Sex and age differences among tramadol users in three Nordic countries

Astrid Blicher Schelde¹, Anne Mette Skov Sørensen¹, Morten Hindsø², Mikkel Bring Christensen¹, ³, ⁴, Espen Jimenez-Solem¹, ⁵, ⁶ & Robert Eriksson¹, ⁷

¹) Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, 2) Department of Endocrinology, Hvidovre Hospital, 3) Department of Biomedical Sciences, University of Copenhagen, 4) Center for Clinical Metabolic Physiology, Gentofte Hospital, 5) Institute of Clinical Medicine, University of Copenhagen, 6) Copenhagen Phase IV unit (Phase4CPH), Department of Clinical Pharmacology and Center of Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, 7) Department of Disease Systems Biology, Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Dan Med J 2020;67(7):A06190336
ABSTRACT

Introduction: The aim of this study was to examine the prevalence and characteristics of tramadol users in Denmark, Norway and Sweden.

Methods: Data from the national prescription databases comprising the entire population of Denmark, Norway and Sweden between 2007 and 2015 were used to assess prescription medicine use and sold amount (in defined daily doses (DDDs)) of tramadol, other opioids and non-steroidal anti-inflammatory drugs.

Results: From 2007 to 2015 the prevalence of tramadol users increased in Denmark from 45 to 52 per 1,000 residents, and in Norway from 20 to 41 per 1,000 residents. In Sweden, the prevalence decreased from 36 to 17 per 1,000 residents. In comparison, the prevalence of other opioid users decreased in Denmark and Norway, but increased in Sweden. During the study period, there were more female than male tramadol users in all three countries, and the prevalence of tramadol users tended to increase with age. The average tramadol DDD per treated patient remained fairly constant in Norway, while it increased in Denmark and Sweden. In Denmark and Norway, women received a higher DDD than men. The amount of sold tramadol and other opioids combined per 1,000 residents was highest in Denmark.

Conclusions: From 2007 to 2015, the prescription patterns of tramadol and other opioids differed between the three countries. Tramadol was generally used more frequently by women. Women received higher DDD then men in Norway and Denmark, but not in Sweden. The prevalence of tramadol users tended to increase with age in all countries.

Funding: none.

Trial registration: not relevant.

Tramadol is a synthetic opioid. Its metabolite O-desmethyltramadol binds opioid receptors with the highest affinity to the µ-opioid receptor. In addition to its opioid actions, tramadol inhibits the neuronal reuptake of noradrenaline and serotonin, which contributes to the analgesic action [1].

Concern has been voiced in Danish media regarding tramadol’s addictive properties and the high prevalence of tramadol users [2, 3]. This has led the Danish Medicines Agency to include tramadol as a drug under stricter reporting requirement as from late 2017, as well as requiring tramadol to be subject to the same laws as other opioids traditionally considered to be strong opioids, as from the beginning of 2018 [4, 5].

A previous study found an increase in the prevalence of tramadol users in Denmark and Norway between 2007 and 2015, and a decrease in Sweden [6]. This study did not focus on sex and age differences among tramadol users. Even so, this is important to investigate as use among the elderly should be avoided [7].

To assess whether use of tramadol is a concern to public health, it is important to analyse utilisation patterns. In this population-based study, we examined and compared the prevalence and characteristics of tramadol users in primary healthcare in Denmark, Norway and Sweden between 2007 and 2015. The prevalence was compared with the use of other opioids and non-steroidal anti-inflammatory drugs (NSAIDs) to assess interactions in prescription patterns.

METHODS
The study cohort constitutes the entire population of Denmark, Norway and Sweden between 1 January 2007 and 31 December 2015, covering approximately 20.7 million inhabitants in 2015 [8-10].

