet inn data fra spesialisthelsetjenesten, Norsk pasientregister, Dødsårsaksregisteret og obduksjonsrapporter.

Resultater: To hundre pasienter som døde i LAR behandling (definert som innen fem dager etter siste rapporterte inntak av LAR medisin) mellom 1. januar 2014 og 31. desember 2015 ble inkludert. Gjennomsnittsalderen ved død var 48,9 år, og 74 % var menn. Dødelighetsraten var 1,4 per 100 person-år, og økte med økende alder. Somatiske dødsårsaker (45 %) var vanligst, etterfulgt av rus-utløste dødsårsaker (42 %) og voldsomme dødsfall (12 %). Økende sykelighet, målt som Charlson indeks score, var assosiert med redusert odds for rus-utløst dødsårsak (OR = 0,72; 95 % konfidensintervall = 0,61–0,86).

Blant de 200 som døde, ble 125 (63 %) obdusert. Vi fikk tak i obduksjonsrapporten til 122 av disse. De hyppigst rapporterte organpatologiene var kronisk leversykdom (84 %), hjerte- og karsykdom (68 %) og lungeemfysem (41 %). To tredjedeler av de obduserte hadde patologiske funn i flere enn to organsystemer. Økende alder var assosiert med hjerte- og

karsykdom (OR = 1,10; 95 % CI = 1,04–1,16) og nyresykdom (OR = 1,06; 95 % CI = 1,01–1,12), justert for kjønn og kroppsmasseindeks.

Blant de obduserte var det gjennomført toksikologiske undersøkelser av perifert blod hos 107 pasienter. I snitt ble det funnet fire rusmidler/legemidler. I tillegg til foreskrevet LAR medikament, var de vanligste rusmidlene/legemidlene benzodiazepiner (76 %), tetrahydrocannabinol (37 %), stimulanter (29 %) og heroin/morfin (28 %). Den totale (morfin-ekvivalente) opioid-konsentrasjonen var signifikant høyere i rus-utløste dødsfall sammenlignet med andre dødsfall (362 ng/mL versus 182 ng/mL, $P < 0,001$), i motsetning til den totale (diazepam-ekvivalente) benzodiazepin-konsentrasjonen (5466 versus 5701 ng/mL, $P = 0,353$). Økende total opioid-konsentrasjon økte oddsen for rus-utløst død (OR = 1,003; 95 % CI = 1,001–1,006), justert for alder, kjønn, LAR medikament og total benzodiazepin-konsentrasjon.

Konklusjoner: I Norge døde 1,4 % av pasientene i LAR i 2014–2015. Både somatiske og rus-utløste dødsårsaker var vanlig. Hepatitt C-relatert leversykdom, hjerte- og karsykdom og emfysem var svært vanlig blant de obduserte. Den totale opioid-konsentrasjonen så ut til å spille størst rolle i rus-utløste dødsfall hos dem som ble obdusert. Samtidig hadde flertallet flere rusmidler/legemidler i blodet, og rollen til forskrevne LAR medikamenter i overdosedødsfall er fortsatt uklar. Pasienter i LAR har behov for en helhetlig behandling som tar hensyn til aldring, fysisk og psykisk helse, rusmiddel- og legemiddelbruk og levekår. For å ytterligere redusere dødelighet knyttet til multimorbiditet og/eller bruk av flere rusmidler/legemidler, er det behov for integrert, tverrfaglig behandling i et livsløpsperspektiv.

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome

aOR: Adjusted Odds Ratio

BMI: Body Mass Index

CI: Confidence Interval

CMR: Crude Mortality Rate

COPD: Chronic Obstructive Pulmonary Disease

COVID-19: Corona Virus Disease of 2019

DALY: Disability-Adjusted Life-Year

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th revision

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction

GP: General Practitioner

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

ICD-10: International Classification of Diseases, 10th revision

MOUD: Medications for Opioid Use Disorder

MRR: Mortality Rate Ratio

NSP: Needle and Syringe Program

OAT: Opioid Agonist Treatment

OR: Odds Ratio

PIN: Personal Identification Number

PY: Person Year

PWID: People Who Inject Drugs

RCT: Randomized Controlled Trial

SMR: Standardized Mortality Ratio

SUD: Substance Use Disorder

US: United States (of America)

WHO: World Health Organization

List of papers

Paper 1

Bech AB, Clausen T, Waal H, Šaltytė Benth J, Skeie I. Mortality and causes of death among patients with opioid use disorder receiving opioid agonist treatment: a national register study. *BMC Health Services Research* 2019; **19**: 440.

Paper 2

Bech AB, Clausen T, Waal H, Delaveris, GJ, Skeie I. Organ pathologies detected post-mortem in patients receiving opioid agonist treatment for opioid use disorder: a nation-wide 2-year cross-sectional study. *Addiction* 2021; 1–9.

Paper 3

Bech AB, Clausen T, Waal H, Vindenes V, Edvardsen HE, Frost J, et al. Post-mortem toxicological analyses of blood samples from 107 patients receiving opioid agonist treatment: substances detected and pooled opioid and benzodiazepine concentrations. *Addiction* 2021; 116:845–55.

Preface

Important terms and phrases

Words matter, and there are ongoing discussions about stigmatizing terms and the importance of respectful terminology and person-first language in the field of addiction [1-3]. In this thesis, the use of the terms "drug" and "drug use" refers to "substances controlled under the international drug control conventions, and their non-medical use" [4]. The terms misuse, non-medical use, illicit use and extra-medical use of prescription drugs are often used interchangeably [5]. In line with Larance et al. [5], I prefer the term extra-medical use of prescription drugs, as this term "encompasses use that is either without a prescription or not as directed by a doctor, without excluding the possibility that the user may have medically driven reasons for using the medication". Controversy also exists surrounding terminology from the diagnostic systems [5]. I prefer to use the term opioid dependence, except when referring to literature using the term opioid use disorder.

The terms opioid substitution treatment and opioid maintenance treatment have been used for years; however, both terms are considered stigmatizing by some reviewers and editors. Opioid agonist treatment is suggested as a non-stigmatizing term [2, 3], or alternatively medications for opioid use disorder (MOUDs). Methadone and buprenorphine are agonists at the μ opioid receptor, while MOUDs also include antagonist medication such as naltrexone. In this thesis, I prefer OAT to MOUD because only methadone and buprenorphine were available as OAT medications in Norway in 2014–2015.

Two expressions describe mortality: CMR and standardized mortality ratio (SMR). The CMR is the total number of deaths against the PYs of follow-up, usually expressed as the number of deaths per 100, 1,000 or 1,000,000 PY observed. In this thesis, the number of deaths is divided by PYs of follow-up (the number of years times the number of the OAT population)

and multiplied by 100 to derive CMR/100 PY, which is equivalent to per cent. Cause-specific mortality rates are the number of deaths assigned to a specific cause divided by PYs of follow-up.

$$\frac{Deaths\ during\ a\ specific\ time\ period}{Person\ years} x\ 100 = CMR\ per\ 100\ PY$$

The SMR compares the observed number of deaths in the sample to the expected number of deaths in a sample of the same age and sex from the general population of that country, at that time. An SMR greater than 1 indicates excess mortality in that sample compared with the general population [6]

1. Introduction

Opioid dependence is associated with high rates of morbidity and mortality [7]. The aim of this thesis was to explore mortality and causes of death among patients receiving OAT for opioid dependence in Norway in the years 2014–2015. In this chapter, the background for the thesis is presented; the extent of drug use with a focus on opioids, diagnostic criteria for opioid dependence, and OAT as an important treatment in the context of harm-reduction and recovery.

1.1 Drug and alcohol use

Drug use and its health consequences continue to be a matter of global concern [8, 9]. The drug market is diverse, dynamic and complex, and globalization and technology influence drug flows, availability and demand [10, 11]. The global drug market has expanded over the past twenty years, in terms of the overall number of people who use drugs, the illicit production and the quantities of drugs seized [4]. Contributing factors to the expansion are population growth, urbanization (e.g., drug use is more common in urban areas) and income [4]. Alcohol use is more common in low-income countries, while illicit drug use, such as the use of heroin and other opioids, cannabis, amphetamines and cocaine, is more common in high-income countries [12]. The number of new psychoactive substances identified and reported to the United Nations Office on Drugs and Crime has increased from 166 in 2009 to 950 in 2019 [4]. New drugs such as synthetic cannabinoids, cathinones and ketamine have entered the market [10], and in 2016, the new, synthetic benzodiazepine etizolam overtook diazepam as the benzodiazepine most frequently reported in opioid-induced deaths in Scotland [13]. The drug marketplace is also less discriminating, with drug users who may substitute one drug for another or use multiple substances [10]. Polydrug use among problem drug users, including the use of alcohol, is common, and increases the risk of both fatal and non-fatal overdoses and other health risks [14].

In 2016, the most common substance use disorders (SUDs) worldwide were alcohol use disorder (100.4 million people), opioid use disorder (26.8 million cases) and cannabis use disorder (22.1 million cases) [12]. The global burden of disease is measured as disability-adjusted life-years (DALYs), which combine premature mortality (years of life lost) and burden due to disability (years of life lived with disability). Alcohol and illicit drug use are important contributors to the global disease burden, but with substantial regional variations [12]. Norway is among the countries in the world with the highest estimated DALY rates related to drug use, especially because of lives lost due to overdose. The global burden of disease attributable to drugs in 2016, measured as age-standardized DALYs per 100 000 people, was 421.0 (95% CI = 363.7–483.3). By comparison, the age-standardized DALY rate in Norway was 591.3 (95% CI = 504.0–679.9) [12].

People who inject drugs (PWID) have a higher mortality risk from overdose, blood-borne infections and suicide [15]. In a systematic review and meta-analysis by Mathers et al. [15], PWID had a pooled CMR of 2.35 per 100 PYs. CMRs were higher in low-and middle-income countries, among males and PWID with human immunodeficiency virus (HIV) infection. The most common causes of death among PWID were drug overdose and acquired immune deficiency syndrome (AIDS). The pooled SMR was almost 15 times the rate among those of comparable age and sex in the general population [15]. Opioids are the type of drug most commonly injected [16].

1.2 Opioid use

Opioids include natural opiates (e.g., morphine and codeine), semi-synthetic opiates (e.g., heroin, buprenorphine, oxycodone) and synthetic opioids (e.g., methadone, fentanyl and tramadol). Opioids have an important role in clinical medicine and are essential in anesthesia and for the treatment of pain. However, opioids can also produce euphoria as well as respiratory depression and have the potential for extra-medical use and dependence.

In line with a dynamic drug market, the opioid market has changed over the past two decades [4, 11]. In North America, extra-medical use of prescription opioids has led to a dramatic increase in overdose deaths [17]. In 2014, around 38% of adults in the USA used prescription opioids, almost 5% engaged in extra-medical opioid use and 0.8% were estimated to have a prescription opioid use disorder [16]. Almost 500 000 people died from opioid overdose from 1999 to 2019 in the US. The Centers for Disease Control and Prevention describe three distinctive waves. The first wave started at the turn of the millennium. Prescriptions of opioid analgesics quadrupled between 1999 and 2010. Following this over-prescribing, fatal overdoses involving prescription opioids increased substantially from 1999. The second wave started in 2010, with rapid increases in fatal overdoses involving heroin, while the third wave started in 2013, involving extra-medical synthetic opioids, particularly illicitly produced fentanyl [18]. Fentanyl and other synthetic opioids caused an estimated six-fold increase in overdose deaths from 2013 to 2016 [16].

One explanation of the emergence of fentanyl is that the availability and dispensing of prescription opioids became more restricted and strictly monitored between 2010 and 2012 due to the increase in opioid overdose deaths. This left large groups of people using opioids with shrinking supplies [19]. In the beginning, fentanyl was used as an adulterant in heroin. However, fentanyl is now the dominant opioid in opioid overdose deaths in North-America [4]. The fentanyl market is mainly supply-driven, and important factors are lower prices, higher potency and ease of transportation [20].

In Europe, there were 1.3 million high-risk opioid users in 2018, and the estimated CMR due to overdose in Europe was 22.3 deaths per million people aged 15-64 [21]. The situation in Scotland is particularly concerning, where the mortality rate is almost 13 times higher than the average in Europe, and even higher than comparable data from the US [22]. However, national mortality rates vary considerably. The use of forensic examinations is unsystematic

in some countries, and different systems are used to compile mortality data. Additionally, differences in risk and protective factors exist, such as the type of drug, route of administration and the availability of treatment [21, 23]. There is also an underreporting of overdose deaths in some countries [21, 24]. This limits the comparability of overdose data in Europe.

In Europe, the illicit opioid market is diverse. Heroin and OAT medications are involved in the majority of overdose deaths. However, in most deaths, multiple drug toxicity is implicated [22]. Although the proportion of deaths involving heroin is decreasing [22], the average purity of heroin has increased by 23% in Europe since 2009, while the price has dropped by 17% [25]. Extra-medical use of tramadol is also emerging [4]. Fentanyl use is less common in Europe, but is known to be an endemic problem in Estonia [26]. Fentanyls have been involved in overdose deaths in all Nordic countries [27]. There have also been overdose deaths in Germany and Greece, primarily linked to diverted fentanyl-based patches [20].

The use of opioids has also changed in Norway [28]. From 2000–2017, there was a declining trend in heroin overdose deaths, but an increase in the detection of methadone, buprenorphine, fentanyl, oxycodone, tramadol and ketobemidone, as well as an increase in the combination of opioids and benzodiazepines detected post-mortem. Whether the medical opioids detected in these deaths were prescribed is not known [28]. The annual number of overdose deaths has been relatively stable in Norway for the last 20 years, despite the increasing number of people receiving OAT. However, the number of overdose deaths increased in Norway in 2020. Suggested explanations for this increase are high potency heroin and changes in health and social services due to the COVID-19 pandemic [29].

In Africa and the Middle East, the use of tramadol has increased, while the use of heroin and pharmaceutical opioids is increasing in India. Extra-medical use of tramadol is also reported

by some countries in East and South-East Asia such as Indonesia and Thailand [4]. Nonetheless, heroin remains one of the most problematic drugs globally because of the relationship between the use of heroin and injecting drug use, blood-borne infections and overdose deaths [4, 8]. To illustrate the extent of the problem, the quantity of heroin seized globally reached a record high of 91 tons in 2016 [30]. Additionally, people over the age of 40 make up an increasing share of those with an opioid problem [31]. This aging trend can be seen in Europe, the USA and Australia [32, 33].

1.3 Opioid dependence

Opioid dependence is associated with high rates of morbidity and mortality as well as wider societal harms, such as harms to family cohesion, reduced employment and financial contribution, and criminal activity [7, 16]. There are considerable geographical variations in the prevalence of opioid dependence, especially in the quality of data on opioid dependence, making estimates uncertain [16]. The prevalence is higher among men, with a male to female ratio of 2.5 [11]. However, women appear to progress from initial use to dependence at a faster rate [16] and to present to treatment with more psychiatric comorbidities and life instability [34]. Opioid dependence is often understood in a biopsychosocial model [16, 35], although this model has been criticized in recent years, e.g., for focusing too much on the biological factors [36]. Genetic factors, adverse early development, mental illness, social norms, drug exposure and availability are all factors that influence opioid use and the progression and development of opioid dependence. Lower socioeconomic status and poor school performance are also risk factors [16].

There are two systems of classification for the diagnosis of opioid dependence internationally: the Diagnostic and Statistical Manual of Mental Disorders, 5th revision (DSM-5) of the American Psychiatric Association [37] and the International Classification of Diseases, 10th revision (ICD-10) of the World Health Organization (WHO) [38]. In the DSM-5, the previous

distinction between opioid abuse and opioid dependence has been replaced with the diagnosis of opioid use disorder, which is measured on a continuum from mild (2-3 symptoms) to severe (6 or more symptoms) within a 12-month period [37]. The ICD-10 distinguishes between harmful use and dependence. Harmful use is defined as a pattern of psychoactive substance use that is causing damage to health, either physically or mentally [38]. Opioid dependence syndrome is characterized by a cluster of cognitive, behavioral and physiological features:

- A strong desire or sense of compulsion to take opioids
- Difficulties in controlling opioid use
- A physiological withdrawal state
- Tolerance
- Progressive neglect of alternative pleasures or interests because of opioid use
- Persisting with opioid use despite clear evidence of overtly harmful consequences.

The ICD-10 defines opioid dependence syndrome as "the presence of three or more of these features present simultaneously at any one time in the preceding year" [38]. In Norway, ICD-10 is most commonly used.

1.4 Opioid agonist treatment

OAT is the most widely used treatment modality for opioid dependence globally [39]. Patients accepted for OAT usually meet the diagnostic criteria for opioid dependence syndrome according to the ICD-10 or the criteria for severe opioid use disorder in DSM-5. Short-acting opioids such as heroin are replaced by long-acting opioids like methadone or buprenorphine. With the right dosage, patients should neither experience euphoria nor withdrawal symptoms. Methadone has been on the WHO "List of essential medicines" since 2005, with buprenorphine as an alternative, for the treatment of opioid dependence [40].

OAT reduces mortality and physical morbidity related to drug use and injection during treatment [39]. Additionally, OAT reduces criminal activity [41, 42] and improves quality of life [43]. There is weak evidence on the effect of OAT on functional outcomes such as cognitive, physical, occupational, behavioural and social outcomes [44]. OAT in combination with psychosocial support is the most effective treatment option. According to the WHO [39], psychosocial support such as cognitive and behavioral approaches and contingency management should be available, but are not mandatory. OAT is provided in various ways globally in terms of access, retention, medication choices, cost and psychosocial support, which probably results in a variation of outcomes based on the different approaches. In Europe, methadone is the most prescribed medication in OAT, used by 63% of OAT patients, while 34% use buprenorphine-based medications. In some countries, slow-release oral morphine, diacetylmorphine (heroin) or the long-acting opioid antagonist naltrexone are also used as medications, but are less frequently prescribed [9].

1.4.1 The Norwegian OAT setting

From the early 1990s, HIV-positive patients in Norway with opioid dependence received methadone as a harm-reduction strategy to reduce HIV-infection among PWID. From 1998, OAT became available as a national treatment program, and patients receiving OAT obtained patients' rights in 2004, following a drug policy reform at the time [45]. OAT in Norway is publicly funded, and is mainly delivered within a national OAT program. Addiction units in the public hospital trusts assess the need and initiate OAT, but the treatment is based on collaboration between addiction units, general practitioners (GPs) and municipal health and social services. Methadone was the only OAT medication available until buprenorphine was introduced in 2001.

In the first years, capacity was limited and waiting lists were long. OAT in Norway was considered high-threshold and abstinence-oriented, and patients who continued to use drugs after initiation of OAT could be involuntarily discharged. The inclusion criteria were strict, and only patients 25 years or older, with long-standing opioid dependence and previous abstinence-oriented treatment episodes received OAT. Patients under 25 years received OAT only if they had severe (i.e., life-threatening) physical health conditions. The number of patients increased substantially during the first decade, and more than tripled from 2002 to 2011 [46]. Clinical practice has gradually changed as the evidence-base has evolved. In 2010, national guidelines [47] were implemented; these state that the aims of OAT are to improve quality of life, improve the individual's levels of functioning, and reduce the harms and the risk of overdose related to opioid use [48]. In addition to the agonist treatment, patients should get help to improve their physical, mental, social and work-related levels of functioning. The goals of treatment are set in collaboration with the patient.

Today, OAT in Norway is characterized by an aging OAT population with high retention in treatment, and buprenorphine as first-line treatment and most prescribed medication [48, 49]. The treatment is not time-limited, and involuntary discharge is rare. At the end of 2020, 8099 patients were receiving OAT [49]. The percentage of women has been around 30% for many years [46]. The national OAT guidelines from 2010 are now under revision.

1.5 OAT, harm-reduction and recovery

OAT and needle and syringe programs (NSP) are the two most important harm-reduction interventions, because the greatest benefit is reported when OAT and NSP are combined and implemented at high coverage [50, 51]. In a systematic review by Larney et al. [50], Norway was among the four countries in the world, together with Austria, the Netherlands and Australia, with the highest coverage of both NSP and OAT.

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines harm-reduction as “interventions, programmes and policies that seek to reduce the health, social and economic harms of substance use to individuals, communities and societies” [51]. The main aims of harm-reduction are to decrease potential harms and maximize the well-being of persons who are unable or unwilling to stop using drugs [52]. In some countries, harm-reduction services also emphasize the goals of attracting people who use drugs into treatment, and reducing crime [53]. Vearrier argued that harm-reduction falls within the scope of both clinical and public health ethics [52]. Within the framework of the four ethical principles of Beauchamps and Childress, harm-reduction enhances autonomy, reduces the harms related to drug use (non-maleficence), advances well-being (beneficence) and provides basic, accessible healthcare to a marginalized group (justice) [52]. Harm-reduction is an official policy of the United Nations [51]. In 2020, United Nations published international guidelines on human rights and drug policy, where access to harm-reduction services is considered a human right [54].

Despite national differences, countries in Europe continue to voice strong support for harm-reduction at the international level [51]. However, harm-reduction is still controversial or not implemented in other parts of the world [55, 56]. Critics have claimed that the concept of “harm” is not objectively defined, and that harm-reduction interventions seem to sanction or enable drug use, thus sending out the wrong message [51]. As an example, up-take of take-home naloxone after prison release was reduced in England because both providers and service users saw accepting naloxone as evidence of insufficient commitment to abstinence [57]. Others criticize harm-reduction interventions for an excessive focus on the short-term consequences of drug use at the expense of more holistic, long-term recovery goals [53]. The terms “abstinence” and “sobriety” in some of the definitions of recovery are also highly

debated, including whether those in OAT should be viewed as being abstinent (i.e., free of drugs) when they use OAT medication [53].

However, harm-reduction and recovery as treatment goals are not mutually exclusive [31]. The holistic goals of OAT in Norway as presented in section 1.4.1 are very similar to the goals of recovery used by the Substance Abuse and Mental Health Services Administration in the US. They define recovery as "a process of change, through which people improve their health and wellness, live self-directed lives and strive to reach their full potential" [58]. Thus, OAT in Norway encompasses both harm-reduction and recovery goals.

2. Factors associated with mortality: status of knowledge

In this chapter, the status of knowledge regarding OAT and factors associated with mortality is presented. The aim is not to provide a complete review of the literature on OAT, but to present an overview of the most important aspects in relation to the overarching theme of this thesis.

When this project started in 2016, only one systematic review and meta-analysis on mortality among regular or dependent users of heroin and other opioids had been published [59]. However, during the course of the project (2016-2021), five additional systematic reviews and meta-analyses on extra-medical opioid use, opioid dependence and mortality have been published [60-64].

2.1 OAT reduces morbidity and mortality

Mortality among people with extra-medical opioid use and/or opioid dependence is substantially higher than in the general population. Systematic reviews and meta-analyses report pooled all-cause CMRs between 1.35-2.09/100 PYs [59, 62, 63], with SMRs 10.3-14.66 times higher than in the general population [59, 63]. The mortality risk is elevated across a range of causes, such as overdose, suicide, accidents, AIDS, liver-related deaths and other physical diseases [63]. Lewer et al. [65] found a life expectancy gap of 15 years when people with opioid dependence receiving OAT were compared with the general population. Men have higher CMRs and lower SMRs than women; the latter is mainly due to lower mortality rates among women at lower ages in the general population [59, 63].

As illustrated in Table 1, systematic reviews and meta-analyses as well as Norwegian studies consistently show that both all-cause and overdose mortality are reduced during OAT compared with untreated periods or after cessation of treatment [60-62, 66, 67]. In a

systematic review and meta-analysis by Lewer et al. [68], OAT was also associated with fewer emergency department visits and hospital admissions among adults who used drugs.

Table 1. CMRs per 100 PYs in persons with extra-medical opioid use and/or opioid dependence on/off opioid agonist treatment

	CMR/ 100 PY	All-cause CMR/100 PY on OAT	All-cause CMR/100 PY off OAT	Overdose CMR/100 PY on OAT	Overdose CMR/100 PY off OAT
Systematic reviews and meta-analyses:					
Degenhardt et al. [59]	2.09				
Sordo et al. [60]		Met: 1.13	Met: 3.61	Met: 0.26	Met: 1.27
		Bup: 0.43	Bup: 0.95	Bup: 0.14	Bup: 0.46
Ma et al. [61]		On: 0.93	Untreated: 4.89	On: 0.24	Untreated: 2.43
			Discharged: 1.69		Discharged: 0.68
		Met: 1.05	Met: 2.03		
		Bup: 0.38	Bup: 0.80		
Bahji et al. [62]	1.35	On: 0.86	Untreated: 2.26	On: 0.28	Untreated: 1.15
		Met: 0.91	Met: 2.68	Met: 0.29	Met: 1.24
		Bup: 0.60	Bup: 0.86	Bup: 0.22	Bup: 0.46
Larney et al. [63]	1.59				Untreated: 0.52
Santo et al. [64]		On: 1.10	Untreated: 2.4	On: 0.30	Untreated: 0.79
Norwegian studies:					
Clausen et al. [66]		On: 1.40	Untreated: 2.40	On: 0.40	Untreated: 1.90
			Discharged: 3.40		Discharged: 2.10
Bukten et al. [67]		On: 1.30	Untreated: 1.97	On: 0.55	Untreated: 1.50
			Discharged: 3.37		Discharged: 2.33

CMR: crude mortality rate; PY: person years; OAT: opioid agonist treatment; Bup: prescribed buprenorphine; Met: prescribed methadone.
Untreated periods may include both pre-treatment periods and/or no treatment, depending on available data on treatment in included studies.

A major limitation of systematic reviews and meta-analyses is the high heterogeneity among the included studies. Thus, differences in mortality might reflect differences in patient characteristics such as sex, percentage of people injecting or HIV status [59, 62, 63], treatment delivery or the socio-political context of the studies [62, 64, 69], and inconsistent coding of causes of death and misclassification of out-of-treatment deaths occurring in-treatment [62, 63]. Study design, cohort size and year of publication also affect mortality rates

[61]. Another limitation is that most studies included in systematic reviews and meta-analysis are from high-income countries [62, 63]. Given these limitations, national mortality studies are important for interpreting national results in the context of treatment provision and cause of death statistics.

