Effect of the Market Withdrawal of Dextropropoxyphene on Use of Other Prescribed Analgesics

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**Key words**

Analgesics; opioids; dextropropoxyphene; drug consumption

**Abstract**

**Background and aims:** Dextropropoxyphene (DXP) is a synthetic opioid that was prescribed worldwide for mild to moderate pain. It was withdrawn from the European market in 2009. In this study we aim to investigate the effect of the market withdrawal of dextropropoxyphene in Norway on overall use of opioids and other analgesics at an individual level.

**Methods:** Data were collected from the nationwide Norwegian Prescription Database (NorPD). It covers all prescription of drugs from 01 January 2004 from Norwegian pharmacies dispensed to individuals outside institutions. The study period was divided in two 2-year periods from 01 September 2008 to 31 August 2010, and from the market withdrawal of DXP on 01 September 2010 to 31 August 2012. We included every individual that filled at least one prescription of dextropropoxyphene in the first 2-year period in our study population. In this study dextropropoxyphene, codeine and tramadol are defined as “weak opioids”, and all other opioids are termed “strong opioids”.

**Results:** 9171 individuals were included in our study population. 4290 filled a prescription of DXP only once and were classified as “single users”, 2990 were users with prescriptions of up to 200 Defined Daily Doses (DDD) over the first 2-year period, or “sporadic users”, and 1886 were classified high users with over 200 DDDs over a 2-year period. After the market withdrawal 8392 continued to be prescribed analgesics or benzodiazepines. In the single user group, the proportion of users of weak opioids decreased from 69.5% to 57.6%, whereas the proportion of users of strong opioids was unchanged. Among the sporadic user group, the proportion of users of weak opioids went from 69.7% to 71.0%, the proportion using tramadol from 39.1% to 43.9%, and the users of strong opioids from 25.8% to 31.3%. In the high user group, there was an increase in the number of users of strong opioids from 37.8% to 51.4%. The amount of strong opioids prescribed in the high user group increased from a mean of 262.5 DDD to a mean of 398.3 DDD in the following two years. The amount of tramadol increased in all groups and was 3 times as high in the high user group after market withdrawal of DXP.

**Conclusions:** Our study showed that the withdrawal of DXP lead to an increase in prescription of other analgesics. The proportion of users increased in all three groups and so did the prescribed amount of other analgesics. Both the proportion of users of other opioids and the amount prescribed increased considerably. However, 1 in 10 earlier users of DXP stopped using prescribed analgesics altogether in the following two years. The increase in use among earlier high users of DXP was most striking.

**Implications:** This study documents markedly increased prescriptions of other opioids after withdrawal of dextropropoxyphene due to its high risk of serious complications. However, consequences of the increased use of opioids among earlier high users of DXP such as changes in risk of poisonings, accidental deaths and suicides remain to be investigated.

**1 Introduction**

Dextropropoxyphene (DXP) is a synthetic opioid structurally similar to methadone which was introduced in the USA in 1957 and became a popular opioid analgesic worldwide. It was most frequently prescribed in a combination with paracetamol sold under a variety of brand names, in Norway as Aporex® and Co-proxamol® in the UK. Aporex was approved for the Norwegian market for the first time in 1968. Dextropropoxyphene was classified as a weak opioid and its main indications were postoperative pain and mild to moderate pain. Side effects included dizziness and a euphoric sensation related to dependency. The analgesic effect of dextropropoxyphene has however been debated. A meta-analysis including several randomized controlled trials showed that there was little to no additional effect of adding dextropropoxyphene to paracetamol in the management of postoperative pain, arthritis and musculoskeletal pain [1]. With unconvincing analgesic effects compared to other common analgesics, the question of potential risks and overdose concerns were raised.

Toxicity of dextropropoxyphene results in similar reactions as opioid intoxication including respiratory distress and disturbed cardiac conduction that could potentially be fatal. In addition, the margin between therapeutic and toxic concentrations is narrow. In 1982 Aporex was classified as a “narcotic” in Norway, in other words a potent opioid like morphine, due to concerns regarding fatal toxicity [2]. The major active metabolite is renally excreted so that individuals with reduced renal function had an increased risk of toxic effects.

