# Prevalence and distribution of long-term opioid therapy in primary care in Uppsala county, Sweden: a retrospective observational study

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# Abstract

**Introduction:** Due to the global increase in opioid prescription rates and the parallel increase in opioid misuse, abuse and opioid-related deaths in many countries, attention on reducing irrational opioid use has become more predominant. Because of the risks related to opioid use and limited evidence for prolonged analgesic effects, the use of long-term opioid therapy (LTOT) in patients with chronic non-cancer pain is questionable. In Sweden, information about the number of patients that are currently on LTOT, how these are distributed among the primary care practices, and what type of opioids that are being prescribed, is lacking. Therefore, this study aimed to investigate the prevalence and distributions of adult patients with LTOT in primary care practices in Uppsala county, Sweden and to investigate the type, quantity and trends of opioid prescriptions in these patients.

**Methods:** A retrospective study of opioid prescription data was conducted using data from both regional (Region Uppsala) and national (Socialstyrelsen) prescription databases in Sweden. The study population consisted of adult patients in Uppsala county with at least one opioid prescription between 01-06-2021 until 31-05-2022 (Region Uppsala) and 01-01-2016 until 01-09-2022 (Socialstyrelsen). LTOT prevalence rates were calculated by dividing the number of identified LTOT patients with the total number of enlisted patients. ATC-codes of different opioids were used to calculate the total number of prescriptions, users and total prescribed defined daily dose (DDD) per 1000 inhabitants for all opioids. Descriptive statistics were used to examine patient characteristics and opioid use. A Chi-square test was performed to analyze the difference of LTOT prevalence rates between individual primary care practices.

**Results:** LTOT prevalence rates of 0.77% and 1.13% were reported for the regional and national dataset, respectively. LTOT prevalence rates differed between public primary care practices. Between 2016 and 2021, an increasing trend in the number of prescriptions, users and total prescribed DDD was mainly found for oxycodone and buprenorphine.

**Conclusion:** LTOT prevalence rates among adult patients in primary care in Uppsala county varied between 0.77% and 1.13% and LTOT patients were not equally distributed among public primary care practices. The use of stronger opioids increased substantially between 2016 and 2021 in Uppsala county, Sweden. Oxycodone and buprenorphine showed the most pronounced increases, whereas only tramadol showed a decreasing trend. Our findings show similarities with results from other European studies, reporting an indication for a shifting trend from the prescription of weaker opioids to stronger opioids. Although our numbers and trends need to be interpreted with caution, the results underline the importance of close monitoring if benefits still outweigh risks and if treatment rationale of opioid use still applies.



**Keywords:** opioids, long-term opioid therapy, prescription data

## Samenvatting (Dutch)

**Introductie:** Door de wereldwijde toename van het aantal voorgeschreven opioïden en de parallelle toename van opioïden-misbruik en opioïd-gerelateerde sterfgevallen in veel landen, is de aandacht voor het terugdringen van irrationeel opioïdengebruik toegenomen. Vanwege de risico's van opioïdengebruik en het beperkte bewijs voor langdurige pijnstillende effecten is het gebruik van langdurige opioïdentherapie (LTOT) bij patiënten met chronische niet-kankerpijn twijfelachtig. In Zweden ontbreekt informatie over het aantal patiënten dat momenteel LTOT gebruikt, hoe deze verdeeld zijn over de eerstelijnspraktijken en welk type opioïden wordt voorgeschreven. Het doel van deze studie is daarom om de prevalentie en verdeling van volwassen patiënten met LTOT in eerstelijnspraktijken in de provincie Uppsala, Zweden te onderzoeken, en om het type, de hoeveelheid en de trends van het voorschrijven van opioïden bij deze patiënten te onderzoeken.

**Methode:** Er is een retrospectieve studie uitgevoerd naar het voorschrijven van opioïden met behulp van gegevens uit zowel regionale (Regio Uppsala) als nationale (Socialstyrelsen) receptendatabases in Zweden. De studiepopulatie bestond uit volwassen patiënten in de provincie Uppsala met ten minste één opioïdenvoorschrift tussen 01-06-2021 tot 31-05-2022 (Region Uppsala) en 01-01-2016 tot 01-09-2022 (Socialstyrelsen). LTOT-prevalentiecijfers werden berekend door het aantal geïdentificeerde LTOT-patiënten te delen door het totale aantal ingeschreven patiënten. ATC-codes van verschillende opioïden werden gebruikt om het totale aantal voorschriften, gebruikers en de totale voorgeschreven gedefinieerde dagelijkse dosis (DDD) per 1000 inwoners voor alle opioïden te bepalen. Beschrijvende statistieken werden gebruikt om de patiëntkenmerken en het opioïdengebruik te onderzoeken. Een Chi-kwadraat toets werd uitgevoerd om het verschil van LTOT prevalentiecijfers tussen individuele eerstelijnspraktijken te analyseren.

