The burden of disease among people with severe substance use disorders

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“Before you heal someone, ask him if he's willing
to give up the things that make him sick”

- *Hippocrates c 400, BC*

Abstract in English

Background

A substance use disorder (SUD) is a potentially severe clinical condition with high co-occurrence of somatic and mental disorders. The burden of disease attributable to substance use contributes to 11.8 million deaths worldwide each year or 1.5% of the global disease burden. Prevalence of chronic hepatitis C (HCV) have reached endemic proportions among people with severe SUD, more than half will experience a mental health disorder at some point during their lives and it may cause poor health-related quality of life (HRQoL). Few studies have assessed HCV treatment uptake, impact of substance use patterns and mental health, or measured HRQoL as health outcome among long-term patients in opioid agonist therapy (OAT).

Methods

In paper I, HCV treatment uptake among OAT patients was estimated by medication dispensation from 2014 to 2017 in Sweden and Norway using data from nationwide registries; The Swedish Prescribed Drug Register and The Norwegian Prescription Database. HCV prevalence was estimated from a mix of primary and secondary data. Paper II and three are nested prospective cohort studies, which recruited 707 and 609 participants, respectively, across nine OAT outpatient clinics and low-threshold municipality clinics in Norway, during 2017-2020.

The ten-item Hopkins Symptom Checklist (SCL-10) and EQ-5D-5L were used to assess symptoms of mental health disorders and HRQoL. The SCL-10 involves ten items, which are each scored on four dimensions from *not bothered at all* (item score = 1) to *extremely bothered* (item score = 4). A linear mixed model analysis examined the impact of substance use patterns and sociodemographic factors on SCL-10 sum score with beta coefficients with 95% confidence intervals (CI). EQ-5D-5L measures five health dimensions on a five-point Likert scale (from *no problems* (item score = 1) to *extreme problems* (item score = 5)). A UK value set was applied to calculate index values (from 0 to 1). Self-perceived health was measured with EQ-VAS (from 0 to 100). Descriptive statistics were derived at baseline and central tendency and dispersion reported by means and standard deviation (SD).

Results

For the HCV treatment uptake study, altogether 3,529 individuals were identified with dispensed OAT in the Swedish cohort and 7,739 individuals in the Norwegian cohort. HCV prevalence was estimated to be over 50%. Calculations showed that annual HCV and DAA treatment uptake increased in both countries. The estimated cumulative HCV treatment uptake among people in need of HCV treatment at

the end of 2017 was 28% in Sweden and 31% in Norway. In Sweden, DAA treatment was associated with increased age (adjusted odds ratio (aOR) 1.8; 95% CI 1.0-3.2) and dispensation of drugs used for diabetes (aOR 3.2; 95% CI 1.8-5.7), whereas in Norway, dispensation of cholesterol modifying agents and antibacterials were associated with decreased odds (aOR 0.4; 95%CI 0.2-0.9, aOR 0.8; 95%CI 0.6-1.0).

Overall, many individuals reported considerable mental distress and impaired HRQoL. The mean (SD) SCL-10 score for all items was 2.2 (0.8) at baseline, which showed that 65% of the cohort had a mean score >1.85, the standard threshold for likely mental health disorders. Among people with frequent use of substances, more symptoms of mental health disorders were observed amid those using benzodiazepines (3.6, 95% CI:2.4;4.8), cannabis (1.3, 0.2;2.5), opioids (2.7, 1.1;4.2) compared to those with no or less frequent use of these substances. On the contrary, less mental health symptoms were observed among people using frequently stimulants (-2.7, -4.1;-1.4). The study also showed that females (1.8, 0.7;3.0), having debt worries (2.2, 1.1;3.3) and unstable living conditions (1.7, 0.0;3.3) were associated with higher burden of mental health symptoms. There were large individual variations in SCL-10 score from baseline to follow-up, but no consistent time trends indicating change over time for the whole cohort.

The mean (SD) EQ-5D-5L index value at baseline was 0.7 (0.3) and EQ-VAS 57 (22) compared to 0.9 (0.2) and 80 (19) for the Norwegian reference population. The study found large individual variations in index values, where 43% had >0.8 and 5% had <0.2 at baseline. The lowest EQ-5D-5L index values were observed for female patients, age groups older than 40 years and for methadone users. At follow-up, improvements in HRQoL were observed across almost all health dimensions. Mean (SD) overall index value and EQ-VAS at follow up were 0.7 (0.2) and 59 (22) respectively.

Conclusion

This thesis has revealed numerous challenges related to people with severe SUD, in addition to being a very heterogeneous population. Despite increased HCV treatment uptake in both Sweden and Norway it was estimated that more than two thirds of the OAT populations in need of treatment were left untreated at the beginning of 2018. While the vast majority is experiencing a high burden of mental health symptoms and considerable impaired HRQoL, around one third had few mental health symptoms and very good HRQoL. These findings emphasize the urgent need for more research, and perhaps more gender-and age-adopted treatment. The wide variations seen in SCL-10 and HRQoL support more focus on individualized treatment and personalized patient care, and the need for regular assessment of these health outcomes in SUD and OAT treatment programs.

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Sammendrag på norsk (abstract in Norwegian)

Bakgrunn

Ruslidelse er en potensiell svært alvorlig klinisk tilstand med høy grad av samtidig forekomst av somatisk og mental sykdom. Sykdomsbyrden som tilskrives rusmidler bidrar til 11.8 millioner dødsfall hvert år eller 1.5% av den totale globale sykdomsbyrden. Forekomst av kronisk hepatitt C (HCV) har nådd endemiske proposisjoner blant mennesker med alvorlig rusavhengighet, mer enn halvparten av dem vil oppleve en psykisk lidelse i løpet av livet, og det kan lede til dårlig helse-relatert livskvalitet. Det er få studier som har undersøkt behandlingsopptak av HCV, hvordan rusmidler kan påvirke psykisk helse, eller som har undersøkt helse-relatert livskvalitet blant langtids behandlede i legemiddelassistert rehabilitering (LAR).

Metode:

I den første studien som inngår i denne avhandlingen benyttet vi data fra befolkningsbaserte registre; läkemedelsregistret i Sverige og reseptregisteret i Norge fra 2014 til 2017.HCV forekomst av kronisk HCV ble modellert på bakgrunn av både primære og sekundære datakilder. De to andre studiene som inngår i denne avhandlingen er prospektive kohort studier med henholdsvis 707 og 609 deltagere fra ni LAR poliklinkker og kommunale mottaks- og omsorgssentre i Norge fra 2017 til 2020.

Vi benyttet Hopkins symptom sjekkliste (SCL-10) og EQ-5D-5L for å evaluere psykisk helse og helse-relatert livskvalitet. Førstnevnte bruker en ti punkts liste over psykiske tilstander hvor hver enkelt dimensjon skåres fra *ikke brydd i det hele tatt* (skår 1) til *ekstremt brydd* (skår 4). En lineær mixed model analyse undersøkte sammenhengen mellom rusmiddelbruk og sosiodemografiske faktorer på SCL-10 sum skår, med beta koeffisienter med 95% konfidensintervall. EQ-5D-5L måler fem helse dimensjoner på en fem punkts skala (fra *ingen problemer* (skår 1) til *ekstreme problemer* (skår 5). For å kunne regne ut indeksverdi (fra 0 til 1) ble ett verdi sett fra Storbritannia benyttet. Selvoppfattet helse ble målt med EQ-VAS (fra 0 til 100). Deskriptiv statistikk ble rapportert fra inklusjons tidspunkt og sentral tendens rapportert med gjennomsnitt og standardavvik (SA).

Resultat

Til sammen ble henholdsvis 3,529 og 7,739 individer identifisert med forskrevet LAR medisiner i de svenske og norske kohortene. HCV forekomsten ble estimert til å være like over 50% i studieperioden. Det årlig behandlingsopptaket økte i begge land. Det estimerte kumulative HCV behandlingsopptaket

blant de som trengte behandling var 28% i Sverige og 31% i Norge ved utgangen av 2017. De direkte-virkende antivirale legemidlene var assosiert med økt alder (justert odds ratio (aOR) 1.8; 95% KI 1.0-3.2) og forskrivning av diabetes medisiner (aOR 3.2; 95% KI 1.8-5.7) i Sverige, mens forskriving av kolesterolsenkende legemidler og antibiotika var assosiert med nedsatt odds (aOR 0.4; 95% KI 0.2-0.9; aOR 0.8; 95% KI 0.6-1.0) i Norge.

Samlet sett ble det rapportert betydelige symptomer på psykiske lidelser og nedsatt helse-relatert livskvalitet blant deltagerne. Gjennomsnitt (SA) SCL-10 skår for de ti psykiske tilstandene var 2.2 (0.8), som viste at 65% hadde gjennomsnitt skår over 1.85, som er foreslått terskel for psykiske lidelser. Blant de som oppga regelmessig rusinntak ble det observert flere symptomer for psykisk lidelser blant de som brukte benzodiazepiner (3.6, 95% KI: 2.4;4.8), cannabis (1.3, 0.2;2.5), og opioider (2.7, 1.1;4.2) sammenlignet med de som hadde intet eller uregelmessig bruk av disse rusmidlene. På den andre siden ble det funnet færre symptomer blant de som oppga regelmessig bruk av simulanter (-2.7, -4.1;-1.4). Resultatet viste også at kvinner (1.8, 0.7;3.0), gjeldsbekymringer (2.2, 1.1;3.3) og ustabil livssituasjon (1.7, 0.0;3.3) var assosiert med høyere mental sykdomsbyrde. Det var også store individuelle variasjoner i SCL-10, men ingen signifikante tidsendringer på gruppenivå.

Gjennomsnitt (SA) EQ-5D-5L indeksverdi ved inklusjon var 0.7 (0.3) og for EQ-VAS 57 (22), sammenlignet med 0.9 (0.2) og 80 (19) for den generelle norske befolkningen. Igjen var det store individuell variasjoner, hvor 43% hadde >0.8 og 5% <0.2 i indeksverdi ved inklusjon. Den laveste indeksverdien ble observert blant kvinner, de eldre enn 40 år og for metadon brukere. Ved oppfølging ble det observert forbedring i nær sagt alle helse dimensjoner. Gjennomsnitt (SA) indeksverdi og EQ-VAS ved oppfølging var henholdsvis 0.7 (0.2) og 59 (22).

Konklusjon

Denne avhandlingen har vist en rekke utfordringer blant personer med alvorlig ruslidelser, men også at det er en heterogen populasjon. Til tross for økning i HCV behandlingsopptak både i Sverige og Norge blant LAR pasienter, er det estimert at vel to tredjedeler av de som trengte behandling var ubehandlet i begynnelsen av 2018. Selv om de fleste samlet sett opplevde en stor psykisk sykdomsbyrde og betydelig nedsatt helse-relatert livskvalitet, oppgir vel en tredjedel få symptomer og har en god livskvalitet. Disse funnene understreker betydningen av mer forskning. Kanskje vil det være gevinster av mer kjønns- og aldersspesifikk behandlingstilnærming i tverrfaglig spesialisert rusbehandling. Evaluering av psykisk helse og helse-relatert livskvalitet anbefales som utfallsmål i tverrfaglig spesialisert rusbehandling og LAR behandling.

Papers included in thesis

Paper I

Aas CF, Vold JH, Skurtveit S, Odsbu I, Chalabianloo F, Lim AG, Johansson KA, Fadnes LT: ***Uptake and predictors of direct-acting antiviral treatment for hepatitis C among people receiving opioid agonist therapy in Sweden and Norway: a drug utilization study from 2014 to 2017***. *Substance abuse treatment, prevention, and policy* 2020, **15**(1):44

Paper II

Aas CF, Vold JH, Gjestad R, Skurtveit S, Lim AG, Gjerde KV, Løberg EM, Johansson KA Fadnes LT: ***Substance use and symptoms of mental health disorders: a prospective cohort of patients with severe substance use disorders in Norway.*** *Substance abuse treatment, prevention, and policy* 2021, **16**(1):20

Paper III

Aas CF, Vold JH, Skurtveit S, Lim AG, Ruths S, Islam K, Askildsen JE, Løberg EM, Fadnes LT, Johansson KA: ***Health-related quality of life of long-term patients receiving opioid agonist therapy: a nested prospective cohort study in Norway***. *Substance abuse treatment, prevention, and policy* 2020, **15**(1):68

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List of tables and figures

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Important terminology and definitions

A substance use disorder (SUD) is a potentially severe clinical condition; it may cause social marginalization, long-term impairments in most aspects of an individual's life, and premature death compared to the general population [1]. According to World Health Organization (WHO), mental and behavioral disorders due to psychoactive substance use are divided into ten classes; alcohol, opioids, cannabinoids, sedative hypnotics, cocaine, other stimulants, hallucinogens, tobacco, volatile solvents, and multiple drug use and use of other psychoactive substances [2]. For the purpose of this thesis, a SUD is defined as harmful use of, or dependency on a substance or class of substances, such as alcohol and or opioids. Harmful use of substances, sometimes termed substance abuse, involves the use of substances that have caused either physical or psychological harm to an individual's health over a certain period of time [3]. Substance dependency, is a more severe chronic relapsing disorder consisting of a cluster of physiological, behavioral, and cognitive phenomena – where the use of the substance or substances have the predominant place compared to other behaviors that had greater value before [4]. Thus, a dependency of a substance is termed *severe SUD* in this thesis when known. Harmful use and dependency are central in WHO's international classification of diseases (ICD-10) diagnostic system [4].

Among several possible definitions of comorbidity, a general medical definition is opted for this thesis meaning simply that there is a presence or coexistence of additional diseases, either somatic or psychiatric, with reference to the initial diagnosis of SUD (or to the index condition being examined) [5].

Important abbreviations

Anti-HCV	Antibodies to hepatitis C virus
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence interval
DAA	Direct-acting antiviral agents
DALY	Disability-adjusted life years
DDD	Defined Daily Dose
HCV	Hepatitis C virus infection
HCV RNA	Ribonucleic acid (either quantitative or qualitative)
HRQoL	Health-related quality of life
NorPD	Norwegian Prescription Database
OAT	Opioid agonist therapy
PWID	People who inject drugs
QoL	Quality of life
SPDR	The Swedish Prescribed Drug Register
SUD	Substance use disorder
SVR	Sustained virologic response
UL	Uncertainty interval
WHO	World Health Organization

1. Introduction

1.1 Substance use disorder

Psychoactive substances have been around for almost as long as humanity, however, it was not until early 19th century scientific classification begun [6].

1.1.1 Burden of disease attributable to substance use disorders

Globally it was projected that almost 100 million disability-adjusted life years (DALY), or some 4% of all DALYs, were attributed to substance use as a risk factor in 2016 [7]. Altogether, substance use contributes to 11.8 million deaths worldwide each year, which is only secondary to cardiovascular diseases, and represent some 1.5% of the global disease burden [7-9]. Premature death, caused by long-term substance use, accounts for most of these deaths, 11.4 million; with smoking (7.1) and alcohol (2.8) representing the most prevalent risk factors [8]. However, a considerable number of individuals also die directly from overdoses each year, where deaths from SUD are differentiated between alcohol and illicit drugs including opioids, cocaine, amphetamines/methamphetamines and cannabis [8]. Of the around 350,000 directly deaths in 2017 worldwide, 185,000 were from alcohol and 167,000 from illicit drugs [8, 9]. Unlike the premature deaths, where most deaths are seen in people aged 70 years and older, direct deaths mainly affect younger people: over 50% of the overdoses are seen in people younger than 50 years old [8]. It was estimated that just over two percent of the world population had a severe SUD in 2016 with vast intercountry differences in terms of prevalence and distribution of substances used [7]. For instance, in the USA and several countries in Eastern Europe, which both saw a prevalence of SUD of over five percent, opioids and other illicit drugs dominate in the former while Russia and eastern European countries reported chronic use of alcohol as the most commonly abused substance [8, 10].

The prevalence of people with severe SUD in Norway was estimated to just over three percent at the start of the millennium; after a slight decline towards 2010, the last couple of years after have seen a flatten curve at just below three percent up until 2016 [8]. There were 621 direct deaths from SUD in Norway in 2018, where alcohol and illicit drugs accounted for 335 and 286 deaths, respectively [11]. When adjusted for population growth in the same time period, alcohol have seen a marked decline on mortality whereas illicit drugs have seen no significant decrease in direct deaths [3]. As seen globally, also in Norway severe SUD represent one of the most important risk factors for premature death and DALYs [3, 11].

1.1.2 Etiology of substance use disorders

Despite the long history of substance abuse, it was only from the 1980s, disorders related to substance use were recognized as a primary mental health disorder [6]. SUD and mental health disorder co-occur; more than half of the people with a SUD will experience a mental health disorder at some point during their lives [12, 13]. However, it is less clear whether mental health disorders develop mostly as a consequence of substance use or vice versa [14]. There seems to be a set of multifactorial risk factors associated with development of SUD, such a genetic vulnerability, childhood trauma, low level of educational and occupational participation, access to substances, emotional- sexual- and physical abuse [3, 15, 16]. There is a considerable genetic influence, studies on alcohol use disorders shows that genetic vulnerability alone contributes for around 50% of the overall risk factors [17, 18]. The co-occurrence of SUD and mental health disorders may thus be attributed to shared genetic vulnerability and pathophysiological processes possibly related to specific neurotransmitter systems, in particular within the dopaminergic system [19, 20]. In addition, genetic influence has also shown to be involved in the processing of illicit drugs, drug-specific changes in gene expression and metabolism [21].

1.1.3 Opioid dependence – a severe substance use disorder

Humans have used derivatives from the opium poppy since the sixth millennium before Christ and opioids are therefore among the oldest known psychoactive drugs. The active ingredient of opium, morphine, was first chemically isolated by Wilhelm Sertürner, before Sir Robert Robinson won the 1947 Nobel Prize in chemistry following his derivation of morphine's structural formula [22]. Opioids are used medically for acute and chronic pain relief, palliative care and for treatment of opioid dependence with opioid agonist therapy (OAT). However, opioids are also consumed for extramedical, or recreational use. Traditionally heroine has been the leading opioid used for these purposes worldwide, with the exceptions of opium producing countries, such as Afghanistan and neighboring nations, and the increased prescriptions of opioids for non-cancer pain in high-income countries such as USA and Canada [23, 24]. The latter have produced an iatrogenic epidemic of opioid misuse, dependence, and overdoses [25]. For instance, almost 50% of the people enrolled in an OAT program in Canada reported their first contact with opioids was through a dispensation for medical use of opioids [26]. Many people initiate using extramedical opioids for their mind-altering affects and pain relief; however, not everyone will develop an opioid dependence [24, 27]. Studies on heroine have shown that around one-third to two-thirds develop opioid dependence within a year of commencement [28, 29].

Opioid dependence is a severe chronic relapsing disorder consisting of a cluster of physiological, behavioral, and cognitive phenomena [4]. Worldwide, opioid use disorders affect over 16 million people and is responsible for over 120,000 deaths per year [30]. In Norway, of the 286 direct deaths recorded from illicit drug use, opioids accounted for 82% of those deaths in 2018 [3]. Of all illegal drugs, opioids denote the highest disease burden, has the highest demand for treatment, it contributes to substantial increased healthcare costs, and has shown a marked increase in opioid related mortality in the last decade [10, 24, 31]. People with opioid use disorders suffer not only an early death, but also severe social marginalization and long-term impairments in most aspects of their lives [1].

1.1.4 Opioid agonist therapy

Opioid treatment programs with methadone dates back to the 1960s in Scandinavia when it was first initiated in Sweden [32]. However, it was not until 1998 it was implemented as a medical treatment for opioid dependence in Norway [33]. Increased focus on, and availability of harm reduction programs, such as OAT have lowered the demand for illegal opioids [31]. OAT is an evidence-based medical intervention and considered the gold standard of treatment for opioid dependence that augments treatment retention, reduces illicit opioid use, improves patients' health and reduces crude mortality rates significantly [24, 34-37]. For instance, results of 22 pooled longitudinal cohort studies showed a crude mortality rate for patients on OAT of 0.90 per 100 person years, compared to 1.63 when OAT was ceased, and 4.91 for any untreated periods [38]. Most patients in Norwegian OAT programs are treated with either buprenorphine, buprenorphine-naloxone, methadone or levomethadone, as other opioids are very rarely used and considered outside national guidelines [39]. There are currently more than 7,500 people enrolled in OAT programs in Norway, which gives an OAT coverage considerably higher compared to the other Scandinavian countries of Sweden and Denmark, and the USA [40-43]. It is estimated that around 60% of people with opioid dependence are currently enrolled in OAT programs in Norway [44].

With an integrated treatment approach, OAT has been put forward to play a significant role in the management of both somatic and psychiatric comorbidities among people with opioid dependence; such as its role in the treatment of chronic hepatitis C (HCV) and to reduce the risk of HCV acquisition [45, 46], increase uptake of HIV testing and treatment [47], and improve the management of mental health disorders [48, 49].

1.2 Somatic comorbidity among people with substance use disorders

A SUD is a multifactorial disorder often leading to adverse social and health complications, hence often termed a biopsychosocial syndrome. The most common somatic complications, especially among people who inject drugs (PWID), are overdoses, injuries, and infections, however, a range of other less common health complications have also much higher prevalence among people with SUD compared to the general population [50-52]. People with severe SUD also have a higher risk of diseases that are more common in the general population, including various cancers and cardiovascular diseases [51, 52]

1.2.1 People who inject drugs

Worldwide, around 11 million people injected drugs in 2017 [53]. PWID are associated with increased risk for both morbidity and mortality compared to the general population, and the risk of premature death is up 15 times higher among people who use illicit opioids [35, 37]. Opioids are the most common drug used by PWID, however, stimulants, which include methamphetamine, amphetamine, and cocaine, represent a significant proportion of injected drugs and contributes to the second highest proportion of disease attributed to SUD globally [53]. In Western Europe around 20% of the PWID report stimulants as their main injected drug, while 40 to 50% of PWID in North America inject stimulants as their main drug [53]. Mortality rates and cause of death of PWID varies according to drug culture, low- to high-income countries, geographical locations, age, and gender; nonetheless, overall overdose was the most common reported cause of death while both HIV and chronic HCV infections are significant risk factors for both opioids and stimulant PWID [35, 37, 54, 55].

In addition to the factors mentioned above, mortality rates and causes of death among people in OAT will also vary according to their OAT continuity and retention in treatment [38]. OAT patients are aging, in fact, Norway has among the oldest populations in Europe with a mean age of almost 45 years in 2017, and it is thus likely that somatic causes of death will increase compared to overdoses and other drug-induced causes of death [41, 56, 57]. In a Norwegian study of all-cause mortality among OAT patients, somatic diseases accounted for 45% of deaths, followed by drug-induced and violent deaths at 42% and 12%, respectively [58]. Furthermore, increased somatic comorbidity was found to reduce the odds of dying from a drug-induced cause of death [58]. Likewise, retention in OAT treatment, with both methadone and buprenorphine, has shown substantial reductions in the risk for drug-induced mortality [59].

Of the 11 million people who injected drugs in 2017 almost 6 million of those were living with chronic HCV, however, as we shall see next, prevalence globally is much higher with the burden of HCV affecting PWID considerably [53, 60].

1.2.2 Hepatitis C virus infection

HCV was formerly known as non-A and non-B hepatitis (NANBH), until the isolation of a cDNA clone from a hepatitis genome by Choo *et. al* in 1989 [61]. This newly discovered virus was found to be responsible for some 90% of the non-A, non-B hepatitis in the USA, and together with hepatitis B the cause of 96% of all hepatitis-related mortality [62, 63]. HCV is classified as an RNA virus belonging to the flaviviridae family, with an affinity for hepatocytes where the viral replication takes place [63]. The HCV RNA genome mutates frequently and has great genetic heterogeneity with at least six known genotypes and more than 50 subtypes [64].

The main route of transmission is by exposure to infected blood, such as contaminated needles or blood products, however, also the sharing of filters and other user equipment among PWID have shown to transmit HCV [65]. There is also a risk for perinatal transmission between mother and fetus, sexual transmission or blood contact [65]. Exposure to the virus may cause both acute and chronic infections. The former is asymptomatic for most, though some 10 to 20% develop jaundice while other signs include mild to severe flu-like symptoms, malaise, lethargy, abdominal pain, dark urine, pale stool, and increased enzymes on liver function tests [65]. Without any treatment, between 15 and 45% of infected people achieve spontaneous clearance of the virus, normally within a year, while the rest will proceed to develop a chronic HCV with progressing stages of liver fibrosis and subsequently cirrhosis [60]. Chronic HCV is defined by the persistence of detectable HCV RNA in a person's blood test at least six months after the onset of the acute HCV infection [63]. After 20 years of chronic HCV infection, the prevalence of cirrhosis may be as high as 20 to 30% [60, 65]. The prognosis for developing a chronic disease is affected by several factors such as age at time of infection, gender, concomitant alcohol consumption; and is poorer among individuals with an advanced age, being male, using alcohol, genotype-3 infections, immunosuppression and having co-infections with hepatitis B and HIV [63, 65]. Furthermore, chronic HCV infection may also contribute to extrahepatic comorbidity often independent of the stage of liver fibrosis; with the most common being depression (24%), diabetes mellitus (15%) and chronic renal disease (10%) [60]. Among patients with cirrhosis, around one in forth will develop hepatocellular carcinoma within a 10 year time line [65].

The global prevalence of HCV among the general population varies considerably; high prevalence is found in East Asia, North Africa/Middle East (>3.5%), moderate prevalence in Southeast Asia, sub-Saharan Africa, Europe and Latin America (1.5-3.5%), low prevalence in Asia Pacific and North America (<1.5%) and between 0.5 to 1% in the Scandinavian countries of Norway, Sweden and Denmark [65, 66]. However, while prevalence may be low to moderate among the general populations, prevalence is significantly higher among SUD and PWID populations at more than 50% [41, 67, 68]. Injecting drug use and sharing of syringes and needles are the major drivers of HCV incidence [69]. Since it was first discovered HCV has become a worldwide epidemic. The WHO has estimated that 71 million people around the world are chronically infected with the virus and that 399,000 die annually from HCV related complications such as liver cirrhosis or hepatocellular carcinoma [60, 66]. Modeling the burden of HCV in Norway suggests that HCV-related liver morbidity and mortality are increasing among PWID and are likely to continue to rise until 2022; with around 7,000 former and current PWID living with chronic HCV at the time of planning this study; with an estimated 400 new cases annually, and around 40 HCV-related deaths yearly [70].

1.2.3 Hepatitis C strategies for control and elimination

Despite the high burden of HCV among people with SUD, and especially PWID, comparatively few have commenced antiviral treatment at the time of study and HCV continues to pose a serious health threat [40]. At the World Health Assembly in 2016, the WHO recognized the Global Health Sector Strategy, which aims to eliminate viral hepatitis (HCV and hepatitis B infection) by 2030 [60]. Eliminating chronic HCV, which is defined as a 90% reduction in incidence and a 65% reduction in mortality compared with the 2015 baseline, requires a significant effort in terms of increasing uptake of testing, diagnosing, and antiviral treatment [60]. Ultimately, it requires that 90% of individuals with chronic HCV must be identified and diagnosed, and of those, at least 80% must be treated [60]. In addition, other preventive strategies have been proposed alongside increasing testing and antiviral treatment, such as OAT scale-up, safe injection sites and needle-syringe programs to reach the above objectives [60, 71].

Alongside the decision made at the World Health Assembly in 2016, Norway also endorsed a comprehensive national strategy against viral hepatitis in the same year [72]. The initial plan was later revised and updated in 2018. Antiviral treatment with direct-acting antiviral agents (DAA) was made readily available for all diagnosed with chronic HCV regardless of stage of liver fibrosis from February 1, 2018, and the ambitious aim of the national strategy was to reduce HCV incidence by 90% by 2023 and stated that nobody should no

longer die from HCV related complications [72, 73]. DAA treatment has been offered as universal health coverage to all chronic infected HCV patients in Sweden from 2017 [74].

1.2.4 Treatment of hepatitis C

The ambition of any antiviral treatment of HCV infection is to eliminate of the virus. Since the discovery and development of ribavirin in the 1970s, it was found to be active against different DNA and RNA viruses [75]. After the discovery of HCV in 1989, there were a few attempts to treat HCV with ribavirin monotherapy in the 1990s, however, while it had some effects on serum alanine aminotransferase levels and patients infected with genotype 2 and 3, little effect was noted on HCV RNA levels and thus not achieving sustained virologic response (SVR) [75]. SVR is defined as absence of HCV RNA 12 weeks after end of treatment. A major advancement in HCV antiviral treatment came in 1998 when ribavirin was added to pegylated-interferon and together played a crucial role the HCV treatment preventing relapses and breakthroughs in the years to come [76]. With this drug combination, SVR was achieved in approximately 50 to 56% of patients [77, 78]. However, the course of treatment was long, 24-48 weeks with weekly injections and sometimes-severe side effects with interferon induced bone-marrow depression, flu-like symptoms, neuropsychiatric disorders and autoimmune-syndromes [79].

