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 cumulative frequency of HCV treatment among OAT patients from 2014 to 2017 in Sweden and Norway. Dispensations of medicines from different therapeutic areas, which served as proxy for co-morbidities in 2017, were adjusted for age, gender, and OAT medications and studied in a logistic regression model.

Results

In total 3,529 individuals were identified with dispensed OAT in the Swedish cohort and 7,739 individuals in the Norwegian cohort. HCV treatment was utilized by 407 persons in Sweden and 920 in Norway during the study period. Annual HCV treatment uptake increased in both countries, giving a cumulative frequency of around one-third in both countries at the end of the study period. DAA treatment was associated with increased age (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) 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).

Conclusions

An increase in DAA treatment and HCV treatment uptake was observed among Swedish and Norwegian OAT patients during the introduction period of new direct-acting treatment regimens. However, a further scale-up is crucial to be able to control and eliminate the HCV endemic among OAT patients.
1. 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 with failing health policies for vulnerable populations. The HCV prevalence is around 50%, or more, among PWIDs [5, 6] and it is estimated that HCV complications will continue to increase within the next few years [7]. In 2016, the World Health Organization’s member states embraced the aim of eliminating viral hepatitis as a public health treat by 2030, which is defined by a 80% reduction in incidence and 65% reduction in mortality, respectively [8].

The coverage of preventive interventions and harm reduction services varies among PWIDs. Although the distribution of needle and syringe programs is relatively poor [9], opioid treatment programs such as opioid agonist therapy (OAT) has higher coverage in many countries [10]. In Norway, approximately 7,500 individuals are enrolled in OAT programs while only around 4,400 are enrolled in Sweden [11, 12], which may suggest that OAT coverage in Sweden is substantially lower. OAT has shown to reduce the risk of HCV acquisition [13], and despite ongoing illicit drug use, patients on OAT are achieving high SVR rates [14]. Hence, OAT programs may be a critical intervention for achieving large reductions in HCV transmissions. Several modelling studies have shown that significant reductions in HCV prevalence can be achieved with an adequate increase in HCV treatment uptake
Nevertheless, HCV treatment uptake has remained low [18, 19]. In Norway, annual HCV treatment uptake among OAT patients ranged from 1.3% to 2.6% in the period from 2004 to 2013 [19]. HCV treatment uptake, and in particular DAA treatment, among OAT patients in Sweden is unknown. Taking into consideration the potential of HCV disease elimination by publicly funded DAA policies in the Scandinavian countries [10, 20] and the high HCV prevalence among the OAT population, it is essential to calculate the DAA treatment uptake within an OAT delivery platform. Such estimates are important for countries aiming for HCV elimination or endemic control in near future.

Despite the high burden of disease and comorbidity among PWIDs and patients on OAT, knowledge is limited regarding any potential country differences among OAT patients receiving DAAs and those who do not. Furthermore, dispensed medicines from various therapeutic areas, such as psychopharmacological drugs, drugs used in diabetes, and cardiovascular disorders, can serve as a proxy for comorbidities.

Thus, this observational study aims to:

1. calculate HCV treatment uptake annually and cumulatively after the introduction of DAAs among patients receiving OAT in Sweden from 2014 to 2017
2. compare DAA treatment uptake between Norway and Sweden among patients receiving OAT from 2014 to 2017
3. evaluate if various dispensed drugs, age, gender and OAT medication can predict DAA treatment uptake among OAT patients in Sweden and Norway in 2017

2. Methods
2.1 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 (SPDR) and The Norwegian Prescription Database (NorPD). The registries cover the entire Norwegian and Swedish populations and record all drugs dispensed from pharmacies. NorPD was established on January 1, 2004 and SPDR on July 1, 2005, administered by The Norwegian Institute of Public Health and The Swedish National
Board of Health and Welfare, respectively. All drugs are classified according to The Anatomical Therapeutic Chemical (ATC) classification system. [21].

2.2 Study population and definitions
The study population included all individuals aged 18 to 75 years who received OAT. OAT was defined as being dispensed at least one defined daily dose (DDD) per day per calendar year of buprenorphine, methadone, buprenorphine-naloxone, and levomethadone in Sweden and Norway 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. Other opioids are very rarely used for OAT and considered outside national guidelines and were therefore not included in the study [22]. 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 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 (Figure S1). ATC/DDDs rendering to 2017 [23] were used to quantify the dispensed OAT medications.

