Prescribed opioid analgesic use developments in three Nordic countries, 2006–2017

Article *in* Scandinavian Journal of Pain · January 2019

DOI: 10.1515/sjpain-2018-0307

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Observational study

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https://doi.org/10.1515/sjpain-2018-0307
Received September 5, 2018; revised December 14, 2018; accepted December 18, 2018

Abstract

Background and aims: While the Nordic countries have considerably stricter controls on opioid prescribing for chronic non-cancer pain than other countries, previous research has warned that prescription of strong opioids is increasing. This study examines consumption of and developments in dispensed prescribed opioids to individuals receiving ambulatory care from 2006 to 2017, using publicly available data from each of three Nordic countries' national prescription registries.
Methods: Repeated, cross-sectional design. One-year prevalence of all dispensed prescribed opioids in ATC N02A group were reported for Norway, Denmark, and Sweden in the period 2006–2017 by gender. One-year prevalence of the weak opioids tramadol and codeine and the strong opioid oxycodone were then reported separately over this period for each country. The mean defined daily dose (DDD) per user per year, an estimate of the amount of opioids prescribed, was reported for each of the three opioids in 2016.
Results: Patterns of dispensed prescribed opioids differ greatly between 2006 and 2017 and between countries, with tramadol increasing in Norway, codeine declining across the board, and oxycodone increasing in all three countries. Norway exceeded Sweden and Denmark in prevalence of all dispensed prescribed opioids, with 12.1% of the female Norwegian population and 9.2% of the male Norwegian population dispensed at least one prescribed opioid as an outpatient in 2016. Norway's high overall prevalence rates are tempered by dispensing the lowest mean doses of both weak opioids compared to Sweden. Similarly, Sweden dispenses the lowest mean doses of oxycodone but to the largest proportion of its population (3.0%).
Conclusions: Significant shifts have occurred in the dispensing of prescribed opioids in Norway, Sweden, and Denmark over the past 12 years. The increasing prevalence of oxycodone in all three countries should continue to be monitored. Prescription registries provide a wealth of publicly available data that can be used to monitor and to guide prescribing policies in a more knowledge-based direction.

Keywords: opioids; chronic non-cancer pain; prescription registry; Nordic; oxycodone; tramadol.

1 Introduction

Opioids are increasingly common in medical pain management. For acute and terminal conditions, the pain condition is expected to be transient, and short-term opioid prescription with the goal of pain reduction has traditionally been widely accepted. The goal of chronic non-cancer pain (CNCP) treatment differs, however, as it is not always expected that the pain origin will go away, and pain may even progress. Modern and up-to-date CNCP treatment aims rather at improving functioning and quality of life, and no strong evidence supports opioids' effectiveness in meeting these goals during long-term use [1, 2].

Nevertheless, opioid prescribing for CNCP has increased in the past decades, and the links between this increase, the prevalence of prescribed and non-prescribed opioid misuse and abuse [3], and opioid-related overdoses [4], are now irrefutable. In the US alone, more than

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200,000 people died from overdoses related to prescription opioids between 1999 and 2016 [5]. Organizations such as the World Health Organization are quick to point out the discrepancies in patient access to pain management globally, and highlight that the overabundance of prescription opioids in the United States, Canada, Australia, and New Zealand does not reflect the limited access of cancer populations in low-income countries. Nevertheless, there is little reason to believe this opioid epidemic will remain ensconced in North American and Australasian borders if appropriate actions are not taken [6].

The lack of common definitions, measurements and clinical practices of prescription opioid consumption make it difficult to compare trends, prevalence and drug use between countries. High-quality longitudinal epidemiological data of prevalence, incidence, and patterns of prescription opioid use are therefore sparse, but needed to update the knowledge base in order to provide better preventive measures.

