ABSTRACT

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

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

Setting Patients who were dispensed OAT opioids from pharmacies.

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

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

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

Conclusions Nearly half of those patients who were dispensed an OAT opioid in Norway and Sweden were dispensed potentially addictive drugs. The differences identified between Norway and Sweden might be related to differences in eligibility guidelines and restrictions with respect to OAT.
hyperactivity disorder (ADHD), personality disorders, depression, other substance use disorders besides opioid addiction or injection-related diseases such as hepatitis C virus infection. The wide range of high-prevalent comorbidities can require coprescriptions of potentially addictive drugs to obtain an optimal medical treatment in the OAT population. Examples such as prescriptions of OAT in order to improve ADHD symptoms and short-term prescriptions of benzodiazepines to treat psychomotor agitation caused by stimulant intoxications or seizure prophylaxis, as in cases of benzodiazepine or alcohol withdrawal, illustrate clinical indications for such coprescriptions.

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

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

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

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

METHODS

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

Inclusion criteria in this study, therefore, identified patients with a high opiate tolerance who had a high degree of continuity in their OAT treatment.

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

Patient and public involvement
Patients and the public were not involved in the development of the study design, planning and recruitment. Study results were not distributed to the patients after...
the study. All data were handled strictly confidentially and anonymously. The Strengthening the Reporting of Observational Studies in Epidemiology Guidance checklist was applied during the preparation of the study.

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

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

Analysis strategy and statistical analyses

Data analysis

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

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

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

Statistical analyses

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

RESULTS

Descriptive characteristics

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

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

Dispensing rates of potentially addictive drugs

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

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

In 2017, the mean doses of dispensed benzodiazepines were 17mg/day diazepam equivalents in Norway, with a corresponding 16mg/day in Sweden (table 3). Further, the mean dose of dispensed z-hypnotics was 8mg/day zopiclone equivalents in both countries in 2017. The mean daily doses of dispensed pregabalin, gabapentin and lisdexamphetamine were higher in Norway than in Sweden (pregabalin: 402mg vs 345mg, gabapentin: 1021mg vs 772mg and lisdexamphetamine: 58mg vs 51mg), while the mean dose of dispensed methylphenidate per day was higher in Sweden compared with Norway (methylphenidate: 80mg vs 57mg). The results
were relatively similar in 2015 and 2016 except for the mean dose of dispensed lisdexamphetamine per day, which was higher (in mg) in Sweden than in Norway in 2015 (lisdexamphetamine: 42 mg vs 13 mg).

Combinations of potentially addictive drugs in 2017
The proportion of patients on OAT being dispensed a single potentially addictive drug was 34% in Norway and 31% in Sweden. A quarter were dispensed potentially addictive drugs from two or more drug groups (see online supplementary table S3). ‘Benzodiazepines and z-hypnotics’ was the most commonly dispensed combination of drugs, whereas ‘benzodiazepines and non-OAT opioids’ and ‘z-hypnotics and gabapentinoids’ were the second most common combinations in Norway and Sweden, respectively.

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

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

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

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

*Patients were categorised in the groups ‘Methadone/Levomethadone’ and ‘Buprenorphine/buprenorphine-naloxone’. The type of OAT opioids was calculated based on the most dispensed OAT opioid measured in DDD per calendar year.

DDD, defined daily dose; No., number of patients; OAT, opioid agonist therapy.
Table 2  Dispensation rates of potentially addictive drugs in patients receiving opioid agonist therapy

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

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

The differences in dispensing rates and mean daily doses of codispensed potentially addictive drugs between Norway and Sweden may also be explained by the composition and heterogeneity of OAT populations. The European Monitoring Centre for Drugs and Drug Addiction, evaluating OAT in 12 European countries,29 points out that restrictive policy, narrow inclusion criteria and costs are seen as substantial challenges limiting the coverage of OAT. In general, patients who repeatedly use illicit drugs in OAT have a higher coverage of OAT, which also includes patients using illegal drugs and accordingly those with a higher burden of comorbid diseases. In Sweden, repeated use of illicit drugs in OAT has more psychiatry and somatic comorbidities and systemic review evaluating OAT in 22 European countries, points out that restrictive policy, narrow inclusion criteria and costs are seen as substantial challenges limiting the coverage of OAT.42