A Norwegian study published in 2008 by Clausen et al. [66] was included in four of the above mentioned systematic reviews and meta-analyses [59-62]. The study by Clausen et al. [66] covered the years 1997-2003, and reported an all-cause mortality rate during OAT of 1.4/100 PY. During OAT, 73% of the deaths were non-overdose deaths [70]. A Norwegian cohort study by Bukten et al. [67] published in 2019 was included in the most recent systematic review and meta-analyses [63, 64]. Bukten et al. [67] found an all-cause CMR of 1.3/100 PYs during OAT in the years 1997-2009. Older age at treatment initiation was associated with higher risk of mortality during OAT.

2.2 Differences between methadone and buprenorphine

Both methadone and buprenorphine provide good outcomes and are effective in retaining people in treatment and reducing opioid use [39]. Additionally, the opioid antagonist naltrexone can be useful in preventing relapse in those who have withdrawn from opioids [39], and is included in some of the reviews and meta-analyses. There are certain differences between the medications.

2.2.1 Retention in treatment

Randomized controlled trials (RCTs) show that there was no difference between methadone and buprenorphine in fixed medium and high doses in retaining people in treatment, while fixed low-dose methadone (≤40 mg) performed better than fixed low-dose buprenorphine (2-6 mg). However, in flexible-dosing approaches, which are more clinically relevant, buprenorphine was less effective than methadone in retaining people in treatment [71]. Better

retention with methadone has also been found in other studies [72, 73]. Retention, and especially retention of over one year, is associated with substantial reductions in the risk for all-cause and overdose mortality [60, 61].

2.2.2 Periods of transition

During treatment, both buprenorphine and methadone reduce all-cause and overdose mortality. Periods of transition, such as initiation of OAT, cessation or discharge from treatment or release from prison without OAT, are periods of increased mortality risk [60, 74-76]. Mortality, especially due to overdose, increases during induction onto methadone, but not onto buprenorphine [60, 61, 75, 77] or naltrexone [75]. *Confounding by indication* is a problem in most observational studies, i.e., that results are confounded by differences in disease severity or other risk factors in patients selected to receive different or no medications for the same condition [77, 78]. However, the study by Kimber et al. [77] was detailed and well powered. Their sensitivity analyses showed that the lower mortality with buprenorphine during the first four weeks of treatment was a robust finding and was not likely to be caused by unmeasured confounding.

The first 2-4 weeks after cessation of OAT is also a period of increased mortality risk [60, 61, 75]. Buprenorphine appears to be safer than methadone and naltrexone immediately after leaving treatment [61, 75]. Ma et al. [61] found that although all-cause CMR for naltrexone was lower than for buprenorphine and methadone during OAT (0.26/100 PYs, 0.38/100 PYs and 1.05/100 PYs, respectively), buprenorphine groups had lower mortality rates compared with methadone and naltrexone after treatment cessation (0.80/100 PYs, 2.03/100 PYs and 1.97/100 PYs, respectively). Naltrexone was not available in OAT in Norway in 2014–2015, and will not be discussed further.

2.2.3 Diversion and extra-medical use

Methadone and buprenorphine are involved in a substantial share of overdose deaths in some countries in Europe, including Norway [22, 27, 28]. Extra-medical use and diversion of OAT medications can lead to poor adherence to treatment, fatal and non-fatal overdoses, compromised public acceptance of OAT and an increased incidence of opioid dependence [9, 31, 79]. It is both a challenge and a responsibility for OAT providers to ensure availability of OAT while implementing effective anti-diversion policies [9]. The WHO emphasizes the importance of a balanced policy, where maximum access to OAT must be balanced against minimum harm. However, this balance will often present difficult trade-offs [9].

To reduce diversion, improved access to OAT is important in countries with low coverage [9]. Other strategies include the use of misuse-deterrent formulations such as buprenorphine-naloxone, clinical prescription guidelines and education [43]. Supervised intake of OAT medications in the beginning of agonist treatment and for patients who are not stable is likely to reduce diversion [39, 43], but the evidence is scarce. Saulle et al. [80] conducted a systematic review on the effect of supervised dosing, but they judged the quality of evidence from very low to low for all the outcomes. They concluded that more research on the effect of supervised dosing, the risk of diversion and safety is needed. Daily supervision is also severely restrictive to patients and limits the acceptability of treatment [39]. Some patients feel stigmatized, trapped and disempowered by the control measures in OAT [81], which ultimately may lead to drop-out from treatment and increased mortality risk.

2.3 Research gaps

To summarize, the drug market is dynamic and flexible, and there are both geographical and cultural variations in drug use (e.g., drug of choice, injection), prevalence of opioid dependence and related mortality. Although OAT for opioid dependence increases quality of

life and substantially reduces morbidity and mortality [39, 59-62, 68], OAT patients still have a higher disease burden, higher rates of hospital admissions and higher mortality [82-84] than age- and sex-matched peers. The high incidence of acute and chronic diseases as well as an increased risk of overdose, suicide and accidents among individuals with opioid dependence lead to excess mortality for both natural and unnatural causes of death and a shorter life expectancy. Additionally, OAT is provided in various ways globally, and the role of prescribed OAT medications in drug-induced deaths among patients receiving OAT is unclear.

Norway has an aging OAT population at increased risk of mortality. When the project started, available mortality data for Norway were old (i.e., from 2003) with no recent linkage with the Cause of Death Registry [85]. Therefore, to improve treatment and prevent premature mortality, more research was needed to better understand mortality among patients receiving OAT in the Norwegian context.

2.4 Objectives

The overarching aim of this thesis was to explore mortality and causes of death among patients receiving OAT in Norway in 2014–2015. The project consisted of two studies. Study 1 aimed to explore CMRs and the distribution of causes of death of all patients who died during OAT in Norway in 2014–2015 (Paper 1). In study 2, we aimed to investigate organ pathology (Paper 2) and toxicology results (Paper 3) in those who died during OAT in 2014–2015 and were subjected to an autopsy. The specific objectives of the three papers were:

Paper 1: To describe the causes of death among OAT patients in Norway, to estimate all-cause and cause-specific CMRs during OAT, and to explore characteristics associated with drug-induced death compared with other causes of death.

Paper 2: To document organ pathologies detected post-mortem and to estimate the extent to which individual characteristics were associated with at least one pulmonary, hepatic, cardiovascular or renal pathology.

Paper 3: To present the substances and their concentrations detected post-mortem stratified by cause of death, estimate the pooled opioid and benzodiazepine concentrations using established conversion factors for blood concentrations from the Norwegian Road Traffic Act**,** and explore the association between causes of death and the pooled opioid and benzodiazepine concentrations.

3. Material and methods

3.1 Design

The two studies had a naturalistic, observational design, and included cross-sectional data from several sources. Study 1 used data from the hospital trusts, the Norwegian Cause of Death Registry and the Norwegian Patient Registry. In addition, information from the annual OAT status reports for 2014 and 2015 was used to estimate CMRs. In study 2, we used data from the autopsy reports in addition to data from hospitals and registers. The reporting of results in the papers followed the Strengthening the Reporting of Observational Studies (STROBE) guidelines [86].

3.2 Participants

We included all patients in the national OAT program who died between 1 January 2014 and 31 December 2015. According to the national OAT guidelines [47], patients who have missed doses for more than four consecutive days have to be restarted on OAT medication by the prescribing doctor because of potential loss of opioid tolerance. Thus, patients were included if they died during ongoing treatment or within five days of the last reported intake of OAT medication.

Initially, the hospital trusts reported that 255 patients had died during OAT. Fifty-five patients did not meet the inclusion criteria and were excluded. Paper I included 200 patients who met the inclusion criteria. Of the 200 patients, 125 (63%) had a medical or forensic autopsy. Paper 2 included all patients who had an autopsy with available autopsy reports (n = 122), while Paper 3 included all patients who had an autopsy with toxicological analyses from peripheral blood (n = 107). The numbers and reasons for exclusion in each paper are presented in Figure 1.

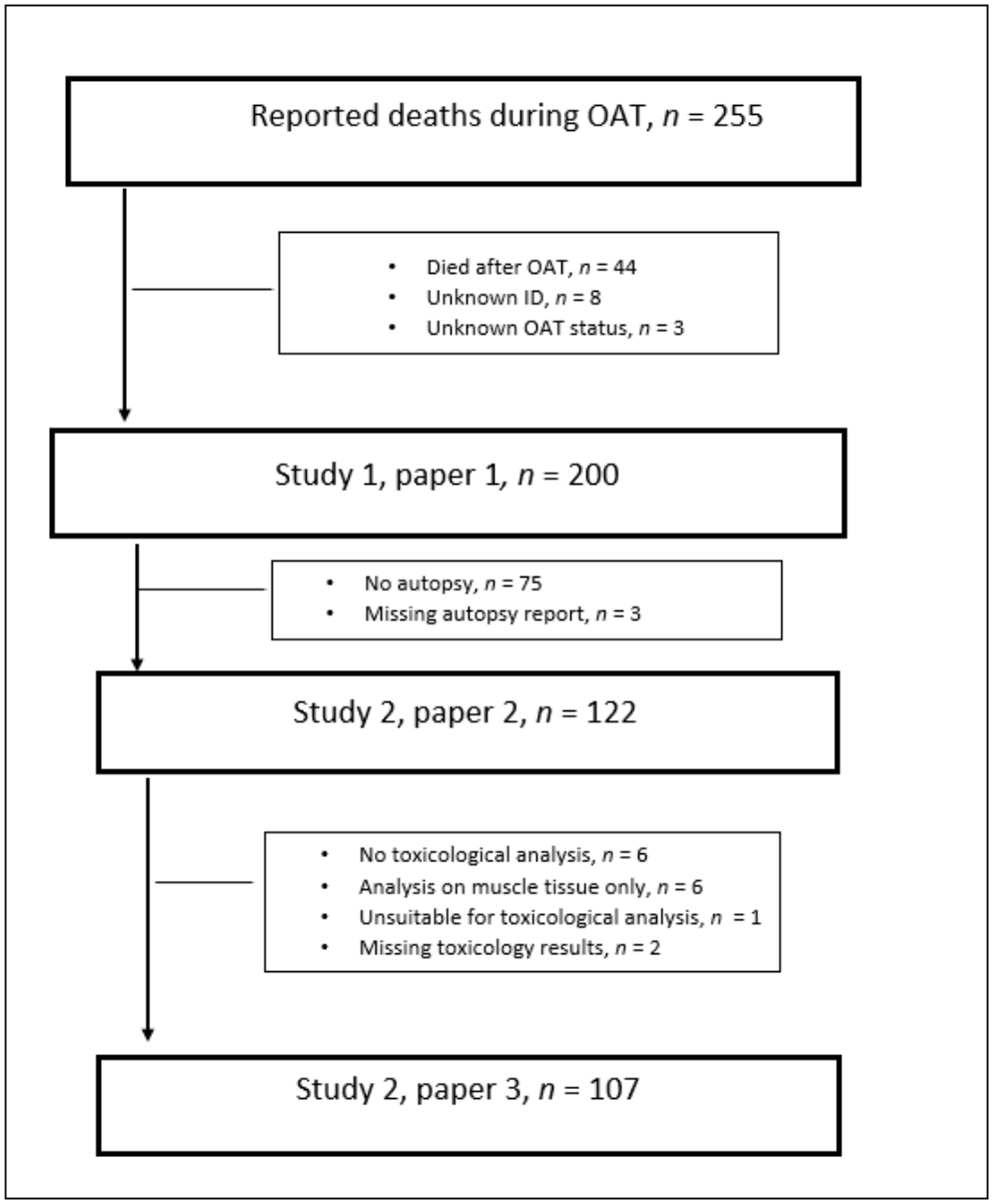

Figure 1. Flow diagram of participants in the three papers.

3.3 Data sources

We collected data from several sources: questionnaires, medical records, register data and autopsy reports.

3.3.1 Questionnaires

A death registration questionnaire was made especially for this study (Appendix 1). This questionnaire was filled out by clinicians responsible for OAT in the hospital trusts, based on their knowledge about the patient and data from the patient's medical record. The questionnaire contained demographic characteristics and information about OAT medication at the time of death, duration of OAT, physical and mental health diagnoses, prescribed medications and information about the fatality and the cause of death. The variables age, sex, region, OAT medication at the time of death (including dose and supervised intake) and duration of OAT were collected from the death registration questionnaire. We also asked the clinicians to fill out a short questionnaire with two questions: whether the patients lived in an urban or rural area and if there had been any previous interruptions of the OAT treatment for more than five days in the five years prior to death (Appendix 1).

3.3.2 Medical records

To access information about the cause of death and treatment received in the five years before death, we retrieved discharge summaries and medical autopsy reports, if existing, from medical records in physical and mental health inpatient and outpatient facilities and specialized drug treatment units within the hospital trusts.

The hospital trusts also provided the patient's individual OAT status reports from the year of death and three years prior to death, if existing. The status report is filled out annually based on the clinician's knowledge of the patient's situation, and preferably in collaboration with the patient. This instrument contains variables such as the patient's demographic status, OAT medication, drug use, mental and physical symptoms and patient satisfaction. For the years covered (2012–2015), the national response rate varied between 76 and 80%. The OAT status

report was validated in 2005 [87]. From the OAT status reports, we used the variables "Disability pension", "Own home" and "OAT prescribed by GPs" in Paper 1.

3.3.3 The Cause of Death Registry

The Norwegian Cause of Death Registry covers all deaths in Norway as well as deaths of Norwegians who die abroad. A death certificate is filled out by physicians based on the ICD-10 diagnosis. The underlying cause of death is defined as "the illness or injury which initiated the train of morbid events leading directly to death or the circumstances of the accident or violence which produced the fatal injury" [38]. The cause and place of death, the main intoxicant and whether the deceased had an autopsy were obtained from the Norwegian Cause of Death Registry.

3.3.4 The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) contains information about all patients waiting for or having received treatment in the specialist health care service in Norway. NPR provides a range of data on patients treated in the specialist health care services, including diagnoses based on ICD-10 codes. Since 2008, the register contains identifiable data on treatment [88]. From the NPR, we collected information about the patient's main or primary ICD-10 diagnosis and up to 20 secondary diagnoses as well as admissions to physical and mental health facilities or specialized drug treatment registered in the NPR in the five years before death. As an example, the variable "Psychiatric admissions" used in Paper 1 was admissions to psychiatric hospitals registered in the NPR.

3.3.5 Autopsy reports

In cases of suspected unnatural death such as overdose, suicide, accidents and homicide, the police or a higher prosecution authority usually request a forensic autopsy to establish the

cause and time of death or to identify the deceased. A forensic autopsy includes macroscopic and microscopic examinations of all organs as well as toxicological analysis. Neuropathological examination is not standard, but assessed in each case. Forensic autopsy reports also include excerpts from police records regarding the circumstances of death and (if available) information from medical records. Most forensic autopsy reports were retrieved from the Norwegian Board of Forensic Medicine. However, a few reports were obtained by contacting the hospitals responsible for the autopsy. In addition to forensic autopsies, physicians can request a medical autopsy to confirm the cause of death or to evaluate treatment. Consent from next of kin is mandatory. The medical autopsy reports were retrieved from the hospital trusts.

From the autopsy reports, we collected information on organ pathology and weight and height, which was used to estimate BMI. We also retrieved information on toxicology if available (i.e., substances detected post-mortem and their concentrations) and circumstances of death (days from death to autopsy, signs of drug use, OAT status described in the report).

3.4 Data collection

Data were collected in three steps as illustrated in Table 2. To minimize recall bias, the death registration questionnaire was filled out shortly after the patient had died in 2014 and 2015. Information from the questionnaires was de-identified when sent to the project, pending approval from the Regional Committee for Medical and Health Research Ethics, which was obtained in December 2016. After ethical approval, the project received the personal identification number (PIN) of all the deceased. We collected additional data from the hospital trust as well as data from the Cause of Death Registry and the NPR between January 2017 and October 2018, based on the PINs. Finally, when we received the information from the Cause of Death Registry about those who had an autopsy, we retrieved forensic autopsy reports from the Norwegian Board of Forensic Medicine as well as medical autopsies from

the hospital trusts. Obtaining all the necessary permits and collecting data was time-consuming and took two and a half years.

Table 2. Data collection during the project

	2014–2015	2017–2018	2018
Death registration questionnaires[a]	x		
Hospital data[b]		x	
Norwegian Patient Registry		x	
Norwegian Cause of Death Registry		x	
Forensic and medical autopsy reports			x

a) The questionnaires were de-identified pending ethical approval.
b) Hospital data included discharge summaries from the five years before death and OAT status reports (if existing) from the three years before death.

3.5 Measurements

3.5.1 CMR

We used period prevalence to estimate CMRs because it takes time to accumulate a sufficient number of deaths in rare diseases such as opioid dependence. The OAT status report is published annually, with information on all patients in the Norwegian OAT program (e.g., number of patients, age, sex and OAT medication). Thus, it was possible to calculate CMRs by dividing the total number of deaths in OAT by the PYs of follow-up (i.e., the number of years times the number of patients in OAT). The number of patients in OAT was 7220 in 2014 and 7439 in 2015 [89, 90], giving an observation period of 14,659 PYs. CMRs were reported per 100 PY, with 95% Poisson CIs [6].

3.5.2 Cause of death

The cause of death was categorized into one of three groups: Death due to somatic disease, drug-induced death and traumatic death. Norway follows the ICD-10 definitions of drug-induced death used by the EMCDDA [38, 91], where drug-induced death is defined as "Deaths happening shortly after consumption of one or more illicit psychoactive drugs, and

directly related to this consumption, although they often may happen in combination with other substances such as alcohol or psychoactive medicines". The term drug-related death is often used interchangeably in the literature. Drug-induced death included accidental poisoning (X42, X41), intentional poisoning (X62, X61), poisoning undetermined intent (Y12, Y11) and SUDs (F11, F12, F14-F16, F19) [91]. Traumatic death comprised deaths due to accidents, suicide (except intentional overdoses) and homicide.

3.5.3 Organ pathology

From the autopsy reports, we collected details on pulmonary, cardiovascular, liver and renal pathology and weights of the heart, liver and spleen. Organ pathology was based on the explicit reporting by the pathologist in the autopsy report, with one exception. To reduce the risk for underestimation due to inconsistent reporting of an enlarged liver, we used the definition of hepatomegaly suggested by Molina et al.: liver weight > 1760 g for women and > 1860 g for men [92, 93]. The definitions of organ pathology are presented in Appendix 2.

3.5.4 Toxicology

Only two laboratories in Norway perform post-mortem toxicological analyses: the Department of Forensic Sciences at Oslo University Hospital and the Department of Clinical Pharmacology at St. Olav's Hospital in Trondheim. We included only cases with toxicological analyses from peripheral blood to reduce post-mortem site- and time-dependent changes [94, 95]. When interpreting toxicological findings from the autopsy reports, the following factors (as listed in Paper 3) were considered:

- Morphine can be detected after intake of heroin, codeine or morphine. Heroin is rapidly metabolized to 6-acetylmorphine (6-AM) and further to morphine. The presence of 6-AM distinguishes heroin use from the use of morphine. If only

morphine is detected, it is not possible to determine if this is a result of heroin or morphine intake.

- Codeine is metabolized to morphine, and may be detected in low concentrations following heroin intake. Codeine was considered as a trace amount when concomitant 6-AM was detected. Codeine was categorized as "Other medications" if a concomitant morphine concentration was less than 10% of the codeine concentrations or if no concomitant morphine was detected in combination with codeine.
- Methamphetamine is partly metabolized to amphetamine *in vivo*. Concentrations of methamphetamine and amphetamine were added together and categorized as stimulants.
- Detection of tetrahydrocannabinol in blood was regarded as positive of tetrahydrocannabinol.
- Since ethanol (alcohol) may be formed post-mortem, ethanol was only included if concomitant findings of its metabolites ethyl glucoronide and ethyl sulfate were present in blood or urine.

3.5.5. Pooled opioid and benzodiazepine concentrations

Driving under the influence of alcohol or drugs is regulated in the Norwegian Road Traffic Act. In 2012, legislative limits for non-alcohol drugs in blood were implemented in Norway [96-98]. If multiple benzodiazepines or opioids are detected, it is possible to convert various benzodiazepines and opioids to diazepam-equivalent or morphine-equivalent concentrations using conversion factors from the Norwegian Road Traffic Act. In this way, it is possible to calculate pooled concentrations of several benzodiazepines or opioids detected in whole blood. The principle of conversion factors for benzodiazepines as well as for opioids (although little studied) used in the Road Traffic Act assumes a linear concentration–effect relationship [96].

We used the conversion factors for blood concentrations established in the Norwegian Road Traffic Act to calculate pooled morphine-equivalent and diazepam-equivalent concentrations of various opioids and benzodiazepines detected in peripheral blood post-mortem. Due to lack of evidence, conversion factors for buprenorphine and tramadol are not established and therefore not included in the conversion table used in the Norwegian Road Traffic Act [96, 99]. For buprenorphine and tramadol, we assumed that the conversion factors for their blood concentrations were similar to the conversion factors for equipotent doses according to Nielsen et al. [100].

In Paper 3, the following opioids were detected post-mortem in our material and pooled: heroin, morphine, methadone, buprenorphine, tramadol. The following benzodiazepines were detected post-mortem and pooled: clonazepam (measured as the metabolite 7-aminoclonazepam), diazepam and/or the active metabolite desmethyldiazepam, alprazolam, oxazepam and nitrazepam. The z-hypnotics zopiclone and zolpidem were also included because of their similar effect to that of benzodiazepines. Conversion factors have not yet been established for pregabalin and gabapentin, which were therefore excluded. The conversion factors used in our study are provided in Appendix 3.

Toxicological results in Norwegian autopsy reports are presented as molar units (µmol/L), while scientific journals prefer mass units (ng/mL). The following formula was used to convert post-mortem concentrations of the different opioids and benzodiazepines in µmol/L to morphine- and diazepam-equivalent concentrations in ng/mL:

Post-mortem blood concentrations in µmol /L x conversion factor x molecular weight of diazepam or morphine = diazepam- or morphine-equivalent concentrations in ng/mL.

Example: Alprazolam 0.16 µmol/L x 20 (conversion factor for alprazolam) x 284.7 g/mol (molecular weight diazepam) = 911 ng/mL = diazepam-equivalent concentration of alprazolam in ng/mL.

3.5.6 Other variables

Different definitions, measurements and combinations of multimorbidity exist [101, 102]. One of the most common methods of measuring the number and severity of diseases is the Charlson comorbidity index [103]. This index is based on ICD-10 diagnoses for 17 disease categories [104]. We used the ICD-10 coding algorithms for Charlson comorbidities developed by Quan et al. [105]. Each disease category has its associated weighting from 1-6, based on severity. In Paper 1, we used the age-adjusted Charlson comorbidity index where age 50-59 years added one point, 60-69 years added two points, etc.

We used several data sources if possible in case of lack of important covariates in Paper 1. The variable "Previous non-fatal overdose(s)" included non-fatal overdoses recorded in the OAT status reports, or hospital admissions due to non-fatal intoxication (ICD-10 codes T4n, T50.9 and T56.9) recorded in the NPR in the five years before death. The variable "BZD/z-hypnotic prescribing" included at least one prescription of benzodiazepines and/or z-hypnotics recorded either in the questionnaire or in the medical record in the year prior to death, while the variable "Psychotropic medication" included antidepressant and/or antipsychotic medication recorded either in the questionnaire or in the medical record in the year prior to death.

3.6 Statistics

The analyses were performed using SPSS software, version 25 and 26 (IBM Corporation, Armonk, NY, USA) or Stata version 15 (StataCorp LLC), while the co-author (Šaltytė Benth)

who provided multilevel regression analyses in Paper I used SAS, version 9.4. Results with $P < 0.05$ were considered statistically significant, and all tests were two-sided.

3.6.1 Mortality rates

We estimated CMRs with 95% CI and CMRs stratified by age, OAT medication and sex. We also estimated mortality rate ratios (MRR = dividing two CMRs) with 95% CI. The Poisson mean CI calculator in Stata, version 15, was used to estimate CIs and MRRs.

3.6.2 Descriptive analyses

Categorical variables were presented as frequencies and proportions, while continuous data were expressed by means and standard deviations or, if non-normally distributed, by medians and minimum and maximum values. To assess normality of continuous variables, the Kolmogorov-Smirnov test was used in addition to inspection of histograms.

3.6.3 Bivariate analyses

Frequencies of categorical variables were compared using a Pearson's chi-square test or a Fisher's exact test (if expected numbers in each cell were below five). Student's t-test was used to compare the means of normally distributed continuous variables. A Mann-Whitney *U* test was used to compare the difference between two groups when the dependent variable was continuous, but non-normally distributed. For example, in Paper 3, the concentrations of the different substances presented were skewed to the right (the means were higher than the medians). Therefore, medians and minimum and maximum values were used as descriptive measures, and a Mann-Whitney *U* test was used for comparison of post-mortem concentrations in drug-induced and other causes of death.

3.6.4 Binary logistic regression

In all papers, bivariate and multiple binary logistic regression models were used to assess the association between the outcome variable and covariates included as fixed effects in the models. Results were presented as ORs with 95% CIs. Only complete cases with no missing values of covariates were included in the multiple models in all three papers.

In Paper 1, patients from Health Region East were older and more often prescribed methadone than patients from other health regions. This finding can probably be explained by the development of the opioid problem in Norway. People who started to use heroin in the 1990s and early 2000s often came to Oslo and the surrounding areas because drugs were more readily available in the capital. Nested or clustered data may not fulfill the major assumption of regression models of independent observations. Random effects try to capture the unexplained or unobserved heterogeneity among clusters [106]. Therefore, to adjust the estimates for within-region correlations in Paper 1, random intercepts for region were included in the models but not reported since the focus in these multilevel models was on the fixed effects.

3.7 Ethical considerations

The study was conducted in accordance with international and national research ethics acts and regulations [107-110]. The Regional Committee for Medical and Health Research Ethics (case number 2016/1204, South East) approved the study. In addition, each participating hospital trust (including data protection officials) approved data collection and disclosure. The Norwegian Cause of Death Registry and the Norwegian Patient Registry approved access to register data, while the Higher Prosecution Authorities approved access to forensic autopsy reports (i.e., the Director of Public Prosecution, the Council for Confidentiality and Research and the Ministry of Justice and Public Security).

