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ORIGINAL ARTICLE

Trends in opioid prescribing in Estonia (2011-2017)

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Abstract

Our objective was to examine the trends and variation in opioid prescribing in Estonia from 2011 to 2017. This retrospective cross-sectional study is based on a nationwide prescription medicines database. We stratified the analysis by treatment indication (cancer vs noncancer pain). Between 2011 and 2017, annual opioid prescribing rates increased by 67% (from 82.9 to 138.6 prescriptions per 1000 population). The annual number of prescriptions per patient did not change substantially (from 2.94 in 2011 to 2.87 in 2017), and was higher among cancer patients (5.07 vs 2.67 annual prescriptions per cancer and noncancer patients, respectively, in 2017). The use of the most potent opioids (morphine, fentanyl) was higher in noncancer than in cancer patients. The use of prescription opioids is low, and raises concern about the potential undertreatment of cancer pain, in parallel with misuse of opioids for either noncancer pain or diversion.

KEYWORDS

Estonia, opioids, prescription drugs

1 | INTRODUCTION

Research from the United States, Australia,[1] Canada,[2] and European countries[3-6] have shown a significant increase in opioid utilization during the past decade to such a scale that several countries (United States, Canada, Australia) have called for an organized response to the opioid crisis.[7-9] In 2017, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reports that while some parallels exist, the overall European situation remains different to that reported from the United States.[10] The highest use of (legal in and outpatient care) opioids (fentanyl, oxycodone, morphine, hydromorphone, pethidine) in 2014-2016 was documented in Germany and Austria (> 20 000 defined daily doses (DDD)/1 000 000), and this use significantly exceeds that described for the United States (16 500 DDD/1 000 000).[11] Yet, the literature highlights the absence of an opioid crisis in Germany[12] or Austria.[13]

Within Europe, there is still a more than 10-fold difference between the highest consumption in the Western/Northern countries and the lowest consumption in the Southern/Eastern countries. In several countries (including Estonia) the estimated opioids use is well below 2000 DDD/1 000 000, with the lowest in the Russian Federation (135 DDD/1 000 000).[11] While high opioid usage is undoubtedly a serious problem, the underuse of opioid analgesia (low opioid prescribing) is also a threat.

Data on the use of prescription opioids dispensing and changes in use over time in Estonia are limited.[6] This study aimed to describe the trends of the most commonly prescribed opioids in Estonia from 2011 to 2017, stratified by cancer and noncancer pain treatment groups.

Abbreviations: DDD, defined daily doses; EHIF, Estonian Health Insurance Fund; OME, oral morphine equivalent; SmPC, Summaries Product Characteristics.

2 | MATERIALS AND METHODS

This time-series analysis included data on all dispensed opioids prescriptions between 2011 and 2017 in Estonia.

2.1 | Data source

Since the early 2000s, the Estonian Health Insurance Fund (EHIF) has maintained a complete record of prescriptions issued for outpatient care. About 94% of the Estonian population is covered by the EHIF.[14] Prescriptions for uninsured individuals are also captured in the EHIF database (although not reimbursed).

2.2 | Data

We use data on all filled prescriptions for opioid analgesics (ATC N02A) issued during the period 1 January 2011 to 31 December 2017 from the EHIF. For each prescription data on medication (including ATC code, amount dispensed), indication for use (ICD-10 diagnosis code), date of filling; patient's age, and gender were retrieved.

2.3 | Utilization measures

We present (a) the number of prescriptions; (b) the number of patients; (c) the DDD[15] for each opioid per patient and/or per year; and (d) the oral morphine equivalent (OME)[16] quantity per patient and/or per year. The annual total amount of each opioid entity dispensed was divided by the DDD of the particular opioid.[17,18] We calculated the oral morphine equivalency to account for the variation in biological strength. The conversion to OMEs was based on the amount of the base form of the substance, according to the Summaries Product Characteristics (SmPC)[19] or by conversion factor[20] from the salt form, if the amount of the base form was not stated in the SmPC. The amount of opioid for each prescription was multiplied by the equi-analgesic ratio of the opioid to derive the OME dose.[16]

2.4 | Cancer and noncancer care use

Patients and corresponding opioid prescriptions were categorized as either 'cancer' group based on the ICD-10 codes for neoplasms (malignant, C00-C97; in situ, D00-D09; benign, D10-D36; or of uncertain or unknown behavior, D37-D48) recorded on the prescription; otherwise, they were included in the "noncancer" group. For annual comparison, each patient was again defined as "cancer" or "noncancer" according to the presence of any neoplasm diagnosis on the prescriptions in the given year.