2.3 Calculating HCV and DAA treatment
HCV treatment was defined as being dispensed either one or more pegylated interferon alpha in combination with ribavirin, or one or more of the DAAs (Table S2) per calendar year during the study period. The annual rates were calculated by dividing number of individuals with dispensed HCV treatment by individuals on OAT. The cumulative frequency, which is the addition 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 number of OAT patients with at least one dispensation of DAA by the total number of OAT patients per year and per country, which represents the annual prevalence of DAA use among OAT patients. Potential predictors of DAA treatment uptake were determined a priori and included OAT medication (methadone/levomethadone vs. buprenorphine-based), age, gender and various dispensed drugs (yes
from different therapeutic areas that were used as proxies for co-morbidities. All dispensations were recorded at the second ATC level (therapeutic subgroup), except for drugs affecting the nervous system, which was recorded at the third, fourth, and fifth ATC level (pharmacological subgroup to chemical substance) respectively (Table S2).

The calculation of HCV treatment uptake among OAT population is described under Table 2.

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

2.5 Data handling and ethical considerations
All data were received anonymous 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) on November 14, 2018 and the Regional Committee for Ethics in Medical Research (no. 2018/939) in Norway on June 19, 2018. Furthermore, the study was conducted in accordance with the Helsinki Declaration and as an observational study in accordance with international accepted STROBE guidelines [24].

3. Results
3.1 Basic characteristics
In Sweden, 3,529 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. 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, 7,739 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.

3.2 DAA and HCV treatment uptake
In Sweden, the annual DAA treatment ranged from 1.4% in 2014, to 4.5% in 2017. The cumulative frequency of DAA treatment was 14.4%. Overall, annual HCV treatment increased from 2.0% in 2014 to 4.5% in 2017, with a cumulative frequency of HCV treatment of 15.1% (Table 2). Overall, 92% of those receiving HCV therapy were treated with DAAs in the study period. Similar observations were noticed in the Norwegian cohort (Table 2).

In Norway, the annual DAA treatment ranged from 1.1% in 2014, to 6.6% in 2017. The cumulative frequency of DAA treatment was 13.3%. Annual total HCV treatment increased from 2.4% in 2014 to 6.8% in 2017, giving a cumulative frequency of HCV treatment of 16.1% (Table 2).

Cumulative frequency of HCV treatment uptake was estimated to 31.5 in Norway and 29.2 in Sweden for the study period.

3.3 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. In Sweden, 123 (4.5%) individuals received treatment. Variations in dispensations 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 binary logistic regression model (Table S3), DAA treatment was associated with increased age (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).

4. 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 was 15% and 16% in Sweden and Norway, respectively. When adjusted for estimated prevalence and incidence the cumulative HCV treatment uptake was higher in Norway with almost 32% during the study period. DAA treatment was associated with increased age and dispensation of drugs used in diabetes in Sweden. Dispensations of lipid modifying agents and antibacterials were associated with lower odds in Norway. Being female was associated with decreased odds for treatment in both countries.

Even if considerable advances have been made in recent year with the introduction of interferon-free treatment regimens for HCV, few have actually engaged in treatment [25]. Several studies have demonstrated continued low treatment uptake among PWIDs and OAT patients [19, 26]. However, concerns about DAA treatment to people who use drugs seems unwarranted as both adherence and high SVR rates in this group have been validated in randomized controlled trials [27, 28]. Our study suggests an increase in HCV treatment in Sweden and Norway, attributed by a complete shift to interferon-free treatment regimens among OAT patients. Treatment with DAAs in Sweden and Norway were previously limited by strict eligibility criteria based on stage of liver fibrosis. However, since 2017 and 2018 in Sweden and Norway, respectively, DAA treatment has been offered as universal health coverage to all HCV patients regardless of genotype and level of liver fibrosis [20, 29]. Treatment demand has naturally soared, especially among former PWIDs [30], while people who are still using drugs have seemingly not been fully able to benefit from the increased accessibility [30]. Arguably, this opts for considering all models of onsite HCV care to people who use drugs in OAT programs, which despite ongoing drug use, may still result in high SVR [14, 18].