The three Nordic countries' complete population-based prescription registries provide an unparalleled opportunity to compare the developments of prescription opioid use in their combined 21 million inhabitants. According to individual country reports, medical (and non-medical) use of prescription opioids has increased in three Nordic countries of Denmark, Sweden, and Norway, which already report persistently high rates of fatal non-prescription opioid overdoses [7] along with prevalences of CNCP from 18 to 30% in their populations, which are gradually ageing [8]. In Denmark, the fastest growing subgroup of long-term prescription opioid users is comprised of women over 40 years, and long-term use is beginning at younger ages [9]. In Norway, the fastest growing subgroup of strong prescription opioid recipients are the elderly [10]. One third of Swedish CNCP patients receiving strong opioids can be considered at risk of dependence due to psychiatric comorbidities, and one fifth of these patients become long-term users, with steadily increasing doses [11]. Seemingly a similar feature across the Nordic countries is a growing number of prescription opioids misusers who have different characteristics than traditional opioid abusers seeking treatment for illicit opioid use, as has been reported in the US [12]. These new users are more frequently female with higher ages than classic illicit opioid users, perceiving pain often from lifestyle-related non-communicable disorders typical of ageing populations. Are potent prescription opioids the right approach to treat this growing group?

The Nordic countries also share many socioeconomic, health system, and health outcome similarities, including unrestricted access to the publicly-financed health system, which facilitates cross-country comparison. Interestingly, opioid management and prescription policies differ markedly. Both Norway and Sweden have guidelines or recommendations for opioid use for CNCP, and the Norwegian guidelines also cover non-pharmacological options [13, 14]. In Denmark, weak opioids were exempted from special prescribing requirements until 2018, and codeine remains exempted [15]. While the regulatory and medical systems differ markedly between these three countries and the US, unless Nordic health professionals are aware of emerging trends in opioid use, a similar opioid epidemic could develop.

The aim of this paper is to use data from each country's complete prescription registry to produce accurate comparisons of their populations' consumption of and developments in the use of weak and strong opioid prescriptions over the past 12 years. Specifically, we will answer the following questions:

1. What is the development of 1-year prevalence of prescribed opioids in the Nordic countries, and how do they differ?
2. How are patterns of prescription of individual opioid substances developing over time across the countries?
3. Are there differences in the average amount of prescribed codeine, tramadol and oxycodone substances across the countries?

2 Methods

This study used a repeated, cross-sectional design, and drew publicly available data from the complete prescription registries of Norway (http://www.reseptregisteret.no/Prevalens.aspx), Denmark (http://www.medstat.dk/en), and Sweden (http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel). The national prescription registries contain data on all prescribed drugs dispensed at pharmacies to individuals receiving ambulatory care. They have been available since 1994 in Denmark, since 2004 in Norway, and since July 2005 in Sweden. This analysis uses comparable Danish data from 2006 to 2016, and Swedish and Norwegian data from 2006 to 2017.

Drugs in these registries are classified according to the Anatomical Therapeutic Chemical classification system [16]. Volume of drug consumption is given in number of Defined Daily Doses (DDD). A DDD is defined as the assumed average maintenance dose per day for a drug used on its main indication in adults. The evaluation of DDDs is based on international use, bearing in mind that national therapy traditions (indications, dosages) often vary greatly. Each DDD should therefore be regarded as a technical measuring unit.

To answer Aim 1, all opioids in the ATC N02A group were aggregated and 1-year prevalence was reported for each year from 2006 to 2017, per country, with each gender examined separately. One-year prevalence was calculated by dividing the amount of people who had been dispensed at least one prescribed opioid drug in the given year by the total number of people in each population, thereby indicating the percentage of each country's population that had been dispensed an opioid at least once in a given year. The analysis of 1-year prevalence of opioid use was based on population data from Statistics Norway, Denmark and Sweden. To answer Aims 2 and 3, the opioids prescribed with the highest prevalence – tramadol and codeine, commonly classified according to their analgesic potency as weak opioids, and oxycodone, a strong opioid – were investigated. The 1-year prevalence rates for each of the three opioid substances were reported in Aim 2. The mean DDD per user per year, an estimate of the amount of opioids prescribed, was reported in Aim 3.

3 Results

3.1 One-year prevalence of all prescribed opioids (Aim 1)

Figure 1 shows 1-year prevalence during the period 2006–2017 in Norway and Sweden, and 2006–2016 in Denmark. The included population consists of those with at least one dispensed opioid drug during the given calendar year, of all ages. For both genders the highest prevalence(s) were observed for Norway in all years. Since 2006 a slight increase in prevalence was observed in Norway and Denmark, from 11.0% to 12.1% among Norwegian women and 8.6–9.2% among Norwegian men (2006–2017), and 7.9–8.9% among Danish women and 5.4–6.6% among Danish men (2006–2016). In Sweden, a slight reduction beginning in 2013 for both genders was observed, and the prevalence in 2017 (8.4% among women and 6.3% among men) was lower than in 2006 (9.3% and 6.6%, respectively).