2.5 | Data analysis

Consumption of opioids was expressed as DDD and the total annual OME in mg (for all opioids by totaling the OMEs of all opioids dispensed).

For each calendar year, we calculated the consumption of opioids expressed as DDD per 1000 population (the mid-year, Statistics Estonia[21]) per day. The percentage change of DDD per 1000 population per day for the total and each opioid from 2011 to 2017 are presented.

We calculated the DDD per 1000 patients receiving opioids per day in outpatient care by totaling the DDDs per 1000 patients per day for each opioid.

Annual opioid prescribing rates were calculated for the total population (by dividing the number of opioid prescriptions by the total number of mid-year population) and patients (by dividing the number of opioid prescriptions by the number of patients filling prescriptions); the rates presented are per 1000 individuals. Linear trend analysis was used to assess changes in time. All analyses were conducted using statistical environment R.[22]

The study procedures were conducted in accordance with local data protection regulations. The analysis used existing records containing only nonidentifiable data and was therefore exempt from ethical review.

3 | RESULTS

In total, 201 890 outpatients (60% female) received opioids during the 7-year study period. Of the total opioid prescriptions, 13.8% were filled for the management of cancer pain and 86% for noncancer pain. The mean age of patients filling opioid prescriptions (at the first prescription in the study period) was 58.8 years (SD 17.8). The patients with cancer diagnosis were older than noncancer patients (mean of 67.3 vs 57.7 years).

From 2011 to 2017, in total, 1 153 385 prescriptions of the opioid analgesics were filled. Tramadol was the most frequently used opioid (n = 699 700 prescriptions), followed by codeine (n = 338 744), oxycodone (n = 45 153), morphine (n = 32 932), dihydrocodeine (n = 22 543), fentanyl (n = 14 050), pethidine (n = 236), and very few (<25 prescriptions) for buprenorphine, tapentadole, or pethidine.

Annual opioid prescribing rates increased by 67% (from 82.9 to 138.6 prescriptions per 1000 population). When taking total oral morphine equivalency into account, the increase was sustained at 66% (from 40.0 to 66.6 g per 1000 population).

During the study period there was a 128% increase in the use of weak (codeine, dihydrocodeine, tramadol) and 164% in the use of strong opioids (morphine, oxycodone, fentanyl) (Table 1). Tramadol had the highest mean annual DDD per 1000 per day. The consumption of codeine increased about 400% (from 0.36 to 1.75 DDD per 1000 population per day); consumption of oxycodone, dihydrocodeine, and fentanyl increased more than twofold, and the use of

TABLE 1 Prescription opioids utilization: annual prevalence, prescription rate per 1000, the number of defined daily dose (DDD) and oral morphine equivalent dose per 1000 population per year for opioids and the percentage of consumption change from 2011 to 2017 in Estonia

	2011	2012	2013	2014	2015	2016	2017	Change: 2011-2017
Annual prevalence (use of any opioid)	2.8%	3.2%	3.5%	3.8%	4.1%	4.3%	4.8%	71%
Number of prescriptions (per 1000)	82.9	94.8	96.2	107.1	116.2	125.3	138.6	67%
OME (mg, all opioids) (per 1000)	39 978	43 204	47 350	54 875	59 231	63 134	66 553	66%
All opioids (DDD per 1000)	698	803	917	1081	1207	1354	1504	115%
Codeine[a] combined	130	186	239	318	401	515	638	391%
Tramadol[a] including combined	461	516	562	617	638	648	665	44%
Oxycodone[a] including combined	42.7	36.4	49	70	79.4	91.5	101.2	137%
Morphine[a]	37.4	34.4	33.2	34.1	36.5	38.9	34.9	–7%
Dihydrocodeine[a]	8.83	9.92	16.18	16.61	16,88	20.39	22.75	158%
Fentanyl[a]	17.6	20.5	16.9	24.6	34.4	40.6	41.2	134%

[a]Codeine (ATC N02AJ06), tramadol (ATC N02AJ13, N02AJ14, N02AX02), oxycodone (ATC N02AA05, N02AA55), morphine (ATC N02AA01), dihydrocodeine (ATC N02AA08), fentanyl (ATC N02AB03).

morphine for outpatient care has remained close to 0.10 DDD per 1000 population per day.

