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Persistent use of high-dose opioids and other addictive medications

SHORT REPORT

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Background

Persistent use of high-dose opioids increases the risk of overdose, particularly when used in combination with other sedatives. The aim of the study was to examine the number of people with persistent use of high-dose opioids in 2011 and 2019, the proportion who received the opioids on a 'blue prescription' (heavily subsidised prescription) and the proportion with concurrent persistent use of benzodiazepines and z-hypnotics.

Material and method

Persistent use of high-dose opioids was defined as the dispensing of more than two defined daily doses or 50 mg of oral morphine equivalents of opioids per day, in at least three out of four quarters. Data from 2011 and 2019 were obtained from the Norwegian Prescription Database.

Results

In 2011 and 2019, a total of 7010 (142 per 100,000 population) and 12,199 patients (228 per 100,000 population), respectively, were given high-dose opioids for persistent use. In 2011, 31 % of these patients received at least one opioid blue prescription; in 2019, the proportion was 51 %. In 2011, 45 % of patients receiving high-dose opioids for persistent use also received over 100 defined daily doses of benzodiazepines, and 35 % received over 100 defined daily doses of z-hypnotics. The corresponding figures for 2019 were 30 % and 32 %.

Interpretation

The proportion of the population receiving high-dose opioids for persistent use was higher in 2019 than in 2011.

Use of opioids for non-cancer-related chronic pain conditions is generally not recommended due to the risk of addiction, overdose and other serious side effects (1). The risk of overdose increases for persistent use of opioids, increasing daily doses and concurrent use of other central nervous system depressants, such as benzodiazepines and z-hypnotics (2). The 'CDC Guideline

for Prescribing Opioids for Chronic Pain' therefore recommends that doctors carefully weigh the benefits and risks before increasing the dose to > 50 mg of oral morphine equivalents, and that the dose is not increased to > 90 mg of oral morphine equivalents (3). Concurrent use of benzodiazepines and other sedatives is not recommended (3).

In Norway, general practitioners (GPs) can apply for patients with severe, persistent pain to receive opioids on a blue prescription up to a daily dose corresponding to 100 mg of oral morphine equivalents daily. For daily doses of oral morphine equivalents exceeding 100 mg, approval must be sought every year by doctors at interdisciplinary pain clinics or doctors in health trusts who have acted as consultants for such units. A ceiling of 300 mg of oral morphine equivalents daily has been set for blue prescriptions (4).

We recently published a study based on the same dataset used here, which showed that 561,917 people collected at least one opioid prescription in 2019, and that 59,996 patients collected more than 0.5 defined daily doses or 12 oral morphine equivalents daily, corresponding to persistent use (5). This represents an increase of 4.6 % and 10.2 % from 2011, respectively, adjusted for population growth. We subsequently found that we lacked corresponding data for the group with the highest risk, namely those with persistent consumption of high doses of opioids. The purpose of this study was therefore to further investigate how many patients were persistent users of high-dose opioids in 2011 and 2019, the proportion who received these medications on a blue prescription, and the proportion who were also persistent users of benzodiazepines and/or z-hypnotics.

Material and method

All data in the study were obtained from the Norwegian Prescription Database, which records all medications dispensed by pharmacies in Norway. The number of defined daily doses was obtained from the Norwegian Prescription Database, and the number of oral morphine equivalents was calculated for all opioids using the method described previously (6). High consumption of the most potent opioids, such as oxycodone, was identified by measuring the amount in oral morphine equivalents. For less potent opioids, such as codeine, high consumption was captured by measuring the amount in defined daily doses. For example, a defined daily dose of oxycodone is 75 mg, which corresponds to 112 mg of oral morphine equivalents, while a defined daily dose of codeine is 120 mg, corresponding to 12 mg of oral morphine equivalents (7). Therefore, in this study, we defined high consumption by measuring opioid use both in defined daily doses and in oral morphine equivalents. To define persistent use, we applied the distribution criterion from Svendsen et al., which involves the dispensing of opioids in at least three out of four quarters in a year (8). We included all individuals over 18 years who, on average, collected prescriptions for opioids corresponding to more than 50 mg of oral morphine equivalents or more than two defined daily doses of opioids per day from pharmacies, and who collected prescriptions for opioids in at least three out of four quarters in the year 2011 and/or 2019.