3.2 Patterns of individual opioid substances (Aim 2)

The three countries exhibited differences in prevalence(s) of prescribed tramadol substances as well as changes in prescribing pattern during the studied periods (Fig. 2). In all years, Denmark had the highest prevalence, which has remained stable since 2012. A steep rise in prevalence has taken place in Norway, while the prevalence has steadily decreased in Sweden with the exception of a slight increase from 2010 to 2012. The prevalence of tramadol in combination with paracetamol is still low in all three countries.

Prevalence of prescribed codeine substances is highest in all years in Norway compared to both Denmark

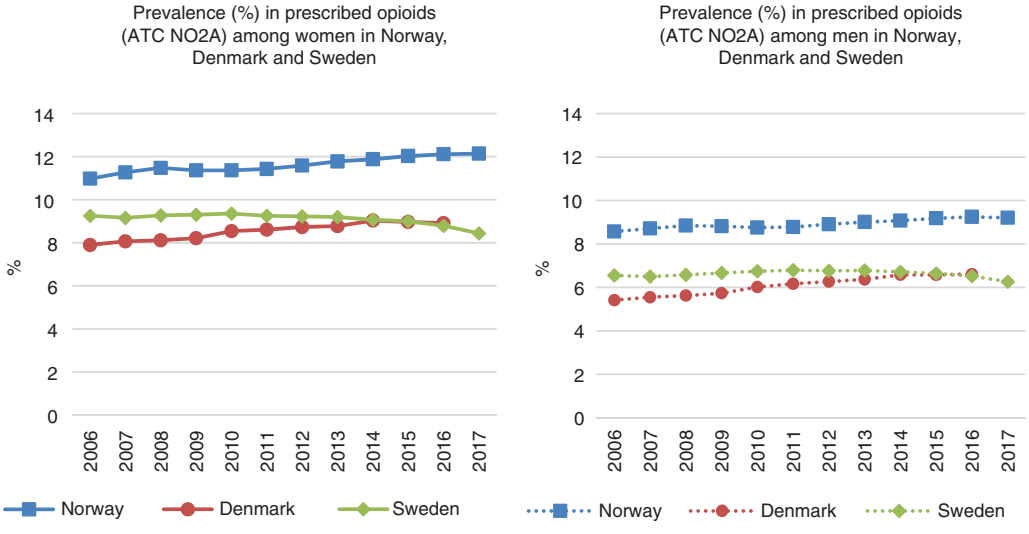

Fig. 1: One-year prevalence of all dispensed prescribed opioids (ATC code NO2A) dispensed in three Nordic countries. Prevalence was calculated by dividing the amount of people who had been dispensed at least one prescribed opioid drug in the given year by the total number of people in each population, thereby indicating the percentage of each country's population that had been dispensed an opioid at least once in a given year. Data were drawn from each country's national prescription registry (Norway: http://www.reseptregisteret.no/Prevalens.aspx, Denmark: http://www.medstat.dk/en, and Sweden: http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel).

