Potentially addictive substances among patients in opioid agonist therapy

- dispensations, use, and fatigue -

Jørn Henrik Vold

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Abstract in English

Background

The current opioid epidemic is a major cause of suffering and overdose deaths globally. It can interact with patients' general well-being and causes fatigue. Opioid agonist therapy (OAT) is a well-documented effective treatment for patients with severe opioid dependence. It protects against opioid overdose deaths and harms from injecting opioids. Over the past decade, reports from several countries indicate a high prevalence of other potentially addictive substances, involving benzodiazepines, z-hypnotics, gabapentinoids, centrally acting stimulants, and opioids, used alongside dispensed OAT opioids. Although potentially addictive substances may increase the risk of fatal and non-fatal overdoses, they can also be essential in treating underlying mental and physical disorders. No studies have evaluated the extent of all potentially addictive substances for the OAT population in Norway and Sweden and how they affect patients' self-reported feeling of fatigue.

Methods

This thesis consists of four papers. Papers I-II evaluated the dispensation rates and dispensed doses of benzodiazepines or z-hypnotics, gabapentinoids, and medications used for attention deficit hyperactivity disorder (ADHD) for 10,371 OAT patients in Norway in 2013-2017 using the Norwegian Prescription Database (NorPD). Paper III compared dispensation rates and dispensed doses of benzodiazepines, z-hypnotics, gabapentinoids, centrally acting substances, strong non-OAT opioids, weak non-OAT opioids among 7176 Norwegian OAT patients and 3591 Swedish OAT patients using data from the NorPD and the Swedish Prescribed Drug Register (SPDR) from 2015 to 2017. The aim of paper IV was three-folded; 1) investigating the extent of some non-dispensed potentially addictive substances (benzodiazepines/z-hypnotics, stimulant substances (amphetamines and cocaine), and opioids), cannabis, and alcohol, 2) measuring fatigue using the nine-item Fatigue Severity Scale (FSS-9), and 3) evaluating how the non-dispensed potentially addictive substances, cannabis, and alcohol were associated with fatigue among substance use disorder (SUD) patients in Bergen and Stavanger, Norway. We defined frequent use of a non-dispensed substance, cannabis, or alcohol as those using a substance at least weekly during the past 12 months. Patients who did not use substances/cannabis/alcohol or use them less than weekly during the past 12 months were categorized as having 'no frequent use' of these substances. To reduce confounding between substance use and fatigue, we adjusted for various sociodemographic and clinical factors. We included 954 FSS-9 measurements from 654 SUD patients, involving 82 % OAT patients, using the INTRO-HCV cohort data in 2016-2020.

Results

In papers I-III, 59 % of the Norwegian OAT patients and 55 % of the Swedish OAT patients were dispensed potentially addictive substances in 2017. In Norway, 46 % of the OAT patients were dispensed a benzodiazepine, 14 % a z-hypnotic, 12 % a weak non-OAT opioid, 10 % a gabapentinoid, 6 % a strong non-OAT opioid, and 4 % a centrally acting stimulant. Among the Swedish OAT population, 26 % were dispensed a z-hypnotic, 19 % a gabapentinoid, 18 % a centrally acting stimulant, 15 % a benzodiazepine, 10 % a strong non-OAT opioid, and 5 % a weak non-OAT opioid. Besides centrally acting stimulants, the mean daily dosages of the dispensed substances were within recommendations. The mean daily dosages of four out of five substances slightly exceeded the recommendations for centrally acting stimulants. Substantial similar results were seen for the period 2013-2016. In addition, being dispensed one benzodiazepine, z-hypnotic, gabapentinoid, non-OAT opioid, or centrally

acting stimulant increased the odds of being dispensed several potentially addictive substances.

The use of non-dispensed potentially addictive substances, cannabis, and alcohol for SUD patients, mainly OAT patients, in Bergen and Stavanger was substantial. Fifty-two percents were frequent users of cannabis, 39 % benzodiazepines or z-hypnotics, 29 % stimulant substances, 26 % alcohol, and 16 % opioids.

Sixty-seven percent of patients exceeded the threshold of severe fatigue (above 36 points). The mean FSS-9 sum score was 43 (standard deviation: 16) on a scale ranging from nine (no fatigue) to 63 points (worst fatigue). A considerable intra-individual variation in fatigue level from first to second fatigue measurement was found. Frequent use of benzodiazepines (adjusted mean difference of FSS-9 sum score: 5.7, 95 % CI: 3.0;8.4) or stimulants (-5.0, -8.0;-2.9) were associated with changes in the FSS-9 sum score compared with less frequent or no use of these substances. Furthermore, females had more fatigue than males (4.1, 1.3;7.0), and having debt difficulties was associated with more fatigue than not having debt difficulties (2.9, 0.4;5.3). In addition, frequent use of benzodiazepines compared with less frequent or no use of these substances over time (-4.4, -8.2;-0.7), and liver fibrosis or cirrhosis compared with healthy liver over time (-5.5, -9.9;-1.0) were associated with slightly less fatigue per year from the first fatigue measurement.

Conclusion
There was extensive use of different dispensed and non-dispensed potentially addictive substances among OAT patients in Norway and Sweden. In addition, substantial fatigue symptoms were widespread. Considering the high prevalence of polysubstance use in the population, it has been paid relatively little attention to OAT research and national guidelines. Focusing on how polysubstance use can be handled in OAT and its impact on health outcomes is of particular interest in further research.

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Sammendrag på norsk (abstract in Norwegian)

Bakgrunn
Den nåværende opioid epidemien er en vesentlig årsak til lidelse og overdosedødsfall globalt. Det kan påvirke pasienters generelle velvære og forårsake utmattelse (fatigue). Legemiddelassistert rehabilitering (LAR) er en veldokumentert behandlingsmetode for pasienter med alvorlig opioidavhengighet. Den beskytter mot opioidrelaterte overdosedødsfall og skader relatert til injiserende sprøytebruk. Over de siste tiårene har det imidlertid kommet reporter fra flere land som tyder på en høy forekomst av andre potensielt vanedannende stoffer som benzodiazepiner, z-hypnotika, gabapentinoider, sentralstimulerende legemidler og opioider som brukes sammen med de utleverte LAR-opioidene. Selv om de vanedannende legemidlene kan øke risikoen for dødelige og ikke-dødelige overdoser, kan de også være en essensielt del av behandlingen for underliggende psykiske og fysiske sykdommer. Ingen studier har tidligere evaluert omfanget av alle disse potentielt vanedannende stoffene for LAR-populasjonen i Norge og Sverige, ei heller om slik bruk påvirker pasienters' selvrapporterte følelse av utmattelse.

Metode
Denne doktorgradsavhandlingen består av fire artikler. Artikkel I-II brukte Reseptregisteret i Norge til å evaluere forskrivningsraten og utskrevne doser av benzodiazepiner eller z-hypnotika, gabapentinoider og ADHD-medisiner for 10 371 LAR-pasienter i Norge for perioden 2013-2017. Artikkel III brukte Reseptregisteret og Läkemedelsregisteret i Sverige til å sammenligne forskrivningsrater og utskrevne doser av benzodiazepiner, z-hypnotika, gabapentinoider, sentralstimulerende legemidler, sterke ikke-LAR opioider, og svake ikke-LAR opioider blant 7176 norske LAR-pasienter og 3591 svenske LAR-pasienter fra 2015 til 2017. Artikkel IV hadde tre formål: 1) å utforske omfanget av noen ikke-forskrevne potensielt vanedannende legemidler/rusmidler (benzodiazepiner/z-hypnotika, sentralstimulerende rusmidler (amfetaminer og kokain) og opioider), cannabis og alkohol, 2) å måle utmattelse ved å bruke Fatigue Severity Scale bestående av ni utmattelsesrelaterte påstander (FSS-9), og 3) å vurdere hvordan de ikke-forskrevne potensielt vanedannende legemidlene/rusmidlene, cannabis og alkohol påvirker utmattelse blant rusavhengige pasienter i Bergen og Stavanger, Norge. Vi definerte hyppig bruk av et ikke-forskrevet potentielt vanedannende legemiddel/rusmiddel, cannabis og alkohol som det å bruke et slikt legemiddel/rusmiddel mer enn ukentlig i løpet av de siste 12 månedene. Pasienter som ikke hadde brukt legemiddelet/rusmiddelet eller hadde brukt dem sjeldnere enn ukentlig i løpet av de siste 12 månedene ble kategorisert som det å «ikke ha et hyppig bruk» av legemiddelet/rusmiddelet. For å redusere effektforveksling mellom legemiddel/rusmiddel bruk og utmattelse, justerte vi for flere sosiodemografiske og kliniske faktorer. Vi inkluderte 954 FSS-9-målinger fra 654 rusavhengige pasienter i 2016-2020 fra INTRO-HCV kohorten, hvor 82 % var LAR-pasienter.

Resultater
I artikkel I-III fant vi at 59 % av norske LAR-pasienter og 55 % av svenske LAR-pasienter fikk foreskrevet et potensielt vanedannende legemiddel i 2017. I Norge fikk 46 % av LAR-pasientene foreskrevet et benzodiazepin, 14 % et z-hypnotikum, 12 % et svakt ikke-LAR opioid, 10 % et gabapentinoid, 6 % et sterkt ikke-LAR opioid og 4 % et sentralstimulerende legemiddel. Blant de svenske LAR-pasientene fikk 26 % foreskrevet et z-hypnotikum, 19 % et gabapentinoid, 18 % et sentralstimulerende legemiddel, 15 % et benzodiazepin, 10 % et sterkt ikke-LAR opioid og 5 % et svakt ikke-LAR opioid. Foruten de sentralstimulerende

legemidlene, var den gjennomsnittlige daglige dosen av de foreskrevne legemidlene innenfor anbefalingene. For fire av fem sentralstimulerende legemidler overskred imidlertid den gjennomsnittlige daglige dosen så vidt anbefalingene. Lignende funn var også funnet for perioden 2013-2016. I tillegg bemerket vi at det å få foreskrevet ett benzodiazepin, z-hypnotika, gabapentinoid, ikke-LAR opioid eller sentralstimulerende legemiddel økte sannsynlighet (odds) for å få foreskrevet flere potensielt vanedannende legemidler.

Bruken av ikke-foreskrevne potentielt vanedannende legemidler/rusmidler, cannabis og alkohol blant rusavhengige pasienter, hovedsakelig LAR-pasienter, i Bergen og Stavanger var betydelig. 52 % var hyppige brukere av cannabis, 39 % benzodiazepiner eller z-hypnotika, 29 % sentralstimulerende rusmidler, 26 % alkohol og 16 % opioider.

Sekstisyv prosent oversteg terskelen for alvorlig utmattelse (poengsum over 36). Den gjennomsnittlige FSS-9-sumskåren ble målt til 43 (standardavvik: 16) på en skala som går fra ni poeng (ingen utmattelse) til 63 poeng (verst tenkelig utmattelse). En betydelig intraindividuell variasjon i utmattelsesnivået fra den første til den andre FSS-9-målingen ble funnet. Hyppig bruk av benzodiazepiner (justert gjennomsnittlig forskjell i FSS-9-sumskår: 5,7, 95 % konfidensintervall: 3,0;8,4) eller sentralstimulerende rusmidler (-5,0, -8,0; -2,9) var assosiert med endringer i FSS-9 sumskåren sammenlignet med mindre hyppig eller ingen bruk av disse legemidlene/rusmidlene. Dessuten var kvinner mer utmattet enn menn (4,1, 1,3;7,0), og det å ha gjeldsproblemer var assosiert med mer utmattelse enn det å ikke ha gjeldsproblemer (2,9, 0,4;5,3). I tillegg var hyppig og vedvarende bruk av benzodiazepiner sammenlignet med mindre hyppig eller ingen bruk av disse stoffene og vedvarende leverfibrose eller skrumplever sammenlignet med det å ha en frisk lever assosiert med mindre utmattelse per år regnet fra den første utmattelsesmålingen.

Konklusjon
Det var et omfattende bruk av ulike foreskrevne og ikke-foreskrevne potensielt vanedannende legemidler/rusmidler blant LAR-pasienter i Norge og Sverige. I tillegg var det utbredt med betydelige utmattelsessymptomer. Tatt i betraktning den hyppige bruken av slike legemidler/rusmidler i denne populasjonen, har det fått lite oppmerksomhet i LAR forskning og i nasjonale retningslinjer. Å fokusere på hvordan bruk av flere rusmidler kan håndteres i LAR og hvordan det påvirker helseutfall vil være av særlig interesse i videre forskning.

Articles in the thesis

Vold JH, Skurtveit S, Aas C, Chalabianloo F, Kloster PS, Johansson KA, Fadnes LT: **Dispensations of benzodiazepines, z-hypnotics, and gabapentinoids to patients receiving opioid agonist therapy; a prospective cohort study in Norway from 2013 to 2017.** *BMC health services research 2020*, 20(1):352.
https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-020-05195-5

Vold JH, Aas C, Skurtveit S, Odsbu I, Chalabianloo F, Halmøy A, Johansson KA, Fadnes LT: **Dispensation of attention deficit hyperactivity disorder (ADHD) medications in patients receiving opioid agonist therapy; a national prospective cohort study in Norway from 2015 to 2017**. *BMC psychiatry 2020*, 20(1):119.
https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-020-02526-y

Vold JH, Aas C, Skurtveit S, Odsbu I, Chalabianloo F, Reutfors J, Halmøy A, Johansson KA, Fadnes LT**: Potentially addictive drugs dispensing to patients receiving opioid agonist therapy: a register-based prospective cohort study in Norway and Sweden from 2015 to 2017.** *BMJ Open 2020*, 10(8):e036860.
https://bmjopen.bmj.com/content/10/8/e036860.long

Vold JH, Gjestad R, Aas CF, Chalabianloo F, Skurtveit S, Løberg E-M, Johansson KA, Fadnes LT: **Impact of clinical and sociodemographic factors on fatigue among patients with substance use disorder: a cohort study from Norway for the period 2016-2020.** *Substance Abuse Treat Prev and Policy* 2020, 15(1):93.
https://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-020-00334-x

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This thesis is a part of the main INTRO-HCV study [1]. INTRO-HCV is a collaboration between Bergen Addiction Research (BAR), Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway, Department of Global Public Health and Primary Care, University of Bergen, Norway, Department of Addiction Medicine (Norwegian: Avdeling for rus- og avhengighetsbehandling), Stavanger University Hospital, Stavanger, Norway, Bergen Municipality, proLAR Nett, and additional researchers from the Norwegian Institute of Public Health, Oslo, Norway, University of Bristol, and Akershus University Hospital. For paper III, we also collaborated with the Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden.

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical
BAR	Bergen Addiction Research
CI	Confidence Interval
DDD	Defined Daily Dose
DSM	The Diagnostic and Statistical Manual of Mental Disorders
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU	European Union
FSS-9	Nine-item Fatigue Severity Scale
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ICPC-2	The International Classification of Primary Care, Version 2
NorPD	Norwegian Prescription Database
OAT	Opioid Agonist Therapy
OR	Odds Ratio
REC	Regional Committee for Medical and Health Research Ethics
SD	Standard Deviation
SPDR	Swedish Prescribed Drug Register
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
SUD	Substance Use Disorder
U.K.	United Kingdom
U.S.	United States of America
WHO	World Health Organization

Introduction

The global opioid crisis and its impact on overdose deaths

Substance use disorder (SUD) is a chronic disease affecting more than 35 million people worldwide [2]. In 2017, it was estimated that 585,000 people died, and more than 42 million years of "healthy" life were lost due to substance use [2]. While hepatitis C virus (HCV) infection is the most prevalent reason for deaths among people with SUDs, opioid dependence itself is the primary reason for the "healthy life" years are lost in the SUD population. During the last decades, deaths attributed to opioid use have been increasing and problematic, causing a global high public health burden and suffering from patients with SUDs [3]. Between 2013 and 2017, a 14-fold increase of non-medical use of the opioid tramadol was seized in Central, West and North African countries, while expanding use of fentanyl and its analogs have accelerated the opioid manufacture during the same period in the U.S. and Canada [2, 4, 5]. In Europe, heroin has dominated as the primary opioid of use among the illegal opioid market during the last decade [6].

Globally, opioid use is an important contributor to overdose deaths among patients with SUDs [2]. The sharp increase in global opioid use has led to more than 49,800 opioid overdose deaths in the U.S. in 2019, an increase of 7 % from the previous year and a two-fold increase in opioid-related deaths from 2013 to 2019 [7]. One out of three of these deaths involved prescribed opioids [5]. In Europe, including the 28 European Union (EU) member states plus Norway and Turkey, 9461 people lost their lives due to overdose deaths in 2017, representing a stable situation compared with the 9397 deaths reported in 2016 [6, 8]. Nearly 80 % of these deaths involved opioids, often in combination with other substances [8]. In European countries, it is estimated that 1.3 million people are high-risk users of opioids, defined as those injecting opioids, with 77 % of these residing in the five most populous EU countries (Germany, Spain, France, Italy, and the U.K.) [6]. In 2017, opioid use dominated among those entering specialized substance treatment, representing 35 % of all first-time entrants [8]. Effective treatment approaches mainly aimed at high-risk opioid users are therefore essential for a global reduction in overdose deaths among the SUD population.

Opioid agonist therapy as a treatment approach

Opioid agonist therapy (OAT) is a well-known and essential treatment approach for some patients with opioid dependence (Figure 1) [9, 10]. In observational studies mainly, the OAT is shown to reduce illicit opioid use [9, 10], all-cause and opioid-related mortality, [11, 12] and risk behavior [13], and improve mental health [14, 15]. The OAT is granted to patients with opioid dependence who meet the opiate *dependence syndrome* criteria defined by the International Classification of Diseases and Health problems, version 10 (ICD-10) (Text box 1) [16] or the criteria for *opioid use disorder* according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Text box 2) [17]. Other additional criteria are applied in some countries [18]. In contrast to the ICD-10, the DSM-5 subdivides drug use disorder into three categories: mild, moderate, or severe, where patients with moderate or severe opioid use disorder are intended for OAT. In the upcoming ICD-11 (Text box 3) [19], ICD-10's 'opioid dependence syndrome' will be replaced with *opioid dependence* with fewer criteria for dependence. However, how this will change the inclusion criteria for OAT remains unknown.

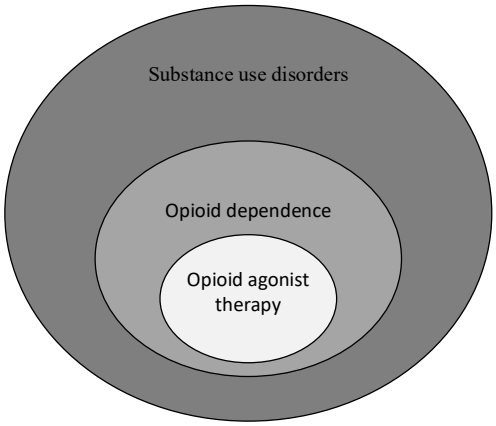

Figure 1: The figure displays the division of commonly used terms in Addiction Medicine and their relations to demand for care; "Substance use disorder", "Opioid dependence", and "Opioid agonist therapy".

Text box 1:

Dependence syndrome according to the International Classification of Diseases and Health problems, version 10

Dependence is usually made only if three or more of the following have been present together at some time during the previous year:

1) A strong desire or sense of compulsion to take the substance;
2) Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use;
3) A physiological withdrawal state when substance use has ceased or have been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4) Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users);
5) Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
6) Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

World Health Organization, 2021.

In Europe, nearly half of high-risk opioid users (approximately 662,000 opioid users) are estimated to have access to OAT, with considerable variations between countries from around 85 % in France down to less than 10 % in Romania [8, 20]. Lack of national guidelines and scarcity of health care resources are reported to restrict the OAT distribution [21]. In addition, excessive regulations on who can prescribe OAT medications to substance users and strict legal regulations around OAT prescribing limit access to the treatment approach in several countries [22].

Text box 2:

Opioid use disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

A problematic pattern of use leading to clinically significant impairment or distress is manifested by two or more of the following within a 12-month period:

1) Opioids are often taken in larger amounts or over a longer period than was intended.
2) A persistent desire or unsuccessful efforts to cut down or control opioid use.
3) A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4) Craving or a strong desire or urge to use opioids.
5) Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6) Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects.
7) Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8) Recurrent opioid use in situations in which it is physically hazardous.
9) Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the opioids.
10) Tolerance.
11) Withdrawal.

Mild: Two or three criteria. Moderate: four to five criteria. Severe: six or more criteria.

American Psychiatric Association, 2013.

Text box 3:

Opioid dependence according to the International Classification of Diseases and Health problems, version 11

Opioid dependence is a disorder of regulation of opioid use arising from repeated or continuous use of opioids. The characteristic feature is *a strong internal drive to use opioids*, which is manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences. These experiences are often accompanied by *a subjective sensation of urge or craving to use opioids*. Physiological features of dependence may also be present, including *tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms*.

The features of dependence are usually evident over a period of at least 12 months but the diagnosis may be made if opioid use is continuous (daily or almost daily) for at least 1 month.

World Health Organization, 2021.

Buprenorphine and methadone are the two most widely used opioids in OAT [22]. Both are long-acting opioids with a duration of approximately 24 hours [23-25]. Overall, methadone is the most commonly prescribed opioid in OAT among European countries, received by over 60 % of the OAT patients [22]. The remaining patients are prescribed buprenorphine-based medications, including buprenorphine-naloxone and depot-formulations of buprenorphine. Slow-releasing morphine, levomethadone, and heroin are more rarely prescribed by a calculated 2 % of the OAT population [22]. Methadone and buprenorphine are usually equal in suppressing illegal opioid use and treatment retention [10]. However, patients receiving methadone have a higher risk of overdose deaths than patients using buprenorphine as an OAT opioid, which are probably related to the methadone's pharmacological properties as a full opioid agonist [26]. Unlike buprenorphine, methadone, by its properties, contributes to a high risk of sedation and overdose if doses are increased and used concomitantly with other opioids. In contrast, buprenorphine is a partial opioid agonist with a partial displacement of other opioids, which usually may protect against opioid overdoses caused by other opioids [27]. Although OAT opioids may lead to overdose itself, they can also induce overdoses if

used in parallel with other competing sedative substances – such as benzodiazepines, z-hypnotics, and gabapentinoids [28-32].

Opioid agonist therapy in Norway and Sweden

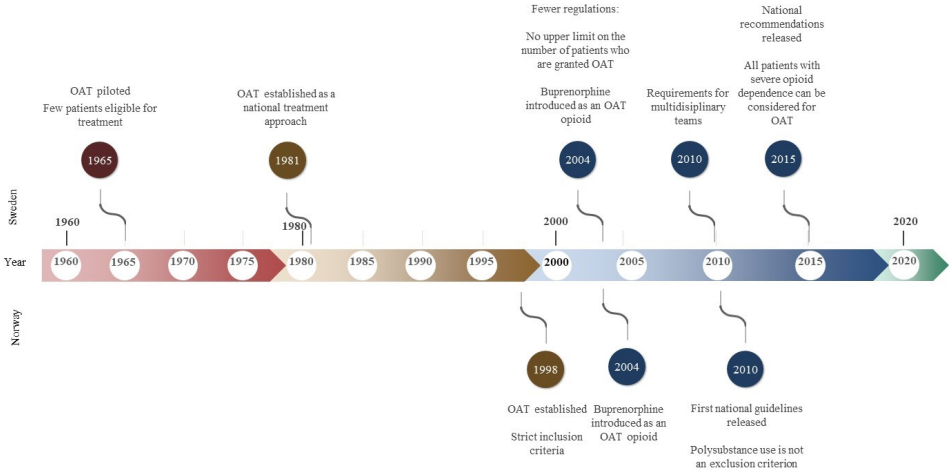

Figure 2: The timeline displays some essential milestones in OAT in Sweden and Norway. OAT: Opioid agonist therapy.

Sweden has treated patients with severe opioid dependence with methadone since the mid-1960s, initially as a pilot scheme for selected patients [33]. During the past four decades, receiving OAT has been made increasingly available. In 2010, patients were offered multidisciplinary teams consisting of professionals from the social services, health professionals in primary care, and consultants in psychiatry or addiction medicine to take care of the patients' rehabilitation. In 2015, when the current national recommendations for OAT were released, patients suffering from opioid dependence caused by other opioids than street heroin were granted OAT [34]. Compared with many other countries, the Swedish OAT is more strictly regulated, especially concerning the additional use of non-dispensed potential addictive substances [35]. Patients with polysubstance use undergoing OAT can be referred to other opioid treatment programs, while those with polysubstance use seeking OAT can be rejected. According to the Swedish Drug Report 2019, 4468 patients received OAT in Sweden in 2017 [35].

Norway implemented OAT in 1998, initially for a few hundred patients with a long-term severe opioid dependence [36]. In 2018, the number of OAT patients had increased to nearly 11,000 patients nationwide. Of those, approximately 700 patients enter or reenter and leave OAT yearly, substantially unchanged for the last decade. In 2010, the Norwegian OAT's first and current national guidelines were released to ensure uniform medical practice for OAT across the country [37]. Following these guidelines, polysubstance use was no longer an absolute criterion for terminating OAT, giving more patients with opioid dependence access to OAT. The Norwegian OAT is organized differently across the country ranging from nurses and general practitioners in primary care to specialized outpatient clinics led by consultants in

Addiction Medicine. However, granting OAT is usually independently assessed by specialized health care [37].

Defining potentially addictive substances and their relationship to OAT opioids

By an additional use of potentially addictive substances in OAT, we mean classes of substances categorized as benzodiazepines, z-hypnotics, gabapentinoids, opioids, and centrally acting stimulants used alongside the OAT opioids.

Benzodiazepines are a collective group name of potentially addictive substances with sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant effects used in a short-term period [38]. They are among the most distributed substances on the illegal market and are chronically used among several SUD patients [31]. Long-term use of benzodiazepines is controversial because of concern about physical and mental dependence, rebound effects, and development of tolerance. Combination therapy, including benzodiazepines and OAT opioids, enhances sedative effects, putting patients at particular risk of overdose and overdose death [28, 29]. In addition, benzodiazepines usually cause long-term withdrawals when abruptly reduced and ceased [39].

Z-hypnotics are similar to benzodiazepine and are used to sleep therapy [40]. In long-term use, physical and mental dependences, rebound withdrawal effects, and tolerance is observed. The tolerance is assumed to be somehow slower to develop than with benzodiazepines in the general population [41], while withdrawals resemble those seen during benzodiazepine withdrawal. Z-hypnotics are sedative agents causing an enhancing effect to OAT opioids, and co-use is controversial [28, 29, 42].

Gabapentinoids, including pregabalin and gabapentin, also having similarities to benzodiazepines, are medically indicated for epilepsy, neuropathy, and anxiety disorders in Europe [43, 44]. During the last decade, both have been reported in observational studies and case reports to cause physical withdrawal, tolerance, and rebound effects [32, 45-47]. The synergistic effects of co-using opioids and gabapentinoids are substantially highlighted, with a risk of overdoses. Pregabalin is under surveillance for abuse potential by the European Medicines Agency for concern about dependence [48]. From June 2018 (Norway) and July 2018 (Sweden), pregabalin was classified as a substance with a potential dependence by the Norwegian Medicine Agencies and the Swedish Medical Products Agency leading to restrictions in dispensing [49, 50].

Opioids are opioid analgesic substances that have effects similar to those of morphine. They are primarily medically indicated for pain relief. For patients in OAT with severe opioid dependence, the additional use of opioids may indicate suboptimal OAT opioid dose and physical accident requiring pain relief [51, 52]. Long-term use can cause tolerance, physical dependence, and withdrawals when abruptly reduced in doses and ceased [53]. Otherwise, euphoria, sedation, and respiratory depression are potential side effects when overdosed [54].

Centrally acting stimulants include methylphenidate, lisdexamphetamine, dexamphetamine, and racemic amphetamine. They are primarily medically indicated substances for attention deficit hyperactivity disorders (ADHD) or hyperkinetic disorders [55]. Higher doses produce euphoria, vigor, decreased appetite, and alertness [56, 57]. In contrast, therapeutic doses may contribute to the successful suppression of ADHD symptoms [55]. Among OAT patients with comorbid ADHD, co-use of centrally acting stimulants and OAT opioids is usually

recommended if taken as prescribed [58]. In Norway, prescribing OAT opioids and centrally acting stimulants in OAT is regulated by national guidelines that require abstinence of illegal substances from at least three months before prescribing centrally acting stimulants [59]. Otherwise, amphetamines and cocaine are the most widely consumed centrally acting stimulant substances for illegal use [8], with some geographic differences. While cocaine dominates in European countries, amphetamines (including methamphetamine) are the most consumed illegal stimulants in the Northern European countries, the Czech Republic, and Slovakia [8, 22, 60, 61].

Dispensing potentially addictive substances to OAT patients

When investigating potentially addictive substances among OAT patients, it is important to keep in mind the distinction between dispensed and non-dispensed potentially addictive substances. While the non-dispensed use addresses illegal or non-medical use, the dispensed potentially addictive substances are dispensed for a medical purpose – such as treating the short-term sleeping disorder with z-hypnotics and severe acute somatic pain with opioid analgesics. Being dispensed potentially addictive substances are usually accepted as an additional treatment in OAT. A survey of comorbidities in the OAT population in general hospitals in Europe demonstrates a high but varying prevalence of several mental disorders [62]. Depression ranges from 34 % to 60 %, anxiety disorders from 3 % to 41 %, psychotic disorders from 20 to 39 %, ADHD from 5 % to 30 %, and personality disorder 20 %. These diseases may contribute to dispensing potentially addictive substances as a first-hand substance or an adjuvant substance to other medical therapy. For example, centrally acting stimulants are usually used as agents for curbing ADHD symptoms, and benzodiazepines are medically indicated for short-term therapy for insomnia and anxiety. In addition, benzodiazepines and gabapentinoids may be essential for patients with substance dependences undergoing detoxifications, while opioids may be needed for acute pain. Otherwise, in some cases, potentially addictive substances can be dispensed on off-label indications to recover mental or physical diseases, protect against injecting behavior, diminish contact with dealers, reduce criminality, and prevent withdrawals, so that non-dispensed substance use is assumingly less likely [63]. Despite this, combining potentially addictive substances with OAT opioids can cause fatal or non-fatal overdoses if taken outside the therapeutic aims, used as a currency in illegal markets, and used alongside non-dispensed potentially addictive substances. Several observational studies investigating dispensed potentially addictive substances for OAT patients have found evidence for an increased risk of all-cause deaths when being co-dispensed OAT opioids and potentially addictive substances compared with being dispensed OAT opioids in monotherapy [28, 29, 52]. However, these studies can be confounded for causality because they did not consider whether patients who were co-dispensed substances had underlying comorbidities and risk behavior, increasing the risk of death.

The use of non-dispensed potentially addictive substances among OAT patients

The use of non-dispensed potentially addictive substances is usually related to benzodiazepines, including z-hypnotics, stimulant substances (amphetamine, methamphetamine, and cocaine), and opioids [8]. The use of these substances for OAT patients is controversial, leading to varying regulations between and within countries in handling [22]. In some countries, patients with non-dispensed potentially addictive substance use, involving opioids and other substances, are excluded from OAT [22, 64], while others allow co-use based on an individual assessment of justifiability [22, 31, 37]. During the past

years, non-dispensed potentially addictive substances have been commonly [22, 31, 65-67], representing now 60 % of patients seeking medical treatment for opioid dependence in some countries [22]. In 2016, based on those entering specialized opioid treatment programs, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated that 12 % misused benzodiazepines, 40 % amphetamines and cocaine, and 4 % 'other substances' [31]. "Misuse" was by the review defined as use without a prescription from a medical practitioner or, if prescribed, when used outside accepted medical practice or guidelines. However, the data regarding non-dispensed potentially addictive substance use among patients with opioid dependence are not fully investigated, and it lacks information of the extent of use from several countries worldwide.

The impact of non-dispensed potentially addictive substance use on fatigue among SUD patients

Fatigue is a subjective health complaint defined as a persistent and overwhelming feeling of exhaustion and lack of energy [68]. Its impact on individuals can vary considerably from an impeccable symptom to a symptom and chronic syndrome affecting job, daily activities, and social life with increased risk of depression and suicide [69-74]. Fatigue is also a common symptom in the general population [74-78], while severe fatigue, impairing daily functioning, is more often seen among patients with chronic diseases – such as those with HCV infection [79-81], Parkinson's disease [82, 83], multiple sclerosis [84-86], or stroke [87-89]. Fatigue has, however, never been investigated thoroughly for SUD patients, despite several potential risk factors concerning; unstable housing situation [90], financial risks [91], unemployment [92, 93], extensive use of substances, and underlying mental disorders with committing suicide attempts [69-74, 94-96]. Substances leading to intoxications and withdrawals may cause mortality [97, 98] and cognitive impairment in several domains – such as deficits in cognitive flexibility [99-101], working memory [102], attention, and impulse control [103]. This might potentially impact fatigue. Surveying the extent of fatigue and how the chaotic life situation patterns, including use of non-dispensed potentially addictive substances, is associated with fatigue will be of particular interest to improve the knowledge of the SUD patients and how the non-dispensed potentially addictive substance use impacts them.

How study the use of dispensed and non-dispensed potentially addictive substances among OAT patients?

There are many ways to investigate the dispensed use of potentially addictive substances among patients in OAT. One way can be to collecting national data of all patients on OAT, which often are laborious and expensive. Another way can be to use national register data. Over the last two-three decades, the Scandinavian countries have developed nationwide prescription registers with information of practically all dispensed medicines delivered from national pharmacies [104, 105]. These data are suitable to identify OAT patients and all their dispensed medicines.

Furthermore, little is known about the non-dispensed substance use and fatigue for SUD patients. However, in Norway, the annual health assessment on all the Norwegian OAT patients gives some information on non-dispensed benzodiazepine and amphetamines used the last four weeks before the assessment [36]. However, detailed information on substance use and its usage pattern lacks. Therefore, creating a new data cohort surveying more detailed information on non-dispensed potentially addictive substances and fatigue is required for SUD patients.

Rationale for the studies

As shown in the introduction, little is known about the extent and doses of dispensed potentially addictive substances in the OAT populations. Differences in OAT regulations may contribute to variations in dispensing substances between and within countries. In Norway and Sweden, the OAT is differently regulated regarding potentially addictive substances. While Sweden referred OAT patients with repeated non-dispensed potentially addictive substance use to other treatment approaches, this repeated use is not an exclusion criterion for receiving OAT in Norway. However, how these inter-country differences impact dispensations of dispensed potentially addictive substances are uncertain. Before these studies, we lacked knowledge of dispensed potentially addictive substances in OAT in Norway and Sweden. In addition, little is known about the differences and similarities in dispensing potentially addictive substances between the countries' OAT programs. Considering this, we have presented data on dispensation rates and dispensed doses of the potentially addictive substances in Norway in papers I and II. In paper III, we have compared dispensation rates and dispensed doses of these substances between Norway and Sweden.

Furthermore, little attention has been paid to the use of non-dispensed potentially addictive substances. In European countries, the prevalence varies considerably, and we lack knowledge of the extent of these substances for the OAT populations. Creating a regional OAT cohort (INTRO-HCV cohort) in Bergen and Stavanger, Norway, we collected information on non-dispensed potentially addictive substance use among almost all SUD patients, mainly OAT patients, in the two cities. Using these data, we have estimated the prevalence of non-dispensed potentially addictive substances in the population from 2016 to 2020 in paper IV.

Finally, fatigue is a symptom that is associated with patients' well-being. As far as we know, no previous studies have investigated fatigue and its relationship to long-term use of non-dispensed potentially addictive substances in a SUD population. Nevertheless, one can assume that the co-use of these substances and other sociodemographic and clinical factors – such as housing situation, debt difficulties, HCV infection, and educational level, may be associated with the level of fatigue in a SUD population. Using the INTRO-HCV cohort, we have investigated the extent and changes in fatigue and how the non-dispensed potentially addictive substance use is associated with fatigue, adjusted for the various clinical and sociodemographic factors.

Aims of the thesis

This thesis's overall objectives were to assess the use of dispensed and non-dispensed potentially addictive substances and investigate the associations between non-dispensed potentially addictive substances and fatigue among OAT patients.

1) To describe the dispensation rates and dosages of dispensed potentially addictive substances among OAT patients in Norway (papers I and II)

2) To describe differences in the dispensation rates and dosages of dispensed potentially addictive substances among OAT patients in Norway and Sweden (paper III)

3) To investigate the extent of non-dispensed potentially addictive substance use among SUD patients, mainly OAT patients, in Bergen and Stavanger, Norway (paper IV)

4) To examine the extent of fatigue symptoms and investigate the associations between non-dispensed potentially addictive substances and fatigue adjusted for various sociodemographic and clinical factors among SUD patients, mainly OAT patients, in Bergen and Stavanger, Norway (paper IV)

Material and methods

Data sources

The data in this thesis are from three different data sources; two nationwide registers from two different countries (Norway: The Norwegian Prescription Database (NorPD), Sweden: The Swedish Prescribed Drug Register (SPDR)) [104, 105], and cohort data from the INTRO-HCV study [1].

The Norwegian Prescription Database

Since January 1, 2004, the NorPD has collected information about all dispensed medicines from Norwegian pharmacies [104, 106]. The pharmacies are obliged by law to register all dispensed substance information electronically and send the information to NorPD monthly. Substances administrated at hospitals, nursing homes, and outpatient clinics are not registered in the NorPD. The NorPD receives information individually identified by an 11-digit person identifier, which are encrypted by a unique identification key number before data reach the researchers. The NorPD contains all information about dispensed substances, including the Anatomical Therapeutic Chemical (ATC) classification system codes, defined daily doses (DDD), date of dispensing, and reimbursement codes. In addition, information on patients (gender, the month and year of birth, and the month and year of death) and prescribers (encrypted prescriber identifier, gender, the year of birth, profession, and specialty) are reported. According to the current World Health Organization (WHO)'s standards [107, 108], the ATC codes and DDD are used. The NorPD is administrated and regulated by the Norwegian Institute of Public Health. There is estimated that about 90 % of the OAT patients are identified using the NorPD [109].