**Resultaten:** LTOT-prevalentiecijfers van 0,77% en 1,13% werden gerapporteerd voor de regionale respectievelijk nationale dataset. LTOT-prevalentiecijfers verschilden significant tussen openbare eerstelijnspraktijken. Tussen 2016 en 2021 werd vooral voor oxycodon en buprenorfine een stijgende trend in het aantal voorschriften, gebruikers en totale voorgeschreven DDD gevonden.

**Conclusie:** LTOT-prevalentiecijfers onder volwassen patiënten in de eerstelijnszorg in de provincie Uppsala varieerden tussen 0,77% en 1,13% en LTOT-patiënten waren niet gelijk verdeeld over de openbare eerstelijnspraktijken. Het gebruik van sterkere opioïden nam aanzienlijk toe tussen 2016 en 2021 in de provincie Uppsala, Zweden. Oxycodon en buprenorfine lieten de meest uitgesproken stijgingen zien, terwijl alleen tramadol een dalende trend liet zien. Onze bevindingen vertonen overeenkomsten met resultaten van andere Europese studies, die een verschuivende trend van het voorschrijven van zwakkere opioïden naar sterkere opioïden rapporteren. Hoewel onze cijfers en trends met de nodige voorzichtigheid geïnterpreteerd moeten worden, onderstrepen de resultaten het belang van nauwgezette evaluatie of de voordelen nog steeds opwegen tegen de risico's en of de rationale van behandelen met opioïden nog steeds van toepassing is.

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# 1. Introduction

Opioids are the most effective and commonly used analgesic in different surgical procedures, the treatment of severe pain and cancer-related pain [1-3]. Over the last decades, an increase of opioid prescriptions has led to an increase of opioid misuse, abuse and opioid-related death [1]. This trend has been most pronounced in North America and to a lesser extent in European countries [1,4]. Within Europe, the impact of higher opioid prescription rates on opioid-related harm differs between countries [4]. According to a recent report by the Organisation for Economic Co-operation and Development (OECD), these higher opioid prescription rates did not necessarily result in increased opioid-related deaths in countries such as the Netherlands, Germany, Austria, Belgium and Denmark [1].

Due to the global increase in opioid prescription rates and especially due to the parallel increase in opioid-related harm, extra attention on reducing opioid use has become more predominant. This is especially the case for clinical situations where evidence for opioid use is limited.

In patients with severe acute pain (e.g. surgical or cancer-related pain), the short-term effects of opioids, such as instant pain relief and improvement of daily functioning, have been established in randomized clinical trials (RCTs) that mainly lasted 12 weeks or less [5-7]. However, only few studies have adequately assessed the long-term effectiveness, leading to inconclusive results [7-9]. Due to the limited evidence for a prolonged analgesic effect, the use of long-term opioid therapy (LTOT) in patients with chronic pain has become increasingly questionable.

Besides the limited long-term evidence, opioid use is associated with several risks and their role in treating long-term non-cancer pain is controversial [10]. One of the main reasons is the risk of opioid addiction, which involves psychological dependence. Second, LTOT is associated with a loss of analgesic potency, leading to an increasing physical tolerance. As a result, effectiveness will decrease over time and increasing dosages are required [10]. Last, opioids can cause multiple severe side effects, such as opioid-induced endocrinopathy and hyperalgesia [11,12]. Given these unique long-term side effects of opioids, it is highly debatable whether the benefits outweigh the risks.

Before starting with opioids, it is of importance that patients receive adequate pain treatment based on a careful and individualized assessment of the benefits and risks of different treatment options. Other treatment options may, depending on the type of pain, include non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-pharmacologic therapy (such as cognitive-behavioral therapy and exercise therapy) [5].