3.7.1 Exemption from informed consent

One of the basic ethical principles in medical research is voluntary informed consent [109, 111], which is based on the principles of human rights and participants' autonomy and personal integrity [109, 110]. Consent must be informed, voluntary, explicit and documentable [109]. Both physical and mental disorders can make individuals temporarily incapacitated to consent. Examples of conditions where drug use may affect the ability to give informed consent are intoxication or strong cravings [112]. Informed consent will normally have to be given by the patient's next of kin if the patient is deceased. Not all patients have close relationship with their families and relatives, and we assumed that contacting the families several years after the patient's death could burden them unnecessarily. The Regional Committee for Medical and Health Research Ethics supported this view and granted an exemption from obtaining informed consent from the next of kin of the deceased.

3.7.2 Exemption from the duty of confidentiality

Privacy, the duty of confidentiality and information security are important aspects of research ethics. The researcher has a duty not to disclose any information about the participants [109, 113]. To gain access to medical record data for the purpose of research and access to register data, the Regional Committee for Medical and Health Research Ethics gave exemptions from the duty of confidentiality. The PhD candidate and the project leader also signed confidentiality agreement under the Police Registry Act [114] to access data from forensic autopsies. The study followed the usual procedures to protect the confidentiality of the data. Only the PhD candidate and the project leader had access to identified data. The data were stored in secure locations on the hospital research server. Data from the hospital trusts with PINs were sent by registered mail using encrypted memory sticks. Print-outs from medical records from the hospital trusts were also sent by registered mail and stored in locked archives

at Innlandet Hospital Trust. The PhD candidate personally received the encrypted memory stick with forensic autopsy reports from the Norwegian Board of Forensic Medicine. The co-authors (other than the project leader) received only de-identified data. Published data were not recognizable on an individual level.

3.7.3 Vulnerable groups

As humans, we are all vulnerable. However, in medical research, people with mental health problems and/or SUDs are often regarded as a vulnerable group [115, 116]. Members of vulnerable groups have an increased risk of being in situations where they can be exploited or exposed to damage or harm [116], e.g., not able to give informed consent due to mental illness, cognitive impairment etc. The principle of vulnerable groups has been criticized for the risk of "stereotyping" and for the absence of clear and workable criteria [115, 117]. People belonging to vulnerable groups should be included in research as long as there is no reason to exclude them [116, 118].

3.7.4 Risks and benefits

OAT in Norway is organized within public specialist health care and it was possible to study mortality in an almost complete national OAT population. Additionally, autopsy rates for unnatural deaths are high in Norway and toxicological analyses are available in most overdose cases [26]. New knowledge on morbidity and mortality is of potential benefit to all patients receiving OAT. The risk was minimal and privacy was protected as far as possible.

3.8 Funding

The study was funded by Innlandet Hospital Trust, grant number 150351. The funder had no role in the study design, data collection or analysis, the decision to publish or preparation of the manuscripts.

3.9 The PhD candidate's independent contributions to the papers

Based on the contributor roles taxonomy (CRediT author statement) [119], the PhD candidate made the following independent contributions in the three papers: project administration, conceptualization of the three papers, data cleaning and curation, formal analyses, investigation, visualization and writing original drafts. The candidate performed the statistical analysis in all three papers, except the multilevel logistic regression analysis in Paper I, which was performed by the co-author Jūratė Šaltytė Benth.

4. Results

The results from study 1 are presented in Paper 1, while the results based on the autopsy reports are presented in Paper 2 and 3. All three papers had a cross-sectional design.

4.1 Study 1

In Paper 1, we aimed to document the causes of death among patients receiving OAT in Norway in 2014–2015 and to estimate all-cause and cause-specific CMRs during OAT. A secondary aim was to explore characteristics of drug-induced death compared with other causes of death.

Data on the cause of death from the Norwegian Cause of Death Registry were combined with data from the Norwegian Patient Registry, medical records and questionnaires. In the two-year observation period, 200 patients receiving OAT died during treatment, defined as within five days of the last reported intake of OAT medication. Among them, 74% were men, and the mean age at the time of death was 48.9 years. Somatic causes of death were most common (45%), followed by drug-induced death (42%) and traumatic death (12%). The CMR was 1.4 per 100 PYs, and increased with age. The CMRs were higher in men than in women (MRR = 1.2; 95% CI = 0.5–1.9) and in patients taking methadone than in those taking buprenorphine (MRR = 2.0; 95% CI = 1.5–2.7). In logistic regression, increasing somatic comorbidity as measured by the Charlson comorbidity index was independently associated with reduced odds of drug-induced death compared with other causes of death (aOR = 0.72; 95% CI = 0.61–0.86).

Conclusions: In 2014–2015, 1.4% of patients receiving OAT died. The CMRs increased with age; however, this increase was steeper for somatic causes of death than for other causes of death. Increasing physical comorbidity reduced the odds of drug-induced death.

4.2 Study 2

4.2.1 Paper 2

In Paper 2, we aimed to document organ pathologies detected post-mortem in those who died during OAT in 2014–2015 and had an autopsy. A secondary aim was to estimate the extent to which individual characteristics (i.e., age, sex and BMI) were associated with pulmonary, cardiovascular, hepatic or renal pathologies**.**

Among the 125 patients who had an autopsy, 122 had available autopsy reports and were included. In this sample, the mean age at the time of death was 48 years, and 75% were men. Pathologies in several organs were common, and 65% of the deceased had more than two organ system diseases. The most common organ pathologies were chronic liver disease (84%), cardiovascular disease (68%) and pulmonary emphysema (41%). In bivariate analysis, only older age was associated with any pulmonary pathology (OR = 1.06; 95% CI = 1.01–1.10), cardiovascular pathology (OR = 1.11; 95% CI = 1.05–1.17) and renal pathology (OR = 1.05; 95% CI = 1.00–1.11). Older age remained independently associated with cardiovascular pathology (aOR = 1.10; 95% CI = 1.04–1.16) and renal pathology (aOR = 1.06; 95% CI = 1.01–1.12) adjusted for BMI and sex.

Conclusions: Among autopsied Norwegians who died during OAT, two-thirds had more than two organ system diseases, despite their mean age of 48 years at the time of death. In multiple regression analysis, only older age was independently associated with at least one cardiovascular or renal pathology after adjusting for sex and BMI.

4.2.2 Paper 3

In Paper 3, we aimed to document the substances and their concentrations detected post-mortem in those with toxicological analyses from peripheral blood, and to estimate the pooled opioid and benzodiazepine concentrations using conversion factors from the Norwegian Road

Traffic Act. We also wanted to explore the association between cause of death and the pooled opioid and benzodiazepine concentrations.

Among the 122 who had an autopsy, 107 had toxicological analyses from peripheral blood and were included in Paper 3. The mean age at the time of death was 47.4 years and 74% were men. A median of four substances was detected across the causes of death. At least one benzodiazepine or z-hypnotic was detected in 76% patients, tetrahydrocannabinol in 37%, stimulants in 29% and heroin/morphine in 28% patients. The median pooled opioid concentration was significantly higher in drug-induced deaths than in other causes of death (362 ng/mL versus 182 ng/mL, $P < 0.001$), in contrast to the pooled benzodiazepine concentration (5466 versus 5701 ng/mL, $P = 0.353$). The multiple regression analysis showed that only increasing pooled opioid concentration in ng/mL was independently associated with increased odds of drug-induced death (aOR = 1.003; 95% CI = 1.001–1.006), adjusted for age, sex, OAT medication and pooled benzodiazepine concentration.

Conclusions: Multiple drug toxicity was common. The pooled opioid concentration seemed to play the most important role in drug-induced deaths during OAT. However, patients prescribed buprenorphine (which is a partial agonist) tended to replace buprenorphine with full agonists such as heroin or methadone, while patients prescribed methadone tended to have high opioid concentrations from methadone as the only opioid.

4.3 Supporting information published online

In Papers 2 and 3, additional information was published online only. Definitions of organ pathology and patient characteristics stratified by autopsy were presented as supporting information in Paper 2 and are provided in Appendix 2 in this thesis. The conversion factors for blood concentrations were presented as supporting information in Paper 3 and are provided in Appendix 3 in this thesis.

5. Methodological considerations

Every study has limitations. Study design, the way the study is conducted or the choice of statistical analysis can produce biased effect estimates [106]. Important aspects of internal validity are statistical validity, selection bias, information bias and confounding. Aspects of internal validity may affect external validity, i.e., the possibility to generalize findings to other populations or treatment settings [106, 111].

5.1 Study design

All three papers had an observational, cross-sectional design. A cross-sectional design is often less time-consuming and easier to conduct than a cohort study. It enables the study of exposure-outcome associations; however, it does not allow for conclusions about causal relationships of the associations [106]. Another limitation is that cross-sectional mortality studies are usually not included in systematic reviews and meta-analysis, in contrast to cohort studies and RCTs.

Only those who died during OAT were included; thus, we could not estimate mortality in versus out of agonist treatment. Additionally, with a cross-sectional design it was not possible to adjust for competing risk, which would require a cohort study design (i.e. survival analysis). If the study participants are older or followed up for a longer period, competing risks are greater. Unless we are studying all deaths, competing risk should be considered [78]. Some of the deceased had several life-threatening conditions, which was illustrated in Paper 1 with two case descriptions. One case involved chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, AA amyloidosis with end-stage kidney failure, chronic obstructive pulmonary disease (COPD) and death due to overdose. The other involved chronic HBV and HCV infections, HIV infection, COPD, acute liver and kidney failure and death due to respiratory failure. Methods for competing risk are increasingly being used in survival

analysis [106]. The regression analysis in Paper 1 should be interpreted with this limitation in mind.

5.2 Type I and type II errors

Statistical validity, and thus internal validity, is strengthened if suitable effect measures and statistical methods and tests are used and if the sample size is sufficient [111].

Opioid dependence is a rare disease, and although we included all patients who died during OAT in Norway in 2014 and 2015, only 200 patients met the inclusion criteria in Paper 1. A small sample size increases the risk of type II error, i.e., that existing associations are not detected due to low statistical power (false negative). In Papers 2 and 3, the sample size limited the number of possible covariates in the regression analyses (including the inclusion of interaction terms). A general rule is that there should be at least ten observations for every term in a regression model [78]. Few covariates were significant in the multiple regression models in our studies, suggesting that either no association existed between the dependent and independent variables, the studies were underpowered (type II error) or important covariates were not included in the models.

In Papers 1 and 3, the dependent variable "Cause of death" was dichotomized into two groups: "Drug-induced death" vs. "Other causes of death". The group "Other causes of death" was used as reference category in both Paper 1 and Paper 3, and consisted of somatic and traumatic causes of death. The group "Traumatic cause of death" was very small (n = 12), and a multinomial regression analysis with drug-induced vs. somatic vs. traumatic cause of death was not possible due to insufficient power.

More men than women have SUDs and the proportion of women in OAT is around 30% [49]. The low proportion of women in Paper 2 (n = 30) increased the risk of an actual difference between men and women not being detected, especially if the difference between men and

women was small. We found that women had lower odds of at least one cardiovascular disease compared with men, but since the 95% CI included 1, this difference was not statistically significant either in bivariate (OR = 0.50; 95% CI = 0.21–1.19) or in multiple analysis (aOR = 0.52; 95% CI = 0.20–1.31). In other post-mortem studies with higher sample size, male sex has been independently associated with cardiovascular disease [120, 121]. The lack of a statistically significant difference in cardiovascular disease between men and women in Paper 2 might represent a type II error, and caution is required when interpreting the results.

Multiple testing increases the risk of type I error; i.e., finding an association by chance when in fact there is none (false positive). Whether and how to adjust for multiple testing is an ongoing debate, since reducing type I error by adjusting for multiple testing also increases the risk of type II error [122]. Rothman argues that not making adjustments is preferable when the data under evaluation are actual observations of nature and not random numbers [123]. We held the opinion that post-mortem concentrations of the various substances and pooled concentrations with p-values presented in Paper 3 were of clinical interest, despite the risk of type 1 error due to multiple testing. If any of the p-values in Table 2 in Paper 3 had been statistically significant (which they were not), it could have been appropriate to adjust for multiple testing.

5.3 Selection bias

Selection bias is a systematic error that may arise if the study participants are not representative of the source population, e.g., if the association between exposure and outcome differs between those who are included in a study and those who are not [78].

In all three papers, the source population was all patients receiving OAT in Norway, with the exception of around a few hundred patients who received OAT in low-threshold OAT

programs [124] outside the hospital trusts in Norway. Patients in low-threshold OAT programs might differ from those in ordinary treatment (e.g., lower retention in treatment, harder-to-reach and/or harder-to-treat). However, the vast majority of patients receiving OAT in Norway were treated in the hospital trusts, including patients with long-standing opioid use and polydrug use. Thus, we considered that those who died during OAT and subsequently were included in study 1 were representative of the source population, and that the risk of selection bias was minimal.

Among those who died during OAT in 2014–2015, 26% were women, while the proportion of women receiving OAT in Norway has been around 30% for many years. This difference was reflected in higher CMRs in males than females in Paper 1. There were also more patients taking methadone among the deceased compared with the total OAT population (55% in the deceased versus around 40% in the whole OAT population in 2014–2015 [89, 90], again reflected in higher CMRs in patients taking methadone than in those taking buprenorphine.

Selection bias was present in Papers 2 and 3 because those who had an autopsy differed from those who did not (Appendix 2). Patients with a known, end-stage disease are not usually autopsied. In Paper 2, those without an autopsy were significantly more likely to have a somatic cause of death and die in a hospital or other health facility, and non-communicable diseases that take time to develop such as COPD and lung cancer were more prevalent. In Paper 2, only cardiovascular and renal pathologies were associated with older age, adjusted for sex and BMI among those who had an autopsy. The lack of association between age and pulmonary or liver pathologies might be explained by this selection bias.

In Paper 3, prescribed methadone was associated with increased odds of drug-induced death in bivariate analysis (OR = 2.53; 95% CI = 1.13–5.68), but not in the multiple model (aOR = 1.2; 95% CI = 0.44–3.73). This bivariate association in Paper 3 contrasts with the results in

Paper 1, where prescribed methadone was not associated with drug-induced death when all 200 deceased patients were included, neither in bivariate (OR = 1.24; 95% CI = 0.64–2.41) nor in multiple regression analysis (aOR = 1.25; 95% CI = 0.63–2.48). The bivariate association in Paper 3 between prescribed methadone and drug-induced death is probably a result of selection bias and should be interpreted with caution. In other words, the distribution of OAT medications in patients autopsied and with toxicological analyses from peripheral blood (n = 107) differed from the distribution of OAT medications in Paper 1 where all deceased patients were included (n = 200).

5.4 Information bias

A systematic error can arise if the information collected about the study participants is erroneous. Two types of information bias are misclassification (e.g., the person is placed in an incorrect category) and recall bias [78]. Although we took measures to reduce information bias, we cannot rule out the possibility of misclassification and recall bias.

We have used routinely collected health data in research, e.g., health administrative data, disease registries (NPR), medical records and autopsy reports. Using routinely collected data in research has several advantages, such as representativeness, generalizability, reduced cost and effort and the possibility to access large datasets that cover long periods [125]. However, there are also several limitations, which may affect internal validity, such as the risk of misclassification, underreporting and lack of transparency [125]. Therefore, we have used the extension to the STROBE statement, the RECORD guidelines (the REporting of studies Conducted using Observational Routinely-collected Data) [126] when preparing the manuscripts. In line with the RECORD guidelines, we have provided descriptions in all the papers of the variables we have created using routinely collected health data, with the aim to improve reporting, reproducibility and replicability.

The cause of death was an important variable in both studies. Both completeness and the degree of coverage are high in the Norwegian Cause of Death Registry [127]. Nonetheless, the cause of death is missing each year in 500-700 deaths nationally, half of which occur abroad [127]. In Paper 1, the cause of death was not recorded or unknown in the Norwegian Cause of Death Registry in eight cases. However, in six of these cases, we found the cause of death in medical records. Thus, a valid cause of death could not be established in only two (1%) of 200 patients. Another objection to the data quality of the Norwegian Cause of Death Registry is that non-specified or non-meaningful diagnoses as the underlying cause of death occur frequently [127]. In our data set, one example was the use of the ICD-10 diagnosis F29 (Unspecified psychosis not due to a substance or known physiological condition) as the underlying cause of death. Based on the autopsy report, we suspected that this was probably a rare coding error with F29 instead of F19. In two more cases, there were discrepancies between the cause of death in the autopsy report and in the Cause of Death Registry. We used the cause of death in the Cause of Death Registry since this is the official data source.

According to Norwegian legislations, a forensic autopsy is required if an unnatural cause of death is suspected, for example deaths due to overdose, suicide or accident. However, autopsy rates can vary with age, sex, manner of death and region [128]. In Paper 1, we reported that 66% of the suicides and 85% of the drug-induced deaths in our data were followed by an autopsy. Five of 84 drug-induced deaths were coded as an intentional drug overdose. In these cases, there was information in the autopsy reports of known suicidal ideations prior to death or suicide notes. However, it is sometimes challenging to distinguish between an unintentional and intentional overdose (suicide). Misclassification between an intentional and unintentional overdose is possible since not all causes of unnatural death in our material were determined by a forensic autopsy.

Autopsies are often regarded as the gold standard in diagnostics and in determining the cause of death, but there are limitations to the use of autopsy reports in research. Forensic autopsies are subject to quality assurance by the Norwegian Board of Forensic Medicine [129]. Nonetheless, reporting in forensic autopsies is not standardized since no national forensic autopsy protocol exists. As discussed in Paper 2, there may have been differences in the degree to which organs were examined and/or the findings included in the autopsy reports. Additionally, there are grey zones between physiological and pathological changes. Although the results in Paper 2 were based on explicit reporting by the pathologist (with the exception of an enlarged liver), and the autopsy reports were assessed by both the PhD candidate and one of the co-authors who is an experienced post-mortem examiner, we cannot rule out the possibility of misclassification of organ pathologies. Medical autopsy reports also have their limitations. In a study published in 2021, 389 medical autopsy reports from 2014 were reviewed. In 18% of these reports, the wrong underlying cause of death was stated, which may have affected the cause of death statistics [130].

Recall bias might be reduced when information from medical records is used to answer surveys or questionnaires [78]. Nurses or social workers in the hospitals filled out 60% of the death registration questionnaires based on their knowledge of the patient and record information. However, clinicians other than doctors did not always have access to medical records of the patient's physical condition because of access regulations. There are also different types of medical records both between and within some of the health trusts, and doctors in one unit did not necessarily have access to medical records in other units or other hospitals. We found that this led to extensive underreporting of the number of diagnoses in the death registration questionnaires. Information on whether the patient lived in an urban or rural area and whether there had been any interruptions of OAT was also difficult and time-

consuming for the clinicians to find and report, and due to extensive missing information, these two variables were not used in any of the published papers.

Different data sources will probably affect the prevalence of multimorbidity [102]. Because ICD-10 diagnoses were generally underreported in the death registration questionnaires, we used diagnoses from the NPR instead when estimating the Charlson comorbidity index score in Paper 1. NPR data have a high level of completeness [131]. However, comorbidity prevalence is lower in administrative data than in chart data [132]. As an example, data from NPR only include diagnoses from specialist health care facilities and thus likely underestimate the prevalence of common diseases that are mainly handled by GPs. Thus, the true Charlson comorbidity index score might be higher than the score we reported in Paper 1 based on ICD-10 diagnoses from the NPR.

5.5 Confounding

Confounding, or the *confusion of effects* is an important issue in epidemiology [78]. A confounder is a measured or unmeasured variable that is associated with the outcome and at the same time could be associated with the exposure [106].

Confounding is more severe in observational studies due to lack of randomization, and can lead to both over- and underestimation of an effect [106, 111]. Stratification is one way of handling confounding. However, the main advantage of multivariable regression models is the ability to control for several confounding variables [78]. Age, sex, BMI and prescribed OAT medications are examples of measured variables potentially confounding the results in our studies. However, unmeasured variables could also have affected the outcomes. In Paper 2, smoking was an example of an unmeasured confounding variable of interest. The association between smoking and excess mortality due to physical causes in individuals with SUD is well established [63, 133]. We did not have information on smoking habits in the present studies,

and smoking was generally not described in hospital medical records. Nonetheless, it was very likely that a majority of the deceased patients in our studies were present or former smokers based on the prevalence of smoking (70-92%) reported in the OAT population both in Norway and internationally [134-136]. But the high proportion of smokers in patients receiving OAT in Norway [136] (and thus the low proportion of non-smokers) also meant that we would have needed a much higher sample size to be able to detect any differences between smokers and non-smokers.

Another unmeasured confounder of interest was details of prescribed benzodiazepines (type of benzodiazepine, dose and last filled prescription). A Scottish study found that co-prescription of benzodiazepine was associated with an increased risk of death from overdose in patients receiving OAT [137]. Although we had good quality data from the hospitals regarding OAT medication and dosage at the time of death, information from the hospitals' medical records on benzodiazepine prescription (especially prescription by GPs) may have been less accurate (i.e., underestimated). In Paper 3, we did not know whether benzodiazepines detected post-mortem were prescribed. Initially, we intended to include data from the Norwegian Prescription Database, which could have provided data on prescriptions of benzodiazepines and psychotropic medication, together with changes in OAT medication in the years prior to death. However, the Norwegian Prescription Database contains only pseudonymous information [138]. Because we had a rich data set with identifiable patients, we were not allowed to use data from the Norwegian Prescription Database due to the risk of reverse identification. On the other hand, it is generally difficult to account for extra-medical use of benzodiazepines. Exposure misclassification would mitigate any mortality increase seen with co-prescribing of benzodiazepines [137]. For this reason, some researchers choose not to include information on benzodiazepine prescription in mortality research [139].

5.6 External validity

Internal validity affects external validity, i.e., the possibility to generalize the findings to other countries or treatment settings. We included only those who died. It is important to note that those who died might be those at highest risk in the OAT population, e.g., the most vulnerable due to longstanding SUDs, multimorbidity or ongoing polydrug use. Thus, the results (e.g., the number of benzodiazepines or the number of organ pathologies detected post-mortem) may not be directly generalizable to living patients receiving OAT in Norway.

The type of drugs, the proportion of individuals who inject, and the treatment provided differ between countries [25, 26, 140]. These differences are also visible in the Nordic countries [26, 27], which are otherwise quite similar. Additionally, buprenorphine is the most prescribed OAT medication in Norway, in contrast to most European countries [9], and the Norwegian OAT population is aging [49]. Nonetheless, older age, smoking and polydrug use are common among people with opioid dependence [4, 22, 25, 134, 141]. Despite the limitations discussed in this chapter, the internal validity is considered fairly good, and our results are probably generalizable to aging OAT populations in other countries with similar characteristics.

5.7 Strengths

One of the main strengths was that those included represented an almost complete national cohort of deceased patients receiving OAT with very few missing cases. The different data sources also had their strengths and limitations. As an example, non-communicable diseases like cancer and liver or kidney failure are generally underestimated in autopsy studies because patients with a known, end-stage physical disease are not usually autopsied. Therefore, our results based on information from several different sources complement both autopsy studies and studies based on mortality registers only. The method of pooling opioid and benzodiazepine concentrations is novel. Despite methodological limitations as discussed in Paper 3, this method provided more information than merely counting the number of

substances. The fact that 63% had a forensic or medical autopsy also strengthened the validity of the causes of death.

6. Discussion of results

First, the results from the two studies will be discussed in relation to existing literature. Then, in section 6.3, the results from all three papers will be discussed in relation to each other and from the perspectives of aging, multimorbidity and polydrug use.

6.1 CMRs and causes of death

In study 1, we found an all-cause CMR of 1.4/100 PY during OAT. This CMR is high and even above the upper 95% CIs of CMRs reported in systematic reviews and meta-analyses [61, 62, 64]. However, CMRs are higher in older individuals [63], and a CMR of 1.4/100 PYs is similar to the CMR of 1.43/100 PYs reported by Santo et al. [64] in OAT patients older than 35 years, as well as CMRs of 1.3-1.4/100 PYs during OAT reported in other Norwegian studies [66, 67]. In study 1, the mean age of those who died while receiving OAT was almost 49 years, and some of them had been in OAT for up to 17 years. OAT in Norway started later than in many other countries in Europe [9]. In the first years (1997 to 2009), the mean age at enrolment in OAT was 36-38 years [67], which was higher than that of most European countries [85]. The age profile, together with high retention in treatment, may explain why Norway still has one of the oldest OAT populations in Europe.

As seen in other studies [60-62], the all-cause CMR was higher in patients taking methadone than in those taking buprenorphine. Methadone was introduced earlier than buprenorphine in most countries, including Norway [9]. In study 1, patients prescribed methadone had been significantly longer in OAT, but were not significantly older than patients prescribed buprenorphine. Therefore, we suggested that in the Norwegian context, the higher CMR in those prescribed methadone might be due to a "veteran-effect" (e.g., longer duration of drug use, earlier initiation of OAT). Mortality may also vary by treatment setting [69]. No deaths were reported during initiation of methadone in our data set, in contrast to findings from

previous studies [60, 64, 77]. In Norway, in-patient detoxification and initiation of OAT are common, especially for methadone. Our result confirms the results from Norwegian studies showing that overdose during initiation of OAT is a rare event [66, 67].

Both somatic (45%) and drug-induced deaths (42%) were common during OAT, and the CMRs for both increased with age. In our material, cancer and cardiovascular and pulmonary causes of death accounted for one-third of all deaths during OAT. As patients age, their healthcare needs are primarily related to non-communicable diseases [65]. Cancer will be an increasingly important cause of death as opioid users live longer [142]. Although cancer incidence rates generally are comparable between patients with and without a history of mental illness and SUDs, cancer case fatality rates are higher among the former [143, 144]. Aging or disease progression may also gradually decrease tolerance of substances and increase the risk of overdose. The increasing vulnerability of an aging cohort of opioid users is illustrated by a 75% increase between 2012 and 2018 in the number of overdose deaths among those > 50 years in Europe [21].