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register has collected information about all dispensed substances from the Swedish pharmacies since July 1, 2005 [105]. Like the NorPD, substances dispensed at hospitals, nursing homes, and outpatient clinics are not captured using this data source. All information delivered from SPDR to researchers are encrypted using patient identification key numbers. The SPDR contains information of dispensed substances using the ATC codes and DDD according to the current WHO's standards [107, 108], information of patients (gender, the current age at the dispensation date), prescribers (profession and specialty), prescribing date, and dispensing date. The Swedish National Board of Health and Welfare has estimated that almost 60 % of the OAT patients are captured using the SPDR [33, 34]. Compared with the NorPD's identification rate of 90 %, this relatively lower patient identification rate is assumingly due to a higher rate of dispensed OAT opioids from outpatient clinics in primary care or specialized care being not linked to the register.

Anatomical Therapeutic Chemical classification system

The Anatomical Therapeutic Chemical classification system is a global classification system governed by the WHO Collaborating Centre for Drug Statistics Methodology [107]. The ATC system classifies the most therapeutic substances for human use worldwide if "*being substances with market authorization in at least one country (…)*" (the relevant part of the

definition is included). The ATC classification system operates a hieratic structure of five levels for substance classification where the substances are given unique codes:

1st level: Anatomical main group (N = the nervous System)

2nd level: Therapeutic subgroup (07 = other nervous system drugs)

3rd level: Pharmacological subgroup (B = drugs used in addictive disorders)

4th level: Chemical subgroup (C = drugs used in opioid dependence)

5th level: Chemical substance (02 = methadone)

Figure 3: The figure displays the hieratic structure of the ATC classification system exemplified using ATC code of methadone (ATC code: N07BC02). ATC: Anatomical Therapeutic Chemical.

The ATC codes represent a crucial role in identifying patients who have received OAT opioids and their dispensations of potentially addictive substances in the NorPD and SPDR. In paper I-III using the ATC system, we defined dispensed substances/substance groups as follow:

Benzodiazepines: Benzodiazepines are the substances categorized under the ATC code groups "N05BA" ("benzodiazepine derivatives"), "N05CD" ("Benzodiazepine derivatives"), and "N03AE01" (clonazepam). Of those, the following have marked authorizations in Norway or Sweden: alprazolam (ATC code: N05BA12), clonazepam (N03AE01), diazepam (N05BA01), flunitrazepam (N05CD03), midazolam (N05CD08), nitrazepam (N05CD02), lorazepam (N05BA06) (Sweden only), and oxazepam (N05BA04).

Z-hypnotics: Zopiclone (N05CF01) and zolpidem (N05CF02).

Gabapentinoids: Gabapentin (N03AX12) and pregabalin (N03AX16).

OAT opioids: Buprenorphine (N07BC01), methadone (N07BC02), levomethadone (N07BC05), and buprenorphine-naloxone (N07BC51). These substances are mainly dispensed in Norway and Sweden. Other countries may dispensed other OAT opioids.

Non-OAT opioids: All opioid categorize under the 3th ATC code level "N02A", including all dispensed opioid analgesics and opioid analgesics combined with non-opioid analgesics or antispasmodics (e.g.: codeine plus paracetamol). The most commonly dispensed non-OAT opioids are: morphine (N02AA01), oxycodone (N02AA05), ketobemidone (N02AB01), fentanyl (N02AB03), and buprenorphine (N02AE01).

Non-OAT opioids (paper I): "Weak non-OAT opioids" are defined as codeine (N02AJ06), tramadol (N02AJ13, N02AX02) and tapentadol (N02AX06). Other opioids (N02A) are

classified as “strong non-OAT opioids”. The term “weak” refers to opioids with lower equipotency relative to other opioids.

Non-OAT opioids (paper III): “Weak non-OAT opioids” are defined as codeine (N02AJ06, N02AJ08, N02AJ09), tramadol (N02AJ13, N02AJ14, N02AX02) and tapentadol (N02AX06). Other opioids (N02A) are classified as “strong non-OAT opioids”.

Centrally acting stimulants: Racemic amphetamine (N06BA01), dexamphetamine (N06BA02), methylphenidate (N06BA04), and lisdexamphetamine (N06BA12).

ADHD medications: All substances defined as “Centrally acting stimulants” plus atomoxetine (N06BA09).

Defined daily doses

ATC code	**Substance name**	**1 DDD is equal to (in mg):**
	Benzodiazepines	
N03AE01	Clonazepam	8
N05BA01	Diazepam	10
N05BA04	Oxazepam	50
N05BA06	Lorazepam	2.5
N05BA12	Alprazolam	1
N05CD02	Nitrazepam	5
N05CD03	Flunitrazepam	1
N05CD08	Midazolam	15
	Z-hypnotics	
N05CF01	Zopiclone	7.5
N05CF02	Zolpidem	10
	Gabapentinoids	
N03AX12	Gabapentin	300
N03AX16	Pregabalin	1800
	ADHD medications	
N06BA01	Racemic amphetamine	15
N06BA02	Dexamphetamine	15
N06BA04	Methylphenidate	30
N06BA09	Atomoxetine	80
N06BA12	Lisdexamphetamine	30
	OAT opioids	
N07BC01	Buprenorphine	8
N07BC02	Methadone	25
N07BC05	Levomethadone	15
N07BC51	Buprenorphine, combinations	8

Table 1: The table displays the relationship between Defined Daily Doses (DDD) and milligrams among potentially addictive substances, according to the WHOs standards per October 2018. ATC: Anatomical Therapeutical Chemical Classification; OAT: Opioid Agonist Therapy.

The defined daily dose is a measurement of the quantity of the dispensed substances. The DDDs are mainly used in research to quantify dispensed substances' consumption and study differences in substance dispensations. The basic definition is "*the assumed average maintenance dose per day for a drug used for its main indication in adults* [110]." Due to a substance having various medical indications, the DDD does not necessarily reflect the recommended dose of a medical indication. The NorPD and SPDR quantify all dispensed substances using the DDDs. In paper I-III, we recalculated all dispensed DDD per substance into milligrams using the table above (Table 1), according to the WHO's standards per October 2018 [110].

INTRO-HCV cohort data

The INTRO-HCV cohort data are data collected from SUD patients in Bergen and Stavanger, Norway. Patients are recruited from the OAT outpatient clinics in the two cities and two municipality clinics in Bergen. The data collection has been ongoing since May 2016, and up to June 2020, approximately 750 patients with SUDs are included. Of those, 82 % receive OAT at baseline. The clinics work in multidisciplinary teams consisting of physicians specialized in Addiction Medicine, psychologists, nurses, and social workers. The patients included are offered an annual health assessment, including a survey of sociodemographic and clinical conditions, self-reported substance use, self-reported physical and mental health, clinical examination, elastography, and complete blood counts. If any health issues are revealed during the health assessment, patients are medically and psychosocially followed up by the multidisciplinary teams. The teams work closely with physicians specialized in family medicine or other clinical consultants in the hospital. The data are collected using electronic data collection software Checkware® under research nurses' supervision.

Study design and specific aims of the papers

Paper I is a prospective observational study that overall investigated dispensations of benzodiazepines, z-hypnotics, and gabapentinoids among the Norwegian patients who were dispensed OAT opioids per calendar year for the study period 2013-2017. In addition, we examined how discontinuing OAT opioids were associated with changes in the dosages of dispensed benzodiazepines or z-hypnotics, and gabapentinoids.

Paper II is a prospective observational study that examined the dispensations of ADHD medications among the Norwegian patients who were dispensed an OAT opioid per calendar year during the study period 2015-2017. In addition, we examined whether the dosage of an ADHD medication was changed substantially per calendar year among those who received both an OAT opioid and ADHD medication yearly throughout the study period. Furthermore, we evaluated how this continuity in dispensed OAT opioids and ADHD medication throughout the study period were associated with being dispensed a benzodiazepine, z-hypnotic, opioid (other than OAT opioids), and gabapentinoid in 2017.

Paper III is a prospective observational study that investigated dispensations of benzodiazepines, z-hypnotics, gabapentinoids, weak non-OAT opioids, strong non-OAT opioids, and centrally acting stimulants among patients who were dispensed OAT opioid per calendar year in the period 2015-2017 in Sweden and Norway.

Paper IV is a prospective cohort study that studied the use of non-dispensed potentially addictive substances (benzodiazepines or z-hypnotics, stimulant substances (amphetamines and cocaine), and opioids), alcohol, and cannabis among SUD patients, mainly OAT patients, who were measured fatigue. Furthermore, we investigated the extent of self-reported fatigue in the population, and how the use of non-dispensed substances, alcohol, and cannabis influenced fatigue, adjusted for sociodemographic and clinical factors in 2016–2020 in Bergen and Stavanger, Norway.

Study samples according to the papers

Table 2	**Paper 1**	**Paper 2**	**Paper 3**	**Paper 4**
Data source	NorPD	NorPD	NorPD and SPDR	INTRO-HCV cohort
Country/region	Norway	Norway	Norway and Sweden	Bergen and Stavanger, Norway
% of coverage (estimated)	90 %	90 %	90 % Norway 60 % Sweden	70 %
Inclusion criteria	Being dispensed an OAT opioid from the Norwegian pharmacies Above 18 years of age during the calendar year included		Being dispensed mean ≥ 1 DDD of OAT opioids from Norwegian or Swedish pharmacies per calendar year Above 18 years of age and below 75 years of age during the calendar year included	Receiving OAT in the outpatient clinics in Bergen or Stavanger, Norway, or receiving health care for substance use in two municipality clinics in Bergen, Norway Conducted at least one health assessments, including a fatigue measurement
Study size	10,371	9235	10,767 (Norway: 7176, Sweden: 3591)	654
Study period	2013-2017	2015-2017	2015-2017	2016-2020

Table 2: The table displays the data sources, country/region, estimated coverage, inclusion criteria, study size, and study period for papers I-IV.

Paper I. All patients above 18 years of age who were dispensed an OAT opioid in the study period from 2013 to 2017 were included. Furthermore, the OAT opioid methadone has two medical indications in Norway: OAT and pain. While the methadone tablet formulation is approved for pain only, the mixture formulation has only the OAT as the medical indication

[37]. Considering this, we excluded the cases who not had any dispensations of methadone mixture from January 1, 2004, to December 31, 2017. In addition, we used reimbursement codes for palliative care (ICD-10: -90; the International Classification of Primary Care, Version 2 (ICPC-2): -90) to exclude patients who were dispensed methadone tablets on these codes during the study period. Unlike methadone, the OAT opioids buprenorphine, buprenorphine-naloxone, and levomethadone dispensations have the OAT as their only medical indication. These dispensations were fully included in our analysis.

In addition, we defined patients who discontinued OAT as all those who were dispensed the last dispensation of an OAT opioid in the inclusion period from January 1, 2017, to September 30, 2017, and then no dispensation until the end of the collected NorPD data on March 31, 2018.

Paper II. The inclusion criteria were similar to paper I, except the study period, which was changed to 2015-2017 due to minimal changes in dispensation rates and doses from one year to another observed in paper I. Moreover, patients who were co-dispensed at least one ADHD medication and OAT opioid yearly in the study period 2015-2017 were defined based on those who fulfilled the inclusion criteria.

Paper III. All Norwegian and Swedish patients above 18 years of age who were dispensed more than mean one DDD of an OAT opioid daily per calendar year during the study period 2015-2017 were included. Due to the OAT opioid methadone could be administered as tablets and injection liquids for non-OAT patients with pain in both countries, we only included the methadone dispensations administrated as a mixture for this paper. Furthermore, to be safer in keeping out patients who received methadone for other medical indications than OAT, we used the total amount of dispensed OAT opioid DDD per day to measure whether patients were likely to be OAT patients.

Paper IV. All patients who received OAT in the OAT outpatient clinics in Bergen or Stavanger, Norway, or received health care for SUD in two municipality clinics in Bergen and measured fatigue at least once using the nine-item Fatigue Severity Scale (FSS-9) were included.

Variables and paper-specific definitions

Variables

In the table below, we showed all variables included in the paper I-IV.

Table 3

Presented data	Paper I	Paper II	Paper III	Paper IV

Independent variables/ confounders in regression analyses	- Age
	- Gender
	- The number of dispensations of OAT opioids
	- The type of dispensed OAT opioid
	- Being dispensed at least one:
	  o non-OAT opioid
	  o gabapentinoid
	  o benzodiazepine/z-hypnotic
		- Age
		- Gender
		- The number of dispensations of OAT opioids
		- The type of dispensed OAT opioid
		- Being dispensed at least one:
		  o non-OAT opioid
		  o gabapentinoid
		  o benzodiazepine or z-hypnotic
				- Age
				- Gender
				- Educational level
				- Housing situation
				- Debt difficulties
				- Injecting substance use
				- Use of non-dispensed substances (stimulant substances (amphetamines and cocaine), benzodiazepines, and opioids), cannabis, and alcohol
				- Being infected by:
				  o hepatitis B virus infection
				  o hepatitis C virus infection
				  ▪ If hepatitis C virus infected, viral load was calculated
				- Liver stiffness (transient elastography and APRI score)
				- Hemoglobin
				- Estimated glomerular filtration rate
				- C-reactive protein

Dependent variables in regression analyses	- Dispensed at least one: o benzodiazepine or z-hypnotic o gabapentinoid	- Dispensed at least one ADHD medication		- Nine-item Fatigue Severity Scale sum score
Other variables	- Mean daily dosages of: o benzodiazepines or z-hypnotics o pregabalin o gabapentin	- Mean daily dosages of: o methylphenidate* o dexamphetamine o lisdexamphetamine o atomoxetine o racemic amphetamine * For methylphenidate, we calculated dosages of short-acting and long-acting methylphenidate.	- Age - Gender - The type of dispensed OAT opioid - Being dispensed at least one: o benzodiazepine o z-hypnotic o gabapentinoid o strong non-OAT opioid o weak non-OAT opioid o centrally acting stimulant - Mean dosage of dispensed: o benzodiazepines o z-hypnotics o pregabalin o gabapentin o methylphenidate o lisdexamphetamine	- Receiving OAT o If received OAT, clarifying whether the therapy was buprenorphine-based or methadone-based.

Table 3: The table lists all independent and dependent variables in regression analyses in the papers I-IV. "Other variables" were variables that not were included in regression analyses. APRI = Aspartate Aminotransferase to Platelets Ratio Index; OAT: Opioid Agonist Therapy.

Definitions

Substance definitions for papers I-III

Text box 4: Essential definitions in the register-based studies

Dispensation: A dispensation is defined as when patients received a medicine from a pharmacy.

Dispensation rate: Dispensation rate was defined as patients who were dispensed at least one dispensation of a potentially addictive substance (e.g. clonazepam) or substance group (e.g. benzodiazepines) divided on the number of patients who were dispensed an OAT opioid per calendar year.

Calculating mean daily dosages: we calculated the mean daily dosages of dispensed potentially addictive substance per calendar year by summarizing the total amount of dispensed DDDs of the substance (e.g. clonazepam) per year. The total amount of DDDs was converted to milligrams according to Table 1. Furthermore, for benzodiazepines and z-hypnotics in paper I, we summarized the total amount of dispensed substances by converting the total amount of each substance to diazepam equivalents using the equations below according to [111, 112] (Text box 5).

Text box 5: Equations to convert benzodiazepines and z-hypnotics with different equipotency into diazepam equivalents:

$$Diazepam\ equivalents_{\ lowest} = diazepam + oxazepam \times \frac{1}{5} + alprazolam \times 10 + clonazepam \times 10 + flunitrazepam \times 10 + nitrazepam + zopiclone + zolpidem \times \frac{1}{2}$$

$$Diazepam\ equivalents_{\ mean} = diazepam + oxazepam \times \frac{1}{4} + alprazolam \times \frac{40}{3} + clonazepam \times \frac{40}{3} + flunitrazepam \times \frac{40}{3} + nitrazepam + lorazepam \times 4 + zopiclone \times \frac{8}{7} + zolpidem \times \frac{2}{3}$$

$$Diazepam\ equivalents_{\ highest} = diazepam + oxazepam \times \frac{1}{3} + alprazolam \times 20 + clonazepam \times 20 + flunitrazepam \times 20 + nitrazepam + zopiclone \times \frac{4}{3} + zolpidem$$

Due to uncertainty regarding equipotency between different benzodiazepines and z-hypnotics relative to diazepam, we created the three equations above based on the lowest, mean, and highest stated equipotency dosages of benzodiazepines. Using these equations, we ran

sensitivity analyses calculating the uncertainty in the dispensed dosage of benzodiazepines and z-hypnotics.

In contrast to paper II, we summarized the total amount of dispensed benzodiazepines and z-hypnotics in two separate equations based on the mean equipotency dosage of the substance groups in paper III. The two equations were created to identify potential differences in dosages of the benzodiazepines and z-hypnotics between Norway and Sweden and were according to [111, 112] (Text box 6).

Text box 6: Equipotency equations to convert benzodiazepines to diazepam equivalents and z-hypnotics to zopiclone equivalents

$$Diazepam\ equivalents_{\ mean} = diazepam + oxazepam \times \frac{1}{4} + alprazolam \times \frac{40}{3} + clonazepam \times \frac{40}{3} + flunitrazepam \times \frac{40}{3} + nitrazepam + lorazepam \times 4$$

$$Zopiclone\ equivalents_{\ mean} = zopiclone + zolpidem \times \frac{12}{7}$$

Finally, the total amount of milligrams of the dispensed potentially addictive substances were divided by 365.25 days to estimate the mean daily dosage per calendar year.

Specific definitions for papers I and II

Categorizing the number of dispensations: The number of dispensations was defined per substance (e.g., oxazepam) or substance group (e.g., 'benzodiazepine or z-hypnotic'). The number of dispensations for each potentially addictive substance group was categorized into three groups: 0, 1-2, and ≥ 3 dispensations per calendar year. The number of dispensations of OAT opioids was divided into five groups: 1-6, 7-12, 13-51, ≥ 52 dispensations per calendar year.

Categorizing the dispensed mean daily dosages: The mean daily dosages of diazepam equivalents were categorized into five groups: 0, ≤ 20, > 20 - ≤ 40, and > 40. Furthermore, pregabalin was categorized into the following three groups (mean mg per day): > 0 - ≤ 300, > 300 - ≤ 600, and > 600, and gabapentin into these three groups (mean mg per day): > 0 - ≤ 900, > 900 - ≤ 3600, and > 3600.

Type of dispensed OAT opioid: we defined the type of dispensed OAT opioid as the last type of OAT opioid dispensed per calendar year (buprenorphine-based or methadone-based).

Discontinuing OAT: For patients who discontinued OAT, we defined three equal periods from 180 days before to 90 days after the discontinuation date. The three periods were: 1) 180 to 90 days prior to the date for the last dispensation, 2) the last 90 days prior to the discontinuation date, and 3) the 90 days after the date for discontinuation. We calculated the mean daily dosage of dispensed 'benzodiazepines and z-hypnotics', pregabalin, and gabapentin for each period.

Specific definition for paper III

The type of dispensed OAT opioid: We defined the type of dispensed OAT opioid (buprenorphine-based or methadone-based) as the OAT opioid that was mostly dispensed per calendar year, calculated in DDDs per year.

Specific definitions for paper IV

Measuring fatigue: We used the FSS-9 to measure the fatigue during the last week, including items considering: mental and physical functioning, motivation, carrying out duties, and interference with work, family, or social life. The FSS-9 was a nine-item questionnaire consisting of a Likert scale per item ranging from one point to seven points, generating a sum score between nine and 63 points. We defined baseline as the first annual health assessment, including FSS-9 measurement, when the health assessments were listed chronologically.

Non-dispensed potentially addictive substances: We defined non-dispensed substances as being dispensed a substance in the following substance groups: opioids (including heroin), stimulants (amphetamines and cocaine), and benzodiazepines (including z-hypnotics).

Sociodemographic and clinical factors: From the INTRO-HCV cohort, we used information from the annual health assessment concerning; non-dispensed potentially addictive substance use plus alcohol and cannabis, injecting substance use, being on OAT (including OAT dosage ratio), educational level, housing situation, debt difficulties, and liver stiffness (measured by transient elastography). In addition, we obtained blood sample results per annual health assessment concerning; C-reactive protein, estimated glomerular filtration rate, hemoglobin, current infectious diseases (hepatitis B virus infection, HCV infection, and human immunodeficiency virus (HIV)), and Aspartate transferase and thrombocytes to calculate the Aspartate transferase to platelets ratio index score (APRI).

Dealing with non-dispensed potentially addictive substances, plus alcohol and cannabis: We classified non-dispensed potentially addictive substances plus alcohol and cannabis in two groups per substance/substance group: frequent users and non-frequent users. A frequent user was defined as using a substance/substance group at least weekly during the past 12 months. Patients using alcohol, cannabis, or non-dispensed potentially addictive substances less than weekly were classified as a 'no frequent user." We presented the prevalence of frequent users and non-frequent users as percentages of the SUD population per substance/substance group (benzodiazepines, opioids (including heroin), stimulants (cocaine and amphetamines), cannabis, and alcohol).

Dealing with no non-dispensed potentially addictive substance factors: We defined 'injecting substance use' as having injected at any time during the past 12 months according to the health assessment. Being on OAT was defined according to whether patients were currently enrolled in OAT at baseline. The OAT dosage ratio was calculated by dividing the received OAT opioid dosage by the expected OAT opioid dosage. The expected dosage was defined as the mean dosage of the lowest and highest recommended dosages according to WHO's guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (18 mg buprenorphine or 18/4.5 mg buprenorphine-naloxone, 90 mg methadone, or 45 mg levomethadone) [25]. Being infected with hepatitis B virus, HIV, or HCV were defined as detecting positive hepatitis B virus surface antigen, HIV antigen/antibodies, or positive HCV polymerase chain reaction at the first annual health assessment. If positive HCV polymerase chain reaction, we used the Helmert contrast in order to classify patients into two groups – transmitted and non-transmitted – and further into two subgroups: whether patients have a

low viral load (< 800 000 IU/ml) or high viral load (≥ 800 000 IU/ml). We classified the educational levels in five groups: 'not completed primary school,' 'completed primary school (nine years),' 'completed high school (12 years),' 'three or fewer years of college or university' or 'more than three years of college or university. Moreover, patients were classified into two groups based on the housing situation the last 30 days prior to the health assessment; "unstable" and "stable." "Unstable housing situation" represented patients who had lived on the street, in a homeless shelter, or with family and friends during the last 30 days. Others who had a more permanent residence were classified as having a stable housing situation. Debt difficulties were defined as striving to pay off legal or illegal debt due to a constrained private economy.

Statistics

Table 4 **Statistical analysis**	**Paper I**	**Paper II**	**Paper III**	**Paper IV**
Frequency tables	x	x	x	x
One-sample t-test	x			
Paired t-test	x	x		
Sensitivity analysis	x			x
Binary logistic regression	x	x		
Expectation-maximization imputation				x
Longitudinal analysis	x	x		x
Mixed model regression				x
Outcome measures				
Dispensation rates	x	x	x	
Mean daily dosages	x	x	x	
Crude odds ratio (cOR)	x	x		
Adjusted odds ratio (aOR)	x	x		
Fixed effects: estimate (baseline) (mixed model)				x
Fixed effects: slope (time trend) (mixed model)				x
Software	IBM SPSS version 24.0	IBM SPSS version 24.0	Stata SE 16.0	Stata SE 16.0 and IBM SPSS version 26.0

Table 4: Statistical methods, outcome measures, and software used in the papers I-IV

Papers I and II. The one-sample t-tests were used to calculate mean daily dosages of dispensed benzodiazepines or z-hypnotics, and gabapentinoids with 95 % confidence intervals. Furthermore, we used the paired sample t-test to compare the differences in the mean daily dosages of benzodiazepines or z-hypnotics (in diazepam equivalents), gabapentinoids (pregabalin or gabapentin), and ADHD medications in defined periods for patients who discontinued OAT and those who were co-dispensed ADHD medications and OAT opioids. Furthermore, we created binary logistic regression models per calendar year with being

dispensed at least one benzodiazepine or z-hypnotic, gabapentinoid, and ADHD medication, respectively, as the dependent variables. The independent and categorical variables were age groups (≤ 25, 26-35, 36-45, 46-55, and ≥ 56 years), gender, the number of dispensed OAT opioids, the type of dispensed OAT, and being dispensed at least one non-OAT opioids. In addition, being dispensed a gabapentinoid was used as an independent and categorical variable when being dispensed a 'benzodiazepine or z-hypnotic' was defined as a dependent variable, and vice versa. We presented the odds ratio (OR) for the analyses. The level of statistical significance was set to $p < 0.05$.

Paper III. We performed descriptive statistics (means, medians, percentiles, and percentages) of dispensation rates and dispensed dosages of potentially addictive substances (benzodiazepines, z-hypnotics, gabapentinoids, ADHD medications, strong non-OAT opioids, and weak non-OAT opioids) per calendar year per country in the study period.

Paper IV. We used a linear mixed model to investigate whether the sociodemographic and clinical factors affected the FSS-9 sum score at baseline and to which extend they impacted changes in the sum score from baseline to the following health assessments. We presented the statistical analyses in a three-step procedure. First, we dealt with missing data using Expectation-Maximization imputation of the sociodemographic and clinical factors. This imputation method is a common and recommended method to input data before running linear mixed model analyses [113]. When running the imputation, the missing values were dealt with as "missing at random." Overall, a total of 2.6 % of the factor variables were replaced with estimated values by imputation. Second, using linear mixed models, we analyzed the factor variables separately as outcome variables as a function of the time (time from baseline). We investigated whether the factor variables changed significantly from baseline to the following health assessments by these analyses. Clinically substantial changes in these outcome variables over time have been handled as time-varying exposure variables in a linear mixed model analysis with the FSS-9 sum score as an outcome variable. However, we did not identify any clinically significant changes in the factor variables. Thus, the factors' (predictors') baseline level were handled as stable predictors in the model. Third, we created a linear mixed model using the FSS-9 sum score as an outcome variable and the sociodemographic and clinical factors at baseline as stable, independent predictor variables. The interactions between these factors and time were added to the model to explore whether predictors changed the FSS-9 sum score (outcome variable) over time. We specified a random intercept fixed slope regression model. Restricted maximum likelihood was set as an estimator. The full information maximum likelihood ensured that all available FSS-9 sum score measurements were used. Additionally, we ran similar analysis models by including OAT patients using methadone or buprenorphine, respectively, at baseline. In all analyses, the level of statistical significance was set to $p < 0.05$. Due to the risk of type I errors caused by the above 40 predictors in the models, we performed a sensitivity analysis by adding Bonferroni corrected p-values for adjusting.

Ethics approval and consent to participate

Paper I and II. The Regional Committee for Medical and Health Research Ethics (REC), REC vest, Norway, has approved the use of registry data for the study (approval number 2018/939/REK Vest, June 19, 2018). No informed consent from included patients was required as the data was received pseudonymous and encrypted.

Paper III. The Regional Committee for Medical and Health Research Ethics West, Norway, and the Swedish Ethical Review Authority in Stockholm, Sweden, have both approved the use of the Norwegian and Swedish registry data for the study (Norway: reference number 2018/939/REK Vest, June 19, 2018; Sweden: reference number 2018/2080-31/1, 14 November 2018 and reference number 2019-04791, November 22, 2019). The Regional Committee for Medical and Health Research Ethics West, Norway, is appointed by the Norwegian Ministry of Education and Research, and the Swedish Ethical Review Authority is under the Swedish Ministry of Education. No informed consent from the patients was necessary.

Paper IV. The INTRO-HCV study is reviewed and approved by the Regional Ethical Committee for Health Research West, Norway (REK Vest 2017/51). All patients provided written informed consent prior to enrollment in the study.

Results

Aim 1: To describe the dispensation rates and dosages of dispensed potentially addictive substances among OAT patients in Norway (papers I and II)

Paper I. In 2017, the dispensation rate of being dispensed a 'benzodiazepine and z-hypnotic' was 50 % per calendar year throughout the study period. Twenty-nine percent were dispensed oxazepam, which was the most dispensed benzodiazepine in 2017. The mean daily dosage was 21 mg (standard deviation (SD): 38 mg) diazepam equivalents in 2013 and 17 mg (SD: 25 mg) in 2017. In 2017, being dispensed at least one benzodiazepine or z-hypnotic was associated with females compared with males (aOR: 1.2, 95 % confidence interval (CI): 1.1;1.3), age above 56 years compared with age below 25 years (1.2, 1.1;1.3), using methadone as OAT opioid compared with using buprenorphine (1.3, 1.2;1.4), and being dispensed a non-OAT opioid (3.0, 2.6;3.5) or gabapentinoid (2.5, 2.1;3.0) compared with not being dispensed these substances. Substantial similar results were seen in 2013-2016.

Gabapentinoids were dispensed to 9 % of the patients in 2013 and 11 % of the patients in 2017. Pregabalin was twice as frequently dispensed as gabapentin per year. For 2017, the mean daily dosage of pregabalin was 386 mg (SD: 454 mg), and for gabapentin, 1047 mg (1450 mg). The mean dosages of gabapentinoids were nearly unchanged during the study period. Being dispensed a gabapentinoid was associated with being dispensed a non-OAT opioid (3.0, 2.5;3.5) and 'benzodiazepine or z-hypnotic' (2.0, 2.1;3.0) compared with not being dispensed these substances.

A total of 693 patients discontinued OAT during the study period. Of those, 156 patients were dispensed benzodiazepines or z-hypnotics for the defined 90-days' periods. We did not identify any changes in the dispensed dosages of benzodiazepines and z-hypnotics, pregabalin, or gabapentin at baseline compared to the following 90 days after the discontinuation date.

Paper II. The dispensation rates of being dispensed an ADHD medication were 3.5 % in 2015 and 4.6 % in 2017. In 2017, above half of the patients with co-dispensed ADHD medication and an OAT opioid received short- and intermediate-acting methylphenidate (55 %), followed by lisdexamphetamine (24 %). Similarly, we found that being dispensed buprenorphine rather than methadone as OAT opioid (1.6, 1.3;2.1), being dispensed a non-OAT opioid compared with not dispensed these opioid substances (1.5, 1.1;1.9), and being below 25 years of age rather than being above 56 years of age (0.3, 0.1;0.6) were associated with being dispensed ADHD medication. Similar results were substantially seen for 2015 and 2016.

We identified 142 patients who were co-dispensed ADHD medication and OAT opioids throughout the period from 2015 to 2017. Of those using methylphenidate, we found an increase in the dispensed mean daily dosages from 63 mg (SD: 43 mg) in 2015 to 76 mg (39 mg) in 2017 ($p = 0.01$). For lisdexamphetamine, we showed a non-significant increase of 64 mg during the three years ($p = 0.10$). Notably, except atomoxetine, the mean daily dosages for all ADHD medications exceeded the recommendations, according to the European Medicines Agency, the Norwegian Medicines Agency, and the Norwegian Medicines Handbook [114-118]. Moreover, 85 out of 142 patients receiving co-dispensed ADHD medication and an OAT opioid throughout the study period also were dispensed other potentially addictive substances concomitantly (gabapentinoids, z-hypnotics, benzodiazepines, and non-OAT opioids).

Aim 2: To describe differences in the dispensation rates and dosages of dispensed potentially addictive substances among OAT patients in Norway and Sweden (paper III)

The proportion of patients who were dispensed at least a substance from one of the substance groups (benzodiazepines, z-hypnotics, gabapentinoids, non-OAT opioids, or centrally acting stimulants) was almost equal between the countries (in 2017: 59 % (Norway) and 55 % (Sweden) (Figure 14). However, there were some substantial inter-country differences in the dispensed substance groups. Most notably, 44 % of the Norwegian patients were dispensed benzodiazepines compared with 14 % among the Swedish OAT patients in 2017. Furthermore, 14 % of the Norwegian OAT patients compared with 26 % of the Swedish OAT patients were dispensed z-hypnotics, whereas gabapentinoids were dispensed to 10 % of the OAT patients in Norway and 19 % of the OAT patients in Sweden. Interestingly, the centrally acting stimulants were dispensed to 4 % in Norway and 18 % in Sweden. Similar results were also seen for 2015 and 2016.

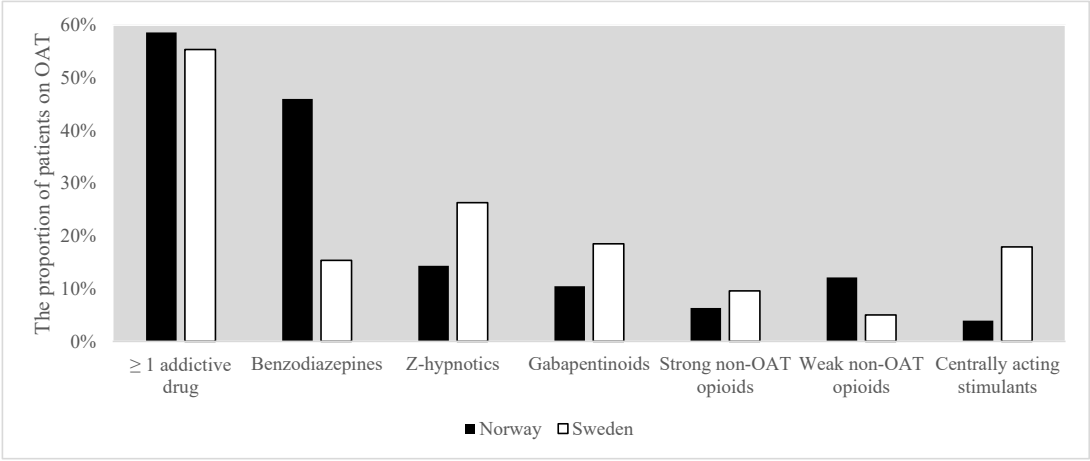

Figure 4: The figure displays the proportion of OAT patients who were dispensed at least one potentially addictive substance (benzodiazepine, z-hypnotic, gabapentinoid, strong non-OAT opioid, weak non-OAT opioid, or centrally acting stimulant) in Norway and Sweden in 2017. Weak non-OAT opioids were defined as all substances containing codeine, tramadol, or tapentadol, while strong non-OAT opioids defined all other opioids. Not mutually exclusive. OAT: Opioid Agonist Therapy.

In 2017, the mean daily dosages of dispensed benzodiazepines were 17 mg (SD: 25 mg) diazepam equivalents in Norway, with a corresponding 16 mg (22 mg) in Sweden. Moreover, the mean dosage of dispensed z-hypnotics was 8 mg (9 mg (Norway), 7 mg (Sweden)) zopiclone equivalents in both countries. For pregabalin, gabapentin, and lisdexamphetamine, the mean daily dosages were higher in Norway than in Sweden (pregabalin: 402 mg (431 mg) (Norway) versus 345 mg (260 mg) (Sweden), gabapentin: 1021 mg (1524 mg) versus 772 mg (1118 mg) and lisdexamphetamine: 58 mg (46 mg) versus 51 mg (37 mg)), while the mean

daily dosage of dispensed methylphenidate was higher in Sweden compared with Norway (methylphenidate: 80 mg (63 mg) vs 57 mg (40 mg)).

Among patients who were co-dispensed OAT opioids and centrally acting stimulants, 34 % in Norway and 31 % in Sweden also dispensed at least one of the other potentially addictive substances (benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids) in 2017. Furthermore, a quarter was dispensed OAT opioids, centrally acting stimulants, and two of the other potentially addictive substances. In 2017, the most commonly dispensed combination of three substances was OAT opioid, centrally acting stimulants, and 'benzodiazepines or z-hypnotics.'

Aim 3: To investigate the extent of non-dispensed potentially addictive substance use among SUD patients, mainly OAT patients, in Bergen and Stavanger, Norway (paper IV)

Of 654 SUD patients who were recruited, approximately one-third completed two or more annual health assessments. Of those included, 82 % received OAT at baseline. At baseline, the self-reported prevalence of frequent users of non-dispensed potentially addictive substances plus alcohol and cannabis, the past 12 months was: cannabis 52 %, benzodiazepines or z-hypnotics 39 %, stimulants 29 %, alcohol 26 %, and opioids 16 %. Furthermore, patients who have ever used substances during the past 12 months had the following prevalence at baseline: cannabis 78 %, alcohol 72 %, benzodiazepines or z-hypnotics 71 %, stimulants 64 %, and opioids 49 % (data not shown in the paper). Using the linear mixed model, we found that the frequent users' substance prevalence was not clinically significantly changed from baseline to the following health assessments.

Aim 4: To examine the extent of fatigue symptoms and investigate the associations between non-dispensed potentially addictive substances and fatigue adjusted for various sociodemographic and clinical factors among SUD patients, mainly OAT patients, in Bergen and Stavanger, Norway (paper IV)

The FSS-9 sum score was 43 (SD: 16) at baseline, representing a mean score for the FSS-9 items of 4.8 (SD: 1.8). Females had a higher score than males (adjusted mean difference of FSS-9 sum score: 4.1, 95 % CI: 1.3;7.0), and frequent use of benzodiazepines (5.7, 3.0;8.4) or stimulants (-5.0, -8.0;-2.0) compared with less frequent or no use of these substances were associated with changes in the FSS-9 sum score at baseline. In addition, patients with debt difficulties were barely associated with more fatigued than those with no debt difficulties (2.9, 0.4;5.3).

Substantial intra-individual changes in the FSS-9 sum score from baseline to the following health assessment were observed (Figure 5). Furthermore, patients with frequent use of benzodiazepines compared with those with less frequent or no use (-4.4, -8.2;-0.7), and patients with liver fibrosis or cirrhosis measured by transient elastography compared with those with healthy liver (-5.5, -9.9;-1.0) over time were associated with less fatigue per year. These differences were unlikely to be clinically significant.