Dextropropoxyphene has been associated with dependency, abuse and in later years especially suicides [3-10]. After reviews of the safety profile the UK Committee on Safety of Medicines (CSM) announced that the drug should be withdrawn from use in the UK in 2005, with final date of withdrawal 31st December 2007 [11]. European Medicines Agency (EMA) recommended withdrawal of dextropropoxyphene from the market in the European Union in 2009 following the UK, with the final date of withdrawal 01 September 2010 in Norway [12]. US Food and Drug Administration (FDA) instructed manufacturers to cease production in 2010 after a randomized double-blind multiple-ascending dose (MAD) study on dextropropoxyphene was conducted on healthy volunteers showing a significant prolongation on QTc interval on daily doses of 600 and 900 mg [13].

Studies in the UK, Ireland and France showed a clear reduction in accidental poisoning deaths and suicides after the withdrawal with little change in deaths and hospital admissions involving other analgesics, and users of dextropropoxyphene often switched to non-opioid analgesics [14-21]. No study on the impact of the withdrawal of dextropropoxyphene has been conducted in Norway.

The market withdrawal of a drug may lead to an increasing use of other drugs. A regular user of dextropropoxyphene could switch to another opioid or a drug with abuse potential and harmful effects. The aims of this study were to analyse to which degree earlier users of dextropropoxyphene switched to other analgesic drugs of interest after dextropropoxyphene was withdrawn from the market, and whether they increased their consumption of these prescribed drugs.

**2 Methods**

**2.1 Data source**

Data for this longitudinal prospective register-based study were drawn from the Norwegian Prescription Database (NorPD). This nationwide database covers all prescriptions of drugs from 1 January 2004 from Norwegian pharmacies dispensed to individuals outside institutions [22]. All drugs in NorPD are classified according to the Anatomical Therapeutic Chemical classification (ATC) system [23]. Data available in our study were encrypted personal identity numbers, birth year and gender for both prescribers and patients, prescription dates, numbers of DDD, drug name and ATC-code. DDD (Defined Daily Dose), being the assumed average maintenance dose per day of a drug used for its main indication in adults defined by the World Health Organization (WHO). One DDD of Aporex® (DXP in combination with paracetamol) is 140 mg, and the equianalgesic ratio compared to oral morphine is 0.15 [24].

**2.2 Study population and study period**

We used data from NorPD from 1 September 2008 to 1 September 2012. The study period was divided into two main parts:

1. 2 years before the withdrawal of DXP from the Norwegian market up until the withdrawal: 1 September 2008 to 31 August 2010.
2. 2 years after the withdrawal: 1 September 2010 to 31 August 2012.

Our study population was composed of all individuals who filled a prescription for DXP at least once during the period from 1 September 2008 to 31 August 2010 (*n* = 10621). Individuals who died before 1 September 2012 were excluded (*n* = 1450), resulting in a total number of 9171 individuals. 39.5% men, 60.5% women, mean age (1 September 2010) 61,2 years (SD = 16,1), median age 62 (range 14 to 102).

For the main analysis we categorized individuals into three groups based on the consumption pattern of DXP from 1 September 2008 to 31 August 2010.

1. Individuals receiving a single prescription of DXP in a 2-year period, termed “single users”.
2. Users who were prescribed a total of 200 DDDs of DXP or less over a 2-year period, termed “sporadic users”. 200 DDDs of DXP is equivalent to 4200mg of oral morphine.
3. Individuals receiving prescriptions of a total of >200 DDDs over a 2-year period, termed “high users”.

**2.3 Analysis strategy**

We first investigated the proportion of DXP-users in each of the three categories who used additional analgesic drugs and sedatives in each 2-year period, before and after the market withdrawal of DXP. 5 groups of drug classes of interest were defined based on ATC-codes.

1. Dextropropoxyphene, ATC-code = N02AC54.
2. Weak analgesics, ATC-code M01A, NSAIDs and other anti-rheumatic drugs, and ATC-code N02B, which includes paracetamol, acetylsalicylic acid and phenazone.
3. Weak opioids, which in Norway in the study period included ATC-code N02AJ06, codeine and paracetamol in combination, and ATC-code N02AX02, tramadol.
4. Strong opioids, selected as ATC-code N02A except the weak opioids, which in our study includes morphine, oxycodone, ketobemidone, pethidine, fentanyl, and buprenorphine (all opioids except DXP, codeine and tramadol).
5. Benzodiazepines, ATC-codes N05B, N05C or N03AE01.