We did not find that the CMR for traumatic causes of death increased with age, and existing literature is inconsistent [70, 145]. In a recent systematic review and meta-analysis [63], the suicide rate was almost eight times higher and the rate of accidental injuries (except unintentional overdose) was almost seven times higher among people with extra-medical opioid use than in the age- and sex-matched general population. However, according to Santo et al. [64], the rate of suicide during OAT was lower than the rate seen without treatment in people with opioid dependence, while the rates of violence and accidents did not differ significantly with or without OAT.

6.2 Autopsy findings

In study 2, organ pathologies detected post-mortem and toxicology results were explored.

6.2.1 Organ pathology

In Paper 2, HCV-related liver disease, cardiovascular disease and pulmonary emphysema were the most common organ pathologies detected post-mortem. Two-thirds of the deceased had more than two organ system diseases. Our results concur with studies reporting excess mortality from respiratory, cardiovascular and hepatic diseases among individuals with opioid use disorder or other SUDs [133, 146]. Patients receiving OAT may have multiple risk factors for both infections and non-communicable diseases such as excessive alcohol, tobacco and drug use (including injection), insufficient physical activity, poor nutrition and dental status and reduced physical health in general. Other factors that might contribute to high mortality due to physical causes are diagnostic overshadowing, barriers to treatment, and lower screening rates [65, 143, 147].

Liver diseases related to HCV infection are common among PWID [148-150]. As expected, liver pathologies (mainly HCV-related) were detected in a majority (81%) of those autopsied. More surprisingly, given the mean age of 48 years, 22% had already developed cirrhosis. Hepatocellular cancer and liver cirrhosis contribute substantially to the global burden of disease [12]. Left untreated, individuals with chronic HCV infection will eventually develop liver sequelae [151] and access to HCV treatment is therefore important. We did not have information on whether those who died in 2014–2015 had ever received treatment for HCV infection. Although new effective antiviral medications were available from 2014, treatment was restricted to those with severe liver affection in the first years as the medication was very expensive for the regional health trusts. Since 2018, however, treatment has been available to all patients with HCV infection in Norway [152].

It is worth noting that more than 2/3 of patients who had an autopsy had at least one cardiovascular disease, with ventricular hypertrophy, myocardial infarction and moderate to

severe atherosclerosis being the most common. Suggested explanations for this high prevalence include smoking, the use of opioids [153] and the use of stimulants or anabolic androgenic steroids [154, 155] (either alone or in combination). The role that systemic chronic inflammation plays in disease risk, biological aging and mortality is still not fully understood [156]. Systemic chronic inflammation associated with HCV infection increases the risk of myocardial infarction and stroke [157]. Chronic inflammation might also be one explanation of increased arterial stiffness and vascular age reported in patients with opioid dependence compared with opioid naïve controls [158]. Buprenorphine has been reported to be milder in its cardiovascular effect than methadone [159]. The high prevalence of smoking in individuals with SUD also contributes substantially to excess mortality for respiratory diseases [63, 133], in common with our finding that 41% of those with an autopsy had pulmonary emphysema.

In Paper 2, 61% of patients autopsied had signs of drug use described in the autopsy reports (i.e., information about recent drug use, drugs or drug paraphernalia on or close to the body or fresh needle marks). Chronic inflammation associated with skin and soft tissue infections due to injection or "skin popping" (subcutaneous injection) is involved in the development of AA amyloidosis [160]. In Paper 1, seven deceased patients (5%) had amyloidosis of the kidneys, all whom developed kidney failure and needed hemodialysis. Among those with AA amyloidosis who had an autopsy, three also had amyloidosis in the liver and one in the spleen. The prevalence of amyloidosis detected post-mortem in PWID ranges from 1.6 to 22.5% [160]. In Norway, AA amyloidosis was not encountered in individuals using opioids until 2005 [161].

6.2.2 Toxicology

In Paper 3, a median of four substances was detected in those with post-mortem toxicological analyses from peripheral blood. Both single opioids (heroin, morphine, buprenorphine or

methadone) and a combination of several opioids contributed to the significantly higher pooled opioid (i.e., morphine-equivalent) concentration in drug-induced deaths compared with other causes of death during OAT. Nonetheless, our results must be interpreted with caution. The conversion factors from the Norwegian Road Traffic Act are based on a limited number of studies investigating psychoactive effects among opioid-naïve individuals [96], while all deceased patients in our study had had opioids prescribed (i.e., tolerance). The conversion factors are used in Norway only, and conversion factors for buprenorphine and tramadol, as well as for pregabalin and gabapentin, have not yet been established.

Among the 66 drug-induced deaths in Paper 3, prescribed methadone was considered the main intoxicant in 30 cases and prescribed buprenorphine in seven cases. The interpretation of the role of prescribed OAT medication in overdose deaths is not straightforward. Post-mortem concentrations cannot be used to reliably calculate the quantity of medication consumed. Additionally, tolerance accounts for part of the overlap between therapeutic and lethal concentrations [162]. Patients prescribed methadone have higher post-mortem concentrations of methadone than those not in OAT at the time of death [163-165]. Injection of buprenorphine and methadone has been found to be a risk factor for overdose death, especially in combination with concomitant intake of benzodiazepines and alcohol [166-168]. An Italian study found that 28% of those receiving OAT had injected their own OAT medication [169]. Other suggested explanations for high post-mortem concentration of methadone or buprenorphine are organ pathologies that may affect metabolism and excretion [170] and post-mortem redistribution [94, 95, 162, 171]. For methadone, a mean +20% change in methadone concentration was observed in a study by Brockbals et al. [95]; however, this change was considered irrelevant in light of post-mortem toxicological interpretation. Low post-mortem concentrations of opioids might be explained by delayed death [165, 166, 172].

Another important finding was that buprenorphine was not detected post-mortem in 12 of 52 patients (23%) prescribed buprenorphine, although they all died within five days of the last reported intake of OAT medication. In contrast, methadone was detected post-mortem in all patients prescribed methadone. Buprenorphine is a partial agonist with antagonist properties. Therefore, patients may stop taking buprenorphine to enhance the effect of other opioids such as heroin or (non-prescribed) methadone. This finding concurs with studies reporting that patients receiving buprenorphine are more often in and out of treatment [173] and have lower retention compared with patients receiving methadone [71].

As expected [13], benzodiazepine use was common, and at least one benzodiazepine was detected in three-fourths of the deceased in Paper 3. We did not know whether these medications were prescribed. Although the pooled benzodiazepine concentrations did not differ by cause of death, we cannot draw the conclusion that benzodiazepines were not involved in these deaths. The mechanisms for additive effects upon respiratory depression when opioids and benzodiazepines are combined are poorly understood [174], and the concentration ranges in our data were wide. Additionally, pregabalin was detected in 18% of the deceased but was not included in the pooled benzodiazepine concentration. The proportion of patients in OAT prescribed benzodiazepines and pregabalin increased from 2013-2017 [175]. Pregabalin, and to a lesser extent gabapentin, have abuse potential and are known to boost a euphoric high and reduce withdrawal symptoms in patients with a history of opioid use disorder or other SUDs [176]. Both are increasingly associated with fatal overdoses (especially in combinations with opioids) in several countries [22, 27, 176-179].

6.3 A complex combination

When the two studies are viewed as a whole, aging, multimorbidity and polydrug use emerge as overarching themes. An aging OAT population is not a problem per se, but rather a desirable development and a consequence of successful OAT reducing all-cause mortality in

individuals with opioid dependence. Multimorbidity significantly increases with age and is associated with poor quality of life, a higher number of prescriptions, high health care utilization and increased mortality risk [101, 102, 180, 181]. Multimorbidity is clearly present in our data, measured with the Charlson index score in Paper 1 and the number of organ pathologies in Paper 2. Polydrug use is also common and multiple drug toxicity is involved in most overdose deaths [22, 25], in line with our results in Paper 3.

Treatment is complex and often less successful for individuals using multiple substances [4]. Motivations for polydrug use in the literature include inadequate doses of OAT medication [182], psychoactive effects, self-medication of physical or mental health conditions or managing withdrawal, cravings or undesirable effects of other drugs [183]. Additionally, most treatments and guidelines target a single index condition. Challenges in managing patients with multimorbidity include lack of guidelines and evidence, conflicting recommendations and competing and shifting priorities [180]. Important goals of managing multimorbidity are to optimize benefit, minimize harm and enhance quality of life [180]. These are very similar to the aims of harm-reduction interventions mentioned in section 1.5: to reduce harms and maximize well-being.

Han et al. argue that there is a lack of awareness of the interplay of aging, chronic medical disease and substance use. Substance use-related comorbidities and health behaviors may accelerate frailty and lead to early onset of geriatric conditions. Therefore, SUD management in this population is complicated [184]. The clinical picture is further complicated by mental ill-health common in individuals with SUDs [185] as well as self-reported conditions such as pain [136], which we have not examined in our studies.

6.3.1 The role of OAT medications in overdose deaths

The combination of aging, multimorbidity and multiple drug toxicity also makes it challenging to determine the cause of death and the role of the OAT medications in overdose deaths. The uncertainty surrounding the cause of death was often explicitly discussed in the autopsy reports in our data. However, the death statistics generally fail to acknowledge the complexity of the interlinked causes of death since each death is classified by only one cause [85], and only one main intoxicant is reported in overdose deaths (usually the most potent opioid). Thus, the results from Papers 2 and 3 add to the results of Paper 1, and provide more detailed information on the sometimes inextricably interwoven factors causing premature morbidity and mortality in individuals with opioid dependence.

In a substantial number of overdose deaths in our data, the prescribed OAT medication was considered the main intoxicant. As the number of patients prescribed buprenorphine and methadone increases, the number of fatal overdoses where OAT medications are detected post-mortem will also increase [9]. Indeed, the number of overdose cases where methadone is coded as the main intoxicant in the Norwegian Cause of Death Registry has increased significantly since 2003 [28], in line with the increasing number of patients receiving OAT in Norway. The pathologist did not report information about the deceased's OAT status in 35% of the autopsies in our data, and we did not know whether this information was available. If the pathologist lacks information on OAT status and prescribed medications in patients recieiving OAT (and thus the deceased person's opioid tolerance), the death statistics might overestimate the role of OAT medications in overdose deaths. According to the EMCDDA [9], information about prescribed OAT medication together with a detailed assessment of the role of OAT medications in overdose deaths should be provided. A national forensic autopsy protocol could reduce variations in practice and reporting in Norway.

In Scotland and England, increasing morbidity is suggested as a risk factor for the sharp increase in methadone-specific mortality among both male and female methadone clients older than 45 years [139, 186]. Disease of the circulatory system was the comorbidity most likely implicated in the quadrupling of methadone-specific overdose among methadone-prescription clients older than 45 years in Scotland, followed by digestive disease (including liver disease) [187]. This is in line with our findings that both cardiovascular and HCV-related liver diseases were common. Other suggested risk factors for methadone-specific overdose are polydrug use, polypharmacy and methadone-related QTc prolongation resulting in torsade des pointes and cardiac arrest [139, 186].

From both a public health and a clinical perspective, it is important to know whether medications involved in overdose deaths are prescribed or not, and if prescribed, whether patients receiving OAT die *from* or *with* their OAT medication. If methadone- and buprenorphine-related deaths are consequences of diversion and extra-medical use of OAT medications due to lack of access to OAT or barriers to treatment, improved access to OAT is one way of reducing diversion [9] and overdose deaths outside treatment. New medications such as injectable depot buprenorphine or heroin-assisted treatment could attract individuals with opioid dependence into treatment who normally do not want OAT due to control measures or the limited range of medications. As an example, injectable depot buprenorphine has been available in Norway since 2020, with promising patient satisfaction [188]. Conversely, if a substantial proportion of methadone- and buprenorphine-related deaths in Norway occurs among patients already receiving OAT, improved follow-up of multimorbidity and polydrug use, patient education and dose titration may reduce methadone- and buprenorphine-related deaths, especially as the patients age.

7. Clinical implications and concluding remarks

The main aim of this project was to explore mortality and causes of death in the Norwegian OAT program. Although the data used in this thesis only provided a snapshot, the results from the three papers add useful information and insights into morbidity and mortality in patients receiving OAT in Norway.

Both somatic and drug-induced deaths were common. Findings from the three papers suggest that important patient-oriented interventions should include regular health checks and regular medication review (including dose titration as patients age), smoking cessation or tobacco harm-reduction interventions, spirometry and lung image tests for heavy smokers, HCV treatment and improved focus on patients' cardiovascular history. Life style interventions need to be implemented, preferably as early in the patients' lives as possible. Additionally, greater focus is needed on suicide and overdose prevention. Reducing drug injection and improving injection practice (e.g., hygiene) are also important to reduce the risks of overdose, infections and chronic inflammation. For those who continue to inject drugs, access to supervised injection facilities and NSP are important harm-reduction interventions.

The combination of aging, multimorbidity and multiple drug toxicity makes it challenging to establish the exact cause of death. The use of (one or more) opioids still plays a major role in overdose deaths among patients receiving OAT, but the role of prescribed OAT medications and benzodiazepines in overdose deaths remains unclear. As a minimum, autopsy reports should include information on prescribed medications and a detailed assessment of the role of prescribed methadone or buprenorphine in overdose deaths among patients receiving OAT. The high prevalence of cardiovascular disease also underlines the importance of an autopsy to distinguish between an overdose and sudden cardiac death.

Given the high risk of mortality outside treatment, it is paramount to retain individuals with opioid dependence in OAT to keep all-cause mortality at a minimum. Patients receiving OAT require comprehensive treatment and care that considers physical and mental health problems, aging, pharmacological treatment and drug use, living conditions, and wider societal factors. To further reduce mortality related to multimorbidity and/or polydrug use, multidisciplinary and integrated treatment and care in a life course perspective is necessary.

8. Future research

The method of pooling blood concentrations detected post-mortem is novel. More studies are needed to evaluate the conversion factors as well as to validate the results in Paper 3. Additionally, conversion factors for buprenorphine and tramadol need to be developed. Although difficult, the combined effect of opioids (including prescribed OAT medication) and benzodiazepines, z-hypnotics and gabapentinoids in drug-induced deaths within OAT should also be further explored, especially since the combination of opioids and benzodiazepines detected post-mortem has increased in recent decades [28]. One possibility is studies linking prescription data and post-mortem toxicological findings.

Males generally have a higher overdose mortality than women. However, large register studies from Scotland and England reported that this female advantage seems to be diminishing as patients receiving OAT are aging, especially for methadone-specific mortality [139, 186]. One might question whether higher multimorbidity rates [103, 189] as well as polydrug use or polypharmacy [175] in women are explanations of the diminishing female advantage in older OAT patients. Unfortunately, we could not explore mortality by age groups and sex due to the small sample size and low proportion of women, and more studies are needed to validate the results from Scotland and England in other treatment settings.

Renal pathologies were probably underestimated in our study because findings not relevant for establishing the cause of death were not always reported in detail in the autopsy reports and we did not have access to histological samples. A decreased kidney function associated with opioid use [190] or aging [191] increases the risk for drug accumulation and medication-related adverse events, including methadone toxicity [190]. Therefore, more studies are needed on age- and disease-related changes in the kidneys in the OAT population.

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RESEARCH ARTICLE Open Access

Mortality and causes of death among patients with opioid use disorder receiving opioid agonist treatment: a national register study

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Abstract

Background: Mortality rates and causes of death among individuals in opioid agonist treatment (OAT) vary according to several factors such as geographical region, age, gender, subpopulations, drug culture and OAT status. Patients in OAT are ageing due to effective OAT as well as demographic changes, which has implications for morbidity and mortality. Norway has one of the oldest OAT populations in Europe. Because of the varying mortality rates and causes of death in different subgroups and countries, research gaps still exist. The aims of this study were to describe the causes of death among OAT patients in Norway, to estimate all-cause and cause-specific crude mortality rates (CMRs) during OAT and to explore characteristics associated with drug-induced cause of death compared with other causes of death during OAT.

Methods: This was a national, observational register study. Data from the Norwegian Cause of Death Registry and the Norwegian Patient Registry were combined with data from medical records. We included all patients in the Norwegian OAT programme who died not more than 5 days after the last intake of OAT medication, between 1 January 2014 and 31 December 2015.

Results: In the 2-year observation period, 200 (1.4%) of the OAT patients died. A forensic or medical autopsy was performed in 63% of the cases. The mean age at the time of death was 48.9 years (standard deviation 8.4), and 74% were men. Somatic disease was the most common cause of death (45%), followed by drug-induced death (42%), and violent death (12%). In general, CMRs increased with age, and they were higher in men and in patients taking methadone compared with buprenorphine. Increasing somatic comorbidity, measured by the Charlson comorbidity index, reduced the odds of dying of a drug-induced cause of death compared with other causes of death.

Conclusions: Both somatic and drug-induced causes of death were common during OAT. Improved treatment and follow-up of chronic diseases, especially in patients aged > 40 years, and continuous measures to reduce drug-induced deaths appear to be essential to reduce future morbidity and mortality burdens in this population.

Keywords: Opioid agonist treatment, Mortality, Cause of death, Multimorbidity, Overdose, Methadone, Buprenorphine

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Background

Opioid use disorder (OUD) is associated with high rates of morbidity and mortality [1]. Individuals who use illicit opioids have up to 15 times the risk of premature mortality compared with the general population [2]. Opioid agonist treatment (OAT) with methadone, buprenorphine or buprenorphine-naloxone is the most common evidence-based treatment modality for individuals with OUD. It is well established that OAT substantially reduces mortality, especially overdose deaths [1–4]. Criminal convictions and somatic morbidity related to substance use and drug injection (e.g., local and systemic bacterial infections) are also reduced during OAT, and quality of life is improved [1, 5–7].

Mortality rates and causes of death among individuals in OAT vary according to factors such as geographical region, age, gender, subpopulations, cohort characteristics, drug culture (i.e., injection), retention in treatment and OAT status [2, 4]. A systematic review and meta-analysis published in 2018 found a pooled all-cause crude mortality rate (CMR) of 0.93 per 100 person-years (PY) (95% confidence interval [CI]: 0.79–1.04) during OAT compared with 4.89/100 PY (CI 3.54–6.23) for untreated periods and 1.69/100 PY (CI 1.47–1.91) after cessation of OAT [4]. In general, CMRs increase with age, especially for somatic causes of death [8], and men have higher CMRs compared with women [2, 4]. CMRs also appear to be higher for individuals taking methadone compared with those taking buprenorphine during induction and treatment, and after cessation of OAT [2–4]. However, retention in treatment is better with methadone [9], and retention in OAT for more than 1 year is associated with a lower mortality rate [4].

OAT patients in Europe are ageing due to effective OAT as well as demographic changes as the post-war baby boom generation ages [10]. This ageing trend can also be seen in Australia and in the USA [10, 11], and has implications for morbidity and mortality. Norway has one of the oldest OAT populations in Europe [12], with a mean age of 44.9 years in 2017 [13]. As OAT patients are getting older, somatic causes of death will likely increase [14], although high drug-induced mortality, irrespective of gender, has been found among ageing methadone patients in recent studies from Scotland and England, including high methadone-specific mortality rates in patients aged > 45 years [15, 16].

Research gaps still exist because of varying mortality rates and causes of death in different subgroups and countries. In Norway, mortality data on individuals receiving OAT are more than 10 years old [8, 17], and no recent studies have linked data to the mortality register [14], which is essential to obtain reliable data about the causes of death. To improve treatment and prevent premature mortality, more research is warranted to better understand mortality rates and the distribution of causes of death in an ageing OAT population. The aims of this study were to describe the causes of death among OAT patients in Norway, to estimate all-cause and cause-specific CMRs during OAT in patients stratified by age, OAT medication and gender, and to explore characteristics associated with drug-induced cause of death compared with other causes of death during OAT.

Methods

Study design and setting

This study was a national, observational study combining register and hospital record data. In Norway, OAT is delivered within a national OAT programme and encompasses both abstinence-oriented treatment and harm-reduction goals. Addiction units in the specialist health care system assess the need for OAT and initiate treatment, and the treatment involves collaboration between addiction units, general practitioners (GPs) and health and social services in the municipalities [18, 19]. At the end of 2017, 7622 patients were enrolled in OAT, 38% of whom used methadone and 59% used buprenorphine or buprenorphine-naloxone [13].

We included all patients in the national OAT programme who died between 1 January 2014 and 31 December 2015. According to the national guidelines, patients who have missed doses for more than 5 consecutive days must be restarted on OAT medication because of potential loss of opioid tolerance. Thus, patients were included if they had died during ongoing treatment or not more than 5 days after the last reported intake of OAT medication. Clinicians in addiction units initially reported 255 deceased OAT patients. Fifty-five patients were excluded: 44 patients who died more than 5 days after the last reported intake of OAT medication, eight patients whom the hospitals were unable to identify further and three patients whose OAT status was unknown at the time of death. A total of 200 patients met the inclusion criteria.

Measurements

Data from the Norwegian Cause of Death Registry and the Norwegian Patient Registry (NPR) were combined with hospital record data. Clinicians completed a questionnaire about the patient's age, gender, health region, OAT medication at the time of death, duration of OAT treatment and information about prescription drugs used before death. At least one prescription of benzodiazepines (BZD) or z-hypnotics during the year before death registered either in the questionnaire or in the medical record was dichotomized into one variable called "BZD/z-hypnotic medication". At least one prescription of antidepressants and/or antipsychotic drugs was dichotomized into one variable called "Psychotropic

medication". From the hospital records, we also collected the OAT status report for the year of death and 3 years before death, if available. The OAT status report is an annual individual report on all OAT patients and is based on the clinician's knowledge of the patient's situation; this report is preferably completed in collaboration with the patient. The variables "Disability/retirement pension", "Own home" and "OAT prescribed by GPs" were collected from the OAT status reports.

Data on the cause of death, place of death, main intoxicant in drug-induced deaths and whether the deceased had an autopsy or not were obtained from the Norwegian Cause of Death Registry [20]. The underlying cause of death is defined as "the illness or injury which initiated the train of morbid events leading directly to death or the circumstances of the accident or violence which produced the fatal injury" [21]. The underlying cause of death was categorized into one of three main groups: death due to somatic disease, drug-induced death and violent death. The definition of drug-induced death is based on the International Classification of Diseases, 10th edition (ICD-10) and includes unintentional overdose or overdose by unknown intent, intentional overdose and substance use disorder [21, 22]. Violent deaths include deaths due to accident, suicide (except intentional overdose) and homicide.

The NPR contains information about all patients referred to or having received treatment in the specialist health care service in Norway [23]. From the NPR, we collected information on admissions to psychiatric hospitals and the diagnoses based on the ICD-10 in the 5 years before death. For each patient, we derived a Charlson comorbidity index score, which is a widely used measure of disease burden based on age and ICD-10 diagnoses for 17 somatic conditions [21, 24, 25]. The variable "Previous non-fatal overdose(s)" refers to either non-fatal overdoses registered in the OAT status report or hospital admission due to non-fatal intoxication (ICD-10 codes T4n, T50.9 and T56.9) registered in the NPR in the 5 years before death.

Data were collected in 2017 and 2018; however, to minimize recall bias, the questionnaire used in the study was filled out by the clinicians shortly after the patients had died in 2014 and 2015. In six cases, the cause of death was not registered or was unknown in the Cause of Death Registry but was found in the medical records. Thus, the cause of death could not be established in only two of 200 patients.

Statistical analysis

The characteristics of all patients and stratified by causes of death were described by frequencies and percentages if categorical, and means and standard deviations (SD) or medians and minimum and maximum values if continuous. Group comparisons were made using Student's t test or Mann–Whitney U test for continuous data and χ^2 or Fisher's exact test for categorical data. To obtain more balanced CMRs, data for the years 2014 and 2015 were combined due to the small number of expected deaths. The CMRs were calculated by dividing the total number of deaths in OAT by the total number of patients in OAT mid-year 2014 and 2015 (i.e., PY), for all patients as well as stratified by age, OAT medication and gender. CMRs are reported per 100 PY, with 95% Poisson CIs [26]. Bivariate and multiple multilevel regression models were estimated to assess the association between drug-induced cause of death and patient characteristics included as fixed effects into the models. Random intercepts for region were included to correctly adjust the estimates for within-region correlations. The results are presented as odd ratios (ORs) and 95% CIs, with other causes of death used as reference category. The regression models were estimated on cases with no missing values of covariates. The results with $p < 0.05$ were considered statistically significant, and all tests were two-sided. The analyses were performed using IBM SPSS Statistics for Windows version 25 (IBM Corp.), Stata Statistical Software version 15 (StataCorp LLC) and SAS version 9.4.

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics South-East (Case number 2016/1204), the Cause of Death Registry, the NPR and the participating hospital trusts, including data protection officials.

Results

Patient characteristics

Table 1 gives an overview of the patient characteristics. The mean age at the time of death was 48.9 years (SD 8.4, ranging from 23 to 71 years), and 74% ($n = 147$) were men. Methadone was used by 55% of patients, at a median dose of 90 mg (ranging from 15 to 200 mg), and buprenorphine was used by 41% at a median dose of 16 mg (ranging from 1 to 52 mg). GPs prescribed OAT medication for 68% ($n = 156$) of the patients. The median total duration of OAT was 8 years (ranging from 1 month to 17 years). Four patients had been in OAT for < 3 months at the time of death.