Further advancements came in 2011 when protease inhibitors, the first generation DAA, where approved for treatment, and three years later when the polymerase inhibitor, sofosbuvir, came into the market patients were offered interferon-free HCV treatment regimens for the first time [65]. As of 2018, the regulatory authorities in USA and Europe has approved 13 DAA from the four classes; NS3/4A (protease) inhibitors, NS5A inhibitors, NS5B polymerase inhibitor (nucleotide analogue), and NS5B polymerase inhibitor (non-nucleoside analogue) [60]. Different combinations of DAA are considered to be pan-genotypic when they achieve high treatment efficacy across all six known genotypes [60]. Combining DAA with ribavirin will still be relevant in certain circumstances, for instance among hard to treat cirrhotic patients with genotype 3 [76]. HCV policies including DAA offer countries an opportunity to eliminate HCV endemics, with less side effects, shorter treatment duration and improved adherence as compared to old interferon-based treatment. Combining two (or three) DAA can achieve SVR of far beyond 90% including patients who have been hard to treat in the past [80-82].

1.2.5 Barriers to hepatitis C treatment and elimination

The era of DAA treatment creates an opportunity to cure a substantial portion of people with chronic HCV among severe SUD populations. However, even if these highly effective

medications have become readily available, treatment have been scarce [69, 83]. One reason was the initial costs of DAA therapy in high-income countries, which ranged from $83,000 to $153,000 per treatment course, prompting restrictive access policies in most settings [84, 85]. Since, costs of DAA therapy has decreased considerably due to increased pharmaceutical competition, production of generic DAA and improved pricing models among others [86]. Subsequently, many high-income countries such as Norway, now offer unrestricted access to DAA treatment [65]. Treatment demand has soared, especially among former PWID, while people who are still using drugs have not been able to benefit equally from the increased accessibility, suggesting that DAA costs alone is not the only substantial barrier to the ambitious elimination targets outlined above [65, 86]. Previous studies have addressed the insufficient linkage to HCV care, testing and screening among people with SUD, while other studies have identified the lack of knowledge of HCV among risk populations as a barrier and demonstrated that psychoeducation may have a positive effect on both SVR rates and adherence to HCV treatment [40, 87-89]. Up to two-thirds of people with SUD may be unaware that they are actually infected with chronic HCV [90].

Another significant obstacle to HCV treatment among people with severe SUD is the physician-perceived risk factors, especially ongoing substance use, as a contraindication for DAA treatment [40]. Despite mounting evidence and the revised HCV treatment guidelines from WHO, which recommend treatment regardless of ongoing substance use, many clinicians seem to still be reluctant to treat people with injecting drug use [60, 91]. In addition to a systematic review that found DAA treatment to be highly favorable among people with severe SUD, including PWID and OAT patients, and supported further access to HCV treatment despite ongoing substance use; it was the SIMPLIFY study that established the efficacy as neither drug use before or during treatment affected the SVR [92, 93]. Thus, DAA treatment should be offered to people with severe SUD, regardless of ongoing substance use [93]. In addition, successful elimination of HCV involves several components, from the global to community level, as suggested by Gore (2020) and outlined in Table 1 on the next page:

Table 1: Key components for HCV elimination.

Global level	Expanded WHO viral hepatitis program
	Enhanced global NGO involvement
	Increased global investment
National level	Political engagement and leadership
	National HCV strategy development
	National HCV-testing policy development
	National surveillance systems to monitor HCV elimination
	Funding for civil-society organizations
Screening level	HCV-testing strategy
	Targeted screening in high-risk populations
	Universal screening in settings with generalized epidemics
	Ongoing monitoring of level of HCV diagnosis
Diagnostic level	Low-cost, simple and rapid HCV diagnostics
	Implementation research on new diagnostics
	Cost-effectiveness evaluation in different settings
Treatment level	Access to DAA therapy without restrictions
	Diverse models of HCV care (specialist and non-specialist prescribers)
	Expanded voluntary generic-DAA licenses
	Education of healthcare providers and affected community
	Targeted strategies among high-risk populations
	Monitoring for reinfection, with access to retreatment
Prevention level	High coverage of harm reduction (NSP and OAT)
	Blood-donor HCV screening in all settings
	Enhanced healthcare infection control
	Antenatal HCV screening and evaluation of DAA therapy in pregnancy
Monitoring and evaluation level	Population-level surveillance monitoring of HCV incidence
	Mathematical modeling
	Monitoring of DAA uptake and outcomes
	Monitoring of HCV-related morbidity and mortality
	Monitoring of HCV-related stigma and discrimination
Community and societal level	Community awareness campaigns
	Enhanced education: school-based, healthcare professional, political
	Drug-law reform
	Reduced stigma and discrimination of people living with HCV and PWID

Source: Dore *et.al*. Global elimination of hepatitis C by 2030: why not?

NGO: non-governmental organizations, DAA: direct-acting antiviral agents, HCV: hepatitis C infection, PWID: people who inject drugs, NSP: needle-syringe programs, OAT: opioid agonist therapy

1.2.6 Prevention and monitoring: Hepatitis C treatment uptake

The coverage of preventive interventions and harm reduction services varies among people with severe SUD. The distribution of needle-syringe programs and OAT are relatively poor in many settings; only around 1% of PWID worldwide lives in areas of high coverage of these preventive measures [94]. In contrast, opioid treatment programs such as OAT has higher coverage in most high-income countries [95]. OAT has shown to reduce the risk of HCV acquisition [45], and despite ongoing substance use, patients in OAT are achieving high SVR rates as seen above [92]. Hence, OAT may be a critical intervention for achieving large reductions in HCV transmissions. Several modeling studies have found that significant reductions in HCV prevalence may be achieved with a reasonable increase in HCV treatment uptake [96-98].

Nevertheless, HCV treatment uptake has remained low among people with severe SUD, including patients enrolled in OAT programs [99-101]. In Norway, annual HCV treatment uptake among OAT patients ranged from 1.3% to 2.6% in the period from 2004 to 2013 [102]. HCV treatment uptake since, and in particular in the DAA era, is largely unknown. The potential for HCV disease elimination by publicly funded DAA policies and the high HCV prevalence among OAT populations, it is essential to calculate the DAA treatment within an OAT delivery platform. At the time of the study planning, such estimates were important for countries aiming for HCV elimination or endemic control in the near future.

1.3 Psychiatric comorbidity among people with substance use disorders

More than half of the people with a SUD will experience a mental health disorder at some point during their lives [12, 13]. Measuring mental distress may be used to predict mental health disorders among people with SUD [103].

1.3.1 A comorbid condition: prevalence and challenges

On the one hand, ongoing substance use or serious abstinence, may present as symptoms of mental health disorders, either as temporary incidents such as stimulant-induced psychosis, or long-term when triggering an underlying psychopathology as seen with cannabis and schizophrenia [19, 20]. On the other hand, having a mental health disorder such as depression, may cause some patients to use for instance stimulants to ease symptoms, and thereby progress to a SUD [104]. Thus, the overlap and fluctuations of mental health symptoms, ongoing substance use with substance-induced symptoms, abstinence, limitations of various assessment methods, and other methodological considerations may well complicate the diagnosing of mental health disorders among people with SUD [104].

Nevertheless, it appears to be a strong association between mental health disorders as a risk factor for SUD, while having a SUD may affect the presence of mental health disorders [104, 105]. Several studies have demonstrated the high co-occurrence of mental health disorders among people with SUD [5, 106, 107]. However, the etiological relationship between both disorders seem less clear [108]. Whether they present at the same time (concurrently) or at different times (successively), mental health disorders and SUD may or may not be causally related, even if they could share a common genetic susceptibility and pathophysiological evolvement [20, 108, 109]. Early exposure to either stress or trauma may also be contributing factors [15, 104].

Epidemiological studies suggest a prevalence of around 27% for anxiety disorders, 35% for affective disorders, 30% for attention-deficit hyperactivity disorder, and 51% for personality disorders among SUD populations [110-112]. Prevalence may even be higher in clinical studies as people with severe problems are more likely to seek help; studies have found prevalence of around 70% for one or more personality disorder and around 66% for childhood trauma among people with SUD, and at least one mental health disorder was seen in around 80% of patients in a study among OAT patients [13, 15, 113]. This comorbid condition may challenge and interfere with treatment of SUD, which seems to be both undertreated and underdiagnosed in clinical settings [114]. One study found a direct association between quantity of substance use and severity of mental health symptoms among patients with schizophrenia [115]. In a follow-up study, both early onset of substance use and depression were found to be independent predictors of relapse among people with SUD [116]. In addition, several studies have shown that treatment outcomes and prognosis may be considerably poorer among patients with comorbid mental health disorders among people with SUD [12, 117, 118]. Thus, identifying patients with comorbid conditions is an essential precondition in treatment settings, and underlines the importance of diagnostic assessment of mental health disorders among people with SUD in order to improve overall treatment outcomes [119].

Integrating treatment approaches of mental health disorders and people with SUD are heralded as more effective and superior compared to separate treatment plans [48, 49, 120]. However, in spite of the mounting evidence most European countries have opted for a separate treatment approach of mental health disorders and SUD, which may cause delayed diagnostics and create a barrier to recovery [5, 119]. In Norway, where psychiatry and addiction medicine are separate medical specialties; people with SUD and milder comorbid mental health disorders, such as mild to moderate depression or anxiety, are treated in a

SUD setting – while people with comorbid severe mental health disorders such as psychosis and bipolar disorders, are treated within a psychiatric health care platform [121].

1.3.2 Identifying mental distress and symptoms of mental health disorders

The high prevalence of mental health disorders among people with SUD, and given the negative impact on treatment outcomes and prognosis; suggest a need for routinely screening individuals entering SUD treatment [122]. However, a consistent finding among people entering SUD treatment is the lack of routine assessment of mental health disorders, which is not always performed as a standard diagnostic procedure upon treatment initiation [104]. Early assessment and detection of comorbidity may therefore be favorable for individuals in need of further examination or psychiatric treatment, especially for more severe mental health disorders such as psychosis, bipolar disorders and severe depression [121]. One such screening instrument, the Hopkins symptom check list (SCL-10), may be used to identify mental distress and symptoms of mental health disorders among the general population and people with SUD [103, 123].

Hopkins symptom check list SCL-90 was first developed at Johns Hopkins University in the 1950s, and originally contained nine primary symptoms dimensions [124]. The SCL-10 consist of two of the original nine dimension with ten items measuring mental distress and symptoms of mental health disorders, and is the short-form of the more comprehensive Hopkins symptoms check list SCL-25 [123]. The instrument is psychometrically sound, brief and easy to complete, thus recommended for both clinical and research applications alike [123, 125]. By introducing a cut-off point one can interpret the proportion of the respondents with likely mental health disorders. In the literature, 1.85 is the established threshold for mental distress and indicator of mental health disorders, and proposes that some 50 to 60% of identified cases above the cut-off will be eligible diagnostically for at least one mental health disorders [123, 126].

Population studies have found that mental distress and symptoms of mental health disorders are consistently higher among female gender; in addition to people with poor social support, low level of education, having financial difficulties, and belonging to an ethnic minority [123, 127-129]. Among people with SUD, being female, receiving prior treatment for mental health disorders and extended use of substances predicted a higher level of symptoms of mental health disorders [103].

1.3.3 Substance use patterns: predictor of poor mental health?

Concurrent substance use, including prescription medicine misuse (e.g. without prescription, higher frequency or dosage than prescribed), is common and prevalent among people with SUD and people enrolled in OAT [130, 131]. Benzodiazepines, which are a class of drugs that bind to the $GABA_A$ receptor producing anxiolytic, sedative and muscle relaxant effects, are not only the most frequent prescribed psychiatric drug, but also among the prescription drugs most commonly misused [132, 133]. Thus, the misuse of benzodiazepines has emerged as a major public health concern, attributed by a dramatic increase in benzodiazepine-related overdoses the last decade [134]. People with SUD, and especially among people using opioids, have a much higher misuse of benzodiazepines compared to the general population [132]. Moreover, benzodiazepines misuse is also prominent among people with alcohol use disorders and people using stimulants, and strongly associated with risk for other prescription drug misuse [132, 135, 136]. Among people enrolled in OAT, the majority of studies report a benzodiazepines use of over 40%, which is similar to findings in Norway among individuals in OAT [131, 132, 137]. There is also some evidence that benzodiazepine misuse is related to increased HIV and HCV risk behavior, poor quality of life (QoL), and contributes to maintain ongoing substance use during SUD treatment [132]. Methamphetamine, amphetamine and cocaine, collectively known as stimulants, are another important risk factor for poor mental health and suicidal ideation [138]. Furthermore, stimulants are associated with increased risk of cardiovascular events and mortality, HIV and HCV infections, injury and violent events [139].

As there are few population-level studies with a longitudinal design addressing the topic of substance use patterns among people with severe SUD, causality remain mostly unknown [132, 138]. Thus, assessing potential predictors of mental health symptoms and change in symptom burden over time from substance use patterns seem warranted.

1.4 Health-related quality of life among people with opioid dependence

Knowledge of health-related quality of life (HRQoL) among people with opioid dependence and long-term OAT treatment is limited [140]. HRQoL, which is a concept that includes both societal perspective and an individual's subjective physical and mental wellbeing, and may be an important outcome measure for SUD treatment programs and patient evolvement [141].

1.4.1 Measuring health-related quality of life among people with opioid dependence

Traditionally most research and clinical practice on OAT have emphasized on "hard outcomes", such as crude mortality rate, opioid abstinence, retention in treatment and reducing concomitant drug use [140]. Amid an opioid epidemic, especially in the USA, there has been renewed interest from scholars regarding treatment of opioid dependence, yet little attention has been given to studying HRQoL outcomes in opioid treatment programs [142]. Several researchers have argued that HRQoL, which is a patient-measured outcome and perhaps better reflect overall health and personal wellbeing, should be included as an outcome when evaluating substance use and OAT treatment [142-145]. In addition, HRQoL and quality adjusted life years are viewed as vital treatment outcomes in policymaking when evaluating health economics, such as cost-effectiveness analyses [142]. Several institutions advocate and encourage the use of validated HRQoL measures, notably The US Food and Drug Administration (USA) and the National Institute for Health and Care Excellence (UK) [142].

A range of several aspects complicates the dynamics of the research. There is a practical and academic distinction between QoL and HRQoL domains. Whereas HRQoL aims to capture a patient's subjective physical and mental wellbeing, QoL has accentuate a more holistic approach to include features beyond health in a patient's everyday life. Some scholars support the use of QoL instruments in opioid use disorders [146], despite a systematic review suggesting that current QoL instruments have limitations that hinders accurate and sensitive measurement in this particular subpopulation [1]. Many different instruments measuring Qol and HRQoL are available, however comparisons and external validity are put into question as different methods are used; among the ten different QoL instruments assessed, none scored perfectly on both content and properties and thus viewed insufficient when measuring QoL among people with opioid dependence [1]. As seen above, others advocate the use of HRQoL as it also allows calculation of quality-adjusted life years and being able to compare disease burden across various populations without being disease-specific, which is especially important in health priority settings [142]. One such HRQoL instrument, which has been validated for opioid use disorders, is the EQ-5D-

5L [147, 148]. The EuroQol Group, which is a network of international multidisciplinary researchers since 1987, has developed both the former EQ-5D-3L and the current EQ-5D-5L [149]. The instrument is a widely used generic measure of HRQoL, which consists of a descriptive (societal) part and a visual analogue scale (self-perceived health) [150]. This is vital when evaluating responsiveness and detect meaningful changes in health status [151].

Measuring HRQoL among patients enrolled in OAT programs represents an opportunity beyond calculating quality adjusted life years, economic evaluations and comparisons across populations – it also offers a real chance to consider a more patient-centered health outcome of OAT treatment [142].

1.4.2 Health-related quality of life among people with opioid dependence

There is building evidence that HRQoL is substantially lower among people with opioid dependence compared to the general population and people with other mental health disorders [142, 152-154]. Factors that seem to be associated with poor HRQoL are age, female gender, and symptoms of mental health disorders and physical comorbidity, while there is more controversy regarding continued substance use and chronic HCV infection [152, 155-157]. As the opioid dependent cohort is aging, they seem to be associated with considerably more medical problems and worse overall health compared to younger patients under 40, which is likely to put additional burden on SUD treatment programs in the future, and to better assess and address the needs of these patients [156, 158, 159]. Similarly, females in OAT consistently report worse HRQoL and more symptoms of mental health disorders compared to their male counterparts [152, 160]. Substance use patterns and HRQoL associations are less clear. In a large cohort of OAT patients, the use of benzodiazepines was identified as a factor for lower mental HRQoL and use of stimulants with higher physical HRQoL compared to non-users of these substances [140]. While the use of stimulants and benzodiazepines are among the most commonly used substances among people with opioid dependence, it is not necessarily a predictor of poor HRQoL in all settings [140, 152, 153].

People enrolled in OAT with chronic HCV have reported lower HRQoL compared to people without HCV in some studies [140, 157]. Conversely, left untreated; OAT patients with chronic HCV were associated with worse HRQoL compared to people with chronic HCV outside an OAT treatment program [161]. Whereas mental health assessment and intervention prior to HCV treatment seem to be a predictor for improved HRQoL, interferon-based treatment of chronic HCV alone seems to either worsen or be non-significantly associated with HRQoL [157, 161]. The poor reported HRQoL might even

persist after achieving SVR with this regimen [162]. In the DAA era, however, when a large clinical trial compared treatment with interferon-based and DAA treatment regimens; the latter was found superior in achieving both high SVR rates and improvements in HRQoL at follow-up [162].

1.4.3 Effect of opioid agonist therapy on health-related quality of life

The demand for street heroin have declined in recent years in Western Europe, including Norway, as the coverage of preventive measures such as OAT have become more available for PWID with opioid dependence [31]. In Western Europe, the estimated coverage of OAT is above 40 OAT patients per 100 PWID [94]. In Norway probably even higher at up to 60 OAT patients per 100 PWID [44]. In contrast, places such as USA and Eastern Europe coverage of OAT is poor and vary between 1 and 20 OAT patients per 100 PWID [94]. Research has shown that is possible to transfer people with heroin dependence rapidly and successfully from low-threshold settings to OAT programs despite the presence of severe social problems, and comorbid somatic and mental health disorders [163]. A consistent finding in the literature is a considerably lower self-reported HRQoL among these patients prior to, and upon, treatment initiation of OAT, as compared to the general population [152, 154, 164]. However, many of the previous studies are cross-sectional rather than longitudinal designs, offers few participants and with non-validated HRQoL measures for opioid dependence, which make comparisons challenging across various disease populations [160, 165].

1.5 Rationale for the studies

As shown in the introduction, people with severe SUD are a marginalized subpopulation with risk of serious somatic and mental health comorbidities and an early death. HCV is an infectious disease, which in particular impact people with severe SUD who inject or have injected drugs. With the emergence of new effective medications for treatment of chronic HCV there is an opportunity to eliminate a deadly infectious disease and prevent hepatitis-related complications and mortality. Elimination strategies at country level demands unrestricted access to these new medications and being able to monitor the treatment uptake and outcomes. As such, OAT has been proposed to play a key role as delivery platform for integrative and upscaling HCV care. At the time of study and study planning, with changing national guidelines and restrictive DAA treatment policies, there was a lack of knowledge concerning the HCV prevalence and treatment uptake among OAT patients, which paper I aimed to fill [166].

While there is building evidence of the vast co-occurrence of mental health disorders among people with severe SUD, considerable less is known about how substances and use patterns influence the symptom burden over time. The second paper used a longitudinal design to address this question [167].

OAT is an evidenced based medical intervention for people with opioid dependence and the most important preventive measure. HRQoL has emerged as an important outcome measure of OAT treatment, however the knowledge is scarce and only infrequently implemented in OAT programs [142]. Research have repeatedly shown a substantially lower HRQoL among these patients before and upon treatment initiation of OAT, while there is still a large gap in the knowledge about long-term OAT patient's HRQoL. This was the rationale for the third paper, which assessed the HRQoL of long-term OAT patients at baseline and after one year follow-up [168].

2. Aims and objectives of the thesis

2.1 Aims

The overall aim of this thesis was to study the burden of disease among people with severe substance use disorders (SUD). The first aim was to study the treatment uptake of chronic hepatitis C (HCV) among people enrolled in opioid agonist therapy (OAT), secondly to assess symptoms of mental health disorders and effect of substance use patterns, and thirdly describe the health-related quality of life (HRQoL) among long-term patients in OAT.

2.2 Objectives

In order to reach the aims of the thesis, the following objectives were addressed:

- Estimate the prevalence of chronic HCV and calculate HCV treatment annually and cumulatively after the introduction of DAA among people in OAT in Sweden and Norway, 2014 to 2017 (paper I)
- Assess symptoms of mental health disorders among people with severe SUD and evaluate how substance use patterns, clinical and sociodemographic factors affect these symptoms over time (paper II)
- Assess the HRQoL and self-perceived health in long-term OAT patients at baseline and follow-up one year later (paper III)

3. Materials and methods

In order to answer the research objectives stated above, this thesis has utilized observational data from nationwide registries and a nested cohort study, and modeled HCV prevalence from both primary and secondary data sources.

3.1 Study settings

The first study about HCV treatment uptake collected data from the entire Swedish and Norwegian populations to identify people with dispensions of OAT (and HCV) treatment from 2014 to 2017. The studies for paper II and three took place in Bergen and Stavanger, which are cities in southwestern parts of Norway with around 280,000 and 130,000 inhabitants each. The target population was individuals with opioid dependence who received OAT treatment in Sweden and Norway (paper I) and in all together nine OAT outpatient clinics (paper II and three) and two low-threshold municipality clinics (paper II) in Bergen. Figure 1 provides an overview of the timeline and study settings:

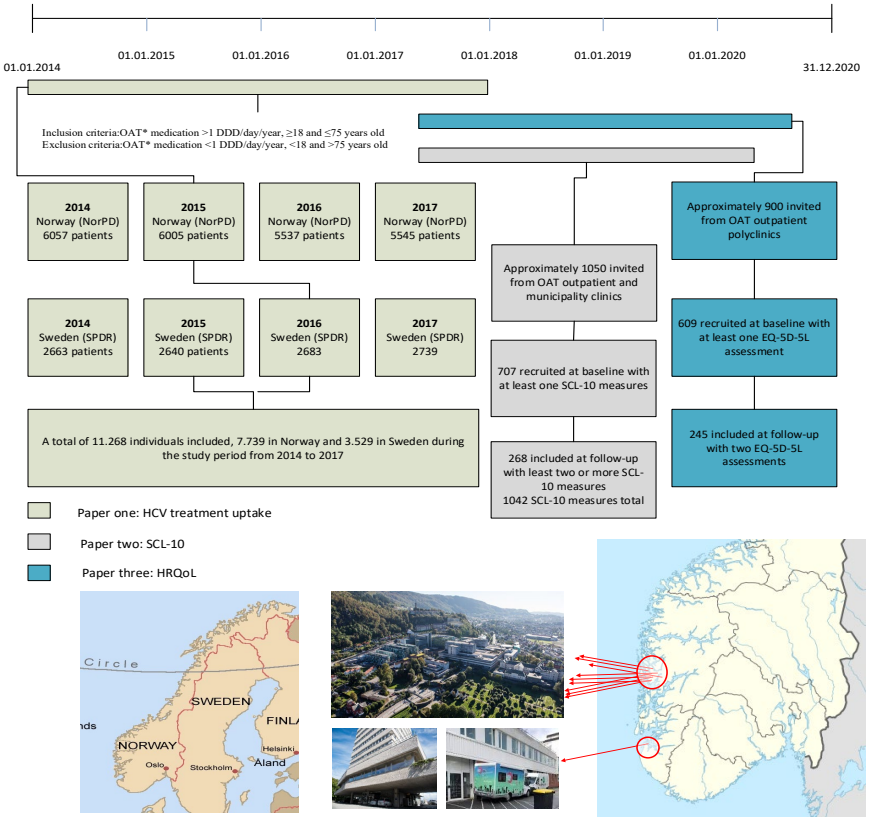

Figure 1: Timeline, settings and papers included in this thesis

3.1.1 Opioid agonist therapy in Sweden and Norway

Sweden and Norway have similar welfare and national healthcare systems where the standard is open access to health care for all inhabitants. As such, and in theory, all residents with a diagnosed opioid dependence according to International Classification of Diseases have free access to opioid agonist therapy (OAT) in Norway, however in Sweden, a diagnosis for at least 12 months is required for treatment entry [33, 169]. Pharmacotherapy with either buprenorphine or methadone, in an integrated program with psychosocial support is the mainstay of treatment even though there are vast intercountry differences to this approach [39, 169, 170].

Whereas the first methadone maintenance treatment program dates back to the 1960s in Sweden, modelled after the Dole and Nyswander program, Norway first implemented OAT in 1998 into the general health and social security system [33, 171]. In both countries, inclusion into the program was strict and thus characterized as high threshold and restrictive. However, this practice was abolished in Norway according to the new OAT guidelines from 2010. Since then, entry requirements have been minimal where opioid dependence has been the absolute inclusion criteria, the whole OAT program has expanded and taken over by the specialist health services, and patients were no longer subject to involuntary termination based on e.g. illicit substance use [33, 39, 41, 172]. This is not the case in Sweden. Even if admittance criteria are currently less strict compared to previous ones [171], in cases of repeated illicit substance use while receiving OAT, the provision of OAT may be ceased and patients referred to other types of treatment [32, 42]. There are currently around 7,500 individuals on OAT in Norway and 4,400 in Sweden [42, 173]. Attempts to estimate OAT coverage among people with opioid dependence have proven difficult due to the criminal nature of illicit drug use, difficulties in identifying injecting drug users and people in need of treatment.

3.1.2 Opioid agonist therapy in Bergen and Stavanger (Norway)

The OAT outpatient clinics in Bergen and Stavanger have implemented an integrated treatment and care model where patients are followed-up on a near daily basis by general and specialized nurses, psychologists and physicians who are under specialization- or specialized in addiction medicine. There are around 1,030 enrolled in OAT in Bergen and surrounding counties, and around 180 patients enrolled in OAT Stavanger [174]. People with severe SUD in the municipality clinics are to some degree overlapping with the OAT clinics in Bergen. They are estimated to be around 700 with frequent weekly contact. Patients are followed-up by social workers, general nurses and physicians specialized in family medicine. The Integrated Treatment of Hepatitis C (INTRO-HCV) study have

employed trained research nurses who collected blood samples and completed the structured patient interviews, which were recorded in a health register using an electronic data collection software (CheckWare®).

3.2 Data sources

The papers included in this thesis are based on data from four sources; two national health registries; The Norwegian Prescription Database (NorPD) and The Swedish Prescribed Drug Register (SPDR) (paper I), a mathematical model for estimating HCV prevalence in Norway and Sweden (paper I), and one observational cohort from the INTRO-HCV study [174] (paper II and III).

3.2.1 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) was established on January 1, 2004 at the Norwegian Institute of Public Health. It covers the entire Norwegian population, and monitors drugs dispensed by prescription in Norway. Pharmacies are obliged to register dispensed drugs made to individuals, and pass the information to NorPD electronically once a month. Drugs that are purchased without prescription, such as over the counter, or supplied to hospitals and nursing homes are not included in NorPD on individual level [175]. Each dispension provides detailed drug information, including Anatomical Therapeutic Chemical Classification System code (ATC), patient information (gender, date of birth, date of death, county of residence and more), and prescriber information (profession, medical specialty, county of occupation). Diagnosis and indication for use is not always evident, however, reimbursement codes can be used as guidance for disease after 2008 [175].

3.2.2 The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) was established in 2005. As with NorPD, the register includes dispensed drugs from all Swedish pharmacies and thereby excludes drugs used in hospitals, nursing homes and drugs purchased over the counter. In addition, SPDR also follows the WHO ATC Classification system [176]. SPDR contains information equal to NorPD in terms of patients and prescriber information. From a research perspective, both National registries provide valuable data on exposure to drugs and is useful to study patterns of drug utilization [177].

3.2.2.1 Anatomical Therapeutic Chemical (ATC) Classification System

All dispensed drugs in Norway and Sweden are classified according to ATC developed by the WHO Collaborating Centre for Drug Statistics Methodology [178]. The ATC system

consists of five levels as shown below, going from a main anatomical or pharmacological group to the actual chemical substance(s):

Table 2: Anatomical Therapautic Chemical (ATC) Classification System

ATC Level 1: The system has 14 main anatomical or pharmacological groups, from A: Alimentary tract to V: Various. E.g. **J**: Antiinfective for systemic use
ATC Level 2: Pharmacological or Therapeutic subgroup. E.g. J**05** Antivirals for systemic use
ATC Level 3: Chemical, Pharmacological or Therapeutic subgroup. E.g. J05 **A** Direct acting antivirals
ATC Level 4: Chemical, Pharmacological or Therapeutic subgroup. E.g. J05 A**P** Antivirals for treatment of hepatitis C infections
ATC Level 5: Chemical substance(s). E.g. J05 AP**54** elbasvir and grazoprevir

Source: World Health Organization Collaborating Centre for Drug Statistics Methodology

3.2.2.2 Defined daily doses (DDD)

By definition the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults according to WHO Collaborating Centre for Drug Statistics Methodology [178]. The DDD is only allocated to drugs that are approved and marketed in at least one country, and assigned an ATC code. However, since the DDD is a unit of measurement it is not always the recommended prescribed daily dose, and especially problematic for opioids with dissimilar indications. One example is methadone (DDD of 25mg/day), which is normally prescribed in doses above 60mg/day as this have better treatment outcomes in OAT compared to lower doses [178, 179].