When opting for opioids, it is the responsibility of clinicians to create an individualized plan that includes treatment duration, dosage and potential discontinuation. In addition, it is essential that potential risks and realistic benefits are evaluated periodically. If long-term effectiveness on pain management does not outweigh the risks of ongoing therapy, treatment rationale no longer applies. Subsequently, clinicians and patients should work together to optimize other therapies and to taper irrational opioid treatment to lower dosages or to taper and discontinue opioids [5].

Even though the practice of opioid tapering is already occurring, evidence for specific tapering and discontinuation strategies is still scarce [13]. The clinical impact of LTOT dose reduction for patients with chronic non-cancer pain remains unclear and could potentially be harmful [14]. Currently, multidisciplinary and modal interventions are generally recommended and successful examples of the involvement of pharmacists in these multidisciplinary interventions exist across different countries and settings [15].

Despite the availability of different treatments for chronic pain, a large proportion of patients still experience inadequate pain control [16,17].

In Sweden, the number of adult people experiencing moderate to severe chronic pain is substantial, with an estimated prevalence of 18% [17]. Prevalence estimates of moderate to severe chronic pain among adults in Europe vary widely with a range between 10-30% [17]. This could be a consequence of differences between patient populations or the adoption of different definitions for and measurements of chronic pain [17]. It is likely that a substantial proportion of these patients are on LTOT, but the exact prevalence of LTOT in Swedish adult patients with chronic non-cancer pain is unknown [18].

Nevertheless, these prevalence estimates of adult people experiencing moderate to severe chronic pain indicate that chronic pain represents an evident public health issue. Given the

fact that further data on its prevalence and epidemiology is limited in Sweden, an accurate estimation of the societal and economic impact of chronic pain is lacking [17]. Still, as the medical use and misuse of opioid analgesics is growing, it is likely to expect that this social and economic burden will increase over time.

In a recent Swedish study by Grelz et al., the prescription patterns of opioids among patients with complex chronic pain conditions were analyzed to better understand the prevalence of LTOT in Swedish patients with chronic non-cancer pain [18]. Even though evidence for LTOT is questionable [5,6,8,9], their results suggest that opioids are prescribed routinely for the treatment of moderate to severe chronic non-cancer pain [18]. According to recent Swedish reports, general practitioners account for one third of all new opioid prescriptions and are responsible for the highest proportion of opioid prescription renewals [19]. Moreover, it is important to note that these prescription patterns of opioids have gradually shifted from the prescription of weaker opioids (e.g. tramadol) to the prescription of stronger opioids (e.g. oxycodone) [16,20].

In recent years, Region Uppsala, the healthcare authority responsible for the quality of and access to healthcare for all 400.000 inhabitants in Uppsala county, has invested in multidisciplinary collaboration including pharmacists in primary care practices. Within this context, a research project has recently been started to investigate the effects of a multidisciplinary team-based approach, including a pharmacist, on pain treatment outcomes in patients with LTOT for chronic non-cancer pain in primary care. A controlled before-and-after intervention study is proposed, where patients' treatment outcomes at four primary care practices with the multidisciplinary team-based approach (intervention) will be compared with primary care practices without this approach and without a pharmacist (control). In preparation of this study, a better understanding of the number of patients that are currently on LTOT for chronic non-cancer pain, and how these are distributed among the primary care practices in Uppsala county, is warranted.

## 1.1 Aim

Therefore, this study aimed to investigate the prevalence and distributions of adult patients with LTOT in primary care practices in Uppsala county, Sweden. The secondary aim of this study was to investigate the type, quantity and trends of opioid prescriptions in adult patients with LTOT in primary care in Uppsala county, Sweden.

# 2. Methods

## 2.1 Design, setting and population

A retrospective observational study of opioid prescription data of adult patients in primary care in Uppsala county, Sweden, was conducted. To be able to compare data from different registries, observational data was collected from both regional and national databases in Sweden. Data from the regional database was obtained from Region Uppsala, which is the regional authority that is responsible for the quality and delivery of health care within Uppsala county and operates the public primary care practices (roughly half of all primary care practices in the county). Data from the national database was obtained from the Swedish National Board of Health and Welfare (Socialstyrelsen) [21].

## 2.2 Outcomes

### 2.2.1 Primary outcome: Prevalence of LTOT

The primary outcome of interest was the prevalence of patients with LTOT prescribed by the general practitioner in Uppsala county. As definitions of LTOT vary in different publications [22], several definitions were adopted in this study to assess the impact on the outcomes.