Comorbid conditions were common, as reflected by a median Charlson comorbidity index score of 2. Only 18% of the patients had a Charlson comorbidity index of zero, which corresponds to no registered somatic medical condition in the NPR and aged < 50 years at the time of death. The most frequent chronic diseases registered in the NPR in the 5 years before death were liver diseases (62%, chiefly hepatitis C),

Table 1 Characteristics of 200 patients who died during opioid agonist treatment, stratified by the cause of death

Variables	N	Total, N (%)	Drug-induced deaths *N* = 84, n (%)	All other causes of death *N* = 116, n (%)
Demographics				
Male gender	200	147 (74)	59 (70)	88 (76)
Age, mean (SD)	200	48.9 (8.4)	46.9 (8.5)	50.3 (8.2)
Region East, incl. Capital Oslo	200	89 (45)	30 (36)	59 (51)
Region South	200	39 (20)	16 (19)	23 (41)
Region West	200	44 (22)	26 (31)	18 (16)
Region Mid-Norway	200	14 (7)	7 (8)	7 (6)
Region North	200	14 (7)	5 (6)	9 (8)
Disability/retirement pension[a]	154	117 (76)	45 (70)	72 (80)
Own home[b]	162	125 (77)	54 (78)	71 (76)
OAT medication				
Methadone	199	109 (55)	46 (55)	63 (54)
Buprenorphine	199	82 (41)	35 (42)	47 (41)
Other	199	8 (4)	2 (2)	6 (5)
OAT prescribed by GPs	156	106 (68)	42 (60)	64 (74)
Dose methadone (met) or buprenorphine (bup)				
< 60 mg met or < 8 mg bup	187	21 (11)	10 (12)	11 (10)
60–120 mg met or 8–24 mg bup	187	141 (75)	62 (77)	79 (75)
> 120 mg met or > 24 mg bup	187	25 (13)	9 (11)	16 (15)
Total duration of OAT				
< 4 years	188	36 (19)	14 (18)	22 (20)
4–8 years	188	56 (30)	30 (38)	26 (24)
8–12 years	188	49 (26)	18 (23)	31 (29)
12–17 years	188	47 (25)	18 (23)	29 (27)
Comorbidities				
Charlson index score, median (min–max)	200	2.0 (0–12)	1.0 (0–9)	3.0 (0–12)
Psychiatric admissions[c]	200	56 (28)	26 (31)	30 (26)
BZD/Z-hypnotics[d]	177	76 (43)	28 (38)	48 (46)
Psychotropic medication[e]	156	44 (28)	12 (20)	32 (33)
Previous non-fatal overdose[f]	200	59 (30)	30 (36)	29 (25)

[a]Only four patients had a retirement pension at the time of death (> 67 years). Among those who did not have a disability or retirement pension, two had paid work and the rest had work assessment allowance or social welfare
[b]Own home, rented or owned. Among those who did not have an own home, two were homeless; the rest lived in shelters, institutions, with friends/family or were in prison
[c]Psychiatric admissions registered in the NPR in the last 5 years before death
[d]BZD/Z-hypnotics prescribed at least once in the year before death
[e]Antidepressants/antipsychotic medication prescribed at least once in the year before death
[f]Non-fatal overdoses registered in the NPR or in OAT status reports in the last 5 years before death

cardio-vascular diseases (19%) and chronic obstructive pulmonary disease (COPD) (19%). Co-prescription was common, and 43% of the deceased had at least one prescription of BZD/z-hypnotics in the year before death, and 28% were prescribed other psychotropic medication. Thirty per cent of the patients had experienced previous non-fatal overdose(s) in the last 5 years before death.

Compared with patients taking buprenorphine, patients taking methadone were significantly more likely to live in Health Region East than the other four health regions (75% vs. 61%/31%/29%/46%; all $p < 0.01$) and they

had been significantly longer in OAT (median 10.1 vs. 6.8 years; $p < 0.001$), but were not significantly older (mean 49.3 vs. 48.1 years; $p = 0.331$) (data not shown in Table 1).

Causes of death

Table 2 provides an overview of the causes of death for all patients as well as stratified by gender; 90 deaths (45%) were caused by somatic disease, 84 (42%) were drug induced, and 23 (12%) were violent deaths.

Cancer and cardio-vascular and pulmonary diseases were the most frequent somatic causes of death. Twenty-six patients died of cancer, and lung cancer alone accounted for one-third of cancer fatalities. COPD, emphysema and pneumonia were the most frequent causes of death for those who died of pulmonary diseases. Cardio-vascular causes of death were more diverse, involving pulmonary embolism, haemorrhagic stroke, endocarditis, chronic ischaemia or myocardial infarction. Among the 14 patients who died of a liver disease, one died of liver cancer. The group "Other somatic cause of death" included four cases of kidney failure, three of diabetes, two of gastrointestinal bleeding, two of bacterial infections/sepsis and one case of epilepsy. Seven patients had a confirmed secondary amyloidosis (amyloid A [AA] amyloidosis) diagnosis with end-stage kidney disease and needed regular haemodialysis, but only two of them had kidney failure as the underlying cause of death. Bacterial infections contributed substantially to mortality: 30 patients (15%) had bacterial infections either as a contributing cause or as an underlying cause of death in the Cause of Death Registry. The most common infections were pneumonia, endocarditis or fatal sepsis. Nine patients (5%) had human immunodeficiency virus (HIV), but no patients died of acquired immune deficiency syndrome (AIDS).

Several patients had more than one potential fatal somatic disease documented in medical records or in the Cause of Death Registry. Two fatalities exemplified the complex of multiple comorbidities: one involved chronic hepatitis B and C, AA amyloidosis with end-stage kidney failure, COPD and death due to overdose; the other involved chronic hepatitis B and C, HIV, COPD, acute liver and kidney failure and death due to respiratory failure.

Among the 84 drug-induced deaths, 71 patients had undergone an autopsy. In the Cause of Death Registry, methadone was reported as the main intoxicant in 31 deaths and heroin in 17. Other opioids, including buprenorphine, were the reported main intoxicant in an

Table 2 Causes of death among 200 patients in opioid agonist treatment in Norway, stratified by gender

	Total	Men	Women
	N = 200, n (%)	*N* = 147, n (%)	*N* = 53, n (%)
Somatic cause of death	90 (45)	69 (47)	21 (40)
Cancer, excl. Liver cancer	26 (29)	19 (28)	7 (33)
Cardio-vascular disease	20 (22)	15 (22)	5 (24)
Pulmonary disease	18 (20)	14 (20)	4 (19)
Liver disease, incl. Liver cancer	14 (16)	12 (17)	2 (10)
Other somatic cause of death	12 (13)	9 (13)	3 (14)
Drug-induced cause of death[a]	84 (42)	59 (40)	25 (47)
Methadone	31 (37)	21 (36)	10 (40)
Heroin	17 (20)	14 (24)	3 (12)
Other opioids (T402, T404, T406)	15 (18)	10 (17)	5 (20)
Substance use disorder (F11, F19)	17 (20)	11 (19)	6 (24)
Non-opioid overdose	4 (5)	3 (5)	1 (4)
Violent cause of death	23 (12)	16 (11)	7 (13)
Suicide	12 (52)	7 (44)	5 (71)
Accident	8 (35)	6 (38)	2 (29)
Homicide	3 (13)	3 (19)	0
Other/unknown cause of death[b]	3 (2)	3 (2)	0

Data are expressed as *n (%)*. The distributions of somatic cause of death, drug-induced, violent and unknown cause of death did not differ between men and women ($p = 0.610$[a])

[a]Five suicides by intentional overdose are included in the group "Drug-induced death". Only four patients < 31 years died during OAT; all four died of overdose

[b]One patient with non-organic psychosis (F29) as the cause of death was included in the group "Other/unknown cause of death"

additional 15 deaths. No drug-induced deaths occurred in the first month after initiation of methadone or buprenorphine. Ten of the 17 patients with substance use disorder as an underlying cause of death had severe medical comorbidities as a contributing cause of death in the Cause of Death Registry.

Half of the violent deaths were suicides, and three-quarters of the suicides were intentional self-harm by hanging. Both men and women died in suicides and accidents (falling, hypothermia, fire and traffic accidents), but all three homicide victims were men.

Forensic or medical autopsies were performed for 125 (63%) of the deaths. The autopsy rate was high for all unnatural deaths: 66% for suicides, 85% for drug-induced deaths, 88% for accidents and 100% for homicides. The most common place of death was the home address (43%), where almost two-thirds of the deaths were drug-induced; 37% died in a hospital or other health institution, three-quarters of whom died of an already known somatic disease. We found no statistically significant differences between men and women in the causes of death, autopsy rates or place of death.

CMRs

Table 3 shows that the mean number of patients in OAT was 7220 in 2014 and 7439 in 2015, giving a total observation period of 14,659 PY. The 2-year all-cause CMR during OAT was 1.4/100 PY (equivalent to 1.4%). In general, CMRs increased with age. The mortality rate for somatic causes of death was twice as high in patients aged > 50 years than in those aged 41–50 (mortality rate ratio [MRR] 2.1, CI 1.3–3.4). The rates for drug-induced deaths also increased with age, although not as steeply as those for somatic causes of death, whereas the rates for violent deaths were the same across all age groups. Men had a slightly higher mortality rate than women (MRR 1.2, CI 0.5–0.9). The mortality rate was twice as high among patients taking methadone than among those taking buprenorphine (MRR 2.0, CI 1.5–2.7).

Characteristics associated with drug-induced cause of death during OAT

Table 4 shows the results from a multilevel logistic regression analysis assessing characteristics associated with drug-induced cause of death compared with all other causes of death during OAT. In bivariate analyses, both increasing age ($p < 0.05$) and increasing Charlson comorbidity index score ($p < 0.001$) were associated with lower odds of dying of a drug-induced cause of death. In the multiple model, only the Charlson comorbidity index remained significant ($p < 0.001$). The variables of male gender, taking methadone (compared with taking buprenorphine), previous non-fatal overdoses, psychiatric admissions and duration of OAT were not associated with dying of a drug-induced cause of death during OAT, neither in the bivariate nor in the multiple analyses.

Discussion

In this study on mortality in the total Norwegian OAT population, both somatic and drug-induced causes of death were frequent during OAT. In the 2-year observation period, 1.4% of the patients died. In general, CMRs increased with age, and this pattern was more pronounced for somatic causes than other causes of death.

Table 3 CMRs/100 PY (95% CI) during OAT, stratified by age, OAT medication and gender

	PY in OAT (%)	Deaths, n (%)	CMR/100 PY (95% CI)	Drug-induced cause of death	Somatic cause of death	Violent cause of death
2014	7220	95 (48)	1.3 (1.1–1.6)	NA	NA	NA
2015	7439	105 (52)	1.4 (1.2–1.7)	NA	NA	NA
Total	14,659	200	1.4 (1.2–1.6)	0.6 (0.5–0.7)	0.6 (0.5–0.8)	0.2 (0.1–0.2)
Age						
< 41 years	5570 (38)	33 (17)	0.6 (0.4–0.8)	0.3 (0.2–0.5)	0.1 (0.1–0.2)	0.2 (0.1–0.3)
41–50 years	5424 (37)	81 (41)	1.5 (1.2–1.9)	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.2 (0.1–0.3)
> 50 years	3665 (25)	86 (43)	2.4 (1.9–2.9)	0.8 (0.6–1.2)	1.4 (1.0–1.8)	0.1 (0.0–0.3)
OAT medication						
Methadone	5707 (39)	109 (55)	1.9 (1.6–2.3)	0.8 (0.6–1.1)	0.9 (0.7–1.2)	0.2 (0.1–0.4)
Buprenorphine	8487 (58)	82 (41)	1.0 (0.8–1.2)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.1 (0.1–0.2)
Gender						
Male	10,261 (70)	147 (73)	1.4 (1.2–1.7)	0.6 (0.4–0.7)	0.7 (0.5–0.9)	0.2 (0.1–0.3)
Female	4398 (30)	53 (27)	1.2 (0.9–1.6)	0.6 (0.4–0.8)	0.5 (0.3–0.7)	0.2 (0.1–0.3)

CMR crude mortality rate, *PY* person-years, *CI* confidence interval, *OAT* opioid agonist treatment, *NA* not applicable
Causes of death $n = 197$, three patients with other/unknown cause of death excluded
OAT medication $n = 191$, other OAT medication excluded. This represents the use of OAT medication at the time of death. We could not obtain information about the changes in OAT medication before death

Table 4 Results of multilevel logistic regression analysis for characteristics associated with drug-induced cause of death during OAT[a]

Characteristics	Bivariate models OR (95% CI)	Multiple model OR (95% CI)
Gender		
Men	1	1
Women	1.37 (0.70; 2.70)	1.59 (0.77; 3.30)
Age	0.95 (0.92; 0.99)*	0.99 (0.95; 1.04)
OAT medication		
Buprenorphine	1	1
Methadone	1.24 (0.64; 2.41)	1.25 (0.63; 2.48)
Charlson index	0.73 (0.62; 0.85)**	0.72 (0.61; 0.86)**
Non-fatal overdoses[b]		
No	1	1
Yes	1.60 (0.83; 3.10)	1.72 (0.82; 3.60)
Psychiatric admissions[c]		
No	1	1
Yes	1.35 (0.70; 2.60)	0.91 (0.44; 1.88)
OAT total duration in years	0.97 (0.90; 1.04)	1.00 (0.92; 1.08)

OAT opioid agonist treatment. Only complete cases are included, $N = 181$.
*$p < 0.05$, **$p < 0.001$
[a]The reference category is "Other causes of death"
[b]Non-fatal overdoses registered in the NPR or in OAT status reports in the last 5 years before death
[c]Psychiatric admissions registered in the NPR in the last 5 years before death

The CMR was also higher in patients taking methadone compared with buprenorphine. In the multiple regression model, we found that increasing somatic comorbidity, as measured by the Charlson comorbidity index, reduced the odds of dying of a drug-induced cause of death compared with other causes of death.

In line with previous Norwegian studies, we found that somatic causes of death among OAT patients predominated [8, 17]. Non-communicable diseases such as cancer and COPD take time to develop and are associated with both age and the lifestyle factors prevalent among OAT patients. High rates of pulmonary diseases and increased cancer risk are consistent with previous findings in ageing OAT patients [27–31]. COPD and emphysema are independent risk factors for lung cancers, together with smoking, and predict reduced survival [32, 33]. Liver cirrhosis and liver cancer due to hepatitis C also contribute substantially to morbidity and mortality among opioid users [34]; however, despite a high prevalence of hepatitis C among the deceased in our study, only 14 patients died of liver disease. Some of the deaths of somatic origin were probably more directly associated with injecting drug use. Acute bacterial skin and soft tissue infections are common among injecting drug users [35], and bacteraemia often causes severe focal infections and sepsis. Persisting infections and inflammation caused by continued injecting and skin popping (subcutaneous injecting) are also associated with AA amyloidosis [36, 37]. AA amyloidosis was not encountered among heroin users in Norway until 2005 [37] but is now an emerging issue among the ageing OAT patients. Injection-related health risks other than blood-borne viral infections in OAT patients who continue to use drugs might be an under-researched topic.

Although the overdose risk is reduced during OAT, nevertheless 42% of the patients in our study had a drug-induced cause of death. None of the patients died of an overdose in the first month after initiating OAT. The increased risk of fatal overdose during initiation of methadone may vary according to treatment setting [4, 38]. According to Norwegian OAT guidelines, both buprenorphine and methadone should be initiated under monitoring and observation, and inpatient detoxification at the initiation of OAT is common [19]. Methadone was judged to be the main intoxicant in 31 of the 84 drug-induced deaths and, in all except two cases, the patient was taking methadone as the OAT medication. The interpretation of this finding is not straightforward. It is difficult to determine the precise role of OAT medication in fatal overdoses [39]. The instituted dose of methadone may become dangerous because of increasing vulnerability as OAT patients age and comorbidity levels rise. The overdose risk among OAT patients is associated with several factors such as somatic and psychiatric comorbidities, co-prescribing, previous non-fatal overdoses and polydrug use [40–42], which may make it difficult to ascertain the exact cause of death. In addition, the post-mortem examiner is not always informed about the OAT status. Thus, the number of methadone deaths might represent an overestimation, and may in fact have been caused by single or multiple somatic causes in combination with regular prescribed methadone doses.

An all-cause mortality rate of 1.4/100 PY during OAT was the same as found in an earlier Norwegian study [17], but higher than the rate of 0.93/100 PY found in a systematic review and meta-analysis [4]. In line with previous studies, CMRs increased with age, and were higher in men and for patients taking methadone compared with buprenorphine [2–4, 8]. Suggested explanations for increased CMRs among patients taking methadone are methadone-induced prolongation of the QTc interval, increasing the risk of ventricular cardiac arrhythmia (torsades de pointes) and "sudden death", ingestion of alcohol and BZD, physical comorbidities and harder-to-support patients [15, 16]. In the Norwegian setting, the difference in CMRs might be explained by a "veteran effect". Until 2001, methadone was the only OAT medication. Patients taking methadone in our study had been treated in OAT for significantly longer than those taking

buprenorphine, and most likely had a longer drug career. In addition, patients with a severe or terminal disease such as cancer taking buprenorphine are often converted to methadone or other opioids.

In the regression analysis, we found an association between increased somatic morbidity and reduced odds of a drug-induced cause of death. The Charlson comorbidity index was moderately correlated with age, which could be one explanation why age did not remain significant in the multiple model. Multimorbidity (i.e., having two or more chronic diseases) is associated with increased risk of mortality, functional decline, polypharmacy, increased number of hospital admissions and poorer quality of life [43]. Multimorbidity usually increases with age [43], but patients in OAT have high rates of chronic diseases across all age groups [44, 45]. Several of the patients in our study had multiple severe and potentially fatal medical conditions, and thus several competing disease end-points.

Somewhat surprisingly, given the superior safety profile of buprenorphine, we did not find that taking methadone increased the odds of drug-induced cause of death compared with buprenorphine. The lack of association between the other covariates and drug-induced cause of death could be because the two groups were quite similar, which makes differences less likely to detect. Risk factors not included in the model (e.g., prescription medication, drug use) could be another explanation.

Our findings have several implications. Multimorbidity in OAT patients calls for a broad range of patient-oriented and organizational measures, such as improved treatment and follow-up of chronic diseases and multidisciplinary teamwork and co-ordination of care [43, 44]. The high prevalence of COPD and pulmonary cancer suggests that a stronger focus on tailored tobacco harm-reduction approaches and smoking cessation is important for this patient group, and as early in their lives as possible, to reduce cumulative risk. OAT patients should be offered spirometry and lung image tests [32, 33]. Overdose prevention is a multifaceted challenge [14]. Further measures may include improved follow-up after non-fatal overdose, reviewing older patients' methadone dosage in the context of somatic comorbidities (e.g., reduced liver and kidney function) and offering regular electrocardiograms to patients aged > 45 years. Distribution of intranasal naloxone to at-risk populations is also relevant [15, 46, 47].

Strengths and limitations

The strengths of our study include the use of register data that were combined with information from hospital medical records. This gave in-depth information about the fatalities that were not accessible using register data alone. The national OAT programme is organized within the public specialist health care service in Norway, and has a monopoly of this treatment modality; thus, we were able to study mortality in a complete, national OAT population. The high rate of forensic or medical autopsy also strengthens the validity of the findings. A valid cause of death was not established in only two patients (1%).

Our study has several limitations. Almost half (47%) of the questionnaires were completed by clinicians other than physicians, who do not always have access to somatic medical records. Thus, we cannot rule out the possibility of information bias. Regarding somatic comorbidity, we have no data on smoking status, but the smoking prevalence among Norwegian OAT patients is high and similar to the 69–94% prevalence reported in earlier studies [27, 45, 48, 49]. In addition, the number of non-fatal overdoses is probably under-estimated, because most overdoses in Norway are attended by the ambulance service only. A higher number of participants would have allowed for more variables in the regression analysis. We did not have information on the changes in variables that can vary over time, such as prescription of BZD, psychotropic medications and changes in OAT medication before death. The broad categories of prescribed medication (at least one prescription of benzodiazepine and psychotropic medication in the year before death) limited their use as covariates in the regression analyses.

Conclusions

In this study on mortality among patients in the Norwegian OAT programme, both somatic and drug-induced causes of death were common during OAT. AA amyloidosis is an emerging issue. As expected, CMRs increased with age, and this increase was steeper for somatic causes than for other causes of death. CMRs were also higher in men and in patients taking methadone. Increasing somatic comorbidity reduced the odds of a drug-induced cause of death. Both improved treatment and follow-up of chronic diseases, especially in patients aged > 40 years, and continuous measures to reduce drug-induced deaths appear to be essential to reduce future morbidity and mortality burdens in this population.

Abbreviations

AA: Amyloid A; AIDS: Acquired immune deficiency syndrome; BZD: Benzodiazepines; CI: Confidence interval; CMR: Crude mortality rate; COPD: Chronic obstructive respiratory disease; GP: General Practitioner; HIV: Human immune deficiency virus; ICD-10: International Classification of Diseases, 10th edition; MRR: Mortality rate ratio; NPR: Norwegian Patient Registry; OAT: Opioid agonist treatment; OR: Odds ratio; OUD: Opioid use disorder; PY: Person-years; SD: Standard deviation

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Authors' contributions

ABB participated in the detail planning of the study, collected the data, conducted the analysis together with and under supervision of IS and TC, and drafted, wrote and revised the manuscript. TC took part in the planning and designing of the study, was co-supervisor, consecutively commented on data analysis and revised the manuscript. HW took part in the original planning of the study and revised the manuscript. JBS has performed statistical analyses including multilevel logistic regression model, contributed with interpretation and description of results and critical input to the manuscript. IS was project leader and main supervisor, planned and designed the study and took part in the writing and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset generated and analysed during the current study is not publicly available to protect the privacy of participants but it is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Regional Committee for Medical and Research Ethics South-East (Case number 2016/1204), the Cause of Death Registry (Norwegian Institute of Public Health), the Norwegian Patient Registry (Norwegian Directorate of Health) and the participating hospital trusts, including data protection officials.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH REPORT

ADDICTION SSA

Organ pathologies detected post-mortem in patients receiving opioid agonist treatment for opioid use disorder: a nation-wide 2-year cross-sectional study

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Abstract

Aims: To document organ pathologies detected post-mortem in patients receiving opioid agonist treatment for opioid use disorder and estimate the extent to which individual characteristics are associated with pulmonary, cardiovascular, hepatic or renal pathologies.

Design: Two-year cross-sectional nation-wide study.

Setting: Norway.

Participants: Among all 200 patients who died during opioid agonist treatment between 1 January 2014 and 31 December 2015, 125 patients (63%) were autopsied. Among these, 122 patients (75% men) had available autopsy reports and were included. The mean age at the time of death was 48 years.

Measurements: Information on pulmonary, cardiovascular, hepatic and renal pathologies were retrieved from forensic or medical autopsy reports, with no (0) and yes (1) as outcome variables and age, sex and body mass index as covariates in logistic regression analyses.

Findings: Pathologies in several organs were common. Two-thirds (65%) of the decedents had more than two organ system diseases. The most common organ pathologies were chronic liver disease (84%), cardiovascular disease (68%) and pulmonary emphysema (41%). In bivariate analyses, only older age was associated with any pulmonary pathology [odds ratio (OR) = 1.06; 95% confidence interval (CI) = 1.01–1.10], cardiovascular pathology (OR = 1.11; 95% CI = 1.05–1.17) and renal pathology (OR = 1.05; 95% CI = 1.00–1.11). Older age remained independently associated with cardiovascular pathology (OR = 1.10; 95% CI = 1.04–1.16) and renal pathology (OR = 1.06; 95% CI = 1.01–1.12) adjusted for body mass index and sex.

Conclusions: Among autopsied Norwegians who died during opioid agonist treatment in 2014 and 2015, two-thirds had more than two organ system diseases, despite their mean age of 48 years at the time of death. Older age was independently associated with at least one cardiovascular or renal pathology after adjusting for sex and body mass index.

KEYWORDS
Ageing, autopsy, buprenorphine, forensic, methadone, multi-morbidity, opioid substitution treatment, pathology, postmortem

INTRODUCTION

Opioid agonist treatment (OAT) for opioid use disorder (OUD) substantially reduces all-cause mortality and somatic morbidity associated with substance use and injections [1–4]. Nonetheless, compared with matched non-dependent controls, patients receiving OAT have higher rates of chronic disease and multi-morbidity (i.e. two or more chronic diseases), higher rates of hospital admissions and emergency department visits and a higher life-time prevalence of blood-borne viral infections and sexually transmitted diseases [5–7]. Individuals receiving OAT have a life expectancy deficit of approximately 15 years [8]. Similar to individuals with severe mental disease, most excess deaths relate to non-communicable physical diseases, especially as they age [8]. Impaired liver, kidney or cardiac function due to ageing or disease progression may also gradually decrease tolerance to substances and thus increase the risk of overdose.

As patients receiving OAT are ageing [9–11], improved knowledge and follow-up of non-communicable diseases have therefore become increasingly important. Autopsies are important in establishing an exact cause and manner of death, and may provide valuable information about organ pathologies that were not diagnosed or were without clinical manifestations before death. However, a paucity of post-mortem data exists concerning organ pathologies in patients receiving OAT, especially in those aged more than 40 years. In addition, few data are available for the prevalence of enlarged organs. An association between a history of chronic alcohol use and cardiomegaly or hepatomegaly has been reported [12]. A clearer understanding of the complex health needs in patients receiving OAT may improve clinical decisions and preventive measures. In the present study, we therefore aimed to:

1. Document organ pathologies detected post-mortem in patients receiving OAT in Norway who died in 2014–15 and were subjected to an autopsy.
2. Estimate the extent to which individual characteristics were associated with at least one pulmonary, hepatic, cardiovascular or renal pathology.

METHODS

Design and setting

This was a cross-sectional nation-wide study using information from hospital records, the Norwegian Cause of Death Registry and autopsy reports. The study reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supporting information, Appendix S1). In Norway, with 5.4 million inhabitants, addiction units in the public specialist health-care service assess and initiate OAT. However, OAT is based on collaboration between addiction units, general practitioners and health and social services in the municipalities. The treatment is publicly funded and time-unlimited. At the end of 2015, 7498 patients were receiving OAT, among whom 58% received buprenorphine or buprenorphine–naloxone, 39% methadone and 2% other opioids [11].

Selection of cases

The present study is part of an extensive nation-wide study examining mortality and causes of death among all 200 patients who died while receiving OAT (i.e. died within 5 days after the last reported intake of OAT medication) in Norway between 1 January 2014 and 31 December 2015. We previously reported that the mean age at the time of death was 49 years, and 74% were men. Somatic causes of death were most common (45%), followed by drug-induced (42%) and violent (12%) deaths. The all-cause crude mortality rate (CMR) was 1.4 per 100 person-years during OAT [13]. Among these 200 patients, 125 (63%) were subjected to a forensic or medical autopsy. We were unable to obtain three autopsy reports. Thus, in the present study, 122 patients were included, 105 (86%) of whom were subjected to a forensic autopsy.

The characteristics and causes of death of all 200 decedents stratified by autopsy are presented in Supporting information, Appendix S2. Those subjected to an autopsy were significantly less likely to have died of a somatic cause of death and in a hospital or health-care institution, and less likely to have other OAT medication than buprenorphine or methadone. They were also younger (mean 48.0 versus 50.3 years), but this difference was not significant ($P = 0.06$, Student's t-test).

