INTRODUCTION

Research from the United States, Australia, Canada, and European countries 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. 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. The highest use of (legal in and outpatient care) opioids (fentanyl, oxycodone, morphine, hydromorphone, pethidine) in 2014-2016 was documented in Germany and Austria (16 500 DDD/1 000 000). Yet, the literature highlights the absence of an opioid crisis in Germany or Austria.

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). 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. 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.
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. 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 for each opioid per patient and/or per year; and (d) the oral morphine equivalent (OME) 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. 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) or by conversion factor 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.

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) 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.

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...
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 opioid 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

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 Kingdom4 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 Kingdom25 and United States26 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 countries34). 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
of codeine and tramadol in cancer pain are controversial.\textsuperscript{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

\begin{table*}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
 & 2011 & 2012 & 2013 & 2014 & 2015 & 2016 & 2017 & Change 2011-2017 \\
\hline
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\% \\
\hline
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\% \\
\hline
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) & 1030 & 1026 & 1068 & 1123 & 1136 & 1129 & 1096 & 6\% \\
\hline
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\% \\
\hline
Opioid consumption (per patient) & & & & & & & & \\
DDD (mean) & 54.2 & 53.3 & 54.3 & 59.3 & 62.2 & 67.5 & 66.2 & 18\% \\
Oral morphine equivalents (mg) & 4682 & 4117 & 4034 & 4524 & 4595 & 4917 & 4597 & -2\% \\
\hline
\end{tabular}
\caption{Annual prescription opioids utilization in Estonia, 2011-2017}
\end{table*}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Prescription opioids use (DDD per user per year) by noncancer and cancer care patients in Estonia, 2011-2017}
\end{figure}
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, and, until 2018, drug overdose mortality in Estonia was the highest in the European Union for over 15 years. 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). 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 under-treatment 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.

ACKNOWLEDGMENT

This work was supported grant # IUT34-17 from the Estonian Ministry of Education and Research.

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.

ORCID

Anneli Uusküla https://orcid.org/0000-0002-4036-3856

REFERENCES

1. Lalic S, Ilomäki J, Bell JS, Korhonen MJ, Gisev N. Prevalence and incidence of prescription opioid analgesic use in Australia. Br J Clin Pharmacol. 2019;85(1):202-215.
2. Fischer B, Jones W, Krahn M, Rehm J. Differences and over-time changes in levels of prescription opioid analgesic dispensing from retail pharmacies in Canada, 2005–2010. Pharmacoepidemiol Drug Saf. 2011;20:1269-1277.
3. Stannard C. Misuse of opioids in Europe. Lisbon Addictions 2017, 24-26.10.2017, Lisbon, Portugal.
4. Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. Lancet Psychiatry. 2019;6(2):140-150.
5. Fredheim OMS, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007: pharmacoepidemiological data from a complete national prescription database in Norway. Eur J Pain. 2010;14:289-294.
6. Oselin K. The Use of Opiates in Estonia (1994–2013). https://www.ravimiamet.ee/sites/default/files/Opiatide%20kasutamine.pdf. Accessed Aug 30, 2019.
7. Belzak L, Halverston J. The opioid crisis in Canada: a national perspective. La crise des opioïdes au Canada: une perspective nationale. Health Promot Chronic Dis Prev Can. 2018;38(6):224-233.
8. Volkow ND, Jones EB, Einstein EB, Wargo EM. Prevention and treatment of opioid misuse and addiction: a review. JAMA Psychiatry. 2019;76(2):208-216.
9. Prescription strong (Schedule 8) opioid use and misuse in Australia – options for a regulatory response. Consultation paper Version 1.0, 2018. Accessed Aug 30, 2019.
10. European Monitoring Centre for Drugs and Drug Addiction, European Drug Report 2017: Trends and Developments, Publications Office of the European Union, Luxembourg: 2017.
11. Bosetti C, Santucci C, Radreza S, Erthal J, Berterame S, Corli O. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990–2016. Eur J Pain. 2019;23(4):677-707.
12. Radbruch L. Rising opioid prescriptions may not be a crisis. BMJ. 2019;367:5823.
13. European Monitoring Centre for Drugs and Drug Addiction, Austria Country Drug Report 2019. http://www.emcdda.europa.eu/countries/drug-reports/2019/austria/drug-induced-deaths_en Accessed Dec 19, 2019.
14. Estonian health insurance fund. 2017. https://statistica.haigekassa.ee/pxweb/pxweb/et/kindlustatut/. Accessed Aug 30, 2019.
15. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2019. www.whocc.no/atc_ddd_index/. Accessed Aug 30, 2019.
16. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016;25(6):733-737.
17. Zin CZ, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain. 2014;18(9):1343-1351.
18. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2013. Oslo, 2012.
19. Estonian State Agency of Medicines. Register of Medicinal Products. https://www.ravimiregister.ee. Accessed Aug 30, 2019.
20. International Narcotics Control Board. Yellow List, 2018. https://www.incb.org/documents/Narcotic-Drugs/Yellow_List/57th_edition_YL_ENG.pdf. Accessed Aug 30, 2019.
21. Statistics Estonia. http://pub.stat.ee/px-web/2001/1_Databases/Population/01Population_indicators_and_composition/04Populati on_figure_and_composition/04Population_figure_and_composition.asp. Accessed Aug 30, 2019.
22. R Core Team R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2016. http://www.R-project.org/. Accessed on April 01, 2019.