According to the Swedish quality indicator *Lm12alla*, opioid therapy can be defined as LTOT when opioid prescriptions for a single patient add up to more than the equivalent of 90 days' full dose of opioids in the last 12 months [23]. As this full dose is different for different opioids, the more compatible method defined daily dose (DDD) was used in this study. The DDD represents a predefined international average daily dose of an opioid, assigned by the World Health Organization [24]. One DDD over 12 months is equivalent to 365 days of the presumed average daily dose. In the *Lm12alla* definition, a cut-off value of 0.25 DDD was chosen as this corresponds with 90 days of using the presumed average daily dose in 12 months [23]. Hence, *DDD > 0.25* was used as the primary definition for the prevalence of LTOT.

As other studies opt for a stricter definition of LTOT, a cut-off value of 0.50 DDD was applied as well [22,25]. This corresponds with 180 days of using the presumed average daily dose in 12 months.

Even though the *Lm12alla* definition uses cumulative opioid dosages as a criterion, it does not necessarily account for consistent use. For example, if patients would occasionally use escalating dosages of opioids due to surgical procedures or incidental severe pain, they could still be labeled as LTOT patients according to this definition. Therefore, an addition to the definition is warranted. To ensure that only patients who chronically use opioids were identified, a time component was added to the *Lm12alla* definition. Based on a recent Swedish study, patients can be labeled as long-term users when they had at least one opioid prescription per quarter for at least 3 out of 4 quarters of the year [18]. This element was added to the two previously described *Lm12alla* definitions. However, this addition could only be made for data from the national dataset from Socialstyrelsen, as no information about specific dates of opioid dispenses was provided in the regional dataset from Region Uppsala (table 1, see also 2.3 Data collection).

Although multiple definitions for LTOT are frequently used, most studies align the definition of LTOT with the definition of chronic pain (more than 3 months) [5,22]. According to Edlund et al., it is highly unlikely that patients would receive opioids for longer than 3 months for acute conditions [26]. Moreover, the definition *DDD > 0.25* is directly derived from the earlier discussed Swedish quality indicator *Lm12alla* [23]. Taking these elements into consideration, the adoption of *DDD > 0.25* as primary definition seemed most appropriate. *DDD > 0.25* plus at least one opioid prescription per quarter for at least 3 out of 4 quarters of the year, *DDD > 0.50* and *DDD > 0.50* plus at least one opioid prescription per quarter for at least 3 out of 4 quarters of the year, were secondary definitions of LTOT (table 1).

Table 1: Overview of different definitions of LTOT that were used for both datasets to measure the prevalence of LTOT (primary outcome).

| Definition | Clinical scenario | Regional dataset (Region Uppsala) | National dataset (Socialstyrelsen) |
|---|---|---|---|
| **DDD > 0.25 (Lm12alla)*** | > 90 days of using the presumed average daily dose in 12 months | Applied | Applied |
| **DDD > 0.25 >= 3 quarters** | DDD > 0.25<br>+ at least one opioid prescription per quarter for at least 3 | Not able to apply | Applied |

| | | | |
|---|---|---|---|
| | out of 4 quarters of the year | | |
| **DDD > 0.50** | > 180 days of using the presumed average daily dose in 12 months | Applied | Applied |
| **DDD > 0.50 >= 3 quarters** | DDD > 0.50<br>+ at least one opioid prescription per quarter for at least 3 out of 4 quarters of the year | Not able to apply | Applied |

* Primary definition of LTOT

### 2.2.2 Secondary outcomes: Type and quantity of opioid prescriptions

Furthermore, the unique Anatomical Therapeutic Classification (ATC) codes of different opioids were used to calculate the total number of prescriptions for all different opioids and to determine the variation in use between weaker and stronger opioids [27,28]. In addition, the total number of patients who had a prescription for a certain opioid and the corresponding total DDD for each opioid were calculated. Subsequently, the mean DDD per prescription and per user were calculated for each opioid type.

## 2.3 Data collection

### 2.3.1 Regional dataset

Data from the regional dataset were obtained from Region Uppsala. Region Uppsala manages the regional healthcare registry that contains all information from the regional electronic health record system, such as prescribed drugs and patient demographics of all public primary care practices in Uppsala county.