Forensic and medical autopsy procedures

According to Norwegian legislation, the police or a higher prosecution authority usually request a forensic autopsy in cases of suspected unnatural death (overdose or violent death such as suicide, accident and homicide). No national forensic autopsy protocol exists; hence, autopsy practice may vary among jurisdictions and institutions, as well as between pathologists. Nonetheless, the general routine for a forensic autopsy in Norway includes macroscopic and microscopic examinations of all major organs, and toxicological analysis from peripheral blood if possible. Neuropathological examination is not standard, but is considered in each case. Forensic autopsy reports include excerpts from police records regarding the circumstances of death and information from medical records if available. In addition to forensic

autopsies, a post-mortem examination in the form of a medical autopsy can be conducted at the request of a physician to confirm the cause of death or to evaluate treatment. As a rule, medical autopsy cases are natural deaths. Unlike forensic autopsy, consent from next of kin is mandatory. All autopsy reports were inspected retrospectively and the results are based on what the pathologists reported in standard forensic or medical autopsies. The definitions of organ pathologies are presented in Supporting information, Appendix S3. Two investigators (A.B.B. and G.J.M.D.) independently extracted data from the autopsy reports and discussed categorization until consensus.

Measurements

Outcome measures

From the autopsy reports, information was collected on details of pulmonary, cardiovascular, hepatic and renal pathologies as well as information on organ weights of the heart, liver and spleen.

Clear definitions of abnormal organ weight are generally lacking [14]. Heart weight is correlated with body surface area, body mass index (BMI), body weight, age and sex; several reference tables and calculators for heart weight exist [15–20], which makes comparisons between studies difficult. Therefore, in addition to the judgement stated by the pathologists on the presence of cardiomegaly, we determined the prevalence of cardiomegaly as defined by the heart-weight calculator described by Vanhaebost *et al*. [18]. Due to inconsistent reporting on hepatomegaly/enlarged liver in the autopsy reports, we defined hepatomegaly as liver weight outside the normal range (i.e. > 1860 g for men and > 1767 g for women) [14,21]. Liver fibrosis may be described in liver cirrhosis, but not vice versa, and we did not report liver fibrosis in cases where the pathologist had described cirrhosis. Aspiration and signs of pulmonary and/or cerebral oedema are also common post-mortem findings in drug-induced deaths but were not reported because organ pathology, rather than cause of death, was the focus of the present study.

Covariates

The hospital trusts responsible for OAT provided information about age and sex. From the autopsy reports, we collected information on the decedents' weight and height, which was used to estimate their BMI.

Other characteristics

The hospital trusts provided information on OAT status and OAT medication at the time of death. The number of substances detected post-mortem and signs of drug use were collected from the autopsy reports, while the cause and place of death were retrieved from the Cause of Death Registry. Norway follows the definition of drug-induced death used by the European Monitoring Centre for Drugs and Drug Addiction; thus, drug-induced deaths included unintentional overdose or overdose by unknown intent, as well as intentional overdose and substance use disorders (SUDs) [22,23].

Analysis

The data were presented as frequencies, proportions, means and standard deviations (SDs) or median, minimum and maximum values for non-normally distributed continuous variables. The differences between men and women and between those subjected to an autopsy or not were tested using Pearson's χ^2 test or Fisher's exact test, as appropriate for categorical variables, and Student's *t*-test or Mann–Whitney *U*-test for normally and non-normally distributed continuous variables, respectively. The outcome variables were defined separately for each of the four pathology types (pulmonary, cardiovascular, hepatic and renal pathology), with yes (1) representing the presence of at least one organ pathology within each type and no (0) representing the absence of any pathology of this type. Bivariate logistic regressions for each pathology type and each covariate were conducted, followed by multiple logistic regressions for each pathology type where all covariates were included. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The significance level was set at < 0.05, and all analyses were two-sided. The analyses were not pre-registered; therefore, the results should be considered exploratory. The data were analysed using SPSS software version 26 (IBM Corporation, Armonk, NY, USA).

Ethics

The Regional Committee for Medical and Health Research Ethics (South-East, case no. 2016/1204), the Cause of Death Registry, the Director of Public Prosecution, the Ministry of Justice and Public Security and the participating hospital trusts, including data protection officials, approved the study.

RESULTS

Case characteristics

The mean age at the time of death was 48 years (SD = 8.7, range = 23–68 years) and 75% were men (Table 1). The total mean duration of OAT was 7.9 years (SD = 4.2, range = 0.1–17 years). Fifty-one per cent of the patients were prescribed methadone and 48% buprenorphine or buprenorphine–naloxone. The median methadone dose was 90 mg daily (range = 15–200 mg) and the median buprenorphine dose was 16 mg daily (range = 1–28 mg). Among those included in the present study, 58% of the deaths were categorized as drug-induced deaths in the Cause of Death Registry, 15% as violent

TABLE 1 Characteristics at the time of death of 122 patients who died during opioid agonist treatment in Norway in 2014–15 by sex

	All, *n* = 122	Men, *n* = 92	Women, *n* = 30
	n (%)	*n* (%)	*n* (%)
Age (years)			
Age, mean ± SD	48.0 ± 8.7	48.3 ± 9.0	47.1 ± 8.0
Treatment			
Total duration of OAT in years, mean ± SD, *n* = 116	7.9 ± 4.2	7.7 ± 4.0	8.5 ± 4.9
Prescribed methadone	62 (51)	46 (50)	16 (53)
Prescribed buprenorphine	58 (48)	45 (49)	13 (43)
Prescribed other/unknown OAT medication	2 (2)	1 (1)	1 (3)
Buprenorphine dose in mg, median (min–max), *n* = 58	16 (1–28)	16 (1–28)	16 (6–24)
Methadone dose in mg, median (min–max), *n* = 61	90 (15–200)	90 (20–200)	85 (15–150)
Cause of death			
Drug-induced death	71 (58)	51 (55)	20 (67)
Somatic cause of death	32 (26)	27 (29)	5 (17)
Violent death	18 (15)	13 (14)	5 (17)
Unknown cause of death	1 (1)	1 (1)	0 (0)
Place of death			
Home	67 (55)	54 (59)	13 (43)
Hospital/nursing home	23 (19)	19 (21)	4 (13)
Other/outdoor	20 (16)	13 (14)	7 (23)
Not reported	12 (10)	6 (7)	6 (20)
Other characteristics			
Number of substances detected, median (min–max), *n* = 112	4 (1–11)*	4 (1–8)*	5 (2–11)*
Signs of drug use,[a] *n* = 113	69 (61)	54 (64)	15 (54)
BMI, mean ± SD, *n* = 116	25.2 ± 5.3	25.2 ± 5.5	25.3 ± 4.8
Organ weights (g), mean ± SD			
Heart weight,[b] *n* = 117	NA	417 ± 100	355 ± 133
Liver weight,[b] *n* = 118	NA	1839 ± 577	1637 ± 469
Spleen weight,[b] *n* = 114	NA	298 ± 176	220 ± 113

NA = not applicable; SD = standard deviation; OAT = opioid agonist treatment.
[a]Information in the autopsy reports about recent drug use and/or drugs or drug paraphernalia on or close to the body, and/or fresh needle marks not related to medical treatment;
[b]reference weights: heart: men 233–383 g, women 148–296 g [19,20], liver: men 968–1860 g, women 603–1767 g, spleen: men 28–226 g, women < 230 g [14,21].
*$P < 0.05$. Valid percentage is presented.

deaths and 26% as natural causes. Of the latter, 14 patients died of acute cardiovascular disease, eight of pulmonary disease, four of cancer and six of other somatic diseases. Two patients had HIV, but none of them died of AIDS. More than half the cases (55%) were found at home. In 61% of the cases, signs of recent drug use were reported in the autopsy reports. The only significant difference between men and women was that, for women, a median of five substances were detected post-mortem compared with four in men ($P = 0.018$, Mann–Whitney *U*-test).

The BMI was 25.2 (median = 25.1, range = 12.2–38.0) in men and 25.3 (median = 24.0, range = 17.8–39.4) in women. The mean heart weight in men was 417 g (median = 400 g, range = 210–709 g), liver weight 1839 g (median = 1750 g, range = 745–3300 g) and spleen weight 298 g (median = 270 g, range = 30–870 g). The corresponding weights for women were mean heart weight 355 g (median = 350 g, range = 230–975 g), liver weight 1637 g (median = 1535 g, range = 730–2675 g) and spleen weight 220 g (median = 195 g, range = 60–470 g). The box-plots for the organ weights are provided in Supporting information, Appendix S4.

The toxicological data from 107 of the 122 cases included in the present study were published previously [24]. In addition to prescribed methadone or buprenorphine, the most common substances detected in peripheral blood were benzodiazepines/z-hypnotics (76%), tetrahydrocannabinol (37%), stimulants (29%) and morphine/heroin (28%) [24] (data not presented in Table 1).

Organ pathology

Organ pathologies in several organ systems were common, as 65% of the decedents had more than two organ system diseases (Table 2). Only four decedents (3%) had no observed organ pathologies. At least one pulmonary pathology was reported in 63% of the cases. The most common pathology was signs of emphysema (41%), followed by pulmonary fibrosis (16%), foreign body granulomas in the lungs (i.e. injected tablets) (9%) and pulmonary embolism (3%), while 16% had pneumonia. Sixty-eight per cent had at least one cardiovascular pathology. The pathologists reported cardiomegaly in 40 (33%) cases, compared with 30 (25%) cases using the heart weight calculator by Vanhaebost *et al*. [18]. Cardiac fibrosis was reported in 26%, left and/or right ventricular hypertrophy in 20%, myocardial infarction (fresh or old infarctions, including micro-infarction) in 17% and endocarditis and/or myocarditis in 5%. In addition, the pathologists reported moderate to severe atherosclerosis of the coronary arteries and/or aorta in 24% of the decedents.

At least one hepatic pathology was reported in 84% of the decedents. More than half (57%) had signs of chronic liver disease (lymphocytic infiltrate). Steatosis was reported in 42% of the decedents, liver fibrosis in 24% and cirrhosis in 22%, while 40% had hepatomegaly. Splenomegaly was reported in 45%. Portal lymphadenopathy (one or several perihepatic lymph node enlargements) was explicitly stated (yes/no) in 71 cases and was reported in 52% of these cases. The pathologists reported at least one renal pathology in 31% of the decedents, with nephrosclerosis being the most common (27%), followed by renal fibrosis in 9% and benign kidney cysts in 8%. Four patients (3%) had amyloidosis in the kidneys; in three of whom, also in the liver and one in the spleen. Other pathologies included six cases of cancer, two cases of fatal bacterial infection (encephalitis/sepsis) and one case of miliary tuberculosis. In addition to macroscopic examination of the brain, neuropathological examination of the brain was performed in 58 (48%) of decedents with no significant findings in almost two-thirds of these cases. Cerebral haemorrhage or infarction was reported in seven cases; all three cases of cerebral haemorrhage were fatal.

Among those subjected to an autopsy, those who died of a natural cause of death had significantly more organ pathologies ($P = 0.001$, Mann–Whitney *U*-test). That is, a median of four organ system diseases was detected compared with three in those who died of other causes (i.e. drug-induced and violent cause of death) (data not presented in Table 2).

Logistic regression

In bivariate analyses, only older age increased the odds of any pulmonary pathology, cardiovascular pathology and renal pathology, but not any liver pathology (Table 3). Adjusted for BMI and sex, older age remained independently associated with cardiovascular and renal pathologies. The covariates BMI and sex were not significant, either in bivariate or in multiple regression analyses.

DISCUSSION

The most common organ pathologies detected post-mortem in patients receiving OAT who were subjected to an autopsy were hepatitis C virus (HCV)-related liver disease, cardiovascular disease, smoking-related pulmonary emphysema and enlarged heart, liver and spleen. Almost two-thirds of the decedents had more than two organ system diseases, despite their mean age of 48 years at the time of death. The prevalence of pulmonary, liver and cardiovascular pathologies was generally higher than findings in other post-mortem studies [25–28], which is probably explained by the older participants in the present study. Our results are in line with studies reporting excess mortality for respiratory, cardiovascular and liver diseases among individuals with SUDs compared with the general population [29–31].

Older age was the only covariate independently associated with at least one cardiovascular or renal pathology. We have previously documented that the CMRs increased with age, and that this increase was steeper for somatic causes than other causes of death [13]. As illustrated in Supporting information, Appendix S2, patients receiving OAT who died naturally of a known, somatic disease during the 2-year study period were generally not subjected to an autopsy, and were subsequently not included in this autopsy study. Therefore, the lack of association between older age and any pulmonary or liver pathology in the regression analyses might be explained by selection bias. That is, patients who died of an unnatural cause and were subjected to an autopsy had fewer pathologies than those who died naturally.

Systemic chronic inflammation has emerged in recent years as a factor in the aetiology of several diseases [32]. For example, HCV infection is associated with cardiovascular disease. A systematic review and meta-analysis [33] reported a pooled risk ratio of 1.28 for stroke and myocardial infarction in individuals with compared with those without HCV infection. Chronic inflammation is also suggested as one explanation for the increased arterial stiffness and vascular age reported in opioid-dependent patients compared with opioid-naive controls, with buprenorphine reported to be milder in its cardiovascular effects than methadone [34,35]. In addition, Seltenhammer *et al*. [36] suggested that hypoxia in the heart tissue associated with opioid use induces apoptosis which, in turn, stimulates cardiac remodelling and fibrosis in almost the same manner as myocardial infarction. Stimulant use [37–40] and the use of anabolic androgenic steroids (AASs) [41] are also associated with cardiac changes, increased heart weight and increased cardiovascular mortality. Stimulants, mainly amphetamine, were detected in 29% of those included with toxicological analysis from peripheral blood. AASs are not included in post-mortem toxicological analyses in Norway; however, in a Norwegian study from 2020 life-time AAS use was reported by 28.3% of the patients in SUD treatment and was highest among men who preferred using stimulants [42]. Thus, chronic inflammation, opioid use, stimulant use and the use of AASs (independently or in combination) may explain the high prevalence of cardiovascular pathology in the present study, in addition to the relatively high age of those included.

TABLE 2 Organ pathology detected post-mortem in 122 patients receiving opioid agonist treatment, by age category and sex

	All	Age category			Sex		Patients with missing data[a] *n*
		< 40 years	40–50 years	> 50 years	Male	Female	
	N = 122 *n* (%)	*n* = 21 *n* (%)	*n* = 47 *n* (%)	*n* = 54 *n* (%)	*n* = 92 *n* (%)	*n* = 30 *n* (%)	
Pulmonary pathology							
Emphysema	49 (41)	2 (10)	18 (39)	29 (56)	39 (44)	10 (33)	3
Fibrosis	19 (16)	1 (5)	11 (24)	7 (14)	15 (17)	4 (14)	5
Pneumonia	18 (16)	3 (14)	6 (14)	9 (18)	12 (14)	6 (21)	8
Foreign body	11 (9)	2 (10)	4 (9)	5 (9)	8 (9)	3 (10)	2
Pulmonary embolism	4 (3)	1(5)	3 (7)	0 (0)	4 (4)	0 (0)	2
At least one pulmonary pathology	75 (63)	7 (33)	31 (67)	37 (71)	56 (63)	19 (63)	3
Cardiovascular pathology							
Myocardial infarction	20 (17)	2 (10)	8 (17)	10 (19)	19 (21)	1 (3)	2
Ventricular hypertrophy	24 (20)	0 (0)	10 (22)	14 (27)	23 (26)	1 (3)	3
Fibrosis	31 (26)	5 (24)	10 (22)	16 (31)	23 (26)	8 (28)	4
Cardiomegaly	40 (33)	2 (10)	15 (33)	23 (43)	35 (39)	5 (17)	2
Mild atherosclerosis	33 (28)	8 (38)	13 (28)	12 (23)	29 (32)	4 (13)	2
Moderate/severe atherosclerosis	29 (24)	0 (0)	4 (9)	25 (47)	22 (24)	7 (23)	2
Endocarditis and/or myocarditis	6 (5)	0 (0)	5 (11)	1 (2)	5 (6)	1 (3)	3
Cerebral infarction/haemorrhage[b] (*n* = 58)	7 (12)	1 (13)	4 (15)	2 (8)	4 (9)	3 (21)	–
At least one cardiovascular pathology	82 (68)	8 (38)	27 (59)	47 (89)	65 (72)	17 (57)	2
(mild atherosclerosis not included)							
Hepatic pathology							
Lymphocytic infiltrate	66 (57)	8 (38)	30 (67)	28 (57)	51 (58)	15 (56)	7
Steatosis	49 (42)	6 (30)	21 (46)	22 (43)	39 (44)	10 (35)	5
Fibrosis	29 (24)	4 (19)	10 (21)	15 (29)	21 (23)	8 (28)	3
Cirrhosis	27 (22)	2 (10)	11 (23)	14 (26)	22 (24)	5 (17)	1
Hepatomegaly	47 (40)	8 (40)	22 (47)	17 (33)	36 (40)	11 (38)	4
Portal lymphadenopathy[c] (*n* = 71)	37 (52)	4 (33)	23 (70)	10 (39)	22 (46)	15 (65)	–
At least one hepatic pathology	102 (84)	15 (71)	44 (94)	43 (81)	77 (85)	25 (83)	1
Renal pathology							
Nephrosclerosis	30 (27)	2 (11)	12 (27)	16 (33)	23 (27)	7 (26)	9
Fibrosis	10 (9)	1 (5)	5 (11)	4 (8)	8 (9)	2 (7)	8
Cysts	10 (8)	0 (0)	3 (6)	7 (14)	9 (10)	1 (3)	2
Amyloidosis	4 (3)	0 (0)	2 (4)	2 (4)	4 (4)	0 (0)	1
At least one renal pathology	37 (31)	3 (14)	14 (30)	20 (38)	30 (33)	7 (23)	1
Other							
Splenomegaly	51 (45)	10 (50)	22 (50)	19 (38)	41 (48)	10 (35)	8
Cancer	6 (5)	1 (5)	1 (2)	4 (7)	5 (5)	1 (3)	0
Systemic infections[d]	3 (3)	0 (0)	2 (4)	1 (2)	2 (2)	1 (3)	1
Several organ system pathologies							
> 1 organ system disease	105 (87)	15 (71)	42 (89)	48 (91)	79 (87)	26 (87)	1
> 2 organ system disease	78 (65)	8 (38)	30 (64)	40 (76)	60 (66)	18 (60)	1

Valid percentage is presented. Definitions of organ pathologies are presented in Supporting information, Appendix S3.

[a]Tissue not suitable for microscopic or microscopic examination;

[b]neuropathological examination was performed in 58 cases. In the remaining cases, the brain was only examined macroscopically;

[c]portal lymphadenopathy was explicitly reported (yes/no) in only 71 cases;

[d]systemic infections: encephalitis/sepsis/tuberculosis.

TABLE 3 Bivariate and multiple logistic regression with any pulmonary, cardiovascular, hepatic or renal pathology reported by the pathologist (no/yes) as outcome variable

	Any pulmonary pathology (yes, *n* = 75)	Any cardiovascular pathology (yes, *n* = 82)	Any hepatic pathology (yes, *n* = 102)	Any renal pathology (yes, *n* = 37)
	OR; 95% CI (aOR; 95% CI)	OR; 95% CI (aOR; 95% CI)	OR; 95% CI (aOR; 95% CI)	OR; 95% CI (aOR; 95% CI)
Age (years)	1.06; 1.01–1.10*	1.11; 1.05–1.17**	1.03; 0.98–1.09	1.05; 1.00–1.11*
	(1.05, 0.99–1.09)	(1.10; 1.04–1.16)**	(1.05; 0.98–1.11)	(1.06; 1.01–1.12)*
Sex				
Male (ref.)	1	1	1	1
Female	1.02; 0.43–2.40	0.50; 0.21–1.19	0.91; 0.30–2.78	0.62; 0.24–1.60
	(1.06; 0.43–2.62)	(0.52; 0.20–1.31)	(0.99; 0.29–3.45)	(0.80; 0.30–2.16)
BMI	1.01; 0.94–1.09	1.00; 0.93–1.08	1.06; 0.96–1.18	0.97; 0.90–1.05
	(1.02; 0.94–1.09)	(1.01; 0.93–1.09)	(1.07; 0.96–1.19)	(0.97; 0.90–1.05)

OR = odds ratio; aOR = adjusted odds ratio; BMI = body mass index.
*$P < 0.05$, **$P < 0.001$. Only cases with no missing covariate values were included in the multiple models: $n = 115$; except any pulmonary pathology: $n = 114$.

Liver pathologies detected post-mortem were probably HCV-related, because more than half the decedents had HCV infection registered in the Norwegian Patient Registry in the 5 years before death [13]. However, alcohol-related liver diseases could not be ruled out in some of the cases. Splenomegaly may facilitate the progression of liver fibrosis to cirrhosis, although the mechanisms remain poorly understood [43]. Splenomegaly was detected in almost half the cases, while 22% had already developed cirrhosis. Portal lymphadenopathy was also common, and is significantly more often detected post-mortem in individuals with HCV infection [28]. Advanced liver disease may alter the pharmacokinetics of several medications; thus, methadone dose-monitoring and adjustments may be appropriate for some patients already in their late 40s. Improved access to treatment for HCV infection is important to reduce the risk for HCV-related liver disease as well as the associated cardiovascular disease.

Pulmonary emphysema (with variable degrees of severity) was detected in 41% of the decedents. This result is in common with studies reporting excess mortality, particularly for respiratory disease in individuals with OUD or SUD compared with the general population [29,30]. Although we lacked information on smoking habits, the reported prevalence of smoking among Norwegian OAT patients is 91% [44], similar to other OAT populations [45–47]. Spirometry and volumetric computerized tomography (CT) screening may be appropriate for long-term heavy smokers for early diagnosis of chronic obstructive pulmonary disease and lung cancer, while smoking harm reduction interventions such as the use of snus (smokeless tobacco) [48] or e-cigarettes might be relevant for some if smoking cessation is difficult or not wanted.

Polydrug use, smoking and other life-style factors as well as barriers to treatment and diagnostic overshadowing contribute to excess all-cause mortality and a reduced life expectancy [8,29,49]. The general benefits and effectiveness of OAT are well documented [1–4] and both access to and retention in OAT programmes are crucial to reduce morbidity and mortality among individuals with OUD. However, with an ageing OAT population, efforts to promote life-style changes and regular health check-ups are increasingly important to further improve their health and survival, preferably as early in their lives as possible. Patients receiving OAT require comprehensive, multi-disciplinary treatment and care that considers polydrug use, somatic and mental health, ageing, living conditions and wider societal factors.

Limitations

Some caveats must be considered. In this cross-sectional study, we were not able to compare organ pathologies in those receiving OAT with individuals with OUD not receiving OAT. However, a recent systematic review and meta-analysis found that people with OUD had a substantial lower risk of suicide, cancer, cardiovascular-, drug- and alcohol-related mortality during OAT compared with time out of OAT [4]. Secondly, different diagnostic grey zones between physiological and pathological changes exist [15], as well as variable degrees of severity, which may have resulted in misclassified cases. Thirdly, the main aim of a forensic autopsy is to establish the cause of death. Findings irrelevant to establishing the cause of death or microscopic changes related to senescence may not be reported in detail. For example, some of the forensic autopsy reports did not have detailed macroscopic and microscopic descriptions of the kidneys, and we did not have access to histological samples. Therefore, renal pathologies are probably underestimated. Additionally, differences in reporting existed (e.g. differences in the degree organs were examined and/or the findings included in the reports), which also may lead to under-reporting. A national forensic autopsy protocol could contribute to

increased quality in monitoring and reporting of autopsy findings. Finally, a lack of statistical power limited the possibility for more advanced statistical analyses of potentially important characteristics, such as sex differences.

Nonetheless, a major strength is that our results illustrate the complexity of multi-morbidity that the cause-of-death statistics fail to capture, and complement results from epidemiological and clinical studies. The results from this nation-wide study are probably generalizable to other ageing OAT populations in which smoking and polydrug use are common.

CONCLUSIONS

In this post-mortem study of patients receiving OAT, two-thirds had more than two organ system diseases. Older age was independently associated with at least one cardiovascular or renal pathology after adjusting for sex and BMI. Policymakers and service providers should prepare to meet the complex health needs of a heterogeneous OAT population, where the combination of polydrug use and multimorbidity is of particular concern.

DECLARATION OF INTERESTS

None.

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AUTHOR CONTRIBUTIONS

Anne Berit Bech: Conceptualization; data curation; formal analysis; investigation; project administration. **Thomas Clausen:** Conceptualization; supervision. **Helge Waal:** Conceptualization. **Gerd Jorunn Møller Delaveris:** Conceptualization; investigation. **Ivar Skeie:** Conceptualization; funding acquisition; investigation; project administration; supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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III

ADDICTION
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Postmortem toxicological analyses of blood samples from 107 patients receiving opioid agonist treatment: substances detected and pooled opioid and benzodiazepine concentrations

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ABSTRACT

Aims To present the substances and their concentrations detected postmortem in patients receiving opioid agonist treatment (OAT) stratified by cause of death, estimate the pooled opioid and benzodiazepine concentrations using established conversion factors for blood concentrations from the Norwegian Road Traffic Act and explore the association between drug-induced cause of death and the pooled opioid and benzodiazepine concentrations. **Design** Cross-sectional nation-wide study. **Setting** Norway. **Participants** One hundred and seven patients who died during OAT (i.e. within 5 days after the last intake of OAT medication) between 1 January 2014 and 31 December 2015, with postmortem femoral blood available for toxicology. Data were collected from hospital records, the Norwegian Cause of Death Registry and autopsy reports. **Measurements** Presence of alcohol and non-alcohol substances in the bloodstream postmortem, determined through records of toxicology of postmortem femoral blood. **Findings** A median of four substances was detected across the causes of death. At least one benzodiazepine was detected in 81 (76%) patients. The median pooled opioid concentration was significantly higher in drug-induced deaths compared with other causes of death (362 versus 182 ng/ml, $P < 0.001$), in contrast to the pooled benzodiazepine concentration (5466 versus 5701 ng/ml, $P = 0.353$). The multivariate regression analysis showed that only increasing pooled opioid concentration (ng/ml) was associated with increased odds of a drug-induced cause of death (odds ratio = 1.003; 95% confidence interval = 1.001–1.006). **Conclusions** In Norway, overall opioid concentration seems to play an important role in drug-induced deaths during opioid agonist treatment in patients prescribed methadone or buprenorphine. Patients prescribed buprenorphine tend to replace their agonist with full agonists, while patients prescribed methadone tend to have high opioid concentrations from methadone as the only opioid.