Data sources

We used information from the three publicly available national prescription databases [11-13] including information on Anatomical Therapeutic Classification (ATC) codes, number of users, number of residents and defined daily doses (DDDs) per year. One DDD is the average maintenance dose per day and the measure can be used to identify differences between healthcare schemes. Each unique combination of drug and administration route is assigned a specific DDD, e.g., only considering the oral administration route, one DDD for tramadol is 300 mg, 100 mg for morphine and 75 mg for oxycodone.

The databases supply the information divided into regions or counties and stratified on age and sex. The databases include information on an individual level and from the primary sector only (i.e., redemptions made at community pharmacies).

Drugs included in the analysis

The ATC codes of tramadol (N02AX02) or tramadol and paracetamol (N02AJ13) were used to define the use of tramadol. For use of other opioids, we used the following ATC codes and subordinate levels: Natural opium alkaloids (N02AA), phenylpiperidine derivatives (N02AB), diphenylpropylamine derivatives (N02AC), benzomorphan derivatives (N02AD), oripavine derivatives (N02AE), morphinan derivatives (N02AF), opioids in combination with antispasmodics (N02AG), codeine and paracetamol (N02AJ06), codeine and acetylsalicylic acid (N02AJ07), codeine and ibuprofen (N02AJ08), codeine and other non-opioid analgesics (N02AJ09), tapentadol (N02AX06) or codeine (R05DA04). For NSAIDs, we used the following ATC codes and subordinate levels: Butylpyrazolines (M01AA), acetic acid derivatives and related substances (M01AB), oxicams (M01AC), propionic acid derivatives (M01AE), fenamates (M01AG), coxibs (M01AH), nabumetone (M01AX01) and anti-inflammatory/antirheumatic agents in combination (M01B).

Data analysis

In the analyses of tramadol, we combined tramadol and combinations containing tramadol. In a separate analysis, we also investigated the proportions of tramadol sold alone or in combinations. All other opioids and NSAIDs described above were binned in two separate groups. Drug use was defined as one or more redeemed prescriptions in a given year. The prevalence was defined as the number of patients redeeming a prescription per 1,000 residents. The prevalence is presented for each country for the years 2007, 2011 and 2015. We used the same years to stratify the tramadol prevalence by age groups (0-4, 5-9, 10-14, 15-19, 20-39, 40-64, 65-79 and ≥ 80 years). The prevalence of male and female tramadol users was investigated for each year during the study period. Furthermore, we estimated the average DDD per 1,000 residents and per treated patient per year for each country.

The combination of codeine and acetylsalicylic acid (N02AJ07) is also sold over the counter (OTC),
but only in Denmark. We therefore applied the following two conditions: We included all sold DDDs of codeine and acetylsalicylic acid in the calculation of the average DDD per 1,000 residents, but only the proportion of codeine and acetylsalicylic acid in combination sold through a prescription when calculating average DDD per treated patient in Denmark.

*Trial registration:* not relevant.

**RESULTS**

**Tramadol use**

Overall, the prevalence of users increased between 2007 and 2015 in Denmark from 45 to 52 per 1,000 residents, and in Norway from 20 to 41 per 1,000 residents, whereas the prevalence decreased in Sweden from 36 to 17 per 1,000 residents (*Figure 1A*).
During the study period and in all three countries, there were more female than male users. The prevalence of users for both sexes increased during the study period in Denmark and Norway, but decreased in Sweden (Table 1).
The average DDD per treated patient for both sexes increased during the study period in Denmark and Sweden. In Norway, the average DDD per treated patient for both sexes remained fairly constant. In Denmark and Norway, women received a higher DDD than men, whereas the DDDs between sexes in Sweden were similar (Figure 2A).

### TABLE 1  
Prevalence: number of patients redeeming a prescription per 1,000 residents, of tramadol users among males and females between 2007 and 2015 in Denmark, Norway, and Sweden.