For ethical and data protection reasons (see 2.5 Ethical considerations) only aggregated data per primary care practice was provided by Region Uppsala. Patients were selected for both LTOT definitions using multiple selection criteria. First, patients had to be enlisted at one of the public primary care practices of Region Uppsala. Also, patients had to be 18 years or older and had to have at least one prescription of an opioid with the ATC-code 'N02A' prescribed by a general practitioner within Region Uppsala in the period 01-06-2021 until 31-05-2022 (12 months). Last, patients had to meet the requirements of the LTOT definitions.

In the data, no information is provided about the indication of the prescription. As this study investigates LTOT in patients with chronic non-cancer pain, the assumption was made that almost all primary care opioid prescriptions contain some form of non-cancer pain as an indication. Still, to assure a higher level of certainty and to be able to quantify the number of patients who use opioids due to cancer or its treatment, all patients who were diagnosed with cancer in the past 12 months were identified. An overview of all included ATC-codes and their corresponding type of opioid is provided in appendix 1. Information about prescription rates, number of users and total sum of DDD were provided for all ATC-codes for each primary care practice for the same privacy reasons. No information about individual use or dosages was provided. Moreover, the number of unique prescribers per patient was provided.

Data about the number of enlisted patients and the socio-economic status for each primary care practice was collected separately with SAS ® Visual Analytics (SAS Institute Inc, Cary, USA), an application for data exploration and analytics that was used by Region Uppsala and available for the researchers. Socio-economic status scores for patients enlisted at each primary care practice were based on the Swedish Care Need Index (CNI) from Statistics Sweden (SCB) [29]. This is a method that computes an index value based on several material, socio-demographic and cultural variables. All these variables are standardized and weighted to calculate a CNI value for each primary care practice. In general, a higher CNI value represents a more deprived status [29]. Last, information on whether a pharmacist is present was collected for each primary care practice through the researcher's professional network.

As only information about public primary care practices from Region Uppsala was available from this dataset (approximately 50% of all primary care practices in Uppsala county), no data on opioid prescriptions from private primary care practices and opioid prescriptions from other drug prescription systems than the regional system were included. In Uppsala county, prescriptions for patients with automated dose dispensing are written in a different (national) system and therefore not included in this data. Consequently, most opioid prescriptions for nursing home residents were not included.

### 2.3.2 National dataset

Data from the national dataset was obtained from Socialstyrelsen. The data contains information on all prescriptions that have been dispensed at community pharmacies in Sweden since 2005 [21]. Important to note is that only regional prescription data from patients in Uppsala county was provided from this national dataset, see below.

In the national dataset, all adult patients (18 years or older) were included. This data contained information on dispensed opioid prescriptions from both primary care and secondary care as well as the private healthcare sector. The period that was adopted ranged from 01-01-2016 until 01-09-2022. As this dataset contained information on more than 900,000 prescriptions from more than 90,000 patients, all patients were given a specific patient number. Last, information was provided whether the patient was a resident of Uppsala county at the time of every prescription. Opioid prescriptions for patients who moved out of the county within the time period were therefore still included in the data.

For every individual patient, this data contained information on the date (year/month) of the first opioid dispensing and the number of days that additional opioid dispenses were registered. Also, the data contained information on the ATC-code and total DDD of each individual prescription and whether the opioids were prescribed by primary care or not. Last, information was collected about how many different prescribers per patient were responsible for those prescriptions. Information about sex, age and other patient characteristics were not provided for ethical and data protection reasons, see 2.5 Ethical considerations.

## 2.4 Data analysis

### 2.4.1 Regional dataset

Characteristics of the study population and prescriber information were analyzed with descriptive statistics. To measure the LTOT prevalence, the 12-month period 01-06-2021 until 31-05-2022 was chosen as time frame, and concern written (and not dispensed) opioid prescriptions, see 2.3 Data collection. The LTOT prevalence rates were determined by dividing the total number of selected patients for each definition of LTOT with the total number of enlisted patients.

Moreover, the number of unique prescribers and CNI for each primary care practice were plotted against the LTOT prevalence of that primary care practice, to investigate the potential association between these variables. Last, a Chi-square test (significance: $p < 0.05$) was used to investigate the differences in LTOT prevalence rates between primary care practices.
Microsoft Excel was used for data management and descriptive statistics.