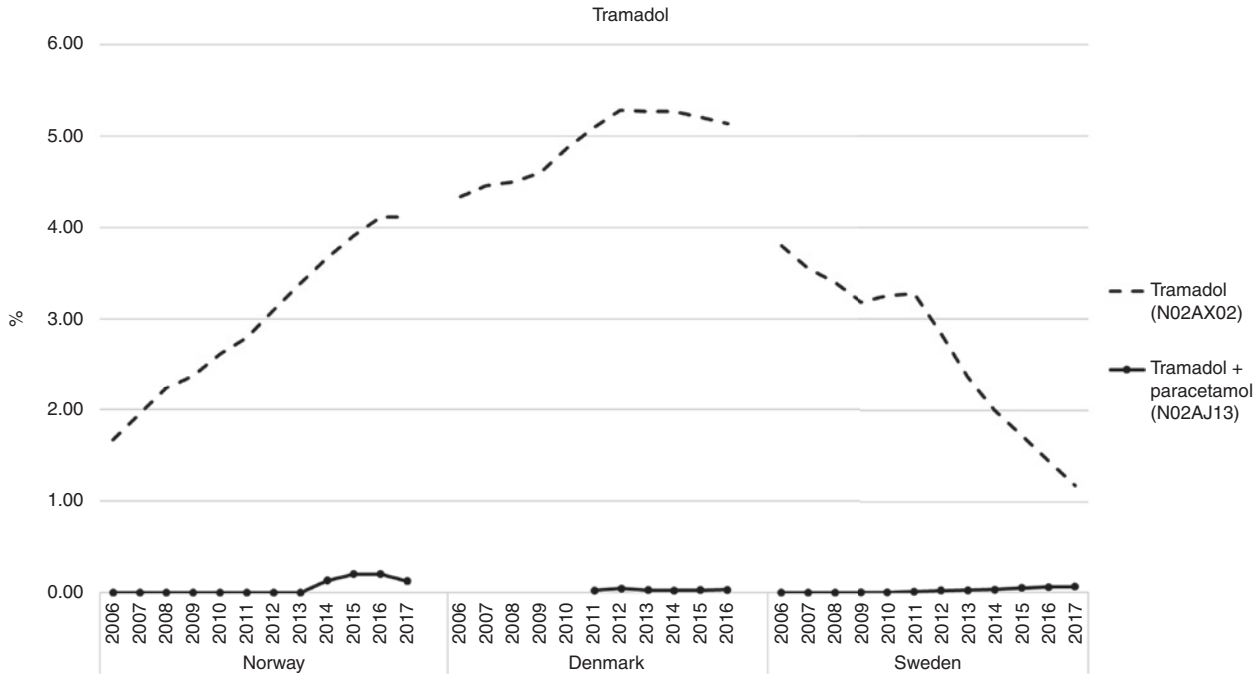

Fig. 2: Prevalence of dispensed prescribed tramadol in three Nordic countries, using publicly available data from each country's national prescription registry. Data from 2006 to 2017 were available for Norway and Sweden, and from 2006 to 2016 for Denmark.