3.2.3 Modelling the prevalence of chronic hepatitis C

Prevalence data of chronic HCV among OAT patients were not readily available for either Norway or Sweden at the time of study. An estimation from the best available primary and secondary sources was thus made. Data was used from the INTRO-HCV study from Bergen and Stavanger as a proxy to estimate prevalence among Norwegian OAT patients [174]. Among 752 patients, blood samples showed a prevalence of anti-HCV of 81% and HCV RNA of 45%. Anti-HCV, which is antibodies to the HCV virus, indicate current infection, clearance of the infection, or that anti-viral treatment has been successful. HCV RNA indicates current infection. History of injecting drug use was also included. Among OAT patients in the cohort, 4.9% answered they have never injected drugs and we subsequently counted those as non-PWID.

Based on the assumption that Norway and Sweden hold similar demographics, including drug cultures and behaviors [180], we generalized the proportion of non-PWID from the Norwegian cohort to also represent the Swedish cohort. It is assumed that anti-HCV prevalence is 0.7% among non-PWID in both Norway and Sweden, which was derived from estimates of HCV prevalence among adults in the general population from a comprehensive global review of HCV epidemiology [181]. In addition, several studies have pointed towards a high prevalence of Anti-HCV among Swedish PWID [182]. For the purpose of estimating prevalence among the Swedish patients we used published data from a large cohort of PWID in Stockholm, which reported a prevalence of anti-HCV of 82% [183]. Moreover, a systematic review have estimated that spontaneous clearance of HCV occurs in approximately 26% (95% confidence interval (CI) 22-29%) of acute HCV infections, with the remaining proportion of cases becoming chronic [184]. The above assumptions enabled us to derive a simple formula to estimate chronic HCV prevalence in Norway and Sweden:

$$\boldsymbol{Expected}\ number\ of\ chronic\ HCV = ((1-\delta) * [\phi * \pi_{PWID} + (1-\phi) * \pi_{NonPWID}] * N) - \tau$$

where N is the size of the study population, δ is the rate of spontaneous HCV clearance, ϕ is the proportion of OAT patients who are PWID, π_{PWID} and $\pi_{NonPWID}$ are the anti-HCV prevalence estimates among PWID and non-PWID, respectively, and τ is the number of HCV treatments given (see *3.3.2*).

3.2.4 The integrated treatment of hepatitis C cohort

The INTRO-HCV is a nested cohort study linked to the multicenter randomized controlled trial and longitudinal observation study [174]. The data included in this thesis was collected from 2016 to 2020, as part of an annual health assessment among people with severe SUD in Bergen and Stavanger. The main aim of the main study is to compare the efficacy of integrated and standard treatment of HCV. The study design is described in detail in the published study protocol [174].

3.3 Study design, sample and assessments

By design, all studies included in this thesis are observational studies as shown below.

Table 3: Overview of study samples in the thesis

	Paper I	Paper II	Paper III
Study design	Population-based	Prospective cohort	Prospective cohort
Study setting	Sweden and Norway	Western Norway	Western Norway
Data sources	NorPD, SPDR, modelling	Intro-HCV cohort	Intro-HCV cohort
Inclusion criteria	OAT* medication >1 DDD/day/year, ≥18 and ≤75 years old No consent required	Opioid dependence according to ICD-10 or having a severe SUD/PWID, ≥18 and ≤75 years old Written informed consent	Opioid dependence according to ICD-10 ≥18 and ≤75 years old Written informed consent
Individuals included	11,268: 3,529 in the Swedish cohort, 7,739 in the Norwegian cohort	707	609
Participation rate, %	100	67*	68*
Follow-up rate, %*	100**	38	40
Assessments	Dispensations	Hopkins SCL-10	EQ-5D-5L and EQ-VAS
Main outcomes studied	HCV treatment uptake among OAT patients	Symptoms of mental health disorders and substance use patterns	Health-related quality of life among long-term OAT patients

NorPD = Norwegian Prescription Database, SPDR = Swedish Prescribed Drug Register, INTRO-HCV = Integrated treatment of Hepatitis C, HCV = hepatitis C, OAT = opioid agonist therapy, SUD = substance use disorder, PWID = people who inject drugs, ICD 10 = WHO international classification of disease, SCL-10 = symptom check list 10

**The participation rate in OAT Bergen among frequent users is around 90%, the above estimate is for Bergen and surrounding counties of all possible invitees. Follow-up is not equal to drop-out since many have a delay and not fallen out of the study*

***This is estimated. In case of hospitalization or incarceration there may be periods without dispensations captured in the nationwide registries*

3.3.1 Paper I

The first study was an observational study among patients in OAT in Sweden and Norway from 2014 to 2017. Data were extracted from SPDR and NorPD. The registries cover the entire Norwegian and Swedish populations, thus have true population-based coverage. HCV prevalence data among OAT patients was unknown, consequently, we employed primary and secondary sources to estimate HCV prevalence as described above. The study sample included all individuals aged 18 to 75 years who were dispensed at least one DDD per day per calendar year of buprenorphine (ATC N07BC01), methadone N07BC02),

buprenorphine-naloxone (N07BC51), and levomethadone (N07BC05) in Sweden and Norway, by summarizing all annually dispensed OAT DDDs divided by 365.25 days. Inclusion criteria was set at a dosage at minimum one DDD per day/per annum to avoid including other medical indications than OAT. The study sample was thus chosen annually for both countries and it was possible for an individual to be included in more than one calendar year. Using this inclusion procedure, a total of 11,268 individuals were included for the main analysis (Figure 2).

3.3.2 Pharmacoepidemiological assessment

HCV treatment was defined as being dispensed either one or more pegylated interferon alpha (L03AB05 and L03AB11) in combination with ribavirin (J05AP01), or one or more of the DAA (group J05AP) per calendar year during the study period. Similarly, considering certain drugs as predictors for DAA treatment, dispensations were recorded at the second ATC level, except for drugs affecting the nervous system, which was recorded at the third, fourth, and fifth ATC levels (Table 2).

3.3.3 Paper II

The second study was a nested prospective cohort study linked to the multicenter INTRO-HCV study, and data was collected from May 2017 until July 2020 as part of an annual health assessment. The study sample was comprised of two groups of patients; individuals diagnosed with opioid dependence (F11.2) according to International Classification of Diseases version 10 (ICD-10) [185] where the majority (83% at baseline, 93% of follow-up) were enrolled in OAT during the study period, and people with severe SUD and injecting drug use being cared for at the municipality clinics. All included individuals were 18 years or older at time of inclusion and signed a written informed consent to partake in the study.

3.3.3.1 Assessment: Hopkins symptom check list (SCL-10)

The SCL-10 is a structured and self-administrated questionnaire, designed to measure symptoms of mental health disorders and psychological distress, and is widely used [123, 125, 186]. The SCL-10 involves ten items (suddenly scared for no reason, feeling fearful, faintness, dizziness or weakness, feeling tense, blaming yourself, difficulties falling asleep, feeling of worthlessness, feeling blue, feeling hopeless, and feeling everything is an effort), which are each scored on four dimensions from *not bothered at all* (item score = 1) to *extremely bothered* (item score = 4). Scores were summed and divided by the number of items answered to derive the mean item score. Mean scores vary between one and four, where the latter assumes *extremely bothered*. SCL-10 mean item scores were used for

descriptive analyses while SCL-10 sum scores were used in linear mixed model (LMM) analyses. Furthermore, the mean item scores were calculated by gender, age, level of education, and living conditions at baseline. By introducing a cut-off point one can interpret the proportion of the respondents with symptoms of mental health disorders. A mean score of 1.85 for SCL-10 has been recommended as a threshold for indicating substantial mental health distress [123].

3.3.4 Paper III

Also the third study was nested prospective cohort study linked to the INTRO-HCV study, and the data was collected from May 2017 until July 2020. The study sample included individuals diagnosed with opioid dependence according to ICD-10 [185], currently enrolled in OAT treatment, aged 18 years or older, and had given a written informed consent to participate in the study.

3.3.4.1 Assessment: Health-related quality of life: EQ-5D-5L

The EQ-5D-5L instrument is a widely used generic measure of HRQoL [149] and validated for opioid use disorders [147, 148]. It consists of two components. The first descriptive system evaluates health in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has five levels of response, ranging from no problems, slight problems, moderate problems, severe problems, to extreme problems [150]. The second part of EQ-5D-5L entails a visual analogue scale (VAS) where the respondent rates the self-perceived health from 0 (worst health imaginable) to 100 (best health imaginable) [150]. A systematic review have supported the use of the EQ-5D-5L in a broad range of patients, and was thus selected to assess the HRQoL among OAT patients [187].

3.4 Statistics analysis

The quantitative analyses for this thesis have been performed by the author in close collaboration with the co-authors. Except for the LMM and expectation-maximization analyses for paper II, which were performed in IBM SPSS version 26.0, all other analyses used STATA/SE 16.0. Statistical significance was set at the $p < 0.05$ level.

3.4.1 Paper I

For this study the *cumulative treatment uptake* of HCV was defined as the proportion of the individuals estimated with chronic HCV exposed to treatment at some point during the study period from 2014 to 2017. The unadjusted annual HCV treatment, was assessed among all patients with dispensed OAT treatment per calendar year (Table 4), and calculated as the

number of treated individuals divided by the number of individuals with dispensed OAT with confidence intervals (CI). Using the above formula (under 3.2.3), *expected number of chronic HCV infections* were calculated, with uncertainty in this quantity arising only from the uncertainty in spontaneous clearance. By dividing the expected number of chronic HCV infections by the total population size in that particular year and setting, prevalence was estimated. HCV treatment uptake was than estimated by dividing the HCV treatments in each year by the estimated number of chronic HCV infections in that same year, yielding a percentage of chronic HCV infections that were treated per year. *The cumulative HCV treatment uptake* was then calculated as the sum of HCV treatment uptake across successive years.

In this paper we presented the descriptive data as frequencies, percentages, and means, with corresponding 95% CI and uncertainty intervals where appropriate. Logistic regression was done to assess whether potential predictors, which were determined a priori; *methadone vs buprenorphine-based* OAT medications, *stratified age*, *gender*, and various dispensed drugs as binary variables (*yes vs no*) from different therapeutic areas affected the outcome variable, which was DAA treatment in 2017, and presented with 95% CI and adjusted odds ratio (OR).

3.4.2 Paper II

In this study we defined baseline as the time when the first SCL-10 measure was completed at the first annual health assessment. Additional SCL-10 measures at the next health assessment(s) were listed chronologically and included as follow-up. OAT was defined as receiving an OAT medication as baseline. Moreover, the OAT ratio, which corresponds to the received dose of OAT medication per day divided by expected mean dose (buprenorphine 18 mg or methadone 90 mg) according to WHO [188], was calculated per OAT patient. Furthermore, *injecting substances* was defined as having any substance injected during last 12 months, while *frequent substance use* was defined as using a substance (alcohol, cannabis, stimulants, non-OAT opioids, and benzodiazepines) more than once weekly during the last year. Most of the sociodemographic data was defined as categorical variables. Any missing values were assumed to be *missing at random* when performing expectation-maximization imputation. Overall, there were missing values for 3.4% of these values, which were subsequently replaced with the estimated values by expectation-maximization imputation according to Enders (2010) [189].

Descriptive data was presented as frequencies, percentages, means and standard deviations (SD), with corresponding 95% CI where applicable. Moreover, in order to evaluate the

impact of substance use patterns, clinical and sociodemographic factors at baseline and over time, we used a longitudinal LMM analyses where time was defined as years from baseline, and impact on the SCL-10 sum score assessed. The model was a random intercept fixed slope model with restricted maximum likelihood regression. Based on the full information maximum likelihood estimator all available data in the outcome variable were used. This was a two-step procedure where first each defined predictor variable was set against time – to evaluate if the predictor variable itself changed over time. However, there was no clinically significant changes when analyzed separately as outcome variables (time variable being the exposure variable). This allowed the model to include the predictor variables as time-independent variables in the second step. A new LMM was subsequently made with the predictor variables (time-independent) set against the SCL-10 sum score as the outcome variable. Furthermore, a time interactional was added to each predictor variable to investigate if time impacted changes of SCL-10 given each predictor. The predictor variables, on the baseline level and change in SCL-10 sum score, represented as main effects and interaction effects with time.

3.4.3 Paper III

Baseline was defined as the time when the first EQ-5D-5L assessment was completed at the first annual health assessment. Additional EQ-5D-5L assessment at the next health assessment was included as follow-up. The mean time between the first and second annual OAT assessment was 375 days (95% CI: 359-392 days). Responses to the five HRQoL dimensions are coded as a five-digit code, which represents a numerical description of a health state. The digits have no arithmetic properties and therefore a single summery number (an index value) needs to be arrived by applying a formula with an appropriate value set, which is a representative sample of the general population. The index value then represents how good or bad a health state is according to the preferences of the general population, ranging from 1 (full health) to 0 (dead, with negative values indicating health states worse than death) [150]. In the absence of a Norwegian value set, we applied an EQ-5D-5L value set for UK to determine the EQ-5D-5L index values for each health state in the OAT cohort [190].

Summary statistics were derived, including proportions and number of patients for the five EQ-5D-5L dimensions by age, gender, and OAT medications. The EQ-VAS score was summarized descriptively by mean, SD, minimum and maximum. A paired t-test of means for the 245 patients with two time points was used in the analysis to investigate whether there was any statistical significance in EQ-5D-5L between the measurements. An ANCOVA model for EQ-VAS changes from baseline to the next OAT health assessment

was conducted where place and treatment were fixed effects and baseline covariate. If data were missing from more than one dimension, participants were excluded. Altogether eight patients missed data on one dimension at baseline but were included in the analyses. There were no missing data from EQ-5D-5L follow-up or EQ-VAS.

To estimate the unbiased treatment effects from baseline to follow-up we used an inverse probability weighted method as we had follow-up data for a subgroup. We calculated population weights based on age, gender and how many times OAT medication was collected during a week in a binominal regression model with follow-up values as the dependent variable. More weight was given to cases with valid data, which were associated with highest probability of having missing data, and less weight was given to cases with lowest probability of missing. The mean for the population weights was 1.0 (SD 0.1) in our model.

3.5 Ethical considerations

All the studies included in this thesis have been approved by the regional committee for ethics in medical research in Norway (REK) and the Regional Ethical Review Committee in Sweden; paper I (no. 2018/939 and no 2018/2080-31/1), paper II and III for the Integrated treatment of hepatitis C virus infection among people who inject drugs: (INTRO-HCV) (REK Vest no. 2017/51) [174]. Furthermore, the studies were conducted in accordance with the Helsinki Declaration. A written informed consent was obtained for all participants in study two and three. In the first study, however, no written informed consent was required by the ethical committees as the data received was received pseudo-anonymous and encrypted. As the registers include sensitive information, data handling requires some caution. Therefore, data have been kept strictly on approved Helse Bergen research servers throughout the study period and in accordance with the Data Protection Impact Assessment, governed by Krister Kleppe; the data protection officer in Helse Bergen.

Even if all three studies were purely observational by design, and did not present any immediate risks or benefits to the participants, their contribution is of utmost importance not only to answer research questions, but ultimately contribute to knowledge that will improve patient care among a hard-to reach population.

4. Results

4.1 Objective I: Estimate the prevalence of chronic HCV and calculate HCV treatment annually and cumulatively after the introduction of DAA among people in OAT in Sweden and Norway, 2014 to 2017 (paper I)

4.1.1 Basic characteristics

Altogether 11,268 individuals were identified with dispensed OAT treatment in Sweden and Norway. In Sweden, 3,529 individuals receiving OAT were included during the study period from 2014 to 2017, where the majority was male (70%) with a mean age (SD) of around 44 (10) and 45 (11) years in 2014 and 2017, respectively. In Norway, 7,739 individuals were included with OAT treatment during the study period; the majority male (70%) with mean age (SD) of 44 (9) in 2014 and almost 46 (9) years in 2017. In both countries most of patients received buprenorphine-based OAT medications (up to 55 and 56% in 2017). Overall, 407 individuals in the Swedish cohort were dispensed HCV treatment, and 920 in Norway during the study period.

4.1.2 Main findings

The main finding from this study was the cumulative treatment uptake; 28% (uncertainty interval (UI): 27-30) of the OAT patients in Sweden and 31% (UI: 29-32) of the OAT patients in Norway, with estimated chronic HCV, received treatment from 2014 to 2017.

Based on our model HCV prevalence was estimated to range from 56% (UI: 53-59) in 2014, to 53 (UI: 51-56) in 2017 for Sweden. In Norway, prevalence was estimated from 54 (UI: 52-58) in 2014 to 50 (UI: 48-53) in 2017. In Sweden, annual HCV treatment uptake was thus calculated to 3.6% (UI: 3.5-3.8) in 2014, and 8.5% (UI: 8.0-8.9) in 2017. In Norway, annual HCV treatment uptake was calculated to 4.5% (UI: 4.3-3.7) in 2014, and 13.6% (UI: 12.8-14.3) in 2017. The proportion of DAA treatment increased throughout the study period and reached 99% and 97% in Sweden and Norway in 2017, respectively. Annual and cumulative estimated HCV treatment uptake in Norway and Sweden for 2014 and 2017 is presented on the next page:

Table 4: Annual and cumulative estimated HCV treatment uptake in Norway and Sweden among OAT patients in 2014 and 2017

	2014		***2017***	
Country	**Norway**	**Sweden**	**Norway**	**Sweden**
HCV treatment n (overall)	148	54	378	124
Study population n,	6057	2663	5545	2739
HCV treatment % (95% CI)	*2.4 (2.1-2.8)*	*2.0 (1.5-2.6)*	*6.8 (6.2-7.5)*	*4.5 (3.8-5.3)*
Expected proportion of OAT patients who are not PWID, n*	303	133	277	137
Expected Anti-HCV, weighted by PWID status, n**	4651	2075	4258	2135
Expected chronic HCV after spontaneous clearance, n (UI)***	3442 (3303-3628)	1536 (1474-1619)	3151 (3023-3321)	1580 (1516-1665)
Expected chronic HCV after treatment, n (UI)	3294 (3155-3480)	1482 (1420-1565)	2773 (2645-2943)	1456 (1392-1541)
Expected chronic HCV after spontaneous clearance and treatment, % (UI)	54.4 (52.1-57.5)	55.6 (53.3-58.8)	50.0 (47.7-53.1)	53.1 (50.8-56.3)
Estimated HCV treatment uptake % (UI)	***4.5 (4.3-4.7)***	***3.6 (3.5-3.8)***	***13.6 (12.8-14.3)***	***8.5 (8.0-8.9)***
Estimated HCV cumulative treatment uptake % (UI)	***4.5 (4.3-4.7)***	***3.6 (3.5-3.8)***	***31.0 (29.3-32.4)***	***28.3 (26.7-29.6)***

OAT = opioid agonist therapy, HCV = hepatitis C virus infection, CI = confidence interval, UI = uncertainty interval,
Anti-HCV = antibodies to hepatitis C virus, PWID = people who inject drugs
Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD), Intro-HCV = Integrated treatment of hepatitis C study, Kåberg et al. (2017): Prevalence of hepatitis C and pre-testing awareness of hepatitis C status in 1500 consecutive PWID participants at the Stockholm needle exchange program, Micallef et al. (2006): Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies

*Expected non-PWIDs among OAT patients set to 5%
**Expected Anti-HCV among PWID in Norway 80.8%, expected Anti-HCV among PWID in Sweden 82%, expected Anti-HCV among non-PWID in both Norway and Sweden is 0.7%
***Expected spontaneous clearance 26% (22-29%)

4.1.3 Secondary findings

Finally, certain predictors, which were determined a priori, were evaluated for any association with DAA treatment in both countries. In Sweden, being dispensed DAA treatment was associated with increased age (adjusted odds ratio (aOR) 1.8; 95% CI 1.0-3.2) and dispensation of drugs used in diabetes (aOR 3.2; 95% CI 1.8-5.7). In Norway, dispensations of cholesterol modifying medications and antibiotics were associated with decreased odds (aOR 0.4; 95% CI 0.2-0.9, aOR 0.8; 95% CI 0.6-1.0) of receiving DAA treatment. Being female was associated with decreased odds in both countries (Sweden: aOR 0.6; 95% CI 0.3-0.9, Norway: aOR 0.8; 95% CI 0.6-1.0).

4.2 Objective II: Mental health symptoms and substance use (paper II)

4.2.1 Basic characteristics

In this study 707 individuals were included from the OAT outpatient clinics and low-threshold municipality clinics. The study sample was similar in basic characteristics to the HCV study; the majority were male (71%), with a mean age of 43 at baseline and 45 years at follow-up. The vast majority of the study sample was enrolled in OAT; 82% at baseline and 93% at follow-up. More than half had injected substances at least once during the last year, while 71% reported frequent substance use; most prevalent substances being cannabis (50%), benzodiazepines (38%), stimulants (28%), alcohol (25%) and non-OAT opioids (16%). A high proportion of the study sample (88%) reported stable living conditions at baseline, while less than half (41%) had a subjective worrying debt situation.

4.2.2 Main findings

A considerable symptom burden was reported among the study sample; the mean (standard deviation, SD) SCL-10 item scores was 2.2 (0.8) at baseline, with 65% of the cohort reporting a SCL-10 score above the validated threshold of 1.85 [123]. The solid black line show the mean SCL-10 scores of the study sample, while the black dotted line represent the cut-off as shown in figure below:

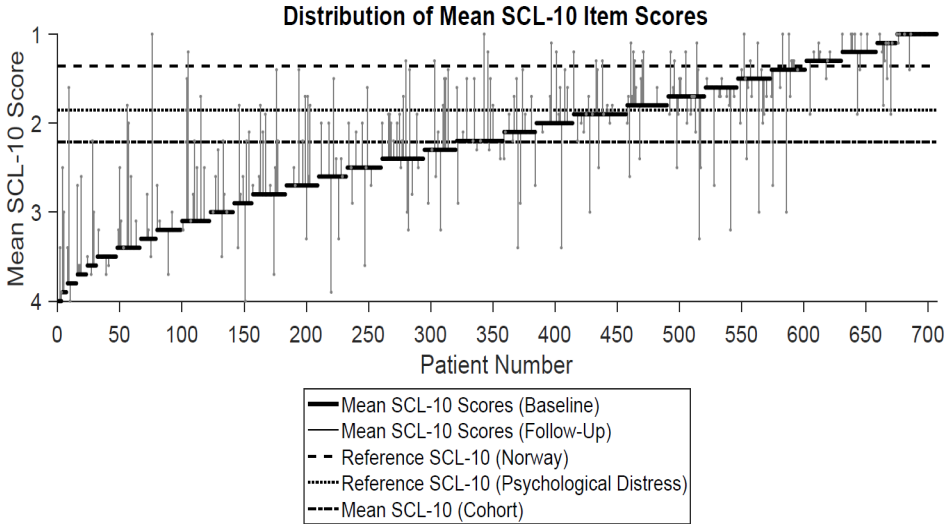

Figure 2: Distribution of Hopkins SCL-10 scores at baseline and follow-up.
HRQoL = Health-related quality of life
Source for general population comparison: Strand et. al (2003): Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36)

Of the 707 individuals recruited at baseline, 268 (38%) had SCL-10 measures at two data points. There was large individual variation in symptoms of mental health disorders and sharp changes in symptom burden, in both positive and negative directions, were observed. A linear mixed model analysis was subsequently conducted with the SCL-10 sum scores; symptoms of health symptoms at baseline were particularly prevalent among females (SCL-10 sum score: 1.8, 95% confidence interval (CI): 0.7 to 3.0), people with frequent use of cannabis (1.3, CI: 0.2 to 2.5), non-OAT opioids (2.7, CI: 1.1 to 4.2), and benzodiazepines (3.6, CI: 2.4 to 4.8) compared to males and people with no or less frequent use of these substances at baseline. Moreover, people with unstable living conditions (1.7, CI: 0.0 to 3.3) and having a worrying debt (2.2, CI: 1.1 to 3.3) had increased mental distress compared to people with stable living conditions and non-worrying debt, respectively. On the other hand, frequent use of stimulants was associated with lower SCL-10 sum score at baseline (-2.7, CI: -4.1 to -1.4) compared with people with no or less frequent use. However, in the time-trend analyses, we found no clear associations between substance use patterns, sociodemographic characteristics and change in mental health symptoms over time.

4.2.3 Secondary findings

Overall, many individuals reported considerable mental distress. The mean (SD) SCL-10 score for all items was 2.2 (0.8) at baseline, which showed that 65% of the cohort had a mean score >1.85, the standard reference score for symptoms of mental health disorders.

4.3 Objective III: HRQoL and self-perceived health in long-term OAT patients at baseline and follow-up one year later (paper III)

4.3.1 Basic characteristics

The target study sample was OAT patients. Six hundred and nine patients were included from the OAT outpatient clinics with a mean (SD) duration of OAT treatment of 7.9 (5.4) years, while total length of OAT treatment ranged from 0 to 25 years for the whole study sample. Included individuals were predominantly male (71%) with a mean age of 44 years. Most received buprenorphine-based medication (60%) followed by methadone (38%).

4.3.2 Main findings

Considerable impairments in HRQoL and self-perceived health (EQ-VAS) were found in many of the OAT patients at baseline; mean overall scores for the five dimensions were 1.7 (95% CI: 1.6-1.8) for mobility, 1.3 (95% CI: 1.2-1.3) for self-care, 1.8 (95% CI: 1.7-1.9) for usual activity, 2.3 (95% CI: 2.2-2.4) for pain/discomfort and 2.7 (95% CI: 2.6-2.8) for anxiety/depression. In addition, females and patients receiving methadone treatment

reported more problems across all EQ-5D-5L domains compared to males and patients on buprenorphine-based medications, respectively.

Patients in the age group 41-60 reported more problems on every domain except pain/discomfort compared to patients under 40 years of age. The mean (SD) EQ-VAS score of OAT patients was 57 (22) for the total sample at baseline, meaning their self-perceived health was considerably lower compared to the Norwegian reference population of 80 (19) [191]. Again, lower scores were observed for females (56, SD 23), patients over 41 years old (54, SD 23), and with methadone treatment (53, SD 22). The mean (SD) EQ-5D-5L index value for OAT patients was 0.699 (0.250) at baseline. However, 43% had an index value above 0.8, meaning they had "no problems" in the five health domains. Thirty-four percent of the sample even had an index value above 0.848 (Norwegian reference population [191]), meaning their HRQoL was better than that of the Norwegian general population and shown in Figure 3 with solid blue line and dotted blue line, respectively. Around five percent had an index value below 0.2, meaning they had "extreme problems" in their HRQoL.

4.3.3 Secondary findings

The large variations in EQ-5D-5L, which were observed between individuals at baseline, were also seen at follow-up analysis one year later. Significant improvement in overall HRQoL (p=0.004) was observed at one-year follow-up with around half of the OAT patients reported some improvement in HRQoL; for both genders (m: p=0.039, f: p=0.016), age group 26-40 (p=0.002) and buprenorphine-based patients (p=0.027). The mean (SD) EQ-5D-5L index value was 0.729 (0.237) at follow-up; 49% had an index value above 0.8 while 37% of the sample had an index value above the Norwegian reference population. Around four percent had an index value below 0.2, as shown in the Pen's Parade below:

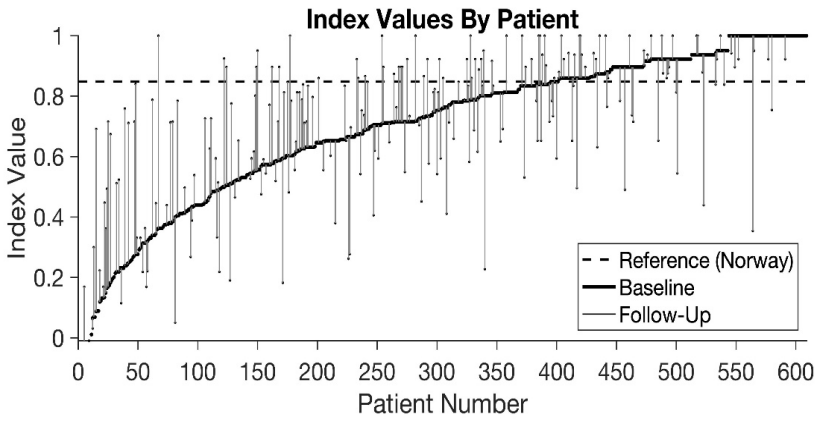

Figure 3: Distribution of HRQoL index values at baseline and follow-up.
Sources: HRQoL index values for the Norwegian general population Stavem et al (2018): General population norms for the EQ-5D-3 L in Norway: comparison of postal and web surveys

5. Discussion

This thesis has described the immense symptom burden and key challenges facing people with severe SUD in Sweden and particularly Norway. There are obvious challenges from a societal, clinical and patient perspectives in terms treatment and improving patient care. The discussion will start by a short summary of the key study findings before discussing key methodological aspect on the basis of research literature and more specific addiction research in light of these findings. Finally, it will discuss some of the study implications and recommendations.