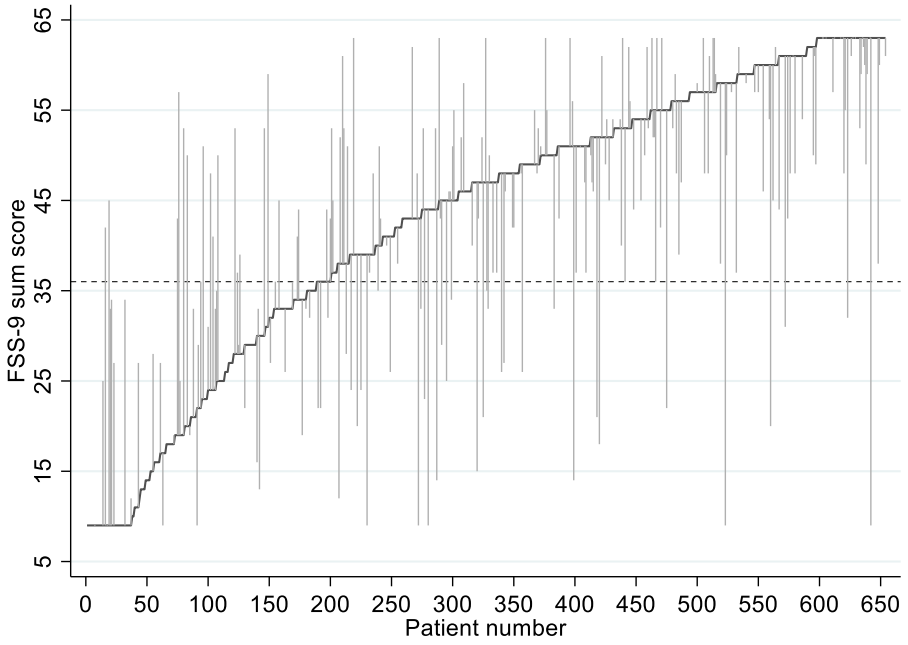

Figure 5: The figure displays the FSS-9 sum scores at the first health assessment (baseline) and the second health assessment when the health assessments are listed chronologically per patient. The darkest line represents the FSS-9 sum scores at baseline, while the grey spikes mark the changes in the FSS-9 score between baseline and the second health assessment if patients completed two or more health assessments. The spikes' endpoints (furthest from the darkest line) demonstrates the FSS-9 sum score at the second health assessment. FSS-9: Nine-item Fatigue Severity Scale.

For patients receiving methadone as an OAT opioid, females had more fatigue than males (7.3, 2.5;12.2), and patients with frequent use of benzodiazepines compared with those with less frequent or no use were associated with higher FSS-9 sum scores (6.0, 1.6;10.5) at baseline. Furthermore, patients with debt difficulties had higher FSS-9 sum score than those with no debt difficulties (4.9, 0.7;9.1). A high versus low hepatitis C viral load was also associated with more fatigue at baseline (31.5, 1.5;61.5). Furthermore, patients with frequent benzodiazepine use compared with those with less frequent or no use (-6.8, -12.5;-1.1) were associated with a decreasing FSS-9 sum score from baseline to the following health assessment. In addition, patients with liver fibrosis or cirrhosis compared with those with healthy liver (-6.2, -11.7;-0.7) and patients with high versus low viral hepatitis C load (-44.6,-81.7;-7.5) were also associated with a decreasing FSS-9 sum score per year from baseline.

For patients receiving a buprenorphine-based OAT opioid, frequent alcohol use compared with less frequent or no use was associated with a higher fatigue score at baseline (4.8, 0.2;9.3). In contrast, frequent stimulant use compared with less frequent or no use was associated with a lower fatigue score at baseline (-5.0, -9.9;-0.1). In addition, patients with frequent benzodiazepine use compared with those with less frequent or no use (-8.0, -14.1;-

1.8), and patients with liver fibrosis or cirrhosis compared with those with a healthy liver were associated with lower FSS-9 sum score per year from baseline (-9.0, -17.1;-0.7).

Discussion

The discussion section begins with a methodological discussion of the papers, followed by a summary and a clinical discussion of the main findings.

Methodological discussion of the papers

The measurement errors are usually classified as either random or systematic errors [119]. *Random errors* cause an unknown and unpredictable condition on one measurement, while systematic errors always affect all measurements with the same amount or by the same proportion. The random errors are considerably reduced and tended towards zero with high precision when using national register databases with thousands of participants. For the INTRO-HCV cohort, the risk of random errors affecting the results is somewhat higher than the national register data due to a smaller study sample and self-reported data concerning fatigue questionnaire or sociodemographic and clinical conditions.

Systematic errors (bias) patterns affect all study's measurements independent of its sample size [119]. These errors skew the results towards a specific direction from the true values, affecting the study's validity. The validity is expressed by *internal validity* and *external validity*. The internal validity expresses how well the results fit the included patients in the study, while the external validity shows the results' generalizability to other populations. Key violations of internal validity are *confounding*, *selection bias*, and *information bias*, which will be handled in more detail in the following paragraphs.

Selection bias

Selection bias expresses the selection of individuals, groups, or data for analysis, not ensuring the population's representativeness that was intended to be analyzed. In paper I-III using the NorPD and SPDR, we received practically all information about dispensed substances in the two countries, eliminating the risk of recall biases entirely. Furthermore, we identified patients who received OAT opioids from pharmacies. These patients were dispensed at least one OAT opioid (paper I-II) or at least one DDD per day (paper III) per calendar year from the pharmacies during the study period. These inclusion criteria could introduce selection bias. Approximately 10 % of the Norwegian OAT patients and 40 % of the Swedish OAT patients received OAT opioids from other health services than pharmacies, which were not linked to the databases' dispensations [34, 109]. These patients were assumed to receive the OAT opioids from specialized addiction outpatient clinics and were missed in our studies. One could assume that these patients were more frequently followed up in the outpatient clinics by health professionals who work daily with patients with substance dependences. Close follow-ups by professionals with expertise in addiction medicine could limit potentially addictive substances dispensing compared with patients receiving OAT medications by pharmacies, contributing to an overestimation of dispensation rates and dosages in papers I-III.

Moreover, methadone has two medical indications in Norway and Sweden: OAT [120, 121] and pain [122, 123]. In papers I and II, we excluded patients receiving methadone due to pain by identifying those who only are dispensed methadone tablets (usually for palliative care) without any dispensation of methadone mixture from January 1, 2004, to December 31, 2017. According to the national OAT guidelines, methadone mixture is the first-hand choice when choosing methadone as an OAT opioid in Norway, indicating that all OAT patients who used

methadone have at any time received methadone mixture. This gave us a reasonable opportunity to exclude those only receiving methadone tablets. In addition, to ensure including most OAT patients and not palliative care patients receiving OAT opioids, we also used reimbursement codes for palliative care to exclude non-OAT patients during the study period. Nevertheless, non-OAT patients with pain who were dispensed methadone mixture as a pain killer on other medical indications than palliative care or were switched from mixture to tablets formulation could still be categorized as OAT patients using these criteria. Thus, we could not be entirely sure that patients using methadone on other medical indications than OAT were not classified as OAT patients.

Furthermore, in paper III, we dealt with the inclusion criteria using the mean defined daily dosages. We included patients who exceeded the threshold on one mean DDD of dispensed OAT opioids per day during a calendar year, independent of which OAT opioid dispensed, corresponding to a mean daily dosage of at least 8 mg buprenorphine/buprenorphine-naloxone, 25 mg methadone, or 15 mg levomethadone [108]. According to the World Health Organization's standard, the recommended mean dosage of OAT opioids was 18 mg buprenorphine and 90 mg methadone [25], a substantially higher dosage than the present study's threshold value. However, patients received OAT opioids on other medical indication, e.g., for palliative care or acute medical conditions, rarely reach a dispensed mean dosage per calendar year above the defined threshold. Nevertheless, with this in mind, we tried to balance the criteria by not including too many patients with pain as an indication (if too low cut-off value) and being aware of excluded OAT patients using a low-dosage OAT opioid (if too high cut-off value). Still, one could assume that our results were less generalizable to patients using a low dosage of an OAT opioid than those using a dosage above the threshold. We have illustrated this approach in the figure below.

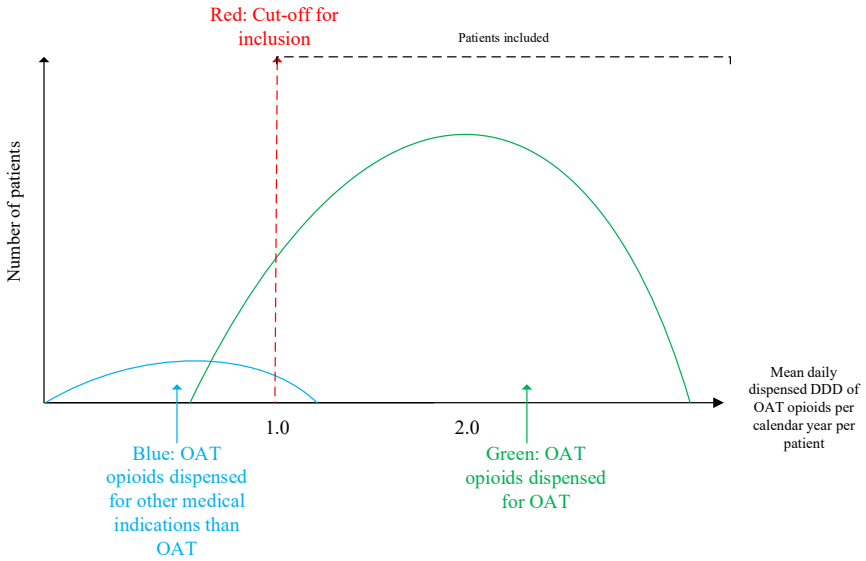

Figure 6: The figure displays a graph of the expected distribution of patients who were dispensed OAT opioids for OAT and other medical indications. We assumed that OAT patients are more likely to be dispensed OAT opioids in doses above mean one DDD daily of OAT opioids per calendar year. DDD: Defined Daily Doses; OAT: Opioid Agonist Therapy.

Another source for bias is that the NorPD and SPDR did not receive information about dispensed substances from hospitals, prisons, and outpatient clinics underlying hospitals. This could limit these papers' internal validity, considering that SUD patients, including OAT patients, are occasionally incarcerated [124, 125], followed up in OAT outpatients clinics, or hospitalized [126-129].

We reached the majority of OAT patients in Bergen and Stavanger by the inclusion criteria in paper IV [1]. However, only a third of patients in the INTRO-HCV cohort completed two or more health assessments within the study period. One could assume that those with the most interest in being followed up met for health assessments, while patients with delayed follow-up or drop-outs could present findings that were not captured by our results. The reasons for delayed follow-up and drop-outs could be multifactorial, involving substance intoxication, substance withdrawals, severe anxiety, hospitalizations, moving from the OAT outpatient clinics to pharmacies, etc. For these cases, a substantial change in the sociodemographic and clinical conditions not capturing could contribute to selection bias affecting the longitudinal fatigue analyses' results. Another bias was patient and system delays and capacity challenges in the outpatient clinics that could postpone the health assessments. During the year 2020, reorganizations of the OAT medication delivery model due to the COVID-19 pandemic delayed some health assessments. In this period, the OAT opioids were provided to patients by home deliveries rather than consultations in the OAT outpatient clinics. These delivery changes reduced the capacity to conduct the annual health assessments and recruit patients to the INTRO-HCV cohort. However, when comparing patients with two or more health assessments with those with one or more health assessments at baseline, substantial changes in sociodemographic and clinical factors, including substance use, were not found.

Moreover, we expected missing values in analysis variables in paper IV when collecting data of patients with a historically high risk of loss-to-follow-ups. Interestingly, the predictors were rarely affected by missing values, representing only 2.6 % of the variables. We handled missing values using the Expectation-Maximization imputation to optimize the data set before running linear mixed models. The Expectation-Maximization algorithm for imputing data is iteratively performing maximum likelihood estimation in latent variables [130, 131]. The method is recommended to estimate missing values for a linear mixed model [113]. By using the Expectation-Maximization imputation, we introduced bias by replacing missing values with estimated values. However, these imputed values represented a relatively small number of the total predictor values in the data set and were calculated using a recommended imputed method for mixed models. Nevertheless, to be transparent about this bias's impact, we could present the linear mixed model analysis with and without imputed data and adjust and unadjusted/crude estimates of the models' predictors in the paper. Furthermore, we simplified the linear mixed models in paper IV by not running the analysis with time-varying predictor variables. This could theoretically introduce bias if they did not capture changes in predictors between the annual health assessments. However, we ran separate analyses with the predictors as the outcome variable and time between the annual health assessments as the independent variable in the linear mixed models. When running these analyses, we did not find any clinically significant changes in the predictor variables from baseline to the following health assessments. This led to this simplification was maintained for the linear mixed model analysis.

Information bias

Information bias is a systematic difference between the truths and results that were presented. The differences may be related to data collection, recall, recording, and handling data in the study. Using the NorPD and SPDR, the bias in handling data, including dealing with missing values, was practically eliminated. On the other hand, the NorPD and SPDR have a few sociodemographic and clinical variables, giving us limited options to adjust for all relevant factors. Unlike the SPDR, the NorPD contains information on month and year of death, and reimbursement codes for chronic diseases, making us able to exclude patients who were not likely to receive OAT in papers I and II. Moreover, the two data sources only receive information on dispensed substances, which prevented us from knowing whether substances were taken as prescribed. The substances could be given to other patients, or for some cases, sold on the illicit market in order to get income [132, 133]. Furthermore, the papers could not accurately identify whether patients co-used potentially addictive substances and OAT opioids concomitantly. Patients could be classified as co-users of substances for a calendar year, although OAT opioid dispensations were terminated when the other potentially addictive substances were dispensed.

Furthermore, the paper IV variables were collected by drawing blood samples, measuring liver stiffness by transient elastography, and self-reporting sociodemographic and substance use variables. Transient elastography can introduce systematic measurement errors for obese patients and those who have eaten during the hours before the measurement. Furthermore, self-reporting itself, e.g., reporting substance use for the past 12 months, could introduce recall bias [134]. Short and long-term benzodiazepine and z-hypnotic use, representing 40 % of the study sample, could impair cognition by reducing nonverbal memory and not recalling specific details of new information [135]. Considering this, we could improve the validity between self-reporting and laboratory variables, e.g., by verifying self-reported substance use with observed urine samples. However, drawing observed urine samples could create a barrier to recruiting and following up, giving us probably fewer patients included. Moreover, self-reporting could also introduce socially-desirability bias related to sensitive topics, such as non-dispensed substance use and debt difficulties [136-138]. This bias could lead to that the patients report as regards what is socially acceptable to respond. Consequently, debt difficulties and non-dispensed substance use could be underreported, especially for OAT patients where non-dispensed substance use could contribute to stricter follow-ups and more frequently observed OAT opioid intakes. To partly avoid the risk of socially desirable reporting bias, we handled some of the information confidentially for clinicians and ensured that research nurses were not involved in OAT-related decisions. However, we could not entirely exclude this bias when using self-reported data.

Moreover, we measured liver stiffness using the gold standard, transient elastography. The measurements were performed using measuring equipment facilitated for patients with body mass index below 30.0 kg/m^2. A proportion of 16.2 % of patients exceeded this threshold (data not shown in the paper), introducing a systematic measuring error for these liver stiffness measurements. This could impact the association between fatigue and liver stiffness.

The nine-item Fatigue Severity Scale is a well-known self-reporting questionnaire to measure fatigue in the general population and patients with chronic diseases [74, 75, 79, 83, 84, 86, 89]. However, the questionnaire items' comprehension regarding item wording, item format, item context, and scale ratings could impact how the items were answered, introducing information bias [139]. For patients with SUDs, we addressed some common challenges. First, overlapping items made it challenging for patients to understand the nuances between the items thoroughly, which significantly impacted patients who were intoxicated by

substances or gone through substance withdrawals. Second, in some formulations, the patients were tempted to respond to the items with what made general sense rather than personally impacting them. For example, item seven, "Fatigue interferes with carrying out certain duties and responsibilities patients with SUDs," which, in some cases, were responded as "of course, getting tired interferes with duties and responsibilities." These patients tended to respond with a high rather than low score on the items. Third, most SUD patients included were unemployed, which were not considered in one item (item nine), concerning their daily functioning on the job. This item could perform answers not fully capture the purpose of the item. Fourth, scale rating could impact how patients respond to an item. Scales including negative numbers (-5 to +5) have shown to not obtain a similar answer than a corresponding scale with only positive numbers (0 to 10), considering that the difference between the highest and lowest values in the two scales was equal [140]. How this influences the FSS-9 sum score was not evaluated but could impact the responses on the FSS-9. Fifth, in a previous study, the FSS-9 was translated to Norwegian from the US-English version with a naïve Norwegian speaking translator and a qualified naïve US-English translator [74]. However, a high-quality translation lacked, according to Wild, D. et al. [141]. Nevertheless, we have recently validated and shortened the FSS-9 questionnaire to a three-item FSS facilitated for SUD patients [142].

Confounding

Confounding is a variable that influences both the outcome and exposure variables, resulting in a spurious association [119]. In the pharmacoepidemiological studies involving the NorPD and SPDR (paper I-III), the exposure variable is often a dispensed substance linked to the outcome variable by a medical indication. This introduces the risk of "confounding by indication" [143]. For OAT patients with a consistently high prevalence of mental diseases and polysubstance use, the potential for confounding between the exposure and outcome in studies is likely. Using only the NorPD and SPDR, we could not sufficiently differentiate between the medical indications for dispensing potentially addictive substances. For example, being dispensed benzodiazepines could be dispensed for approved short-term medical indications, such as jet-lag, panic attacks, sleeping disorders, agents to curb status epilepticus, and short-term treatment of alcohol withdrawal. However, in several cases, the number of dispensations indicated long-term use of some substances. Although long-term use of benzodiazepines is discouraged, in some cases, it may help treat chronic mental disorders or replace non-dispensed benzodiazepine use with dispensed benzodiazepine use for patients undergoing detoxification. Furthermore, we also found a strong association between being dispensed a gabapentinoid and a benzodiazepine or z-hypnotic, which could be co-dispensed for withdrawal treatment, anxiety disorder, or neuropathic pain. These examples illustrate a spectrum of potential underlying causes (confounders) for dispensing, which could not be addressed using information from the NorPD and SPDR. Considering this, we were unable to conclude with causality in paper I-III, and the presented indications for dispensing and their associations should therefore be interpreted in caution. The figure below illustrates some reasons for dispensing potentially addictive substances for OAT patients.

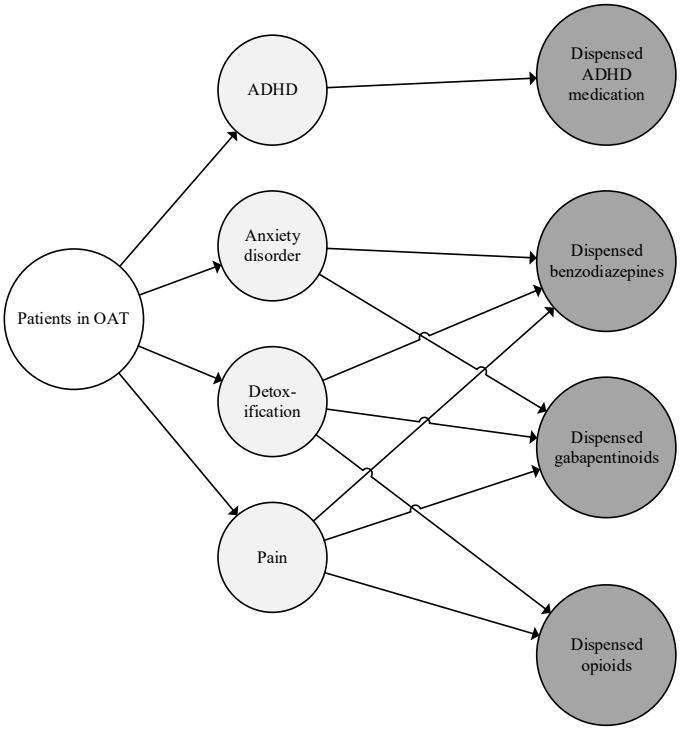

Figure 7: The figure displays a biomedical model on potential medical disorders/conditions (confounders) that may explain the associations between SUD patients and dispensed substances. SUD: Substance use disorder

Fatigue is a subjective health complaint that is considerably affected by various medical and psychosocial factors. We dealt with confounding by surveying sociodemographic and clinical factors, including non-dispensed potentially addictive substances in the annual health assessments that we thought influenced the patients' fatigue level. We illustrate the potential associations by arrows in the figure below.

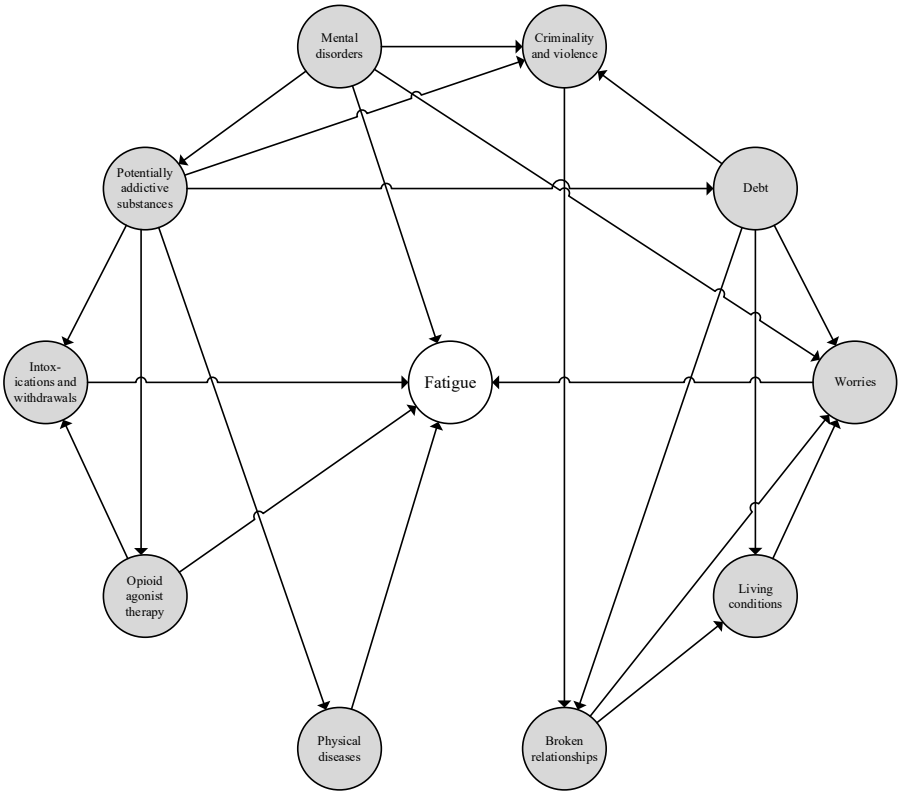

Figure 8: The figure displays direct acyclic graphs of potential relationship between sociodemographic and clinical factors and fatigue among patients with substance use disorders.

The results pointed out a higher fatigue level in the SUD population than a general Norwegian population, and being on the level for other severe chronic diseases – such as HCV infection [79-81], Parkinson's disease [82, 83], multiple sclerosis [84-86], or stroke onset [87-89]. Despite adjusting for the sociodemographic and clinical variables, the fatigue level and its predictors were unlikely to fully cover all causes of the populations' high fatigue level. Most notably, the frequent use of benzodiazepines increased the fatigue sum score by five points, and the frequent use of stimulants decreased the score by five points compared with those with less frequent or no use of these substances. Other underlying factors could, therefore, explain more of the fatigue level presented. For example, using benzodiazepines frequently could be confounded by depression (mental disorder), giving them higher fatigue level, while criminality and violence related to difficulties in repaying illegal substance debt, broken relationship to family and friends, and poor living condition could usually increase the fatigue level in some cases (Figure 9). Other underlying medical and psychosocial aspects – such as intoxication, withdrawal, and physical diseases – could also confound the FSS-9 score at the

moment when surveying fatigue. However, adjusting for these complex individual events was challenging. Thus, the selection of variables in models without concern for causal interferences could give higher risks of inappropriate conclusions without transparently showing potential short-comings. Paper IV has presented this transparently in contrast to several other published studies.

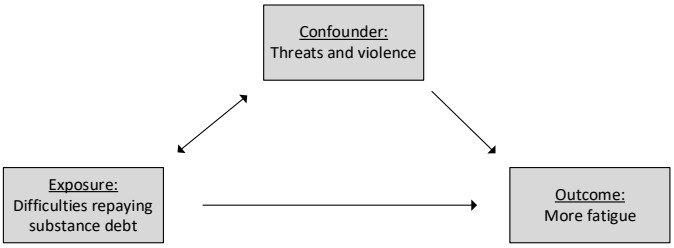

Figure 9: The figure displays potential confounder (threats and violence) between having difficulties repaying substance debt (exposure) and being more fatigued

Assessing type I and type II errors

Avoiding false associations and differences between exposure and outcome is of interest in all research. To handle this, we differentiate between type I errors revolving around false positive values (rejection of a true null hypothesis) and type II errors expressing false negative values of tests (rejection of a false null hypothesis) [144]. Type I and II errors can be dealt with in different ways; reduce alpha if many tests, ensure adequate sample size and statistical power, assess the precision of confidence intervals etc. Although the potential factors affecting type I and II errors in this dissertation have been partly discussed in the previous sections, we point out some crucial errors in the following paragraphs.

Despite high power with large populations in paper I-III, type II errors could be introduced. The current inclusion criteria of being dispensed an OAT opioid (paper I-II) or achieving the threshold of mean one DDD per day of dispensed OAT opioids per calendar year (paper III) to be included, could include patients who not were OAT patients. These non-OAT patients could introduce type II errors by having a different prevalence of disorders and dispensing patterns of dispensed potentially addictive substances than OAT patients. For example, a third of the SUD population had comorbid SUDs and ADHD, which was substantially higher than expected for the general population and non-OAT patients dispensing methadone for pain. This could introduce type II errors by impacting the dispensation rates of ADHD medication in the study sample and reducing the generalizability and transferability to other SUD populations.

In paper IV, the linear mixed model analyses were more prone to type I errors. With 20-21 predictors used for baseline and time trend assessments, we estimated the risk of one estimate distributed outside a 2.5-97.5 % distribution when drawn from a random sample (type I error) to be 87 %. Considering this, we introduced Bonferroni corrected p-values as a conservative method to handle the risk of error, leading to the number of significant predictors declined from six to two: frequent use of benzodiazepines or stimulants compared with less frequent or no use of these substances.

Furthermore, in paper IV, the predictors of being infected with the HIV or hepatitis B virus infections presented wide confidence intervals in the linear mixed model analyses. This corresponded to a low prevalence of these diseases in the SUD population, reducing the analysis's statistical power, and gave us potential false-negative associations (type II errors). However, previous studies investigating fatigue in these populations have shown an association between these diseases and fatigue [145-147]. The similar potential false-negative association with fatigue could also be the case for severe kidney diseases measured by estimated glomerulus filtration rates, considering that few patients had severe disease associated with substantial fatigue symptoms in this study [148-150]. The longitudinal analyses (slope estimates) could also introduce type II errors because only a third had more than one measuring point for fatigue. Loss of patients reduced the statistical power, which could provide false associations.

Causation

Bradford Hill suggested nine criteria to evaluate whether the associations were causal in epidemiological studies [151]. The criteria are the strength (effect size), consistency, specificity of the association, temporality (i.e., the causal predictor preceding the outcome), biological gradient (dose-response relationship), plausibility, coherence with current knowledge, and experiment and analogous examples. In the following, we discuss our results according to the criteria illustrated by examples from the papers.

Paper I-III. Using the NorPD and SPDR, the strength was reached by including a high proportion of OAT patients, giving us high precision and statistical power for most analyses. However, a weakness could be the cases in some subgroup analyses, e.g., patients who were dispensed an ADHD medication where the number of patients did not count more than 349 in 2017 (paper II). The consistency criterion was sufficiently met in all the analyses. This could be illustrated by the fact that the predictors for being dispensed a potentially addictive substance were maintained from one calendar year to another. For example, being dispensed a gabapentinoid or being female rather than male reached unchanged odds for being dispensed a benzodiazepine per calendar year throughout the study period 2013-2017. Similar consistency was also found in other analyses.

Furthermore, it was more challenging to evaluate the specificity of the associations. A broad specter of underlying medical diseases/conditions for being dispensed a potentially addictive substance could impact the predictors' associations with being dispensed a potentially addictive substance. For example, some OAT patients were well-functioning by living a life with family and work with no other substance dependences than opioids. In these cases, benzodiazepine could be dispensed for short-term sleeping disorders for a few days or weeks according to the preapproved medical indication. Other OAT patients were polysubstance users living on the street with broken family and friend relationships with several hospitalizations due to intoxications where long-term use was more likely. The fact that we lacked information on comorbidities to study participants and the indication for dispensing could make the results less specific. Furthermore, the temporality was weakened. We did not consider whether some predictors (e.g., being dispensed a potentially addictive substance) had preceded before or after the outcome. For example, being dispensed a gabapentinoid (exposure) could be dispensed after patients were dispensed a benzodiazepine or z-hypnotic (outcome) during the same calendar year.

The dose-response relationship criterion evaluates whether a greater exposure leads to a greater/lower incidence of the effect. A potential age gradient was found regarding patients above 56 years of age who had an increased odds of being dispensed a benzodiazepine or z-hypnotic compared with those below 25 years of age (paper I). Similarly, a potential age gradient was also found for patients above 56 years of age who had a reduced odds for being dispensed an ADHD medication compared with those were below 25 years of age. Other predictors were not created for evaluating dose-response relationships. Moreover, due to other studies investigating the underlying reasons for dispensed potentially addictive substances were lacked in the literature, the plausibility evaluation was also challenging. However, our results were substantially in line with what was clinically expected. For example, we found that being dispensed one potentially addictive substance, e.g., benzodiazepines, increased the odds of being dispensed one of the remaining potentially addictive substances, e.g., gabapentinoids or non-OAT opioids, according to paper I. This finding could be explained by patients' comorbidities, e.g., anxiety disorders and substance withdrawals, making more substance dispensations medically indicated [62]. Additionally, patients using methadone as an OAT opioid were associated with being dispensed a benzodiazepine or z-hypnotic, or a gabapentinoid, contrary to what were shown for those using buprenorphine. One potential plausible cause of this was that patients on methadone could be more comorbid than patients on buprenorphine, so that dispensing on benzodiazepines, z-hypnotics, or gabapentinoids was more likely.

Furthermore, although little is known about the associations with potentially addictive substances in the SUD population, the results were substantially coherent with existing clinical knowledge. On the aspect of analogy, two studies evaluating mortality in the OAT population in the U.K. and Sweden showed that the dispensation rates of benzodiazepines and gabapentinoids were in line with our results [28, 29]. However, the studies did not evaluate the same associations for being dispensed a potentially addictive substance, which gave us not analogous examples of similarities to the existing SUD patient literature in line with our identified associations.

Paper IV. The OAT cohort also met some of the Bradford Hill criteria. Although the study's strengths were insufficient to conclude with causal associations, the study's large sample of SUD patients gave us sufficient statistical power to point out some associations between predictors and fatigue. Moreover, the consistency criterion was partly fulfilled, although substantial intra-observer reliability between the FSS-9 measurements was found. The consistency could be shown by the fact that the comparable predictors went in the same direction in the analyses. For example, the non-significant predictors 'having debt difficulties' and 'being females rather than males' went in the same direction as the significant predictor 'the frequent use of non-dispensed benzodiazepines compared with less frequent or no use,' consistent with what was expected clinically. In addition, the non-significant 'frequent use of non-dispensed benzodiazepines compared with less frequent or no use' reduced fatigue over time (time trend, slope), which was expected since persistent benzodiazepine use could lead to less fatigue induced by increasing substance tolerance.

The specificity criterion was partly met by including a specter of sociodemographic and clinical predictors describing the SUD population. Although several predictors impacted fatigue, they did not thoroughly explain the high fatigue score in the population compared with the general population. For example, the frequent use of benzodiazepines only increased the fatigue score by five points. This could indicate that other underlying factors than those were assessed impact fatigue in this study. Moreover, we could not be sure that the exposure

variables preceded the fatigue level (temporality). Although most predictor variables were substantially stable over time, some predictors could be affected by being collected either after the FSS-9 measurement. For example, predictors involving blood samples could be drawn after the outcome had occurred. This could be in conflict with the temporality criterion to some degree. Moreover, the dose-response relationship was found for persistent liver fibrosis or cirrhosis compared with a healthy liver, contributing to less fatigue. Other dose-response relationships between the fatigue level and the predictors (age, liver stiffness (transient elastography and APRI), hemoglobin, estimated glomerulus filtration rate, and C-reactive protein), were not found in the SUD population.

Moreover, since fatigue has not been studied well in the SUD population, the plausibility and coherence evaluations were challenging. Although our study's results were partly in line with what was clinically expected, further research was needed to assess the plausibility before transferring to other SUD populations. For example, contrary to other studies [79-81, 145, 152], we did not estimate more fatigue among patients infected with HCV and HIV infections. Unstable housing situations or injecting substance use did not affect fatigue, although clinical experience suggest that this may be the case. Furthermore, analogous examples of fatigue measurements for the SUD population do not exist as far as we know. However, similar studies evaluating fatigue among patients with chronic diseases have shown a high fatigue level compared with the general population [74, 81-86, 89], corresponding to our SUD population's result.

External validity and transferability

Exploring the extent of dispensing potentially addictive substances in a national OAT population is most relevant for health professionals and national health governments working with OAT patients. Before generalizing our results to other OAT populations, it is important to interpret the results according to regulations and organizations of the OAT in Norway and Sweden. It is also important to underline that paper III included only patients receiving more than one mean DDD daily of an OAT opioid per calendar year. This made our results less transferable to OAT patients who were dispensed the lowest dosages of OAT opioids. Furthermore, changes in dispensing rates have occurred from 2013-2017 to 2021. For example, the stricter dispensation practice of pregabalin introduced in June/July 2018 by the Norwegian Medicine Agencies and the Swedish Medical Products Agency has probably reduced the dispensation rate for pregabalin during the last three years. One can also assume that the dispensation rates of lisdexamphetamine have increased from 2017 to 2021, considering facilitation in the pre-approved reimbursement of lisdexamphetamine introduced in October 2018.

As far as we know, research on fatigue for SUD patients, mainly OAT patients, has not earlier been studied. However, it is essential to keep in mind that 18 % of the SUD patients in the OAT cohort do not receive OAT as the treatment approach. These patients were included because they received low-threshold primary health care frequently for substance-related harms, thus representing many of the same health conditions as OAT patients. This can increase the generalizability of our results to other SUD populations and those with similar comorbidities in high-cost countries with cultural and health system similarities with Norway. Moreover, this study was also mainly aimed at patients who were marginalized with extensive substance use. This can make the study less transferable to OAT and SUD patients with high daily functioning, those with only one mild to moderate substance dependence, or patients with recreational substance use without severe substance dependences.

Neutrality and interests

Concerning neutrality, all papers in this thesis have strengths. Using national register data, we analyzed data having high completeness and precision compared with data collected by self-reporting. Data were collected with low cost and no use of clinical health professional resources and were automatically collected from the pharmacies in Norway and Sweden. For the INTRO-HCV cohort, all data were collected by research nurses employed by our research group. The researchers were not involved in patient consultations when collecting data. We could not altogether remove the chance for research nurses had affected the participants' answers during the health assessments. However, the data collection information was presented as neutral as possible from the researchers with no interest in influencing the results in a particular direction.

Concerning interests, all authors and research nurses in these studies were employed and funded by governmental funding, including the University of Bergen, Haukeland University Hospital, the Norwegian Institute of Public Health, the University of Oslo, and/or the Research Council of Norway. No authors had any conflicting interests, including financial interests by receiving salary and remunerations from organizations or the pharmaceutical industry related to these studies. The funders were independent of the studies and were not involved in data collecting, analyzing, and publishing.

Proper reporting of data is essential. According to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist [153], we addressed the reported data for all the published papers to ensure accuracy and completeness of reporting the observational studies.

Ethical considerations

Collecting large data of all dispensations of substances from Norwegian and Swedish patients who were dispensed OAT opioids and the INTRO-HCV cohort have some ethical considerations. First, the data were stored on a protected research server with access only for pre-approved users involved in the research project. The researchers were approved by the Regional Ethic Committee, REC Vest, before getting access to the data. Second, data from register research are exempted from obtaining informed consent from patients. Data were therefore delivered anonymously with identification keys for each patient. There were not at any time possible to expose the identity of the included patients. However, using local geographical knowledge of the individuals based on region, gender, birth year, dispensed substances, etc., one can theoretically be able to identify patients. However, it is improbable that this could happen. Third, all included patients in the INTRO-HCV cohort had obtained informed consent for using the collected data on research before being enrolled in the study. The collected data were personally identifiable and were stored on a protected research server with user-controlled accesses. Fourth, all HCV-infected participants included in the INTRO-HCV cohort were offered HCV treatment with direct-acting antiviral agents. These participants were followed up closely regarding HCV treatment adherence and potential treatment complications. However, the harm of participating in the INTRO-HCV cohort could be the time spent conducting an annual health assessment. Some participants spent several consultations before completing. Overall, data, including tables and figures with variables with less than five individuals, were grouped ("< 5") to maintain anonymity in all papers.