There was a simultaneous increase in both the total annual number of prescriptions (66% increase from 2011 to 2017) and the annual number of opioid-using patients (70% from 2011 to 2017). The increase in the annual numbers of patients receiving opioids was more pronounced among noncancer patients (75% vs 29% increase from 2011 to 2017) (Table 2).

The annual number of prescriptions per patient did not change substantially (from 2.94 in 2011 to 2.87 in 2017) (Table 2). The mean number of annual opioids prescriptions was higher among cancer patients during the period of observation (ie, 5.07 vs 2.67 annual prescriptions per cancer and noncancer patients, respectively, in 2017). In 2017 the mean annual OME for cancer patients exceeded that dispensed by noncancer patients more than four times (4600 vs 1100 mg per patient per year). The mean annual OME per cancer pain patient fluctuated from 4000 mg (in 2013) to 4900 mg (in 2016). We did not observe a change in the annual amount of opioids (expressed in OME per patient) prescribed to noncancer patients during the period of observation.

Throughout the period, morphine consumption per patient among noncancer patients exceeded that of the cancer patients; also per patient consumption of fentanyl and dihydrocodeine was higher among noncancer patients than cancer patients in some years (Figure 1).

4 | DISCUSSION

Our study covers complete (all medical specialists) opioid analgesic prescribing (outpatient care) data for the whole of Estonia.

First, utilization of prescription opioids in Estonia is considerably lower than in developed countries in Europe, the United States and Australia. At population-level, the amount of opioids prescribed in Estonia in 2017 was almost 10 times lower than in the United States,[23] approximately six times lower than in the United Kingdom[4] and two times lower than in Scandinavian countries.[24] At the level of outpatient care, in 2017 in Estonia the annual average opioid consumption per user was at least two to three times lower than in Scandinavian countries.[24] It is important to note that tramadol is the most used prescription opioid in Estonia. This synthetic weak μ-opioid receptor agonist was classified as a controlled substance in the United Kingdom[25] and United States[26] in 2014, and re-classification is under consideration in Canada.[27] Tramadol is not classified under controlled substances in Estonia. However, its abuse potential cannot be underestimated.[28]

Second, the use of prescription opioids is increasing—we found a substantial rise in opioid prescribing between 2011 and 2017, with important differences between certain opioids. Codeine use has increased by more than 300% and use of fentanyl, oxycodone, and dihydrocodeine has increased more than 100%, whereas morphine use decreased by 7%. Increasing codeine sales have received attention in Europe in relation to abuse affecting diverse groups of patients, from children to older people and among all social classes.[29] Decreasing morphine use in parallel with the sharply increasing use of oxycodone is described in Scandinavian countries,[30,31] the United Kingdom,[4,17] Australia,[32] and the United States.[33] Escalating use of fentanyl for the treatment of chronic noncancer pain has also been documented elsewhere (Australia,[32] Scandinavian countries[34]). Pharmaceutical fentanyl, with a potency 50-100 times higher than morphine, greatly increases opioid-related risks (eg, high overdose and abuse potential).[35-37]

Third, irrespective of the generally low use of prescription opioids, noticeable signs should raise an alert. The role and utility

TABLE 2 Annual prescription opioids utilization in Estonia, 2011-2017

	2011	2012	2013	2014	2015	2016	2017	Change 2011-2017
All patients								
Number of prescriptions	110 020	125 338	126 832	140 746	152 807	164 919	182 599	66%
Number of patients	37 473	42 729	45 738	49 736	53 563	57 070	63 713	70%
Number of prescriptions per patient	2.9	2.9	2.8	2.8	2.9	2.9	2.9	−2%
Noncancer care patients								
Number of patients	33 509	38 411	41 190	44 946	48 638	52 148	58 607	75%
Number of prescriptions per patient	2.7	2.7	2.6	2.6	2.7	2.7	2.7	−2%
Opioid consumption (per patient)								
DDD (mean)	21.0	21.7	23.3	25.3	26.3	27.8	28.0	33%
Oral morphine equivalents (mg) (mean)	1030	1026	1068	1123	1136	1129	1096	6%
Cancer care patients								
Number of patients	3964	4308	4543	4790	4925	4922	5106	29%
% female	48.1	49.5	49	50.1	50.1	50.1	49.7	3%
Age in years (mean)	66.9	67.6	67.8	67.8	67.8	68.3	68.3	
Number of prescriptions per patient	4.8	4.8	4.6	4.7	4.8	5.1	5.1	6%
Opioid consumption (per patient)								
DDD (mean)	56.2	53.3	54.3	59.3	62.2	67.5	66.2	18%
Oral morphine equivalents (mg) (mean)	4682	4117	4034	4524	4595	4917	4597	−2%