### 2.4.2 National dataset

For the national dataset, the LTOT prevalence rates were determined in a similar way to the regional dataset. For comparison reasons, the same 12-month period from the regional dataset (01-06-2021 until 31-05-2022, see 2.3 Data collection) was chosen as time frame to measure the LTOT prevalence for the national dataset as well.
As the national dataset contains information on dispensed opioid prescriptions from 01-01-2016 until 01-09-2022, the total number of dispensed opioid prescriptions, users and total sum of DDD were calculated by year and stratified by ATC-code. To ensure that the potential impact of population growth on the total number of opioid prescriptions, users and total DDD was addressed, these outcomes were calculated per 1000 capita. To do so, the outcomes had to be corrected by the annual population of Uppsala county. An overview of this population is provided in appendix 2.
Furthermore, the variation between weaker and stronger opioids was analyzed as well. Subsequently, potential trends in general opioid use were assessed for both individual opioid types and for aggregated opioid types (weaker/stronger). An overview of the classification between weaker and stronger opioids is provided in appendix 1 [27,28].

Second, to investigate the distribution of opioid use among LTOT patients, skewness of opioid use was analyzed by generating a Lorenz curve for opioid prescriptions from 01-01-2016 until 01-09-2022. The Lorenz curve is a statistical tool that was used as an indicator for intensity and proportional use of opioids within the population of opioid users. The Gini coefficient, a measurement of distribution often used in economic inequality studies [30], was calculated by using the Lorenz curve's area under the curve. The resulting Gini coefficient is a value between zero and one that represents full equality (zero) until full inequality (one) of opioid use [31]. Microsoft Excel was used for data management, descriptive statistics and the generation of the Lorenz curves.

## 2.5 Ethical considerations

The regional dataset only contained aggregated and anonymized patient data. With regards to the dataset from the national database, only anonymized prescription data without patient characteristics were collected. Hence, no identifiable sensitive individual personal data was used in this analysis. Therefore, ethical approval from the Swedish Ethical Review Authority was not required according to Swedish law [32,33].

# 3. Results

## 3.1 Prevalence of LTOT

### 3.1.1 Regional dataset

From the 209980 enlisted patients at the primary care practices, 1915 were identified as LTOT patients (DDD > 0.25; table 2). Of these patients, 1190 patients (62.1%) were female. Between primary care practices, the number of selected patients with LTOT ranged from 14 to 281. Furthermore, the median age ranges from 46 to 71 years old.

The median number of unique prescribers per patient ranged from 1 to 4 for each primary care practice. For only six primary care practices, the median number of unique prescribers per patient was one. This indicates that in many cases, multiple prescribers are responsible for a patient's opioid prescriptions. Moreover, the CNI score ranged from 0.71 ([redacted] to 1.87 ([redacted]). Based on the plots in appendix 3, there seemed to be no association between either the number of unique prescribers or CNI, and the prevalence for LTOT.

Based on prescription data from public primary care practices, a combined total of 1617 and 1187 non-cancer patients were selected for the definitions *DDD > 0.25* and *DDD > 0.50* respectively (table 3). As a result, the non-cancer LTOT prevalence, defined as *DDD > 0.25* and *DDD > 0.50,* was 0.77% and 0.57% respectively.

The LTOT prevalence rates differed between the primary care practices (Chi-square p-value < 0.001).

Table 2: An overview of prevalence of LTOT (DDD > 0.25), LTOT patient demographics, number of unique opioid prescribers per LTOT patient, and whether a pharmacist is working at the practice, for each primary care practice and in total.