To further analyse the use pattern, in each study period we investigated the amount of drug consumption (in DDDs) in patients who were prescribed drugs in each of the five categories. We used the same three categories of DXP users.

**3 Results**

A total of 9171 individuals had filled at least one prescription for DXP during the 2-year period from 01 September 2008 to the market withdrawal. Of these, 4290 (46,8 %) were individuals receiving a single prescription – single users, 2995 (32,7 %) were sporadic users and 1886 (20,6 %) were high users. Of the additional drugs of interest, the single users were mainly using weak analgesics (78,2 %) and weak opioids (69,5 %). The sporadic users used weak analgesics (79,5 %) and weak opioids (69,7 %) mainly but also strong opioids (25,8 %). Among the high users the pattern was similar, but the proportion using strong opioids was considerably higher (37,8 %) **(Table 1)**. Users of benzodiazepines were present in all three groups and at a higher prevalence than the average Norwegian population [25]. Proportion of users increasing from the single users (55.8%), to the sporadic users (69.1%) and to the high users (77.8%).

There was a large variability in the amounts of drugs prescribed in each group. High users of DXP were also the highest users of other analgesics. **Table 2** presents the amount of analgesics prescribed in DDDs, among the three consumer groups of DXP in the first 2-year period. The amounts received in all five categories were higher in the high user group, compared to the other two groups. Amounts of strong opioids were considerably higher.

After the market withdrawal 01 September 2010, a total of 779 (8.5%) individuals did not receive any prescription of an analgesic (or benzodiazepine) during the full 2-year period from 01 September 2010 to 31 August 2012. Hence, 8392 individuals continued to be prescribed analgesics or benzodiazepines. In the single users group, 3732 (87%) continued to use analgesics in the second 2-year period, while 2793 (93.3%) among the sporadic users and among the high users 1867 (99%) continued to be prescribed analgesic drugs.

**Table 3** shows the number and proportion of individuals in the three DXP groups who received DXP, weak analgesics, weak opioids, strong opioids and benzodiazepines in the second 2-year period from 01 September 2010 to 31 August 2012. A total of 188 individuals continued to be prescribed DXP after the market withdrawal through “compassionate prescribing”. In the single users group, the users of weak analgesics and weak opioids went down (from 78.2% to 68.3%, and 69.5% to 57.6% respectively) and the proportion of users of strong opioids changed little. In the sporadic user group, the users of strong opioids increased slightly (25.8% to 31.3% respectively), whereas the numbers of users of weak analgesics and weak opioids were about the same (**Table 1** and **Table 3**). Among the high users of DXP the proportion using all five classes of analgesics increased, and particularly strong opioids (from 37.8% to 51.4%). The proportion of weak opioid users increased from 66.0% to 79.7%. The proportion using tramadol increased in sporadic and especially in high users (39.9% to 53.9%). In total there were 421 new users of strong opioids after the market withdrawal, all among the sporadic user group and high user group. The proportion of users of benzodiazepines changed little, however it was still high compared to the normal population.

The amounts of prescribed analgesics increased in all three study groups after the market withdrawal. **Table 4** presents the amounts of prescribed analgesics in the 2-year period from 01 September 2010 to 31 August 2012. The amount of weak analgesics received increased in all three groups. The use of weak opioids also increased, except in the sporadic user group where it stayed about the same, while the amounts of strong opioids received went substantially up in all three DXP user groups (**Table 2** and **Table 4**). The increase was particularly striking in the high user group with a mean amount of 262.5 DDD in the first 2-year period, increasing to a mean of 398.3 DDD in the second 2-year period. Interestingly, the amount of tramadol dispensed increased in all groups and was more than doubled in high users. The amounts of benzodiazepines changed marginally after the market withdrawal.

**4 Discussion**

This is the first nationwide study of earlier DXP users and their consumption pattern after the market withdrawal of DXP. There was an increase in opioid use among the earlier sporadic users, and especially among the earlier high users of DXP after the market withdrawal. Both numbers of users and amounts of opioids prescribed increased, however among the high users the increase was most substantial. Among the single users the proportion went down in all drug classes, but those who continued to be prescribed analgesics, increased the amount of drug received. In the high user group both the proportion of users of opioids, and the amount of drug prescribed increased dramatically, indicating that long-term pain patients receiving high amounts of DXP, either became new users of potent opioids or increased their dosage of other opioids considerably.