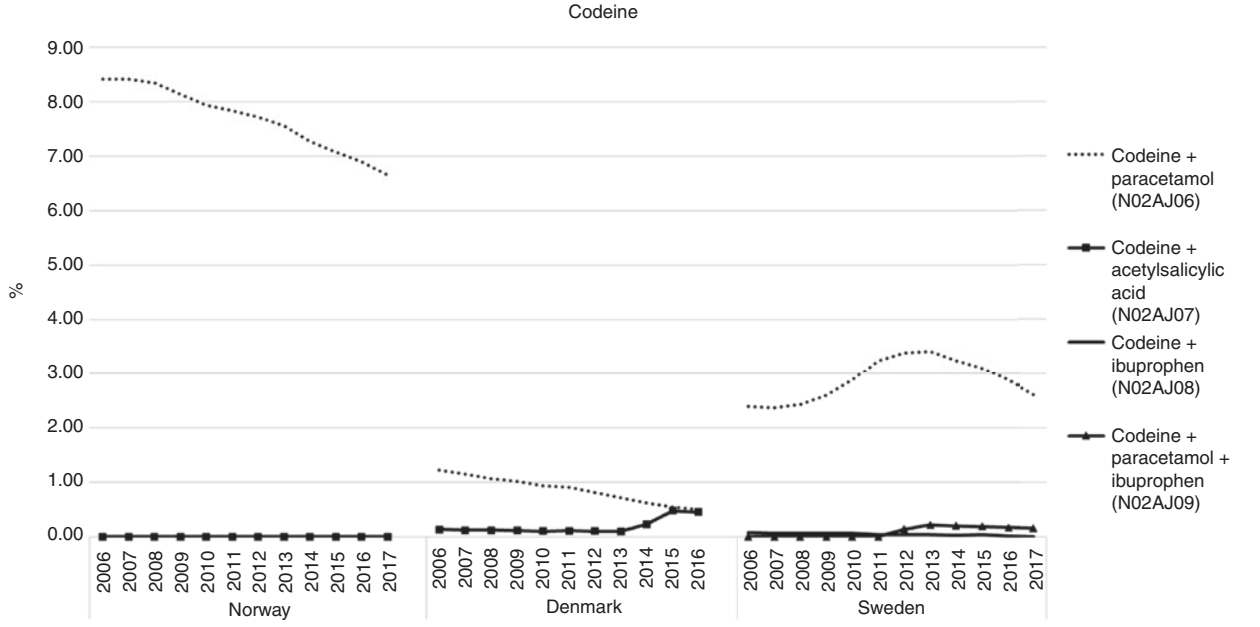

Fig. 3: Prevalence of four formulations of dispensed prescribed codeine in three Nordic countries, using publicly available data from each country's national prescription registry. Data from 2006 to 2017 were available for Norway and Sweden, and from 2006 to 2016 for Denmark.

and Sweden (Fig. 3). The most frequently dispensed codeine substance is a paracetamol combination, with a prevalence in Norway in 2016 (6.9%) 13.8 times higher than in Denmark (0.5%), and 2.4 times higher than in Sweden (2.9%). Norway and Denmark have decreased this prevalence since 2006, while the prevalence in Sweden increased from 2007 to 2013 (from 2.4 to 3.4%), and as of 2017 (2.6%), is nearly back to its 2006 level (2.4%). The codeine and acetylsalicylic acid combination, used in Norway and Denmark, has a significantly lower

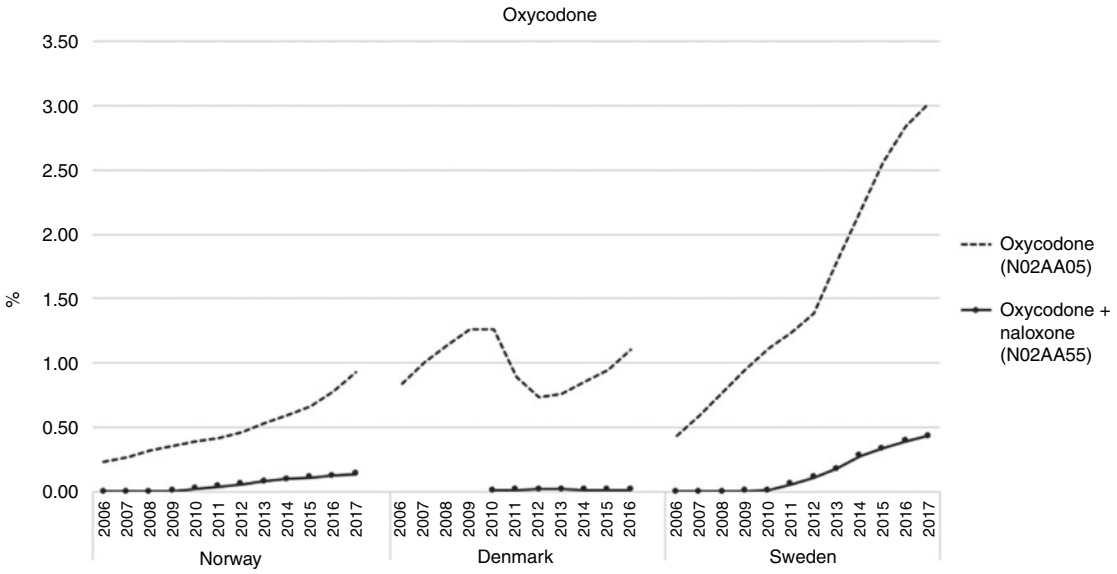

Fig. 4: Prevalence of dispensed prescribed oxycodone in three Nordic countries, using publicly available data from country's national prescription registry. Data from 2006 to 2017 were available for Norway and Sweden, and 2006–2016 for Denmark.

prevalence, as does codeine and ibuprophen (used only in Sweden), and a codeine, paracetamol, and ibuprophen combination (used in Denmark and Sweden).

The prevalence of prescribed oxycodone is very high in Sweden compared to Norway and Denmark (Fig. 4). In 2017, more than 3% of the Swedish population were dispensed oxycodone at least once, compared to approximately 1% in both Denmark and Norway. Prevalence in Sweden has been consistently rising, from 0.4% in 2006 to 3.0% in 2017, while the increase in Norway from 2006 to 2017 has been more modest (0.2%–0.8%). The development in Denmark differs markedly, with a 2-year decline beginning in 2011 that reversed in 2013. The most recent prevalence in Denmark (1.1%) is again approaching 2010s peak (1.3%).