| Primary care practice | Patients enlisted, no. | Patients with LTOT (DDD>0.25), no.(%) | Female sex, % | Age, median yrs (MIN-MAX) | Unique prescribers, median no. (MIN-MAX) | CNI | Pharmacist present (yes/no) |
|---|---|---|---|---|---|---|---|
| [redacted] | 4997 | 60 (1.20%) | 51.7% | 57 (24-95) | 1 (1-6) | 0.76 | No |
| [redacted] | 4221 | 25 (0.59%) | 52.0% | 46 (30-88) | 2 (1-9) | 0.73 | No |
| [redacted] | 8293 | 102 (1.23%) | 69.6% | 59 (20-98) | 1 (1-5) | 0.88 | Yes |
| [redacted] | 8075 | 73 (0.90%) | 67.1% | 58 (24-98) | 2 (1-6) | 1.09 | No |
| [redacted] | 8493 | 32 (0.38%) | 62.5% | 64 (26-90) | 2 (1-6) | 1.09 | No |
| [redacted] | 10001 | 94 (0.94%) | 67.0% | 57 (20-92) | 1 (1-5) | 0.74 | No |
| [redacted] | 3992 | 68 (1.70%) | 64.7% | 61 (19-89) | 3 (1-9) | 0.98 | No |
| [redacted] | 13961 | 91 (0.65%) | 58.2% | 63 (31-96) | 2 (1-6) | 1.87 | Yes |
| [redacted] | 10098 | 82 (0.81%) | 61.0% | 62 (28-90) | 1 (1-5) | 1.18 | No |
| [redacted] | 6950 | 67 (0.96%) | 59.7% | 63 (28-90) | 3 (1-11) | 1.06 | No |
| [redacted] | 12024 | 63 (0.52%) | 61.9% | 61 (29-87) | 2 (1-5) | 0.88 | No |
| [redacted] | 9428 | 41 (0.43%) | 61.0% | 70 (31-93) | 2 (1-5) | 0.87 | Yes |
| [redacted] | 13962 | 106 (0.76%) | 60.4% | 65 (27-95) | 2 (1-6) | 1.13 | Yes |
| [redacted] | 9337 | 130 (1.39%) | 65.4% | 60 (20-97) | 1 (1-6) | 1.18 | No |
| [redacted] | 3773 | 14 (0.37%) | 71.4% | 62 (39-82) | 2 (1-4) | 1.68 | No |
| [redacted] | 8308 | 64 (0.77%) | 60.9% | 62 (28-91) | 3 (1-11) | 0.75 | No |
| [redacted] | 16682 | 123 (0.74% | 65.0% | 67 (44-94) | 1 (1-6) | 0.90 | No |
| [redacted] | 19544 | 281 (1.44%) | 61.2% | 62 (25-96) | 2 (1-11) | 1.05 | Yes |
| [redacted] | 15500 | 115 (0.74%) | 57.4% | 71 (29-94) | 2 (1-8) | 1.07 | Yes |
| [redacted] | 5741 | 55 (0.96%) | 58.2% | 65 (25-89) | 2 (1-9) | 0.71 | No |
| [redacted] | 3640 | 58 (1.59%) | 58.6% | 64 (30-95) | 2 (1-7) | 0.97 | No |
| [redacted] | 6389 | 105 (1.64%) | 70.5% | 63 (28-87) | 3 (1-8) | 0.91 | No |
| [redacted] | 6561 | 66 (1.01%) | 54.5% | 66 (33-90) | 4 (1-7) | 0.91 | No |
| **Total** | 209980 | 1915 (0.91%) | 62.1% | (19-98)* | (1-11)* | NA | NA |

* Median value not able to calculate due to aggregated data

Table 3: Number of LTOT patients and LTOT prevalence rates for different definitions and with or without patients with a cancer diagnosis in the past 12 months. Only primary care prescriptions included within the time period 01-06-2021 until 31-05-2022 were included.

| Definition | Patients enlisted, no. | Patients with LTOT, no. (%) | Patients with cancer diagnosis in past 12 months, no. | Non-cancer patients with LTOT, no. (%) |
|---|---|---|---|---|
| **DDD > 0.25** | 209980 | 1915 (0.91%) | 298 | 1617 (0.77%) |
| **DDD > 0.50** | 209980 | 1410 (0.67%) | 223 | 1187 (0.57%) |

### 3.1.2 National dataset

The total number of enlisted patients was 286294 in 2016 and this number increased to 311766 in 2021 (table 4). The number of LTOT patients declined over time, resulting in a declining LTOT prevalence rate from 1.37% in 2016 to 1.11% in 2021.

Table 4: LTOT (DDD > 0.25) prevalence rates in primary care per year.

| Year | Patients enlisted, no. | Patients with LTOT, primary care, no. (%) |
|---|---|---|
| **2016** | 286294 | 3923 (1.37%) |
| **2017** | 291433 | 3806 (1.31%) |
| **2018** | 296823 | 3658 (1.23%) |
| **2019** | 302488 | 3611 (1.19%) |
| **2020** | 306321 | 3584 (1.17%) |
| **2021** | 311766 | 3460 (1.11%) |

In the calculation of the prevalence rates for different definitions, the time period 01-06-2021 until 31-05-2022 was chosen (table 5). The total population of Uppsala county for 2021 was used as denominator, as data for 2022 is not available yet (table 4) [34].