The pattern of use of weak opioids in Norway is changing. Particularly, there is an increase in use of tramadol. The one-year period prevalence of tramadol use in the adult Norwegian population increased approximately threefold from 1.7% in 2004 to 4.7% in 2014 [26]. This tendency is also obvious in our study.

The proportion using benzodiazepines stayed about the same, and so did the prescribed amount. This indicates that the use of benzodiazepines was unaffected by the market withdrawal of DXP and these drugs did not serve as replacement for earlier users of DXP. However, a much higher prevalence of users of benzodiazepines was observed among earlier users of DXP than the average Norwegian population [25].

Studies performed in Europe and USA also show that earlier users of DXP switched to other opioids and increased the dosage of opioids already received, in particular an increased use of tramadol, codeine and paracetamol [3, 6, 14, 18-21]. Our study shows that the consumption of strong opioids increased markedly, especially among the high users of DXP. A French study based on aggregated data on drug consumption performed in 2018 showed that in the two years following the market withdrawal, the total consumption of weak opioids went down due to DXP no longer being prescribed, while the consumption of tramadol and codeine increased. This indicates the same worrisome increase in use of other opioids replacing the earlier use of DXP. Also, consumption of strong opioids increased. However, the use of paracetamol increased more than the weak opioids, due to safety concerns regarding tramadol and codeine according to the author [27]. A study performed in Norway on another drug with abuse potential, carisoprodol, showed no worrisome increase in the numbers of users of opioids after the market withdrawal of this drug [28].

The toxicity of dextropropoxyphene has been a great concern and a motivator to the withdrawal. A study from Finland investigated the fatal toxicity index (FTI) for 70 medicinal drugs, where FTI is the number of fatal poisonings caused by a particular drug divided by drug consumption, in this study expressed as number of deaths per million DDD over three study years. Dextropropoxyphene scored as the second highest FTI in this study, only surpassed by methadone. Oxycodone, tramadol and morphine did only have one fifth of the FTI score of DXP, and codeine even lower. Thereby this study supports the concerns regarding DXP toxicity [29]. A review study was performed in USA where it was stated that DXP offers no therapeutic advantages over any other opioid, risks outweigh any perceived benefits and drugs with a better risk-benefit-ratio are available. The acute toxicity is described in this study as similar to opiate intoxication with respiratory depression, circulatory collapse and coma. DXP in combination with CNS-depressants, such as alcohol, proved to be a major cause of drug-related deaths [30].

As the aim of our study was to study the effect of withdrawal of DXP, the population consists solely of individuals who have received at least one prescription of DXP at some point in the first 2-year period. The total opioid use in the entire population of Norway is not studied, and we cannot draw conclusions regarding total opioid consumption in the Norwegian population over time.

The main strength of this study is that the data provided was from a nationwide prescription database NorPD covering every drug dispensed to non-institutionalised individuals. Due to Norwegian legislation and automatic electronic admission of the prescriptions from all pharmacies to the database, the NorPD includes all filled prescriptions in Norwegian pharmacies, and close to 100 % of the records are linked to personal identity numbers. This allows a detailed surveillance of prescription drugs for the entire population over a longer period of time and eliminates the potential for recall bias, which is a major source of error in cohort studies based on self-reporting drug consumption. Primary non-adherence is also eliminated because only drugs prescribed by a physician and thereafter retrieved in a pharmacy will be registered in the NorPD. Basing data only on prescriptions which might not be filled and retrieved, could prove to be a source of error [31].

The weaknesses of the study are that the data is dispensed drugs from pharmacies, and there is no way to ensure that the individuals actually ingested the drugs and when they did it and in what amounts. Drugs used in nursing homes and hospitals, are not recorded at the individual level in NorPD which will lead to an underestimation of total drug use, especially in the elderly population. In this study, individuals who died before 01 September 2012 were excluded. To which degree the death of these individuals was linked to high use of prescribed drugs is unknown. Two of the weak analgesics in this study, NSAIDs and paracetamol, are sold without a prescription in low doses and small pack sizes in grocery stores etc in Norway. However, chronic users and users in need of higher dosages get NSAIDs and paracetamol prescribed by their physician. The clinical implications of increased prescription of strong opioids have not been studied. Linkage between NorPD and the Norwegian Patient Register might provide useful information.