3.3 Mean amounts of selected opioids (Aim 3)

Figure 5 displays the differences in the mean amount of prescribed codeine, tramadol and oxycodone dispensed in 2016, the most recent year for which data for all three countries is available. Mean amount was calculated as the mean DDD per user per year.

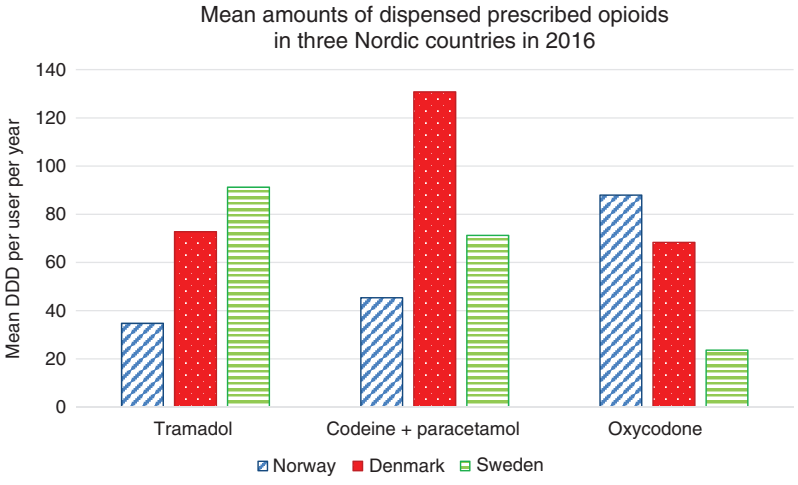

Fig. 5: Mean amounts of weak and strong prescription opioids dispensed in Norway, Denmark, and Sweden in 2016. Mean amounts were calculated as the mean defined daily dose (DDD) per user per year, using data from each country's national prescription registry.

First, each country has different prescription patterns regarding highest and lowest opioid amounts. The average amounts dispensed in Norway of both weak opioids, codeine and tramadol, are lower compared to the other Nordic countries. The mean amount of codeine dispensed in Norway was 45 DDD/user/year, compared to 71 DDD in Sweden and 131 DDD in Denmark. The mean amount of tramadol in Norway was 35 DDD, nearly half of the amount in Denmark (72 DDD), with the highest amount in Sweden (91 DDD). In contrast, Norwegians are prescribed the highest amount of the strong opioid oxycodone (88 DDD), almost quadruple the amount that the average Swedish outpatient is prescribed (24 DDD).

4 Discussion

In this analysis of 12 years of publicly available prescription registry data from three Nordic countries, Norway exceeded Sweden and Denmark in opioid prescribing prevalence, with 12.1% of the female Norwegian population and 9.2% of the male Norwegian population being dispensed at least one opioid prescription in 2016. Prescribing to both genders is increasing slightly in Norway and Denmark and decreasing slightly in Sweden. Patterns of strong and weak opioid prescribing differ greatly between 2006 and 2017 and within and between countries, with the weak opioid tramadol increasing in Norway, the weak opioid codeine declining across the board, and the strong opioid oxycodone increasing in all three countries. Sweden's high oxycodone prescribing is tempered by low doses, while Norway prescribes the highest amounts of oxycodone per patient.

Norway displayed a consistently higher prevalence of opioid prescribing than Denmark and Sweden during the period 2006–2017, for the entire populations. A similar finding was also reported among only children in the period 2006–2016 [17]. This high prevalence may be due to single prescriptions of weak opioids in Norway. A previous study reported that 56% of adult Norwegian users of weak opioids received only one prescription in the course of 2013 [10]. In Denmark, however, this may not be the case: in 2013, 43% of CNCP opioid users nationally received 1–2 prescriptions, while 41% were chronic users [9].

Prevalence rates must also be examined alongside mean amounts. The higher prevalence of Norwegian opioid prescribing among the whole population was mainly due to the large amount of Norwegians who received small doses of the weak opioids codeine (7% prevalence) and tramadol (4% prevalence). In comparison, Sweden displayed the highest prevalence of prescribing the strong opioid oxycodone (3% prevalence), but by far the lowest average amount per user. This amount, according to a previous study reporting DDD/prescription, has steadily decreased during this time period [18].