<table>
<thead>
<tr>
<th>Year</th>
<th>Denmark, n/1,000</th>
<th>Norway, n/1,000</th>
<th>Sweden, n/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>2007</td>
<td>37</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>2008</td>
<td>37</td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>2009</td>
<td>38</td>
<td>54</td>
<td>19</td>
</tr>
<tr>
<td>2010</td>
<td>41</td>
<td>57</td>
<td>21</td>
</tr>
<tr>
<td>2011</td>
<td>43</td>
<td>59</td>
<td>23</td>
</tr>
<tr>
<td>2012</td>
<td>45</td>
<td>61</td>
<td>26</td>
</tr>
<tr>
<td>2013</td>
<td>45</td>
<td>61</td>
<td>28</td>
</tr>
<tr>
<td>2014</td>
<td>45</td>
<td>61</td>
<td>32</td>
</tr>
<tr>
<td>2015</td>
<td>44</td>
<td>60</td>
<td>35</td>
</tr>
</tbody>
</table>
The average sold amount of tramadol per 1,000 residents was consistently higher in Denmark than in Norway and Sweden. The average DDD per 1,000 residents increased in Denmark and Norway, whereas it decreased in Sweden (Figure 2B). Combinations of tramadol were only marketed in Norway and Sweden during the study period. We identified combinations of tramadol redeemed in Norway the last two years of the study period. During these two years, the majority of tramadol was sold as tramadol alone. Formulations consisting of tramadol alone accounted for 6,906,881 DDDs (99%) in 2014 and 7,241,348 DDDs (97%) in 2015. In Sweden, a single patient redeemed a combination of tramadol and paracetamol in 2015.

For all three countries in 2007, 2011 and 2015, the prevalence of users increased with age, except for Sweden in 2015, where the prevalence of users remained fairly steady among people aged 40 years and above. Among the elderly (≥ 65 years of age), considerable differences were observed in the prevalence of users between the three countries. In 2015, the prevalence of users among the elderly aged 80 years or above was two and six times higher in Denmark than in Norway and Sweden, respectively (Table 2).
Use of other opioids

We observed different trends between the countries in the prevalence of patients using other opioids than tramadol. The prevalence decreased in Denmark from 59 to 56 per 1,000 residents and in Norway from 96 to 87 per 1,000 residents, while it increased in Sweden from 59 to 78 per 1,000 residents (Figure 1B).

The average DDD per treated patient decreased during the study period for both sexes in Denmark and Sweden, while it remained stable in Norway. In Denmark and Norway, women consistently received a higher DDD than men, whereas the sexes received close to the same DDD in Sweden (Figure 2A).

During the study period, the average sold amount per 1,000 residents decreased in Denmark and Norway, while it was stable in Sweden (Figure 2B). Combining the sold amount of all opioids, residents in Denmark redeemed more opioids per 1,000 residents than was the case in the other two countries.

Use of nonsteroidal anti-inflammatory drugs

The prevalence of NSAID users decreased during the study period in all three countries. Norway had the highest prevalence, followed by Denmark and Sweden. Between 2007 and 2015, the average DDD per 1,000 residents decreased in Denmark and Sweden, whereas it increased in Norway (Table 3).

### TABLE 2

<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>Denmark, n/1,000</th>
<th>Norway, n/1,000</th>
<th>Sweden, n/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-14</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15-19</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>20-39</td>
<td>26</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>40-64</td>
<td>58</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>65-79</td>
<td>103</td>
<td>113</td>
<td>108</td>
</tr>
<tr>
<td>≥ 80</td>
<td>165</td>
<td>173</td>
<td>170</td>
</tr>
</tbody>
</table>
**DISCUSSION**

In this population-based cohort study, we observed a higher prevalence of tramadol users among women than among men in all three countries. It has previously been shown that women report
pain more often than men, and that women more frequently suffer from pain disorders such as migraine and fibromyalgia [14]. A recent Danish report concluded that a larger proportion of women than men has reported pain or discomfort within the past 14 days, and that they more often have consulted their general practitioner within the past 12 months [15]. These factors might explain why women more often than men were prescribed analgesics, including tramadol.