This study has assessed changes in prescriptions and drug use. Long-term studies on clinical implications such as accidental poisonings, suicides and deaths should also be performed.

**5 Conclusions**

This study indicates that the market withdrawal of dextropropoxyphene lead to an increase of prescriptions of other analgesics. There was a general increase in both users of other analgesics and amounts prescribed in all three groups of earlier DXP users, except for the use of benzodiazepines which remained unchanged. The increased use of both weak and strong opioids among the earlier high users of DXP was most striking. Opioid use was also increased in the single user and sporadic user group. On the other hand, after the market withdrawal approximately 1 in 10 earlier users of DXP stopped receiving analgesics completely in the following two years.

DXP has an extensive toxicity profile, while the opioid alternatives do not prove to be as toxic. According to other studies, the switch from DXP to other opioid analgesics is probably not harmful, even if an increased consumption may be an unwanted effect of the market withdrawal.

**6 Implications**

This study provides an attempt to characterize and quantify changes in individual use of weak analgesics, weak opioids, strong opioids and benzodiazepines after the opioid dextropropoxyphene was withdrawn from the Norwegian market. DXP is no longer available in Europe and no longer being manufactured in the USA. Potential harmful effects of the increased consumption of other opioids in the group of earlier high users of DXP should be further investigated.

**Authors’ statements**

**Ethics**

The Norwegian Prescription Database (NorPD) is a nationwide database with its own regulations. The database contains data on an individual level, but in pseudonyms, so that information that can identify an individual will not be accessible. When the NorPD is not linked to any other data source, approval from the Regional Ethics Committee is not needed.

**Conflict of interest**

The authors have no conflict of interest to declare.

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| Table 1: Number of users of DXP, NSAIDs and paracetamol (weak analgesics), weak opioids, tramadol, strong opioids and benzodiazepines in the first 2-year period before DXP was withdrawn from the market (1 Sep 2010), among the three groups of DXP users. Also given in percent of the total DXP use pattern group. | | | | | | |
|  | **Dextropropoxyphene  (*N* = 9171)** | **Weak analgesics\*   (*N* = 7127)** | **Other weak opioids\*\* (*N* = 6312)** | **Tramadol  (*N*=3461)** | **Strong opioids\*\*\*  (*N* = 2318)** | **Benzodiazepines  (*N* = 5930)** | |
| 1) Single users (*N* = 4290) | 4290 (100%) | 3356 (78.2%) | 2980 (69.5%) | 1538 (35.6%) | 834 (19.4%) | 2395 (55.8%) | |
| 2) Sporadic users (*N* = 2995) | 2995 (100%) | 2382 (79.5%) | 2088 (69.7%) | 1170 (39.1%) | 772 (25.8%) | 2068 (69.1%) | |
| 3) High users (*N* = 1886) | 1886 (100%) | 1389 (73.7%) | 1244 (66.0%) | 753 (39.9%) | 712 (37.8%) | 1467 (77.8%) | |

\*M01A, N02B \*\*N02AJ06, N02AX02 \*\*\*N02A except N02AJ06 and N02AX02.

Also given in percent of the total DXP use pattern group.

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| Table 2: Amounts of DXP, weak analgesics, weak opioids, tramadol, strong opioids and benzodiazepines in defined daily doses (DDDs) among users of DXP in the first 2-year period before DXP was withdrawn from the market (1 Sep 2010), in the same three consumption pattern groups. | | | | |
|  | **DDDs** | **Single users** | **Sporadic users** | **High users** |
| Dextropropoxyphene (*N* = 9171) | Mean (SD)  Median (IQR) | 22.0 (15.6)  20.0 (14.5) | 83.9 (53.6) 73.5 (80.0) | 733.3 (614.5)  549.0 (605.0) |
| Weak analgesics \*  (*N* = 7127) | Mean (SD)  Median (IQR) | 236.1 (330.4)  100.0 (265.0) | 318.8 (411.1)  153.7 (355.6) | 381.2 (435.5)  216.7 (477.2) |
| Other weak opioids \*\*  (*N* = 6312) | Mean (SD)  Median (IQR) | 167.4 (348.3)  36.7 (124,8) | 236.8 (408.6)  70.0 (236.0) | 274.3 (422.5)  87.5 (344.2) |
| Tramadol  (*N* = 3461) | Mean (SD)  Median (IQR) | 69.1 (178.4)  16.7 (36,7) | 88.0 (189.7)  20.0 (65.4) | 94.6 (217.5) 20.0 (71.7) |
| Strong opioids \*\*\*  (*N* = 2318) | Mean (SD)  Median (IQR) | 109.1 (330.1)  13.4 (48.6) | 116.2 (298.2) 18.7 (76.3) | 262.5 (852.1)  35.0 (180.9) |
| Benzodiazepines  (*N* = 5930) | Mean (SD)  Median (IQR) | 534.4 (857.3)  240.0 (688.3) | 669.9 (959.4)  372.9 (750.0) | 1076.8 (1255.6)  780.0 (1036.0) |