Clinical discussion of the results

Extensive use of potentially addictive substances among patients in OAT

Nearly three out of five Norwegian and Swedish patients were dispensed a potentially addictive substance per calendar year during 2015-2017. In Norway, 46 % were dispensed a benzodiazepine and 14 % a z-hypnotic in 2017, of which 42 % (absolute value) received three or more dispensations of either a benzodiazepine or z-hypnotic during the same calendar year. In Sweden, 15 % were dispensed a benzodiazepine and 26 % a z-hypnotic in 2017. Being dispensed a benzodiazepine or z-hypnotic was associated with females rather than males, using methadone compared with buprenorphine as OAT opioids, and being dispensed a gabapentinoid or non-OAT opioid in Norway in 2017. The amount of dispensed benzodiazepines tended to be slightly reduced during 2015-2017 in both countries. The proportion of patients who were dispensed a gabapentinoid increased slightly by 2 % from 2015 to 2017 in Norway and by 1 % in Sweden. Further, the dispensation rate of pregabalin was worryingly twice as high as for gabapentin. Moreover, the dispensation rate of weak opioids was twice as high as for the strong opioids in Norway in 2017, which was the opposite of what was seen between strong and weak opioids in Sweden. Furthermore, we found a slight increase in dispensation rates of centrally acting stimulants from 3 % (2015) to 4 % (2017) in Norway and from 17 % (2015) to 18 % (2017) in Sweden, and for four out of five ADHD medications, the mean dosage exceeded the recommendations [114-118]. In Norway, being dispensed an ADHD medication was associated with patients below 25 years of age compared with those above 56 years of age, being dispensed buprenorphine rather than methadone as an OAT opioid, and being dispensed non-OAT opioids. Moreover, in Bergen and Stavanger, 39 % of SUD patients reported frequent use of non-dispensed benzodiazepines or z-hypnotics during the past 12 months prior to the first health assessment. A similar proportion for cannabis use was 52 %, stimulant use 29 %, alcohol use 26 %, and opioids use 16 %. In these two cities, the FSS-9 sum score was 43 (SD: 16) at baseline. The sum score was higher for females than males, those with frequent use of benzodiazepines compared with those with less frequent or no use of these substances, and patients having debt difficulties compared with not having these difficulties at baseline. In addition, patients with frequent use of stimulant substances were associated with lower FSS-9 sum scores than those with less frequent or no use. Furthermore, patients with frequent use of benzodiazepines compared with those with less frequent or no use over time and patients with liver fibrosis or cirrhosis measured by transient elastography compared with those with healthy liver over time were associated with lower the FSS-9 sum score per year from baseline. These trend effects were less likely to be clinically significant. Group differences in fatigue between patients using buprenorphine and methadone as OAT opioids in sociodemographic and clinical factors were also identified.

The Norwegian and Swedish dispensation rates of benzodiazepines and z-hypnotics were substantially in line with European and North-American countries' rates, although some inter-country differences existed between countries [28, 29, 154-156]. When comparing the dispensation rates for benzodiazepines and z-hypnotics among OAT patients in Sweden in 2005-2015 with our findings for 2015-2017, the rates seemed to decrease [28]. In contrast, the Norwegian dispensation rates of benzodiazepines and z-hypnotics increased compared with the dispensation rates in 2005 [154]. This could correspond to the change in criteria to granting OAT in 2010, making it possible for patients with polysubstance use to receive OAT [37]. Furthermore, comparing the use of non-dispensed benzodiazepines and z-hypnotics in Bergen and Stavanger, Norway, with other European countries, the prevalence was also

substantially equal [31]. The EMCDDA examining the non-dispensed benzodiazepine use among high-risk opioid users admitted to treatment facilities in some European countries detected that the prevalence of benzodiazepine use varied considerably from one country to another, with a range from 70 % in Germany down to 45 % in France [31], with a tendency towards an increased use with the length of stay in OAT [157]. When including all SUD patients using benzodiazepines in Bergen and Stavanger, they ranked between the prevalence of benzodiazepine use in France and Germany but just below France when we only assessed the prevalence of frequent users of the substances. However, compared with all other European countries, France has the highest coverage of OAT among opioid dependence (approximately 80 %), alluding to more polysubstance users using non-dispensed benzodiazepines compared with the SUD patients in Bergen and Stavanger [22]. This could explain the lower prevalence in Bergen and Stavanger compared with France. However, our findings only represented non-dispensed benzodiazepine and z-hypnotic use from two cities in Norway, and intra-country variations in non-dispensed benzodiazepine use were therefore likely.

Not surprisingly, we found a substantially higher proportion of patients who used non-dispensed benzodiazepines or z-hypnotics (71 %) than those dispensed these substances (2017: 50 %) in Norway. When considering the annual national self-reporting survey pointing out that half of the Norwegian OAT patients consumed benzodiazepines the four weeks prior to the survey [36], our results regarding non-dispensed benzodiazepine or z-hypnotic use were expected. Nevertheless, benzodiazepines are discouraged in Norway according to national guidelines, signifying that most Norwegian OAT patients did not fulfill the criterion in guidelines [37]. In Sweden, the use of non-dispensed potentially addictive substances is uncertain; however, dispensed potentially addictive substances reached almost equal rates in Sweden as in Norway in 2015-2017, indicating that non-dispensed substance use among Swedish OAT patients also is likely.

The mean dosages of dispensed benzodiazepines and z-hypnotics were considerably lower during the period 2013-2017 compared with the dispensed mean dosages of these substances in 2005 in Norway and an Australian cross-sectional study examining benzodiazepine dosages among OAT patients [154, 158]. The current Norwegian OAT guidelines discouraging benzodiazepine use could play an important role in reducing the dispensed dosages [37]. In Sweden, there does not exist comparable data of dispensed mean dosages before publishing this study; however, both countries presented similar trends towards decreasing mean daily dosages of dispensed benzodiazepines during the study period. Nevertheless, the decreasing mean daily dosage of dispensed benzodiazepines could also cause increased use of non-dispensed substances for patients with substance dependence. Considering that 71 % of SUD patients in Bergen and Stavanger reported non-dispensed benzodiazepines use, often high-potency benzodiazepines – such as clonazepam, diazepam, alprazolam – likely, the total mean dosage per patient was considerably above the mean daily dosages estimated using the NorPD and SPDR. This could affect the consumed dosage trends of non-dispensed and dispensed benzodiazepine use in the population without being obtained in our studies.

The use of dispensed gabapentinoid was slightly increased in Norway and Sweden in 2015-2017, corresponding to other countries' prevalence and trends [29, 159]. Interestingly, 22 % of the Swedish OAT patients were dispensed a gabapentinoid in 2005-2012, indicating a slight reduction in dispensation rate compared with our finding on 19 % in 2017 [28]. For the non-dispensed gabapentinoid use, no data were collected in Norway and Sweden; however,

other countries showed a diverging prevalence from 18 % to 37 % in different SUD populations during the past years [66, 160, 161]. Globally, several worries regarding gabapentinoid misuse and dependence have been reported among SUD patients, which for 2012-2016 had led to 634 published reports of gabapentinoids' side effects [162]. Some reports indicated that opioid dependent patients particularly preferred gabapentinoids due to their sedative and euphoric effects when taken alongside opioids [28, 32, 45, 159]. A systematic review of gabapentinoid misuse found that gabapentinoids often were sold and bought on the illegal substance market [32], exemplified by 70 % of 30 U.K. heroin users who reported gabapentinoid use [163]. Interviews concerning gabapentinoid misuse presented that they often were co-administrated with other sedative substances to enhance their effects, being a barrier to access of other substances, synergism with other substances, or to self-treat withdrawal or pain [46, 164-167]. From June 1, 2018, the Norwegian Medicines Agency decided to put pregabalin under stricter dispensing regulation [49], and Sweden introduced similar regulation on July 24, 2018 [50]. Both regulations can reduce pregabalin's dispensation rate among SUD patients in the future, even though it might lead to more non-dispensed gabapentinoid use. Considering these worries, dispensing gabapentinoid itself and its co-dispensing involving other potentially addictive substances among SUD patients should be thoroughly and individually assessed before dispensing, especially among OAT patients with a particular risk of fatal and non-fatal overdose when combining. Further monitoring of dispensed and non-dispensed gabapentinoid use is needed to understand its benefit and harms, in particular the impact on dependence and misuse.

Moreover, a slight increase in OAT patients who were dispensed ADHD medications in Norway and Sweden in 2015-2017 was found, corresponding to a slight increase from Norway's prevalence in 2008-2010 [168]. In addition, the dispensation rate of ADHD was almost four-fold higher in Sweden than in Norway. In both countries, the dispensation rates were higher than those in general Northern countries [169, 170], but still considerably lower than the estimated ADHD prevalence for SUD patients in the Northern countries [171]. This difference between dispensation rates and the prevalence of ADHD could demonstrate some differences in handling ADHD medications between countries. First, there are differences in national guidelines for dealing with dispensed ADHD medications in OAT. Besides SUD patients initiating ADHD medication in hospitals, the Norwegian guidelines for ADHD require at least three months abstinence of non-dispensed potentially addictive substances prior to ADHD medication were initiated for SUD patients who are followed up at outpatient clinics [59]. This criterion for ADHD medication is not noted in the national recommendations for ADHD treatment in Sweden, which could explain a higher dispensation rate of ADHD medication in Sweden than in Norway [172]. Otherwise, the three-month criterion was also not mentioned in a consensus report involving experts' advice from several European countries [58]. However, the experts did not reach any consensus about whether patients should abstain or reduce/recover their substance use before starting dispensing centrally acting stimulants. Second, the criteria for granting OAT are stricter in Sweden than Norway, e.g., by having a higher threshold for accepting non-dispensed substances. Considering this, one can also assume that the differences in dispensation rates were addressed more polysubstance users in OAT in Norway than Sweden, so dispensed ADHD medication was less justifiable in the former country.

The mean daily dosage for four out of five dispensed ADHD medications exceeded recommendations [114-118]. Some evidence suggests that SUD patients who received ADHD medication should be dispensed dosages equal to or higher than the recommendations [173, 174]. Although high-dosage ADHD medication itself did not show more effect on patients'

ADHD symptoms, they may increase the adherence to the treatment among SUD patients. However, a Norwegian study found that half of the OAT patients with comorbid ADHD initiating ADHD medication discontinued it during two years [175]. The reasons were relapsing to non-dispensed substance use, poor perceived effect, substance craving, adverse effects, and failure to meet the driver's license regulation. For OAT patients with ADHD using non-dispensed substances in doses that considerably exceed the dispensed ADHD medication dosages, one could also assume that the substance was terminated because it did not meet the patient's expectations.

Moreover, nearly 30 % of the SUD patients in Bergen and Stavanger self-reported at least weekly use of non-dispensed amphetamines or cocaine over the past 12 months. This was twice as high as reported in the annual national self-reported assessments in Norway [36, 109]. On the other hand, the result was lower than reported among 60 OAT patients in Finland but within the range of stimulant use in some U.S. regions [66, 176]. The higher availability of non-dispensed stimulant substances in the Bergen and Stavanger than nationwide may be one of several substantial reasons for this finding. However, it does not seem that patients with ADHD are more likely to use non-dispensed stimulants than those without ADHD [177], giving less evidence for the fact that low dispensation rate of ADHD medication nationwide can address a high use of non-dispensed stimulant substances. However, patients with non-dispensed stimulant substance use are often comorbid, and depression, psychosis, suicide attempts, worsening psychosocial functioning, and hospitalizations are frequently reported [178-181]. Therefore, addressing reasons for the high prevalence of non-dispensed stimulant use is of interest for further research.

The dispensation rate of weak non-OAT opioids was twice the rate for strong non-OAT opioids in Norway, opposed to Sweden's picture. In Norway, the total dispensation rate of weak and strong opioids was 12 % in 2005, representing a slight increase in the proportion of OAT patients dispensed non-OAT opioids [51]. The introduction of the Norwegian guidelines for OAT in 2010 represented a shift in OAT by not excluding patients with non-dispensed substance use. This encompasses patients with polysubstance use preserving more complex medical and psychosocial health challenges than those with solely opioid dependence. This could address some of the increase in the dispensed non-OAT opioid use from 2015 to 2017. On the other hand, we were surprised that weak non-OAT opioids were dispensed to OAT patients, in particular, above the dispensation rate for strong non-OAT opioids in Norway. When considering the equipotency between opioids, the weak non-OAT opioids have a lower opioid-acting effect per tablet, with recommended daily dosages far below dosages needed to curb pain for patients who received OAT opioids. For example, patients with acute moderate to severe pain usually need 20 % more of their daily OAT opioids to curb pain. For patients with a daily dosage of 90 mg methadone, 20 % are equal to approximately 20 mg methadone, converting into short- or intermediate-acting opioids as morphine is equal to almost 80 mg morphine per day [182]. For weak non-OAT opioids, 80 mg morphine represents 480 mg codeine (1.0 mg codeine is almost equal to 0.2 mg morphine) or 800 mg tramadol (1.0 mg tramadol is almost equal to 0.1 mg morphine) daily, which are far above the recommendations for tramadol or codeine (weak non-OAT opioids) [183, 184]. This example illustrated that dispensing weak non-OAT opioids for OAT patients using OAT opioids in recommended dosage does not usually meet the dosages needed for great analgesic effects for most patients with high opioid tolerance using OAT opioids daily. Still, we wondered why the dispensation rate of weak non-OAT opioids was higher than the rate for strong OAT opioids in Norway. This could indicate that OAT patients were suboptimal pain treatment and the opioid analgesic dosages not considering the considerably opioid tolerance among these patients.

Sixteen percent of SUD patients, mainly OAT patients, used non-dispensed opioids at least weekly during the past 12 months. Compared with national self-reported data, the use of non-dispensed opioids in Bergen and Stavanger was higher than nationwide, stable for the past years [36]. Our finding of non-dispensed opioid use was also higher than detected among the Finnish OAT patients [66]. Although we did not fully understand why they used non-dispensed opioids when undergoing OAT, one could assume that suboptimal pain treatment or too low OAT opioid dosage could address the use in some cases. Nevertheless, these results were uncertain and will need more attention in research before concluding with causal relationships.

Patient characteristics associated with dispensed potentially addictive substances

Being dispensed a 'benzodiazepine or z-hypnotic' or gabapentinoid was associated with females rather than males in Norway, corresponding to results also were seen in the general population [185-188]. In addition, we found a strong association between being dispensed a benzodiazepine or z-hypnotic and using methadone rather than buprenorphine as an OAT opioid. Unlike males, females have a higher prevalence of anxiety disorders and sleeping disorders, and they more often seek medical and psychosocial treatment for health challenges [189-191]. This could address the higher dispensation rates of 'benzodiazepine or z-hypnotic' and gabapentinoids among females than males. Furthermore, methadone is a second-hand substance in OAT used in many cases who were insufficiently medicated with buprenorphine-based therapy. Methadone's full opioid agonistic properties could be feasible for OAT patients suffering from underlying painful diseases and patients with severe opioid dependence who were inadequately treated by buprenorphine. Thus, one could assume that patients using methadone were more comorbid than those on buprenorphine, attributing to more dispensed benzodiazepine or z-hypnotic than those using buprenorphine-based medication.

The Norwegian OAT patients who were dispensed benzodiazepine or z-hypnotic showed an association with being dispensed a gabapentinoid, and vice versa. A similar dispensing pattern was also observed in other countries [29, 192]. Although co-users' underlying reasons are not thoroughly understood, the overlapping medical indications for benzodiazepine and gabapentinoid dispensing could play an important role in addressing these associations [193]. Benzodiazepines and gabapentinoids are both medically indicated for epilepsy and anxiety disorder, and gabapentinoids for neuropathic pain [43, 44]. Among SUD patients, the prevalence of anxiety disorder is substantially higher than the general population [62], contributing to the co-use of benzodiazepines and gabapentinoids could be dispensed in several cases. Although co-use may indicate a higher risk of non-fatal and fatal overdose death [28, 29], co-dispensing of benzodiazepines/z-hypnotics and gabapentinoids could exceptionally be the way to reach a higher functioning level with complex co-occurring diseases, e.g., by reducing criminality, treating underlying diseases, and stopping non-dispensed potentially addictive substance use and injecting substances in some of these cases [63].

The odds of being dispensed an ADHD medication were lower for patients above 56 years of age than those below 25 years of age, corresponding to the general population's findings [170, 194]. Additionally, being dispensed a ADHD medication was associated with patients who were dispensed buprenorphine rather than methadone as an OAT opioid and those who were dispensed non-OAT opioids compared with those who were not dispensed non-OAT opioids

in 2017. Little is known about why buprenorphine rather than methadone was associated with being dispensed ADHD medication; however, previous studies showed that patients on methadone were less likely to have ADHD symptoms and had greater dependence severity than those on buprenorphine [195-197]. In addition, some other characteristics of patients on methadone could contribute to lower ADHD medication rates than those using buprenorphine. First, methadone is the second-hand OAT opioid in Norway, probably used on patients having more severe opioid dependence and other substance dependence [37]. This could make the methadone cases less available to be treated with ADHD medication. Second, sedation is more likely for patients using full opioid agonist as methadone than those receiving the partial opioid agonist buprenorphine [198], potentially reducing the efficacy, acceptability, and tolerability of ADHD medications [58]. Third, according to paper I, more patients on methadone were co-dispensed benzodiazepines and z-hypnotics, potentially enabling prescribers to withhold the ADHD medication dispensations.

Fatigue among SUD patients

Paper IV is, as far as we know, the first study evaluating fatigue quantitatively for patients receiving SUD worldwide. The overall finding was that SUD patients had substantially higher fatigue levels than the general population [74], with seven out of 10 patients who presented severe fatigue symptoms, defined as at least 40 points on the FSS-9 sum score. Although it was considerable intra-individual variations in fatigue over time, the SUD patients' fatigue level at baseline was in line with other chronic diseases evaluated – such as post-stroke fatigue [199], myasthenia gravis [200], and HCV infection [80, 152, 201].

Non-dispensed potentially addictive substance impact on fatigue among SUD patients

The frequent use of non-dispensed benzodiazepines was associated with more fatigued than less frequent or no use of these substances at baseline, while the fatigue level was associated with a slight decrease per year when the frequent use of benzodiazepines was maintained from the baseline. We were not surprised that the frequent benzodiazepine use was associated with more fatigued; however, the underlying reasons for this are uncertain in this population. A report of high-risk opioid users showed that benzodiazepine and opioid users have poorer physical and psychological health, more hospitalizations, lower quality of life, and more disability than those only using opioids without benzodiazepines [31]. In addition, they are significantly more vulnerable to overdose, overdose deaths, and mental disorders – such as depression, anxiety disorders, personality disorders, and psychosis [62]. These underlying comorbidities and their treatments could also increase fatigue. Thus confound the association between patients with frequent use of non-dispensed benzodiazepines and those with less frequent or no use of these substances, e.g., by being depressed [72, 202] or using antipsychotic agents with sedative properties [203]. However, the frequent use of benzodiazepines over time was associated with decreasing fatigue levels, which could be related to changes in mental health or higher tolerance to benzodiazepines over time, giving a reduced sedative effect.

Moreover, the frequent use of non-dispensed stimulant substances was associated with less fatigue than those with less frequent or no use at baseline. This fatigue level was unchanged per year from baseline. Lower levels of fatigue for stimulant users could be related to stimulant substances' toxicological properties, including invigorating, euphoria, suppressing appetite, and lack of lethargy [56, 57]. However, frequent use of these substances is also well-documented to facilitate a wide range of harms in health associated with increased fatigue

[178, 179]. Reviews examining the health challenges of methamphetamine use indicated a higher risk of psychosis, violence, suicidality, depression, criminality, and injecting substance use [204, 205]. Considering this, one can assume that the reduced fatigue level could be related to stimulant intoxication, suppressing underlying comorbidities associated with higher fatigue levels. This could also partly address the considerable intra-individual changes in fatigue level presented in Figure 5.

Non-dispensed potentially addictive substance impact on fatigue among OAT patients

The type of OAT opioid used could affect which non-dispensed potentially addictive substances, including alcohol and cannabis, were associated with fatigue changes among OAT patients. The frequent use of non-dispensed benzodiazepine, which is taken alongside methadone, enhances these substances' sedative properties, probably making patients more fatigued than those with less frequent or no non-dispensed benzodiazepine use [31]. Compared with patients on methadone, we were surprised that the buprenorphine patients with frequent use of non-dispensed benzodiazepines were not associated with more fatigued than those on buprenorphine with less frequent or no use of non-dispensed benzodiazepines. The reasons are uncertain, although more differences in underlying comorbidities among patients with frequent use of benzodiazepines than those with less frequent or no use of benzodiazepines could have played a role. As shown earlier in this thesis, patients on methadone are likely to suffer from more comorbidities than patients with buprenorphine [195-197]. This could also have contributed to using a higher dose of non-dispensed benzodiazepines cause more fatigued among patients on methadone than those on buprenorphine. However, little is known about why frequent alcohol use was associated with less fatigue, and frequent stimulant use was associated with more fatigued than less frequent or no use of these substances among patients with buprenorphine. Why not similar findings were found for patients using methadone as an OAT opioid is not understood and needs further research before drawing causal relationships. The results and their potential reasons should, therefore, be interpreted in caution.

No other studies have evaluated fatigue in the OAT population and how the non-dispensed potentially addictive substances were associated with fatigue in this population. For these OAT patients often having a chaotic life situation, fatigue and its changes could be widely affected by individual confounding factors; being affected by substances, going through substance withdrawals, quarreling with family and friends, and exposing to treats and violence from other substance users, etc. The large intra-individual variations in the FSS-9 sum score found could support this suggestion. However, one can assume that improving medical and psychosocial conditions – such as treating HCV infection, reducing substance use, treating underlying mental disorders, and protecting against injecting substance use – will reduce the population's overall suffering and give lower fatigue levels.

Conclusions

This thesis has shown that nearly three out of five OAT patients were dispensed at least one potentially addictive substance in Norway and Sweden in 2015-2017, with some inter-country differences between substances. Besides four out of five ADHD medications, all mean daily dosages of potentially addictive substances assessed were estimated within recommendations. The considerable extent of dispensed potentially addictive substances in the OAT population compared with the general population could be understood with the high prevalence of mental and physical comorbidities in the OAT population. Furthermore, we presented that more than half of SUD patients in Bergen and Stavanger used non-dispensed potentially addictive substances, including alcohol, more than weekly during the past 12 months before the first health assessment. Moreover, the SUD patients in the two cities were more fatigued than the general population and on the level with other chronic diseases. The sociodemographic and clinical factor associated with the most increase in fatigue was the frequent use of benzodiazepines compared with less frequent or no use of these substances.

The dispensation rates of potentially addictive substances varied between Norway and Sweden. This could be related to substantial inter-country differences in the organization of OAT. In 2010, when Norway introduced the first and current OAT guidelines, non-dispensed substance use itself was not a criterion to be excluded from the OAT. In contrast, Sweden has a lower threshold to transfer patients to other treatment if OAT patients use non-dispensed substance use. This could lead to different OAT populations, with a higher prevalence of polysubstance users in Norway than in Sweden, with more dispensed potentially addictive substance use in Norway.

Non-dispensed potentially addictive substances were prevalent among OAT patients in Bergen and Stavanger, Norway, illustrating by nearly three out of four OAT patients had used non-dispensed benzodiazepine during the past 12 months. Not surprisingly, self-reported use of non-dispensed substances was substantially higher than the rates of dispensed potentially addictive substances in Norway and Sweden. However, the prevalence of non-dispensed substances corresponded to the prevalence of non-dispensed substances in other European countries.

Moreover, SUD patients in Bergen and Stavanger had high fatigue levels, with significant intra-individual changes between the annual health assessments. The underlying factors for being fatigued and the intra-individual fluctuations in fatigue were associated with some included sociodemographic and clinical factors. However, other factors beyond those investigated in this thesis could probably explain a larger degree of the variance in fatigue.

Consideration for future research

Limited attention has been paid to research on patients with polysubstance dependences in OAT, their comorbidities, and the overdose death risk. We lack knowledge on how these patients can be reached with OAT and how we best tackle their polysubstance dependences when receiving OAT opioids. Polysubstance dependence is also a substantial problem when it comes to ADHD medications. Unfortunately, little is known about how ADHD medication improves ADHD symptoms among patients with polysubstance dependences with comorbid ADHD. Furthermore, besides OAT, we lack knowledge about how we best protect against overdoses and reduce the risk of injecting substance use for patients with non-dispensed substance dependences. Can dispensing stimulants and benzodiazepines for dependences for these substances recover patients from criminality and diminish contact with dealers so that overdoses and injecting substance use are less likely? Finally, more knowledge of subjective health complaints – such as fatigue, quality of life, and psychological distress, can be essential to evaluate SUD populations, compare SUD populations to other chronic disease populations, and identify factors that might improve subjective health complaints in this population in the future.

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Errata

Thesis

- Page 1: Paragraph 2: “In 2017, opioid use dominated those entering specialized substance treatment, representing 35 % of all first-time entrants” should be replaced with “In 2017, opioid use dominated among those entering specialized substance treatment, representing 35 % of all first-time entrants”.

- Page 1: Paragraph 3: “However, whether this change will affect the criteria for granting OAT is still unknown” should be rewritten to “How this will change the inclusion criteria for OAT remains unknown”.

- Page 2: Figure 1 legend: “The figure displays the division of commonly used terms in Addiction Medicine and how these realte to demand for care; “Substance use disorder”, “Opioid dependence”, and “Opioid agonist therapy” should say “The figure displays the division of commonly used terms in Addiction Medicine and their relations to demand for care: “Substance use disorders”, “Opioid dependence”, and “Opioid agonist therapy”.

- Page 11: Non-OAT opioids: “e.x.: codeine plus paracetamol” should be rewritten to “e.g.: codeine plus paracetamol.”

- Page 19: “Discontinuing OAT”: “For patients who discontinued OAT, we defined three equal periods from 180 days prior to the discontinuation date to 90 days” should be rewritten to “For patients who discontinued OAT, we defined three equal periods from 180 days before to 90 days after the discontinuation date.”

- Page 37: Paragraph 4: “Other OAT patients were polysubstance users living on the street with broken family and friend relationships with several hospitalizations due to intoxications where the risk of long-term use was more likely” should be edited to “Other OAT patients were polysubstance users living on the street with broken family and friend relationships with several hospitalizations due to intoxications where long-term use was more likely”.

- Page 39: Paragraph 1: “The other predictors measuring dose-response relationships: age, liver stiffness (transient elastographyand APRI), hemoglobin, estimated glomerulus filtration rate, and C-reactive protein, a dose-response relationship was not seen in the SUD population” should be rewritten to “Other dose-response relationships between the fatigue level and the predictors (age, liver stiffness (transient elastographyand APRI), hemoglobin, estimated glomerulus filtration rate, and C-reactive protein) were not found in the SUD population.”

- Page 39: paragraph 2: “Unstable housing situations or injecting substance use not affected fatigue, although they could do se based on clinical experience” should be rewritten to “Unstable housing situations or injecting substance use did not affect fatigue, although clincial experience suggest that this may be the case.”

- Page 40: paragrah 4: “The Regional Ethic Committee, REC Vest, approved the users before data became available” should be rewritten to “The researchers were approved by the Regional Ethic Committee, REC Vest, before getting access to the data.”

- Page 42, paragraph 3: “In Sweden, there not exists comparable data of dispensed mean dosages prior to this study (…)” should be rewritten to “In Sweden, there does not exist comparable data of dispensed mean dosages before publishing this study (…)”

- Page 57: Reference 143: The paper has been published and should be referred as: "Vold JH, Gjestad R, Aas CF, Meland E, Johansson KA, Fadnes LT: **Validation of a three-item Fatigue Severity Scale for patients with substance use disorder: a cohort study from Norway for the period 2016-2020**. *Health Qual Life Outcomes* 2021, **19**(1):69."

Paper II

- Page 4: Statistical analyses: Chi-square test was not used and should be removed.

Paper IV

- Page 11: Reference 25 refers to a wrong paper. The correct paper should be: "World Health Organization: Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. 2009. [Available from: https://www.who.int/publications/i/item/9789241547543].

Paper I

Vold JH, Skurtveit S, Aas C, Chalabianloo F, Kloster PS, Johansson KA, Fadnes LT: **Dispensations of benzodiazepines, z-hypnotics, and gabapentinoids to patients receiving opioid agonist therapy; a prospective cohort study in Norway from 2013 to 2017.** *BMC health services research 2020*, 20(1):352.

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BMC Health Services Research

RESEARCH ARTICLE Open Access

Dispensations of benzodiazepines, z-hypnotics, and gabapentinoids to patients receiving opioid agonist therapy; a prospective cohort study in Norway from 2013 to 2017

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Abstract

Background: Dispensations of benzodiazepines, z-hypnotics, and gabapentinoids to patients on opioid agonist therapy (OAT) are common and have pros and cons. The objectives of the current study are to define the dispensation rates of these potentially addictive drugs, and whether the number and the mean daily doses of dispensed OAT opioids and discontinuing OAT, are associated with being dispensed benzodiazepines, z-hypnotics and gabapentinoids among patients on OAT in Norway in the period 2013 to 2017.

Methods: Information about all dispensed opioids, benzodiazepines, z-hypnotics and gabapentinoids were recorded from the Norwegian Prescription Database (NorPD). A total of 10,371 OAT patients were included in the study period. The dispensation rates were defined as the number of patients who were dispensed at least one of the potentially addictive drugs divided among the number of patients who have dispensed an OAT opioid per calendar year. Mean daily doses were calculated, and for benzodiazepines and z-hypnotics, stated in diazepam equivalents. The association between dispensed potentially addictive drugs, and the number and the type of dispensed OAT opioids were calculated by using logistic regression models.

(Continued on next page)

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Results: Half of the OAT patients received at least one dispensation of a benzodiazepine or z-hypnotic, and 11% were dispensed at least a gabapentinoid in 2017. For dispensed benzodiazepines or z-hypnotics, the mean daily dose was reduced from 21 mg (95% confidence interval (CI): 20–23) diazepam equivalents in 2013 to 17 mg (95% CI: 16–17) in 2017. The mean daily dose of pregabalin increased from 365 mg (95% CI: 309–421) in 2013 to 386 mg (95% CI: 349–423) in 2017. Being dispensed a gabapentinoid (adjusted odds ratio (aOR) = 2.5, 95% CI: 2.1–3.0) or a non-OAT opioid (aOR = 3.0, 95% CI: 2.6–3.5) was associated with being dispensed a benzodiazepine or z-hypnotic. Discontinuing OAT did not affect the number of dispensations and the doses of potentially addictive drugs.

Conclusion: The dispensation rates of potentially addictive drugs are high in the OAT population. Treatment indications, as well as requirements for prescription authority, need to be debated and made explicit. Randomized controlled trials evaluating the benefits and risks of such co-prescription are required.

Keywords: Opioid substitution treatment, Benzodiazepines, Zopiclone, Zolpidem, Pregabalin, Gabapentin, Opioids, Drug prescriptions

Background

Dispensations of benzodiazepines, z-hypnotics, and gabapentinoids to patients on opioid agonist therapy (OAT) have pros and cons. These drugs may increase the mortality among patients on OAT and are associated with criminality, psychosocial problems, and injecting drug use [1, 2]. The use of several potentially addictive drugs is particularly challenging in an OAT program aimed at reducing mortality and injecting drug use and achieve rehabilitation among marginalized and comorbid patients with opioid addiction [3–8]. However, dispensations of benzodiazepines among highly comorbid patients with polydrug use may decrease the mortality if such dispensations make patients abstinent of illegal drugs, and they are followed up strictly by health professionals [2].

The proportion of OAT patients who were dispensed benzodiazepines or z-hypnotics varies across countries. In the United Kingdom, the proportion of OAT patients who were dispensed benzodiazepines and z-hypnotics was 42 and 20%, respectively, between 1998 and 2014 [9]. In Sweden, 32% of OAT patients were dispensed a benzodiazepine, and 41% received a z-hypnotic in the period from 2005 to 2012 [1]. Further, the proportion of Norwegian OAT patients who were dispensed benzodiazepine was 40% in 2005. Regulations of OAT are a typical reason for differences in the proportion of patients who are dispensed, potentially addictive drugs between countries [10]. In some countries, OAT has been a subject for strict regulation, implying that OAT is stopped if used potentially addictive drugs concomitantly [11–13]. Others, e.g., Norway, such discontinuation of OAT in case of benzodiazepine, and z-hypnotic use has become less common compared to during the early 2000s [14, 15].

The knowledge of gabapentinoid use among patients on OAT is lacking. However, for the last couple of years, gabapentinoids, particularly pregabalin, are consumed significantly more often among patients with opioid addiction compared to patients with other drug addictions [16]. Withdrawal symptoms are described if dose reduction or discontinuation [17–20], while using high-dosed gabapentinoids may cause euphoric effects, sedation, hallucinations, dissociation, conspicuous behavior, and the reinforced effect of OAT opioids [8, 16]. Dispensing gabapentinoids among patients with opioid addiction not necessarily indicated misuse or addiction. However, it is worrying if adverse side effects occur when combining with highly potent opioids with OAT opioids [16].

In Norway, opioid agonist therapy has been applied increasingly as an available treatment approach for opioid addiction [15]. In 2017, about 7500 patients received OAT opioids, and the majority received their OAT opioids at least once per week from pharmacies. A decreasing proportion of patients discontinued OAT during the past few years, and in 2017, 681 patients, including those who died, left the treatment [15]. Although, little is known about dispensations of benzodiazepines and z-hypnotics and gabapentinoids among patients on OAT. Thus, this observational study aims to investigate the dispensation rates and doses of these potentially addictive drugs among patients who were dispensed at least one OAT opioids in Norway in the period 2013 to 2017 and those who discontinued OAT. This study has three objectives:

(1) To define dispensation rates and mean daily dose of benzodiazepines, z-hypnotics, and gabapentinoids per calendar year.
(2) To assess the association between OAT opioids in terms of the number of dispensations and mean daily dose of OAT opioids, and whether patients are dispensed a benzodiazepine, z- hypnotic, or gabapentinoid, or not per calendar year.
(3) To evaluate whether discontinuations of OAT affect the number of dispensations and the mean daily dose of dispensed benzodiazepines and z-hypnotics, or gabapentinoids.

Methods

Data source

All data were register data and were drawn from the Norwegian Prescription Database (NorPD) (www.norpd.no). From January 1, 2004, all pharmacies in Norway are obliged by law to submit all the dispensed drugs data electronically to the Norwegian Institute of Public Health. NorPD contains information of all dispensed drugs, including reimbursements, dispensed from pharmacies in Norway, except for dispensations dispensed during hospitalizations or at outpatient clinics. Anatomical Therapeutic Chemical (ATC) classification system was employed according to the determination by the World Health Organization (WHO) collaborating centre for drug statistics per October 2018 [21]. NorPD data were collected from January 1, 2013, to March 31, 2018, in this study. The STROBE checklist was applied in the preparation of the study (Additional file 1).

Study population

All patients above 18 years of age who received at least one dispensation of an OAT opioid, including methadone, levomethadone, buprenorphine, and buprenorphine-naloxone, from January 1, 2013, to December 31, 2017, were included. The patients using methadone tablets to achieve pain relief in palliative care were excluded by identifying those who only were dispensed methadone tablets without any dispensations of other OAT opioids or methadone mixture in the period from January 1, 2004, to December 31, 2017. Discontinuing OAT was defined as all patients who had the last dispensation of an OAT opioid in the inclusion period from January 1, 2017, to September 30, 2017, and then, no dispensations until the end of the collected NorPD data on March 31, 2018.

Analysis strategy and statistical analyses

Definitions of opioids, benzodiazepines, z-hypnotics, gabapentinoids, age, the number of dispensations, mean daily doses, and the type of dispensed OAT opioid

Opioid agonist therapy opioids, non-OAT opioids, and gabapentinoids, including gabapentin and pregabalin, were defined according to their ATC codes (Additional file 2). Benzodiazepines and z-hypnotics were defined as all benzodiazepines and z-hypnotics that have or have had marketing authorizations in Norway during the study period, including alprazolam, clonazepam, diazepam, flunitrazepam, nitrazepam, oxazepam, zolpidem, and zopiclone. Dispensations of benzodiazepines and z-hypnotics were pooled.

All included OAT patients were categorized into age groups per calendar year. The age groups were ≤ 25, 26–35, 36–45, 46–55, and ≥ 56. The number of dispensations was defined as all dispensations of a drug per calendar year. Further, the type of OAT opioid was defined as the last type of opioid that was dispensed per year. The mean daily doses of benzodiazepines, z-hypnotics, and gabapentinoids per year were calculated by using daily defined doses (DDD) stated in NorPD defined by the WHOs standards [21]. For benzodiazepines and z-hypnotics, dispensed DDDs of each benzodiazepine or z-hypnotic were summarized per year and converted to milligrams. For each benzodiazepine or z-hypnotic, the doses per year (in milligrams) were converted to diazepam equivalents, according to a benzodiazepine and z-hypnotic equipotency table stated in the Norwegian national guidelines for addictive drugs (Additional file 3) and WHOs standards [21, 22]. The total doses of each benzodiazepine or z-hypnotic were summarized (in diazepam equivalents) and divided on 365.25 days to calculate the mean daily doses per year. For gabapentinoids, the number of DDDs of gabapentin and pregabalin, respectively, were summarized per calendar year, and further, converted to milligrams by using WHOs standards [21]. The total dispensed doses of pregabalin and gabapentin were divided similarly on 365.25 days to calculate the mean daily dose per year. For OAT opioids, the number of DDDs of any defined OAT opioid were summarized and divided this by the number of days between the date of the first and the last dispensation per year. Due to this estimation, all patients that only were dispensed one dispensation of an OAT opioid per year were censored.