The prevalence of chronic pain conditions increases with age [16]. This is in agreement with the analgesic utilisation observed in our study, where the prevalence of tramadol users in general increased with age. However, other factors might also contribute to the observed pattern.

The prevalence of tramadol users was markedly lower among the elderly (≥ 65 years of age) in Sweden than in Denmark and Norway. During the study period, the National Board of Health and Welfare in Sweden published an updated guideline stating that tramadol should be avoided in the elderly due to a high risk of adverse drug reactions and an increased risk of clinically relevant drug interactions [17]. Our observations might reflect the Swedish physicians’ compliance with this guideline.

Our findings regarding the prevalence of tramadol users during the study period are in line with a recently published study that reported a high prevalence of tramadol users in Denmark and Norway compared with Sweden in 2015 [6].

The increase in Denmark and Norway may possibly be attributed to a decrease in the number of other opioid users, and the decrease in Sweden might be explained by an increase in users of other opioids. Tramadol is commonly called a “weak” opioid, which may lower the barrier for initiating treatment with the drug [18]. However, since the active metabolite of tramadol has high affinity to the µ-opioid receptor, tramadol should not be classified as a weak opioid. Furthermore, caution against NSAID use might have led to an increase in tramadol use [18]. We observed a decrease in the prevalence of NSAID users in all three countries between 2007 and 2015. For Denmark and Norway, part of this decrease might be due to a shift from NSAIDs to tramadol.

Within many areas, the Scandinavian countries’ healthcare legislation is rather similar. However, tramadol requires a special prescription in Norway and Sweden [19]. Until 1 January 2018, this was not the case in Denmark, where tramadol could be prescribed with a regular prescription. This circumstance might explain the higher prevalence of tramadol users observed in Denmark than in Norway and Sweden. With regards to Denmark, it would be of interest to conduct further studies to investigate whether changes in legislation will change Danish physicians’ prescription patterns.

Despite the previously stated similarities between the Scandinavian countries, we observed that the amount of tramadol sold and all opioids combined (i.e., tramadol and all other opioids combined) per resident was markedly higher in Denmark than in the other two countries. We argue that the large differences at the population level alone are an incitement to investigate further the use of tramadol and opioid in general, and to assess the impact and possible health
consequences of the larger opioid use in one of three similar populations.

A major strength of this study includes access to national registries covering the entire population in all three countries. The healthcare systems of Denmark, Norway and Sweden are fairly similar [20], making comparisons of analgesic use between the countries feasible. A limitation of our study is that we are likely underestimating the number of DDDs per treated patient. This is due to the properties of the data exported from the national prescription databases. The data extracts contain the number of patients and DDDs sold for each ATC code, but since we cannot link patients from different ATC groups, we are likely overestimating the number of patients treated with the sum of the DDDs. The opposite applies to the prevalence estimations, as it is possible that individual patients redeemed prescriptions from different ATC groups within one of the three prespecified analgesic groups (tramadol, other opioids and NSAIDs) during our study period, resulting in an overestimation of the prevalence. Furthermore, NSAIDs and combinations of codeine and acetylsalicylic acid are also available OTC, and we therefore cannot estimate the number of patients obtaining these types of medications. Lastly, our study did not investigate the use of other analgesics, such as paracetamol, gabapentinoids or tricyclic antidepressants, and an exposure switch to these analgesics cannot be excluded.

CONCLUSIONS

The prevalence of tramadol users was higher among women than among men; and in Denmark and Norway, women received a higher DDD than men. During the study period, there was a trend in all three countries that the prevalence of tramadol users increased with age. Between 2007 and 2015, the prevalence of tramadol users increased in Denmark and Norway whereas it decreased in Sweden. The changes might be explained, in part, by shifts between analgesics.

Correspondence: Robert Eriksson. E-mail: robert.eriksson@cpr.ku.dk

Accepted: 18 May 2020

Conflicts of interest: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

LITERATURE

4. Danish Medicines Agency. Stricter reporting requirements.