\*M01A, N02B \*\*N02AJ06, N02AX02 \*\*\*N02A except N02AJ06 and N02AX02

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Table 3: Number of users of DXP, NSAIDs and paracetamol (weak analgesics), weak opioids, tramadol, strong opioids and benzodiazepines in the second 2-year period from 01 September 2010 to 31 August 2012, among the three groups of DXP users (termed from the first 2-year period). | | | | | | |
|  | **Dextropropoxyphene  (*N* = 188)1** | **Weak analgesics\*  (*N* = 6665)** | **Other weak opioids\*\*  (*N* = 6104)** | **Tramadol  (*N =* 3653)** | **Strong opioids\*\*\*  (*N* = 2745)** | **Benzodiazepines  (*N* = 5686)** |
| 1) Single users  (*N* = 4290) | 15 (0.4%) | 2930 (68.3%) | 2472 (57.6%) | 1320 (30.8%) | 840 (19.6%) | 2263 (52.8%) |
| 2) Sporadic users (*N* = 2995) | 60 (2.0%) | 2247 (75.0%) | 2128 (71.0%) | 1316 (43.9%) | 936 (31.3%) | 1974 (65.9%) |
| 3) High users  (*N* = 1886) | 113 (6.0%) | 1488 (78.9%) | 1504 (79.7%) | 1017 (53.9%) | 969 (51.4%) | 1449 (76.8%) |

1 : 188 individuals continued to be prescribed DXP after the market withdrawal through “compassionate prescribing”.

\*M01A, N02B \*\*N02AJ06, N02AX02 \*\*\*N02A except N02AJ06 and N02AX02

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 4: Amounts of DXP, weak analgesics, weak opioids, tramadol, strong opioids and benzodiazepines in defined daily doses (DDDs) among users of DXP in the second 2-year period from 01 September 2010 to 31 August 2012, in the same three consumption pattern groups. | | | | |
|  | **DDDs** | **Single users** | **Sporadic users** | **High users** |
| Dextropropoxyphene (*N* = 188) | Mean(SD)  Median (IQR) | 13.8 (11.2)  10.0 (0.0) | 25.3 (16.5)  20.0 (24.5) | 94.8 (144.6)  49.0 (79.8) |
| Weak analgesics \*  (*N* = 6665) | Mean (SD)  Median (IQR) | 271.0 (359.3)  133.3 (301.8) | 344.5 (412.6)  188.3 (440.0) | 465.8 (491.6)  300.0 (562.5) |
| Other weak opioids \*\*  (*N* = 6104) | Mean (SD)  Median (IQR) | 200.7 (399.0)  46.7 (180.3) | 234.6 (392.0)  73.3 (243.3) | 425.5 (496.0)  275.4 (516.7) |
| Tramadol (*N* = 3653) | Mean (SD)  Median (IQR) | 97.8 (247.6)  16.7 (60.0) | 107.3 (219.5) 33.3 (93.3) | 216.5 (334.4)  90.0 (263.3) |
| Strong opioids \*\*\*  (*N* = 2745) | Mean (SD)  Median (IQR) | 176.3 (480.4) 22.4 (128.6) | 193.9 (542.7)  35.3 (143.2) | 398.3 (1033.1)  117.6 (375.1) |
| Benzodiazepines  (*N* = 5686) | Mean (SD)  Median (IQR) | 568.6 (839.7)  300.0 (715.0) | 694.4 (1088.8)  420.5 (765.0) | 1012.1 (1098.8)  745.0 (977.7) |

\*M01A, N02B \*\*N02AJ06, N02AX02 \*\*\*N02A except N02AJ06 and N02AX0