Tramadol deserves particular attention, because of the heterogeneity in prescribing developments in the three countries. First, Norway displays a steady increase since 2006, when the 1-year prescribing prevalence was approximately one third of the prevalence in Denmark and Sweden. At this time, codeine was the most prevalent weak opioid in Norway, likely due to the influence of an early Norwegian study showing that tramadol was not different from placebo at doses of 50 mg and 100 mg in treating acute post-operative pain, and that codeine + paracetamol was more effective [19]. This study was probably less influential in Denmark and Sweden, and in Denmark, tramadol prevalence increased until 2013 guidelines recommended avoiding long-term treatment with opioids [9]. Tramadol use also increased in Sweden from 2009 to 2012, at which point it was classified as an addictive substance. Bäckryd et al. speculated that the overall increase in average amount of tramadol prescribing in Sweden despite reduction in prevalence is due to tramadol being increasingly used for chronic (persistent) pain rather than acute post-operative pain [18].

The obvious popularity of tramadol in Norway is contradicted by its safety profile. Originally marketed as a painkiller without addictive potential – as well as without follow-up studies of long-term effectiveness – tramadol remains among the most commonly used opioid for CNCP the Nordic countries. This is despite the now recognized addictive potential and an adverse event profile that includes anxiety, panic attacks, hallucinations, and gastrointestinal complications, as well as unusual central nervous system side effects such as disassociation and paranoia [20, 21]. Chronic users are the group with the highest risks. A recent analysis of first-time tramadol users in Norway concluded that one out of 20 began a path of long-term opioid use combined with other addictive behaviors including increasing doses, graduating to strong opioids, and benzodiazepine and Z-hypnotic co-prescriptions [22].

Codeine is prescribed at the highest average doses in Denmark, which also has the lowest prevalence. The opposite pattern in seen in Norway, in which low doses are prescribed to the largest percentage of residents. Codeine has been decreasing in prevalence in all three countries for at least the past 5 years, and there is a likely substitution effect with tramadol in Norway. Given that tramadol may have a more negative side effect profile than codeine, the

wisdom of this strategy should be questioned. The combination of codeine + paracetamol could be a particularly effective alternative to tramadol, although may be perceived less "modern" by some prescribers and/or patients.

Finally, Sweden's steep and steady increase in oxycodone prescription prevalence over the past 10 years is worrying, as an increase in the oxycodone + naloxone combination, with lower misuse potential, is modest at best. However, the increased availability of oxycodone in all three of these countries needs to be addressed, particularly given oxycodone has been identified as the driver of the North American opioid crisis [23]. While low doses to a high number of patients is the trend in Sweden, high doses to a low number of patients is a trend in Norway; nevertheless, both countries have reported a steady increase in oxycodone-related deaths in toxicological forensic examinations, along with the increase in oxycodone availability [24, 25]. Denmark instituted a national and regional campaign to encourage prescribers to substitute oxycodone for morphine and temporarily succeeded in lowering oxycodone prevalence, but as soon as the campaign ceased, oxycodone prescribing began increasing and is almost back to pre-campaign levels [26, 27]. This indicates the need for long-term strategies to change patterns of prescription consistently.

The appropriateness of prescription opioids for pain must be critically re-considered, beginning with a differentiation of acute pain from CNCP. Opioids are likely not the treatment of choice for CNCP patients and are not recommended as the first line of treatment in any case. All pain treatment should begin with evaluable treatment goals developed in concert with patients: if such goals have not been met with one strategy after a pre-defined period of time, then an alternative strategy employed [6]. As the Norwegian professional guidelines for CNCP and opioid use specify, non-pharmacological options (such as exercise, psychological and behavioral therapy, and transcutaneous electrical nerve stimulation) should always be the first choice for CNCP, supplemented thereafter with non-opioid pharmacological options. These prior treatments must be documented before starting opioid therapy, as must poor quality of life and functional capacity due to pain, the ability of the general practitioner to closely monitor, and the capacity of the patient to use the opioid as prescribed [13]. When screening patients and selecting therapy types, it is also important that the descriptor *weak* opioids not be confused with *no/low-risk* [28, 29].