5.1 Key findings

The first study was a population-based observational study assessing the HCV, including DAA, treatment uptake among individuals enrolled in OAT in Sweden and Norway from 2014 to 2017. The study found a cumulative HCV treatment uptake of 28% across all age groups in Sweden, and 31% in Norway. Annual treatment uptake was low in the beginning of the observation at 3.6% and 4.5%, respectively, but increased steadily towards the end of the study period to 8.5% in Sweden and 13.6% in Norway. Our results showed a complete shift towards DAA treatment regimens among OAT patients, however there was still a considerable gap between those individuals receiving HCV treatment and those estimated to being infected with chronic HCV until the end of the study period in both Sweden and Norway. Treatment uptake was associated with increasing age, being female and being dispensed certain drugs in both countries. By 2018, only a handful of European countries were on track to achieve the ambitious elimination target set out by WHO; namely France, Italy, United Kingdom, Spain, Switzerland, and among the Nordic countries only Iceland [86]. Key components of their HCV effort seem to be a clear national HCV strategy coupled with determined political leadership and will, high coverage of preventive measures such as needle-syringe programs and OAT, satisfactory monitoring and broad access to affordable DAA treatment [86]. Other key components of successful HCV elimination is shown in Table 1. Although Norway has several key components in place, such as a comprehensive and ambitious national hepatitis strategy since 2016, unrestricted access to DAA therapy since 2018 and high coverage of OAT [65, 72], a further essential component is enhanced monitoring and evaluation, which is crucial for the tracking of the DAA response on prevalence and incidence. Without sufficient surveillance and monitoring of HCV and HCV treatment uptake, the efficacy of these programs cannot be fully assessed. It has been compulsory to notify The Norwegian Surveillance System for Communicable Diseases since 1990, however, since there has been no distinction between anti-HCV, HCV RNA or HCV core antigen reporting before 2016, it is impossible to assess whether cases were acute or chronic, or whether patients achieved SVR on their own, or how many cases were actually

notified [102]. The result is that accurate HCV prevalence and incidence data prior to 2016 are not readily available, nor is the treatment uptake in the DAA era among people with severe SUD.

In the second study on mental distress, SCL-10 was used to assess symptoms of mental health disorders among people with severe substance use disorders. The vast majority of these individuals, 65%, have symptoms of mental health disorders and psychological distress. The mental symptom burden was particularly prevalent among females, people with frequent use of cannabis, non-OAT opioids, and benzodiazepines compared to males and people with no or less frequent use of these substances. The frequent use of stimulants indicated less symptoms of mental health disorders compared to subject with less or no frequent use. Hence, our findings are in line with other research that suggests that benzodiazepine misuse are associated with other substance use, in addition, worsening mental health symptoms and disorders, especially anxiety, mood disorders, and among people with personality disorders are observed [132, 192-194]. Correspondingly, having a SUD, or a mental health disorder, is also likely to increase the risk for misuse of opioids [195, 196]. In addition, substance use patterns of cannabis, especially frequent use, are found to be associated with residual cognitive impairment and poor mental health [138, 139, 197]. While it seems clear that stimulants may exacerbate psychosis in for instance, people with underlying schizophrenia, it seems less clear whether they contribute to increase the risk of new cases on their own [198, 199]. However, one population based study found that people with stimulant use disorder had a higher risk of developing schizophrenia compared to people with other SUD (excluding cannabis) [200]. In a systematic review, the odds were doubled and tripled for developing psychosis among people with any use of stimulants and people with a stimulant use disorder, respectively [138]. This association remained significant after adjusting for other substance use and pre-existing mental health disorders [138]. Frequency and dosage also seem to play a role. In one of the few studies with a longitudinal design, an increase of psychotic symptoms were observed secondary to dose and periods with frequent use [200]. On the contrary, no significant associations have been found between people with stimulant use disorders and anxiety [138]. Nor is the evidence compelling when it comes to major depression, though several studies indicate an association with depressive symptoms both among frequent users of stimulants and upon entering SUD treatment [138, 201-203]. We found no clear associations between substance use patterns and changes in mental health symptoms over time.

The final study assessed the HRQoL in long-term OAT patients. It was among the first studies to examine changes in HRQoL in a sample of long-term OAT patients over a one-

year follow-up period. The literature on HRQoL and OAT patients show improvements in HRQoL upon treatment entry, but data on long-term patients' HRQoL is mostly unknown. We found considerable impairments in HRQoL and self-perceived health (EQ-VAS) in many of the OAT patients in the cohort. However, large variations in EQ-5D-5L index values were observed between individuals, both at baseline and at follow-up. Significant improvement in overall HRQoL was observed at one-year follow-up with around half of the OAT patients reported some improvement in HRQoL while around one-third experienced worse HRQoL at one-year follow up, again, with great individual variations. Only males reported significant improvement in their self-perceived health at follow-up. There is supporting evidence that HRQoL improves after commencing OAT and during the first few months of treatment [152, 154, 204, 205]. For instance, among a cohort of people with heroin dependence, which were recruited from a low-threshold setting and subsequently initiated OAT, showed a considerable improved HRQoL from baseline to follow-up three months after [206]. In a study with longer follow-up, QoL was assessed every three months from OAT initiation; found a rapid improvement during the three first months of OAT, however, the effect ultimately waned off [207]. Another study on HRQoL found the same initial effect upon OAT introduction and until follow-up six months later [208]. However, during the next six months of follow-up, HRQoL than unexpectedly declined [208]. In a study among a larger OAT cohort with one-year follow up, no improvements in HRQoL were observed [209]. In addition, a recent systematic review suggests there is still limited knowledge regarding HRQoL outcomes in OAT treatment programs and therefore rarely used [142]. Hence, while there is evidence that OAT is effective in improving HRQoL at treatment uptake and a few months after treatment, the effect of long-term OAT treatment upon HRQoL remains largely unknown except for the study presented in this thesis [140]. With the prospect of an aging OAT population in Western Europe, understanding the needs of these patients – not only as a whole group, but also including the various subpopulations, seem crucial in order to provide suitable care in existing health care systems [1, 165].

5.2 Research fundamentals – research among a hard-to reach population

The scientific classification of psychoactive substances and research emerged around the same time when morphine addiction was studied by Levinstein (1875) who revealed the main drivers for opioid dependence; the fixation and priority over others to take the substance and the phenomenon of withdraw that could be cured by simply giving more opioids [6, 210]. However, the reality is that research among people with SUD may be very challenging for a number of reasons. Research among people from socially disadvantaged groups, such as people with SUD, is often labelled hard-to-reach (or hidden) populations, secondary to the struggles to get access and keep those participants in studies and in public

health programs [211, 212]. The lack of research, and especially quality research with designs that can address causality, may lead to decisions and treatment recommendations not grounded on evidence-based-medicine, which requires the integration of both the best available evidence, clinical judgement and patients value [213]. Within this context, it is useful to consider the term best available evidence, which is founded upon certain criteria from *high* to *very low* to interpret the hierarchy of evidence and how it can be used to guide a grade of recommendations as shown below:

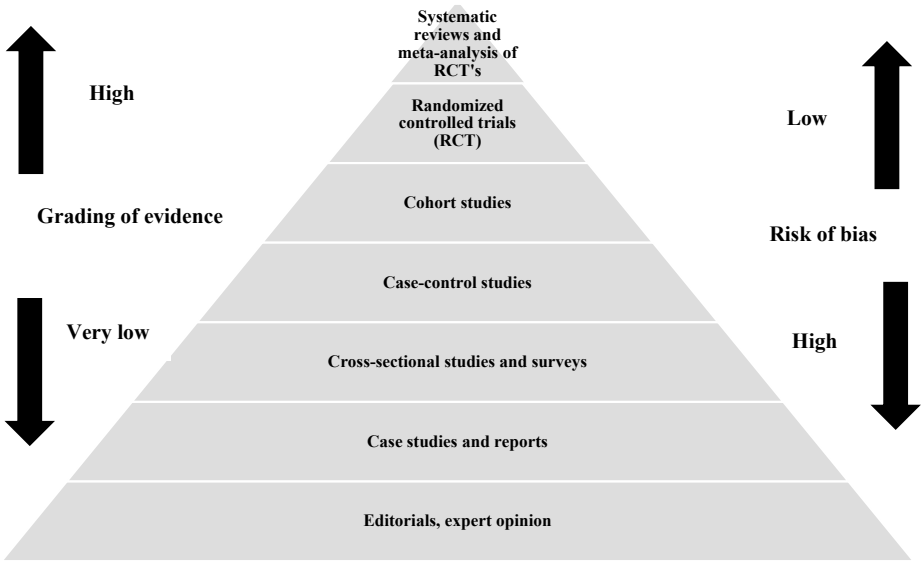

Figure 4: The hierarchy of evidence and likelihood of bias.
Source: Modified from Atkins et. al (2004) Grading quality of evidence and strength of recommendations

In addition, lack of research and knowledge about substance abuse and people with SUD may advocate a reduced amount of interest and even funding. For example, there seems to be limited knowledge - and inclusion, of substance abuse and SUD among health personnel and medical educations in Norway, and perhaps even viewed as "low status" compared to other more prestigious research fields [214, 215]. This is further amplified at country levels in the skewness of research on substance abuse and dependencies. In fact, based on number of publications and citations, research has shown that approximately two-thirds of all publications origin in the USA compared to ten countries in Europe (England, Germany, France, Italy, Spain Netherlands and the Nordic countries) [216]. Pending on the external validity, research from the USA may arguably benefit beyond American borders, however, it prove difficult to adapt findings between rather different settings and continents [217].

Then there is a question about the quality of addiction research. For instance, if we consider the prophylactic treatment with thiamin among people with alcohol dependency to prevent the onset of Wernicke-Korsakoff syndrome. A search in Cochrane Library database suggests that there is only one study in the last 20 years with a randomized, double-blind design, which investigated the therapeutic effect of thiamin in this group [218, 219]. This could be a coincident, or point toward a systematic lack of quality research among people with SUD compared to more "high status" diseases.

Thus, European and Norwegian research is needed to add to the overall knowledge and contribute towards best available evidence in the field of substance abuse and dependencies.

5.3 Internal validity

The key research question is whether, or to which degree, inference can be drawn from study findings to represent the "truth" in the real world [220]. Therefore, understanding bias is essential for the conduct of quality research studies. In the context of research methodology, bias refers to systematic deviation of results or inferences from the truth [221]. Bias is defined by Last and Abramson (1995) as *any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth* [222]. A bias can take place at any phase of the clinical research process; from the planning phase, to implementation/data collection, and publication. The validity, which describes the accuracy of the research, is normally divided into internal and external validity. The following subsections will discuss key aspects of the internal validity of this thesis. According to the definition of Porta (2008), internal validity is the degree to which a study is free from bias and depends on the soundness of study design, conduct and analysis [221].

5.3.1 Study design

All studies included in this thesis are with an observational design, i.e. the included individuals were observed without any controlled interventions. Whereas paper I was a register-based cohort study, following large cohorts of OAT patients in Sweden and Norway, paper II and three followed a cohort of OAT and SUD patients nested to the multicenter INTRO-HCV study. Having a prospective design have some advantages compared to retrospective or cross-sectional designs. During the planning process of paper I, the exposure (OAT) and outcome (HCV treatment) were clearly defined prior to data collection together with inclusion and exclusion criteria of the study. Despite several limitations as will be discussed, the study design of paper I was regarded as sufficient to answer the research questions in a cost-effective manner. Similarly, the study design of

paper II and III were planned and adopted according to the research questions. Also these studies have some limitations, such as an imperfect number of measuring points and lack of control groups. Hence, making any causal interpretations difficult and was not the scope of these studies. All studies used quantitative data to answer the research questions. Data collection methods included the use of national registries for paper I, and a combination of semi-structured interviews and questionnaires for the other two papers in this thesis. By standardizing the study protocols for data collection, which included trained research nurses entering the data into a data management program (Checkware®), is likely to have reduced punching (information) errors. Also, by applying validated questionnaires and close follow-up by the research nurses throughout the study period are likely to have reduced the inter-observer variability. Blinding of research nurses to the participants exposure (OAT) and outcomes (SCL-10 and HRQoL) was not possible in these studies. However, since the research nurses did not take part in any clinical evaluations or decisions regarding OAT treatment for the participants, this could also decrease bias.

5.3.2 Selection bias

Selection bias can arise from procedures used to select the subjects or result from factors that influence loss to follow-up [223]. In paper I; nationwide registry data from SPDR and NorPD was used for Sweden and Norway. Since participation is compulsory in both registries, they cover the entire populations of these two countries. Hence, in theory they should not be subject to any selection bias. Yet in practice, this is unfortunately not the case. Selection bias could arise in the inclusion criteria for dosage, route of drug administration, duration of exposure, and the prospect of some patients not being recorded in either SPDR or NorPD at all. It is estimated that approximately 10% of OAT patients in Norway and 40% in Sweden receive their OAT medications from outpatient polyclinics not captured in either NorPD or SPDR [41, 224]. Also, we included patients each calendar year with dosage criteria based on DDD. Therefore, an individual who commenced OAT treatment late or quit early during the year may not obtain sufficient exposure to be included that particular year. Similarly, an individual with a low OAT dose below the one DDD/day would not be included in the study. In addition, there is also a possibility that individuals on methadone mixture in the study were not true OAT patients despite excluding those on tablets and injections and setting dosage criteria of minimum one DDD per day per calendar year. Most individuals are dispensed OAT medications at pharmacies while some receive the medicine at OAT outpatient clinics, which means that the latter may not be fully identified in this study. This is also the case for OAT and HCV medications administered directly to hospitalized and institutionalized patients, which may not be recorded in the registries. Overall, we opted to use these strict selection criteria to make sure those who fulfilled the

criteria were reached and in fact true OAT patients. This probably reduced the selection bias of including non-OAT patients in the study sample, despite risk of underestimating the total OAT samples in both countries.

In paper II and three selection bias could occur both during the identification of the study samples and at loss to follow-up, which is a particular concern for studies among hard-to-reach populations and could thus represent a threat to the internal validity of the estimates derived from these studies [211, 220]. We dealt with the former by clearly defining the study samples, having continuous access to the patients in the outpatient OAT clinics and low-threshold municipality clinics for the research nurses during the study period, and individuals with increased risk to develop the outcome of interest; measures symptoms of mental health disorders and HRQoL. In addition, by having a prospective design of the studies, where the outcomes (SCL-10 and EQ-5D-5L) were unknown at the time of inclusion, is likely to be less prone to selection bias [225]. Follow-up was conducted on a sub-group of the initial samples in both cohort studies. From around 900 patients invited to participate in the HRQoL study, a total of 609 (68%) patients completed the EQ-5D-5L questionnaire at baseline, and of those, 245 (40%) were included in the follow-up analyses. To reduce the selection bias due to the loss-to-follow-up (or more correctly, delayed follow-up) we performed an inverse probability weighted method as described in the methods chapter [226]. The mean for the population weights was 1.0 (SD 0.12) in our model, implying few differences between those with valid and missing EQ-5D-5L measurements from baseline to follow-up. In the second paper, where the study sample consisted of both OAT patients and people with severe SUD, the loss to follow-up was greater in the latter group. Individuals enrolled in OAT accounted for 83% and 93% of the study sample at baseline and follow-up, respectively. Of the 707 participants with SCL-10 measures at baseline and 268 (38%) were included in a follow-up analyses with 67 (10%) having at least three annual measuring points. To reduce the potential for selection bias between the sub-group with follow-up SCL-10 measurements again an inverse probability weighted analysis was used and revealed a mean for the population weights similar to paper II (comparing the 268 patients at follow-up with those at baseline). In addition, secondary to selection bias, missing data on entire observations or a subset of variables can distort the effect estimate of interest [227]. Missing values of SCL-10, clinical and sociodemographic variables, which included substance use, injecting substance use, educational level, worrying debt situation, and living conditions were assumed to be *missing at random*. Hence, the missing values are systematically dissimilar from the observed values, however, the systematic differences are fully accounted for by measured covariates [227]. There were missing values for

approximately 3.4% of these values, which were subsequently replaced with the estimated values by expectation-maximization imputation [189].

5.3.3 Information bias

Information bias, or sometimes called measurement error, is related to the way information is processed and resulting from the problems with the measurement of study variables [223]. Such errors are often termed either non-differential (random) or differential information bias [228]. The former implies that errors in measurements happen equally across comparison groups and tend to lead to an underestimation of effect, while the latter implies there are different levels of inaccuracy between the groups and could either over- or underestimate the true effect [228]. Such problems may arise for different reasons including recall of information among study participants, over- or underreporting, sub-optimal measuring tools, or during interviewer interaction with participants. In addition, the use of substances, either during an acute intoxication or in a withdrawal phase, can influence all these and represent a bias when differentially distributed among the comparison groups [220].

One of the advantages with prescription databases is that they practically remove the recall bias. The dispensations are registered with pharmacies and participants do not need to remember them. The information in SPDR and NorPD is consistent with a participant both being prescribed the medication and having collected the dispensation at a pharmacy. However, the registries do not have information about adherence or compliance. In the instances an individual do not choose to collect the prescription, often termed primary non-compliance, or when an individual collect the dispensation, one cannot be sure if the subject actually took the medication as prescribed (secondary non-compliance) [229]. As mention above, another source for information bias is that medications administered directly to hospitalized and institutionalized patients are not captured by the prescription databases, which may underestimate the actual medications used. For instance, it is estimated that NorPD captures around 90% of the patients with dispensed OAT from pharmacies [41]. The other 10% could represent OAT patients with more need for follow-up in the OAT outpatient clinics, and as such, may represent patients with higher disease burden and in need of HCV treatment. This could skew our results toward underestimating the HCV treatment uptake. On the other hand, our estimates can also be overestimates. OAT patients have successfully entered the health care system and therefore more likely to accept medical treatment, and thus bias our results toward improved HCV treatment uptake. In regard to dispensation of HCV treatment, almost all HCV treatment is initiated in outpatient polyclinics and thus are included in the prescription database [102, 230].

Much of the information in the cohort studies in paper II and III are based on self-reporting information from study participants with semi-structured interviews with research nurses, which challenges several aspects of the information assessment process. Firstly, in the event a participant do not remember or inaccurately remember, this may introduce recall bias. The outcomes of interest, SCL-10 and HRQoL had a short recall at both baseline and follow-up, however many of the other clinical and sociodemographic questions had weeks, months and ever recall questions, which may increase the risk of recall bias. The preferred recall period seems to be dependent upon the objectives of the study; a longer period implies more information and lower recall bias when data analysis are aggregated [231]. We aimed to further reduce the risk for recall of information by having a prospective cohort design, and by research nurses asking for information at the time of inclusion or around the annual health assessments. In addition, questions were carefully selected, using validated questionnaires when possible, and balanced toward asking too many extensive question, which could risk fatigue response among participants.

A perhaps bigger concern for the cohort studies is the introduction of social desirability bias among people with SUD. The core of this bias is on the one hand to underreport socially undesirable attitudes and behaviors such as substance use, while on the other over report more socially desirable attributes [232]. While this has not been studied well among people with SUD, there is some evidence pointing toward social desirability bias being associated with severity of substance use and socially desirable changes in the use of both alcohol and other substances [233-235]. Another study among cocaine and opioid users found that those with high levels of socially desirable responding also report considerably fewer symptoms of depression and lower frequency of substance use [232]. Depressive symptoms are assessed in both SCL-10 and EQ-5D-5L. This could imply that among participants who would answer a more socially desirable response may actually underreport depressive symptoms in both studies. While this bias is hard to overcome and fully address in a clinical setting, central in the INTRO-HCV study have been to communicate that these studies may be potentially useful to the participants. Secondly, by employing independent research nurses not being involved in any clinical decisions may have motivated the participants to provide more accurate and trustworthy information, especially when asked about substance use. However, the research nurses may themselves introduce an interview bias, which refers to any systematic difference between how information is asked, stored, or understood [225]. The effect of the interviewer may have significant impact on the collected data, in particular when sensitive information is asked about for instance substance use, income, risk behavior for infectious diseases, or mental health symptoms [236]. The regular training of the research nurses is likely to reduce most of these problems. While the exposure was well

known to the research nurses, this was not the case for the outcomes in the cohort studies, thus, interview bias seem more unlikely when the outcome of interest is unknown to the interviewer [225]. Another method to minimize interview bias could perhaps be to have sociodemographic interviewer-respondent matching, though there is little evidence supporting this to substantially increase response rates or data validity [236].

5.4 Confounders and causality

One of the key aims, and challenges, in epidemiological research is to evaluate if the exposure is the cause of outcomes of interest. In order for an exposure to be a cause of the disease, the exposure must than have preceded the outcome of interest. This condition is referred to as the basic temporality criterion in epidemiology [223]. In the opposite event, when the disease or outcome of interest has a causal effect on the exposure, a situation of reverse causality occurs [223]. As shown in the illustration below; when substance use, as the exposure causes mental health disorders, the reverse causality occurs when the outcome causes the exposure, in this case, substance use.

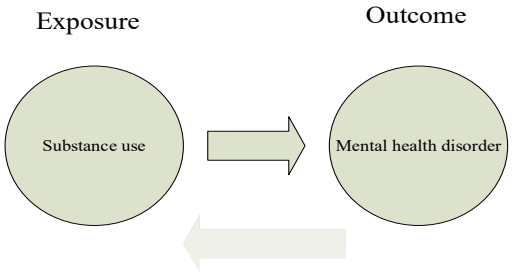

Figure 6: Temporality and reverse causation

In observational studies, when a prospective cohort observes an association between the exposure and outcome, a number of possible explanations need to be addressed before it can infer that a cause-effect relationship truly exists. As discussed under the internal validity, it may be caused by any systemic errors (biases) or can be simply by chance (referred to as random error, which is discussed in the subsection below). A third probability is that the observed association may in fact be due to the effects of confounding. A confounder affects both the exposure and outcome, thus, distorts the measurement of the association between them. Van den Broeck (2013) explains this concept further; confounding hinders our ability to see the true casual effect of the exposure on the outcome and can mask associations when they truly exist – or indicate spurious associations when in fact there are no casual relationships [223]. In other words, several potential situations may

arise. If we add to the illustration above, a confounder can cause both the exposure and the outcome, or be non-causally associated with either the exposure or outcome:

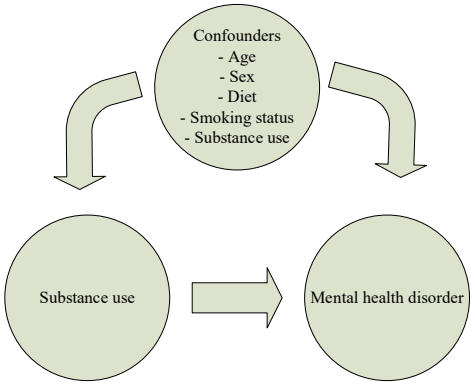

Figure 7: Confounding

In order to cause confounding, a variable should be either unequally distributed among exposure levels, be a cause of the outcome (or strongly associated) or be outside the causal pathway between the exposure and outcome [223]. The main prevention of the effect of confounding is study design and data analysis (such as regression). The former includes randomization and matching, which were not feasible for the studies included in this thesis, however, we applied restriction by the introduction of exclusion criteria especially for paper I to make sure we were actually capturing true OAT patients in both Sweden and Norway. However, since the exposure in most pharmaepidemiological studies is often a drug prescription, this may introduce a confounding factor known as confounding by indication, since the determinant of the outcome is present, and with HCV medication, which are not commonly prescribed, and therefore not likely to be present in any comparison groups [237]. Controlling for such an evet is only theoretically possible since we did not have any information about the prescriber identity in SPDR and NorPD, and thus not being able to adjust for the same prescriber. In the cohort studies included in this thesis known confounders were adjusted for in multivariable analyzes, yet, all studies in this thesis are at risk for confounding as the effect of any unknown confounders only can be fully adjusted by true randomization [225].

Thus, an observed statistical association between an exposure and outcome in this thesis does not necessarily infer a causal relationship. On the other hand, a lack of such association does neither imply an absence of such causal relationship taking place. The evaluation of whether an observed association represent a true cause-effect seems reliant on certain

criteria. One set of such criteria was proposed by Hill (1965), which involves an assessment of the strength of association; where a strong association is more likely to be casual compared to a weak one; is there temporality as described above, i.e. cause must precede outcome, is the findings consistent with other findings, is there a dose-response relationship (or biological gradient), specificity of the association – is there a one to one relationship between cause and outcome, plausibility and coherence; does the removal of exposure lead to altered outcome occurrence [223, 238]. While some of Hill's criteria were partly met in the included papers, such as consistency, coherence of current knowledge and to a certain degree dose-relationship in paper I-III, others could be in conflict with both the temporality criterion to a certain extent, specificity and one to one relationship between potential cause and outcome. However, the scope of these papers were not to conclude strictly on a causal interpretation. In line with Hernan and Robins (2020) casual inference framework, where there is some hesitation to endow observational associations (unless ideal randomized assignments take place), we used a combination of theory and literature review to construct our models and analyses [239]. For instance, in paper II where the outcome was mental distress (SCL-10), earlier research has shown several sociodemographic factors being associated with mental health disorders, such as debt, gender, and living conditions. Other factors, such as substance use patterns and injecting behavior are less studied and we therefore constructed a priori theory for these selected variables as shown in the figure below:

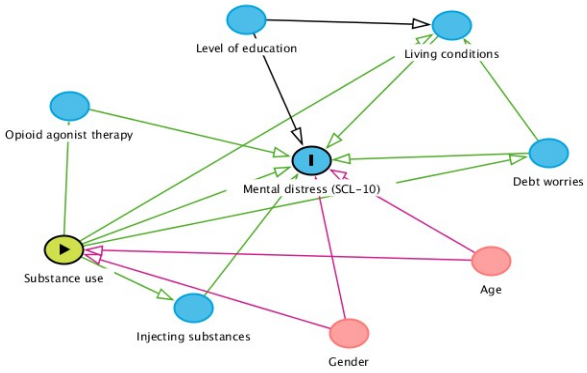

Figure 8: Causal diagram made with DAGitty for SCL-10
SCL-10 = Hopkins Symptom Check list 10

By using a combination of existing knowledge and theory, testing the potential relationship between these clinical (and sociodemographic) variables in a casual inference framework may contribute to reduce the risk of unfortunate selection of variables and a more reasonable interpretations of the findings [239].

5.5 External validity

As illustrated in the figure below, the internal validity is the precondition for external validity. Porta (2008) defines external validity to which degree the results of a study may apply, be relevant, or be generalized to populations or groups that did not participate in the study [221]. If the study design is sound, with an acceptable sample size, when biases and confounders are adjusted for, the question remains; is the presented evidence trustworthy? [223]. In line with what have been discussed previously regarding both quantity and quality of research in addiction medicine, there seems to be another aspect which in particular reduces the external validity of many studies according to a systematic review; the high rate of exclusion criteria in studies among people with SUD [240]. In paper I we opted for very strict inclusion criteria to minimize selection bias among OAT patients, however, this is likely to have also influenced the external validity of the study to some degree. In clinical and cohort studies, there is also a need to balance the eligibility criteria in order to protect the safety of the participants (and to ensure the internal validity), and make sure to include the study sample of interest to preserve good external validity [240]. In the cohort studies in this thesis, where the target study sample were people with severe SUD and opioid dependence we therefore opted for broader inclusion criteria. However, a particular concern is the high co-occurrence of SUD and mental health disorders in these cohorts. Since many of these patients live a very unstable life, they are difficult to recruit to studies, challenging to engage and retain in treatment may lead to the exclusion from controlled studies, resulting in limited validity of existing research – which likely also have affected our studies [241-244]. Thus there seems to be an urgent need to shift research on addiction medicine more toward effectiveness studies to facilitate evidence-based interventions in clinical settings and improve external validity [241].

5.6 Strengths of the thesis

The main strength of this thesis is the relatively large sample sizes among people with severe SUD. Paper I presents a very large sample of OAT patients being treated for HCV, which was estimated by a model. At the time of the study, there were few papers on HCV treatment uptake after the introduction of new medications. By using national registries like SPDR and NorPD, with near complete databases with few entry errors, we were able to design a time- and cost-effective quality cohort study, which could answer our main research questions. Similarly, the major strengths of paper II and three are the relatively large sample size of a “hard-to-reach” population of people with severe SUD in an observable clinical setting. Both studies were designed as nested prospective cohort studies, avoiding many of the biases addressed earlier in this chapter. In addition, a particular strength of paper II is

the longitudinal design whereas paper III is the first major study on HRQoL among long-term OAT patients.

5.7 Other methodological considerations

5.7.1 Random and other potential errors

Errors in measurement estimations are normally referred to as either systematic errors, as seen above, or errors that incur randomly. A random error, which affects the reliability of the study, introduces greater variation in the estimates as it may occur by chance [245]. One way to control for random errors is by having a larger sample size. In our first study, which was register-based data from NorPD and SPDR which captures the entire Norwegian and Swedish populations, effectively reduces the chance for random errors while also increasing the precision in measured estimates. While it is not possible to completely eliminate random errors, we can assume that for the first paper in this thesis, will limit such errors substantially. For the cohort studies from Intro-HCV (paper II and three) with a study sample of 707 and 609, respectively, random errors are slightly more prone to random errors. Thus, we tried to control for it by efficient statistical analysis and expressed the estimations quantitatively with confidence intervals (and p-values where appropriate).