The patients were divided into three dose categories. The group with the lowest dose consisted of patients who received more than the recommendation in the US guideline, i.e. 50 oral morphine equivalents (3), but who could still receive the opioid amounts on a blue prescription in primary care. They collected prescriptions for amounts corresponding to 2–4 defined daily doses or 50–100 mg of oral morphine equivalents per day for at least three out of four quarters in the year.

Dose group 2 consisted of patients who received amounts exceeding the recommended limit for primary care prescriptions, but which can be prescribed by doctors in the specialist health service. This group collected prescriptions for amounts corresponding to 4–12 defined daily doses or 100–300 mg of oral morphine equivalents per day for at least three out of four quarters in the year.

Dose group 3 consisted of patients who received amounts exceeding the recommended limit for prescriptions in the specialist health service for non-cancer-related chronic pain (1). This group collected prescriptions for amounts corresponding to > 12 defined daily doses or > 300 mg of oral morphine equivalents per day for at least three out of four quarters in the year.

We also examined how many patients concurrently received more than 100 defined daily doses of benzodiazepines and/or z-hypnotics in the year and for whom at least one opioid prescription was dispensed on a blue prescription with reimbursement code -71 under the blue prescription regulation (strong chronic pain) (4). Patients who received at least one prescription with reimbursement code -90 (palliative end-of-life care) were excluded. The proportion of the population using opioids was calculated based on the average population in Norway in 2011 (4,953,088) and 2019 (5,347,896) (9).

The study is part of the research project 'Preventing an Opioid Epidemic in Norway: Focusing on Treatment of Chronic Pain (POINT)' (10) and was approved by the Regional Committee for Medical and Health Research Ethics (REC South-East 2019/656, REC South-East C 2020/1871 (amendment – extended project period)). A data protection impact assessment was also conducted for the project, which was approved by the data protection officer at the Norwegian Institute of Public Health.

Results

Table 1 shows the percentages and number of patients with persistent use of high-dose opioids in 2011 and 2019, categorised by dose groups and whether the recipients received the opioids on a white or blue prescription. The total number of patients was 7010 (142 per 100,000 population) in 2011 and 12,199 (228 per 100,000 population) in 2019, representing a 61 % increase. The difference between the two years was greatest in the group that received at least one opioid blue prescription, from 44 per 100,000 population in 2011 to 117 per 100,000 population in 2019. Corresponding figures for those who received the opioids exclusively on a white prescription were 97 per 100,000 population in 2011 and 111 per 100,000 population in 2019, an increase of 14 %. The proportion of patients with persistent use of high-dose opioids who also

received more than 100 defined daily doses of benzodiazepines was 45 % in 2011 and 30 % in 2019. Corresponding figures for z-hypnotics were 35 % and 32 %, respectively.

Table 1

Patients with persistent use of high-dose opioids (more than two defined daily doses or 50 mg of oral morphine equivalents per day for at least three out of four quarters in the year), categorised into three dose groups based on the total amount of opioids dispensed in 2011 and 2019. The study population is divided into two groups based on whether they received the opioids exclusively on a white prescription or received at least one blue prescription with reimbursement code -71. We have also included the total for both groups. Additionally, we show the percentage of these patients who received more than 100 defined daily doses of benzodiazepines and/or z-hypnotics in the same year. The percentage of the population using opioids was calculated based on the average population in Norway in 2011 (4,953,088) and 2019 (5,347,896) (9). DDD = defined daily doses; OMEQ = oral morphine equivalents.