Moreover, patients were stratified into different categories according to the number of dispensations and the mean daily doses of dispensed benzodiazepines and z-hypnotics, gabapentinoids, and OAT opioids, respectively. Benzodiazepines and z-hypnotics, and gabapentinoids had three dispensation groups: 0, 1–2, and ≥ 3 dispensations per calendar year, and the OAT opioids were categorized into four groups: 1–6, 7–12, 13–51, and ≥ 52 dispensations per calendar year. Benzodiazepines and z-hypnotics were divided into three groups according to the mean daily doses (in milligrams) were dispensed: 0, ≤20, > 20 - ≤40, and > 40 diazepam equivalents. The mean daily doses of pregabalin and gabapentin were categorized into three groups. For pregabalin (mg per day): > 0 - ≤300, > 300 - ≤600, and > 600, and for gabapentin (mg per day): > 0 - ≤900, > 900 - ≤3600, > 3600. OAT opioids were defined as the mean daily DDDs, and the following three groups were used: 0- < 1, 1- < 2, and ≥ 2 mean DDDs per day. The ratio between DDD and milligrams are presented in Additional file 3.

Analysis strategy according to the aims

Dispensation rates were defined as all OAT patients who were dispensed one or more of the defined benzodiazepines or z-hypnotics, or gabapentinoids, respectively, per calendar year divided on all included OAT patients the same year.

Diazepam equivalents were used to adjust for equipotency of benzodiazepines and z-hypnotics. Due to the

absence of consistent international guidelines of equipotency for these drugs, a sensitivity analysis was conducted [22]. The lowest and highest stated equipotency for each benzodiazepine and z-hypnotic, as well as a mean of them, respectively, were used to create three equipotency equations to convert all dispensed doses per year of each benzodiazepine or z-hypnotic into diazepam equivalents. The mean equivalent equation was as follow (in milligrams (mg)):

$$\begin{aligned} Diazepam\ equivalents_{mean} = {} & diazepam + oxazepam \\ & \times \frac{1}{4} + alprazolam \times \frac{40}{3} \\ & + clonazepam \times \frac{40}{3} \\ & + flunitrazepam \times \frac{40}{3} \\ & + nitrazepam \\ & + zopiclon \times \frac{8}{7} \\ & + zolpidem \times \frac{2}{3} \end{aligned}$$

The lowest and the highest equivalent equations are presented in Additional file 4.

The number of dispensations of benzodiazepines and z-hypnotics, gabapentinoids, and OAT opioids, respectively, was plotted against the number of dispensations of an OAT opioid per year. Furthermore, the mean daily doses of dispensed benzodiazepines and z-hypnotics, and gabapentinoids, respectively, were plotted against mean daily DDD of OAT opioids per year.

The associations between being dispensed a benzodiazepine or z-hypnotic, or a gabapentinoid, and age, gender, type of OAT opioid, the number of dispensed OAT opioids, and being dispensed a non-OAT opioid were assessed per calendar year by using logistic regression models.

Dispensation rates and the mean daily doses of benzodiazepines and z-hypnotics, and gabapentinoids were evaluated for patients who discontinued OAT. For the baseline, the dispensation rates and the mean daily doses of dispensed benzodiazepines or z-hypnotics (stated in diazepam equivalents), and gabapentinoids, respectively, were calculated for the period 180 to 90 days before discontinuation date. Furthermore, the dispensation rates and the mean daily doses of benzodiazepines or z-hypnotics, and gabapentinoids, during the last 90 days before and the 90 days after discontinuation date, respectively, were summarized separately and

Table 1 Baseline characteristics of patients on opioid agonist therapy in Norway

Baseline characteristics	2013		2014		2015		2016		2017	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Patients	7709		7914		7958		7804		7709	
Deaths	165		151		138		114		124	
Patients, excl. deaths	7544		7763		7820		7690		7585	
Age										
- ≤ 25	211	3	185	2	171	2	135	2	120	2
- 26-35	1590	21	1570	20	1551	20	1403	18	1333	18
- 36-45	2724	36	2730	35	2605	33	2508	33	3292	32
- 46-55	2283	30	2449	32	2544	33	2540	33	2548	34
- ≥ 56	736	10	829	11	949	12	1104	14	1192	16
Mean (SD)	*43 (10)*		*44 (10)*		*44 (10)*		*44 (10)*		*45 (10)*	
Gender										
Men	5221	69	5390	69	5430	69	5354	70	5245	69
Women	2323	31	2373	31	2390	31	2336	30	2340	31
OAT opioids[a]										
Methadone, included levomethadone	3406	45	3264	42	3216	41	3066	40	2981	39
Buprenorphine[b]	4138	55	4499	58	4604	59	4624	60	4604	61
Potentially addictive drugs										
Dispensed a benzodiazepine and z-hypnotic[c]	3747	50	3809	49	3714	47	3758	49	3762	50
Dispensed a gabapentinoid	708	9	662	9	717	9	762	10	845	11

NorPD Norwegian Prescription Database, *OAT* Opioid agonist therapy, *SD* Standard deviation
[a]The last type of dispensed OAT opioid per year
[b]Include buprenorphine-naloxone
[c]Z-hypnotic includes zolpiclone and zolpidem

compared to dispensation rates and mean daily doses at baseline.

Statistical analyses

Means, median, percentiles, percentage, 95% confidence interval (CI), odds ratio (OR), and *p*-value are presented when appropriate. The one-sample t-test was used to calculate mean daily doses of dispensed benzodiazepines or z-hypnotics, or gabapentinoids with 95% CI. The paired sample t-test was used to compare the differences in the mean daily dose of benzodiazepines or z-hypnotics and gabapentinoids, respectively, per year among OAT patients who discontinued OAT. Multivariable analyses for categorical variables were performed per year by creating logistic regression models. For these models, being dispensed a gabapentinoid, or a benzodiazepine or z-hypnotic were dependent variables, respectively, per year. Age groups, gender, type of OAT opioid, the number of dispensed OAT opioids, and being dispensed a non-OAT opioid were independent variables and defined categorically. In addition, being dispensed a gabapentinoid was used as an independent and categorical variable when being dispensed a benzodiazepine, or a z-hypnotic was defined as a dependent variable, and vice versa. The level of statistical significance was $p < 0.05$. All patients were excluded from the calendar year they died. SPSS version 24 was used for all analyses.

Ethical considerations

The Regional Committee for Medical and Health Research Ethics, REC vest, Norway, has approved the use of registry data for the study (approval number 2018/939/REK Vest, June 19, 2018). No informed consent from included patients was necessary.

Results

Basic characteristics

A total of 10,371 patients were dispensed at least one OAT opioid from pharmacies in Norway in the period 2013 to 2017 (Table 1). In 2017, 69% were men. The mean age increased from 43 (standard deviation (SD): 10) years in 2013 to 45 (SD: 10) years in 2017. A total of 690 participants died during the study period.

Dispensation rates and mean daily doses of dispensed benzodiazepines, z-hypnotics, and gabapentinoids

The proportion of patients who received at least one dispensation of benzodiazepines or z-hypnotics was 50% in 2017, and 42% received three or more such dispensations (Fig. 1). Similar findings were found yearly from 2013 to 2016. The dispensation rates of benzodiazepines

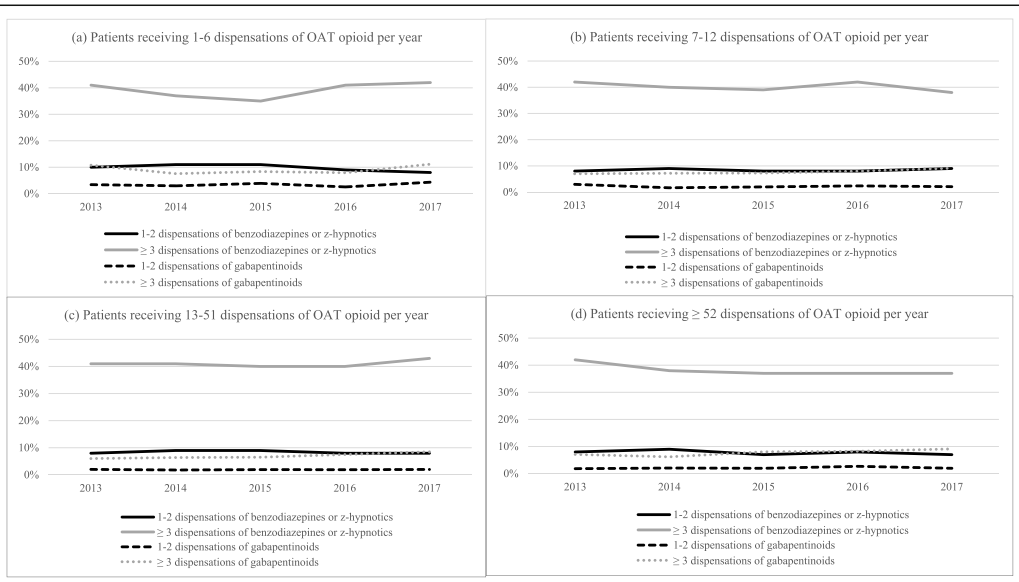

Fig. 1 The proportion of patients on OAT were dispensed a benzodiazepine or z-hypnotic, and a gabapentinoid. Legend: OAT = opioid agonist therapy. The figures display the proportion of patients who were dispensed 1–2 or 3 or more dispensations of benzodiazepines or z-hypnotics and gabapentinoids, respectively, of those who dispensed an OAT opioid per calendar year in the study period. Each figure **a**) to **d**) displays patients on OAT categorized on the number of dispensations of OAT opioids per year: **a**) 1–6 dispensations, **b**) 7–12 dispensations, **c**) 13–51 dispensations, and **d**) 52 or more dispensations

and z-hypnotics declined from 21 mg (95% CI: 20–23 mg) diazepam equivalents per day in 2013 to 17 mg (95% CI: 16–17 mg) diazepam equivalents per day in 2017 (Table 2a and Table 2b). A quarter of patients was dispensed oxazepam, which was the most frequently dispensed benzodiazepine per year throughout the study period (Table 3). Zopiclone was the most frequently dispensed z-hypnotic per patient per year.

Gabapentinoids were dispensed to 9 % of the patients in 2013 and 11% of the patients in 2017. Pregabalin was almost twice as frequently dispensed per patient as gabapentin per year throughout the study period. The mean daily doses of dispensed pregabalin increased with 1% per year from 365 mg (95% CI: 309–421 mg) in 2013 to 386 mg (95% CI: 349–423 mg) in 2017, and gabapentin increased with 4% per year from 911 mg (95% CI: 753–1068 mg) to 1047 mg (95% CI: 885–1209 mg) in the same period.

The dispensation rates of benzodiazepines and z-hypnotics, and gabapentinoids related to the number of dispensations and mean daily DDD of dispensed OAT opioids

The number of dispensations and the mean daily DDD of OAT opioids was not associated with changes in dispensation rates or the number of dispensations of benzodiazepines and z-hypnotics or gabapentinoids per year in the study period (Additional files 5, 6 and 7). However,

Table 2 The daily doses of dispensed potentially addictive drugs

a)

All indications		**2013**	**2014**	**2015**	**2016**	**2017**
Benzodiazepine and z-hypnotic dose per patient (in diazepam equivalents)		**mean (lowest-highest)**				
	Mean (mg/day)	21 (17–29)	20 (16–27)	19 (15–25)	17 (14–23)	17 (14–22)
	Median (mg/day)	10 (9–12)	10 (9–12)	10 (8–12)	10 (8–12)	10 (8–11)
	25 percentile (mg/day)	3 (2–3)	2 (2–3)	3 (2–3)	3 (2–3)	3 (2–3)
	75 percentile (mg/day)	23 (20–29)	22 (19–27)	21 (18–26)	21 (18–26)	20 (18–25)
All indications		**2013**	**2014**	**2015**	**2016**	**2017**
Pregabalin dose per patient	Mean (mg/day)	365	365	371	381	386
	Median (mg/day)	205	230	249	285	255
	25 percentile (mg/day)	46	74	62	84	69
	75 percentile (mg/day)	506	552	552	561	552
All indications		**2013**	**2014**	**2015**	**2016**	**2017**
Gabapentin dose per patient	Mean (mg/day)	911	970	997	960	1047
	Median (mg/day)	411	488	493	493	513
	25 percentile (mg/day)	82	124	82	82	164
	75 percentile (mg/day)	1228	1314	1383	1286	1430

b)

All indications		**2013**	**2017**
		Mean dose (95 % CI)	Mean dose (95% CI)
	Diazepam equivalents per patient		
Benzodiazepine and z-hypnotic dose per patient (in diazepam equivalents)	Mean (mg/day)	21 (20–23)[a]	17 (16–17)[b]
Pregabalin dose per patient	Mean (mg/day)	365 (309–421)[c]	386 (349–423)[d]
Gabapentin dose per patient	Mean (mg/day)	911 (753–1068)[e]	1047 (885–1209)[f]

Df Degrees of freedom, *Lowest* Lowest equipotency dose, *Highest* Highest equipotency dose, and Mean = Min + Max divided by 2

[a]One sample t-test, df = 3746, [b]one sample t-test, df = 3761, [c]one sample t-test, df = 486, [d]one sample t-test, df = 590, [e]one sample t-test, df = 260, and [f]one sample t-test, df = 309

The table a) displays the daily doses (mean, median, 25 percentile, and 75 percentile) of dispensed benzodiazepines or z-hypnotics (calculated in diazepam equivalents), pregabalin and gabapentin per year among patients on OAT in Norway in period 2013 to 2017

The table b) displays the mean daily doses of dispensed benzodiazepines or z-hypnotics (calculated in diazepam equivalents), pregabalin and gabapentin in 2013 and 2017. The 95% confidence intervals were calculated by one-sample t-test analyses

For table a) and b), an equipotency table for benzodiazepines and z-hypnotics were used to make sensitivity analyses displaying the lowest equipotency dose and the highest equipotency dose of the included benzodiazepines and z-hypnotics. The results were presented in parentheses. All dispensed benzodiazepines and z-hypnotics were summarized per year

Table 3 The proportion of patients who were dispensed benzodiazepines, z-hypnotics, and gabapentinoids, respectively

Year	2013		2014		2015		2016		2017	
Benzodiazepines or z-hypnotics	**No.**	**%[a]**	**No.**	**%[a]**	**No.**	**%[a]**	**No.**	**%[a]**	**No.**	**%[a]**
Oxazepam	2094	28	2091	27	2124	27	2183	28	2229	29
Diazepam	1216	16	1251	16	1222	16	1272	17	1289	17
Zopiclone	1026	14	964	12	932	12	936	12	863	11
Nitrazepam	757	10	759	10	747	10	737	10	701	9
Clonazepam	479	6	432	6	362	5	331	4	268	4
Zolpidem	351	5	359	5	333	4	315	4	327	4
Alprazolam	305	4	304	4	237	3	206	3	196	3
Flunitrazepam	41	1	38	0	37	0	32	0	36	0
Gabapentinoids	**No.**	**%[a]**	**No.**	**%[a]**	**No.**	**%[a]**	**No.**	**%[a]**	**No.**	**%[a]**
Pregabalin	487	6	449	6	491	6	523	7	591	8
Gabapentin	260	3	240	3	277	4	291	4	310	4

No. Number of patients, *OAT* Opioid agonist therapy
[a]Percent of all patients who were dispensed an OAT opioid
The table displays the proportion of all OAT patients who were dispensed different benzodiazepines, z-hypnotics, and gabapentinoids

being dispensed a benzodiazepine or z-hypnotic was associated with aging 46–55 years or being above 56 years of age rather than aging below 25 years, gender women, using methadone rather than buprenorphine as OAT opioid, or being dispensed at least one dispensation of non-OAT opioids, or gabapentinoids in 2017 (Table 4, Additional file 8). Further, being dispensed a gabapentinoid was associated with being dispensed a benzodiazepine or z-hypnotic or a non-OAT opioid. Similar results were substantially found per year in the period 2013 to 2016.

Dispensation rates and mean daily doses of dispensed benzodiazepines and z-hypnotics, and gabapentinoids related to discontinuation of OAT

We identified 693 patients who discontinued OAT during the inclusion period. Of those, 156 patients were dispensed at least one dispensation of a benzodiazepine or z-hypnotic in the period from 180 days before to 90 days after discontinuation. The mean daily dose of dispensed benzodiazepine and z-hypnotic was not changed compared to the mean daily dose at baseline when patients discontinued OAT (Δ mean daily dose (in mg): 0, 95% CI: − 3 − 3) (Fig. 2).

Furthermore, 42 patients were dispensed a benzodiazepine or z-hypnotic only during the 90 days after discontinuation. Of these patients, the mean daily dose of benzodiazepines or z-hypnotics during the 90 days after discontinuation was about half of the mean daily dose of these patients who were dispensed benzodiazepines or z-hypnotics at baseline and until 90 days after the discontinuation. Pregabalin and gabapentin were prescribed to 50 and 23 patients, respectively, during the 180 days before to 90 days after discontinuation of OAT (Additional file 9). No changes in mean daily doses of these drugs were found when comparing the mean daily doses at baseline with the mean daily doses the first 90 days after the discontinuation (pregabalin: Δ mean daily dose (in mg): 50, 95% CI: − 47 − 149, gabapentin: Δ mean daily dose (in mg): 190 mg, 95% CI: − 789 − 1168).

Discussion

In the period 2013 to 2017, a steady proportion of the Norwegian OAT population received at least one prescription of a benzodiazepine or z-hypnotic. Furthermore, the number of patients who were dispensed at least one dispensation of a gabapentinoid increased slightly in the study period. The mean daily dose of benzodiazepines and z-hypnotics was declining, while the mean daily dose of pregabalin and gabapentin were increasing. The number of dispensations and the mean daily DDD of OAT opioids did not affect the number of dispensations of benzodiazepines and z-hypnotics, or gabapentinoids. Being dispensed a benzodiazepine or z-hypnotic was associated with aging 46–55 years or being above 56 years of age rather than aging below 25 years, gender women, using methadone rather than buprenorphine as OAT opioid or being dispensed at least once a non-OAT opioid, or a gabapentinoid in 2017. Similar results were substantially found in the period from 2013 to 2016. Oxazepam and zopiclone were the most frequently dispensed benzodiazepine and z-hypnotic, respectively, and pregabalin was prescribed twice as often per patient per year as gabapentin throughout the study period. Discontinuation of OAT was not associated with changes in the dispensation rates or the mean daily doses of benzodiazepines or z-hypnotics, or gabapentinoids.

Our findings were in line with dispensation rates of benzodiazepines, z-hypnotics, and gabapentinoids in the OAT population in the United Kingdom in the period from

Table 4 Logistic regression analyses of variables associated with being dispensed a benzodiazepine or z-hypnotic, and a gabapentinoid

a)

2017	Dispensed a benzodiazepine or z-hypnotic			
	N = 3764			
	cOR	***p*-value**	**aOR (95% CI)**	***p*-value**
Age				
- ≤ 25	1.0 (ref.)		1.0 (ref.)	
- 26-35	1.0	.80	0.9 (0.6–1.4)	.76
- 36-45	1.0	.85	1.0 (0.7–1.5)	.94
- 46-55	*1.6*	*.02*	*1.7 (1.1–2.5)*	*.05*
- ≥ 56	*1.9*	*< .01*	*1.2 (1.1–1.3)*	*.01*
Gender				
- Men	1.0 (ref.)		1.0 (ref.)	
- Women	*1.2*	*< .01*	*1.2 (1.1–1.3)*	*< .01*
The number of dispensations of OAT opioids				
- ≥ 52	1.0 (ref.)		1.0 (ref.)	
- 13-51	*1.3*	*< .01*	*1.2 (1.1–1.5)*	*.01*
- 7-12	1.1	.27	1.0 (0.9–1.3)	.73
- 1-6	*1.3*	*.03*	1.1 (0.9–1.4)	.23
OAT opioids[a]				
- Buprenorphine (incl. combinations)	1.0 (ref.)		1.0 (ref.)	
- Methadone (incl. Levomethadone)	*1.4*	*< .01*	*1.3 (1.2–1.4)*	*< .01*
Dispensed a non-OAT opioid	*3.5*	*< .01*	*3.0 (2.6–3.5)*	*< .01*
Dispensed a gabapentinoid	*3.0*	*< .01*	*2.5 (2.1–3.0)*	*< .01*

b)

2017	Dispensed a gabapentinoid			
	N = 845			
	cOR	***p*-value**	**aOR (95% CI)**	***p*-value**
Age				
- ≤ 25	1.0 (ref.)		1.0 (ref.)	
- 26-35	1.1	.71	1.2 (0.6–2.2)	.60
- 36-45	1.0	.90	1.1 (0.6–2.0)	.79
- 46-55	1.0	.99	0.9 (0.5–1.7)	.75
- ≥ 56	1.0	.95	0.8 (0.4–1.5)	.45
Gender				
- Men	1.0 (ref.)		1.0 (ref.)	
- Women	1.3	< .01	1.1 (1.0–1.3)	.16
The number of dispensations of OAT opioids				
- ≥ 52	1.0 (ref.)		1.0 (ref.)	
- 13-51	0.9	.62	0.9 (0.7–1.1)	.31
- 7-12	1.0	.95	0.9 (0.7–1.3)	.72
- 1-6	*1.5*	*.01*	1.2 (0.9–1.7)	.26
OAT opioids[a]				
- Buprenorphine (incl. combinations)	1.0 (ref.)		1.0 (ref.)	
- Methadone (incl. Levomethadone)	1.1	.46	1.1 (0.9–1.3)	.41
Dispensed a non-OAT opioid	*3.7*	*< .01*	*3.0 (2.5–3.5)*	*<.01*
Dispensed a benzodiazepine or z-hypnotic	*3.0*	*< .01*	*2.5 (2.1–3.0)*	*<.01*

cOR crude odds ratio, *aOR* adjusted odds ratio, *CI* Confidence interval, and *OAT* Opioid agonist therapy

[a]The last type of dispensed OAT opioid

Table a) and b) display unadjusted (crude) and adjusted odds ratio for all independent variables of patients who were dispensed at least a benzodiazepine or z-hypnotic, and a gabapentinoid, respectively, in 2017 in Norway. a) Being dispensed at least a benzodiazepine or z-hypnotic was defined as a dependent variable, and age, gender, 'the number of dispensations of OAT opioids,' 'OAT opioids,' 'dispensed a non-OAT opioid,' and 'dispensed a gabapentinoid' were defined as categorical and independent variables. b) Being dispensed a gabapentinoid was defined as a dependent variable, and age, gender, 'the number of dispensations of OAT opioids,' 'OAT opioids,' 'dispensed a non-OAT opioid,' and 'dispensed a benzodiazepine or z-hypnotic' were defined as categorical and independent variables

1998 to 2014 [9]. Further, the dispensation rates were higher for being dispensed a benzodiazepine or a gabapentinoid and lower for being dispensed a z-hypnotic compared with the OAT population in Sweden in the period 2005 to 2013 [1]. In Norway, the proportion of OAT patients who were dispensed benzodiazepines or z-hypnotics was at least as high as comparable descriptive analyses of benzodiazepine dispensations in 2005 [23]. Moreover, the proportion of the general Norwegian population was dispensed a benzodiazepine or z-hypnotic decreased relatively on 1.2% per year from 10.8% in 2015 to 10.4% in 2017, whereas pregabalin increased by 3.5% per year, and gabapentin increased by 5.8% per year in the same period [24]. The dispensation rates of all these potentially addictive drugs were substantially higher in the OAT population. For gabapentinoids, the dispensation rates were increasing in both the OAT population and the general Norwegian population in the study period.

The reasons for the increasing use of gabapentinoids in the OAT population are lacking. In the past decade, gabapentinoids, particularly pregabalin, were placed under scrutiny due to the risk of addiction [16], and prescribers have become aware of the risk of prescribing these drugs to patients with a history of drug addiction [1]. Although, it is remarkable that the dispensation rate of gabapentinoids was increasing, and pregabalin was dispensed twice as frequently as gabapentin. The reason may be a high prevalence of psychiatric comorbidities like anxiety in the OAT population [25–27]. Further

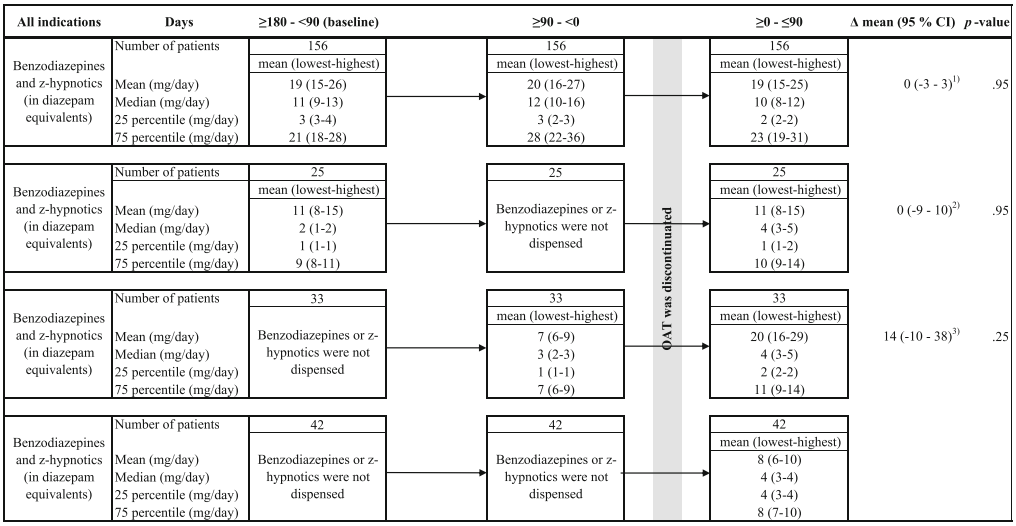

Fig. 2 Daily doses of benzodiazepines and z-hypnotics among patients who discontinued OAT. Legends: CI = Confidence interval, df = degrees of freedom, lowest = lowest equipotency dose, highest = highest equipotency dose, and OAT = opioid agonist therapy. [1)] Paired t-test, df = 155, comparing mean daily dose ≥0 - ≤90 days to baseline related to discontinuation. [2)] Paired t-test, df = 24, comparing mean daily dose ≥0 - ≤90 days to baseline related to discontinuation. [3)] Paired t-test, df = 32, comparing mean daily dose ≥0 - ≤90 days to ≥90 - < 0 days related to discontinuation. Displays the daily doses of dispensed benzodiazepines and z-hypnotics, in the following period related to the date of the last dispensation of an OAT opioids: 1) 180–90 days before discontinuation (baseline), 2) 90–0 days before discontinuation, and 3) 0–90 days after discontinuation. Discontinuation was defined as all patients on OAT who had the last dispensation of an OAT opioid in the period January 1, 2017, to September 30, 2017, and no dispensation until the end of March 31, 2018. The daily doses were stated in mean, median, 25 percentile, and 75 percentile. An equipotency table for benzodiazepines and z-hypnotics were used to make sensitivity analyses, displaying the lowest equipotency dose and the highest equipotency dose of the included benzodiazepines and z-hypnotics. The results were presented in parentheses. All dispensed benzodiazepines and z-hypnotics were summarized per year

studies evaluating reasons for the increasing gabapentinoid use among patients on OAT is required.

Being dispensed a benzodiazepine or z-hypnotic was particularly associated with being dispensed non-OAT opioids, and gabapentinoids, as well as methadone rather than buprenorphine as the type of OAT opioid. Chronic non-malignant pain like pain in muscles and skeleton is highly prevalent in the OAT population using methadone as an OAT opioid and affects up to 68% in some studies [28–31]. Having chronic non-malignant pain on OAT is strongly associated with using benzodiazepines [26, 27], and the presence of psychiatric comorbidities such as anxiety and depression [31]. Even though the prevalence of chronic non-malignant pain in the Norwegian OAT population is uncertain, one can assume that chronic non-malignant pain was an essential explanation for the association between the dispensation of benzodiazepines and gabapentinoids and using methadone on OAT in this study.

Overall, there is substantial evidence that OAT protects against overdose-related deaths and injecting opioid use [32, 33]. Nevertheless, the mortality increases significantly among patients on OAT if dispensed benzodiazepines, z-hypnotics, or gabapentinoids [1, 2]. Therefore, the guidelines in several European countries recommend careful dispensation of potentially addictive drugs to these patients on OAT [34, 35]. However, being dispensed of a potentially addictive drug is not necessarily wrong, and the reasons for these dispensations may be multifactorial. Physical and mental comorbidities are highly prevalent among patients on OAT, which predict and defend the dispensations of potentially addictive drugs [25–27]. In a few marginalized cases with several addictions, it is argued that dispensations of benzodiazepines decrease mortality if low dosed benzodiazepines replace illegal drug consumption [2]. Nevertheless, it should be a better awareness of whether such dispensations are medically indicated on patients on OAT taken our findings into consideration. Improving prescription routines among general physicians, application of strict monitoring systems, and a close co-operation with specialized addiction health care center may be considered as some of the essential approaches to strive for optimal conditions in cases

on OAT where several potentially addictive drugs are medically indicated.

Strengths and limitations

Using Norwegian registry data had some strengths. Pharmacy records are viewed to be more valid than both medical records and data collected from questionnaires and interviews. Because practically all dispensed drugs are registered in the database, completeness, and precision of all received information is high, and the potential for information biases is low.

This study also had some limitations. The NorPD only receives information about dispensed drugs, and we cannot know whether the drugs have been consumed. Second, due to that a minor part of reimbursed prescriptions being received through the Norwegian Health Economics Administration (HELFO), the medical indications for these dispensations are not available for the researchers through NorPD. For example, clonazepam, pregabalin, and gabapentin may be dispensed on the medical indication of epilepsy, while oxazepam or diazepam may be used preferably for detoxifications, or treatment of short-term anxiety or sleeping disorder. Third, the number of dispensations may be incomplete registered by the pharmacies. For OAT opioids, the self-reporting survey of OAT showed that the mean number of dispensation per patient was four times a week [15]. This finding may indicate that the number of dispensations is underestimated in our study. In order to adjust for this uncertainty to some extent, the mean daily dose calculated by summing the dispensed DDD, divided by the number of days between the first and the last dispensation were used. Fourth, slightly less than 10% of OAT opioids are dispensed in addiction specialist outpatient clinics, and those are not necessarily registered in NorPD. Some of these outpatient clinics ordered OAT opioids directly from pharmacies without linking to a personal identification number. These patients were lost in this study [15].

Conclusion

The dispensation rates of benzodiazepines, z-hypnotics, and gabapentinoids to patients receiving OAT in Norway are high. A high burden of disease among patients on OAT may be an essential explanation. Future policies need to debate the indications for dispensations of benzodiazepines, z-hypnotics, and gabapentinoids explicitly in guidelines on OAT as well as make requirements for dispensation authority. More randomized controlled trials evaluating the benefits and risks of such co-dispensation with sufficient power are required.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12913-020-05195-5.

Additional file 1. STROBE Statement. Checklist of items that should be included in reports of cohort studies.

Additional file 2. Anatomical Therapeutic Chemical (ATC) codes for opioids, benzodiazepines, z-hypnotics and gabapentinoids. Legends: OAT = opioid agonist therapy, and WHO = World Health Organization. * Defined by the WHO collaborating centre for drug statistics. The table displays ATC codes and the corresponding drugs defined by WHO.

Additional file 3. Daily defined doses (DDD) and equipotency of opioid agonist therapy (OAT) opioids, benzodiazepines and z-hypnotics, and gabapentinoids that have marketing authorizations in Norway. Legends: Lowest = Lowest equipotency dose, Highest = Highest equipotency dose.

Additional file 4. Equations to calculate diazepam equivalents. Legends: Equations used to calculate lowest, mean, and highest equipotency dose of included benzodiazepines and z-hypnotics.

Additional file 5. Dispensations of benzodiazepines or z-hypnotics, and gabapentinoids plotted against the number of dispensations of OAT opioids per year. Legends: No. = number of patients, OAT = opioid agonist therapy. Patients categorized on 0, 1–2 and ≥ 3 dispensations of benzodiazepines or z-hypnotics, and gabapentinoids per year, and plotted against the number of dispensations of OAT opioids per year in the period 2013 to 2017 in Norway.

Additional file 6. The mean daily DDDs of dispensed OAT opioids plotted against the mean daily doses of dispensed benzodiazepines and z-hypnotics. Legends: DDD = daily defined dose, and No. = number of patients. The table displays the mean daily DDDs of dispensed OAT opioid plotted against the mean daily doses of dispensed benzodiazepines or z-hypnotics. The number of included patients on OAT in this table were only those who have > 1 dispensation of an OAT opioid per calendar year.

Additional file 7. The mean daily DDD of dispensed OAT opioids plotted against the mean daily doses of dispensed pregabalin and gabapentin. Legends: DDD = daily defined dose, and No. = number of patients. The table displays the mean daily DDD of dispensed OAT opioid plotted against the mean daily doses of pregabalin and gabapentin, respectively. The number of included patients on OAT in this table were only those having > 1 dispensation of an OAT opioid per calendar year.

Additional file 8. Logistic regression analyses of variables associated with being dispensed a benzodiazepine or z-hypnotic, and a gabapentinoid. Legends: cOR = crude odds ratio; aOR = adjusted odds ratio; CI = confidence interval, and OAT = opioid agonist therapy. * The last type of dispensed OAT opioid. Table a) and b) display unadjusted (crude) and adjusted odds ratio for all independent variables of patients who were dispensed a benzodiazepine or z-hypnotic, and a gabapentinoid in 2017 in Norway. a) Being dispensed a benzodiazepine or z-hypnotic was defined as a dependent variable, and age, gender, 'the number of dispensations of OAT opioids,' 'OAT opioids,' 'dispensed a non-OAT opioid,' and 'dispensed a gabapentinoid' were defined as categorical and independent variables. b) Being dispensed a gabapentinoid was defined as a dependent variable, and age, gender, 'the number of dispensations of OAT opioids,' 'OAT opioids,' 'dispensed a non-OAT opioid,' and 'dispensed a benzodiazepine or z-hypnotic' were defined as categorical and independent variables.

Additional file 9. Changes in the mean daily doses of gabapentinoids among patients who discontinued OAT. Legends: CI = Confidence interval, df = degree of freedom, and OAT = opioid agonist therapy. [1)] Paired samples t-test, df = 25, comparing mean daily dose ≥0 - ≤90 days to baseline related to discontinuation. [2)] Paired samples t-test, df = 6, comparing mean daily dose ≥0 - ≤90 days to baseline related to discontinuation. [3)] Paired samples t-test, df = 6, comparing mean daily dose ≥0 - ≤90 days to ≥90 - < 0 days related to discontinuation. The tables a) and b) display the daily doses of dispensed pregabalin and gabapentin, respectively, in the following period related to the date of the last dispensation of an OAT opioids: 1) 180–90 days before discontinuation (baseline), 2) 90–0 days before discontinuation, and 3) 0–90 days after discontinuation. Discontinuation was defined as all patients on OAT who had the last dispensation of an OAT opioid in the period January 1, 2017, to September 30, 2017, and no dispensation until the end of March 31, 2018. The daily doses were stated in mean, median, 25 percentile, and 75 percentile.

Abbreviations
AOR: Adjusted odds ratio; ATC: Anatomical Therapeutic Chemical; CI: Confidence interval; DDD: Defined Daily Doses; HELFO: The Norwegian Health Economics Administration; NorPD: The Norwegian Prescription Database; OAT: Opioid agonist therapy; OR: Odds ratio; WHO: World Health Organization

Acknowledgments
Not applicable.

Authors' contributions
JHV was involved in the study design, led analysis, and writing the article preparation. SS, CA, FC, PK, KAJ and LTF contributed in the study design, analysis, and writing the article preparation. All authors have read and approved the final article.

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Availability of data and materials
Supplemental tables and data sources in this observational study are available in this published article and its additional files.

Ethics approval and consent to participate
The Regional Committee for Medical and Health Research Ethics, REC vest, Norway, has approved the use of registry data for the study (approval number 2018/939/REK Vest, June 19, 2018). No informed consent from the patients was necessary.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

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RESEARCH ARTICLE Open Access

Dispensation of attention deficit hyperactivity disorder (ADHD) medications in patients receiving opioid agonist therapy; a national prospective cohort study in Norway from 2015 to 2017

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Abstract

Background: It is estimated that up to a third of patients on opioid agonist therapy (OAT) have attention deficit hyperactivity disorder (ADHD). Treatment by ADHD medication, including a centrally acting stimulant (CAS) or atomoxetine is one of the essential approaches. This study evaluates the use of dispensed ADHD medications in the Norwegian OAT population in the period from 2015 to 2017. Types and doses of ADHD medications, co-dispensations of other potentially addictive drugs like benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids, as well as direct-acting antivirals (DAA) against hepatitis C infection, are investigated.

Methods: Information about all dispensed ADHD medication, OAT opioids, and the defined potentially addictive drugs were recorded from the Norwegian Prescription Database. Dispensation rates, the types, and the doses of dispensed ADHD medications were estimated by summarizing the number of dispensations, and the dispensed doses. Logistic regression analyses were employed to assess the associations between ADHD medication, and OAT opioid use, and dispensations of other potentially addictive drugs and DAAs against hepatitis C infection.

(Continued on next page)

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Results: A total of 9235 OAT patients were included. The proportion of patients who were dispensed ADHD medication increased from 3.5 to 4.6% throughout the study period. The three most dispensed CAS were short- and intermediate-acting methylphenidate (55%), lisdexamphetamine (24%), and dexamphetamine (17%) in 2017. Buprenorphine, rather than methadone, as OAT opioid (adjusted odds ratio: 1.6, CI: 1.2–2.1) was associated with being dispensed ADHD medication. Among patients who received CAS and OAT opioids each calendar year, the dispensed doses of methylphenidate increased from 63 mg/day in 2015 to 76 mg/day in 2017 ($p = 0.01$). Sixty percent of patients receiving ADHD medications were also dispensed other addictive drugs concomitantly in 2017. Similar results were found in 2015 and 2016.

Conclusion: Co-prescription of ADHD medications was low among patients on OAT in Norway, considering a high prevalence of ADHD in this patient group. On the other hand, concurrent dispensations of multiple addictive drugs were common in this population. Understanding the underlying reasons for such prescribing is essential, and research on how to optimize ADHD medication of patients with ADHD receiving OAT is needed.