Unlike random errors, systematic errors are not affected by study size alone. Our main strategy in dealing with systematic errors were laid out in the study designs of the three papers following an observational cohort design and clear data collection strategy in the INTRO-HCV project to minimize information, selection and confounding biases as described above.

Other common impediments, especially in pharmacoepidemiological studies, are how to control for the *immortal time bias* and *left-truncation*. Simply put, in study one; the former arises when OAT patients included in the study by definition cannot have experienced outcome (as they would then have been excluded) during some period of follow-up time when the immortal time is either misclassified or excluded during the analysis as shown below [246]:

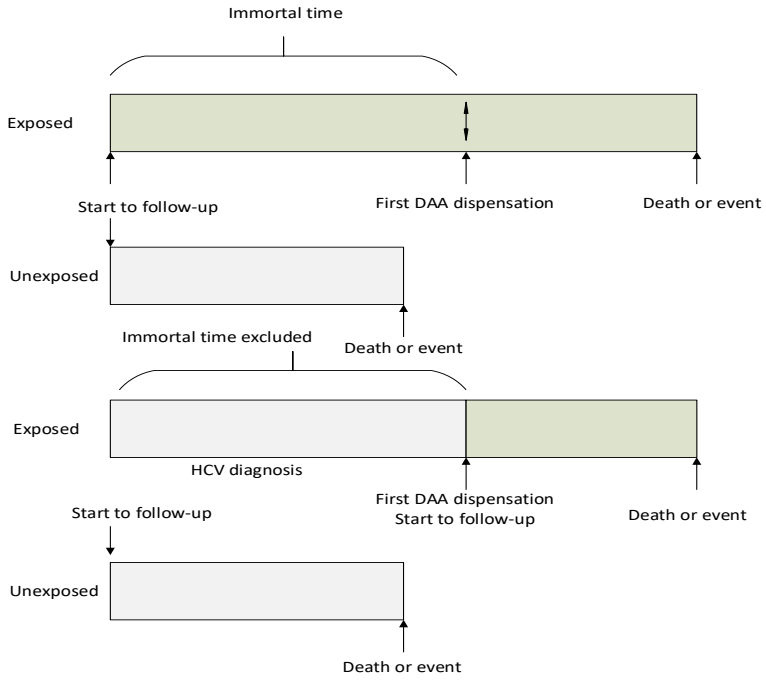

Figure 8: Immortal time bias in cohort studies.
Sources: Lévesqueet. al (2009) Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes

The immortal time bias may therefore in particular skew the results in favor of the HCV treatment group. Our way of dealing with this was designing the study with clear separation of exposure and outcome windows (dispensed OAT with certain DDD during a time period to be included, and dispension of HCV treatment as outcome), with the participants in the exposure group assigned to that group at time-zero during the start of each calendar year. While patients could enter and leave the cohort every calendar year based on inclusion criteria, we prevented over-counting individuals in the HCV treatment group by only including them once during the whole study period (when the first HCV/DAA dispension occurred). Other methods to avoid immortal time bias are time-dependent- or a time-matched, nested case-control analyses [246].

The problem with left truncation happens when certain individuals who have already passed the milestone, in our study receiving HCV treatment, at the time of study recruitment, are not included in the study [247]. In addition, the data presented in study one was cumulative data on HCV treatment uptake for the whole period from 2014 to 2017, and was not linked between individuals diagnosed with HCV (see section below) and individuals receiving HCV treatment. We tried to limit the impact left truncation simply by including only the

first dispension of HCV treatment. Although low, there is a risk for patients with several treatment courses; secondary to re-infection, non-adherence and therapeutic failure not being included.

5.7.2 Unlinked data and model limitations

One of the key limitations in our first study is the absence of HCV diagnosis on an individual level and the linkage of this data to individuals' actually receiving HCV treatment according to NorPD and SPDR. During the study planning and design we opted to not link our data to The Norwegian Surveillance System for Communicable diseases due to the low notification rate and the uncertainty whether HCV infections were acute, chronic or passed infections. In a previous study, when these data was linked, around 40% of the treated individuals according to NorPD were not notified in the Norwegian Surveillance System for Communicable diseases [102]. Using the above model, we calculated the expected number of chronic HCV infections in 2014-2017 for Norway and Sweden, with uncertainty in this quantity arising only from the uncertainty in spontaneous clearance. However, our model may itself have several limitations. The model has not been adjusted for treatment failure or non-adherence. While DAA have a very high curation rate, however, some individuals in the study received interferon-based therapies that may only achieve an SVR of less than 60%. The Norwegian Centre for Addiction Research have estimated prevalence of HCV in Norway among OAT patients, based on Anti-HCV and self-reports. [41, 159, 248, 249]. Mean prevalence during the study period ranged from 51% in 2014 to 43% in 2017. With these estimates, we could calculate a cumulative treatment uptake of HCV of 31.5% in Norway and 29.2% for Sweden by 2017. Finally, self-awareness of HCV may be low and underreported among PWIDs [183], and thus could represent an underestimate of HCV prevalence.

5.8 Study implications and recommendations for future research

5.8.1 Paper I

Whereas most previous studies on HCV treatment uptake have focused on smaller cohorts of PWID during the interferon-era, our study was among the first evaluating HCV treatment uptake among OAT patients at population level after the introduction of DAA therapy. Our study has revealed a large increase in DAA treatment uptake among OAT patients in both Sweden and Norway from 2014 to 2017, compared to several earlier studies that demonstrated continued low treatment uptake among PWIDs and OAT patients [102, 250]. In Norway prior to the introduction of DAA, annual HCV treatment uptake among OAT patients ranged from 1.3% to 2.6% in the period from 2004 to 2013 [102]. However, despite the availability of unrestricted DAA treatment regimen in Norway since 2018, people with

SUD in active substance abuse have not been able to benefit from the increased accessibility [65]. At the time of study, there was still a considerable "gap" between those estimated to be infected with chronic HCV and those receiving treatment. The study implies that there are still significant barriers to HCV treatment among OAT patients, which need to be addressed. The scale of the HCV endemic among people with severe SUD is tragic and is a result of years with failing health policies for vulnerable populations. By 2018, only a handful of high-income countries were considered on a pathway to accomplish the WHOs HCV elimination targets, and among the Nordic countries only Iceland [86]. In Norway, it is estimated that HCV complications will even continue to increase within the next few years [70].

The study also revealed that being female was associated with decreased odds for treatment in both countries. In addition, increased age and certain pharmacoepidemiological associations were identified in Sweden and Norway, respectively. Especially gender and increased age, which were also associated with poor HRQoL in the third study, seems to be linked to psychosocial vulnerabilities, which requires more research and probably more gender and age specific care in OAT clinics. For both Sweden and Norway, which already have a unifying and committed political leadership, a sound national hepatitis strategy, in addition to unrestricted access to DAA therapies, which are the three main components for any country elimination strategy – there seem to be a need for more health policies, which will be addressing local epidemiological challenges among affected populations [86]. OAT has been suggested to play a vital role in the management of chronic HCV among people with opioid dependence and has been shown to reduce the risk of HCV acquisition, and this study have provided insight into the relative contribution of HCV treatment in an OAT setting. [45]. It will require coordinated efforts to increase the treatment uptake, probably at multiple levels of both the primary and secondary health care system. While OAT as an integrated delivery platform may seem promising, since the facilities and infrastructure are already in place for high levels of HCV screening and linkage to HCV care, at least in some places in Norway; however, there still seem to be insufficient evidence [251]. Large clinical trials are needed to test these hypotheses in order to rapidly be able to scale-up treatment uptake and confirm the best available HCV treatment platform among marginalized and vulnerable subpopulations. Finally, enhanced HCV monitoring, including DAA treatment uptake, is essential if we are to reach the ambitious hepatitis strategical targets.

5.8.2 Paper II

The second paper in this thesis assessed symptoms of mental health disorders and impact of substance use patterns and other factors among people with severe SUD. Overall, a

considerable symptom burden was revealed with two-thirds reporting symptoms of mental health disorders. These results are generally in line with multiple studies, both clinical and epidemiological, which indicate high rates of co-occurring mental health disorders among people with SUD and anxiety disorders (27%) [103, 104, 110-112]. We found that mental health symptoms were particularly prevalent among females, people with frequent use of cannabis, non-OAT opioids, and benzodiazepines compared to men and people with no or less frequent use of these substances. However, there were no changes in time trends between use of substances and the burden of mental health symptoms. One assumption could be that the associations at baseline might be due to reverse causality, i.e. that participants with substantial mental health symptoms use substances to self-medicate symptoms [252]. It is also possible that there is a "flattening effect" and that potential negative impact of substances are more substantial at an earlier phase and that the change in later phases are less pronounced. On the other hand, a study that followed SUD patients from treatment entry to discharge found a substantial decrease in symptoms of mental health disorders; over 80% reported above the SCL-10 cut-off score at admission, while around half the study sample reported above this score at discharge [253]. The more severe substance used predicted a larger reduction in symptom burden, which may imply that it is the use of the substances attributed by the removal of both intoxication and abstinence, that lead to the reduction [103, 253]. Other studies have shown that, especially anxious and depressive symptoms, resolve or change rapidly after entry in SUD treatment [254, 255]. Nevertheless, the overall symptom burden in our study is still much higher compared to the patients with reduced mental distress at discharge. Around 85% of our study sample was long-term OAT patients with a mean treatment time of almost eight years, which may suggest that symptoms of mental health disorders do persist despite enrollment in an opioid treatment program such as OAT. In addition, compared to the general population in Norway, were around 11.4% scored above the SCL-10 cut-off, our study found significant higher scores on all measured variables as shown on the next page:

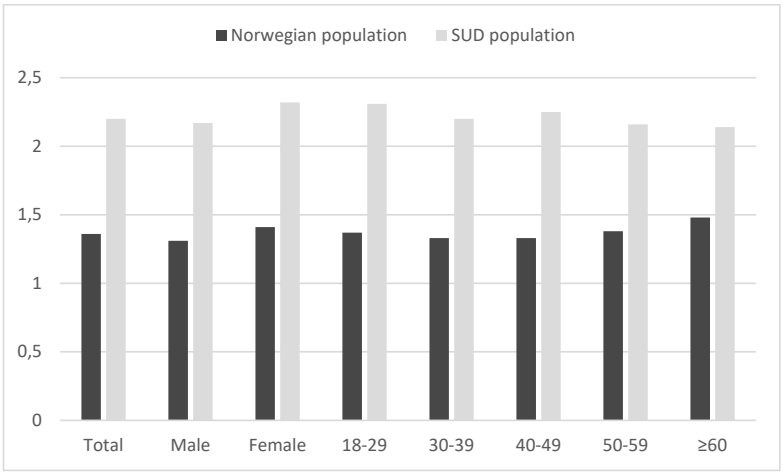

Figure 9: Hopkins SCL-10 scores among the general Norwegian population and people with severe substance use disorders, mean per group
Hopkins SCL-10 = Hopkins symptoms check list 10. Source: Strand et. al (2003). Measuring the mental health status of the Norwegian population: A comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36)

Our study has exposed that screening for mental health disorders among people with severe SUD is important given the high prevalence and co-occurrence of mental health symptoms. Mental health disorders are likely to impact the long-term course of SUD, while treatment of mental health disorders is likely to impact treatment outcomes in SUD treatment [256, 257]. For example, depression and opioid use disorders often co-occur, while having a major depression in one longitudinal study was the disorder that most regularly impacted treatment outcomes negatively for people with opioid dependence, which is of special concern attributed by the very questionable efficacy of antidepressants in this subpopulation [116, 255]. In addition, the presence of comorbid mental health disorders and SUD have been found to be associated with poor treatment outcomes and show a higher psychopathological severity compared to people with a single disorder [109, 258, 259]. Thus, we advocate the assessment of mental health status in clinical settings among people with SUD, not just at treatment entry, but also in long-term and maintenance treatment. There is also a need for more research, especially clinical trials and studies with longitudinal design evaluating impact of substance use patterns, leading toward a better understanding of the dynamics of these dual disorders, be age and gender-sensitive and follow and integrated treatment approach, which have been found superior compared to separate treatment plans among people with mental health disorders and SUD [48, 49, 120].

5.8.3 Paper III

The third paper in this thesis studied the HRQoL among OAT patients with a follow-up one year later. While many studies have demonstrated a poor HRQoL and QoL among people with SUD and opioid dependence, especially at treatment entry, there is a lack of knowledge among people in long-term OAT treatment. Our results at baseline were in line with many of the findings from other studies; overall we observed a generally poor HRQoL, hereunder EQ-5D-5L and EQ-VAS, especially when compared to other chronic disease, and to the general reference population. Compared to the latter, OAT patients reported in average consistently higher percentages of problems across all EQ-5D-5L domains, especially pain/discomfort and anxiety/depression where only 36% and 23% respectively, reported no problems. The same was found for both the EQ-5D-5L index value and EQ-VAS. This finding is consistent with results from another study among OAT patients in Germany [140]. In addition, in line with previous research, females and increased age reported more overall problems compared to males and those younger than 40 years [152, 260]. Increased age has also been strongly correlated to poor physical HRQoL in another study [140]. In our sample the mean age was 44, which is consistent with an aging OAT population in Norway [41, 159]. Increased age of OAT patients coupled with poorly reported HRQoL, could not only lead to increased demand for health care, but also specialized health care in both primary and secondary settings.

Previous research has demonstrated that HRQoL improved considerably at OAT treatment entry and the first few months [206]. Yet other studies only saw improvements in the beginning of observation or even decline [152, 208, 261]. Our study challenges that belief and is among the first to show that changes in HRQoL, including positive changes, are possible. At one year follow-up, we found significant improvement in overall HRQoL with around half of the OAT patients reported some improvement in HRQoL while around one-third experienced worse HRQoL at one-year follow up, with substantial individual variations. Clearly there is a need for more longitudinal studies on OAT patients to either confirm or dismiss this finding. While health states of OAT patients are so diverse and dynamic, this has implications for personalized patient care, and we belive there is a need for regular assessment of HRQoL as an outcome in OAT programs.

Along with more research, especially clinical trials and studies with longitudinal design as mention above, we need to better understand what drives the extreme and rapid changes in HRQoL in both positive and negative directions among OAT patients. We need to know how to best prevent the large drops in index score and how to increase and maintain the increases in index score over time.

6. Conclusion

This thesis has described the immense burden of disease affecting people with severe SUD. The first study calculated the HCV treatment uptake in the DAA era among patients enrolled in opioid agonist therapy at a population level in both Sweden and Norway. In Sweden annual HCV treatment uptake increased from 3.6% in 2014 to 8.5% in 2017, and 4.5% to 13.6% in Norway. The estimated cumulative HCV treatment uptake at the end of 2017 was thus 28% in Sweden and 31% in Norway, which means that around two-third of OAT patients had yet to receive HCV treatment at the beginning of 2018. There seem to be several challenges and still barriers to treatment with the new and effective medications.

Overall, many individuals reported considerable mental distress and impaired HRQoL. Among people with frequent use of substances, more symptoms of mental health disorders were observed amid those using benzodiazepines cannabis, opioids compared to those with no or less frequent use of these substances. Overall, 65% of the cohort had a mean score above the threshold for symptoms of mental health disorders. Although there were large individual variations in SCL-10 score from baseline to follow-up, no consistent time trends indicated change over time for the whole cohort. While HRQoL was substantially lower compared to the general population, also this study revealed large individual variations in index values, where 43% had a good HRQoL and 5% had extremely poor HRQoL at baseline. At follow-up, improvements in HRQoL were observed across almost all health dimensions. This shows that people with severe SUD is a very heterogeneous population.

These findings emphasize the urgent need for more research, and perhaps more gender-and age-adopted treatment. – and arguably there is a need to include screening for mental health disorders both at treatment entry and during maintenance of opioid agonist therapy in order to improve individualized patient care. In addition, there is a need to implement health-related quality of life as an outcome measure when we evaluate the treatment success in both substance use programs and opioid treatment programs. Overall, quality research including clinical trials, which can address the magnitude of confounders and other biases in this subpopulation, is urgently needed. Only then we can start to integrate the recommendations from the best available evidence along with clinical judgement, patients' values and self-perceived health - in what we collectedly know as evidence-based medicine. *Why should the field of addiction medicine lag behind in innovation and evidence?*

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Appendices

Article 1

Aas CF, Vold JH, Skurtveit S, Odsbu I, Chalabianloo F, Lim AG, Johansson KA, Fadnes LT: ***Uptake and predictors of direct-acting antiviral treatment for hepatitis C among people receiving opioid agonist therapy in Sweden and Norway: a drug utilization study from 2014 to 2017***. *Substance abuse treatment, prevention, and policy* 2020, **15**(1):44

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Uptake and predictors of direct-acting antiviral treatment for hepatitis C among people receiving opioid agonist therapy in Sweden and Norway: a drug utilization study from 2014 to 2017

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Abstract

Background: Treatment with direct-acting antiviral agents (DAAs) offers an opportunity to eliminate hepatitis C virus (HCV) endemic among people who inject drugs (PWID) and people enrolled in opioid agonist therapy (OAT) programs. The objective of this study was to estimate and to compare HCV treatment uptake after the introduction of DAAs among patients receiving OAT in Sweden and Norway. We also aimed to evaluate predictors of DAAs treatment among OAT patients in both countries.

Methods: This observational study was conducted with data from The Swedish Prescribed Drug Register and The Norwegian Prescription Database. We studied dispensed medications to calculate HCV treatment among OAT patients from 2014 to 2017 in Sweden and Norway. HCV prevalence was estimated from primary and secondary sources. Dispensations of medicines from different therapeutic areas, which served as proxy for co-morbidities in 2017, were conditionally adjusted for age, gender, and OAT medications. Logistic regression was used to evaluate these parameters.

Results: In total 3529 individuals were identified with dispensed OAT in the Swedish cohort and 7739 individuals in the Norwegian cohort. HCV treatment was utilized by 407 persons in Sweden and 920 in Norway during the study period. Annual HCV and DAA treatment uptake increased in both countries. The estimated cumulative HCV treatment uptake at the end of 2017 was 31% in Norway and 28% in Sweden. DAA treatment was associated with increased age (aOR 1.8; 95% CI 1.0–3.2) and the dispensation of drugs used for diabetes (aOR 3.2; 95% CI 1.8–5.7) in Sweden. In Norway, lipid modifying agents and antibacterials were associated with decreased odds (aOR 0.4; 95%CI 0.2–0.9, aOR 0.8; 95%CI 0.6–1.0).

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Conclusions: An increase in DAA treatment and HCV treatment uptake was observed among Swedish and Norwegian OAT patients whilst introducing new direct-acting antiviral treatment regimens. However, more than two thirds of the OAT population in Norway and Sweden were untreated at the beginning of 2018. A further scale-up is crucial in order to control and eliminate the HCV endemic among OAT patients.

Keywords: Hepatitis C, Chronic hepatitis C, Treatment uptake, Direct-acting antivirals, Opioid substitution treatment

Background

Treatment of chronic hepatitis C virus (HCV) infection has been subject to vivid changes in the last few years with the introduction of direct-acting antiviral agents (DAAs) [1]. The ambition of any antiviral treatment of HCV infection is elimination of the virus. In that sense, standard treatment prior to 2011 was a combination of pegylated interferon alpha and ribavirin, which saw a sustained virologic response (SVR) in approximately 50 to 56% of patients [1, 2]. SVR is defined as absence of HCV RNA 12 weeks after end of treatment. However, since 2011 various DAAs have become readily available and should make interferon-based therapies almost obsolete. HCV policies including DAA offer countries an opportunity to eliminate HCV endemics, with less side effects, shorter treatment periods and improved adherence as compared to old interferon treatment. Combining two (or three) DAAs have led to a SVR of far beyond 90% also among patients who have been hard to treat in the past [3, 4].

The scale of the HCV endemic among people who inject drugs (PWID) is tragic and is a result of years of failing health policies for vulnerable populations. The HCV prevalence is around 50%, or more, among PWIDs [5, 6], and around 50% among patients on opioid agonist therapy (OAT) [7]. It is estimated that HCV complications will continue to increase within the next few years [8]. DAA treatment has been offered as universal health coverage from 2017 and 2018 in Sweden and Norway, respectively [9, 10]. It seems, however, that the increased accessibility has not benefitted active-PWIDs [11].

The coverage of preventive interventions and harm reduction services varies among PWIDs. Although the distribution of needle and syringe programs is relatively poor [12], opioid treatment programs such as OAT has higher coverage in many countries [13]. OAT has shown to reduce the risk of HCV acquisition [14], and despite ongoing illicit drug use, patients on OAT are achieving high SVR rates [15]. Hence, OAT programs may be a critical intervention for achieving large reductions in HCV transmissions. Several studies have shown that significant reductions in HCV prevalence can be achieved with an adequate increase in HCV treatment uptake [16–18]. Nevertheless, HCV treatment uptake has remained low [19, 20]. In Norway, annual HCV treatment uptake among OAT patients ranged from 1.3 to 2.6% in the period from 2004 to 2013 [20]. HCV treatment uptake, and in particular DAA treatment, among OAT patients in Sweden is unknown. Norway and Sweden share a basic cultural unity, have a comparable socioeconomic and political structure with similar health care systems that are based on the Nordic welfare model [21]. Taking into consideration the potential for HCV disease elimination by publicly funded DAA policies in these countries [9, 13] and the high HCV prevalence among the OAT population, it is essential to calculate the DAA treatment within an OAT delivery platform. Such estimates are important for countries aiming for HCV elimination or endemic control in the near future.

Therefore, this observational study aims to:

1) calculate HCV treatment annually and cumulatively after the introduction of DAAs among patients receiving OAT in Sweden from 2014 to 2017
2) compare DAA treatment between Sweden and Norway among patients receiving OAT from 2014 to 2017 and estimate the HCV treatment uptake
3) evaluate if various dispensed drugs (proxy for comorbidities), age, gender and OAT medication is associated with DAA treatment among OAT patients in Sweden and Norway in 2017

Methods

Study design and data sources

This is an observational study among patients on OAT in Sweden and Norway from 2014 to 2017. Data were extracted from The Swedish Prescribed Drug Register and The Norwegian Prescription Database. The registries cover the entire Norwegian and Swedish populations and record all drugs dispensed from pharmacies. All drugs are classified according to The Anatomical Therapeutic Chemical (ATC) classification system [22]. HCV prevalence data is not readily available for Norway and Sweden. Consequently, we employed primary and secondary sources to model HCV prevalence. Data from the INTRO-HCV study in Norway [23] was used in addition to published data on HCV prevalence among a large cohort of Swedish PWIDs [24]. See additional file 1 for a comprehensive description of methodology and data sources.

Study population and definitions

The study population included all individuals aged 18 to 75 years who received OAT in Sweden and Norway. OAT was defined as being dispensed at least one defined daily dose (DDD) per day per calendar year of buprenorphine, methadone, buprenorphine-naloxone, or levomethadone by summarizing all annually dispensed OAT DDDs divided by 365.25 days.

Moreover, OAT medication per individual was noted as the last dispensation per calendar year. To avoid including other medical indications than OAT, we excluded methadone preparations on the basis of route of administration (injections and tablets), and introduced a dosage criteria in order to make sure that actual patients on OAT were captured. The dosage criteria was set at minimum one DDD daily throughout each calendar year as an inclusion criteria. The study populations were thus chosen annually for both countries and it was possible for an individual to be included in more than one calendar year. See additional file 2 for a flow chart. ATC/DDDs according to 2017 [25] were used to quantify the dispensed OAT medications. A more detailed description of OAT and HCV treatment in Sweden and Norway is provided in additional file 3.

Calculating HCV and DAA treatment and estimating treatment uptake

HCV treatment was defined as being dispensed either one or more types of pegylated interferon alpha in combination with ribavirin, or one or more of the DAAs per calendar year during the study period (additional file 4). For each country, the annual HCV treatment rates were calculated by dividing the number of individuals with dispensed HCV treatment by the number of individuals on OAT. The cumulative HCV treatment frequency, which is the sum of successive years of treatment, was then calculated as the proportion of patients with dispensed HCV treatment at some point during the study period. Similarly, DAA treatment was calculated by dividing the number of OAT patients with at least one dispensation of DAA by the total number of OAT patients per year, which represents the annual prevalence of DAA use among OAT patients. Using primary and secondary sources, along with several assumptions, as described in detail in additional file 1, we derived a formula to estimate the chronic HCV prevalence in Sweden and Norway as follows;

$$\textit{Expected Number of Chronic HCV} = ((\mathbf{1}-\boldsymbol{\delta})*[\boldsymbol{\phi}*\boldsymbol{\pi}_{\boldsymbol{PWID}}+(\mathbf{1}-\boldsymbol{\phi})*\boldsymbol{\pi}_{\boldsymbol{NonPWID}}]*\boldsymbol{N})-\boldsymbol{\tau}$$

where N is the size of the study population, δ is the rate of spontaneous HCV clearance, ϕ is the proportion of OAT patients who are PWID, π_{PWID} and $\pi_{NonPWID}$ are the anti-HCV prevalence estimates among PWID and non-PWID, respectively, and τ is the number of HCV treatments given. Using the above formula, we calculate the expected number of chronic HCV infections in 2014–2017 for Norway and Sweden, with uncertainty in this quantity arising only from the uncertainty in spontaneous clearance. The chronic HCV prevalence was then calculated by dividing the expected number of chronic HCV infections by the total population size in that particular year and setting (i.e. Norway or Sweden). HCV treatment uptake was then estimated by dividing the HCV treatments in each year by the estimated number of chronic HCV infections in that same year, yielding a percentage of chronic HCV infections that were treated per year. The cumulative HCV treatment uptake was then calculated as the sum of HCV treatment uptake across years.

Potential predictors associated with DAA treatment uptake were determined a priori and included OAT medication (methadone/levomethadone vs. buprenorphine-based), age, gender and various dispensed drugs (yes vs. no) from different therapeutic areas that were used as proxies for comorbidities. All dispensations were recorded at the second ATC level (therapeutic subgroup), except for drugs affecting the nervous system.

Statistical analyses

All data analyses was conducted in STATA SE 16.0 (StataCorp, TX, USA). Descriptive data was presented as frequencies, percentages, and means, with corresponding 95% confidence intervals where appropriate. Logistic regression was used to estimate whether DAA treatment uptake was associated with gender, age, OAT medication, and dispensations of other drugs in 2017. Statistical significance was set at the $p < 0.05$ level.

Data handling and ethical considerations

All data were received pseudonymised from registry administrators and subsequently analyzed, therefore, no written consent was obtained from any of the individuals in the study. The study was approved by the Regional Ethical Review Committee in Stockholm, Sweden, (no 2018/2080–31/1) and the Regional Committee for Ethics in Medical Research (no. 2018/939) in Norway. Furthermore, the study was conducted in accordance with the Helsinki Declaration and as an observational study in accordance with international accepted STROBE guidelines [26].

Results

Basic characteristics

In Sweden, 3529 individuals receiving OAT were identified. Around 70% were male, with a mean age of approximately 44 years and 45 years in 2014 and 2017, respectively. See additional file 5. The majority of the

OAT patients were treated with buprenorphine-based OAT medication (52% in 2014 and 56% in 2017). Altogether 407 individuals in the Swedish cohort received HCV treatment during the study period. In Norway, 7739 individuals were identified during the study period from 2014 to 2017. 70% were male and mean age was 44 in 2014 and almost 46 years in 2017. 55% received treatment with a buprenorphine-based OAT medication in 2017. Altogether 920 individuals in the Norwegian cohort received HCV treatment during the study period (Table 1).

Estimated HCV prevalence and treatment uptake

For Sweden, chronic HCV prevalence was estimated to range from 55.6% (uncertainty interval (UI) 53.3 to 58.8) in 2014, to 53.1 (UI: 50.8–56.3) in 2017. In Norway, prevalence was estimated from 54.4 (UI: 52.1–57.5) in 2014 to 50.0 (UI: 47.7–53.1) in 2017. The cumulative HCV treatment uptake was thus projected to be 31% in Norway and 28% in Sweden for the study period (Table 2). Unadjusted treatment rates for both countries are shown in additional file 6, (Fig. 1).

Dispensations and predictors of DAA treatment in 2017

OAT patients in Norway and Sweden were stratified according to whether they received DAA treatment or not, and compared in 2017. In the Norwegian cohort 366 individuals (6.6%) received DAA treatment whereas in Sweden, 123 (4.5%) individuals received treatment. Variations in treatment within countries were few, except for drugs used for diabetes (Table 3). However, among individuals receiving DAA treatment in Norway, half were also dispensed benzodiazepines compared to only 15% in Sweden. In contrast, 24 and 31% of the Swedish patients treated with DAA also received dispensations of z-hypnotics and antidepressants compared to 15 and 20% in the Norwegian cohort, respectively.