Keywords Autopsy, benzodiazepine, buprenorphine, drug-induced, forensic, methadone, opioid agonist treatment, overdose, polydrug, toxicology.

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INTRODUCTION

Although opioid agonist treatment (OAT) for opioid use disorder (OUD) substantially reduces the risk of overdose [1–4], drug-induced deaths still occur among patients receiving OAT [5–7]. Methadone and buprenorphine are associated with drug-induced deaths in several countries [8–10], but the role of the OAT medications and their interaction with other substances in drug-induced deaths within OAT is little explored. Most overdoses involve multiple substances, and a median of three to four substances has been detected postmortem in patients receiving OAT [11,12]. Benzodiazepines in combination with opioids increase the risk of respiratory depression and non-fatal and

fatal overdoses [13,14]. Thus, concurrent use of benzodiazepines during OAT, whether prescribed or not, is a matter of considerable concern.

In the Norwegian Road Traffic Act, legal limits for non-alcohol drugs in blood were implemented in 2012 to evaluate driving under the influence of drugs and ensure equal jurisdiction [15]. Concentration limits corresponding to impairment comparable to blood alcohol concentrations were defined and conversion factors for concentrations of opioids and benzodiazepines were established [15,16]. Using the conversion factors from the Norwegian Road Traffic Act to estimate the pooled concentrations found in postmortem blood provides more information than only presenting the number of drugs detected. In a study from 2017, Edvardsen *et al.* [17,18] used these conversion factors to estimate and compare the pooled opioid and benzodiazepine concentrations in cases of fatal intoxication and driving under the influence of drugs. This method may expand our understanding of the total loads of opioids and benzodiazepines in fatal overdoses among patients receiving OAT. Thus, we aimed to:

1 Present substances and concentrations detected in postmortem blood from patients receiving OAT as stratified by cause of death (i.e. drug-induced cause of death compared with other causes of death during OAT).
2 Estimate pooled concentrations of opioids and benzodiazepines as stratified by cause of death using the established conversion factors from the Norwegian Road Traffic Act.
3 Explore whether pooled opioid and benzodiazepine concentrations differ in drug-induced and other causes of death.

METHODS

Study design and setting

This was a cross-sectional nation-wide study using data from hospital records, the Norwegian Cause of Death Registry and forensic and medical autopsies. In Norway, with 5.3 million inhabitants nation-wide, the national OAT programme is organized within the public specialist health-care service. At the end of 2015, 7498 patients received OAT with either buprenorphine (36%) or buprenorphine–naloxone (22%) sublingual tablets, methadone (39%, mainly syrup) and other opioids (3%) [19].

Participants

Between 1 January 2014 and 31 December 2015, 200 patients in total died during OAT in Norway (defined as within 5 days after the last reported intake of OAT medication). As reported previously [6], 90 (45%) of the 200 died of a somatic disease, 84 (42%) of a drug-induced cause of death and 23 (12%) of a violent cause of death. A forensic or medical autopsy was requested and performed in 125 (63%) of the 200 cases [6]. In the present study we included data from 107 of these patients, who were subjected to an autopsy and where femoral blood was collected for toxicological analyses. We excluded 18 autopsy reports; i.e. six medical autopsy reports where toxicological analyses were not performed, one case where the samples were unsuitable for toxicological analyses, six where toxicological analyses were performed on muscle tissue only and five cases where either the toxicology results or the whole autopsy report were missing.

The hospital trusts responsible for OAT provided information regarding age, sex and treatment (e.g. OAT status, duration of OAT, medications and coprescribing), while information regarding fatality and toxicology was obtained from the autopsy reports. The 107 patients were categorized into two groups based on the cause of death obtained from the Norwegian Cause of Death Registry. Group 1 consisted of 66 patients with drug-induced cause of death. Norway has implemented the International Classification of Diseases, 10th revision (ICD-10) coding for drug-induced deaths used by the European Monitoring Centre for Drugs and Drug Addiction [20–22]. Thus, the 66 drug-induced deaths included unintentional overdose or overdose by unknown intent (n = 57), intentional overdose (n = 4) and substance use disorder (n = 5). Results from both drug-induced and other causes of death were included to explore the differences between non-fatal and fatal concentrations in patients receiving OAT. Therefore, group 2 included 41 patients who died of other causes of death: i.e. 23 patients who died of a somatic disease, 17 who died of a violent cause of death [accident, homicide or suicide (except intentional overdose)] and one patient with a psychiatric diagnosis (F29) as an underlying cause of death.

Procedures

Only two laboratories in Norway perform toxicological analyses in postmortem cases: the Department of Forensic Sciences at Oslo University Hospital and the Department of Clinical Pharmacology at St Olav's Hospital Trondheim University Hospital. Details regarding the analytical procedures are described elsewhere [17].

The principle of equipotent doses, where the relative potencies of different opioids and benzodiazepines are considered, is widely acknowledged [15]. Comparable to this, we have used separate conversion factors for blood concentrations that were already implemented in the Norwegian Road Traffic Act to estimate pooled diazepam- and morphine-equivalent concentrations of opioids and benzodiazepines detected postmortem in patients receiving OAT. The principle of conversion factors for blood concentrations of alcohol and benzodiazepines assumes a linear concentration–effect relationship [15]. For opioids,

this relationship has been little investigated, but two studies [23,24] also suggested a linear concentration–effect relationship for opioids [15]. Due to the partial antagonist effect of buprenorphine and lack of evidence regarding the impairing effects of tramadol on driving, the conversion factors for concentrations of buprenorphine and tramadol are not included in the conversion table used in the Norwegian Road Traffic Act [15,16]. We consider the inclusion of buprenorphine and tramadol when investigating drug-induced deaths to be important, and we have assumed that the conversion factors for their blood concentrations are similar to the conversion factors for equipotent doses of buprenorphine and tramadol [25]. The conversion factors used in the present study are provided in the Supporting information, Appendix S1.

Substances

The following substances were detected in the present study. The detected opioids were heroin/morphine, methadone, buprenorphine, tramadol and codeine. Heroin is rapidly metabolized to 6-acetylmorphine (6-AM) in blood and further to morphine. The presence of 6-AM in blood or urine distinguishes heroin use from that of morphine [26]. If only morphine is detected, it is impossible to determine if this is a result of heroin or morphine intake. Codeine is a prodrug metabolized to the psychoactive metabolite morphine. Codeine was regarded as a trace amount/pollutant when concomitant 6-AM was detected, and was categorized as 'other medications/substances' if a concomitant morphine concentration was < 10% of the codeine concentrations or when no concomitant morphine was detected in combination with codeine.

The detected benzodiazepines were clonazepam, measured as the metabolite 7-aminoclonazepam (7-AK), diazepam and/or desmethyldiazepam (active diazepam metabolite), alprazolam, oxazepam and nitrazepam. Because of their effect similar to benzodiazepines, the Z-hypnotics zopiclone and zolpidem were added. Pregabalin was presented separately. Methamphetamine is partly metabolized to amphetamine *in vivo*; thus, concentrations of methamphetamine and amphetamine were summed and categorized as stimulants. Detection of tetrahydrocannabinol in blood was regarded as positive for tetrahydrocannabinol. Ethanol was only included if concomitant findings of its metabolites ethyl glucuronide and ethyl sulphate were present in blood or urine to exclude ethanol formed postmortem.

The detected psychotrophic medications (antipsychotics/antidepressants) were at least one of the following: quetiapine, flupentixol, risperidone, levomepromazine, olanzapine, chlorprothixene, aripiprazole, trimipramine, citalopram, mirtazapine, mianserin, sertraline, amitriptyline and fluoxetine. Other detected medications/substances were paracetamol, codeine, promethazine, dexchlorpheniramine, lamotrigine, hydroxyzine, gabapentin, valproic acid, levetiracetam, alimemazine, metoprolol, carbamazepine, 10-OH carbazepin, salicylic acid, phenytoin, *gamma*-hydroxybutyric acid and 4-fluoroamphetamine (a new psychoactive substance).

Statistical analysis

Data are presented as means, standard deviation (SD), frequencies and proportions. We used a Student's *t*-test to compare continuous data and a χ^2 or Fisher's exact test for categorical data. The concentrations of substances were not normally distributed, and were therefore presented with median, minimum and maximum values. A Mann–Whitney *U*-test was used for comparisons. Bivariate and multiple regression models were estimated to assess the association between drug-induced cause of death and pooled opioid and benzodiazepine concentrations, with other causes of death as a reference category. The results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Only cases with no missing covariate values were included in the multiple model. Because of the wide concentration range, the covariate pooled benzodiazepine concentration was re-scaled in the regression analyses (divided by 1000). All analyses were two-sided and significance was set at $P < 0.05$. The analyses were not pre-registered; therefore, the results should be considered exploratory. Results were presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Appendix S3). Data were analysed using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics South-East (case number 2016/1204), the Cause of Death Registry, The Director of Public Prosecution, the Ministry of Justice and Public Security and the participating hospital trusts.

RESULTS

Characteristics

The mean age at the time of death was 47.4 years (SD = 8.8) for the whole group, and 79 (74%) were men (Table 1). The total duration of OAT was almost 8 years (SD = 4.3). All but two patients were prescribed methadone or buprenorphine and 71 (68%) had doses within the recommended range [19]. There were more patients prescribed methadone in those who died of a drug-induced cause of death compared with other causes of death (58

Table 1 Sample characteristics and circumstances at the time of death of 107 patients receiving opioid agonist treatment, stratified by cause of death.

	All-cause deaths	*Drug-induced deaths*	*Other causes of death*	*Missing data*
	N = 107	*n = 66*	*n = 41*	
Age and sex				
Age, mean ± SD	47.4 ± 8.8	46.9 ± 9.1	48.2 ± 8.3	0
Male, *n* (%)	79 (74)	47 (71)	32 (78)	0
OAT treatment, n (%)				
Duration of OAT in years, mean ± SD	7.7 ± 4.3	8.0 ± 4.3	7.3 ± 4.3	4
Prescribed methadone[a]	53 (50)	38 (58)*	15 (37)*	0
Prescribed buprenorphine[a]	52 (49)	26 (39)*	26 (63)*	0
Prescribed other/unknown OAT medication	2 (2)	2 (3)	0 (0)	0
Dose within recommended range[b]	71 (68)	41 (64)	30 (73)	2
Dose above recommended range[b]	13 (12)	8 (13)	5 (12)	2
Dose below recommended range[b]	21 (20)	15 (23)	6 (15)	2
Supervised intake 1–2 times a week[c]	9 (11)	4 (8)	5 (14)	22
Supervised intake 3–7 times a week[c]	74 (89)	44 (92)	30 (86)	22
Benzodiazepines/Z-hypnotics prescribed[d]	37 (40)	23 (42)	14 (38)	15
Circumstances				
OAT status described in autopsy reports	69 (65)	44 (67)	25 (61)	6
Found 0–48 hours after time of death	94 (88)	57 (86)	37 (90)	0
Median (min–max) days from death to autopsy	3 (0–14)	3 (1–14)	3 (0–11)	2
Signs of drug use[e]	64 (60)	49 (74)**	15 (37)**	4
Fresh needle marks	29 (27)	20 (30)	9 (22)	6
Median (min–max) number of substances	4 (1–11)	4 (1–11)	4 (1–8)	0
Single substance detected	7 (7)	4 (6)	3 (7)	0

*$P < 0.05$; **$P < 0.001$. [a]Median dose (min-max) prescribed at the time of death: methadone 90 mg (15–200 mg), buprenorphine 16 mg (1–28 mg). [b]Recommended dosing range methadone 80–120 mg, buprenorphine 12–24 mg [19]. [c]Supervised intake of OAT medication in the year before death. In addition to the 22 with missing data, two patients did not have supervised intake of OAT medication. [d]Benzodiazepines/Z-hypnotics prescribed at least once in the year before death according to hospital records. [e]Information in the autopsy report about substance use, drugs or drug paraphernalia detected on or close to the body, or fresh needle marks not related to medical treatment. SD = standard deviation.

versus 37%, $P = 0.025$). According to information from the hospitals, 37 (40%) patients were prescribed at least one benzodiazepine/Z-hypnotic in the year before death (mainly oxazepam, Z-hypnotics and/or diazepam).

In the autopsy reports, the pathologist had described OAT status in two-thirds (65%) of the reports. In two reports, the pathologist stated that the OAT status was unknown, and in the remainder the OAT status was not stated. Signs of drug use (fresh needle marks and/or drugs or drug paraphernalia) were described significantly more often in those who died of a drug-induced cause of death compared with other causes of death (74 versus 37%, $P < 0.001$). A median of four substances was detected postmortem.

Substances and concentrations

Methadone was detected in 60 (56%) patients, and among these, 53 had had methadone prescribed (Table 2). In contrast, buprenorphine was not detected in 12 of 52 patients (23%) prescribed buprenorphine. Methadone was detected in five patients where only buprenorphine prescription was documented in their hospital records. Morphine was detected in 30 (28%) patients and the heroin metabolite 6-AM was also found in 19 of them. In the Cause of Death Registry, an opioid was registered as the main intoxicant in 58 of the 66 drug-induced deaths; i.e. methadone in 30 cases, heroin or morphine in 21 and buprenorphine in seven cases.

The two most common benzodiazepines were clonazepam and alprazolam, which were detected in 58 (54%) and 25 (23%) of the patients, respectively. Pregabalin was detected in 19 (18%) patients, stimulants in 31 (29%) patients and tetrahydrocannabinol in 40 (37%) patients. In addition to the substances presented in Table 2, 34 (32%) patients had at least one antipsychotic and/or antidepressant medication detected, while at least one other medication/substance, as previously listed, was detected in 32 (30%) patients.

The median concentration of buprenorphine was lower in drug-induced deaths compared with other causes of death, in contrast to the concentrations of methadone, morphine and tramadol. The median concentrations of the specific benzodiazepines and other substances did not show any consistent pattern in drug-induced compared with other causes of death. There were no significant

Table 2 Substances detected post-mortem in 107 patients receiving opioid agonist treatment, with median (min–max) concentrations (ng/ml), stratified by cause of death.

	All-cause deaths, N = 107		*Drug-induced death, n = 66*		*Other causes of death, n = 41*		*Mann–Whitney U test*
	n (%)	*Median (min–max)*	*n (%)*	*Median (min–max)*	*n (%)*	*Median (min–max)*	*P*
Opioids							
Methadone	60 (56)	881.9 (22.28–4023)	44 (67)	897.4 (24.45–4023)	16 (39)	634.4 (22.28–1764)	0.273
Buprenorphine	40 (37)	5.38 (0.89–93.53)	18 (27)	3.79 (0.89–93.53)	22 (54)	6.08 (1.40–39.28)	0.366
Morphine[a]	30 (28)	228.3 (10.56–3425)	25 (38)	371.0 (11.42–3425)	5 (12)	94.18 (10.56–196.9)	0.136
Tramadol	3 (3)	421.4 (368.7–1580)	2 (3)	1001 (421.4–1580)	1 (2)	368.7 (368.7–368.7)	0.667
Benzodiazepines							
7-AK[b]	58 (54)	185.7 (8.57–3715)	39 (59)	142.9 (8.57–3715)	19 (46)	200.0 (28.57–1143)	0.506
Alprazolam	25 (23)	43.23 (3.71–176.0)	19 (29)	43.23 (3.71–176.0)	6 (15)	17.60 (3.71–61.75)	0.221
Diazepam	10 (9)	205.0 (74.02–939.5)	5 (8)	111.0 (74.02–304.6)	5 (12)	210.7 (187.9–939.5)	0.222
Desmethyldiazepam	18 (17)	188.4 (64.97–758.0)	10 (15)	215.2 (64.97–758.0)	8 (20)	188.1 (108.3–649.7)	0.897
Oxazepam	12 (11)	246.6 (174.9–630.8)	10 (15)	233.7 (174.9–630.8)	2 (5)	329.7 (258.0–401.4)	0.485
Nitrazepam	1 (1)	5.91 (5.91–5.91)	0 (0)	0	1 (2)	5.91 (5.91–5.91)	NA
Zopiclone	7 (7)	31.88 (5.83–222.8)	3 (5)	38.49 (8.94–222.8)	4 (10)	21.58 (5.83–36.16)	0.400
Zolpidem	1 (1)	768.5 (768.5–768.5)	1 (2)	768.5 (768.5–768.5)	0 (0)	0	NA
Other substances							
Pregabalin	19 (18)	5414 (1274–16082)	15 (23)	5573 (1274–16082)	4 (10)	4458 (3185–8280)	0.469
Stimulants	31 (29)	431.0 (29.74–5814)	19 (29)	365.0 (43.27–5814)	12 (29)	498.5 (29.74–4910)	0.389
THC[c]	40 (37)	4.56 (1.04–150.9)	24 (36)	3.77 (1.04–150.9)	16 (39)	5.19 (1.1–16.98)	1.0
Ethanol[d], ‰	9 (8)	1.30 (0.30–3.90)	5 (8)	1.30 (0.60–3.90)	4 (10)	1.25 (0.30–2.10)	0.556

NA = not applicable. To convert concentrations from SI units: µmol/l × molecular weight = ng/ml. Example: methadone 1.3 µmol/l × 309.4 g/mol [molecular weight (Mw) methadone] = 402.2 ng/ml. [a]Nineteen patients also had 6-AM detected in blood or urine (heroin metabolite); [b]7-aminoclonazepam (clonazepam metabolite); [c]THC = tetrahydrocannabinol, *n* = 104; [d]ethanol, *n* = 106.

differences in the median concentrations of each of the various substances according to cause of death.

Pooled concentrations

The median pooled opioid concentration was significantly higher in drug-induced deaths compared with other causes of death (362 versus 182 ng/ml, $P < 0.001$; Table 3). At least one benzodiazepine was detected in 81 (76%) of the cases, but the median pooled benzodiazepine concentrations did not differ significantly according to cause of death (5466 versus 5701 ng/ml, $P = 0.353$).

Factors associated with drug-induced death

Table 4 shows the results from a regression analysis assessing covariates associated with drug-induced cause of death compared with other causes of death during OAT. In bivariate analyses, both taking methadone as OAT medication (compared with taking buprenorphine) and increasing pooled opioid concentration were associated with higher odds of dying of a drug-induced cause of death. However, only pooled opioid concentration remained significant in the multiple-model estimation (OR = 1.003, CI = 1.001–1.006). The covariates of age, sex and pooled benzodiazepine concentration were not significant in neither bivariate nor multiple analyses.

The pooled opioid concentration was significantly higher in drug-induced cause of death compared with other causes of death in both patients prescribed buprenorphine and methadone. Figure 1 presents the pooled concentrations of the various opioids in drug-induced deaths. As illustrated, 23 (36%) of 64 patients had used more than one opioid. In patients prescribed buprenorphine, other opioids contributed substantially to the pooled opioid concentration, while patients prescribed methadone tended to have high concentrations of methadone as the only opioid (i.e. above therapeutic ranges for methadone).

DISCUSSION

In the present study, a median of four substances was detected in postmortem blood from patients receiving OAT. At least one benzodiazepine was detected in 76% of the patients. The median pooled opioid concentration was significantly higher in drug-induced cause of death compared with other causes of death, in contrast to the median pooled benzodiazepine concentration. In the multiple regression model, only increasing pooled opioid concentration was associated with increased odds of a drug-induced cause of death.

A median pooled opioid concentration of 362 ng/ml in drug-induced deaths was higher than the median of 211 ng/ml in all overdose autopsy cases and 225 ng/ml

Table 3 Pooled median (min–max) morphine- and diazepam equivalent concentrations of opioids and benzodiazepines (ng/ml) in 107 patients receiving opioid agonist treatment, stratified by cause of death.

	Total, N = 107		*Drug-induced death, n = 66*		*Other causes of death, n = 41*		*Mann–Whitney U test*
	n (%)	*Median (min–max)*	*n (%)*	*Median (min–max)*	*n (%)*	*Median (min–max)*	*P*
Pooled opioids[a]	104 (97)	314.7 (10.56–3489)	64 (97)	362.1 (20.34–3489)	40 (98)	181.9 (10.56–899.0)	< 0.001
Pooled benzodiazepines[b]	81 (76)	5466 (28.61–177652)	51 (77)	5466 (49.82–177652)	30 (73)	5701 (28.61–54794)	0.353

To convert concentrations from SI units: µmol/l × conversion factor × molecular weight for morphine or diazepam = morphine- or diazepam equivalent concentration in ng/ml. Example conversion methadone to morphine-equivalent concentration: methadone 1.3 µmol/l × 0.375 (conversion factor methadone) × 285.4 g/mol (Mw morphine) = 139.1 ng/ml. 7-aminoclonazepam, alprazolam, oxazepam, nitrazepam, zopiclone and zolpidem. All opioids and benzodiazepines as morphine- or diazepam-equivalents are presented in Supporting information, Appendix S2. [a]Pooled concentrations of opioids from Table 2: morphine and morphine-equivalent concentrations of methadone, buprenorphine and tramadol; [b]pooled concentrations of benzodiazepines from Table 2: diazepam and diazepam-equivalent concentrations of desmethyldiazepam.

Table 4 Factors associated with drug-induced cause of death versus other causes of death (reference) during opioid agonist treatment.

	Bivariate models	*Multiple model*
	OR (95% CI)	*OR (95% CI)*
Age	0.983 (0.940–1.028)	0.998 (0.942–1.057)
Gender		
Men	1	1
Women	1.437 (0.578–3.576)	1.902 (0.596–6.072)
OAT medication		
Buprenorphine	1	1
Methadone	2.533 (1.129–5.683)*	1.276 (0.436–3.733)
Pooled opioid concentration in ng/ml	1.003 (1.001–1.006)*	1.003 (1.001–1.006)*
Pooled benzodiazepine concentration[a] in ng/ml	1.009 (0.985–1.033)	1.007 (0.983–1.031)

*$P < 0.05$. Only complete cases are included in the multiple model, $n = 76$. [a]The covariate pooled benzodiazepine concentration is rescaled (divided by 1000). OAT = opioid agonist treatment; OR = odds ratio; CI confidence interval.

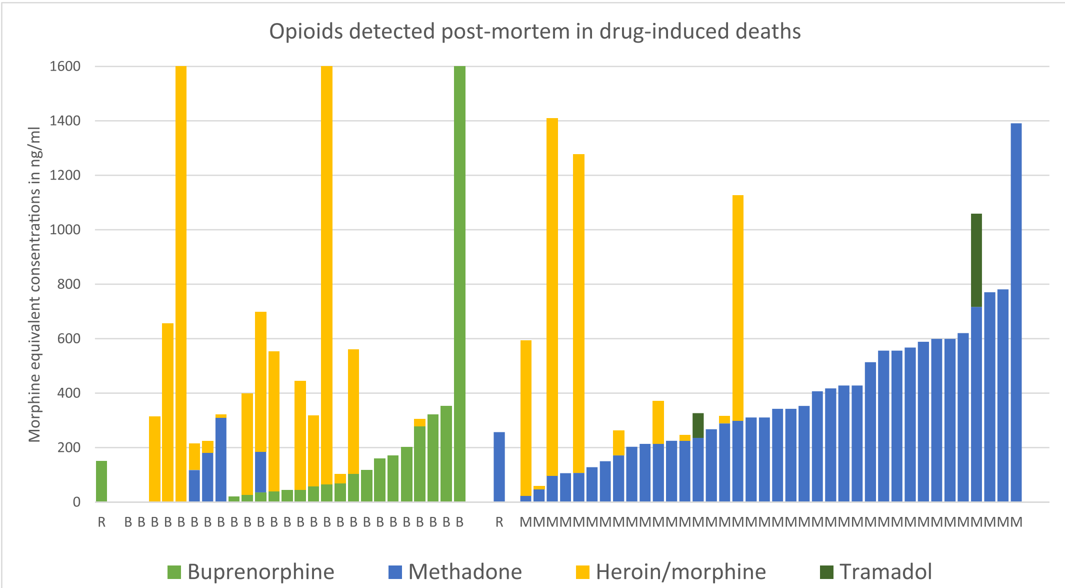

Figure 1 Pooled morphine-equivalent concentrations (ng/ml) of opioids in 64 drug-induced deaths during opioid agonist treatment. B = 26 patients prescribed buprenorphine, M = 38 patients prescribed methadone. Concentrations above 1600 ng/ml are 2140, 2483 and 3425 ng/ml. R = reference concentrations from patients in our sample who died of other causes than drug-induced death, and with the prescribed OAT medication as the only opioid detected post-mortem: 18 patients prescribed buprenorphine (morphine-equivalent concentration 150 ng/ml) and 14 patients prescribed methadone (morphine-equivalent concentration 257 ng/ml). [Colour figure can be viewed at wileyonlinelibrary.com]

in the heroin/morphine-positive autopsy cases reported by Edvardsen *et al.* [17,18]. In their study, however, the pooled opioid concentrations might have been underestimated because buprenorphine and tramadol were not included. The pooled median benzodiazepine concentrations were higher in both groups in the present study (5466 and 5701 ng/ml) compared with 1765 ng/ml in all overdose cases and 2078 ng/ml in heroin/morphine-positive autopsy cases in the same study by Edvardsen *et al.* [17,18]. The median concentrations of most substances in Table 2 in our study were higher than the corresponding findings in postmortem femoral blood from all-cause deaths in a study reported by Ketola & Ojanpera [27]. The higher median concentrations, as well as the wide concentration ranges of benzodiazepines and opioids in both groups in the present study, are probably due to variable development of tolerance. Regular intake of benzodiazepines in doses exceeding the normal therapeutic range have been reported in OAT populations [28]. Previous studies have also reported higher median/mean methadone concentrations in autopsy cases in patients receiving OAT compared with individuals not in treatment at the time of death [11,29,30], indicating, as expected, an increased opioid tolerance among patients receiving OAT.