23. Schieber LZ, Guy GP, Seth P, et al. Trends and patterns of geographic variation in opioid prescribing practices by State, United States, 2006–2017. JAMA Netw Open. 2019;2(3):e190665.

24. Jarlbæk L. Opioid prescribing habits differ between Denmark, Sweden and Norway - and they change over time. Scand J Pain. 2019;19(3):491-499.

25. Monthly Index of Medical Specialities. Tramadol reclassified as a controlled drug. 2019. https://www.mims.co.uk/tramadol-reclassified-ed-controlled-drug/surgery/article/1297952. Accessed Aug 30, 2019.

26. Harrigan TM. Schedules of controlled substances: placement of tramadol into schedule IV. 2013. https://www.deadversion.usdoj.gov/fed_regs/rules/2013/fr1104.htm. Accessed Aug 30, 2019.

27. Health Canada. Forward Regulatory Plan 2019–2021: Regulations amending Schedule I to the Controlled Drugs and Substances Act and the Schedule to the Narcotic Control Regulations to add tramadol and related substances. 2019. https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/tramadol.html. Accessed on July 17, 2019.

28. Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. BMJ. 2019;365:l1849.

29. Finnegan G. Europe’s silent opioid epidemic. Horizon. The EU Research & Innovation Magazine 2018, 04 April. https://horizon-magazine.eu/article/europes-silent-opioid-epidemic.html. Accessed Aug 30, 2019.

30. Muller AE, Clausen T, Sjagren P, Odsbu I, Skurtveit S. Prescribed opioid analgesic use developments in three Nordic countries, 2006–2017. Scand J Pain. 2019;19(2):345-353.

31. Mikkelsen C, Andersen SE. Morphine: oxycodone interventions in Denmark. Eur J Hosp Pharm. 2012;19(6):546.

32. Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. Br J Clin Pharmacol. 2014;78(5):1159-1166.

33. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am J Public Health. 2009;99(2):221-227.

34. Hamunen K, Paakkari P, Kalso E. Trends in opioid consumption in the Nordic countries 2002–2006. Eur J Pain. 2009;13:954-962.

35. Fox LM, Hoffman RS, Vlahov D, Manini AF. Risk factors for severe respiratory depression from prescription opioid overdose. Addiction. 2018;113(1):59-66.

36. Friesen KJ, Woelk C, Bugden C. Safety of fentanyl initiation according to past opioid exposure among patients newly prescribed fentanyl patches. CMAJ. 2016;188(9):648-653.

37. Schepis TS, McCabe VV, Boyd CJ, McCabe SE. The epidemiology of prescription fentanyl misuse in the United States. Addict Behav. 2019;96:89-93.

38. Ripamonti CI. Pain management. Annals of Oncology. 2012;23(Suppl 10):x294-x301.

39. Wiffen PJ, Wee B, Derry S, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2017;7(7):CD012592.

40. Chen Y, Shiels MS, Thomas D, Freedman ND, Berrington de González A. Premature mortality from drug overdoses: a comparative analysis of 13 organisation for economic co-operation and development membership countries with high-quality death certificate data, 2001 to 2015. Ann Intern Med. 2019;170(5):352.

41. European Monitoring Centre for Drugs and Drug Addiction. Statistical Bulletin 2018 — overdose deaths. 2018. http://www.emcdda.europa.eu/data/stats2018/dr_d_enAccessed Aug 30, 2019 .

42. Uuskula A, Jarlais DD, Vorobjov S. The fentanyl epidemic in Estonia: opportunities for a comprehensive public health response. Lancet Psychiatry. 2019;6(12):985.

How to cite this article: Uusküla A, Raag M, Kurvits K, Laius O, Uusküla M, Oselin K. Trends in opioid prescribing in Estonia (2011-2017). Pharmacol Res Perspect. 2020;e00577. https://doi.org/10.1002/prp2.577