In a logistic regression model (additional file 7), DAA treatment was associated with increased age (adjusted odds ratio (aOR) 1.8; 95% CI 1.0–3.2) and dispensation of drugs used in diabetes (aOR 3.2; 95% CI 1.8–5.7) in Sweden. Dispensations of lipid modifying agents and antibacterials were associated with decreased odds (aOR 0.4; 95% CI 0.2–0.9, aOR 0.8; 95% CI 0.6–1.0) of receiving DAA treatment in Norway. Moreover, being female was associated with decreased odds in both countries (S: aOR 0.6; 95% CI 0.3–0.9, N: aOR 0.8; 95% CI 0.6–1.0).

Table 1 Basic characteristics of patients receiving OAT in 2014 and 2017 in Sweden and Norway

	2014		*2017*	
Country	*Sweden*	*Norway*	*Sweden*	*Norway*
OAT studypopulation, n	2663	6057	2739	5545
Gender, n (%)				
Male	1911 (72)	4266 (70)	1961 (72)	3870 (70)
Female	752 (28)	1791 (30)	778 (28)	1675 (30)
Age, n (%)				
18–35	671 (25)	1219 (20)	647 (24)	878 (16)
36–45	817 (31)	2181 (36)	819 (30)	1747 (32)
46–55	744 (28)	2044 (34)	713 (26)	1998 (36)
56–75	431 (16)	613 (10)	560 (20)	922 (17)
Mean age (SD)				
Male	44 (10)	44.1 (9)	45.1 (11)	46.1 (9)
Female	43.5 (11)	43.1 (9)	44.3 (12)	45.2 (10)
OAT medication, n (%)[a]				
Methadone/ levomethadone	1267 (48)	2810 (46)	1198 (44)	2504 (45)
Buprenorphine	875 (33)	2049 (34)	1075 (39)	2190 (40)
Buprenorphine/naloxone	521 (20)	1198 (20)	466 (17)	851 (15)

Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD)
OAT Opioid agonist therapy, *SD* Standard deviation
[a]Last registered OAT medication each calendar year

Discussion

Amid the hepatitis C endemic among PWIDs and individuals enrolled in OAT programs in Sweden and Norway, the study has revealed a large increase in DAA treatment uptake among OAT patients in both countries from 2014 to 2017. As such, our findings reflect the immense progress, which has been achieved in HCV treatment during the recent years with almost a complete shift from interferon-based treatment to solely treatment with DAAs among OAT patients. The cumulative frequency of HCV treatment in the OAT population between 2014 and 2017 was estimated to be 28 and 31%% in Sweden and Norway, respectively.

Despite substantial increase in HCV treatment uptake in advanced health systems like Sweden and Norway, as found in our study, the treatment uptake is still too low and progress too slow globally [20, 28, 29]. Treatment demand has soared after the introduction of DAAs, especially among former PWIDs [11], while people who are still using drugs actively have seemingly not been fully able to benefit from the increased accessibility [11]. In order to reach universal health coverage of DAAs and elimination of HCV, more efforts are needed in countries. Coverage of DAAs varied substantially across European countries, ranging from 0.6 to 10.2% in 2015 [30]. Restrictions in DAA access policies may explain these variations. Among European countries, England, Hungary, Croatia and Slovakia experienced one of the most restricted access policies to DAA treatment compared to Poland, Ireland, the Netherlands, France and Germany, which had the least restrictions during the study period [31]. Our findings saw Sweden with a greater DAA treatment uptake than Norway in 2015, and roughly in the

Table 2 Annual and cumulative estimated HCV treatment uptake in Norway and Sweden among OAT patients 2014–2017

	2014		*2015*		*2016*		*2017*	
Country	Norway	Sweden	Norway	Sweden	Norway	Sweden	Norway	Sweden
HCV treatment n (overall)	148	54	178	105	216	124	378	124
Study population n,	6057	2663	6005	2640	5537	2683	5545	2739
HCV treatment % (95% CI)	*2.4 (2.1–2.8)*	*2.0 (1.5–2.6)*	*3.0 (2.5–3.4)*	*4.0 (3.2–4.7)*	*3.9 (3.4–4.4)*	*4.6 (3.8–5.4)*	*6.8 (6.2–7.5)*	*4.5 (3.8–5.3)*
Expected proportion of OAT patients who are not PWID, n[a]	303	133	300	132	276	134	277	137
Expected Anti-HCV, weighted by PWID status, n[b]	4651	2075	4612	2057	4252	2091	4258	2135
Expected chronic HCV after spontaneous clearance, n (UI)[c]	3442 (3303–3628)	1536 (1474–1619)	3413 (3274–3597)	1523 (1461–1605)	3147 (3019–3317)	1547 (1485–1631)	3151 (3023–3321)	1580 (1516–1665)
Expected chronic HCV after treatment, n (UI)	3294 (3155–3480)	1482 (1420–1565)	3235 (3096–3419)	1418 (1356–1500)	2931 (2803–3101)	1423 (1361–1507)	2773 (2645–2943)	1456 (1392–1541)
Expected chronic HCV after spontaneous clerance and treatment, % (UI)	54.4 (52.1–57.5)	55.6 (53.3–58.8)	53.9 (51.6–56.9)	53.7 (51.4–56.8)	52.9 (50.6–56.0)	53.1 (50.7–56.2)	50.0 (47.7–53.1)	53.1 (50.8–56.3)
Estimated HCV treatment uptake % (UI)	***4.5 (4.3–4.7)***	***3.6 (3.5–3.8)***	***5.5 (5.2–5.7)***	***7.4 (7.0–7.7)***	***7.4 (7.0–7.7)***	***8.7 (8.2–9.1)***	***13.6 (12.8–14.3)***	***8.5 (8.0–8.9)***
Estimated HCV cumulative treatment uptake % (UI)	***4.5 (4.3–4.7)***	***3.6 (3.5–3.8)***	***10.0 (9.5–10.4)***	***11.1 (10.5–11.5)***	***17.4 (16.4–18.1)***	***19.8 (18.7–20.7)***	***31.0 (29.3–32.4)***	***28.3 (26.7–29.6)***

Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD), Intro-HCV = Integrated treatment of hepatitis C study, Kåberg et al. [24]: Prevalence of hepatitis C and pre-testing awareness of hepatitis C status in 1500 consecutive PWID participants at the Stockholm needle exchange program
Micallef et al. [27]: Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies.
OAT Opioid agonist therapy, *HCV* Hepatitis C virus infection, *CI* Confidence interval, *UI* Uncertainty interval
Anti-HCV Antibodies to hepatitis C virus, *PWID* People who inject drugs
[a]Expected non-PWIDs among OAT patients set to 5%
[b]Expected Anti-HCV among PWID in Norway 80.8%, expected Anti-HCV among PWID in Sweden 82%, expected Anti-HCV among non-PWID in both Norway and Sweden is 0.7%
[c]Expected spontaneous clearance 26% (22–29%)
For more comprehensive details on sources and model calculation, see Additional file 1

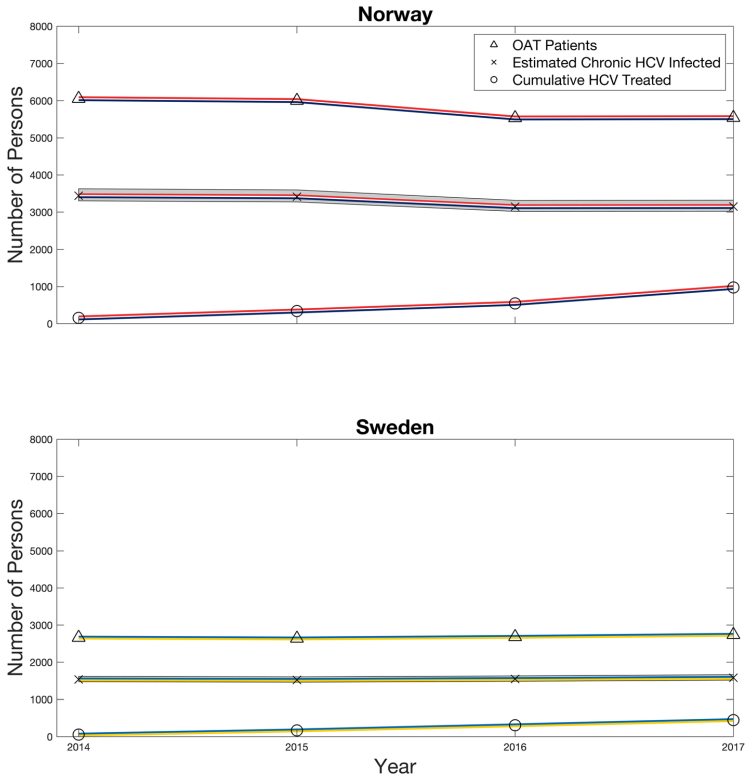

Fig. 1 Estimated HCV treatment uptake in Norway and Sweden among OAT patients from 2014 to 2017. HCV = hepatitis C virus infection, OAT = opioid agonist therapy. Sources OAT and HCV treatment: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD). Prevalence: Intro-HCV = Integrated treatment of hepatitis C study, Kåberg et al. [24]: Prevalence of hepatitis C and pre-testing awareness of hepatitis C status in 1500 consecutive PWID participants at the Stockholm needle exchange program, Micallef et al. [27]: Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. For more comprehensive details on sources and model calculation, see additional file 1.

middle among its European counterparts, similar to the last Scandinavian country, Denmark, at close to 4% [30]. Another reason for the low treatment uptake might be concerns about treatment compliance among PWIDs and OAT patients; however, this seems unwarranted as both good adherence and high SVR rates in this group have been documented in several randomized controlled trials [32, 33].

Arguably, poor treatment uptake of DAAs globally and a hard to reach population opts for countries to consider alternative health service delivery platforms. Addressing barriers to HCV treatment and testing are important. Between 60 and 70% of people enrolled in various opioid treatment programs are offered onsite testing for HCV [29], which is too low. OAT programs could thus benefit from introducing universal HCV testing and linkage to care in OAT settings. Perhaps OAT programs, together with infectious disease and gastroenterology/hepatology specialists, could explore any opportunities for non-specialists to dispense DAA regimens to increase treatment uptake. Psychoeducation to improve knowledge among OAT patients regarding treatment, possible side effects and HCV infection seems to improve both SVR rates and adherence to treatment and should also be considered implemented in an OAT setting [34]. Furthermore, current drug use or any fear of reinfection in patients already treated for HCV should not hinder treatment with DAA. Reinfections seems to be low (1–5%), even if treated patients return to active drug use [35].

The differences between Sweden and Norway are interesting and relevant for other settings. Prevalence of anti-HCV among PWIDs seems consistently higher in Sweden compared to Norway [36, 37]. Coverage of OAT is higher in Norway than Sweden. Waal et al. estimate an overall OAT coverage of around 60% among people

Table 3 Dispensed drugs to patients receiving OAT and OAT/DAAs in Norway and Sweden in 2017

Year	*2017*		*2017*	
Country	Norway		Sweden	
OAT study population, n	5543		2739	
	Only OAT	DAA + OAT	Only OAT	DAA + OAT
	5177	366	2616	123
Drugs	No. (%)	No. (%)	No. (%)	No. (%)
Drugs used in Diabetes	197 (4)	14 (4)	161 (6)	18 (15)
Antithrombotic agents	529 (10)	35 (10)	217 (8)	8 (7)
Cardiovascular system drugs [a]	842 (16)	67 (18)	622 (24)	37 (30)
Lipid modifying agents	271 (5)	10 (3)	121 (5)	4 (3)
Sex hormones and modulators of genital system	654 (13)	51 (14)	430 (16)	14 (11)
Antibacterials for systemic use	1901 (36)	112 (31)	915 (35)	33 (27)
Anti-inflammatory and ant-rheumatic products	1155 (22)	69 (19)	570 (22)	25 (20)
Drugs for obstructive airway diseases	1048 (20)	68 (19)	410 (16)	14 (11)
Benzodiazepines[b]	2368 (46)	181 (50)	402 (15)	19 (15)
Hypnotics and sedatives[c]	797 (15)	54 (15)	691 (26)	30 (24)
Antiepileptics[d]	823 (16)	57 (16)	629 (24)	25 (20)
Antidepressants[e]	960 (19)	73 (20)	1008 (39)	38 (31)
Antipsychotics[f]	1401 (27)	85 (23)	602 (23)	28 (23)

Source: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD). All drugs on ATC Level 2, except under Nervous system. See Supplement Table S2
OAT Opioid agonist therapy, *DAA* Direct-acting antiviral agents
[a]C01, C02, C03, C07, C08, C09
[b]N05BA01, N05BA04, N05BA06, N05BA12, N05CD02, N05CD03, N05CD08, N03AE01
[c]N05CF01 and N05CF02
[d]N03AA, N03AB, N03AF, N03AG, N03AX
[e]N06AA, N06AB, N06AF, N06AG, N06AX
[f]N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN, N05AX

with opioid dependence in Norway [38] compared to 10 to 50% OAT coverage in Sweden [39]. Differences in OAT eligibility criteria could explain lower coverage of OAT in Sweden as compared to Norway. Norway altered its OAT guidelines in 2010, making opioid addiction the absolute criteria for inclusion and being retained in treatment, and there is a high threshold for discharging patients from OAT. However in Sweden, current OAT guideline has lower thresholds for OAT cessation in the case of repeated illicit drug use [7, 40]. The two populations may therefore be different and Swedish OAT patients could have less ongoing drug use, which could lower the risk of HCV and increase the chance for HCV treatment success. However, the Norwegian strategy could be more effective at a population level since hard to reach groups are included and illicit drug use is not considered as an exclusion criterion for OAT.

With the provision of DAA treatment available for all Swedish and Norwegian patients, it may be tempting to argue that this is the beginning of the end for the HCV endemic. In addition to OAT, maintaining a high coverage of needle and syringe availability in these countries, together with continued scale-up of DAA treatment, it may be possible to reduce incidence by 90% by 2030 as shown in a modeling study from the UK [41]. On the other hand it may still seem embryonic as there may be shortcomings in current HCV surveillance systems. HCV has been notified to The Norwegian Surveillance System for Communicable Diseases since 1990, yet, there has been no distinction between anti-HCV, HCV RNA or HCV core antigen reporting before 2016 [20]. Hence, accurate HCV prevalence and incidence data prior to 2016 are not readily available. Furthermore, in order to eliminate HCV as a public health threat by 2030, which both countries have embraced, a coherent and structured national plan is essential. The Norwegian Health Ministry introduced a national hepatitis C strategy in 2016, and was later revised in 2018, which focuses on DAA treatment, HCV surveillance, and prevention, and aims to reduce HCV incidence by 90% within 2023 [42]. On the contrary, an ambitious national Swedish hepatitis C plan has not yet been established [43].

Our findings suggest few inter-country differences in dispensed drugs among those treated with DAAs and those not, except for drugs used for diabetes in the Swedish cohort, which was significantly higher and demonstrated a

strong association with DAA treatment. Chronic HCV might be a risk factor for developing immune system disorders, heart disease and diabetes, especially diabetes type II as the viral infection may increase insulin resistance [44, 45]. This finding was not mirrored in the Norwegian cohort. Dispensed drugs can serve as a proxy for comorbidity and it is well-established that both somatic and especially mental illness are underdiagnosed and undertreated among individuals with substance use disorders [46]. This does not explain the vast differences we observed among dispensations of benzodiazepines, z-hypnotics, and antidepressants comparing Sweden and Norway. Older patients are more likely to have cirrhosis and longer HCV treatment courses compared to younger patients. A reason for the observed age difference may be that the younger patients are usually harder to reach due to an unstable life situation and drug abuse related behavior. Similarly, the analyses point toward women being less likely to be treated for HCV, however, this could be due to women being underrepresented in services.

Strengths and limitations

The national prescription registries capture large populations, and as such, provide researchers with precise and near complete databases. The main strength of this study is that it offers a large sample of OAT patients being treated for HCV.

However, this study has several limitations. As the patients were included each calendar year with a dosage criteria, a patient who commenced treatment late or quit early during the year may not obtain sufficient exposure to be included in that particular year. Moreover, OAT treatment in Norway and Sweden is not uniform. Most individuals are dispensed OAT medications at pharmacies while others receive the drugs at OAT outpatient clinics, which means that those latter patients are not identified in this study. OAT and HCV treatment administered to hospitalized and institutionalized patients are also not recorded in the registries. In addition, DDD does not necessarily reflect the prescribed daily dose.

Furthermore, HCV treatment uptake data was not linked on an individual level to diagnosis codes of HCV according to International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) or the International Classification of Primary Care (ICPC), rather, it was estimated from published reports and modelled where adequate data sources were missing. Thus, there is some uncertainty in the denominator of people with HCV in need of treatment. The predictors for DAA treatment were limited to the main dispensed drugs and sociodemographic variables and so did not fully acknowledge that there could be other vital reasons why access to DAAs would be limited in this group of patients.

Finally, PWID are a heterogeneous group of individuals, and one should be careful not to generalize OAT patients to include all PWIDs.

Conclusion

This study indicates a large scale-up in DAA treatment among Swedish and Norwegian OAT patients. Cumulative HCV treatment uptake was around one-third from 2014 to 2017 in both countries, attributed by a complete shift to DAA treatment regimens. Amidst a HCV endemic among PWIDs, it seems that two-thirds of OAT patients in need of treatment were untreated in the beginning of 2018. Coupled with the prospect of HCV elimination, there is a need for further scale-up of the most effective HCV treatment strategies, by identifying possible predictors of treatment and to establish more accurate surveillance systems in order to provide better care to this group of marginalized people.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13011-020-00286-2.

Additional file 1. *Methodology description: estimating chronic hepatitis C (HCV) prevalence among people on opioid agonist therapy (OAT) in Norway and Sweden:*

Additional file 2. *Flowchart of study populations in Norway and Sweden from 2014 to 2017.* According to World Health Organization Collaborating Centre for Drug Statistics Methodology, ATC/DDD Index. OAT = opioid agonist therapy, DDD = defined daily dose. The DDDs are the assumed average maintenance dose per day for a drug used for its main indication. *Therapeutic subgroup, chemical subgroup, or chemical substance. **Including clonazepam. ***Excluding clonazepam

Additional file 3. *Opioid agonist therapy and hepatitis C treatment in Norway and Sweden*

Additional file 4. *Anatomical Therapeutic Chemical Classification and defined daily dose for OAT medications.* OAT = opioid agonist therapy; SD = standard deviation; Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD). *Last registered OAT medication each calendar year

Additional file 5. *Basic characteristics of patients receiving OAT from 2014 to 2017 in Sweden and Norway.* OAT = opioid agonist therapy, HCV = hepatitis C virus infection, DAA = direct-acting antiviral agent, CI = confidence interval. Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD). *Exluding Ribavirin (J05AP01)

Additional file 6. *Annual and cumulative DAA and HCV treatment among patients receiving OAT from 2014 to 2017.* OAT = opioid agonist therapy, DAA = direct-acting antiviral agent, OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval. Source: The Norwegian Prescription Database (NorPD) and The Swedish Prescribed Drug Register (SPDR). *N05BA01, N05BA04, N05BA06, N05BA12, N05CD02, N05CD03, N05CD08, N03AE01. **N05CF01 and N05CF02. ***N03AA, N03AB, N03AF, N03AG, N03AX. ****N06AA, N06AB, N06AF, N06AG, N06AX. *****N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN, N05AX. For ATC codes see additional file 4

Additional file 7. *Logistic regression on factors associated with DAA treatment among patients receiving OAT in 2017.* OAT = opioid agonist therapy. Sources: The Swedish Prescribed Drug Register (SPDR) and the Norwegian Prescription Database (NorPD). *Methadone, levomethadone, buprenorphine and buprenorphine-naloxone

Abbreviations

OAT: Opioid agonist therapy; DAA: Direct-acting antiviral agents; HCV: Hepatitis C virus; PWID: People who inject drugs; NorPD: The Norwegian Prescription Database; SPDR: Swedish Prescribed Drug Register; ATC: Anatomical Therapeutic Chemical classification system; DDD: Defined daily dose; Anti-HCV: Antibodies to the Hepatitis C virus; SVR: Sustained virologic response; INTRO-HCV: Integrated treatment of hepatitis C study

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Authors' contributions

This observational study was led by CFA in terms of study design, analyzes, drafting and writing the article. All authors contributed to the conception, writing, and revising the draft(s) critically. All authors have read and approved the version to be published.

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Availability of data and materials

Supplemental tables, figure and data sources in this observational study are available in this published article and its additional files.

Ethics approval and consent to participate

The study was approved by the Regional Ethical Committee (no. 2018/939), Norway, on June 19, 2018 and by the Regional Ethical Review Committee in Stockholm (no 2018/2080–31/1), Sweden, on November 14, 2018. No informed consent from the participants was required.

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. None of the other authors have competing interests.

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Article 2

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Substance use and symptoms of mental health disorders: a prospective cohort of patients with severe substance use disorders in Norway

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Abstract

Background: There is high co-occurrence of substance use disorders (SUD) and mental health disorders. We aimed to assess impact of substance use patterns and sociodemographic factors on mental health distress using the ten-item Hopkins Symptom Checklist (SCL-10) over time.

Methods: Nested prospective cohort study of 707 participants with severe SUD across nine opioid-agonist-therapy outpatient clinics and low-threshold municipality clinics in Norway, during 2017–2020. Descriptive statistics were derived at baseline and reported by means and standard deviation (SD). A linear mixed model analysis was used to assess the impact of substance use patterns and sociodemographic factors on SCL-10 sum score with beta coefficients with 95% confidence intervals (CI).

Results: Mean (SD) SCL-10 score was 2.2 (0.8) at baseline with large variations across patients. We observed more symptoms of mental health disorders among people with frequent use of benzodiazepines (beta 3.6, CI:2.4;4.8), cannabis (1.3, CI:0.2;2.5), opioids (2.7, CI:1.1;4.2), and less symptoms among people using frequent stimulant use (–2.7, CI:-4.1;-1.4) compared to no or less frequent use. Females (1.8, CI:0.7;3.0) and participants with debt worries (2.2, CI:1.1;3.3) and unstable living conditions (1.7, CI:0.0;3.3) had also higher burden of mental health symptoms. There were large individual variations in SCL-10 score from baseline to follow-up, but no consistent time trends indicating change over time for the whole group. 65% of the cohort had a mean score > 1.85, the standard reference score.

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Conclusions: People with SUD have a considerable burden of mental health symptoms. We found no association between substance use patterns and change in mental health symptoms over time. This could suggest that the differences observed were indicating flattening of effects or self-medication to a larger degree than medication-related decline in mental health. This call for better individualized mental health assessment and patient care.

Keywords: Substance use disorder, Substance abuse, Mental disorder, Psychological distress, Mental health problems, Opioid substitution treatment, Opioid dependence

Background

Substance use disorders (SUD) contribute to 11.8 million deaths globally per year and 1.5% of the global disease burden [1]. It is estimated that 2% of the world population has a SUD, with some countries reporting a prevalence of SUD greater than 5% [1]. More than half of the people with a SUD will experience a mental health disorder at some point during their lives [2, 3], yet it is less clear whether mental health disorders develop mostly as a consequence of substance use or vice versa [4]. The co-occurrence of SUD and mental health disorders may be attributed to shared genetic vulnerability and pathophysiological processes possibly related to specific neurotransmitter systems [5, 6]. Even though most research has been in relation to amphetamines, cannabis and alcohol, comorbid mental health symptoms are probably also the case for the more severe forms of SUD like opioid dependence. However, less is known about the prevalence, predictors and change over time of mental health symptoms in these patient groups, limiting optimal clinical care. It has been suggested that these comorbidities often are under-recognized in clinical settings [7, 8].

Among people with SUD in Europe, the most prevalent mental health disorders in epidemiological studies are personality disorders (51%), mood disorders (35%), attention-deficit hyperactivity disorder (30%) and anxiety disorders (27%) [9–12]. Poor quality of life [13], concurrent drug use, including benzodiazepine misuse (e.g. without prescription, higher frequency or dosage than prescribed), is common and prevalent among SUD and people enrolled in opioid agonist therapy (OAT) [14, 15]. Some research suggest that benzodiazepine misuse are associated with other substance use, aggressive behavior and worsening mental health symptoms and disorders [16, 17]. Having a SUD, or a mental health disorder, is also likely to increase the risk for misuse of opioids [18, 19]. Opioid dependence is the most severe SUD, and of all illegal drugs, opioids represents the most fatal risk factor, the highest disease burden and most urgent demand for treatment [20, 21]. In addition, substance use patterns of cannabis and simulants especially frequent use, are found to be associated with residual cognitive impairment and poor mental health [22–24].

Attention to mental health symptoms could perhaps better facilitate and optimize individualized mental health care and SUD treatment to these marginalized and vulnerable populations in low-threshold settings and OAT programs. It is therefore vital to identify and assess mental health among the SUD population, as the co-occurrence of SUD and mental health disorders are likely to be underserved by current mental health systems [25, 26].

The aims of this prospective cohort study was to examine prevalence and change over time of mental health symptoms using the ten-item Hopkins Symptom Checklist (SCL-10) among people with severe substance use disorders (SUD) in Norway. In addition, the study aimed to assess potential predictors of mental health symptoms and change in symptom burden over time from substance use patterns and injecting use while also adjusting for level of education, living conditions, age and gender.

Methods

Study design and setting

This study is a nested prospective cohort study linked to the multicenter INTRO-HCV study [27]. The data was collected from May 2017 until July 2020 as part of an annual health assessment among people with SUD in nine OAT outpatient clinics in Bergen and Stavanger and two low-threshold municipality clinics in Bergen. The OAT clinics have implemented an integrated treatment and care model where patients are followed-up on a near daily basis by general and specialized nurses, psychologists and physicians who are under specialization- or specialized in addiction medicine. Buprenorphine-based and methadone are the two main OAT medications [28]. People with SUD in the municipality clinics are followed-up by social workers, general nurses and physicians specialized in family medicine. The INTRO-HCV study have employed trained research nurses who collected and completed the structured patient interviews, which were recorded in a health register using an electronic data collection software (CheckWare).

Study sample

The study sample was comprised of two groups of patients; individuals diagnosed with opioid dependence

(F11.2) according to World Health Organization's International Classification of Diseases version 10 (ICD-10) [29], which were enrolled in OAT during the study period and accounted for 83% of the total study sample at baseline. The other participants were recruited from low-threshold municipality clinics among people who inject drugs. For the purpose of this paper, a SUD was defined as harmful use of, or dependency of a substance, and a *severe SUD* was defined as dependency of one or more substances. All included individuals were 18 years or older at time of inclusion and signed a written informed consent to partake in the study. Altogether 1042 SCL-10 measurements were included from 707 participants. Of the 707 participants with SCL-10 measures at baseline and 268 (38%) were included in a follow-up assessment with 67 (10%) having at least three annual measuring points. The mean time between SCL-10 measurements was 364 days (standard deviation (SD) 133). Table 1 shows details on clinical and sociodemographic characteristics of the study sample.

Assessment

Measuring mental health status: Hopkins symptom check list (SCL-10).

Table 1 Basic characteristics of study sample

Participants, n (%)	Baseline (n = 707)	Follow-up (n = 268)
Gender		
Male	500 (71)	208 (78)
Female	207 (29)	60 (22)
Age, n (%)		
18–29	83 (12)	25 (9)
30–39	203 (29)	71 (26)
40–49	217 (31)	87 (32)
50–59	161 (23)	71 (26)
≥ 60	43 (6)	14 (5)
Mean (SD)	43 (11)	45 (10)
Highest education completed, n (%)		
Not completed lower secondary school	41 (6)	15 (6)
Completed lower secondary school (9 years)	309 (44)	128 (48)
Completed upper secondary school (12 years)	285 (40)	99 (37)
Completed under or postgraduate studies (≥ 12 years)	72 (10)	26 (10)
Current living conditions, n (%)		
Stable (owned, rented or incarcerated)	619 (88)	242 (90)
Unstable (homeless, with family/friends)	88 (12)	26 (10)
Worrying debt situation	292 (41)	116 (43)
Participants enrolled in OAT, n (%)	590 (83)	248 (93)
OAT medications of those; n (%)		
- Methadone	224 (38)	110 (44)
- Buprenorphine-based	357 (61)	134 (54)
OAT treatment ratio*, mean (SD)	0.9 (0.4)	0.9 (0.3)
Injecting and frequent substance use past 12 months, n (%)		
Injected at least once	352 (54)	142 (53)
Alcohol	165 (25)	67 (25)
Cannabis	329 (50)	145 (55)
Stimulants (amphetamine/methamphetamine/cocaine)	183 (28)	73 (27)
Opioids (other than OAT)	103 (16)	29 (11)
Benzodiazepines	248 (38)	104 (39)

SD = standard deviation, OAT = Opioid agonist therapy,
*OAT ratio = ratio between daily OAT medication dose divided by expected mean daily dose; for buprenorphine 18 mg, buprenorphine-naloxone 18/4.5 mg or methadone 90 mg
Frequent substance use was defined as using substance at least weekly during the past 12 months

The SCL-10 is a structured and self-administrated questionnaire, designed to measure symptoms of mental health disorders and psychological distress, and is widely used for both clinical and epidemiological purposes [30–32]. The SCL-10 involves ten items (suddenly scared for no reason, feeling fearful, faintness, dizziness or weakness, feeling tense, blaming yourself, difficulties falling asleep, feeling of worthlessness, feeling blue, feeling hopeless, and feeling everything is an effort), which are each scored on four dimensions from *not bothered at all* (item score = 1) to *extremely bothered* (item score = 4). Scores were summed and divided by the number of items answered to derive the mean item score. Mean scores vary between one and four, where the latter assumes *extremely bothered*. SCL-10 mean item scores were used for descriptive analyses while SCL-10 sum scores were used in linear mixed model (LMM) analyses. Furthermore, the mean item scores were calculated by gender, age, level of education, and living conditions at baseline. By introducing a cut-off point one can interpret the proportion of the respondents with symptoms of mental health disorders. A mean score of 1.85 for SCL-10 has been recommended as a threshold for indicating substantial mental health distress [31].