	Group 1: > 2–4 DDD / > 50–100 mg OMEQ per day		Group 2: > 4–12 DDD / > 100–300 mg OMEQ per day		Group 3: > 12 DDD / > 300 mg OMEQ per day		Total for groups 1–3: > 2 DDD or > 50 OMEQ per day	
Year	**2011**	**2019**	**2011**	**2019**	**2011**	**2019**	**2011**	**2019**
Persistent use of high-dose opioids								
Percentage (number per 100,000 population)	91	137	39	73	11	19	142	228
No. of patients	4 529	7 307	1 923	3 881	558	1 011	7 010	12 199
Concurrent > 100 DDD benzodiazepines, % of persistent users of high-dose opioids	42	26	48	33	62	48	45	30
Concurrent > 100 DDD z-hypnotics, % of persistent users of high-dose opioids	36	32	35	32	28	29	35	32
White prescription only								
Percentage (number per 100,000 population)	70	72	22	30	5	9	97	111
No. of patients	3 449	3 829	1 103	1 626	264	484	4 816	5 939
Age (median, interquartile range)	54 (45–66)	59 (48–72)	53 (43–66)	56 (47–68)	48 (42–57)	52 (44–60)	54 (44–66)	57 (47–70)
At least one blue prescription for opioids								
Percentage (number per 100,000 population)	22	65	17	42	6	10	44	117
No. of patients	1 080	3 478	820	2 255	294	527	2 194	6 260

	Group 1: > 2–4 DDD / > 50–100 mg OMEQ per day		Group 2: > 4–12 DDD / > 100–300 mg OMEQ per day		Group 3: > 12 DDD / > 300 mg OMEQ per day		Total for groups 1–3: > 2 DDD or > 50 OMEQ per day	
Age (median, interquartile range)	59 (48–75)	62 (50–75)	57 (47–69)	59 (49–70)	53 years (46–63)	55 (46–65)	57 (47–71)	60 (50–72)

Discussion

We have previously shown that the proportion of the population with persistent opioid use was 10.2 % higher in 2019 compared to 2011 (5). The results from this study, based on the same dataset, show that the subgroup with persistent use of high-dose opioids increased by 61 %.

The proportion of those with persistent use of high-dose opioids on a blue prescription increased more than the proportion receiving them exclusively on a white prescription. This was particularly evident in the group receiving less than 100 mg of oral morphine equivalents per day. In 2016, GPs were given the opportunity to apply for reimbursement for up to 100 mg of oral morphine equivalents per day, which may partly explain the higher numbers in 2019 compared to 2011. However, the proportion receiving opioids on a white prescription also increased. Additionally, the group receiving doses exceeding 100 mg of oral morphine equivalents per day increased, without a corresponding decrease in the group receiving opioids on a white prescription.

Use of opioids in combination with benzodiazepines and z-hypnotics increases the risk of overdose (1, 11). Compared to 2011, we found that the proportion of patients receiving persistent high doses of opioids while also taking these other addictive medications was lower in 2019. The proportion of patients receiving benzodiazepines was highest in the group that received more than 300 mg of oral morphine equivalents of opioids exclusively on a white prescription. Despite the observed decrease, it is still extremely concerning that many patients with persistent use of high-dose opioids are concurrently using these other addictive medications. In 2023, the heads of the four pain clinics at university hospitals in Norway published an article in which they presented a collective proposal for seven measures to address excessive opioid use and harmful co-medication (12).

The Norwegian Prescription Database provides a good overview of medications dispensed to individuals, but a limitation of the data is that it does not include medications administered in hospitals. Another weakness of the study is that the most recent data were collected in 2019, meaning that it may not accurately reflect the current situation. The data were also not adjusted for changes in the population composition between the two years. Chronic pain conditions are more common in older adults, and since the study population in 2019 was

older, the increasing age of the population may have impacted on the results. Although we excluded all patients who received opioids that were reimbursed under the palliative care reimbursement code (-90), it is possible that some patients with an active cancer diagnosis received opioids that were reimbursed under the code for chronic pain (-71) since they are not in a palliative setting. Registry-based research requires resources, but these results suggest that there is a need for newer and more comprehensive data to monitor developments over time.

Conclusion

We found a significant increase in the proportion of the population persistently prescribed high-dose opioids in 2019 compared to 2011. The increase was greatest in the group that received opioids on a blue prescription. A reduction was observed in the proportion of patients with persistent use of high-dose opioids who were also receiving other addictive medications.

The article has been peer-reviewed.

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