Explanations for the high postmortem opioid concentrations in drug-induced deaths include taking extra or

'topping up' with heroin [31]. High prevalence of organ pathology (e.g. liver and kidney disease) [6,32,33] may impair metabolism and excretion and hence lead to higher blood concentrations of methadone, while lower concentrations of buprenorphine and methadone have been detected in delayed deaths compared with immediate poisonings [30,34]. Another risk factor is injecting of OAT medication instead of taking it sublingually or orally [29,35–37]. In an Italian study [38], 28% reported injecting their own OAT medication, with no differences between the different OAT medications.

Buprenorphine is considered to have a better pharmacological safety profile than methadone, and is therefore often recommended as the preferred OAT medication [39]. However, the risk of fatal overdose is increased if buprenorphine is injected or combined with benzodiazepines or alcohol [13,28,34,35,40] and, as our study suggests, if buprenorphine is replaced by other opioids. Buprenorphine is a partial agonist with antagonist properties; thus, it is likely that patients may stop taking or reduce the dose to enhance the effect from opioid agonists such as heroin [41]. When choosing between methadone and buprenorphine, it is important to consider the medications' stabilizing effect and their ability to prevent or minimize inappropriate use of the medication and other psychoactive drugs.

As expected, the pooled opioid concentration (the total opioid load) seemed to play the most important role, in line with the hierarchy of the most dangerous drug in multiple drug deaths in the ICD-10 [22]. Even though the pooled benzodiazepine concentration was comparable in drug-induced and other causes of death, we cannot draw the conclusion that benzodiazepines were not involved in these deaths. The concentration ranges were wide and the mechanisms for additive effects upon respiratory depression when opioids and benzodiazepines are combined are poorly understood [13]. Additionally, other factors not included in the present study may increase the risk of a drug-induced cause of death, such as comorbidities and the combination of opioids and substances other than benzodiazepines with central nervous system depressant effect (e.g. pregabalin).

The number of cases where an opioid, including the patient's prescribed OAT medication, was considered the main intoxicant is a cause for concern. Nevertheless, systematic reviews and meta-analyses have consistently shown higher mortality outside and after OAT [1–3], and it is imperative to keep patients with OUD in agonist treatment. The Norwegian OAT programme is low-threshold, and one-quarter of the patients had harm reduction as a treatment goal in 2015 [19]. For those who continue to use drugs during OAT, harm-reduction strategies such as information about safer use training and distribution of intranasal naloxone are essential [42,43], as well as treatment tailored to the patient's individual needs. Improved follow-up of somatic diseases and methadone dose adjustments are also important to prevent methadone toxicity as patients age.

Strengths and limitations

To our knowledge, this paper is the first to present postmortem pooled opioid and benzodiazepine blood concentrations in an OAT population, including concentrations in patients who died of causes other than overdose. We also present information concerning prescribed OAT medication. Thus, our findings broaden the understanding of the toxicology in drug-induced deaths among patients receiving OAT and complement the results from larger registry-based studies. Norway has high autopsy rates (90%), and most drug-induced deaths are based on toxicological confirmation [44]. Another strength is that the two laboratories use similar analytical methods and instruments; thus, a very low variation within the results would be expected.

The present study has some limitations. The cross-sectional design cannot address causation [45], and a higher number of participants would have allowed for more covariates in the regression analysis. postmortem re-distribution leads to site- and time-dependent changes in the measured concentrations of certain drugs [26,46,47]. Brockbals *et al.* [46] reported a median/mean +20% postmortem increase in methadone concentrations, ranging from −9 to +71%, and concluded that changes were regarded as irrelevant with respect to forensic toxicology interpretation. postmortem re-distribution will take place in both groups; thus, comparing the concentration levels will provide important information in these cases. To reduce site-dependent postmortem variation, we have included analytical results from femoral blood only. The number of days from estimated time of death to autopsy in the two groups did not differ (median = 3 days, $P = 0.517$). The Norwegian OAT population is among the oldest in Europe, and buprenorphine is the most prescribed OAT medication [19]. Thus, the results may not be fully generalizable to other countries or treatment settings. Finally, data from the Norwegian Prescription Database would have provided updated information about benzodiazepines prescribed by general practitioners, which hospital records may lack.

The conversion factors for blood concentrations are based on a limited number of studies investigating psychoactive effects among opioid-naive individuals [15]. In the present study, we have estimated and compared pooled concentrations in patients with tolerance to opioids. Tolerance is an important aspect, but the development of tolerance differs between opioids and benzodiazepines. Thus, further research is needed, and partial antagonists such

as buprenorphine should be included when this method is used to assess concentrations in drug-induced deaths. Nevertheless, the conversion factors in the present study, except those for buprenorphine and tramadol, are used to mete out legal sanctions in Norwegian driving under the influence of drugs cases.

CONCLUSIONS

The pooled opioid concentration seemed to play the most important role in drug-induced deaths during OAT in patients prescribed methadone or buprenorphine. Patients prescribed buprenorphine tended to replace their agonist with full agonists, while patients prescribed methadone tended to have high opioid concentrations from methadone as the only opioid. Deaths due to other causes had significantly lower pooled opioid concentration compared with drug-induced deaths, but comparable concentrations of pooled benzodiazepines. More research is required on the combined effect of opioids and benzodiazepines in drug-induced deaths within OAT.

Declaration of interests

None.

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Author contributions

Anne Berit Bech: Conceptualisation; project administration; formal analyses; investigation, writing - original draft; visualisation. **Thomas Clausen:** Conceptualisation; writing - review and editing; supervision. **Helge Waal:** Writing - review and editing. **Vigdis Vindenes:** Methodology; formal analyses; writing - review and editing. **Hilde Erøy Edvardsen:** Methodology; formal analyses; writing - review and editing. **Joachim Frost:** Methodology; writing - review and editing. **Ivar Skeie:** Conceptualisation; investigation; writing - review and editing; supervision; project administration; funding acquisition.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Conversion factors for morphine- and diazepam-equivalent blood concentrations.

Appendix S2: Median (min–max) morphine-and diazepam-equivalent concentrations (ng/mL) of the various opioids and benzodiazepines presented in Table 2, in 107 patients receiving opioid agonist treatment.

Appendix S3: STROBE Statement.

Appendix 1

Questionnaires

Registreringsskjema for pasienter som døde under LAR-behandling i 2015

Mortalitet i LAR. Det gjennomføres i 2014 og 2015 en registrering av alle dødsfall under LAR-behandling. Også dødsfall det første året etter avsluttet LAR-medisinering skal registreres dersom de er kjent av LAR-tiltaket, uavhengig av om pasienten fremdeles er inkludert i LAR eller ikke. Dette registreringsskjemaet er utarbeidet for at LAR-tiltakene skal kunne sammenlikne informasjon og eventuelt kople data sammen med statusdata. Det skal slik som statuskjemaene inngå som del av journal, og oppbevares tilpasset rutiner i det enkelte tiltak. Uten særskilt tillatelse kan tiltaket samle informasjonen som ledd i egen kvalitetssikring, men ikke videreformidle personidentifiserbare funn.

SERAF vil søke om tillatelser til en nasjonal undersøkelse basert på personidentifiserbare opplysninger. Denne vil basere seg på dette registreringsskjemaet med tillatelse til kopling til statusdata.

Hvem fyller ut? Skjemaet bør fortrinnsvis fylles ut av ansvarlig lege i LAR-tiltaket i samarbeid med pasientens hovedkontakt i LAR (den som kjente pasienten best).

Hvilken informasjon skal utfyllingen bygge på? Utfyllingen skal bygge på samlet informasjon i LAR-tiltaket og fra andre instanser som var involvert i behandlingen (ruskonsulent i kommune/NAV, fastlege, sykehus m.m.). I tilfeller der pasienten er obdusert og LAR-tiltaket er kjent med funnene, skal disse registreres.

Tidspunkt: Innen 1.februar 2016.

Målgruppe: Alle pasienter som døde mens de var inkludert i LAR i løpet av 2015. Også pasienter som hadde avsluttet medisineringen, men fremdeles var inkludert i LAR, skal registreres. Det vil framgå av skjemaet hvorvidt pasienten faktisk inntok LAR-medisiner ved dødstidspunktet.

Skjemaet er delt i fire deler:
Del 1 – Bakgrunnsdata
Del 2 – Spørsmål om dødsfallet
Del 3 – Helsetilstand
Del 4 – Åpent spørsmål om utfyllers samlede vurdering

Skjemaet skal lagres som del av pasientens journal i det enkelte LAR-tiltak. Det enkelte tiltak bes sammenstille opplysningene i dette skjemaet med statusskjema. Skjemaet har derfor et felt for personnummer som gjør sammenkoplingen enklere.

SERAF vil informere om hvordan aggregerte anonymiserte opplysninger fra skjemaene skal sendes etter at det er avgjort hvilke typer tillatelse som foreligger

Del 1 - Bakgrunnsdata

1.0 Utfyllers yrke

Lege ☐ 0

Annet, spesifiser _____ ☐ 1

Informasjon om avdøde

Personnummer (til bruk ved kobling mot statusundersøkelsen)

☐☐☐☐☐☐☐☐☐☐☐

NB: Slettes ved innsending av aggregerte data.

1.1 Pasientens kjønn

Mann ☐ 0

Kvinne ☐ 1

1.2 Alder ved død (år) ☐☐

1.3 Helseforetak _____

1.4 Samlet varighet av LAR-behandlingen, i en eller flere perioder

☐☐ år ☐☐ mndr.

1.5 Varighet av siste behandlingsperiode i LAR fram til død

☐☐ år ☐☐ mndr.

1.6 LAR-medikament ved dødsfallet

Metadon ☐ 0

Buprenorfin (Subutex eller kopipreparater) ☐ 1

Buprenorfin/nalokson (Suboxone) ☐ 2

Andre, spesifiser: _____ ☐ 3

Uten LAR-medisinering, men inkludert i LAR (se også 1.8) ☐ 4

Ukjent ☐ 9

1.7 Døgndose i mg. ved dødstidspunkt

Metadon ☐☐☐

Buprenorfin ☐☐

1.8 Var pasienten i aktiv medikamentell LAR-behandling ved dødstidspunktet (**ett kryss**)

Ja, i fast dosering (samme dose siste 14 dager)	☐ 0
Ja, men skiftet LAR-medikament siste 14 dager	☐ 1
Ja, men dose økt siste 14 dager	☐ 2
Ja, men under frivillig nedtrapping (dose redusert siste 14 dager)	☐ 3
Ja, men under ikke frivillig nedtrapping (dose redusert siste 14 dgr)	☐ 4
Nei, trappet ned til 0 etter avtalt plan	☐ 5
Nei, ikke hentet medisin i periode på …….. dager (ikke avtalt)	☐ 6
Ukjent	☐ 9

1.9 Medisinering i tillegg til LAR-medikament (**medikament og dose**) fra LAR-tiltak, fastlege eller annen lege ved dødstidspunkt (**kan ha flere kryss**)?

Andre opioider enn LAR-medikamentet (smertebehandling)
☐ Nei - 0
☐ Ja -1
☐ Ukjent - 9

Hvis ja, angi medikament: _____ Døgndose: _____

Benzodiazepiner og z-hypnotika (zopiklone/zolpidem)
☐ Nei - 0
☐ Ja -1
☐ Ukjent – 9

Hvis ja, angi medikament: _____ Døgndose: _____

Sentralstimulerende medikamenter (ADHD-medisin)
☐ Nei - 0
☐ Ja -1
☐ Ukjent – 9

Hvis ja, angi medikament: _____ Døgndose: _____

Antidepressiva
☐ Nei - 0
☐ Ja -1
☐ Ukjent – 9

Hvis ja, angi medikament: _____ Døgndose: _____

Antipsykotika
☐ Nei - 0
☐ Ja -1
☐ Ukjent – 9

Hvis ja, angi medikament: _____ Døgndose: _____

Andre medikamenter (”somatiske”)
☐ Nei - 0
☐ Ja -1
☐ Ukjent – 9

Hvis ja, angi medikament(er): _____ Døgndose: _____

1.10 Overvåkede inntak av LAR-medikament ved dødsfallet

Overvåket inntak 7 dager per uke	☐ 0
Overvåket inntak 3-6 ganger per uke	☐ 1
Overvåket inntak 1-2 ganger per uke	☐ 2
Ingen overvåkede inntak	☐ 3
Ikke i aktiv LAR-medisinering	☐ 4
Ukjent	☐ 9

1.11 Utleveringsordning ved dødsfallet

Utlevering 7 dager per uke	☐ 0
Utlevering 3-6 ganger per uke	☐ 1
Utlevering 1-2 ganger per uke	☐ 2
Utlevering sjeldnere enn 1 gang per uke	☐ 3
Ikke i aktiv LAR-medisinering	☐ 4
Ukjent	☐ 9

Del 2 – Spørsmål om dødsfallet

2.1 Dødsdato (**dato, måned, år)** ☐☐ ☐☐ ☐☐☐☐
NB: Slettes ved innsending av aggregerte data.

2.2 Dødssted

Hjemme i egen bolig	☐ 0
I annen privat bolig	☐ 1
Offentlig sted	☐ 2
I trafikken	☐ 3
Sykehus	☐ 4
Sykehjem	☐ 5
Annet, spesifiser: _____	☐ 6
Ukjent	☐ 9

2.3 Ble den døde obdusert?

Nei	☐ 0
Ja, rettsmedisinsk obduksjon (rekvirert av politi)	☐ 1
Ja, vanlig sykehusobduksjon	☐ 2
Ukjent	☐ 9

2.4 Antatt dødsårsak, basert på opplysninger LAR-tiltaket sitter inne med?

Sykdom ☐ 0
Diagnose (om mulig ICD-10):

_____

Overdose ☐ 1
Hvis obdusert, stoff som var hovedårsak til dødsfallet:

_____

Andre stoffer påvist ved obduksjon:

_____

_____

Voldsomt dødsfall (ulykke, selvmord, drap) ☐ 2
Spesifiser:

_____

Ukjent ☐ 9

2.5 Hvilke opplysninger baseres antatt dødsårsak på (evt flere kryss)?

Obduksjon/toksikologisk rapport	☐ 0
Epikrise sykehus	☐ 1
Opplysning fra behandlende lege	☐ 2
Andre opplysninger, spesifiser:	☐ 3

_____

2.6 Avsluttet "skjermet tilværelse" (fengsel, institusjon, langvarig sykehusbehandling) siste 6 måneder før dødsfallet?

Ja	☐ 0
Nei	☐ 1
Ukjent	☐ 9

Hvis ja, hvor mange **dager** før dødsfallet ☐☐☐

Hvis ja, hvilken form for "skjermet tilværelse":
_____

2.7 Ved overdosedødsfall og voldsomme dødsfall: Var det kjente "krisetegn" (f. eks. overdoser, suicidforsøk, problematferd som vold og truser) i perioden (dager/få uker) før dødsfall?

Ja	☐ 0
Nei	☐ 1
Ukjent	☐ 9

Hvis ja, beskriv kort:_____

2.8 Ved overdosedødsfall og voldsomme dødsfall: Var det noen viktige hendelser i personens liv siste måned før dødsfallet (relasjonstap, dødsfall, økonomisk krise, påvist somatisk lidelse eller andre)

Ja	☐ 0
Nei	☐ 1
Ukjent	☐ 9

Hvis ja, beskriv kort:_____

Del 3 – Helseopplysninger (skal baseres på journalopplysninger)

3.1 Blodsmittestatus (flere kryss)

	Nei	Ja	Ukjent
Antistoff mot HIV ("HIV-smittet")	☐ 0	☐ 1	☐ 9
Aktiv hepatitt B ("smitteførende")	☐ 0	☐ 1	☐ 9
Hepatitt C antistoff ("har vært smittet")	☐ 0	☐ 1	☐ 9
Hepatitt C PCR positiv ("kronisk hepatitt C")	☐ 0	☐ 1	☐ 9

3.2 Kroniske somatiske lidelser – ICD-10 diagnose

Spesifiser:

Diagnose (tekst) ICD-10

_____

_____

_____

_____

_____

_____

_____

_____

3.3 Der dødsfallet skyldes kjent, kronisk somatisk lidelse: Var pasienten i aktiv behandling/oppfølging for lidelsen (sykehusinnleggelse siste år, ambulant oppfølging ved poliklinikk/privat spesialist, hos fastlege)?

Nei	Ja	Ukjent
☐ 0	☐ 1	☐ 9

3.4 Kroniske psykiatriske lidelser – ICD-10 diagnose

Spesifiser:

Diagnose (tekst) ICD-10

_____

_____

_____

_____

_____

_____

_____

_____

Del 4 - Åpent spørsmål om utfyllers vurdering av om mulige tiltak fra behandlingsapparatet kunne ha forhindret dødsfallet

Grovt sett vil dødsfallene kunne deles i tre kategorier: overdosedødsfall, sykdom og voldsomme dødsfall (ulykker, selvmord, drap). Er det noe, ut fra din samlede kjennskap til pasienten, omstendighetene rundt dødsfallet og den behandling/oppfølging som ble gitt forut for dødsfallet, som etter din vurdering kunne vært gjort annerledes fra behandlingsapparatets side slik at dødsfallet kanskje kunne vært unngått?

Beskriv i så fall kort: behandlingstiltak som ble gitt og hvilke andre tiltak som eventuelt kunne ha forhindret dødsfallet. Det er viktig at det her tas utgangspunkt i hvordan situasjonen for pasienten og behandlingsapparatet var *før* dødsfallet, og hvilke tiltak som *med rimelighet* kunne vært satt inn.

Svar i fritekst:

PRAKTISK VEILEDNING FOR UTFYLLING

1. Generelle råd: Les nøye gjennom spørsmålene. Ved de fleste spørsmål skal du bare sette kryss i en rute, ved noen spørsmål kan det krysses av i flere ruter, dette er da presisert i skjemaet. Alle spørsmålene skal besvares. Om nødvendig innhenter du informasjon fra journal eller medarbeidere. Dersom du likevel ikke har nødvendig kjennskap, brukes svaralternativet "Ukjent" .

2. Det skal utfylles ett skjema for hver pasient som er død mens vedkommende har vært *inkludert i LAR*. Det vil framgå av skjemaet om pasienten faktisk inntok LAR-medikamentet ved dødstidspunktet.

3. Skjemaene skal lagres som del av pasientens journal. Aggregerte anonymiserte data sendes SERAF etter nærmere avtale. Dersom SERAF senere får tillatelse til å innhente identifiserbare data, vil LAR-tiltakene senere få konkret informasjon om hvordan innhentingen vil skje.

4. Skjemaet skal – om mulig – fylles ut av ansvarlig lege i LAR-tiltaket i samarbeid med pasientens LAR-kontakt (den som kjente pasienten best).

5. Til del 4 – det åpne vurderingsspørsmålet: det presiseres at det vi spør etter er din vurdering av mulige alternative behandlingstiltak som kanskje kunne ha forhindret dødsfallet. Vi tenker da på eventuelle tiltak som *med rimelighet* kunne vært satt inn. *Med rimelighet* innebærer at de foreslåtte tiltak burde settes inn i *alle liknende situasjoner*, ikke bare enkeltsituasjonen der "fasiten" viste at pasienten døde.

Tilleggsopplysninger

Mortalitet i LAR

Det er gjennomført en registrering av alle dødsfall under LAR-behandling i Norge i 2014 og 2015 og dødsfallene studeres i et eget forskningsprosjekt. Som et ledd i dette prosjektet gjennomføres en kasus-kontroll-studie, der det trekkes ut en kontroll som ikke er død for hver pasient som er død. Dette registreringsskjemaet skal brukes både for de som døde under LAR-behandling i 2014 og 2015 og for kontrollene. Skjemaet skal bare brukes i denne studien og ikke oppbevares som del av journal. Skjemaet bør fortrinnsvis fylles ut av lege i LAR-tiltaket i samarbeid med pasientens hovedkontakt i LAR (den som kjente pasienten best).

Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK), saksnr. 2016/1204.

Skjemaene skal sendes **rekommandert i lukket konvolutt** til Nasjonal kompetansetjeneste ROP, att: Anne Bech, Sykehuset Innlandet HF, Pb. 104, 2381 Brumunddal

Dersom skjema gjelder en av de døde (kasus), skal det oppgis personnummer (til bruk ved kobling mot statusundersøkelsen)

☐☐☐☐☐☐☐☐☐☐☐

Dersom skjema gjelder en av kontrollene, skal det oppgis løpenummer (til bruk ved kobling mot statusundersøkelsen)

☐☐☐

1. Avbrudd i medikamentell LAR-behandling siste fem år. For de døde (kasus) fem år før dødstidspunktet, og for kontroller siste fem år før 31.12.15 (**ett kryss**)

Avbrudd er her ikke knyttet til formell inklusjon/eksklusjon i LAR, men perioder på mer enn fem dager hvor pasienten har vært uten substitusjonsmedikamenter

Aldri	☐ 0
1-3 ganger	☐ 1
4 ganger eller mer	☐ 2
Ukjent	☐ 9

2. Bosted - grad av urbanitet. For de døde (kasus) på dødstidspunkt, for kontroll per 31.12.15 (**ett kryss**)

Storbyområde (100 000 innbyggere eller mer)	☐ 0
Mindre byområde (10 000-100 000 innbyggere)	☐ 1
By/tettsted/bygd (under 10 000 innbyggere)	☐ 2

Appendix 2

Definitions of organ pathology

Characteristics stratified by autopsy

Definitions of organ pathology

The results are based on what the pathologists have explicitly reported in forensic or medical autopsy reports, except hepatomegaly (see definition below).

1. **Pulmonary pathology**

At least one of the following: emphysema, pulmonary fibrosis, pneumonia, pulmonary embolism, foreign body granulomas.

2. **Cardiovascular pathology**

At least one of the following: myocardial infarction (fresh, old or micro-infarction), left and/or right ventricular hypertrophy, cardiac fibrosis not defined as infarction, moderate to severe atherosclerosis of the coronary arteries and/or aorta stated by the pathologist, endocarditis and/or myocarditis, cardiomegaly stated by the pathologist, cerebral infarction or haemorrhage based on neuropathological examination (not traumatic bleeding).

3. **Hepatic pathology**

At least one of the following: lymphocytic infiltrate of the portal tracts and/or parenchyma (inflammation), steatosis, hepatic fibrosis or cirrhosis (we did not report liver fibrosis if the pathologist described cirrhosis), portal lymphadenopathy (i.e. one or several enlarged perihepatic lymph nodes), hepatomegaly defined as liver weight > 1860 g for men and > 1767 g for women.

4. **Renal pathology**

At least one of the following: nephrosclerosis, renal fibrosis, renal cysts, amyloidosis.

5. **Splenomegaly**

Splenomegaly stated by the pathologist.

6. **Other pathology**

At least one of the following: cancer or systemic infection (i.e. miliary tuberculosis or encephalitis/sepsis).

The groups “Splenomegaly” and “Other pathology” are not included in the regression analyses (Table 3).

Several organ system diseases: one or several organ system diseases based on the previous six groups (minimum zero–maximum 6).

Characteristics and causes of death of all 200 patients who died during OAT in Norway in 2014–2015 stratified by autopsy

	All patients who died during OAT n = 200 *n* (%)	Subjected to an autopsy n = 125 *n* (%)	No autopsy n = 75 *n* (%)
Age and sex			
Age, mean ± SD	48.9 ± 8.4	48.0 ± 8.7	50.3 ± 7.9
Men	147 (74)	94 (75)	53 (71)
Treatment			
Total duration of OAT in years, mean ± SD, n = 188	8.2 ± 4.4	8.0 ± 4.2	8.7 ± 4.8
OAT medication,* n = 199			
Methadone	109 (55)	65 (52)	44 (59)
Buprenorphine	82 (41)	58 (47)	24 (32)
Other OAT medication[a]	8 (4)	1 (1)	7 (9)
Buprenorphine daily dose, median (min–max)	16 mg (1–52 mg)	16 mg (1–28 mg)	16 mg (4–52 mg)
Methadone daily dose, median (min–max)	90 mg (15–200 mg)	90 mg (15–200 mg)	90 (15–150 mg)
Cause of death**			
Somatic causes of death	90 (45)	35 (28)	55 (73)
Cancer, excl. liver cancer	*26*	*4*	*22*
Cardiovascular disease	*20*	*14*	*6*
Pulmonary disease	*18*	*8*	*10*
Liver disease, incl. liver cancer	*14*	*4*	*10*
Other somatic causes of death	*12*	*5*	*7*
Drug-induced death[b]	84 (42)	71 (57)	13 (17)
Violent death	23 (12)	18 (14)	5 (7)
Other/unknown cause of death	3 (2)	1 (1)	2 (3)
Place of death**			
Home	85 (43)	67 (54)	18 (24)
Hospital/nursing home	75 (38)	26 (21)	49 (65)
Other/outdoor	22 (11)	20 (16)	2 (3)
Not reported	18 (9)	12 (10)	6 (8)

*$P < 0.05$. **$P < 0.001$. Valid per cent is presented.

a) Morphine prescribed as OAT medication.

b) Drug-induced deaths included unintentional overdose or overdose by unknown intent, intentional overdose and substance use disorders.

Appendix 3

Conversion factors

Conversion factors for morphine- and diazepam-equivalent blood concentrations

Compound	Conversion factor
Morphine equivalents	
Morphine	1.0
Methadone	0.375
Buprenorphine[a]	37.5
Tramadol[a]	0.2
Diazepam equivalents	
Diazepam	1.0
Desmethyldiazepam	0.5
Alprazolam	20.0
7-Aminoclonazepam (7-AK)	48.0
Nitrazepam	3.3
Oxazepam	0.33
Zolpidem	2.0
Zopiclone	6.7

(a) Conversion factors for buprenorphine and tramadol are from Nielsen et al., 2016. The other conversion factors are from Strand et al., 2017.
To convert concentrations from SI units: µmol/L x conversion factor x molecular weight for morphine or diazepam = morphine- or diazepam equivalent concentration in ng/ML.
Example conversion alprazolam to diazepam-equivalent concentration:
Alprazolam 0.16 µmol/L x 20 (conversion factor) x 284.7 g/mol (molecular weight diazepam) = 911 ng/mL.