Study variables; baseline, OAT, clinical and sociodemographic factors

Baseline was defined as the time when the first SCL-10 measure was completed upon the participant's first annual health assessment. Subsequent SCL-10 measures at the next health assessment(s) were listed chronologically and included as follow-up. Being on OAT was defined as receiving either buprenorphine-based or methadone medication at baseline. Moreover, the OAT ratio, which corresponds to the received dose of OAT medication per day divided by expected mean dose (buprenorphine 18 mg or methadone 90 mg) according to World Health Organization [33], was calculated per OAT patient. For the clinical factors we defined *injecting substances* as having injected any substance during the last 12 months, and *frequent substance use* as using a substance more than once weekly during the last 12 months according to the subcategories of *alcohol*, *cannabis*, *stimulants* (amphetamine/methamphetamine/cocaine), *opioids* (non-OAT), and *benzodiazepines* (including z-hypnotics).

Statistical analysis

All descriptive analyses were performed using STATA/SE 16.0. Expectation-maximization (EM) imputation and LMM analyses were performed in IBM SPSS version 26.0. Statistical significance was set at the $p < 0.05$ level. Missing values of SCL-10, clinical and sociodemographic variables, which included substance use, injecting substance use, educational level, worrying debt situation, and living conditions were assumed to be *missing at random* when performing EM imputation. There were missing values for 3.4% of these values, which were subsequently replaced with the estimated values by EM imputation according to Enders (2010) [34].

A LMM analyses were used to evaluate the impact of clinical and sociodemographic factors on the SCL-10 sum score. Time was defined as years from baseline Firstly, we ran a LMM analysis where each defined predictor variable was set against time, to assess whether the predictor variable changed over time. There were no clinical significant changes in these variables when analyzed separately as outcome variables – with the time variable being the exposure variable (data not shown). Thus, these predictor variables were included as constant and time-independent variables in further analyses. Secondly, a new LMM analysis was generated where these time-independent predictor variables were set against the SCL-10 sum score being the outcome variable. In addition, we added a time interactional to each predictor variable to investigate if time impacted changes of SCL-10 given each predictor. The predictor variables, on the baseline level and change in SCL-10 sum score, represented as main effects and interaction effects with time. The model was a random intercept fixed slope model with restricted maximum likelihood set as the estimator. This model uses all available data in the outcome variable.

Results

Basic characteristics of the study sample

Seventy-one percent of the study sample were male, mean (SD) age of 43 (11) at baseline and 45 (10) at follow-up for the whole cohort (Table 1). Approximately 40% had completed upper secondary school. Most participants (88%) had a stable living condition and 41% had a concerning debt situation. Eighty-two percent of the study sample was in OAT, of which 61 and 38% received buprenorphine-based medication and methadone, respectively. Over half had injected substances at least once during the last year, while 71% reported frequent substance use; most prevalent substances being cannabis (50%) and benzodiazepines (38%).

SCL-10 scores at baseline and follow-up

The mean (SD) of the SCL-10 item scores was 2.2 (0.8) (Table 2) at baseline. The distribution was sharply-peaked (kurtosis: 2.2) and slightly right-skewed (skewness: 0.4). The lowest mean (SD) item score (SD) was found for *suddenly scared for no reason* at 1.9 (1.1) and the highest score 2.5 (1.2) for *difficulty in falling asleep* (Fig. 1 and Additional File 1). Overall, females reported

Table 2 Baseline SCL-10 mean item scores and standard deviation (SD) by gender, age and sociodemographic factors

Baseline n = 707	SCL-10	
	Mean	SD
Total	**2.22**	**0.76**
Gender, n 707		
Male	2.17	0.76
Female	2.32	0.75
Age, n 707		
18-29	2.31	0.78
30-39	2.20	0.75
40-49	2.25	0.79
50-59	2.16	0.72
≥60	2.14	0.73
Highest level of education, n 705		
Not completed lower secondary school	2.46	0.78
Completed lower secondary school (9 years)	2.24	0.78
Completed upper secondary school (12 years)	2.14	0.72
Completed undergraduate studies (≤ 15 years)	2.28	0.77
Completed postgraduate studies (≥ 15 years)	2.16	0.66
Current living conditions, n 705		
Stable (owned, rented or incarcerated)	2.19	0.74
Unstable (homeless, with family/friends)	2.40	0.84
Enrolled in OAT and by medication, n 583		
Methadone	2.28	0.71
Buprenorphine	2.15	0.77

SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress, SD =standard deviation, OAT = opioid agonist therapy

mean (SD) SCL-10 item score of 2.3 (0.8) and men 2.2 (0.8) [31].. People with unstable living conditions reported more symptoms of mental disorders than people with stable living conditions. Among OAT treatment, people on methadone reported mean (SD) SCL-10 of 2.3 (0.7) and buprenorphine-based medications at 2.2 (0.8).

SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress.

The figure displays the proportion of patients responses on the ten item scale, from *not bothered at all* (item score = 1) to *extremely bothered* (item score = 4).

We found vast individual dissimilarities in subjective mental health symptoms at baseline (Additional File 2); minimum and maximum mean SCL-10 item score was one and four, respectively. Thirty-three participants (4.7%) reported a mean of one; meaning *not bothered at all* on any items, while three participants (0.4%) were *extremely bothered* on all items. Sixty-five percent of the cohort reported a mean SCL-10 above the 1.85 cut-off point, which is recommended as a predictor of mental disorder [31] as shown in the Pen's Parade below.

Pen's Parade: SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress.

The figure displays distribution in SCL-10 mean values at baseline ($n = 707$) and follow up ($n = 268$), represented by fixed black line and vertical grey lines. The dotted lines represent the mean reported SCL-10 score of the Norwegian reference population (1.36) and standard reference of 1.85 indicating one or more mental disorders above this cut-off, respectively. Source: *Strand BH, Dalgard OS, Tambs K, Rognerud M: Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). Nordic journal of psychiatry 2003* [31].

Altogether 268 (38%) of the 707 participants at baseline had SCL-10 measures at two data points. As shown in Fig. 2, individual SCL-10 score at first follow-up are indicated with grey points and individual changes from baseline with vertical lines. Sharp changes go in both positive and negative directions and appear considerable for some.

Impact of substance use patterns, clinical and sociodemographic factors on baseline level and change in SCL-10 sum score

Using a LMM analysis, we found higher SCL-10 sum scores at baseline for females (SCL-10 sum score: 1.8, 95% confidence interval (CI): 0.7 to 3.0) compared to men, people with unstable living conditions (1.7, CI: 0.0 to 3.3) and having a worrying debt (2.2, CI: 1.1 to 3.3) compared to people with stable living conditions and non-worrying debt, respectively. For substances, frequent use of cannabis (1.3, CI: 0.2 to 2.5), other opioids (2.7, CI: 1.1 to 4.2) and benzodiazepines (3.6, CI: 2.4 to 4.8) were associated with higher SCL-10 scores at baseline compared to people with no or non-frequent use of these substances (Table 3). On the other hand, frequent use of stimulants was associated with lower SCL-10 sum score at baseline (– 2.7, CI: – 4.1 to – 1.4) compared with people with no or less frequent use. There were no significant time interactions between any of the substance use patterns and changes in the SCL-10 sum score, nor were there any significant time interactions with sociodemographic characteristics.

Discussion

In this study, we found that 65% of people with SUD have symptoms of mental health disorders and psychological distress. Mental health symptoms were particularly prevalent among females, people with frequent use of cannabis, non-OAT opioids, and benzodiazepines compared to men and people with no or less frequent use of these substances. Interestingly, there were no clear associations between substance use patterns and

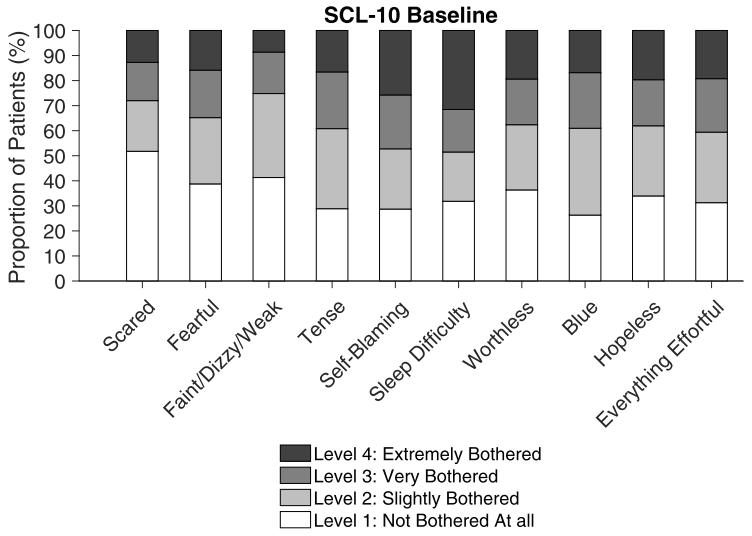

Fig. 1 Proportion of SCL-10 item scores at baseline. SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress. The figure displays the proportion of patients responses on the ten item scale, from not bothered at all (item score= 1) to extremely bothered (item score = 4)

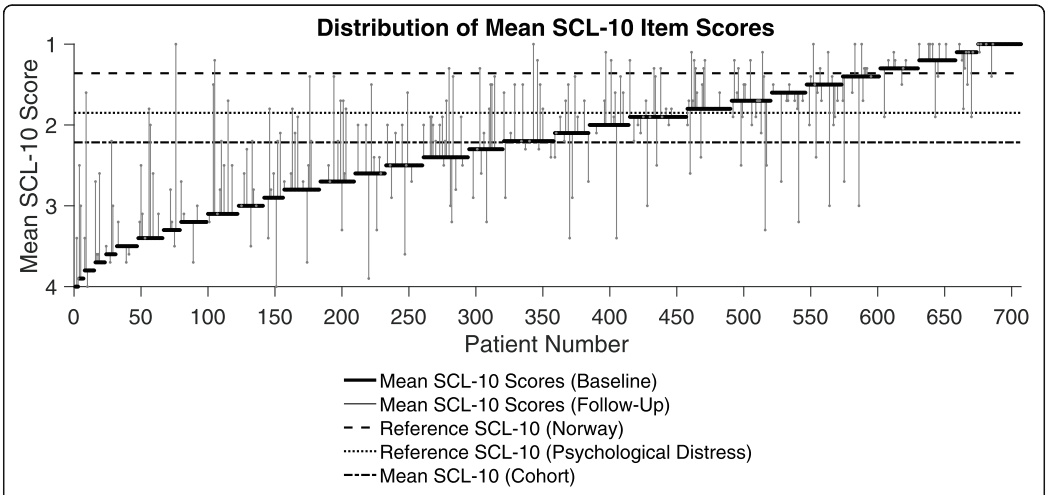

Fig. 2 Pen's Parade: Distribution of mean SCL-10 item scores at baseline and follow-up. Pen's Parade: SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress. The figure displays distribution in SCL-10 mean values at baseline (n=707) and follow up (n=268), represented by fixed black line and vertical grey lines. The dotted lines represent the mean reported SCL-10 score of the Norwegian reference population (1.36) and standard reference of 1.85 indicating one or more mental disorders above this cut-off, respectively. Source: Strand BH, Dalgard OS, Tambs K, Rognerud M: Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). Nordic journal of psychiatry 2003 [31]

Table 3 Linear mixed model of SCL-10 adjusted for clinical and sociodemographic factors

	Fixed effects	
	Baseline	**Change per year**
n = 707	Estimate (95% CI)	Slope (95% CI)
Factor impact* on SCL-10 sum score at baseline and changes per year from baseline		
SCL-10 sum score	18.1 (15.9 to 20.2)	0.6 (−1.6 to 2.9)
Female	*1.8 (0.7 to 3.0)*	0.4 (−0.9 to 1.8)
Age per 10 years	0.0 (−0.1 to 0.0)	0.0 (0.0 to 0.1)
Clinical factors		
Injecting substance use		
Injecting at least once last 12 months	0.6 (−0.7 to 1.8)	−0.3 (−1.6 to 1.0)
Frequent use of substances		
Alcohol	0.7 (−0.6 to 1.9)	0.1 (−1.2 to 1.4)
Cannabis	*1.3 (0.2 to 2.5)*	0.3 (−0.9 to 1.4)
Stimulants (amphetamines/ cocaine)	*−2.7 (−4.1 to − 1.4)*	− 0.2 (−1.6 to 1.3)
Opioids (other than opioid dispensed on OAT)	*2.7 (1.1 to 4.2)*	−2.6 (− 4.7 to − 0.4)
Benzodiazepines	*3.6 (2.4 to 4.8)*	− 0.4 (− 1.7 to 0.8)
Sociodemographic factors		
Level of education	−0.1 (− 0.7 to 0.6)	−0.6 (− 1.3 to 0.1)
Unstable living conditions	*1.7 (0.0 to 3.3)*	1.1 (−1.0 to 3.3)
Worrying debt situation	*2.2 (1.1 to 3.3)*	0.4 (−0.7 to 1.6)

SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress, CI = confidence interval
*Age per 10 years (centered according to mean age 43 years), level of education was coded 0–4 with 4 as the highest educational level, living conditions; unstable situation homeless or non-permanent residence, worrying debt situation: including any legal or illegal fees and debt, injecting substance use: during last 12 months

change in mental health symptoms over time. This could suggest that the differences observed were indicating self-medication to larger degree than medication-related decline in mental health.

People with SUD are a heterogeneous population; fifteen and 35 % reported lower mean SCL-10 item scores compared to the general population and the standard reference score for symptoms of mental health disorders, respectively. Despite vast intra-individual variations in SCL-10 score from baseline to first follow-up, going in both directions, there were no time trends indicating change over time for the total study sample. This indicates that mental health disorders and psychological distress persist over time for this group and we are not able to explain the huge shift, positive and negative, in mental status of many individuals.

The mean SCL-10 for our cohort was 2.2, which is considerable lower compared to the general Norwegian population at 1.4, estimated to be around 11% of the population [31]. Around two-thirds of the total study sample reported symptoms of mental health disorders. This was somewhat higher symptom burden compared to cohort among people with SUD in Sweden [35], however, lower compared to a study among people entering SUD treatment in Norway, which found that over 80% had a level of mental distress above the 1.85 cut-off for SCL-10 at admission [36]. This could reflect that initiating SUD treatment, often combined with strict detoxification, is a very stressful event, whereas most of the patients included in our cohort were long-term OAT patients with a mean treatment time of almost eight years [13]. Correspondingly, follow-up studies have shown that there may be a significant reduction in SCL-10 symptoms when these individuals are discharged from inpatient treatment, however, presence of mental health disorders and severity of substance use seem to be independent predictors of considerable symptoms of mental health disorders in the long-term [37, 38]. We found that mental health symptoms at baseline were associated with a worrying debt situation, unstable living conditions and a frequent use of some of the substances. Severe debt has been found to correlate with poor mental health in a systematic review summarizing a number of studies [39]. There are also several studies suggesting a strong relationships between substance use and psychological distress, despite hardship to establish exact causality [40–42]. In the above study among people entering SUD treatment, severity of substance use, although stratified into alcohol use, illicit drug use and number of substances used– but not the actual substances used; was the most significant predictor of symptoms of mental health disorders [36]. However, again the question

arises whether these symptoms are the direct result of the substance use or symptoms of mental distress presenting upon treatment admission [36].

In our study, use of cannabis, non-OAT opioids and benzodiazepines were co-occurring with mental health distress at baseline, while the opposite was seen for stimulants. There were no changes in time trends between use of substances and mental health symptoms. One hypothesis for these findings could be that the associations at baseline might be due to reverse causality, i.e. that participants with substantial mental health symptoms use substances to self-medicate symptoms [43]. It is also possible that there is a "flattening effect" and that potential negative impact of substances are more substantial at an earlier phase and that the change in later phases are less pronounced. Other research indicate that high doses of benzodiazepines reduce social functioning, and that it may also increase psychological distress and worsen mental health [16, 44], and misuse of benzodiazepines is seen among both SUD and psychiatric populations alike [45]. Similarly, the use of stimulants, in particular methamphetamine, has been associated with poor mental health outcomes [23]. Self-medication of attention deficit hyperactivity disorder (ADHD) with stimulants could be one explanation for these findings. Yet one study found that high ADHD symptom burden was associated with higher mental distress and use of simulants among OAT patients [46]. It is estimated that up to a third of patients in OAT have ADHD and previously we have found that coverage of central acting stimulants in this patient group is very low [12, 47, 48]. An alternative explanation could be that stimulants have a direct positive impact on mental health symptoms among these patients. However, the time trend analyses does not support these hypotheses.

Although prevalence of mental disorders and SUD comorbidity has been found to vary among European countries; research consistently shows a high total prevalence of around 50%, with depression, anxiety disorders and personality disorders being the most frequent [9]. However, some facility based studies indicate an even higher comorbidity prevalence as people with severe symptoms are more likely to seek support; 70% for personality disorders [3] and a lifetime substance-independent mental disorder was found in nine out of ten patients enrolled in treatment facilities [49]. Comorbid mental health disorders and SUD have been found to be associated with poor treatment outcomes and show a higher psychopathological severity compared to people with a single disorder [50–52], and this underlies the importance of assessing mental health status in clinical settings among people with SUD. We endorse that evaluation of mental health and linkage to mental health care services should be included in OAT programs and low-threshold SUD clinics; be gender-sensitive and follow and integrated treatment approach, which have been found superior compared to separate treatment plans [53–55].

The major strength of this study is the relatively large sample size of a "hard-to-reach" population of people with SUD as well as a cohort design. However, there are some limitations. Firstly, only a minority contributed to the prospective analyses (268/707). To reduce the potential for selection bias between the sub-group with follow-up SCL-10 measurements presented in Fig. 2 and the baseline cohort, we conducted an inverse probability weighted analysis. Our study sample is also mainly relevant for people with opioid dependence being enrolled in OAT treatment as most were in this group. Thus, our research might not be generalized to other groups with SUD. Moreover, both in the OAT and low-threshold SUD clinics, patient- and system delays contributed to non-accurate annual health assessments, which could in turn affect both answers and results. Thirdly, the SCL-10 has limitations. It is not a diagnostic tool for mental health disorders and is no replacement for clinical interviews and more comprehensive psychiatric instruments among people with SUD. Literature also suggests that the SCL-10 predicts depression and anxiety better than other diagnosis, and that some 50–60% of the patients identified with symptoms of mental disorders qualify for at least one or more mental disorders when assessed clinically [31, 56, 57].

Conclusion

People with SUD have considerable symptoms of mental health disorders and psychological distress. However, this is a diverse and dynamic population with extreme individual variations. Around one-third have few symptoms of mental health disorders. This emphasizes the importance of consideration and evaluation of symptoms of mental health disorders and psychological distress in both OAT and low-threshold SUD clinics to further improve personalized patient care. Mental health problems were particularly observed among females, people with frequent use of cannabis, opioids, and benzodiazepines, and less among people using amphetamines. Time trend analyses could suggest that the differences observed indicates self-medication or a flattening effect rather than medication-related decline in mental health. Studies with long term follow-up or experimental design is needed to confirm these potential effects better.

Abbreviations

ADHD: Attention deficit hyperactivity disorder; EM: Expectation-maximization imputation; INTRO-HCV: Integrated treatment of hepatitis C virus infection; HCV: Hepatitis C virus infection; LMM: Linear mixed model; OAT: Opioid agonist therapy; SCL-10: Hopkins Symptom Check List 10; SCL-25: Hopkins Symptom Check List 25; SUD: Substance use disorder

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13011-021-00354-1.

Additional file 1. SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress, SD = standard deviation,

Additional file 2. Pen's Parade: SCL-10 = Symptoms checklist 10; ten items scale for measuring mental health status/psychological distress. The figure shows distribution in SCL-10 mean values at baseline ($n = 707$) by fixed black line. The dotted lines represent the mean reported SCL-10 score of the Norwegian reference population (1.36) and standard reference of 1.85 indicating one or more mental disorders above this cut-off, respectively. Source: *Strand BH, Dalgard OS, Tambs K, Rognerud M: Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). Nordic journal of psychiatry 2003.*

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Ethical approval and consent to participate

The study was approved by the Regional committee for medical and health research ethics (no. 2017/51/REK vest). It was conducted in accordance with the Helsinki Declaration and STROBE guidelines All included participants signed a written consent to partake in the study.

Authors' contributions

This observational study was led by CFA in terms of study design, analyzes, drafting and writing the article. JHV, RG and AGL were particularly involved with acquisition of data, analyses and interpretation. Figures were made by AGL. KAJ, LTF, SS, JHV, AGL, KVG, RG and EML contributed to the conception, writing, and revising the draft(s) critically. All authors have read and approved the version to be published.

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Availability of data and materials

Dataset used for SCL-10 for this publication may be available in an anonymous and shortened version upon contacting the corresponding author.

Consent for publication

Not applicable. No personal details on any of the participants are reported in the manuscript, tables or figures.

Competing interests

None of the authors have competing interests.

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Publisher's Note

Article 3

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Substance Abuse Treatment, Prevention, and Policy

RESEARCH Open Access

Health-related quality of life of long-term patients receiving opioid agonist therapy: a nested prospective cohort study in Norway

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Abstract

Background: Opioid dependence carries the highest disease burden of all illicit drugs. Opioid agonist therapy (OAT) is an evidence-based medical intervention that reduces morbidity and mortality. There is limited knowledge on the health-related quality of life (HRQoL) of long-term patients in OAT. This study measures HRQoL and self-perceived health of long-term patients on OAT, compares the scores to a Norwegian reference population, and assesses changes in these scores at 1-year follow up.

Methods: We conducted a nested prospective cohort study among nine OAT outpatient clinics in Norway. 609 OAT patients were included, 245 (40%) followed-up one year later. Data on patient characteristics, HRQoL, and self-perceived health was collected. HRQoL was assessed with the EQ-5D-5L, which measures five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on a five-point Likert scale (from "no problems" to "extreme problems"). An UK value set was applied to calculate index values (from 0 to 1) for the EQ-5D-5L and compare them to a Norwegian reference population. Self-perceived health was measured with EQ-VAS (from 0 to 100).

Results: Mean (standard deviation (SD)) EQ-5D-5L index value at baseline was 0.699 (0.250) and EQ-VAS 57 (22) compared to 0.848 (0.200) and 80(19) for the Norwegian reference population. There were large variations in EQ-5D-5L index values, where 43% had > 0.8 and 5% had < 0.2 at baseline. The lowest EQ-5D-5L index values were observed for female patients, age groups older than 40 years and for methadone users. At follow-up, improvements in HRQoL were observed across almost all dimensions and found significant for mobility and pain/discomfort. Mean (SD) overall index value and EQ-VAS at follow up were 0.729 (0.237) and 59 (22) respectively.

(Continued on next page)

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Conclusion: The average HRQoL and self-perceived health of OAT patients is significantly lower than that of the general population, and lower than what has been found among other severe somatic and psychiatric conditions. Around 34% had very good HRQoL, higher than average Norwegian values, and around 5% had extremely poor HRQoL.

Keywords: Health related quality of life, Quality of life, EQ-5D, Opiate substitution therapy, Opioid agonist therapy, Opioid dependence, Epidemiology

Background

Opioid dependence is a severe chronic relapsing disorder consisting of a cluster of physiological, behavioral, and cognitive phenomena [1]. Worldwide, opioid use disorders affect over 16 million people and are responsible for over 120.000 deaths per year [2]. Of all illegal drugs, opioids denote the highest disease burden, have the highest demand for treatment, contribute to substantial increased healthcare costs, and have given rise to a marked increase in opioid related deaths in the last decade [3–5]. People with opioid use disorders suffer not only from a shorter life-span as compared to the general population, but also severe social marginalization and long-term impairments in most aspects of their lives [6]. Research consistently shows that people with opioid use disorders have inferior quality of life (QoL) compared to the general population [7, 8]. This is partly explained by the extensive co-occurrence of substance use disorder and mental disorders, which both seem underdiagnosed and undertreated [9], in addition to high prevalence of somatic disorders such as chronic hepatitis C of almost 50% [10]. Epidemiological studies suggest a prevalence of around 27% for anxiety disorders, 35% for affective disorders, 30% for attention-deficit hyperactivity disorder, and 51% for personality disorders in patients with substance use disorders [11–13]. However, prevalence may be even higher in clinical studies as people with severe problems are more likely to seek help; studies have found prevalence of around 70% for one or more personality disorder [14] and around 66% for childhood trauma among people with substance use disorders [15], and at least one comorbid psychiatric disorder in approximately 80% of patients on opioid agonist therapy (OAT) [16].

Increased focus on, and availability of harm reduction programs, such as OAT have lowered the demand for heroin in Western Europe including Norway [5]. OAT is an evidence-based medical intervention that reduces illicit opioid use, improves patients' health and reduces crude mortality rates significantly [3, 17–20]. For instance, results of 22 pooled longitudinal cohort studies showed a crude mortality rate for patients on OAT of 0.90 per 100 person years, compared to 1.63 when OAT was ceased and 4.91 for untreated periods [21]. Most research on OAT has emphasized on crude mortality rate, abstinence and retention in treatment, rather than what may be most important for each individual patient; personal wellbeing. In turn, several researchers argued that health related quality of life (HRQoL) should be included as an outcome when evaluating substance use and OAT treatment [22–25]. Thus, to evaluate real life outcome of OAT, changes in objective and self-perceived health, including the individual's own experience, should be examined. In addition, for more individualized OAT treatment and management, it is important to understand the relationship between clinical and demographic characteristics and HRQoL.

Factors associated with poor HRQoL among OAT patients are older age, female gender, and mental and physical comorbidity [7, 26, 27]. There is building evidence that HRQoL is substantially lower among people with opioid dependence and that HRQoL improves at OAT initiation and during the first few months of treatment [27–30]. However, a recent systematic review suggests there is still limited knowledge regarding HRQoL outcomes in OAT treatment programs and HRQoL outcomes are rarely used [22]. Many of the previous studies are cross-sectional rather than longitudinal designs, offers few participants and with non-validated HRQoL measures for opioid dependence, which make comparisons difficult across opioid dependence and other diseases.

The principal aim of this study is to evaluate the HRQoL and self-perceived health of a large cohort of long-term patients with opioid dependence enrolled in an integrated OAT program in Norway. The HRQoL of OAT patients will also be compared to that of the general population in Norway. Finally, an assessment of changes in HRQoL and self-perceived health at one-year follow-up will be conducted.

Methods

Study design and setting

This study is a nested prospective cohort study linked to the Integrated Treatment of Hepatitis C study (INTRO-HCV) [31]. The observational study recruited participants from May 2017 until January 2020 [31]. HRQoL baseline data was collected at the first OAT health assessment, and follow-up data was collected one-year

after baseline for each patient. Trained research nurses, who were not responsible for clinical patient follow-up, collected the research data via structured patient interviews. The data was recorded directly in an electronic data entry system (CheckWare). The study took place in Bergen and Stavanger, which are cities in southwestern parts of Norway with around 280,000 and 130,000 inhabitants each. The target population was individuals with opioid dependence who received OAT treatment and care in all together nine OAT outpatient clinics. The clinics have adopted an integrated treatment and care model where patients are charted on a nearly daily basis by health professionals; including social workers, specialized and general nurses, psychologists, and physicians specialized in addiction medicine. OAT medications include mostly methadone or buprenorphine-based medications, often with directly observed intake [32].

Study sample

The study sample included individuals diagnosed with opioid dependence according to International Classification of Diseases version 10 (ICD-10) [33], currently enrolled in OAT treatment, aged 18 years or older, and have given a written informed consent to participate in the study. Individuals were eligible for inclusion regardless of the type of OAT medication or administration form. Remuneration, of around euro 20, was provided once for the participants upon inclusion to participate in the study. Of the 900 patients invited, a total of 609 (68%) patients completed the EQ-5D-5L questionnaire at baseline, and of those, 245 (40%) were followed up with a follow-up questionnaire approximately 1 year after the first visit. Nineteen patients (2%) were excluded because they did not complete the interview or due to missing data of the EQ-5D-5L instrument The mean time between the first and second annual OAT assessment was 375 days (95% confidence interval (CI): 359–392 days). See Table 1 for details on clinical and demographic characteristics and additional file 1 for flowchart of study sample.