Keywords: Opioid substitution treatment, Centrally acting stimulants, Hyperkinetic disorder, Attention deficit hyperactivity disorder, Substance-related disorders, Dispensed drugs, Register data

Background

The strong association between opioid addiction and attention deficit hyperactivity disorder (ADHD) is well known [1]. Studies indicate that up to a third of patients receiving opioid agonist therapy (OAT) meet the criteria for ADHD [1–5]. Both opioids used in OAT and centrally acting stimulants (CAS) may have properties associated with euphoria and addiction. Current treatment guidelines and previous reviews, therefore, recommend stable psychosocial surroundings and close follow-ups by health professionals in case of prescription of these high-potent drugs [6–10]. The use of other reinforcing, potentially addictive drugs such as benzodiazepines, z-hypnotics, non-OAT opioids, and gabapentinoids should be considered carefully to prevent adverse interactions and risk of new addictions [11, 12]. However, about 50% of patients receiving OAT and ADHD medication, including CAS and atomoxetine, concomitantly discontinue ADHD medication during the first 2 years after the start of the treatment [13]. Reasons for discontinuation include illicit drug use, side effects, and lack of psychosocial stability [13]. Long-term therapy of ADHD medication seems to have the highest chance of adequate adherence when combining psychosocial treatment with ADHD medication and OAT in the absence of other reinforcing, potentially addictive drugs [14, 15].

Little is known about the prevalence of co-existing ADHD and the utilization and the dose of prescribed ADHD medication among patients with ADHD on OAT. Additional use of other potentially addictive drugs makes ADHD assessment and treatment with ADHD medications more challenging. Psychosocial factors and medical conditions among these patients may also complicate diagnosis and the co-therapy with ADHD medication. Therefore, studies show substantial inter-country differences in co-existing ADHD prevalence (5–30%) [2, 16], and variations in utilization and the dose of prescribed ADHD medication [7, 9, 10, 17, 18]. There is evidence that CAS have an effect by suppressing ADHD symptoms among patients with drug use disorders and comorbid ADHD [18]. Some studies also point towards that the high-dosed CAS increases patients' retention to treatment, and prevents discontinuation [19, 20]. However, individual assessment taking into consideration medical and psychosocial conditions will be of particular interest to ensure a proper prescription of CAS to patients on OAT with comorbid ADHD.

During the past years, the guidelines for ADHD worldwide recommend prescribing ADHD medication to patients on OAT with comorbid ADHD and those with other drug use disorders if they are abstinent from any illegal drugs [7, 9, 10, 17]. However, the evidence supporting this recommendation is weak. In Norway, prescribing ADHD medication has been recommending for patients with ADHD on the OAT program since 2014 [21]. A total of 7500 Norwegian patients are given OAT [22], and, in 2016, about 15% self-reported the use of illegal and legal CAS during the last 4 weeks. Although the proportion that was dispensed ADHD medication, on medical indication is uncertain after the guidelines were revised. To be able to improve the treatment of ADHD, it is essential to know more about the current prescription rates of ADHD medications and the prescription patterns of other potentially addictive drugs among patients on OAT who were dispensed an ADHD medication.

Thus, this observational study was aimed to define dispensation rates of attention deficit hyperactivity disorder (ADHD) medications and potentially addictive drugs among patients on opioid agonist therapy (OAT) in the period from 2015 to 2017 in Norway. The aims were to:

1. define the dispensation rates of ADHD medication and the types of ADHD medication dispensed per calendar year.
2. assess whether the dispensations of ADHD medication per calendar year were associated with dispensations of benzodiazepines, z-hypnotics, gabapentinoids, non-OAT opioids, as well as direct-acting antivirals (DAA) against hepatitis C infection, types of OAT opioids, the number of dispensed OAT opioids, gender, and age in the study period.
3. define the mean daily doses of dispensed ADHD medications, and the dispensation rates of benzodiazepines, z-hypnotics, gabapentinoids, and non-OAT opioids in 2017 among patients who were dispensed ADHD medication in the calendar year throughout the study period.

Methods

Data source

All data were register data and were drawn from the Norwegian Prescription Database (NorPD). From January 1, 2004, all pharmacies are obliged to submit data for all dispensed drugs electronically to NorPD underlying the Norwegian Institute of Public Health (www.norpd.no). The NorPD contains information on all drugs dispensed from pharmacies, except for drugs administrated at hospitals, nursing homes, and outpatient clinics [23]. The Anatomical Therapeutic Chemical (ATC) classification system was employed in accordance with the World Health Organization (WHO) standards per October 2018 [24].

Study population

All patients above 18 years of age who received at least one dispensation of OAT opioids per calendar year, including methadone, levomethadone, buprenorphine, and buprenorphine-naloxone from January 1, 2015, to December 31, 2017, were included. In addition, some patients in palliative care use methadone tablets to achieve pain relief. These patients were excluded by identifying those who only were dispensed methadone tablets without any dispensations of other OAT opioids or methadone mixture in the period from January 1, 2004, to December 31, 2017.

Analysis strategy and statistical analyses

Definitions of drugs, including ADHD medications and opioid agonist therapy opioids, the number of dispensations of OAT opioids, and diagnoses

Attention deficit hyperactivity disorder medications were defined as all CAS that had marketing authorizations in Norway in the period 2015 to 2017, including racemic amphetamine, dexamphetamine, methylphenidate, and lisdexamphetamine. In addition, we included the non-stimulant atomoxetine, which is also authorized and recommended in the treatment of ADHD according to guidelines and reviews [6–10, 18, 25]. For methylphenidate, the dispensations were classified by whether the formulation was 'short- or intermediate-acting' or 'long-acting.' Long-acting methylphenidate included depot formulations (Concerta®, Delmosart®, Equasym Depot®, or Methylphenidate Sandoz®), while short- or intermediate-acting methylphenidate included all other formulations (capsules or tablets). All included OAT opioids, ADHD medications, non-OAT opioids, benzodiazepines, z-hypnotics, gabapentinoids, including gabapentin and pregabalin, and DAAs were categorized according to their ATC codes (Additional file 1). The type of OAT opioid that patients were dispensed was defined as the last type of OAT opioid that was dispensed per calendar year.

The number of dispensed OAT opioids was defined as the number of dispensations of any OAT opioid per patient per calendar year. The number of dispensations was stratified according to four categories: 1–6, 7–12, 13–51, and ≥ 52 dispensations per calendar year. Age was defined according to the patient's age in the calendar year and categorized into five groups: ≤ 25, 26–35, 36–45, 46–55, and ≥ 56 years.

All reimbursable and non-reimbursable ADHD medication dispensations were included. The prescribing physician needs to specify the medical condition that is treated by the particular drug, using codes from the 10th revision of International Classification of Diseases (ICD-10) or International Classification of Primary Care 2 (ICPC-2) to get public drug expenses reimbursed in Norway. The diagnostic codes of reimbursed drugs are recorded in the NorPD. Only two medical indications are approved for ADHD medication expense reimbursements in Norway: Hyperkinetic disorder/ADHD (ICD-10: F90 and ICPC-2: P81) or narcolepsy (ICD-10: G47 and ICPC-2: P81). For narcolepsy, only CAS are reimbursed. The information on diagnostic codes for non-reimbursable dispensations are not collected in the NorPD.

Analysis strategy according to the aims

One-year's dispensation rates of ADHD medication during the study period were assessed by summing all patients who received at least one dispensation of an ADHD medication per the calendar year. Furthermore, patients were divided into two groups "all medical indications" and "ADHD" for the years in the study period. The group named "ADHD" only included patients who were dispensed ADHD medications with reimbursement codes for ADHD. The group named "all medical indications" included all patients who received dispensations of ADHD medications, either they were reimbursed or not. Less than five patients were dispensed CAS on the reimbursement code for narcolepsy in the study period.

The association with being dispensed ADHD medication, or not adjusted for age, gender, type of dispensed OAT opioids, the number of dispensed OAT opioids, being dispensed benzodiazepines, z-hypnotics, gabapentinoids, or non-OAT opioids were calculated per calendar year in the study period. Age and the number of dispensed OAT opioids were categorized according to the predefined categories or groups per year. All dispensed ADHD medication, and potentially addictive drugs were identified and categorized into four drug groups: "benzodiazepines or z-hypnotics," "gabapentinoids," "non-OAT opioids," and "ADHD medication" per year. For each group, categorical variables were created by whether patients were dispensed one or more of the drugs in the drug groups or not. Dispensations of DAA were also included due to the frequent use of illicit stimulant drugs in the OAT population and the fact that DAA against hepatitis C infection has made treatment more applicable for these patients. Patients were defined to be dispensed treatment with DAA if they had at least one dispensation of DAA from 2011 and until the end of 2015, 2016, or 2017, respectively.

The mean daily dose of each ADHD medication and the dispensation rates of benzodiazepines or z-hypnotics, gabapentinoids, and non-OAT opioids in 2017, were calculated among patients with at least one dispensation of ADHD medication and OAT, respectively, for each calendar year in the study period. These patients were assumed to have achieved medical continuity in their ADHD treatment and follow up treatment according to national guidelines. The mean daily doses of ADHD medication were calculated by summarizing the total volume of defined daily doses (DDD) of each drug that was dispensed for each patient per year [26]. Further, the number of DDDs dispensed per patient was converted to milligrams according to WHO's standards (Additional file 2). The mean daily dose for each ADHD medication was calculated by dividing the total dose (in milligram) of each drug per year by 365.25 days. The drug groups of each potentially addictive drugs were used to calculate dispensation rates. Each drug group was defined as categorical variables according to whether patients were dispensed at least one drug defined into the drug group or not during 2017.

Statistical analyses

Means, medians, percentiles, percentages, 95% confidence intervals (CI), odds ratios (OR), and *p*-values are presented when appropriate. Multivariable analyses for categorical variables were performed by binary logistic regression. Being dispensed ADHD medication, as well as OAT at least once, respectively, during a calendar year, were defined as a dependent variable in the logistic regression model. Independent variables were age, gender, 'the number of dispensations of OAT opioids,' 'benzodiazepines or z-hypnotics,' 'gabapentinoids,' 'non-OAT opioids,' and 'DAA.' All these variables were defined categorically. The level of statistical significance was defined as $p < 0.05$. The Chi-square test and paired sample t-test were used to estimate differences in dispensed mean daily doses of ADHD medication in 2015 compared to 2017 among patients with at least one dispensation of ADHD medication and OAT, respectively, during a calendar year throughout the study period. All patients were censored from the calendar year they died. SPSS version 24 was used for all analyses.

Ethical considerations

The Regional Committee for Medical and Health Research Ethics, REC vest, Norway, has approved the use of registry data for this study (approval number 2018/939/REK Vest, June 19, 2018). No informed consent from included patients was necessary. The STROBE checklist was applied in the preparation of the study (Additional file 3).

Results

Baseline characteristics

A total of 9235 patients received at least one OAT opioid from pharmacies in Norway in the period 2015 to 2017. In 2017, 69% were male, and the mean age was 45 years (Table 1). A total of 376 participants died during the study period.

One-year prevalence and the types of dispensed ADHD medications

The proportions of OAT patients who received at least one dispensation of an ADHD medication increased from 3.5% in 2015 to 4.6% in 2017. A vast majority of them, i.e., 74% received buprenorphine or buprenorphine-naloxone, whereas the remaining 26% were dispensed methadone or levomethadone. In 2017, the most dispensed CAS was short- and intermediate-acting methylphenidate (55%), followed by lisdexamphetamine (24%), dexamphetamine (17%), long-acting methylphenidate (9%), and racemic amphetamine (2%) (Table 2ab). The non-stimulant atomoxetine was dispensed in 6% of these patients. These findings were substantially similar to the results in 2015 and 2016.

Dispensations of potentially addictive drugs to patients receiving OAT opioids and ADHD medication concomitantly

In the period from 2015 to 2017, being dispensed ADHD medications were associated with being dispensed buprenorphine rather than methadone as OAT opioid (2017: adjusted odds ratio (aOR): 1.6, 95% confidence interval (CI): 1.3–2.1) (Table 3). Further, in 2017, being dispensed ADHD medications were associated with being dispensed

Table 1 Baseline characteristics

	2015		2016		2017	
Patients	7958		7804		7709	
Deaths	138		114		124	
Patients, excl. Deaths	7820		7690		7585	
	OAT	**OAT + AM**[b]	**OAT**	**OAT + AM**[b]	**OAT**	**OAT + AM**[b]
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Dispensed ADHD medication	–	274 (3.5)	–	312 (4.1)	–	349 (4.6)
Age						
≤ 25	171 (2.2)	5 (1.8)	135 (1.8)	7 (2.2)	120 (1.6)	9 (2.6)
26–35	1551 (19.8)	81 (29.6)	1403 (18.2)	90 (28.8)	1333 (17.6)	84 (24.1)
36–45	2605 (33.3)	107 (39.1)	2508 (32.6)	118 (37.8)	2392 (31.5)	134 (38.4)
46–55	2544 (32.5)	69 (25.2)	2540 (33.0)	79 (25.3)	2548 (33.6)	97 (27.8)
≥ 56	949 (12.1)	12 (4.4)	1104 (14.4)	18 (5.8)	1192 (15.7)	25 (7.2)
Mean (SD)	*43.9 (9.7)*	*41.0 (8.5)*	*44.5 (9.8)*	*40.8 (8.7)*	*45.0 (9.9)*	*41.8 (9.0)*
Gender						
Male	5430 (69.4)	193 (70.4)	5354 (69.6)	221 (70.8)	5245 (69.1)	254 (72.8)
Female	2390 (30.6)	81 (29.6)	2336 (30.4)	91 (29.2)	2340 (30.9)	92 (26.4)
OAT opioids[a]						
Methadone (included levomethadone)	3216 (41.1)	72 (26.3)	3066 (39.9)	74 (23.7)	2981 (39.3)	92 (26.4)
Buprenorphine (included combinations)	4604 (58.9)	202 (73.7)	4624 (60.1)	238 (76.3)	4604 (60.7)	257 (73.6)

ADHD Attention deficit hyperactivity disorder, *AM* ADHD medication (atomoxetine, racemic amphetamine, dexamphetamine, lisdexamphetamine, and methylphenidate), *NorPD* Norwegian Prescription Database, *SD* standard deviation, and *No* Number of patients
[a] The last dispensed OAT opioid in the calendar year
[b] On all medical indications
The table displays the baseline characteristics of patients who were dispensed at least one OAT opioid per year in the period from 2015 to 2017

a non-OAT opioid (aOR 1.5, 95% CI: 1.1–1.9) and a DAA against hepatitis C infection (aOR 1.6, 95% CI: 1.2–2.2). The odds ratio (OR) of being dispensed DAA increased steadily during the study period. Being dispensed ADHD medications were not statistically associated with being dispensed gabapentinoids, benzodiazepines, or z-hypnotics per year in the study period.

Mean daily doses of dispensed ADHD medications and dispensation rates of other potentially addictive drugs

We identified 142 patients who received at least one dispensation of ADHD medication per calendar year throughout the study period. We found a substantial increase in the dispensed mean daily doses of methylphenidate from 63 mg in 2015 to 76 mg in 2017 ($p = 0.01$) (Fig. 1). The mean doses of other dispensed ADHD medications were not statistically significantly different in 2017 compared to 2015. However, the mean daily dose of lisdexamphetamine increased from 21 mg in 2015 to 83 mg in 2017. The mean doses of amphetamine, dexamphetamine, methylphenidate, and lisdexamphetamine were near the highest recommended doses for each drug, according to the European Medicines Agency (EMA) [27]. Furthermore, 85 of the 142 patients (60%) who were dispensed an ADHD medication per year throughout the study period also received at least one dispensation of z-hypnotics or benzodiazepines, gabapentinoids, or non-OAT opioids in 2017 (Fig. 2). The most frequent combination of dispensed drugs was 'OAT opioid, ADHD medication, and benzodiazepines, or z-hypnotics.' Seven patients received 'OAT opioid, ADHD medication, benzodiazepines, or z-hypnotics, gabapentinoids, and non-OAT opioids.'

Discussion

In the period 2015 to 2017, the proportion of patients receiving ADHD medication in the OAT population increased from 3.5 to 4.6%. Short- and intermediate-acting methylphenidate and lisdexamphetamine were the most frequently dispensed CAS. Dispensation of buprenorphine rather than methadone as an OAT opioid was associated with being dispensed ADHD medication. In 2017, being dispensed non-OAT opioids and DAA against hepatitis C infection were associated with being dispensed ADHD medication. For four out of five ADHD medication, the mean doses were near the highest recommended doses. Furthermore, the dose of methylphenidate increased significantly throughout the study period. Eighty-five of 142 patients who were dispensed ADHD medication each year throughout the

Table 2 The proportion of patients on OAT were dispensed ADHD medication categorized on medical diagnoses and types of CAS

a)						
Year	**2015**		**2016**		**2017**	
	All indications					
Number of patients	274		312		349	
ADHD medication	*No.*	*%*[a]	*No.*	*%*[a]	*No.*	*%*[a]
Methylphenidate	194	71	217	70	207	59
- short- and intermediate-acting[b]	*182*	*66*	*206*	*66*	*193*	*55*
- long-acting[c]	*38*	*14*	*30*	*10*	*33*	*9*
Dexamphetamine	63	23	64	21	60	17
Atomoxetine	23	8	26	8	21	6
Lisdexamphetamine	14	5	47	15	84	24
Racemic amphetamine	< 5	0	< 5	1	8	2
b)						
Year	**2015**		**2016**		**2017**	
	ADHD					
Number of patients	223		270		312	
ADHD medication	*No.*	*%*[a]	*No.*	*%*[a]	*No.*	*%*[a]
Methylphenidate	171	76	198	72	194	62
- short- and intermediate-acting[b]	*163*	*73*	*190*	*70*	*182*	*58*
- long-acting[c]	*32*	*14*	*26*	*10*	*29*	*9*
Dexamphetamine	45	20	55	20	53	17
Atomoxetine	12	5	19	7	16	5
Lisdexamphetamine	12	5	39	14	72	23
Racemic amphetamine	< 5	< 5	< 5	< 5	7	2

ADHD Attention deficit hyperactivity disorder, *ADHD* medication = atomoxetine, racemic amphetamine, dexamphetamine, lisdexamphetamine, and methylphenidate, *ICD-10* 10th Revision of International Classification of Diseases, *ICPC2* International Classification of Primary Care 2, and *OAT* opioid agonist therapy

[a] Per cent of patients who received OAT and CAS, [b] Include all tablets and capsules with short- and intermediate-acting methylphenidate, [c] Include depot formulations of methylphenidate (Concerta®, Delmosart®, Equasym Depot®, or Methylphenidate Sandoz®)

The tables display patients on OAT who were dispensed an ADHD medication in the period 2015 to 2017 categorized on a) all medical indications, and b) ADHD (ICD-10 code: F90 or ICPC2 code: P81)

study period were also dispensed benzodiazepines, z-hypnotics, gabapentinoids, or non-OAT opioids in 2017.

Short- and intermediate-acting methylphenidate is the most dispensed CAS throughout the study period. These formulations, particularly the short-acting formulation, are associated with euphoria and addiction compared to long-acting formulation [18, 28]. However, the short- and intermediate-acting methylphenidate might be preferable in situations where more focus and concentration is needed for shorter periods. In Norway, the reimbursement for methylphenidate for adults is pre-approved for intermediate-acting formulations as opposed to long-acting formulations [29], which may explain that few patients were dispensed long-acting formulations. A study evaluating the dispensations of ADHD medications in the general population among the Nordic countries showed that Denmark and Norway, in contrast to Finland, Iceland, and Sweden, were substantially dispensed intermediate-acting rather than long-acting methylphenidate in the treatment of ADHD [30]. The Norwegian guidelines for treating ADHD do not mention the formulation of methylphenidate to patients on OAT in their recommendations [7]. However, a European consensus report recommends long-acting formulations of CAS to prevent misuse among patients with drug use disorders and ADHD [18].

The proportion of patients who received ADHD medication increased in the inclusion period. Nevertheless, the dispensation rates were still in the lower range of what was expected. It is estimated that as much as a third of patients with drug addictions in Norway have comorbid ADHD [16], and the proportion of those with opioid use disorder is supposed to be 11–33% [3–5]. Assuming that 40–50% of patients with ADHD were dispensed ADHD medication in the general population [18], one would expect that about 4–16% of those with opioid use disorder receive ADHD medication. Our findings showed that only 4–5% of the patients on OAT also were dispensed ADHD medication during the study period. This might have several explanations. A consensus report evaluating screening, diagnosis, and treatment of patients with drug use disorders and ADHD, recommends the use of CAS when potentially therapeutic pros and cons are considered in advance [18]. In addition, the Norwegian guidelines for ADHD discourage dispensations of ADHD medication to patients on OAT who used other potentially addictive drugs concomitantly [7]. Furthermore, low dispensation rates of CAS may also be explained by medical illnesses or psychosocial conditions, and active illicit drug use, which may disturb the diagnostic assessment of ADHD and delay pharmacological treatment.

Retention to treatment is generally challenging in the treatment of drug addictions, particularly among patients with comorbid ADHD. Inadequate knowledge of pharmacological properties of different ADHD medications may explain a low coverage. For example, unlike CAS, the non-stimulant atomoxetine may need several weeks to give optimal clinical response [18]. Late-onset of the effect of atomoxetine or careful dose-escalation of methylphenidates and amphetamines may conflict with patient's expectations on a quick reduction of ADHD symptoms. In addition, removing factors leading to discontinuation of CAS treatment may play an essential role in preventing relapse to illicit stimulant drug use and sustained stimulant injections, as well as improving the quality of life by keeping complications such as

Table 3 Logistic regression analyses of variables associated with dispensed ADHD medication and OAT

	2015		2016		2017	
Dispensed ADHD medication	*N* = 274		*N* = 312		*N* = 349	
Not dispensed ADHD medication	*N* = 7546		*N* = 7378		*N* = 7236	
	Crude OR	**Adjusted OR (95% CI)**	**Crude OR**	**Adjusted OR (95% CI)**	**Crude OR**	**Adjusted OR (95% CI)**
Age						
- ≤ 25	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
- 26–35	1.8	1.8 (0.7–4.5)	1.3	1.3 (0.6–2.9)	0.8	0.8 (0.4–1.7)
- 36–45	1.4	1.5 (0.6–2.7)	0.9	1.0 (0.5–2.2)	0.7	0.7 (0.4–1.5)
- 46–55	0.9	1.0 (0.4–2.6)	0.6	0.7 (0.3–1.6)	0.5	0.5 (0.2–1.0)
- ≥ 56	0.4	0.5 (0.2–1.4)	0.3	0.4 (0.2–0.9)	0.3	*0.3 (0.1–0.6)*
Gender						
- Female	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
- Male	1.1	1.0 (0.8–1.4)	1.1	1.0 (0.8–1.3)	1.2	1.2 (1.0–1.6)
The number of dispensations of OAT opioids per calendar year						
- ≥ 52	1.0 (ref.)	1.0 (ref.)	1.00 (ref.)	1.0 (ref.)	1.0 (ref.)	1.00 (ref.)
- 13–51	0.9	1.0 (0.7–1.4)	0.7	0.8 (0.6–1.2)	1.1	1.1 (0.8–1.7)
- 7–12	0.7	0.8 (0.5–1.3)	0.8	0.9 (0.6–1.3)	1.3	1.3 (0.9–2.0)
- 1–6	0.7	0.7 (0.4–1.2)	0.9	1.0 (0.7–1.6)	1.0	1.0 (0.6–1.7)
OAT opioids[a]						
- Methadone (incl. Levomethadone)	1.0 (ref.)	1.00 (ref.)	1.00 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
- Buprenorphine (incl. combinations)	*2.0*	*1.7 (1.3–2.3)*	*2.2*	*1.9 (1.4–2.5)*	*1.9*	*1.6 (1.3–2.1)*
Dispensed opioids (excl. OAT opioids)	1.0	1.1 (0.8–1.5)	1.0	1.1 (0.8–1.5)	*1.4*	*1.5 (1.1–1.9)*
Dispensed gabapentinoids	0.8	0.9 (0.5–1.4)	1.2	1.2 (0.8–1.7)	1.1	1.0 (0.7–1.4)
Dispensed benzodiazepines and/or z-hypnotics	0.8	1.0 (0.7–1.2)	0.8	0.9 (0.7–1.2)	1.0	1.0 (0.8–1.3)
Dispensed DAA	0.8	1.0 (0.5–2.1)	1.1	1.4 (0.9–2.3)	*1.4*	*1.6 (1.2–2.2)*

ADHD Attention deficit hyperactivity disorder, *ADHD medication* Atomoxetine, racemic amphetamine, dexamphetamine, lisdexamphetamine, and methylphenidate, *CI* confidence interval, *DAA* direct-acting antivirals against hepatitis C infection, and *OAT* opioid agonist therapy

[a] The last OAT opioid was dispensed during a calendar year recorded in the Norwegian Prescription Database

The table displays odds ratios for each independent variable among patients who were dispensed ADHD *medication* (dependent variable) and OAT. For example, the adjusted odds of being dispensed opioids in 2017 was 1.5 among patients who were dispensed ADHD *medication*. Each independent variable is stated as crude (unadjusted) and adjusted for each calendar year. Italics display significant values

hepatitis C infection low [31]. Integrating ADHD treatment in OAT, or vice versa, maybe a way to facilitate the diagnostics and treatment and improve follow-up approaches among marginalized patients on OAT with comorbid ADHD [32].

In this study, the mean doses of ADHD medications were in the highest range of usual recommended doses. The benefits of high-dose ADHD medication on the treatment of ADHD in the OAT population are not clear. Two placebo-controlled randomized trials, including patients with ADHD and addictions to amphetamines or cocaine, have found a decrease of ADHD symptoms by using doses up to 180 mg methylphenidate [19] and 80 mg racemic amphetamine daily compared to placebo [20]. The former study [19] also found that high-dose of methylphenidate reduced relapse to illicit stimulant use and contributed to higher retention in treatment. Previous research has also confirmed similar findings [33]. The latter study [20], evaluating racemic amphetamine to placebo, showed that doses of 60 mg and 80 mg racemic amphetamine per day, respectively, inhibited cocaine-related craving. Although, a dose of 80 mg racemic amphetamine did not seem to reduce ADHD symptoms more than a dose of 60 mg per day. Overall, one can assume that using higher doses of methylphenidate or racemic amphetamine may improve the effect of these medications on ADHD by keeping patients in treatment, reducing the craving for illicit stimulant drugs, as well as by alleviating ADHD symptoms.

The proportion of patients who were dispensed lisdexamphetamine increased significantly from 2015 to 2017. In addition, the mean dose rose markedly in the same period, although it was not statistically significant. A meta-analysis evaluating the efficacy, acceptability, and tolerability of ADHD medication among patients with ADHD without drug addiction favored amphetamines as

All medical indications		Year 2015	2016	2017	Upper recommended dose (mg)*	Δ mean (95 % CI)**	*p* -value
Methyl-phenidate (all)	Number of patients	88	88	88			
	Mean (mg/day)	63	82	76	80***	13 (4 - 22)[1)]	0.0
	Median (mg/day)	60	76	73			
	25 percentile (mg/day)	26	50	52			
	75 percentile (mg/day)	92	106	104			
Methyl-phenidate****	Number of patients	80	80	80			
	Mean (mg/day)	58	79	72			
	Median (mg/day)	54	76	72	80***	14 (4 - 23)[2)]	0.0
	25 percentile (mg/day)	20	43	45			
	75 percentile (mg/day)	91	106	99			
Methyl-phenidate (long-acting)	Number of patients	11	11	11			
	Mean (mg/day)	51	58	57			
	Median (mg/day)	38	52	59	80***	6 (-8 - 27)[3)]	0.5
	25 percentile (mg/day)	13	9	18			
	75 percentile (mg/day)	68	80	72			
Dex-amphetamine	Number of patients	27	27	27			
	Mean (mg/day)	42	48	50	40	8 (-3 - 19)[4)]	0.2
	Median (mg/day)	40	47	49			
	25 percentile (mg/day)	27	34	27			
	75 percentile (mg/day)	52	60	64			
Lisdex-amphetamine	Number of patients	6	6	6			
	Mean (mg/day)	21	82	83	70	62 (-6 - 131)[5)]	0.1
	Median (mg/day)	22	84	100			
	25 percentile (mg/day)	6	61	22			
	75 percentile (mg/day)	30	109	127			
Atomoxetine	Number of patients	5	5	5			
	Mean (mg/day)	55	63	51	100	-4 (-84 - 75)[6)]	0.9
	Median (mg/day)	48	69	69			
	25 percentile (mg/day)	24	25	7			
	75 percentile (mg/day)	89	98	85			
Racemic amphetamine	Number of patients	< 5	< 5	< 5			
	Mean (mg/day)	60	42	65	45	-	-
	Median (mg/day)	60	42	65			
	25 percentile (mg/day)	60	42	65			
	75 percentile (mg/day)	60	42	65			

Fig. 1 (See legend on next page.)

(See figure on previous page.)
Fig. 1 Doses of dispensed ADHD medication among patients who received OAT opioids from 2015 to 2017. Legends: ADHD = Attention deficit hyperactivity disorder, ADHD medication = atomoxetine, racemic amphetamine, dexamphetamine, lisdexamphetamine, and methylphenidate, CI = confidence interval, and Df = degrees of freedom. [1)] Paired-samples t-test, df = 87, [2)] Paired-samples t-test, df = 79, [3)] Paired-samples t-test, df = 10, [4)] Paired-samples t-test, df = 26, [5)] Paired-samples t-test, df = 5, and [6)] Paired-samples t-test, df = 4. * = Upper recommended doses according to The European Medicines Agency (EMA) per July 2019, ** = Calculation of the differences in mean daily doses between 2015 and 2017, *** = Upper recommended daily dose of short- and intermediate-acting methylphenidate according to the EMA, and **** = Include short- and intermediate-acting methylphenidate (tablets or capsules), not depot formulations. The figure displays the mean daily doses of each dispensed ADHD medication among patients who were dispensed at least one dispensation ADHD medication and OAT opioid, respectively, each calendar year in the study period from 2015 to 2017

the first drug group of choice in the short-term treatment of ADHD in adults [25]. By comparing methylphenidate and amphetamines, the latter was more efficacious and showed higher acceptability (i.e., fewer patients leaving the study). National Institute for Health and Care Excellence (NICE) guidelines [9] and a consensus report [18] evaluating patients with drug addictions and ADHD recommend methylphenidate or lisdexamphetamine as the first drugs of choice in the treatment of ADHD in adults. A risk assessment of the potential of misuse of lisdexamphetamine and methylphenidate has been completed by the WHO, which pointed towards that methylphenidate and lisdexamphetamine still have low harmful profiles compared to other stimulants such as racemic amphetamine and methamphetamine in treatment of ADHD [34]. The use of ADHD medication in the Norwegian OAT population was in line with these recommendations. In addition, it is essential to mention that the lisdexamphetamine named Aduvanz® was granted the Norwegian marketing authorization in September 2017, and the upcoming facilitation in the pre-approved reimbursement of lisdexamphetamine was introduced in October 2018 [35]. These changes may also explain some of the increasing dispensation rates found in this study.

Eighty-five of 142 patients who were dispensed ADHD medication and OAT opioids concomitantly received either benzodiazepines, z-hypnotics, gabapentinoids, or

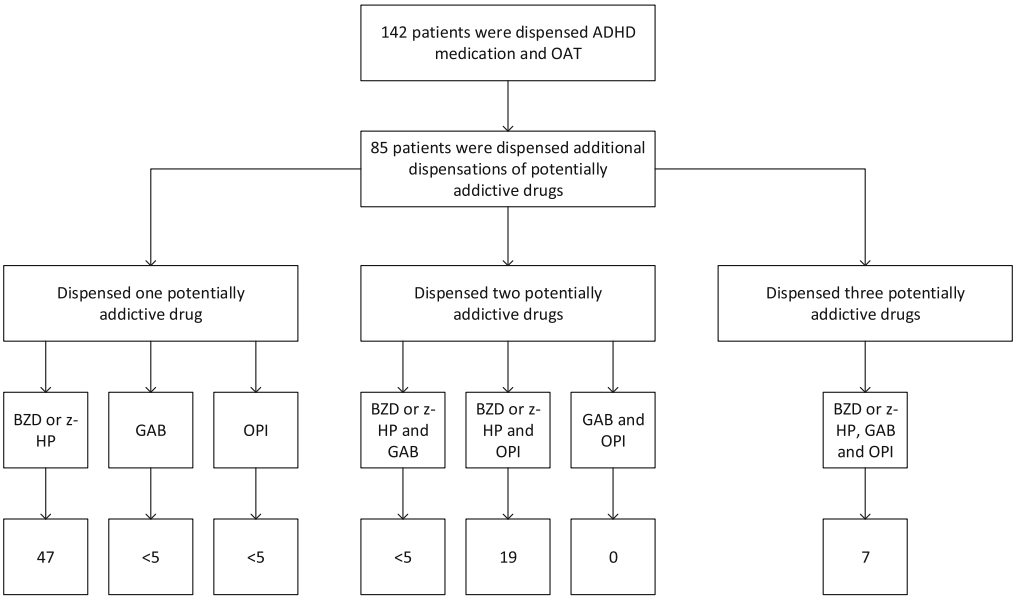

Fig. 2 Patients on ADHD medication who were dispensed other potentially addictive drugs in 2017. Legends: ADHD = Attention deficit hyperactivity disorder, ADHD medication = atomoxetine, racemic amphetamine, dexamphetamine, lisdexamphetamine, and methylphenidate, BZD = benzodiazepines, GAB = gabapentinoids, OAT = Opioid agonist therapy, OPI = non-OAT opioids, and z-HP = z-hypnotics. The figure displays dispensations of BZD, GAB, OPI, and z-HYP in 2017 among patients who were dispensed at least one dispensation of ADHD medication and OAT opioids each calendar year in the period from 2015 to 2017. Eighty-five patients were dispensed BZD or z-HP, GAB, or OPI in this population

non-OAT opioids at least as frequent as in the remaining OAT population not were dispensed ADHD medications in 2017. Our findings confirm previous studies on the OAT population, showing that about half of patients on OAT were dispensed other potentially addictive drugs [11, 36]. The fact that a substantial proportion of patients were dispensed CAS concomitant with dispensations of other potentially addictive drugs may point towards the need to improve the prescribing practice of addictive drugs in this comorbid population in order to keep the risk of adverse interactions low [11, 12, 37]. On the other hand, the prevalence of psychiatric and somatic comorbidities in OAT is high [38–40], and it may predict the high dispensation rates of potentially addictive drugs when these comorbidities are treated. In some cases, prescribing potentially addictive drugs may be used to keep the patients completely abstinent from illicit potentially addictive drugs if health professionals follow up strictly, and the prescribing practices are considered proper [14, 15].

Strengths and limitations

The use of national registry data has some clear strengths, by capturing whole cohorts of the studied populations. Pharmacy records are considered more valid than both medical records and data collected from questionnaires and interviews. Because practically all dispensed drugs are registered in the NorPD database, completeness, and precision of all received information is high, and the potential for information biases is low.

This study also had some limitations. First, because non-reimbursed dispensations of ADHD medication were not received through the Norwegian Health Economics Administration (HELFO), the medical indications for these dispensations are not available for the researchers through NorPD. Further, gabapentinoids, benzodiazepines, z-hypnotics, and non-OAT opioids have different medical indications, and the indications have not been evaluated in this study. Second, the number of dispensed OAT opioids may be incompletely registered by the pharmacies. The self-reporting survey of OAT in Norway in 2017 showed that the mean frequency of dispensations of OAT opioids was four times a week [22]. This finding may indicate that the number of dispensations is underestimated. Third, the NorPD only receives information about dispensed drugs, and we cannot know whether the drugs have been consumed. All addictive drugs are coveted for illegal consumption, and the drugs may be re-distributed. Illicit use is common in this population and cannot be covered using register data. Fourth, slightly less than 10% of OAT opioids are dispensed in addiction specialist outpatient clinics, and those are not necessarily registered in the NorPD. Some of these outpatient clinics order OAT opioids directly from pharmacies without linking to a personal identification number. These patients were missed in this study, and those could have higher dispensation rates of addictive drugs than patients included in this study [22].

Conclusion

Co-prescribing of CAS and atomoxetine was low in the OAT population in Norway, relative to the expected prevalence of ADHD in this patient group. Considering that up to a third of the OAT population is estimated to have ADHD, only 3.5 to 4.6% of patients received both ADHD medication and OAT opioids in Norway in the period from 2015 to 2017. Furthermore, 85 of 142 OAT patients who were dispensed ADHD medication each year throughout the study period were dispensed at least one dispensation of other potentially addictive drugs concomitantly in 2017. Generally, the polydrug use, including CAS, OAT, and other potentially addictive drugs, may lead to adverse side effects; however, a treatment combining several potentially addictive drugs in OAT patients using CAS has only been scarcely studied. Randomized-controlled trials evaluating ADHD medication in different doses are needed to improve the treatment of ADHD in the OAT population.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12888-020-02526-y.

Additional file 1. ATC codes for included drugs, or drug groups. ADHD = Attention deficit hyperactivity disorder, ATC = Anatomical Therapeutic Chemical (ATC) classification system, and OAT = opioid agonist therapy. An overview of drugs and drug groups included in this study.

Additional file 2. Converting table of DDD to milligrams according to WHO's standards. ATC = The Anatomical Therapeutic Chemical (ATC) classification system, ADHD = Attention deficit hyperactivity disorder, DDD = defined daily doses, mg = milligram, WHO = World Health Organization.