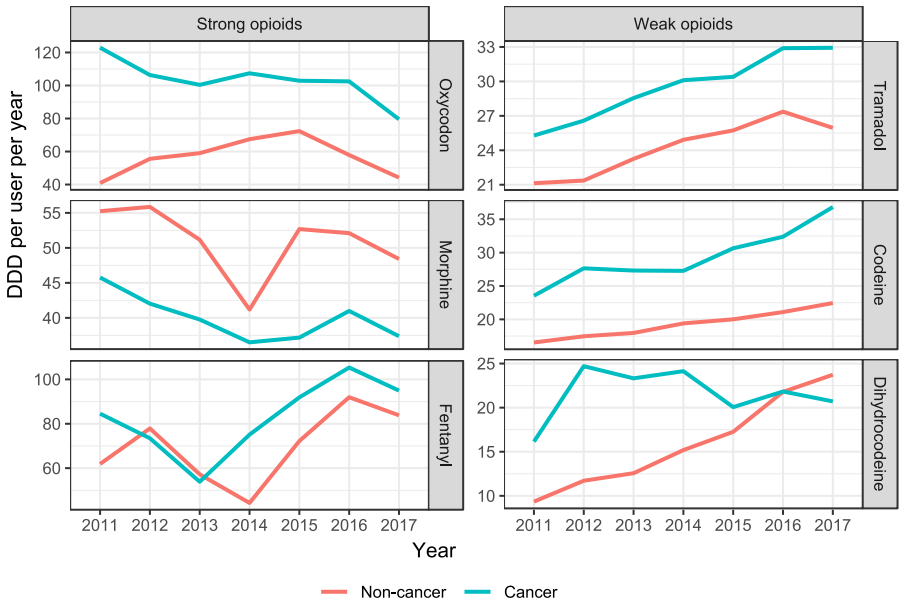

FIGURE 1 Prescription opioids use (DDD per user per year) by noncancer and cancer care patients in Estonia, 2011-2017

of codeine and tramadol in cancer pain are controversial.[38,39] Excluding these opioids from the outpatient care received by cancer patients in Estonia could indicate alarmingly low adequate pain management. In 2017, 86% of prescribed opioids were used for alleviation of noncancer pain in Estonia. The increase in the use of strong opioids (mainly fentanyl) as being largely attributable to prescribing for noncancer patients. Larger doses of morphine and similar doses of fentanyl among noncancer compared to cancer patients could either represent good management for patients with acute or chronic noncancer pain or unwarranted and dangerous prescribing in pain care and/or drug diversion. Quantifying the extent of diversion is difficult. Anecdotal evidence from Estonia indicates a sharp increase in the misuse of prescription medicines, in parallel with episodes of an illicit drugs (mainly fentanyl) shortage and the low quality of the fentanyl sold on the illicit market during the past couple of years (A. Kurbatova, head

of the Centre for Prevention of Drug Addiction and Infectious Diseases at the National Institute for Health Development; personal communication 18 July 2019). Combined with self-misuse, a frequent form of diversion is reselling the prescribed medicines at a higher price (A. Uusküla, unpublished data).

Last but not least, Estonia is one of the countries hardest hit by the opioid crisis: in 2015, Estonia ranked second after the United States in drug overdose deaths in men,[40] and, until 2018, drug overdose mortality in Estonia was the highest in the European Union for over 15 years.[41] This epidemic of overdose mortality cannot be attributed to prescription opioids use, and was caused by the use of illicitly manufactured fentanyls (3-methylfentanyl, fentanyl, carfentanyl, narfentanyl).[42] Data from Estonia support a critical role of the illicit opioids use to the crisis.

5 | CONCLUSION

Monitoring data nationally for potentially problematic prescribing might help to highlight areas where action is most required, and can have a valuable role in improving clinical and public health practice. In Estonia, overall levels of opioid prescribing have increased substantially since 2011 but, despite this increase, indicate the undertreatment of cancer-related pain and potentially some mistreatment in noncancer pain.

6 | AUTHOR CONTRIBUTORS

AU conceived the project, with input from OL, KE, KK, and MU. AU and MR designed the methods and interpreted the findings, with input from OL, KE, KK, and MU. MR performed the analyses in R. AU wrote the first draft. All authors contributed to and approved the final manuscript.

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DISCLOSURES

There are no competing interests to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Estonian Health Insurance Fund. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Estonian Health Insurance Fund.

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