Further, it is noteworthy that population-based studies have demonstrated that long-term opioid treatment for chronic pain is ineffective in providing the essential goals of therapy, namely pain relief, improved quality of life and functional capacity [30, 31]. Besides unsatisfactory analgesic response and the increased risk of addiction, long-term therapy is associated with numerous serious adverse effects on respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine and central nervous systems. The negative long-term consequences include opioid tolerance, hyperalgesia, hypogonadism, sexual dysfunction, immunosuppression and cognitive dysfunction [32–37].

Further research should identify whether some subgroups of CNCP patients are more likely to achieve improved functioning and quality of life, or other patient-physician-identified goals, with opioids. If so, physicians must be able to screen for these patients, and add opioid treatment as a future treatment option, after the aforementioned non-opioid alternatives, while keeping in mind the side effects and risks associated with opioid prescription for CNCP patients. Patient selection and risk stratification is a common recommended feature of several national guidelines, as is an opioid cessation plan [6]. The Nordic countries' complete health and social registries provide important follow-up data sources, and patients receiving opioids for CNCP could be extracted from the prescription registries and their data linked to other registries in high-quality, longitudinal outcome studies.

5 Strengths and limitations

The Nordic prescription databases allow for continuous post-marketing surveillance of drug dissemination and using database data for research has several strengths. Pharmacy records are considered more complete than both medical records and information elicited from interviews and questionnaires. Because information about all drugs dispensed and purchased by patients is automatically entered into the databases, primary non-compliance is not an issue. Completeness and accuracy of pharmacy records is high, due to legislation or other incentives motivating pharmacies to collect and send the data electronically to their national databases on all prescription drugs dispensed to and picked up by individuals in ambulatory care. In pharmacy records, drug use can be measured in detail and the potential for recall and selection bias associated with survey data is eliminated.

Prescription registries contain some limitations, however, the most important being that a dispensed drug may not have been consumed. The publicly available data we used did not allow for the identification of "short-term" or "long-term" users, or between cancer patients

and CNCP patients. Another limitation is that indication for use and the prescribed dose of each medicine are not easily available to researchers from these databases, neither are they available from all websites. Many drugs, including opioids, may be used for different indications, such as moderate or strong pain, and evaluating the amount of all opioids used based on DDD can cause problems for interpretation. We therefore conducted separate analysis on different substances when we calculated the amount of use. Our analysis was limited to outpatient prescriptions of opioids, as medicines given in hospitals and other institutions are not routinely collected in the prescription databases on the individual level.

There are several subgroups with unknown patterns of opioid use who are in need of additional research. Cancer patients and cancer survivors with chronic pain due to malignant tumors or nerve damage from chemotherapy, surgery or radiation; opioid-dependent people in maintenance treatment with chronic pain, who may also have increased tolerance and hyperalgesia; and the elderly, who are more susceptible to both chronic pain and fatal poisonings at lower doses, are only a few of these important subgroups. Each of the Nordic countries has additional high-quality national health and administrative registries that provide individual-level data on risk factors and outcomes of opioid use, which can help us to monitor particularly vulnerable patients in future studies.

6 Conclusion

While the prevalence(s) of strong and weak prescription opioids dispensed to the populations of Norway, Denmark, and Sweden have remained stable in the period 2006–2017, significant shifts have occurred between types of opioids prescribed in each country. The increasing availability of the strong opioid oxycodone in all three of these countries needs to be addressed, particularly given that oxycodone-related deaths are increasing along with increased availability, in settings with prescribing of both low and high average doses. The prescription of opioids for CNCP must be critically re-considered, and in the majority cases, is not the right treatment option. National prescription registries provide a wealth of publicly available data that can be used to inform prescribing policies and thereby improve clinical practice in the future.

Authors' statements

Research funding: The authors state no funding was involved. IO is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities and contract research organizations) for performance of drug safety and drug utilization studies. These entities had no role in the data collection or analysis, neither were they involved in the interpretation of results, writing, revision, or approval of the manuscript.

Conflict of interest: The authors state no conflict of interest.

Informed consent: No informed consent was necessary.

Ethical approval: Not applicable.

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