Additional file 3. STROBE Statement. Checklist of items that should be included in reports of cohort studies

Abbreviations

ADHD: Attention deficit hyperactivity disorder; AOR: Adjusted odds ratio; ATC: Anatomical Therapeutic Chemical; CAS: Centrally acting stimulants; CI: Confidence interval; DAA: Direct-acting antivirals; DDD: Defined Daily Doses; EMA: The European Medicines Agency; HELFO: The Norwegian Health Economics Administration; ICD-10: 10th revision of International Classification of Diseases; ICPC 2: International Classification of Primary Care 2; NICE: National Institute for Health and Care Excellence; NorPD: The Norwegian Prescription Database; OAT: Opioid agonist therapy; OR: Odds ratio; WHO: World Health Organization

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Authors' contributions

J.H.V. was involved in the study design, led analysis, and writing the article preparation. C.A., S.S., F.C., I.O., A.H., K.A.J., and L.T.F. contributed in the study

design, analysis, and writing the article preparation. All authors have read and approved the final article.

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Availability of data and materials

Except supplemental tables with some additional data, no additional data are available due to data protection requirements.

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics (REC), REC West, Norway, has approved the use of registry data for the study (reference number 2018/939/REK Vest, June 19, 2018). The REC committee is appointed by the Norwegian Ministry of Education and Research. No informed consent from the patients was necessary.

Consent for publication

Not applicable

Competing interests

I.O. is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies, unrelated to this work.

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Paper III

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Potentially addictive drugs dispensing to patients receiving opioid agonist therapy: a register-based prospective cohort study in Norway and Sweden from 2015 to 2017

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ABSTRACT

Objectives To compare the use of benzodiazepines, z-hypnotics, gabapentinoids, opioids and centrally acting stimulants (CAS) among patients who had received opioid agonist therapy (OAT) in Norway and Sweden during the period 2015 - 2017.

Design A register-based prospective cohort study using information about dispensed drugs from the Norwegian Prescription Database and Swedish Prescribed Drug Register.

Setting Patients who were dispensed OAT opioids from pharmacies.

Participants A total of 7176 Norwegian and 3591 Swedish patients on OAT were included.

Outcome measures The number and frequency of potentially addictive drugs dispensed were calculated for the two countries. The mean daily doses of dispensed benzodiazepines and z-hypnotics were summarised by calculating benzodiazepines in diazepam equivalents and z-hypnotics in zopiclone equivalents.

Results In 2017, 46% of patients in Norway, and 15% in Sweden, were dispensed a benzodiazepine. Moreover, 14% in Norway and 26% in Sweden received z-hypnotics. Gabapentinoids were dispensed to 10% of patients in Norway and 19% of patients in Sweden. In Norway, 6% and 12% of the patients received strong and weak non-OAT opioids, respectively, whereas in Sweden 10% were dispensed strong non-OAT opioids and 5% weak non-OAT opioids . CAS were dispensed to 4% in Norway and 18% in Sweden. The mean daily doses of benzodiazepines were 16 and 17 mg diazepam equivalents in Norway and Sweden, respectively. For z-hypnotics, the mean daily dose was 8 mg zopiclone equivalents in both countries. 'Benzodiazepines and z-hypnotics' was the most dispensed drug combination in 2017. Similar results were found in 2015 and 2016.

Conclusions Nearly half of those patients who were dispensed an OAT opioid in Norway and Sweden were dispensed potentially addictive drugs. The differences identified between Norway and Sweden might be related to differences in eligibility guidelines and restrictions with respect to OAT.

Strengths and limitations of this study

- This study used national register-based data of drugs dispensed from pharmacies in Norway and Sweden.
- This study did not capture patients who were dispensed opioid agonist therapy (OAT) opioids from entities other than pharmacies.
- There is potential for misclassification of patients if dispensed opioids were dispensed on medical indications other than OAT.
- About 40% and 10% of OAT patients in Sweden and Norway, respectively, were not identified by using these national register-based data.

INTRODUCTION

Several studies indicate that around 50% of those patients who receive opioid agonist therapy (OAT) are dispensed benzodiazepines (e.g., diazepam and oxazepam), z-hypnotics (zolpidem and zopiclone), gabapentinoids (pregabalin and gabapentin), non-OAT opioids (e.g., morphine and oxycodone) or centrally acting stimulants (CAS) (e.g., methylphenidate and lisdexamphetamine) yearly[1–5], notwithstanding the use of any potentially addictive illicit drugs.[1 6 7] Prescribing potentially addictive drugs to patients on OAT is controversial and comes with pros and cons.[1 8] Combinations of several potentially addictive drugs may increase the risk of non-fatal or fatal overdoses,[1] as well as amplify negative complex medical and psychosocial challenges such as unemployment,[9] criminal behaviour[10] and discontinuation of OAT.[6 11–13] However, the majority of patients on OAT have psychiatric and physical comorbidities, including psychotic disorders, attention deficit

hyperactivity disorder (ADHD), personality disorders, depression, other substance use disorders besides opioid addiction or injection-related diseases such as hepatitis C virus infection.[14–16] The wide range of high-prevalent comorbidities can require coprescriptions of potentially addictive drugs to obtain an optimal medical treatment in the OAT population. Examples such as prescriptions of CAS in order to improve ADHD symptoms[17] and short-term prescriptions of benzodiazepines to treat psychomotor agitation caused by stimulant intoxications[18] or seizure prophylaxis, as in cases of benzodiazepine or alcohol withdrawal,[19] illustrate clinical indications for such coprescriptions.

The prevalence of potentially addictive drugs dispensed among patients on OAT varies between countries.[1 5 20–23] In the USA, in 2013, between 22% and 65% of patients on OAT were dispensed benzodiazepines, and 42% and 20% were dispensed benzodiazepines and z-hypnotics, respectively, in the UK between 1998 and 2014.[20 24] In Sweden, 41% of OAT patients were dispensed z-hypnotics in the period 2005–2012.[1] Furthermore, epidemiological studies have shown that a wide range of OAT patients, from 8% to 22%, were dispensed gabapentinoids in different countries,[1 3 24] while between 12% and 34% were dispensed non-OAT opioids.[21 22 25] In contrast, no studies have evaluated CAS dispensing among patients on OAT. Overall, there are substantial intercountry differences regarding patients on OAT who were dispensed potentially addictive drugs; however, there is a gap in knowledge concerning whether these differences still persist.

OAT has in recent decades been increasingly applied as an effective and well-documented treatment for opioid addiction.[26–29] In Norway, around 7500 patients currently receive OAT,[28] while the corresponding number for Sweden is nearly 4400 patients.[30] Research on differences and similarities in the dispensing practice of potentially addictive drugs in these countries needs to be investigated to optimise the use of these drugs in the OAT population. In addition, evaluating dispensed doses of benzodiazepines, z-hypnotics, pregabalin, gabapentin and the CASs methylphenidate and lisdexamphetamine - the first hand of choice in the treatment of ADHD - are of particular interest due to the risk of overdoses and intoxications. It is also important for the study of possible variations in dispensed doses between the two countries.

Thus, this study aims to describe the rates and doses of potentially addictive drugs dispensed from Norwegian and Swedish pharmacies to patients receiving OAT in the period 2015–2017. We aim to describe the following:

1. The dispensing rates of benzodiazepines, z-hypnotics, gabapentinoids, non-OAT opioids and CAS per calendar year.
2. The mean daily doses of dispensed benzodiazepines, z-hypnotics, pregabalin, gabapentin, lisdexamphetamine and methylphenidate per calendar year.
3. The most commonly dispensed combinations of potentially addictive drug groups: benzodiazepines, z-hypnotics, gabapentinoids, non-OAT opioids and/or CAS among patients on OAT in 2017.

METHODS

Data sources

Data were retrieved from the Norwegian Prescription Database and Swedish Prescribed Drug Register. From 1 January 2004 in Norway and 1 July 2005 in Sweden, all pharmacies are obliged to submit electronically all data regarding dispensed drugs to the Norwegian Prescription Database and Swedish Prescribed Drug Register. The Norwegian Prescription Database and Swedish Prescribed Drug Register are administered and regulated by the Norwegian Institute of Public Health and Swedish National Board of Health and Welfare, respectively. Both registers contain information on all drugs dispensed from pharmacies, with unique patient identifiers, except for drugs administered at hospitals, nursing homes and outpatient clinics.[31 32] The Anatomical Therapeutic Chemical (ATC) classification system was used in accordance with the WHO standards per 2018.[33] A recent report evaluating OAT stated that the Swedish Prescribed Drug Register identifies about 60% of patients on OAT,[27] while the Norwegian Prescription Database is assumed to identify about 90% of the patients.[28] Moreover, in 2016, Sweden changed the OAT eligibility criteria by including long-term use of opioids (not only opiates like heroin, opium and morphine) as analgesics for chronic, severe pain.[26 27] Inclusion criteria in this study, therefore, identified patients with a high opiate tolerance who had a high degree of continuity in their OAT treatment.

Study population

All patients between 18 and 75 years of age who received at least one mean defined daily dose (DDD) of one or more defined OAT opioids per day during 2015, 2016 or 2017 were included (see online supplementary table S1). A minimum of one mean DDD per day was set as a criterion for inclusion to exclude patients who were dispensed low-dosed OAT opioids on medical indications other than OAT. The DDD of OAT opioids was calculated for each calendar year separately, which means that patients were only included in the calendar year when the mean dispensed DDD per day of OAT opioids, measured in DDD divided by 365.25 days, was one or more. The type of OAT opioids that were the latest dispensed (calculated in DDD) per year determined which type of OAT opioid category the patients belonged to in a calendar year. Dispensing methadone tablets or injections as well as buprenorphine formulations (ATC code: N02AE01) that have other medical indications besides OAT in Norway and Sweden, were excluded in the calculation of mean DDD of OAT opioids per day.

Patient and public involvement

Patients and the public were not involved in the development of the study design, planning and recruitment. Study results were not distributed to the patients after

the study. All data were handled strictly confidentially and anonymously. The Strengthening the Reporting of Observational Studies in Epidemiology Guidance checklist was applied during the preparation of the study.

Definitions of OAT opioids, other potentially addictive drugs and drug groups

All the potentially addictive drugs in the drug groups of benzodiazepines, z-hypnotics, gabapentinoids, OAT opioids, non-OAT opioids and CAS, which had marketing authorisations in Norway or Sweden in the period from 2015 to 2017, were included. All included drugs were defined according to their ATC codes. In addition, the non-OAT opioids were divided into two groups: 'strong non-OAT opioids' and 'weak non-OAT opioids' according to their analgesic potency.

Analysis strategy and statistical analyses

Data analysis

The age of included patients per year was calculated by subtracting the dispensing year from the birth year. The age of patients was categorised into four groups: 18–35, 36–45, 46–55 and 56–75.

The dispensing rates per year were defined as all included patients who were dispensed at least one potentially addictive drug during a calendar year divided by the number of included patients in the same year. The rates were calculated for each drug and the respective drug groups.

The mean daily doses per year of all dispensed benzodiazepines, z-hypnotics, pregabalin, gabapentin, lisdexamphetamine and methylphenidate were calculated by summing all dispensed DDD of each potentially addictive drug per calendar year in the study period. The DDD of each drug was converted to milligrams by using the definitions of the WHO Collaboration Centre for Drug Statistics Methodology (see online supplementary table S2).[33] The dispensed doses (in milligrams) of each drug were divided by 365.25 days to calculate the mean daily doses per year. Further, the mean daily dose per year of each dispensed benzodiazepine was converted to mean daily dispensed diazepam equivalents according to the equivalency table stated by the Norwegian Directorate of Health and a study evaluating the equipotency of lorazepam versus diazepam (see online supplementary figure S1).[34 35] The dispensed diazepam equivalents per day were used to calculate the total sum of all dispensed benzodiazepines per day per year. The mean daily doses of dispensed z-hypnotics were calculated by converting mean dispensed zolpidem dose per day to zopiclone equivalents according to the guidelines of the Norwegian Directorate of Health.[34] Furthermore, the total mean doses per day of zopiclone and zolpidem in zopiclone equivalents for a calendar year were summed.

Statistical analyses

Means, medians, percentiles and percentages were used to calculate dispensing rates, and the dispensed doses of benzodiazepines, z-hypnotics, pregabalin, gabapentin, lisdexamphetamine and methylphenidate. Stata SE V.16.0 statistical software was used for all analyses.

RESULTS

Descriptive characteristics

A total of 7176 Norwegian and 3591 Swedish patients on OAT were included in the study period (table 1). In 2015, 6007 patients in Norway, and 2640 in Sweden fulfilled the inclusion criteria (see online supplementary figure S2). A further 5542 OAT patients in Norway, and 2683 OAT patients in Sweden were included in 2016, with 5556 Norwegian OAT patients and 2739 Swedish OAT patients having fulfilled the eligibility criteria in 2017.

In 2017, 72% and 70% of the Norwegian and Swedish patients were male, respectively. The mean age of the patients included was 46 years in Norway and 45 years in Sweden. Buprenorphine/buprenorphine-naloxone was the most dispensed OAT opioid throughout the study period, having been dispensed to 55% of patients in Norway and 57% of patients in Sweden. The findings in 2015 and 2016 were similar.

Dispensing rates of potentially addictive drugs

In Norway, 56% of patients on OAT were dispensed benzodiazepines, z-hypnotics, gabapentinoids, non-OAT opioids or CAS in 2015 (table 2). In 2017, the proportion was 59%. In Sweden, the proportion of patients on OAT who received at least one dispensation of these potentially addictive drugs was 56% in 2015 and 55% in 2017 (figure 1). In 2017, the proportion of patients receiving benzodiazepines was 46% in Norway and 15% in Sweden. Furthermore, 14% in Norway and 26% in Sweden received z-hypnotics, and 10% of the Norwegian patients and 19% of the Swedish patients were dispensed gabapentinoids. CAS were dispensed to 4% of the Norwegian patients and 18% of the Swedish patients on OAT. Similar results were also achieved in 2015 and 2016 (see online supplementary figure S3).

Dispensed doses of benzodiazepines, z-hypnotics, gabapentin, pregabalin, lisdexamphetamine, and methylphenidate

In 2017, the mean doses of dispensed benzodiazepines were 17 mg/day diazepam equivalents in Norway, with a corresponding 16 mg/day in Sweden (table 3). Further, the mean dose of dispensed z-hypnotics was 8 mg/day zopiclone equivalents in both countries in 2017. The mean daily doses of dispensed pregabalin, gabapentin and lisdexamphetamine were higher in Norway than in Sweden (pregabalin: 402 mg vs 345 mg, gabapentin: 1021 mg vs 772 mg and lisdexamphetamine: 58 mg vs 51 mg), while the mean dose of dispensed methylphenidate per day was higher in Sweden compared with Norway (methylphenidate: 80 mg vs 57 mg). The results

Table 1 Basic characteristics of patients receiving opioid agonist therapy in Norway and Sweden

	2015				2016				2017			
	Norway		Sweden		Norway		Sweden		Norway		Sweden	
Baseline characteristics	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patients	6007		2640		5542		2683		5556		2739	
Age												
≥18–35	1132	19	648	25	958	17	649	24	881	16	647	24
>35–45	2043	34	786	30	1815	33	806	30	1751	32	819	30
>45–55	2096	35	737	28	1961	35	708	26	2000	36	713	26
>55–≤75	736	12	469	18	808	15	520	19	924	17	560	20
Mean (SD)	45 (9)		44 (11)		45 (9)		45 (11)		46 (9)		45 (11)	
Gender												
Male	4225	70	1886	71	3897	70	1939	72	3878	70	1961	72
Female	1782	30	754	29	1645	30	744	28	1678	30	778	28
OAT opioids*												
Methadone/levomethadone	2747	46	1229	47	2389	43	1209	45	2533	46	1191	43
Buprenorphine/buprenorphine-naloxone	3260	54	1411	53	3153	57	1474	55	3023	54	1548	57

*Patients were categorised in the groups 'Methadone/Levomethadone' and 'Buprenorphine/buprenorphine-naloxone'. The type of OAT opioids was calculated based on the most dispensed OAT opioid measured in DDD per calendar year.
DDD, defined daily dose; No., number of patients; OAT, opioid agonist therapy.

were relatively similar in 2015 and 2016 except for the mean dose of dispensed lisdexamphetamine per day, which was higher (in mg) in Sweden than in Norway in 2015 (lisdexamphetamine: 42 mg vs 13 mg).

Combinations of potentially addictive drugs in 2017

The proportion of patients on OAT being dispensed a single potentially addictive drug was 34% in Norway and 31% in Sweden. A quarter were dispensed potentially addictive drugs from two or more drug groups (see online supplementary table S3). 'Benzodiazepines and z-hypnotics' was the most commonly dispensed combination of drugs, whereas 'benzodiazepines and non-OAT opioids' and 'z-hypnotics and gabapentinoids' were the second most common combinations in Norway and Sweden, respectively.

DISCUSSION

The proportion of patients on OAT who were dispensed a potentially addictive drug was unchanged during the study period, with about half of the patients in both countries. There were, however, substantial variations between the countries in all dispensed drug groups. Benzodiazepines and weak non-OAT opioids were more commonly dispensed in Norway than in Sweden. In contrast, z-hypnotics, gabapentinoids, CAS and strong non-OAT opioids were more frequently dispensed in Sweden compared with Norway. Similar variations between Norway and Sweden have also been found regarding dispensing weak and strong non-OAT opioids in the general population.[36] The most frequent combinations of potentially addictive drugs with OAT medications in 2017 were observed for benzodiazepines and z-hypnotics in both countries. The mean daily doses of dispensed benzodiazepines and z-hypnotics were also similar between the countries, while pregabalin, gabapentin and lisdexamphetamine doses were higher (in mg) in Norway. The mean daily dose of methylphenidate was higher (in mg) in Sweden compared with Norway. Similar results were found in 2015 and 2016.

The Swedish OAT guidelines recommend restrained practice in dispensing potentially addictive drugs,[26 27] while Norway goes further by downright discouraging benzodiazepine use in OAT. It was, therefore, particularly surprising that only 15% of the patients in Sweden were dispensed benzodiazepines, whereas, in Norway, benzodiazepines were dispensed to about half of the OAT patients. However, the dispensing rates of z-hypnotics and gabapentinoids were higher in Sweden than in Norway. The fact that the prevalence of mental and physical disorders is high among patients on OAT - and that there is a broad spectrum of medical indications for the use of benzodiazepines, gabapentinoids and z-hypnotics - makes it challenging to determine whether our results point towards inappropriate dispensing practice in the OAT populations in each country.[14 15 37–39] It is nevertheless noteworthy that the dispensing rates of these drugs deviated considerably between the two countries.

Sweden had dispensing rates nearly four times higher for CAS compared with Norway, which indicates that coverage of ADHD treatment in patients on OAT is higher in Sweden. In both countries, guidelines for ADHD treatment recommend abstinence from other potentially addictive drugs when CAS are dispensed to patients on OAT.[40] In addition, the Norwegian guidelines recommend

Table 2 Dispensation rates of potentially addictive drugs in patients receiving opioid agonist therapy

Year	2015		2016		2017	
	Norway	Sweden	Norway	Sweden	Norway	Sweden
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Country	**6007**	**2640**	**5542**	**2683**	**5556**	**2739**
Dispensed addictive drugs						
Dispensed addictive drug	3383 (56)	1478 (56)	3203 (58)	1542 (57)	3256 (59)	1517 (55)
Benzodiazepines						
All benzodiazepines	2622 (44)	438 (17)	2503 (45)	451 (16)	2556 (46)	421 (15)
Oxazepam	1656 (28)	126 (5)	1605 (29)	133 (5)	1659 (30)	119 (4)
Diazepam	923 (15)	179 (7)	893 (16)	191 (7)	924 (17)	188 (7)
Nitrazepam	574 (10)	62 (2)	533 (10)	63 (2)	514 (9)	46 (2)
Clonazepam	267 (4)	49 (2)	240 (4)	64 (2)	199 (4)	49 (2)
Alprazolam	182 (3)	102 (4)	145 (3)	80 (3)	137 (2)	73 (3)
Flunitrazepam	30 (0)	22 (1)	24 (0)	23 (1)	28 (0)	19 (1)
Z-hypnotics						
All z-hypnotics	912 (15)	750 (28)	834 (15)	760 (28)	798 (14)	721 (26)
Zopiclone	715 (12)	653 (25)	661 (12)	675 (25)	614 (11)	627 (23)
Zolpidem	252 (4)	151 (6)	220 (4)	134 (5)	232 (4)	122 (4)
Gabapentinoids						
All gabapentinoids	503 (8)	463 (18)	509 (9)	497 (19)	582 (10)	507 (19)
Pregabalin	348 (6)	330 (13)	359 (6)	331 (12)	413 (7)	317 (12)
Gabapentin	192 (3)	164 (6)	183 (3)	203 (8)	207 (4)	213 (8)
Strong non-OAT opioids						
All strong non-OAT opioids	309 (5)	280 (11)	314 (6)	275 (10)	353 (6)	262 (10)
Methadone tablets or injections*	94 (2)	120 (5)	85 (2)	105 (4)	130 (2)	108 (4)
Oxycodone	100 (2)	111 (4)	114 (2)	128 (5)	127 (2)	131 (5)
Morphine	63 (1)	54 (2)	71 (1)	44 (2)	71 (1)	32 (1)
Buprenorphine	42 (1)	26 (1)	44 (1)	25 (1)	32 (1)	19 (1)
Ketobemidone	21 (0)	13 (0)	21 (0)	11 (0)	12 (0)	8 (0)
Fentanyl	18 (0)	10 (0)	18 (0)	6 (0)	16 (0)	8 (0)
Weak non-OAT opioids						
All weak non-OAT opioids	768 (13)	169 (6)	675 (12)	150 (6)	674 (12)	137 (5)
Codeine	562 (9)	125 (5)	500 (9)	107 (4)	470 (8)	98 (4)

Continued

Table 2 Continued

Year	2015		2016		2017	
	Norway	Sweden	Norway	Sweden	Norway	Sweden
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Country	**6007**	**2640**	**5542**	**2683**	**5556**	**2739**
Tramadol	289 (5)	53 (2)	233 (4)	49 (2)	274 (5)	36 (1)
Centrally acting stimulants						
All centrally acting stimulants	184 (3)	437 (17)	200 (4)	484 (18)	218 (4)	491 (18)
Methylphenidate	143 (2)	400 (15)	151 (3)	392 (15)	143 (3)	346 (13)
Dexamphetamine	45 (1)	12 (0)	45 (1)	16 (1)	42 (1)	24 (1)
Lisdexamphetamine	9 (0)	82 (3)	28 (1)	144 (5)	51 (1)	183 (7)

Less than six patients were dispensed tapentadol, hydromorphone, petidine, lorazepam and midazolam (data not shown).
*Methadone tablets and injections medically indicated for pain.
No., Number of patients; OAT, opioid agonist therapy.

documented abstinence from potentially addictive drugs at least 3 months prior to the initiation of CAS in OAT patients when indicated.[41] This may partly explain a lower dispensing rate of CAS in Norway compared with Swedish OAT patients. Furthermore, unlike Norway, Sweden seems to terminate OAT in cases of repeated illicit drug use, which indicates that the coverage of OAT among patients with severe opioid addiction may be lower in Sweden.[30 42] This can explain why the proportion of OAT patients who meet the criteria for codispensing CAS is higher in Sweden compared with Norway.

The differences in dispensing rates and mean daily doses of codispensed potentially addictive drugs between Norway and Sweden may also be explained by the composition and heterogeneity of OAT populations. The European Monitoring Centre for Drugs and Drug Addiction, evaluating OAT in 12 European countries,[29] points out that restrictive policy, narrow inclusion criteria and costs are seen as substantial challenges limiting the coverage of OAT. In general, patients who repeatedly use illicit drugs in OAT have more psychiatric and somatic comorbidities.[43–45] In Sweden, repeated use of illicit drugs in OAT may cause patients to be terminated from OAT against their will.[42] This is to believe that Norway probably has a higher coverage of OAT, which also includes patients using illegal drugs and, accordingly, those with a higher burden of comorbid diseases. In addition, the divergent dispensing practices in the two countries could reflect the lack of consensus and evidence-bases concerning the treatment of underlying disorders in OAT patients.

Moreover, a tenth of the Norwegian OAT patients were dispensed a gabapentinoid in 2017, whereas nearly twice as many were dispensed this drug in Sweden. During the last decade, the dispensing of gabapentinoids has increased substantially in the general population in Norway and Sweden despite studies that point out that gabapentinoids are potentially addictive.[7 24 31 32 46] Systematic reviews evaluating the use of gabapentinoids indicate that patients with opioid addiction were at a particular risk of misusing pregabalin and gabapentin,[7 46] and euphoria and sedative effects were described when combining with opioids. Therefore, it is worrying that dispensing rates of gabapentinoids were high and increasing among patients on OAT.

Overall, based on our data and existing knowledge, we are unable to sufficiently evaluate whether dispensing rates of potentially addictive drugs were disproportionately high or even low among patients on OAT in Norway and Sweden during the study period. Some patients may have been undertreated considering their high burden of disease. On the other hand, a recent study has found that being dispensed gabapentinoids, z-hypnotics or benzodiazepines is associated with overdose death among patients on OAT.[1] To stay on the safe side of this challenging matter, lower dispensing rates of these drugs may be preferable considering a high number of overdose deaths in Norway and Sweden during the last decade.[30 47] Stricter dispensing practices with clearer defined medical

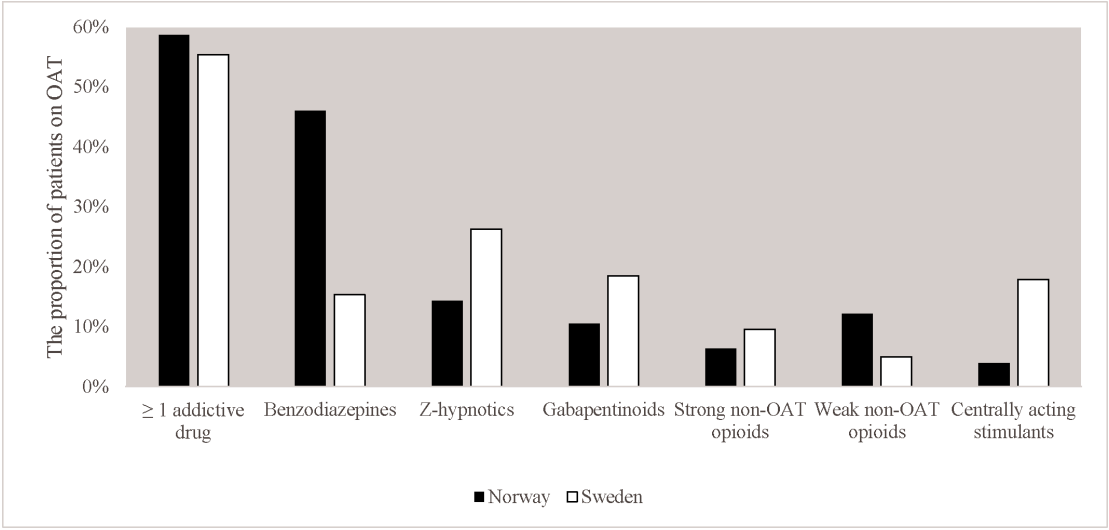

Figure 1 The proportion of patients on OAT who were dispensed potentially addictive drugs in 2017. The figure displays the proportion of patients on OAT who were dispensed at least one potentially addictive drug, benzodiazepine, z-hypnotic, gabapentinoid, strong non-OAT opioid, weak non-OAT opioid and centrally acting stimulant in Norway and Sweden in 2017. Strong non-OAT opioids were defined as all opioid expect codeine, tramadol and tapentadol. Weak non-OAT opioids were defined as all drugs that contain codeine, tramadol or tapentadol. OAT, opioid agonist therapy.

indications, regular urine testing to prevent concomitant street drug use, and close collaboration between prescribers of OAT opioids and those dispensing potentially addictive drugs may be important measures to decrease future overdose deaths and ensure more reasonable and safe treatment approaches among the highly morbid patients on OAT.

STRENGTHS AND LIMITATIONS

The use of national registry data has some advantages, as it can capture whole cohorts of the studied populations. The Norwegian Prescription Database and Swedish Prescribed Drug Register have advantages in that they receive all information concerning dispensed drugs from pharmacies in Norway and Sweden, except for those administered at hospitals, nursing homes and outpatient clinics. These registers are the most useful databases that identify reliable information regarding drug dispensing among patients on OAT.[31 32]

However, this study also has some limitations, mainly related to possible differences in selection bias between the studied populations. First, in both countries, patients may use methadone mixture for a medical indication other than OAT yet still be included in the OAT population. To account for this, only patients who had been dispensed a mean dose of one or more DDD of methadone mixture, levomethadone or buprenorphine/buprenorphine-naloxone during a calendar year were included. Second, mean daily doses were calculated by summing all dispensed doses of the respective drugs during a calendar year divided by 365.25 days. Dividing the dispensed doses per year by 365.25 have some limitations. Some patients may have been dispensed drugs in a higher mean daily dose within a shorter period than the calculations of mean daily doses per year indicate. Further, the drugs that were dispensed at the end of December for consumption in the following months were calculated as consumed in the year the drugs were dispensed. The latter could potentially signify that the mean daily doses were calculated higher than the dose recommended by the prescribers. Third, it is estimated that only about 60% of patients on OAT are identified through the Swedish Prescribed Drug Register; the remaining proportion may receive OAT opioids from specialised addiction outpatient clinics within specialist healthcare.[27] In Norway, it is estimated that 90% of patients who were dispensed OAT opioids were registered in the Norwegian Prescription Database.[28] The fact that 40% of the Swedish patients were lacking could skew the results and affect the conclusion. Patients who received OAT opioids from outpatient clinics may have more psychiatric and physical comorbidities and need more follow-ups than patients who were dispensed OAT opioids by pharmacies. Therefore, these comorbid patients who could not be captured by our study may have had higher dispensing rates of potentially addictive drugs, meaning that the dispensing rates may have been underestimated in this study. Fourth, the Swedish Prescribed Drug Register does not provide data on patients who died during the study period. Due to this, patients were censored from the year with no dispensing

Table 3 Dispensed dose of potentially addictive drugs in the period from 2015 to 2017

Year	2015		2016		2017	
Country	Norway	Sweden	Norway	Sweden	Norway	Sweden
Benzodiazepines						
Diazepam equivalents						
Number of patients	2622	438	2503	451	2556	421
Mean (mg/year)	6920	6896	6585	6437	6216	5936
Mean (mg/day/year)	19	19	18	18	17	16
Median (mg/day/year)	10	10	10	9	10	9
25 percentile (mg/day/year)	3	2	3	2	3	2
75 percentile (mg/day/year)	21	22	21	21	20	21
Z-hypnotics						
Zopiclone equivalents						
Number of patients	912	750	834	760	798	721
Mean (mg/year)	2867	3037	2904	2951	2942	3008
Mean (mg/day/year)	8	8	8	8	8	8
Median (mg/day/year)	5	7	6	6	6	7
25 percentile (mg/day/year)	1	2	1	2	1	2
75 percentile (mg/day/year)	10	12	10	12	11	12
Gabapentinoids						
Gabapentin						
Number of patients	192	164	183	203	207	213
Mean (mg/year)	335409	256505	334730	276083	372966	282017
Mean (mg/day/year)	918	702	916	755	1021	772
Median (mg/day/year)	376	324	492	329	492	329
25 percentile (mg/day/year)	82	82	82	82	164	82
75 percentile (mg/day/year)	1287	992	1232	986	1203	986
Pregabalin						
Number of patients	348	330	359	331	413	317
Mean (mg/year)	134777	123510	144551	119335	146684	126122
Mean (mg/day/year)	369	338	396	327	402	345
Median (mg/day/year)	261	277	319	260	275	287
25 percentile (mg/day/year)	66	138	92	117	82	149
75 percentile (mg/day/year)	561	480	592	483	575	501
Centrally acting stimulants						
Methylphenidate						
Number of patients	143	400	151	392	143	346
Mean (mg/year)	18957	28966	21364	29248	20845	29305
Mean (mg/day/year)	52	79	58	80	57	80
Median (mg/day/year)	48	69	52	71	57	70
25 percentile (mg/day/year)	16	35	18	31	20	28
75 percentile (mg/day/year)	75	109	85	112	85	114
Lisdexamphetamine						
Number of patients	9	82	28	144	51	183
Mean (mg/year)	4778	15238	18158	17649	21033	18514
Mean (mg/day/year)	13	42	50	48	58	51
Median (mg/day/year)	14	29	37	42	42	48

Continued

Table 3 Continued

Year	2015		2016		2017	
Country	Norway	Sweden	Norway	Sweden	Norway	Sweden
25 percentile (mg/day/year)	2	11	14	21	20	20
75 percentile (mg/day/year)	20	60	87	68	99	72

The table displays the mean doses and mean daily doses of dispensed benzodiazepines, z-hypnotics, pregabalin, gabapentin, methylphenidate and lisdexamphetamine per calendar year in the period from 2015 to 2017. The mean daily dose of each drug was calculated by summarising all dispensed DDD per year. The summarised DDD were converted to milligrams according to the WHOs standard. In addition, for benzodiazepines and z-hypnotics, all doses of dispensed benzodiazepines were converted into diazepam equivalents and z-hypnotics into zopiclone equivalents. We used equipotency tables from the Norwegian Directorate of Health[34] and a study evaluating the equipotency of lorazepam vs diazepam[35] when calculating the doses to diazepam and zopiclone equivalents. Further, all dispensed doses (benzodiazepines, z-hypnotics, gabapentin, pregabalin, methylphenidate and lisdexamphetamine) per year were divided by 365.25 days to calculate the mean and median daily doses, and the daily doses at the 25 percentile, and the 75 percentile.

OAT opioids in both countries. The annual self-reported survey on the Norwegian OAT population indicated that the death rate is approximately 1.5% per 100 patient-year, which could constitute about 125 patients yearly in our Norwegian and Swedish population.[28] Fifth, because no dispensed drugs in Sweden nor all non-reimbursed dispensations in Norway are necessarily linked to medical diagnostic codes, such as the International Statistical Classification of Diseases and Related Health Problems version 10, or the International Classification of Primary Care, the medical indications for the dispensations are not available to the researchers through the prescription register-based databases. Sixth, in 2016, Sweden changed the inclusion criteria to be granted OAT by including opioid-addicted patients with extensive opioid use caused by chronic severe pain.[26 27] The proportion of patients receiving OAT opioids due to pain was not estimated in this study.

CONCLUSION

About half of patients who were dispensed an OAT opioid were codispensed potentially addictive drugs in Norway and Sweden. There were remarkable differences in the dispensing rates and dispensed doses of potentially addictive drugs between OAT patients in these countries. This might be related to differences in national guidelines, a lack of evidence-based knowledge and international consensus on the treatment of comorbid conditions among patients on OAT or differences in the criteria required to be included and kept in OAT, which again may contribute to varying clinical practice and treatment approaches in OAT populations across the countries. We call for further research to investigate proper approaches for the treatment of comorbid conditions in patients undergoing OAT.

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Patient consent for publication Not required.

Ethics approval The Regional Committee for Medical and Health Research Ethics West, Norway, and the Swedish Ethical Review Authority in Stockholm, Sweden, have both approved the use of the Norwegian and Swedish registry data for the study (Norway: reference number 2018/939/REK Vest, 19 June 2018; Sweden: reference number 2018/2080-31/1, 14 November 2018 and reference number 2019-04791, 22 November 2019). The Regional Committee for Medical and Health Research Ethics West, Norway, is appointed by the Norwegian Ministry of Education and Research, and the Swedish Ethical Review Authority is under the Swedish Ministry of Education. No informed consent from the patients was necessary.

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Paper IV

Vold JH, Gjestad R, Aas CF, Chalabianloo F, Skurtveit S, Løberg E-M, Johansson KA, Fadnes LT: **Impact of clinical and sociodemographic factors on fatigue among patients with substance use disorder: a cohort study from Norway for the period 2016-2020.** *Substance Abuse Treat Prev and Policy* 2020, 15(1):93.

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Substance Abuse Treatment, Prevention, and Policy

RESEARCH Open Access

Impact of clinical and sociodemographic factors on fatigue among patients with substance use disorder: a cohort study from Norway for the period 2016–2020

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Abstract

Background: The impact of clinical and sociodemographic factors on fatigue remains unknown among patients with substance use disorders (SUD). This study aims to evaluate fatigue among patients with SUD using a nine-item fatigue severity scale (FSS-9) and identify the impact that clinical and sociodemographic factors – such as injecting substance use, chronic infectious diseases, liver fibrosis, opioid agonist therapy (OAT), debt difficulties, and housing situation – have on fatigue.

Methods: We used data from a cohort of patients with SUD in Norway with annual health assessments surveying FSS-9 and some clinical and sociodemographic factors. A total of 915 FSS-9 measurements were collected from 654 patients during the period 2016–2020. We defined baseline as the first annual health assessment when the health assessments were listed chronologically. Time was defined as years from baseline. We used a linear mixed model to analyse whether the clinical and sociodemographic factors affected the FSS-9 sum score, presented with beta coefficients (β) with 95% confidence intervals (CI).

Results: The mean sum score of the FSS-9 was 43 (standard deviation: 16) at baseline. Females compared with males (adjusted mean difference of FSS-9 sum score: 4.1, 95% CI: 1.3–7.0), having debt difficulties compared with having no debt difficulties (2.9;0.4–5.3), and frequent use of benzodiazepines (5.7;3.0–8.4) or amphetamines (-5.0;-8.0– -2.0) compared to less frequent or no use of these substances changed the FSS-9 baseline sum score. The other clinical and sociodemographic factors did not predict any clinically relevant change in the FSS-9 sum score from baseline to the following health assessments.

Conclusion: Patients with SUD suffer from high levels of fatigue. Female patients, patients with debt difficulties, and those with extensive use of benzodiazepines are at particular risk of being fatigued. This should be taken into consideration when planning health services.