Instruments

Health related quality of life: EQ-5D-5L

The EQ-5D-5L instrument is a widely used generic measure of HRQoL [34] and validated for opioid use disorders [35, 36]. It consists of two components. The first descriptive system evaluates health in five dimensions (Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression). Each dimension has five levels of response, ranging from no problems, slight problems, moderate problems, severe problems, to extreme problems [37]. The second part of EQ-5D-5L entails a visual analogue scale (VAS) where the respondent rates the self-perceived health from 0 (worst health imaginable) to 100 (best health imaginable) [37]. A systematic review supports the use of the EQ-5D-5L in a broad range of patients [38]. We therefore selected this instrument to assess the HRQoL of patients in OAT and to compare their HRQoL to the general population.

Statistical analysis

Responses to the five HRQoL dimensions are coded as a five-digit code, which represents a numerical description of a health state. The digits have no arithmetic properties and therefore a single summery number (an index value) needs to be arrived by applying a formula with an appropriate value set, which is a representative sample of the general population. The index value then represents how good or bad a health state is according to the preferences of the general population, ranging from 1 (full health) to 0 (dead, with negative values indicating health states worse than death) [37]. In the absence of a Norwegian value set, we applied an EQ-5D-5L value set for UK, i.e. the societal preference weights for the health state, to determine the EQ-5D-5L index values for each health state in the OAT cohort [39]. Summary statistics were derived, including proportions and number of patients for the five EQ-5D-5L dimensions by age, gender and OAT medications. The EQ-VAS score was summarized descriptively by mean, standard deviation (SD), minimum and maximum as the data was not particularly skewed. A paired t-test of means for the 245 patients with two time points was used in the analysis to investigate whether there was any statistical significance in EQ-5D-5L between the measurements. An ANCOVA model for EQ-VAS changes from baseline to the next OAT health assessment was conducted where place and treatment were fixed effects and baseline covariate. If data were missing from more than one dimension participants were excluded. Altogether eight patients missed data on one dimension at baseline but were included in the analyses. There were no missing data from EQ-5D-5L follow-up or EQ-VAS. To estimate the unbiased treatment effects from baseline to follow-up we used an inverse probability weighted method as we had follow-up data for a subgroup. We calculated population weights based on age, gender and how many times OAT medication was collected during a week in a binominal regression model with follow-u*p* values as the dependent variable. More weight was given to cases with valid data, which were associated with highest probability of having missing data, and less weight was given to cases with lowest probability of missing. The mean for the population weights was 1.0 (SD 0.12) in our model. Statistical significance was set at $p < 0.05$ level. All analyses were made with STATA SE 16.0.

Table 1 Baseline characteristics of study sample

	Percentages or Mean (SD)
Patients, n[a]	
Gender, *n* = 609	
Male	71%
Female	29%
Age, *n* = 609	
< 25	3%
26–40	39%
41–60	53%
≥ 61	5%
Mean age (SD)	44 (10)
Current OAT medication, *n* = 588	
Methadone	38%
Buprenorphine	56%
Buprenorphine/naloxone	4%
Other	2%
Duration of OAT treatment in years, mean (SD), *n* = 583	7.9 (5.4)
Background demographics	
Highest level of completed education, *n* = 588	
Did not complete primary and secondary school	5%
Completed primary and secondary school	45%
High school	40%
Undergraduate education ≤3 years	8%
Postgraduate education ≥3 years	2%
Main source of income, several answers possible, *n* = 611	
Paid work (full time or part time)	7%
Sick pay or unemployment benefits	10%
Social or disability benefits	79%
Savings or scholarships	1%
Other	3%
Accommodation last 30 days several answers possible, *n* = 606	
Owned property	9%
Rented property	68%
Temporary property	7%
Prison	1%
Homeless	1%
At friends or family	12%
Other	2%
Living conditions *n* = 586	
Living alone	63%
Living with others	37%
Children *n* = 587	
Do not have children	44%
Have children	56%
For those having children < 18 years old, *n* = 152	
Having children < 18 with visiting rights	79%
Having children < 18, but no visiting rights	21%

OAT Opioid agonist therapy, *SD* Standard deviation,
[a]n = number of respondents, some questions allow multiple answers

Results

Baseline characteristics of study sample

The patients were predominantly male (71%) with a mean (SD) age of 44 years (10). The age range of the study sample was 23–74 years. Most received buprenorphine-based medication (60%) followed by methadone (38%). Duration in OAT treatment ranged from 0 to 25 years, with a mean (SD) of 7.9 (5.4) years. Results therefore reflects HRQoL of patients that have received OAT over a long period of time. Of the participants, 45% had completed secondary school and 40% completed high school. Almost 80% received either disability pension or social benefits as main source of income. Of the 152 OAT patients with children under 18 years, 21% reported they had no visiting rights (Table 1). The distributions of sociodemographic variables were similar for the baseline- and the follow-up samples. However, the proportion of males increased from 71 to 76% in the follow-up sample and mean (SD) age increased from 44 (10) to 45 (10) years compared to the sample at baseline.

HRQoL of OAT patients at baseline

The distributions of unadjusted EQ-5D-5L scores are presented as norm sets according to gender, age groups, and OAT medications (Fig. 1). Overall, mean scores for the five dimensions were 1.7 (95% CI: 1.6–1.8) for mobility, 1.3 (95% CI: 1.2–1.3) for self-care, 1.8 (95% CI: 1.7–1.9) for usual activity, 2.3 (95% CI: 2.2–2.4) for pain/discomfort and 2.7 (95% CI: 2.6–2.8) for anxiety/depression (additional file 2). "No problems" were reported by 62% for mobility, 85% for self-care, 58% for usual activities, 36% for pain/discomfort, and only 23% for anxiety/depression. This means that the majority of patients had no problems with mobility and conducting usual activities and self-care. On the other hand, extreme problems" with pain/discomfort were noted by 5 % and 7 % reported "extreme problems" with anxiety/depression. Under 1 % reported "extreme problems" with mobility, self-care and usual activities. Females and patients receiving methadone treatment reported more problems across all EQ-5D-5L domains compared to males and patients on buprenorphine-based medications, respectively. Patients in the age group 41–60 reported more

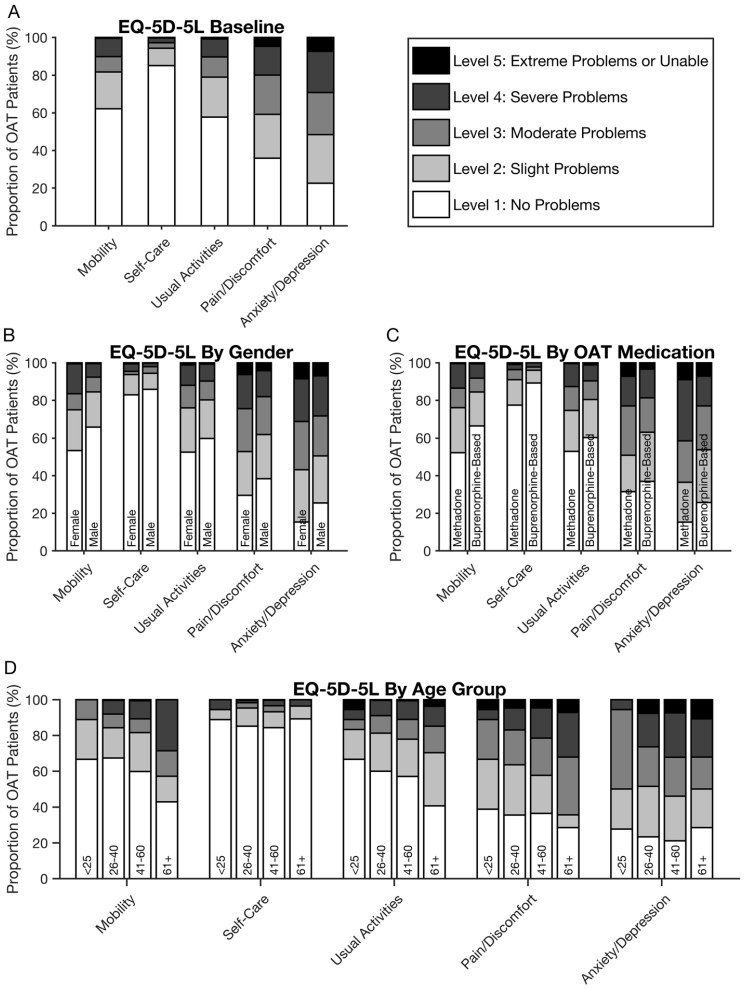

Fig. 1 Proportion of individuals reporting problems by EQ-5D-5L domain; overall, by age, gender and OAT medication. OAT = opioid agonist therapy. Altogether 609 respondents, 8 patients missed values on one dimension. 11 patients, which did not receive either methadone or buprenorphine-based medications are left out of the illustration but not analysis. Proportions (%) and dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). 1A: Overall, 1B: Gender 1C: OAT medication 1D: Age groups

problems on every domain except pain/discomfort compared to patients under 40 years of age, while patients over 60 years of age reported most problems for mobility and pain/discomfort (additional file 2).

The mean (SD) EQ-5D-5L index value for OAT patients was 0.699 (0.250) at baseline. Forty-three percent had an index value above 0.8, meaning they had "no problems" in the five health domains. Thirty-four percent of the sample even had an index value above 0.848 (Norwegian reference population [40]), meaning their HRQoL was better than that of the Norwegian general population. Around 5 % had an index value below 0.2, meaning they had "extreme problems" in HRQoL. The distribution in baseline EQ-5D-5L index values are shown in the Pen's Parade (Fig. 2). The parade shows the HRQoL distribution, and is defined as a succession of every OAT patient included, with their height proportional to their EQ-5D-5L index value, from lowest to highest.

The mean (SD) EQ-VAS score of OAT patients was 57 (22) for the total sample at baseline, meaning their

self-perceived health was considerably lower compared to the Norwegian reference population of 80 (19) [40]. Females reported an EQ-VAS of 56 (23), while 54 (22) for patients aged 41–60, and 51 (23) for patients older than age 60. Patients on methadone reported 53 (22), which was lower EQ-VAS compared to buprenorphine with 58 (22) and buprenorphine-naloxone 65 (21).

Changes in HRQoL of OAT patients at follow up

Altogether 245 (40%) of the 609 patients at baseline were included for the follow-up analyses. As shown in the Pen's Parade (Fig. 2), individual changes in EQ-5D-5L index values for patients with follow-up data (n = 245) are indicated with vertical lines. For instance, a patient with an index value of 0.563 at baseline and a long vertical line going up to 0.840 at follow-up means this patient reported a significant improvement in HRQoL. A patient with a vertical line going down from baseline shows worsen HRQoL between baseline and follow-up. Patients with no follow-up data (n = 364) or no change at follow-up (n = 26) has no vertical line. Figure 2 also shows that the majority of patients have a lower index value than the Norwegian reference population, meaning worse HRQoL, illustrated by values below the dotted line. However, changes go in both directions and appear substantial for some. This means that patients receiving long-term OAT are at risk of relatively rapid changes in index values in both better and worse directions. Overall, around 54% reported improvement in HRQoL, around 35% reported worse HRQoL while 11% reported no changes at follow up compared to baseline values. The mean (SD) observed change was 0.038 (0.20) with minimum and maximum values of − 0.646 and 0.639, respectively. Females reported a mean (SD) change of 0.056 (0.17) compared to males 0.032 (0.21). Variation in individual EQ-5D-5L index value changes from baseline to follow-up is illustrated in additional file 3.

EQ-5D-5L index values improved significantly overall (p = 0.004) and for both genders (m: 0.039, f: 0.016), age group 26–40 (p = 0.002) and buprenorphine-based patients (p = 0.027) as shown in Table 2. The mean (SD) EQ-5D-5L index value was 0.729 (0.237) at follow-up; 49% had an index value above 0.8 while 37% of the sample had an index value above the Norwegian reference population. Around 4 % had an index value below 0.2. Significant improvements in EQ-5D-5L scores were found for mobility (p = 0.008) and pain/discomfort (p = 0.025) (Fig. 3 and Table 3).

Significant improvement in self-perceived health (EQ-VAS) were found for males (p = 0.038).

Discussion

This study is one of the first to examine changes in HRQoL in a sample of long-term OAT patients over a one-year follow-up period. Most studies on HRQoL demonstrate improvements in HRQoL upon treatment entry, but data on long-term patients' HRQoL is scarce. Considerable impairments in HRQoL and self-perceived health (EQ-VAS) were found in many of the OAT patients. However, large variations in EQ-5D-5L index values were found between individuals, both at baseline and at follow-up. Significant improvement in overall HRQoL was observed at one-year follow-up with around half of the OAT patients reported some improvement in HRQoL while around one-third experienced worse HRQoL at one-year follow up, with great individual variations. Males reported significant improvement in their self-perceived health.

Compared to the general Norwegian population, which reported no problems regarding mobility (85%), self-care (98%), usual activities (82%), pain/discomfort (54%) and anxiety/depression (79%) [40], OAT patients reported in average consistently higher percentages of problems across all EQ-5D-5L domains, especially pain/discomfort and anxiety/depression where only 36 and 23% respectively, reported no problems. The mean (SD) EQ-5D-5L index value for the Norwegian reference population 0.848 (0.200) [40] was considerably higher compared to the OAT patients at baseline. Mean (SD) total EQ-VAS for the OAT patients at baseline was considerably lower than the Norwegian reference population who reported overall mean (SD) of 80 (19); females 80 (20) and older age 77 (19) [40].

Our findings are consistent with prior research, such as Strada *et. al* (2019) study of a large OAT cohort in Germany; found that OAT patients had a lower HRQoL than the general population [41]. Several studies have demonstrated that female OAT patients report worse overall HRQoL compared to males [8, 27]. However it is unclear why that is the case and gender-focused research is urgently needed. Perhaps females are more vulnerable for stigma, traumatizing events or maybe have a poorer function upon entering OAT in the first place. Age is also strongly correlated to poor physical HRQoL [41]. In our sample the mean age was 44, which is consistent with an aging OAT population in Norway [32, 42]. Increased age of OAT patients coupled with poorly reported HRQoL, may place an increased demand for health care services in the future. This raises a debate on how level of OAT and various integrated treatment policies and strategies could better benefit OAT patients. Even if OAT patients treated with methadone reported worse HRQoL than those with buprenorphine, the results should be interpreted carefully. In current Norwegian OAT guidelines buprenorphine is usually recommended as first line substitution medication and considered safer compared to methadone due to its partial antagonistic effect [43]. It is also likely that patients

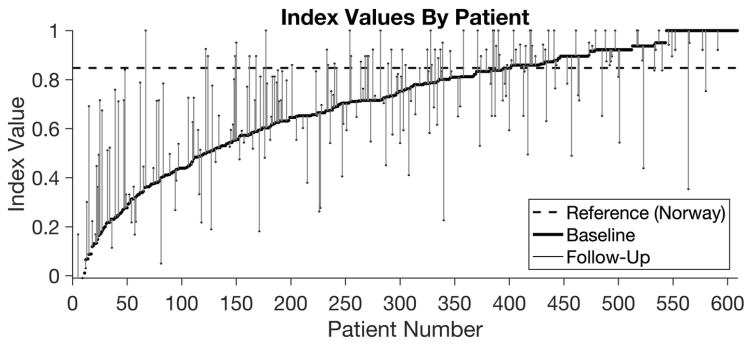

Fig. 2 Pen's Parade: distribution from lowest to greatest health. Pen's Parade: The distribution in baseline EQ-5D-5L index values, where 43% had > 0.8 and 5% had < 0.2 at baseline. The dotted line represent the average reported index value of the Norwegian reference population

may prefer buprenorphine because it is less sedative than methadone, and that both younger and perhaps more stable patients are dispensed buprenorphine, and as such, results could be highly confounded.

Previous research has revealed that HRQoL improves considerably at OAT treatment initiation and the first few months [44]: however, not much research to date has investigated the long-term effect of OAT on patients' HRQoL [7, 22, 29]. For instance, one study among patients on methadone maintenance treatment found that QoL increased markedly in the beginning of the observation, but decreased after 6 months [45] while other studies only saw improvements in the beginning of observation [27, 46]. There is therefore the general belief, based on limited data, that once patients are enrolled in OAT, their HRQoL will remain low and does not change substantially anymore. Our study challenges that belief and is among the first to show that changes in HRQoL, including positive changes, are possible. Additionally, our findings also show that many patients had extreme variations in index values from baseline to follow-up, in both positive and negative directions. This

Table 2 OAT patients' HRQoL and self-perceived health at baseline and follow up as measured by the EQ-5D-5L

	EQ-5D-5L VAS, baseline		EQ-5D-5L VAS, baseline[a]		EQ-5D-5L VAS, follow-up		EQ-5D-5L Index		EQ-5D-5L Index		EQ-5D-5L Index	
	n 609		n 245		n 245		n 609, baseline		n 245, baseline[a]		n 245, follow-up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Overall	57	22	57	22	59	22	0.699	0.250	0.691	0.237	**0.729**	0.237
Gender												
Female	56	23	57	25	57	23	0.653	0.260	0.613	0.273	**0.669**	0.261
Male	57	22	57	21	**60**	22	0.718	0.243	0.716	0.220	**0.748**	0.226
Age group												
< 25	58	18	55	19	61	25	0.787	0.164	0.766	0.211	0.678	0.390
26–40	61	22	59	22	60	22	0.724	0.242	0.689	0.234	**0.745**	0.205
41–60	54	22	55	22	58	22	0.684	0.253	0.686	0.238	0.716	0.253
≥61	51	23	56	16	58	16	0.613	0.292	0.714	0.257	0.754	0.210
OAT medication												
Methadone	53	22	54	21	58	23	0.636	0.260	0.657	0.228	0.686	0.236
Buprenorphine	58	22	58	22	60	22	0.726	0.235	0.716	0.238	**0.758**	0.232
Buprenorphine/naloxone	65	21	59	30	54	26	0.775	0.242	0.558	0.352	**0.737**	0.335

OAT Opioid agonist therapy, *SD* Standard deviation
Index obtained from Devlin, N., Shah, K., Feng, Y., Mulhern, B. and van Hout, B., 2018. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Health Economics
[a]Baseline values for the 245 patients who were eligible for follow-up analysis
The possible range of scores for EQ-5D-5L (0–1, 0 = dead (scores < 0 is possible), 1 = full health) and EQ-VAS (0–100, 0 = worst health imaginable, 100 = best health imaginable
Statistically significant changes are marked in bold ($p < 0.05$)

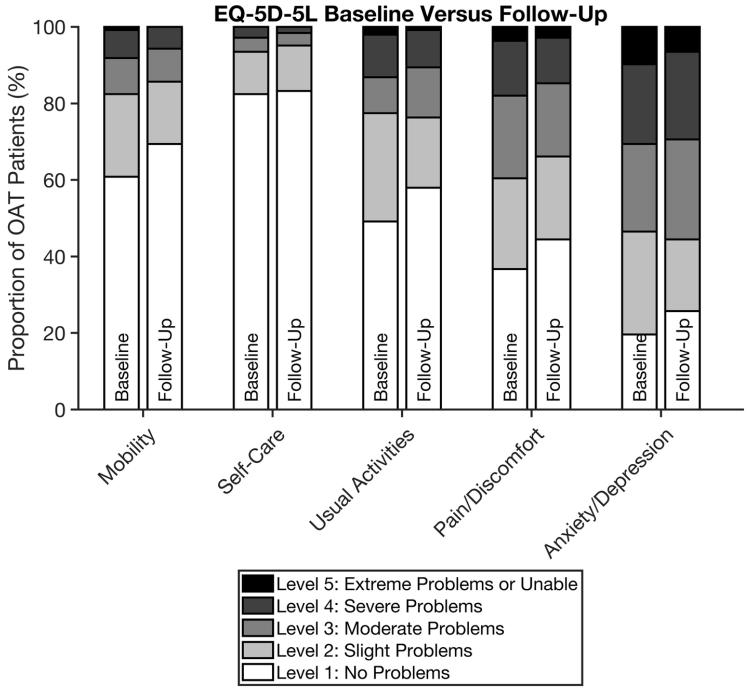

Fig. 3 EQ-5D-5L domains at baseline versus follow-up. OAT = opioid agonist therapy. Proportions (%) and dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Baseline and follow-up for the 245 patients who were eligible for follow-up analysis

suggests that OAT populations are susceptible to severe impairment and also rapid improvements in their HRQoL. Such swift alterations are perhaps less common among other patient groups and future research should examine what causes these changes in HRQoL in long-term OAT patients.

HRQoL in the long-term OAT population was lower in average compared to what is found in other patient groups, such as diabetes type 1 and 2 [47], HIV/AIDS patients [48] and patients with psychiatric comorbidities such as mild to moderate anxiety and depressive disorders, and residual state of bipolar disease [49]. Using the inverse of disability weights (health state valuations) reported in the Global Burden of Disease study (2017), makes comparisons between HRQoL index values and disability weights possible [50]. Research have shown there is a high comorbidity of psychiatric disorders among people with substance use disorders and individuals on OAT [11, 12, 16], while a six-year follow-up study demonstrated that the high psychiatric comorbidity persisted in long-term OAT patients [51]. This may have severe HRQoL impacts and patients with mental disorders may therefore be overrepresented in the lower extreme of the reported index values. Given the wide distribution of severity of disease within the long-term OAT population, treatment needs to be individualized and better adapted to patient functioning and needs. This opts for rethinking and reassessing OAT programs to better facilitate for integrated treatment, which have found to be consistently superior to treatment of substance use and mental disorders with separate treatment plans [52].

Furthermore, as HRQoL profiles of OAT patients are diverse and dynamic this has implications for personalized patient care and the need for regular assessment of HRQoL as an outcome. We need to better understand what drives the extreme and rapid changes in HRQoL in both positive and negative directions among OAT patients. We need to know how to best prevent large drops in index score and how to increase and maintain the increases in index score over time. Additionally, females have worse HRQoL scores compared to men, which indicates that OAT programs should particularly focus on how to improve HRQoL of females and find explanations for why females have lower HRQoL. Similarly, we found that patients older than 40 years have worse

Table 3 Distribution of EQ-5D-5L dimensions at baseline and at follow-up

Mean time between baseline and follow-up is 375 days (95% CI: 358,6–391.9)

Baseline: 609 patients Follow-up: 245 patients

Dimension	Baseline	Baseline[a]	Follow-up	*p* value
Mobility mean (95% CI)	**1.7 (1.6–1.8)**	**1.7 (1.5–1.8)**	**1.5 (1.4–1.6)**	
No problems n (%)	378 (62.1)	149 (60.8)	170 (69.4)	0.0081
Slight problems n (%)	119 (19.5)	53 (21.6)	40 (16.3)	
Moderate problems n (%)	49 (8.1)	23 (9.4)	21 (8.6)	
Severe problems n (%)	59 (9.7)	18 (7.4)	14 (5.7)	
Unable to walk about n (%)	3 (0.5)	2 (1.0)	0 (0)	
Self-care mean mean (95% CI)	**1.3 (1.2–1.3)**	**1.3 (1.2–1.4)**	**1.2 (1.2–1.3)**	
No problems n (%)	517 (84.9)	202 (82.5)	204 (83.3)	0.4
Slight problems n (%)	56 (9.2)	27 (11.0)	29 (11.8)	
Moderate problems n (%)	18 (2.9)	9 (3.7)	8 (3.3)	
Severe problems n (%)	15 (2.5)	7 (2.9)	4 (1.6)	
Unable to wash or dress n (%)	2 (0.2)	0 (0)	0 (0)	
Usual activities mean (95% CI)	**1.8 (1.7–1.9)**	**1.9 (1.8–2.1)**	**1.8 (1.6–1.9)**	
No problems n (%)	350 (57.5)	120 (49.0)	142 (58.0)	0.1
Slight problems n (%)	129 (21.1)	69 (28.2)	45 (18.4)	
Moderate problems n (%)	64 (10.5)	23 (9.4)	32 (13.1)	
Severe problems n (%)	58 (9.5)	27 (11.0)	24 (9.8)	
Unable to do usual activities n (%)	5 (0.8)	5 (2.0)	2 (0.8)	
Pain/discomfort mean (95% CI)	**2.3 (2.2–2.4)**	**2.2 (2.1–2.4)**	**2.1 (1.9–2.2)**	
No pain/discomfort n (%)	218 (35.8)	90 (36.7)	109 (44.5)	0.0245
Slight pain/discomfort n (%)	142 (23.3)	58 (23.7)	53 (21.6)	
Moderate pain/discomfort n (%)	127 (20.9)	53 (21.6)	47 (19.2)	
Severe pain/discomfort n (%)	92 (15.1)	35 (14.3)	29 (11.8)	
Extreme pain/discomfort n (%)	29 (4.8)	9 (3.7)	7 (2.9)	
Anxiety/depression mean (95% CI)	**2.7 (2.6–2.8)**	**2.7 (2.6–2.9)**	**2.7 (2.5–2.8)**	
Not anxious/depressed n (%)	137 (22.5)	48 (19.6)	63 (25.7)	0.3
Slightly anxious/depressed n (%)	157 (25.8)	66 (26.9)	46 (18.8)	
Moderately anxious/depressed n (%)	136 (22.3)	56 (22.9)	64 (26.1)	
Severely anxious/depressed n (%)	132 (21.7)	51 (20.8)	56 (22.9)	
Extremely anxious/depressed n (%)	45 (7.4)	24 (9.8)	16 (6.5)	

CI Confidence interval

P-value: based on paired t-test of means for the 245 patients with two time points

[a]Baseline values for the 245 patients who were included for follow-up analysis

HRQoL. This shows that we need to re-examine health care needs of older patients are met and how we can address their needs better. This is particularly important as long-term OAT patients are now aging and we need to plan for aging populations receiving OAT.

A strength of this study is the large sample size of long-term OAT patients at baseline who are receiving the same level of integrated OAT treatment across their respective OAT outpatient clinics in the two cities. However, there are also limitations to our study. Follow-up was conducted on a sub-group of the initial sample. To reduce the selection bias due to the loss-to-follow-up we performed an inverse probability weighted method. In general, it is problematic to compare HRQoL between studies as setting, population, and level of OAT integrated treatment varies and different instruments are being used. This is also the case for comparisons between results based on EQ-5D-3L and EQ-5D-5L, and when different national value sets are being used. Comparative performance across patient groups is driven by differences in the descriptive systems and associated value sets [37] Another weakness is the absence of a

Norwegian value set. Both our study and the study of the Norwegian reference population had to use value sets that resembles the Norwegian population, and for this reason the UK value set was chosen. Studies have confirmed that the latter version of EQ-5D significantly increase both reliability and sensitivity and can potentially reduce the possible ceiling effects encountered in the EQ-5D-3L earlier version [53, 54].

Conclusion

We found considerably lower HRQoL among long-term OAT patients in average compared to the general Norwegian reference population. However, this is a heterogeneous population. Around one-third had very good HRQoL, higher than average Norwegian values. Improvements in HRQoL were found over the one-year follow-up across most EQ-5D-5L dimensions with some uncertainties on why this was seen. More research is urgently needed to identify and understand why females and older patients have worse HRQoL and shows there is a need for more gender-and age-specific treatment in OAT programs. The wide variations in HRQoL support more emphasis on individualized treatment and personalized patient care, and the need for regular assessment of HRQoL in OAT programs. Our study is among the first to show that changes in HRQoL, including positive changes, are possible even several years after initiation of treatment. Future research should examine what causes these changes in HRQoL in long-term OAT patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13011-020-00309-y.

Additional file 1. OAT = opioid agonist therapy. Flow chart of study sample.

Additional file 2. EQ-5D-5L, descriptive health profile at baseline (frequencies and proportions reported by dimensions and level). OAT = opioid agonist therapy, CI = confidence interval. * = total number of respondents. 8 patients who missed data on one dimension were included in the analysis. ** = long acting morphine sulphate and other opioid prescriptions.

Additional file 3. Changes in EQ-5D-5L index value per patient from baseline to follow-up. 609 patients included at baseline, 245 patients at follow-up one year later.

Abbreviations

HRQoL: Health related quality of life; INTRO-HCV: Integrated treatment of hepatitis C virus infection; OAT: Opioid agonist therapy; QoL: Quality of life

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Authors' contributions

This observational study was led by CFA and KAJ in terms of study design, analyzes, drafting and writing the article. KAJ, JHV and LTF was particularly involved with acquisition of data, analyzes and interpretation. Figures were made by AGL and KAJ. KAJ, LTF, SS, JHV, AGL, SR, KI, JEA, and EML contributed to the conception, writing, and revising the draft(s) critically. All authors have read and approved the version to be published.

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Availability of data and materials

The INTRO-HCV study is ongoing and as such the dataset is not publically available. However, parts of the dataset used for EQ-5D-5L used for this publication may be available in an anonymous and shortened version upon contacting the corresponding author: Christer F. Aas: christer.frode.aas@helse-bergen.no

Ethics approval and consent to participate

The study was approved by the Regional committee for medical and health research ethics (no. 2017/51/REK vest). It was conducted in accordance with the Helsinki Declaration and STROBE guidelines All included participants signed a written consent to partake in the study.

Consent for publication

Not applicable. No personal details on any of the participants are reported in the manuscript, tables or figures.

Competing interests

None of the authors have competing interests.

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