Even if the cumulative frequency of DAA treatment uptake seems to be similar in Sweden and Norway, there may still be discrepancy not fully captured in our results. Estimated HCV treatment uptake is at best imprecise as accurate prevalence and incidence data among OAT individuals from
Sweden do not exist to our knowledge. In Norway it is estimated that mean prevalence among OAT patients was 52% and 43% in 2014 and 2017, respectively, with annual incidence of chronic HCV among PWIDs around 400 per year [7, 11]. However, if we consider the prevalence of Anti-HCV among PWIDs it seems higher in Sweden with 82% compared to 63% among PWIDs in Norway [31, 32]. Secondly, the coverage of OAT seems dissimilar. Sweden, with similar demography and roughly twice the general population compared to Norway has significantly less patients enrolled in OAT programs. Waal et al. estimate an overall OAT coverage around 60% among people with opioid dependence in Norway [33] compared to 10-50% OAT coverage in Sweden [34]. Part of the answer may lay in the current guidelines. Norway altered its OAT guidelines in 2010, making opioid addiction the absolute criteria for inclusion and being retained in treatment, however in Sweden, current OAT guidelines allow lower thresholds for OAT cessation in the case of repeated illicit drug use [11, 12]. Hence, it is not unlikely that the Swedish OAT population represents a remarkably smaller and more selected group of patients with less ongoing drug use and may for this reason be viewed more eligible for HCV treatment.

With the provision of DAA treatment available for all Norwegian and Swedish patients, it may be tempting to argue that this is the beginning of the end for the HCV endemic in Sweden and Norway. In addition to OAT, by 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 [35]. However, on the other hand it may still seem embryonic without sufficient surveillance and monitoring of the disease. 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, it is therefore impossible to assess whether cases were acute or chronic, or whether patients achieved SVR on their own, or how many cases were actually notified [19]. The result is that accurate HCV prevalence and incidence data prior to 2016 are not readily available. Furthermore, in order to eliminate HCV as a public health treat by 2030, which both countries have embraced, a coherent and structured national plan seems 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 [36]. On the contrary, there is not yet established an ambitious national Swedish hepatitis C plan [37]. Coupled with lower OAT coverage and a higher Anti-HCV prevalence, HCV elimination may seem more challenging and distant in Sweden compared to Norway.

Our findings suggest few intercountry differences in dispensed drugs among those treated with DAAs and not, except for drugs used for diabetes in the Swedish cohort, which was significantly higher and a predictor for 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 [38, 39]. This finding was not mirrored in the Norwegian cohort however. Even if dispensed drugs can serve as a proxy for co-morbidity it is well established that both somatic and especially mental illness are underdiagnosed and undertreated among individuals with substance use disorders [40], and 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, which may explain the reported association between DAA treatment among patients aged 46–55 in Sweden. Although, a reason for the observed age difference with regard to being treated for HCV may be that the younger patients are usually harder to reach due to an unstable life situation and drug abuse related behavior. Similarly, the analyzes point toward that women are less likely to be treated for HCV, however, this could just as much be that women having lower prevalence and incidence of chronic HCV.

5. 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, observational studies have 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 that particular year. We may also have included patients on methadone mixture that are not true OAT patients. However, to amend for this we did not only exclude methadone preparations on the basis of route of administration, such as tablets and injections, but also introduced a dosage criteria of minimum one DDD per day per calendar year, for all medications used for OAT. Furthermore, 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. In addition, DDD does not necessarily reflect the prescribed daily dose. Also, OAT and HCV treatment administered to hospitalized and institutionalized patients are not recorded in the registries. 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).

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

6. Conclusion
This observational study has demonstrated a large scale-up in DAA treatment among Swedish and Norwegian OAT patients. Both countries have an increased cumulative HCV treatment uptake of around one-third from 2014 to 2017, recognized by a complete shift to DAA treatment regimens. Midst a HCV endemic among PWIDs it is less clear whether people who currently use drugs have benefitted from the increased availability of interferon-free treatment. 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 establishing more accurate surveillance systems to provide a better care to this group of marginalized people.

Abbreviations
OAT Opioid agonist therapy
DAA Direct-acting antiviral agents
HCV Hepatitis C virus
Declarations

**Ethical 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.

**Availability of data and material**

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

**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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**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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Tables
Due to technical limitations, the tables are only available as a download in the supplemental files section.

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