Keywords: Substance-related disorders, Fatigue, Fatigue severity scale, Quality of life, Comorbidities, Illicit drugs, Viral human hepatitis, HIV, Kidney disease

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Background

Patients with Substance Use Disorders (SUD) suffer from a broad range of health-related difficulties that may contribute to fatigue [1–3]. Fatigue presents itself as a persistent and overwhelming feeling of exhaustion and loss of energy. The condition is mainly associated with chronic diseases and may mitigate treatment adherence and exacerbate comorbid disorders [4, 5]. In SUD populations, a myriad of external factors can interact with fatigue and affect these patients' general well-being [6–8]. Injecting substance use, internal organ dysfunctions (predominantly kidney and liver diseases), mental disorders, as well as low income, unemployment, and homelessness are some of the external factors that interact with fatigue. Despite this, relatively little attention has been paid to the extent of fatigue and how much various external factors influence fatigue among patients with SUD. Therefore, understanding the key factors affecting fatigue is essential to improve treatment outcomes and adherence in this population.

Fatigue is associated with several sociodemographic and clinical factors. Among patients with the Hepatitis C Virus (HCV) infection, 50–70% have reported fatigue [9–11], while 33–88% of those with the Human Immunodeficiency Virus (HIV) infection have presented the same symptom [12]. A more uncertain prevalence of fatigue is seen among patients with the Hepatitis B Virus (HBV) [13, 14]. In addition, females, patients with lower educational levels, and those with opioid use disorders undergoing Opioid Agonist Therapy (OAT) with methadone or buprenorphine generally have a greater risk of fatigue [15, 16]. Disentangling the effects of the potential factors influencing fatigue in patients with SUD is essential for individualised treatment and developing clinical guidelines.

Fatigue is a subjective concept, and various definitions and instruments are used in the literature to capture it, which makes interpretations more complicated [17–19]. The nine-item fatigue severity scale (FSS-9) is a well-known questionnaire used to quantify fatigue treatment effects. It shows excellent validity and reliability across various chronic neurological and infectious diseases, such as multiple sclerosis [17], HCV infection [20], stroke [5], and Parkinson's disease [21]. The fact that FSS-9 shows a high consistency across various chronic diseases makes it particularly suitable to estimate fatigue among patients suffering from SUD with complex and challenging comorbidities.

Thus, this prospective cohort study aims to investigate fatigue using the nine-item Fatigue severity scale (FSS-9) among patients with substance use disorders (SUDs) and predict the impact of sociodemographic and clinical factors on FSS-9, including educational level, housing situation, debt difficulties, chronic infectious diseases, injecting substance use, substance use, liver fibrosis, and kidney disease. Moreover, we estimate:

1) using annual health assessments, the FSS-9 sum score and whether and to what extent the sociodemographic and clinical factors impact this score;
2) the impact of sociodemographic and clinical factors on changes in the FSS-9 sum score from the first health assessment to the following annual health assessments;
3) for two separate subgroups – patients receiving methadone as opioid agonist therapy (OAT) and those receiving buprenorphine as OAT – the FSS-9 sum score, whether and to what extent the sociodemographic and clinical factors affect the FSS-9 sum score at baseline, and any changes in the FSS-9 sum score from the first health assessment to the following annual health assessments.

Methods

Data source

We used data from a cohort nested to the INTRO-HCV trial on patients with SUD in Bergen and Stavanger, Norway [22]. We collected data from May 2016 to January 2020, and recruited patients on OAT from outpatient clinics in Bergen and Stavanger, as well as patients with various SUDs receiving primary healthcare from the municipality clinics in the city of Bergen.

Data collections

All included patients were assessed yearly with a health assessment, including FSS-9 measurements, sociodemographic data, and current substance use. Additionally, blood samples and liver fibrosis measurements using transient elastography were conducted. We collected all data in a health register using electronic data collection software (Checkware®) under research nurses' supervision. All the clinical data, including information regarding OAT, OAT medication, substance use, and possible comorbid clinical conditions, were collected from the electronic medical record.

Study sample

We included 915 FSS-9 measurements from 654 patients in the study period. In total, 225 had follow-up data and conducted the health assessment, including the FSS-9 questionnaire, twice ($n = 188$) or thrice ($n = 37$), providing 487 repeated measurements. The median time interval between the baseline health assessments, and any subsequent assessments in the same patients, including FSS-9 measurements, was 11 months (interquartile range (IQR): 9–14) (Additional file 1).

Measuring fatigue

We measured fatigue during the last week using FSS-9, including items considering: mental and physical functioning, motivation, carrying out duties, and interference with work, family, or social life. An FSS-9 measurement was completed when all nine items in the questionnaires were entirely conducted during an annual health assessment. The FSS-9 items were answered on a Likert scale – ranging from 1 (no fatigue) to 7 (worst fatigue) – that demonstrates the fatigue level. A high score of FSS-9 items notes a high level of fatigue, while a mean FSS-9 item score greater than 4.0 revealed severe fatigue. The data collection software only allowed valid responses to each question and prompted empty questions before submission to minimise missing data. The FSS-9 was also translated and back-translated from the US-English version into Norwegian by qualified native Norwegian-speaking translators (Additional file 2) [23].

Measuring liver stiffness and assessing blood samples

We assessed liver stiffness using transient elastography (Fibroscan®) to reveal liver fibrosis and cirrhosis. The elastography was reported as a median score of 10 measurements conducted by research nurses. A liver stiffness above 10 kilopascals (kPa) was defined as liver fibrosis, while a value above 12.5 kPa indicated liver cirrhosis [24]. We also collected blood samples, including hemoglobin, thrombocytes, C - reactive protein, aspartate aminotransferase, estimated glomerular filtration rate, hepatitis B surface antigen, HIV antigen/antibodies, HCV antibodies, and HCV polymerase chain reaction (HCV PCR) during the annual health assessment. Liver stiffness was estimated by calculating the AST to platelet ratio index (APRI) score and using transient elastography (Fibroscan®) (Additional file 3). Moreover, the hematological and biochemical samples were analysed to detect anemia (Hemoglobin), infection or inflammation (C – reactive protein), kidney disease (estimated glomerular filtration rate), liver disease (APRI), or chronic infectious diseases (HIV, HCV, and HBV), which could affect the FSS-9 score. Both elastography and blood samples were examined annually and simultaneously when conducting the annual health assessments. We analysed the blood samples at the Department of Laboratory Medicine, Haukeland University Hospital, Bergen, Norway, and at the Department of Medical Biochemistry and Microbiology, Stavanger University Hospital, Stavanger, Norway (accredited by ISO-standard 15,189).

Definition of study variables, including sociodemographic and clinical factors

We defined baseline for patients as the first annual health assessment that included an FSS-9 measurement when we listed the health assessments chronologically. We dealt with each FSS-9 measurement as a sum score by summarising the value (one to seven) from each item and as a mean score calculated by dividing the sum score by nine (nine items). We defined being on OAT according to whether patients received buprenorphine or methadone (OAT opioids) at baseline. Further, in accordance with the World Health Organization's standards, we calculated the daily dose of received OAT opioids as a ratio between the received dose per day divided by the expected mean dose of OAT opioids (buprenorphine 18 mg, buprenorphine-naloxone 18/4.5 mg or methadone 90 mg) [25]. We categorised educational level into five groups: 'not completed primary school,' 'completed primary school (nine years),' 'completed high school (12 years),' 'three or fewer years of college or university' or 'more than three years of college or university.' Patients' housing situations in the 30 days prior to the FSS-9 measurement were classified into two groups: "stable" and "unstable." The latter category involved patients who had lived on the street, in a homeless shelter, or with family and friends during the past 30 days. Others who had a more permanent residence were classified as having a stable housing situation. Debt difficulties were defined as striving with paying off legal or illegal debt due to a constrained private economy. We set 'injecting substance use' as having injected at any time during the past 12 months, whereas frequent substance use was categorised as consuming at least one of the substance groups, including 'benzodiazepines or z-hypnotics,' 'cannabis,' 'stimulants (amphetamines or cocaine),' 'alcohol,' and 'heroin or other illicit opioids', more than weekly during the 12 months prior to a health assessment. Patients who did not use substances or used them less than weekly during the past 12 months were categorised as having 'no frequent use of substance'. Having chronic infectious diseases was defined as detecting HCV PCR (HCV), hepatitis B surface antigen (HBV), or HIV antigen/antibodies (HIV) in the blood samples. For HCV PCR, we used the Helmert contrast in order to classify patients into two groups – transmitted and non-transmitted – and further into two subgroups: whether patients have a low viral load (< 800,000 IU/ml) or high viral load (≥ 800,000 IU/ml). By this two-fold division, we investigated whether the level of viral HCV load was associated with changes in the fatigue level.

Statistical analyses

We used Stata/SE 16.0 (StataCorp, TX, USA) for descriptive analysis and IBM SPSS version 26.0 for expectation-maximisation imputation and linear mixed model analyses. The threshold for statistical significance was set to $P < 0.05$ for all analyses unless otherwise stated. In all analyses, we defined time as years from baseline.

We dealt with any missing values concerning sociodemographic and clinical factors – such as educational level, housing situation, debt difficulties, receiving OAT, OAT opioid dose ratio, injecting substance use, substance use, and the results of defined blood samples and transient elastography – as 'missing at random' when running expectation-maximisation imputation. We identified missing values in 2.6% in these factors and all were replaced with estimated values by imputation.

The FSS-9 sum score at baseline was calculated by summarising the nine items' points. Linear mixed model analyses were used to investigate whether the sociodemographic and clinical factors affected the FSS-9 sum score and to what extent they impacted any changes in the score from baseline to following the health assessments. First, the factor variables were analysed separately as outcome variables as a function of the time (time from baseline). We did not identify substantial significant changes in the sociodemographic and clinical factors between the annual health assessments (data not shown). Thus, baseline levels were used as stable predictors in the prediction of the level and changes in FSS-9. We specified the linear mixed models as a random intercept fixed slope regression model. The estimator was set to Restricted Maximum Likelihood. To explore whether predictors predicted changes in outcome, the interactions between these factors and time were added to the model. The full information maximum likelihood ensured that all available FSS-9 sum score measurements were used. Additionally, we presented sub-group analyses for OAT patients using methadone or buprenorphine, respectively. For these analyses, we added the OAT opioid ratio as a predictor. The potential correlations between sociodemographic and clinical factors and fatigue are presented in Additional file 4. We performed a sensitivity analysis by adding Bonferroni corrected p-values to adjust for Type I errors in all analyses.

Ethics approval and consent to participate

The study is reviewed and approved by the Regional Ethical Committee for Health Research West, Norway (REK Vest 2017/51). Each patient provided written informed consent prior to enrolling in the study.

Results

Patients characteristics at baseline

Seventy-one percent of patients were male, and the mean age was 43 years (standard deviation (SD): 11 years) at baseline (Table 1). Six percent had not completed primary school, or 44% had primary school as their highest educational level. 82% received OAT, of which 60% received buprenorphine or buprenorphine-naloxone as an OAT opioid. Further, 13% had an unstable housing situation in the last 30 days leading up to the FSS-9 measurement. 73% had used at least one substance weekly during the past 12 months.

FSS-9 sum scores at baseline

The mean sum score for the FSS-9 was 43 (SD: 16), representing a mean score for the FSS-9 items of 4.8 (2.6) (Table 2). A total of 69% of patients had severe fatigue. The mean FSS-9 sum score was slightly left-skewed (skewness: – 0.7) and tended towards a flattened distribution (kurtosis: 2.4).

The mean scores for the FSS-9 were 43 (SD: 16) for patients receiving methadone and 43 (17) for those using buprenorphine (Additional file 5), corresponding to a mean score for the FSS-9 items of 4.8 (1.8) for patients receiving methadone and 4.7 (1.9) for those using buprenorphine. Severe fatigue was identified in 77% of patients receiving methadone and 67% of those using buprenorphine. In these two sub-groups, the FSS-9 sum scores were slightly left-skewed (skewness: – 1.0 (methadone group), – 0.6 (buprenorphine group)) and flattened distributed (kurtosis: 3.0 (methadone group), 2.2 (buprenorphine group)).

The sociodemographic and clinical factors' impact on the FSS-9 sum score at baseline and the factors' influence on changes in the FSS-9 sum score from baseline to the following annual health assessments

At baseline, we found that the FSS-9 sum score was higher for females than males (adjusted mean FSS-9 sum score difference: 4.1, CI 1.3;7.0, $p = 0.005$), for patients with debt difficulties compared with those without debt difficulties (2.9, CI 0.4;5.3, $p = 0.022$), and for patients with frequent benzodiazepine use compared with those with less frequent or no use (5.7, CI 3.0;8.4, $p < 0.001$) (Table 3). In contrast, the FSS-9 sum score was lower for patients with frequent stimulant use than those with less frequent or no use (– 5.0, CI -8.0;-2.0, $p = 0.001$). Moreover, we saw a small non-clinical significant reduction of the FSS-9 sum score from baseline to the following annual health assessments for patients with frequent benzodiazepine use compared to those with less frequent or no use (– 4.4, CI -8.2;-0.7, $p = 0.021$) and for patients having significant liver fibrosis or cirrhosis measured by transient elastography compared with those with non-significant fibrosis or normal liver stiffness (– 5.5, CI -9.9;-1.0, $p = 0.016$). With Bonferroni corrected p-values, we only found that patients with frequent benzodiazepine or stimulant use compared with those with less frequent or no use of these substances changed the fatigue levels at baseline.

The sociodemographic and clinical factors' impact on changes in the FSS-9 sum score from baseline to the following annual health assessments among patients on OAT

Among patients receiving methadone as an OAT opioid, we found that the FSS-9 sum score was higher for

Table 1 Sociodemographic and clinical characteristics at baseline for all patients and for patients with more than one annual health assessment

	All patients (*N* = 654)	Patients with ≥2 health assessments (*N* = 225)
Age (years), n (%)		
18–29	81 (12)	23 (10)
30–39	185 (28)	63 (28)
40–49	205 (31)	75 (33)
50–59	148 (23)	53 (24)
≥ 60	35 (5)	11 (5)
Mean (SD)	43 (11)	44 (10)
Gender, n (%)		
Male	461 (71)	170 (76)
Female	193 (29)	55 (24)
Highest educational level, n (%)		
Not completed primary school	40 (6)	15 (7)
Completed primary school (9 years)	286 (44)	105 (47)
Completed high school (12 years)	259 (40)	81 (36)
≤ 3 years of college or university	57 (9)	20 (9)
> 3 years of college or university	12 (2)	<5 (2)
Receiving opioid agonist therapy, n (%)	537 (82)	205 (91)
OAT opioid (%)		
Methadone	209 (39)	96 (43)
Buprenorphine/Buprenorphine-naloxone	321 (60)	107 (48)
OAT opioid dose ratio (median (IQR))[a]	0.9 (0.8–1.1)	1.0 (0.9–1.1)
Housing situation the past 30 days, n (%)		
Stable[b]	569 (87)	203 (90)
Unstable[c]	85 (13)	22 (10)
Injected substances the past 12 months, n (%)	338 (56)	116 (52)
Frequent substance use the past 12 months, n (%)[d]		
Alcohol	154 (26)	56 (25)
Benzodiazepines	238 (39)	87 (39)
Cannabis	313 (52)	124 (55)
Opioids	97 (16)	27 (12)
Stimulants (amphetamines and cocaine)	176 (29)	60 (27)
Chronic infectious diseases, n (%)		
Hepatitis C virus infection	315 (48)	184 (82)
Low virulent (< 800,000 IE/ml)	168 (25)	92 (41)
High virulent (≥ 800,000 IE/ml)	147 (22)	92 (41)
Hepatitis B virus infection	5 (0)	< 5 (< 1)
Human immunodeficiency virus	< 5 (< 1)	< 5 (< 1)
Hematological and biochemical samples, median (IQR)		
Hemoglobin (g/dl)	14 (13–15)	14 (13–15)
Estimated glomerulus filtration rate (ml/min/1.73 m^2)	104 (89–122)	105 (91–124)
C-reactive protein (mg/L)	4 (1–9)	3 (1–8)
Aspartate transaminase (U/L)	31 (23–50)	40 (30–65)

Table 1 Sociodemographic and clinical characteristics at baseline for all patients and for patients with more than one annual health assessment *(Continued)*

	All patients (*N* = 654)	Patients with ≥2 health assessments (*N* = 225)
Liver stiffness, median (IQR)		
Transient elastography (kPa)	5 (4–7)	6 (5–8)
Aspartate transaminase to platelets ratio index	0.3 (0.2–0.6)	0.4 (0.3–0.8)

The table displays the sociodemographic and clinical characteristics for all included patients, and for patients with two or more health assessments, including FSS-9 measurements at baseline

FSS-9 nine-item fatigue severity scale (Likert scale), *IQR* interquartile range, *kPa* kilopascal, *OAT* opioid agonist therapy, *SD* standard deviation

[a]OAT opioid ratio is a ratio between the received dose of OAT opioids per day and the expected median daily dose (18 mg buprenorphine, 18/4.5 mg buprenorphine-naloxone or 90 mg methadone). A ratio on 1.0 indicates that patients received the expected daily dose; [b]A stable housing situation was defined as having owned or rented housing situation or being imprisoned; [c]Unstable housing situation was defined as living in a homeless shelter, with family or friends, or on the street; [d]Frequent substance use was defined as using substance at least weekly during the past 12 months

females than males (7.3, CI 2.5;12.2, $p = 0.003$), for patients having debt difficulties compared with those not having debt difficulties (4.9, CI 0.7;9.1, $p = 0.023$), for patients having frequent benzodiazepine use compared with those having less frequent or no use (6.0, CI 1.6; 10.5, $p = 0.008$), and for patients with a high HCV viral load compared with those with a low HCV viral load (31.5, CI 1.5;61.5, $p = 0.040$) at baseline (Additional file 6). Among patients receiving buprenorphine as an OAT opioid, we found that patients with frequent alcohol use had higher the FSS-9 sum score (4.8, CI 0.2;9.3, $p = 0.039$), while patients with frequent stimulant use had lower the FSS-9 score (− 5.0, CI -9.9;-0.1, $p = 0.047$) compared with patients with less frequent or no use of these substances at baseline (Additional file 7). For both subgroups, no sociodemographic and clinical factors were clinically associated with substantial changes in the FSS-9 sum score from baseline to the following annual health assessments. With Bonferroni corrected *p*-values, we did not identify any predictors that changed the fatigue score at baseline and between the annual health assessments.

Discussion

This study showed that 69% of SUD patients had severe fatigue symptoms. The sociodemographic and clinical factors that substantially contributed to higher fatigue scores at baseline were females compared with males (four points), frequent benzodiazepine use compared with less frequent or no use (six points), and debt difficulties compared with no debt difficulties (three points). However, the fatigue score was five points lower for patients with frequent stimulant use than those with less frequent or no use. For patients using buprenorphine as an OAT opioid, we found five points lower fatigue score for patients with frequent stimulant use and five points higher fatigue score for patients with frequent alcohol

Table 2 Mean (Standard deviation (SD)) item scores for single items on FSS-9 at baseline and follow-up

	Baseline (N = 654)	*Follow-up (N = 225)*
FSS-9		
I1: My motivation is lower when I am fatigued	5.4 (2.0)	5.6 (2.0)
I2: Exercise brings on my fatigue	4.7 (2.1)	5.0 (2.0)
I3: I am easily fatigued	4.5 (2.1)	4.8 (2.1)
I4: Fatigue interferes with my physical functioning	4.9 (2.1)	5.1 (2.0)
I5: Fatigue causes frequent problems for me	4.4 (2.2)	4.5 (2.2)
I6: My fatigue prevents sustained physical functioning	4.6 (2.2)	4.4 (2.2)
I7: Fatigue interferes with carrying out certain duties and responsibilities	5.0 (2.1)	5.0 (2.1)
I8: Fatigue is among my three most disabling symptoms	4.6 (2.3)	4.8 (2.3)
I9: Fatigue interferes with my work, family, or social life	4.9 (2.2)	4.6 (2.3)
Mean score of all items	4.8 (1.8)	4.9 (1.7)
Sum score of all items	43.2 (15.9)	43.8 (15.2)

Follow-up: FSS-9 score on the last health assessment during the study period among patients with two or more annual health assessments; *FSS-9* nine-item fatigue severity scale (Likert scale ranging from 1 (no fatigue) to 7 (worst fatigue)), *I* Item, *SD* standard deviation

Table 3 Linear mixed model of fatigue (FSS-9) adjusted for sociodemographic and clinical factors (N = 654)

Fixed effects				
	Effect estimate		**Time trend (per year)**	
	Estimate (95% CI)	***p*-value**	**Slope (95% CI)**	***p*-value**
FSS-9 sum score	42 (26–58)	< .001	3.6 (−23.5–30.7)	0.792
Female	*4.1 (1.3–7.0)*	*0.005*	−0.3 (−4.5–3.8)	0.877
Age per 10 years[1)]	0.2 (−1.0–1.4)	0.755	−0.2 (− 2.1–1.7)	0.844
Educational level	− 1.1 (− 2.6–0.3)	0.132	−0.3 (− 2.3–1.7)	0.754
Unstable housing situation	0.0 (−3.7–3.7)	0.992	2.6 (− 3.6–8.8)	0.408
Debt difficulties	*2.9 (0.4–5.3)*	0.022	−0.2 (− 3.8–3.3)	0.898
Injecting substance use	−0.1 (− 2.9–2.7)	0.944	−0.7 (− 4.6–3.3)	0.740
Frequent use of substances				
Benzodiazepines	*5.7 (3.0–8.4)*	*< .001*[a]	*−4.4 (−8.2 − − 0.7)*	*0.021*
Alcohol	1.8 (−1.1–4.6)	0.221	0.6 (−3.5–4.7)	0.776
Cannabis	1.2 (− 1.4–3.8)	0.356	1.8 (− 1.7–5.3)	0.309
Opioids	3.3 (− 0.3–6.9)	0.069	−4.6 (− 10.8–1.7)	0.149
Stimulants[2)]	*− 5.0 (− 8.0– − 2.0)*	*0.001* [a]	2.1 (− 2.1–6.3)	0.327
Chronic infectious diseases				
Hepatitis B virus infection	3.3 (− 10.4–16.9)	0.638	−2.6 (− 16.8–11.5)	0.715
Hepatitis C virus infection				
- Detected	3.0 (− 5.4–11.4)	0.484	0.7 (− 18.7–20.1)	0.941
- Low vs. high viral load	− 0.4 (− 10.3–10.9)	0.948	− 7.0 (− 17.1–3.0)	0.169
HIV	− 0.1 (− 15.3–15.5)	0.994	13.0 (− 6.8–32.7)	0.197
Liver stiffness				
Transient elastography per 10 kPa	1.2 (−1.6–4.0)	0.391	*−5.5 (− 9.9 − − 1.0)*	*0.016*
APRI score per 1 unit	0.5 (− 0.6–1.5)	0.378	1.4 (− 0.9–3.6)	0.230
Hematologic and biochemical blood samples (continuous variables)				
Hemoglobin per 1 unit (g/dL)	−0.3 (− 1.1–0.6)	0.513	0.3 (− 0.9–1.5)	0.622
eGFR per 30 units (ml/min/1.73m^2)	0.0 (− 2.0–0.9)	0.453	0.0 (− 2.0–1.9)	0.973
CRP per 10 units (ml/L)	−0.1 (− 0.6–0.7)	0.848	0.0 (− 0.1–0.2)	0.682

The table displays a linear mixed model analysis (Restricted Maximum Likelihood regression) evaluating sociodemographic and clinical factors' (predictors) changes in the FSS-9 sum score at baseline and the predictors' influence on changes in the FSS-9 sum score (time trend) per year from baseline. The predictors' effect estimates and time trends estimate adjusted mean differences in the FSS-9 sum score

APRI aspartate transaminase to platelet ratio index, *CI* confidence interval, *CRP* C-reactive protein, *FSS-9* nine-item fatigue severity scale, *eGFR* estimated glomerular filtration rate, *HIV* human immunodeficiency virus, *kPa* Kilopascal, *OAT* opioid agonist therapy

[1)] Age per 10 years was centred according to mean age (43 years) in the study sample at baseline. [2)] Includes amphetamine or cocaine use. The educational level: highest level of education was coded 0–4 with 4 as the highest educational level. Unstable housing situation: living on the street, homeless shelter, or with family and friends at any time during the past 30 days prior to the health assessment. Debt difficulties: struggling with repaying current illegal and legal debt. Injecting substance use: Having injected substance during the past 12 months prior to the health assessment. Frequent use of substances: at least weekly during the past 12 months prior to the health assessment. Viral load of HCV: From − 0.5 to 0.5, where the range ≥ − 0.5 to < 0 represents the low viral load (HCV PCR < 800,000 IE/ml), and the range ≤ 0.5 to > 0 identifies the high viral load (HCV PCR ≥ 800,000 IE/ml). Zero (0) defined patients without HCV infection

[a)] Statistically significant results when using Bonferroni corrected *p*-values ($\alpha_{altered} = 0.05 / 41 = 0.0012$)

use compared with those with less frequent or no use of these substances at baseline. For patients receiving methadone as an OAT opioid, the fatigue score was higher for females than males (seven points), for patients with frequent benzodiazepine use compared with those with less frequent or no use (six points), for patients with debt difficulties compared with those without difficulties with debt (five points), and for patients with a high versus a low viral load of HCV (32 points) at baseline. The latter finding suggesting an extreme difference between a high and a low viral load of HCV was surprising. Other studies assessing HCV viral load and correlation based on clinical and histological features have also not found HCV viral load to impact other related outcomes [26–28]. This finding is likely related to random variability within the data, and it should be interpreted with caution. Moreover, no sociodemographic and clinical factors were associated with clinically significant changes in the fatigue score from baseline to the following health assessments.

In the present study, patients with SUD had a mean fatigue score (4.8) comparable to some of the most severe chronic diseases. In recent studies, patients infected with HIV or HCV, or those co-infected with both of them, have a mean FSS-9 score that ranged from 3.3 to 4.5 [10, 29, 30]. Patients with myasthenia gravis have reported a comparable fatigue score of 4.7 [31], and similarly, so have patients who have suffered from a stroke at least 6 months after the stroke onset (4.8) [32]. One can assume that a high prevalence of underlying mental disorders, extensive polysubstance use, and lower social status could have attributed to the high level of fatigue in the SUD population.

We found that females were weakly more fatigued than males. For both genders, patients with frequent use of benzodiazepines were weakly more fatigued than those with less frequent or no use. Recent studies evaluating fatigue in the general population and patients with chronic disorders have demonstrated similar gender differences in fatigue levels [15, 23, 31, 33]. Gender inequalities regarding household responsibilities and caring for the family have generally been highlighted as explanations for females' fatigue levels [34]. Additionally, females with SUD may be worse off than males in many domains. They may have less financial resources, experience more physical trauma caused by exchanging sex for drugs and money, and face more stigma related to family failures [34]. Moreover, in the general population and among patients with SUDs, females are more likely to use benzodiazepines than males, with a similar tendency found in different countries [2, 35–38]. Females' higher prevalence of anxiety disorders, sleeping disorders and the fact that they are more likely to seek medical care may contribute to more prescriptions of hypnotics and anxiolytics, such as benzodiazepines and z-hypnotics [39–41]. One can believe that these medical, psychological, and social challenges may overall explain the gender gap concerning a higher fatigue level among females in the SUD population.

Our findings revealed that patients with frequent use of benzodiazepines were weakly more fatigued than those with less frequent or no use. Among patients with frequent use of stimulants, we found that they were less fatigued than those with less frequent or no use. These group differences were overall small. In the general population, previous studies assessing the effect of benzodiazepine use have suggested that patients using benzodiazepines have a lower quality of life, self-reported physical health, and more disability than those not using benzodiazepines [42, 43]. This is parallel with the higher fatigue levels shown in the present study. Furthermore, using stimulants, particularly illicit amphetamines, is generally associated with poor mental health and stimulant withdrawal symptoms in the SUD populations [44, 45]. A temporary sense of better self-perceived mental health and fewer withdrawal symptoms may arise when consuming stimulant substances, which contributes to a temporary reduction of fatigue compared to the experience without stimulants. However, our trend analyses indicate that the fatigue levels remained stable over time when the frequent use of stimulants is persistent.

The present study showed no clear associations between fatigue and chronic infectious diseases or kidney disease. For patients with HBV, HIV or end-stage kidney disease, the low prevalence of HBV and HIV and a mean renal function within the normal range could explain why no associations with fatigue were detected. Furthermore, we are surprised that SUD patients with HCV infections did not demonstrate a higher fatigue level compared to patients with SUD without HCV infection, considering that the prevalence of fatigue is up to 70% in populations with HCV [9–11], which is considerably higher than in general population [23]. However, the large extent of polysubstance use in the present population (75%) could have temporarily displaced the HCV infection's change on fatigue.

We found that 77% of patients using methadone as an OAT opioid and 67% of those using buprenorphine had severe fatigue symptoms. Four sociodemographic and clinical factors significantly changed fatigue levels among methadone users, while two factors influenced fatigue among those using buprenorphine. Methadone is a full opioid agonist associated with more euphoria and analgesia than the partial opioid agonist buprenorphine [46]. In a quantitative study evaluating patients' experience of using methadone and buprenorphine in OAT, unwanted physical effects, for example, over-sedation, were particularly pointed out in some methadone cases [47]. These effects might explain methadone users' high prevalence of severe fatigue symptoms and why more sociodemographic and clinical factors influenced methadone users' the fatigue levels than those using buprenorphine.

Overall, no single sociodemographic and clinical factor was associated with substantial changes in fatigue at baseline or over time in the SUD population. This signifies that fatigue was substantially constant between patients. However, the mean fatigue level significantly exceeded the threshold for severe fatigue in the SUD population, which underlies the importance of identifying patients who simultaneously have several sociodemographic and clinical risk factors for severe fatigue. Identifying these patients and treating the underlying causes of fatigue should be the way to reduce the fatigue in the population.

Strengths and limitations

This study has several strengths. We have included 654 patients with SUD that usually are difficult to reach in health care. Of those, 225 patients were followed up by two or three annual health assessments, making longitudinal analyses possible. This study does, however, have some limitations. First, the patients were mainly recruited from outpatient clinics receiving OAT. The majority had opioid dependence, although this was often combined with other dependencies, which could affect the generalisability of our results to other SUD populations. Second, we had a prospective follow-up of only a third of those patients recruited at baseline. This also causes weakness in our results and makes it necessary to carefully interpret the longitudinal analyses. Third, due to clinical challenges, including systematic and patient delays, the annual health assessments were not precisely conducted one year after the previous health assessment. This may affect the interpretation of the predicted fatigue level changes from baseline. Fourth, due to data imputation and inclusion of up to 42 predictors in the linear mixed model analyses, there is a risk of Type I error. We dealt with this by presenting the Bonferroni corrections to all *p*-values in the analyses.

Conclusion

The present study shows a high symptom burden of fatigue among patients with SUDs, particularly among females, patients with debt difficulties, and those with extensive use of benzodiazepines. Identifying severe fatigue and considering fatigue in the follow-ups could help optimise SUD treatment for these patients. Policymakers could take this into consideration when planning health services.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13011-020-00334-x.

Additional file 1. The number of months from baseline to the second or third health assessment. No.: Number of patients; SD: Standard deviation; ref.: Reference. The table displays the number of patients with one, two, and three health assessments, including a nine-item Fatigue Severity Scale score. The table displays the time between baseline and the second and third health assessments.

Additional file 2. The US-English and the Norwegian versions of FSS-9. Description: Legends: FSS-9; Nine-item Fatigue Severity Scale. All items in the FSS-9 are ranged as a Likert scale from 1 to 7, where 1 indicates "strongly disagree" and 7 "strongly agree".

Additional file 3. Aspartate aminotransferase to platelet ratio index (APRI). Description: APRI: Aspartate aminotransferase to platelet ratio index. The figure displays the APRI score equation. The AST upper limit of normal range was defined as 45 IU/L (male) and 35 IU/L (female).

Additional file 4. Potential correlations between sociodemographic and clinical factors and fatigue. The figure shows that potential sociodemographic and clinical comorbidities may affect fatigue among patients with substance use disorders.

Additional file 5. Mean (SD) item scores for single items on the FSS-9 at baseline and follow-up. Legend**:** FSS-9: Nine-item Fatigue Severity Scale; I: Item; OAT: Opioid agonist therapy; SD: Standard Deviation. Follow-up: The FSS-9 score on the last health assessment during the study period among patients with two or more annual health assessments. Mean (SD) item scores for single items on the FSS-9 for patients using methadone or buprenorphine as OAT opioid.

Additional file 6. Linear mixed model of fatigue (FSS-9) adjusted for sociodemographic and clinical factors among patients receiving methadone as an OAT opioid at baseline ($N = 209$). Legends**:** APRI: Aspartate transaminase to platelet ratio index; CI: Confidence interval; CRP: C-reactive protein; FSS-9: Nine-item Fatigue Severity Scale; eGFR: estimated glomerular filtration rate; HIV: Human Immunodeficiency virus; kPa: Kilopascal; OAT: Opioid Agonist Therapy. [1)] Age per 10 years was centred according to mean age (43 years) in the study sample at baseline. [2)] Includes amphetamine or cocaine use. The OAT opioid ratio: a ratio between the received dose of OAT opioids per day divided by the expected mean dose of OAT opioids (buprenorphine 18 mg, buprenorphine-naloxone 18/4.5 mg or methadone 90 mg). The educational level: highest level of education was coded 0–4 with 4 as the highest educational level. Unstable housing situation: living on the street, homeless shelter, or with family and friends at any time in the past 30 days prior to the health assessment. Debt difficulties: struggling with repaying current illegal and legal debt. Injecting substance use: Having injected a substance in the past 12 months prior to the health assessment. Frequent use of substances: at least weekly during the past 12 months prior to the health assessment. Viral load of HCV: From − 0.5 to 0.5, where the range ≥ − 0.5 to < 0 represents the low viral load (HCV PCR < 800,000 IE/ml), and the range from ≤0.5 to > 0 identifies the high viral load (HCV PCR ≥ 800,000 IE/ml). Zero (0) defined patients without HCV infection. When using the Bonferroni corrected *p*-values ($\alpha_{altered} = 0.05 / 43 = 0.0012$), the predictors did not affect the FSS-9 sum score significantly. The table displays a linear mixed model analysis (Restricted Maximum Likelihood regression) evaluating sociodemographic and clinical factors' (predictors) changes in the FSS-9 sum score at baseline and their influence on changes in the FSS-9 sum score (time trend) per year from baseline among patients receiving methadone as an OAT opioid. The predictors' effect estimates and time trends estimate adjusted mean differences in the FSS-9 sum score.

Additional file 7. Linear mixed model of fatigue (FSS-9) adjusted for sociodemographic and clinical factors among patients receiving buprenorphine as an OAT opioid at baseline ($N = 321$). Legends**:** APRI: Aspartate transaminase to platelet ratio index; CI: Confidence interval; CRP: C-reactive protein; FSS-9: Nine-item Fatigue Severity Scale; eGFR: estimated glomerular filtration rate; HIV: Human Immunodeficiency virus; kPa: Kilopascal; OAT: Opioid Agonist Therapy. [1)] Age per 10 years was centred according to mean age (43 years) in the study sample at baseline. [2)] Includes amphetamine or cocaine use. The OAT opioid ratio: a ratio between the received dose of OAT opioids per day divided by the expected mean dose of OAT opioids (buprenorphine 18 mg, buprenorphine-naloxone 18/4.5 mg or methadone 90 mg). The educational level: highest level of education was coded 0–4 with 4 as the highest educational level. Unstable housing situation: living on the street, homeless shelter, or with family and friends at any time during the past 30 days prior to the health assessment. Debt difficulties: struggling with repaying current illegal and legal debt. Injecting substance use: Having injected a substance during the past 12 months prior to the health assessment. Frequent use of substances: at least weekly during the past 12 months prior to the health assessment. Viral load of HCV: From − 0.5 to 0.5, where the range ≥ − 0.5 to < 0 represents the low viral load (HCV PCR < 800,000 IE/ml), and the range ≤ 0.5 to > 0 identifies the high viral load (HCV PCR ≥ 800,000 IE/ml). Zero (0) defined patients without HCV infection. When using the Bonferroni corrected p-values ($\alpha_{altered} = 0.05 / 43 = 0.0012$), the predictors did not affect the FSS-9 sum score significantly. The table displays a linear mixed model analysis (Restricted Maximum Likelihood regression) evaluating sociodemographic and clinical factors' (predictors) changes in the FSS-9 sum score at baseline and their

influence on changes in the FSS-9 sum score (time trend) per year from baseline among patients receiving buprenorphine as an OAT opioid. The predictors' effect estimates and time trends estimate adjusted mean differences in the FSS-9 sum score.

Abbreviations

APRI: Aspartate transaminase to platelet ratio index; CI: Confidence interval; FSS-9: Nine-item Fatigue Severity Scale; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HCV PCR: HCV Polymerase Chain Reaction; HIV: Human Immunodeficiency Virus; IQR: Interquartile Range; kPa: Kilopascal; OAT: Opioid Agonist Therapy; SUD: Substance Use Disorder; SD: Standard Deviation

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Authors' contributions

Jørn Henrik Vold and Rolf Gjestad have led the study design, analysis, and article preparation. Christer F. Aas, Fatemeh Chalabianloo, Svetlana Skurtveit, Else-Marie Løberg, Kjell Arne Johansson, and Lars Thore Fadnes have contributed by leading the study design, analysis, and article preparation. All authors have read and approved the final article.

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Availability of data and materials

No additional data are available due to data protection requirements.

Ethics approval and consent to participate

The study has been reviewed and approved by the Regional Ethical Committee for Health Research (REC) West, Norway (reference number: 2017/51/REK Vest, dated 29.03.2017/20.04.2017). Each patient provided written informed consent prior to enrolling in the study.

Consent for publication

Participants have consented for publication.

Competing interests

Not applicable.

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