Moreover, a tenth of the Norwegian OAT patients were dispensed a gabapentinoid in 2017, whereas nearly twice as many were dispensed this drug in Sweden. During the last decade, the dispensing of gabapentinoids has increased substantially in the general population in Norway and Sweden despite studies that point out that obstetric, policy factors, narrow inclusion criteria and costs are seen as substantial challenges limiting the coverage of OAT.42 43

Table 2 Continued

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

Less than six patients were dispensed tapentadol, hydromorphone, pentidine, lorazepam and midazolam (data not shown).

*Methadone tablets and injections medically indicated for pain.

No., Number of patients; OAT, opioid agonist therapy.
indications, regular urine testing to prevent concomitant street drug use, and close collaboration between prescribers of OAT opioids and those dispensing potentially addictive drugs may be important measures to decrease future overdose deaths and ensure more reasonable and safe treatment approaches among the highly morbid patients on OAT.

**STRENGTHS AND LIMITATIONS**

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

However, this study also has some limitations, mainly related to possible differences in selection bias between the studied populations. First, in both countries, patients may use methadone mixture for a medical indication other than OAT yet still be included in the OAT population. To account for this, only patients who had been dispensed a mean dose of one or more DDD of methadone mixture, levomethadone or buprenorphine/buprenorphine-naloxone during a calendar year were included. Second, mean daily doses were calculated by summing all dispensed doses of the respective drugs during a calendar year divided by 365.25 days. Dividing the dispensed doses per year by 365.25 have some limitations. Some patients may have been dispensed drugs in a higher mean daily dose within a shorter period than the calculations of mean daily doses per year indicate. Further, the drugs that were dispensed at the end of December for consumption in the following months were calculated as consumed in the year the drugs were dispensed. The latter could potentially signify that the mean daily doses were calculated higher than the dose recommended by the prescribers. Third, it is estimated that only about 60% of patients on OAT are identified through the Swedish Prescribed Drug Register; the remaining proportion may receive OAT opioids from specialised addiction outpatient clinics within specialist healthcare. In Norway, it is estimated that 90% of patients who were dispensed OAT opioids were registered in the Norwegian Prescription Database. The fact that 40% of the Swedish patients were lacking could skew the results and affect the conclusion. Patients who received OAT opioids from outpatient clinics may have more psychiatric and physical comorbidities and need more follow-ups than patients who were dispensed OAT opioids by pharmacies. Therefore, these comorbid patients who could not be captured by our study may have had higher dispensing rates of potentially addictive drugs, meaning that the dispensing rates may have been underestimated in this study. Fourth, the Swedish Prescribed Drug Register does not provide data on patients who died during the study period. Due to this, patients were censored from the year with no dispensing during a calendar year.
Table 3  Dispensed dose of potentially addictive drugs in the period from 2015 to 2017

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

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

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

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

The table displays the mean doses and mean daily doses of dispensed benzodiazepines, z-hypnotics, pregabalin, gabapentin, methylphenidate and lisdexamfetamine per calendar year in the period from 2015 to 2017. The mean daily dose of each drug was calculated by summing all dispensed DDD per year. The summarised DDD were converted to milligrams according to the WHO’s standard.

In addition, for benzodiazepines and z-hypnotics, all doses of dispensed benzodiazepines were converted into diazepam equivalents and z-hypnotics into zopiclone equivalents. We used equipotency tables from the Norwegian Directorate of Health34 and a study evaluating the equipotency of lorazepam vs diazepam35 when calculating the doses to diazepam and zopiclone equivalents. Further, all dispensed doses (benzodiazepines, z-hypnotics, gabapentin, pregabalin, methylphenidate and lisdexamfetamine) per year were divided by 365.25 days to calculate the mean and median daily doses, and the daily doses at the 25 percentile, and the 75 percentile.
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