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

Jørn Henrik Vold ,[1,2] Christer Aas ,[1,2] Svetlana Skurtveit,[3,4] Ingvild Odsbu,[5] Fatemeh Chalabianloo,[1,2] Johan Reutfors,[5] Anne Halmøy,[6,7] Kjell Arne Johansson,[1,2] Lars Thore Fadnes [1,2]

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For numbered affiliations see end of article.

Correspondence to
Jørn Henrik Vold;
jorn.vold@uib.no

ABSTRACT

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

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

Setting Patients who were dispensed OAT opioids from pharmacies.

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

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

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

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

Strengths and limitations of this study

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

INTRODUCTION

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

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

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

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

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

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

METHODS

Data sources

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

Study population

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

Patient and public involvement

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

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

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

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

Analysis strategy and statistical analyses

Data analysis

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

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

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

Statistical analyses

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

RESULTS

Descriptive characteristics

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

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

Dispensing rates of potentially addictive drugs

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

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

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

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

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

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

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

Combinations of potentially addictive drugs in 2017

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

DISCUSSION

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

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

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

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

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

Continued

Table 2 Continued

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

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

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

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

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

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

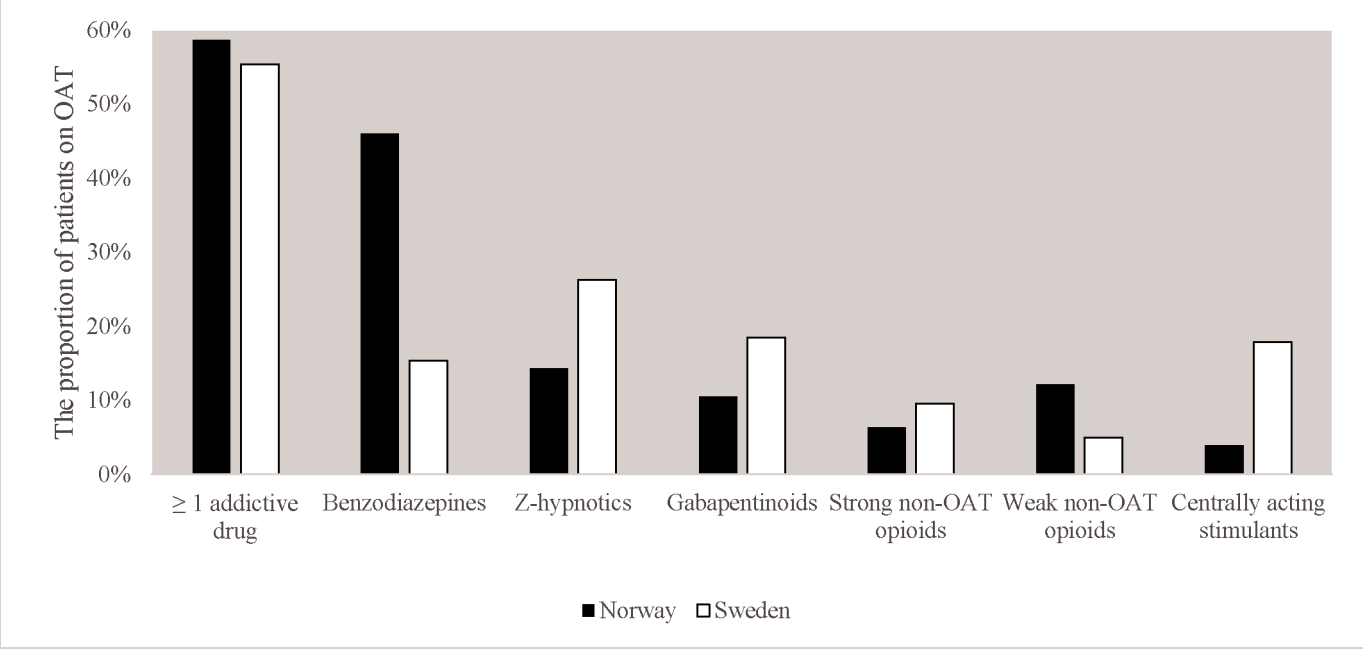

Figure 1 The proportion of patients on OAT who were dispensed potentially addictive drugs in 2017. The figure displays the proportion of patients on OAT who were dispensed at least one potentially addictive drug, benzodiazepine, z-hypnotic, gabapentinoid, strong non-OAT opioid, weak non-OAT opioid and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

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

STRENGTHS AND LIMITATIONS

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

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

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

Year	2015		2016		2017	
Country	Norway	Sweden	Norway	Sweden	Norway	Sweden
Benzodiazepines						
Diazepam equivalents						
Number of patients	2622	438	2503	451	2556	421
Mean (mg/year)	6920	6896	6585	6437	6216	5936
Mean (mg/day/year)	19	19	18	18	17	16
Median (mg/day/year)	10	10	10	9	10	9
25 percentile (mg/day/year)	3	2	3	2	3	2
75 percentile (mg/day/year)	21	22	21	21	20	21
Z-hypnotics						
Zopiclone equivalents						
Number of patients	912	750	834	760	798	721
Mean (mg/year)	2867	3037	2904	2951	2942	3008
Mean (mg/day/year)	8	8	8	8	8	8
Median (mg/day/year)	5	7	6	6	6	7
25 percentile (mg/day/year)	1	2	1	2	1	2
75 percentile (mg/day/year)	10	12	10	12	11	12
Gabapentinoids						
Gabapentin						
Number of patients	192	164	183	203	207	213
Mean (mg/year)	335 409	256 505	334 730	276 083	372 966	282 017
Mean (mg/day/year)	918	702	916	755	1021	772
Median (mg/day/year)	376	324	492	329	492	329
25 percentile (mg/day/year)	82	82	82	82	164	82
75 percentile (mg/day/year)	1287	992	1232	986	1203	986
Pregabalin						
Number of patients	348	330	359	331	413	317
Mean (mg/year)	134 777	123 510	144 551	119 335	146 684	126 122
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)	18 957	28 966	21 364	29 248	20 845	29 305
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	15 238	18 158	17 649	21 033	18 514
Mean (mg/day/year)	13	42	50	48	58	51
Median (mg/day/year)	14	29	37	42	42	48

Continued

Table 3 Continued

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

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

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

CONCLUSION

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

Author affiliations
[1]Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway
[2]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[3]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway
[4]Norwegian Centre for Addiction Research, University of Oslo, Oslo, Norway
[5]Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[6]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[7]Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

Contributors JHV led the analysis and was involved in the study design and writing of the article. CFA, SS, IO, FC, JR, AH, KAJ and LTF contributed to the study design, analysis, and writing of the article. All authors have read and approved the final article.

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Patient consent for publication Not required.

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

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ORCID iDs
Jørn Henrik Vold http://orcid.org/0000-0001-8701-7638
Christer Aas http://orcid.org/0000-0002-6469-9354
Lars Thore Fadnes http://orcid.org/0000-0001-8757-2092

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