From the total of 311766 enlisted patients, 3516 patients with LTOT were identified in primary care (*DDD > 0.25)*. As a result, a LTOT prevalence of 1.13% is calculated. Based on prescription data from Socialstyrelsen, the LTOT prevalence seems to be substantially lower in secondary care than in primary care for all definitions of LTOT. Moreover, the addition of the time component to the definition of LTOT leads to a smaller prevalence. However, this difference is only marginal.

Table 5: LTOT prevalence rates for different definitions. Both primary and secondary care prescriptions included within the time period 01-06-2021 until 31-05-2022 were included.

| Definition | Patients enlisted, no. | Patients with LTOT, primary care, no. (%) | Patients with LTOT, secondary care, no. (%) | Patients with LTOT, combined, no. (%) |
|---|---|---|---|---|
| **DDD > 0.25** | 311766 | 3516 (1.13%) | 1155 (0.37%) | 4672 (1.50%) |
| **DDD > 0.25 >= 3 quarters** | 311766 | 3264 (1.05%) | 965 (0.31%) | 4322 (1.39%) |
| | | | | |
| **DDD > 0.50** | 311766 | 1967 (0.63%) | 670 (0.21%) | 2708 (0.87%) |
| **DDD > 0.50 >= 3 quarters** | 311766 | 1914 (0.61%) | 621 (0.20%) | 2627 (0.84%) |

## 3.2 Type and quantity of written opioid prescriptions - regional dataset

### 3.2.1 Total number of prescriptions, users and sum of DDD

Between 01-06-2021 until 31-05-2022, a total of 9549 opioid prescriptions have been prescribed for LTOT patients (*DDD > 0.25*) (table 6). The prescription data show that oxycodone and codeine plus paracetamol, tramadol and buprenorphine are most prescribed and most used. The other opioid types show a substantially lower number of users and are prescribed less frequently.

Subsequently, the mean DDD per prescription and per user were calculated for each opioid type (appendix 4). Codeine plus other non-opioid analgesic (NOA) and tapentadol provide the highest mean DDD per prescription and per user. When adopting *DDD > 0.*50 as definition for LTOT, no substantial changes can be observed.

Table 6: Total number of prescriptions, users and prescribed DDD for LTOT (DDD > 0.25) patients, for each opioid type in the time period 01-06-2021 until 31-05-2022.

| ATC-code | Drug | Total no. prescriptions | Total no. users | Total prescribed DDD |
|---|---|---|---|---|
| N02AJ06 | Codeine + PCM | 2834 | 766 | 7388 |
| N02AJ09 | Codeine + other NOA | 231 | 69 | 1206 |
| N02AX02 | Tramadol | 1565 | 444 | 3370 |
| N02AA05 | Oxycodone | 2930 | 493 | 5624 |
| N02AA55 | Oxycodone + naloxone | 180 | 54 | 271 |
| N02AE01 | Buprenorphine | 1206 | 401 | 2646 |
| N02AA01 | Morphine | 199 | 57 | 349 |
| N02AB03 | Fentanyl | 96 | 24 | 217 |
| N02AX06 | Tapentadol | 214 | 63 | 867 |
| N02AB01 | Ketobemidone | 91 | 28 | 196 |
| N02A | Other | 3 | 3 | 8 |

## 3.3 Type and quantity of dispensed opioid prescriptions - national dataset

The total number of patients with at least one opioid prescription in primary care was 14940 in 2016 and this number declined to 14180 in 2021. Subsequently, the number of LTOT patients declined from 3923 in 2016 to 3460 in 2021.

### 3.3.1 Total number of opioid prescriptions per year

Based on the national prescription data, codeine plus paracetamol, tramadol and oxycodone show the highest number of prescriptions per 1000 capita (figure 1). Codeine plus paracetamol was the most prescribed opioid type in 2016, while it was oxycodone since 2019. Per 1000 capita, the total number of oxycodone prescriptions increased from 22.4 in 2016 to 55.7 in 2021. Other opioid types that show an increasing trend are oxycodone plus naloxone and buprenorphine. Fluctuation in prescription rates of other opioids is present, but less substantial. The same trends can be observed when adopting a stricter definition for LTOT (appendix 5).

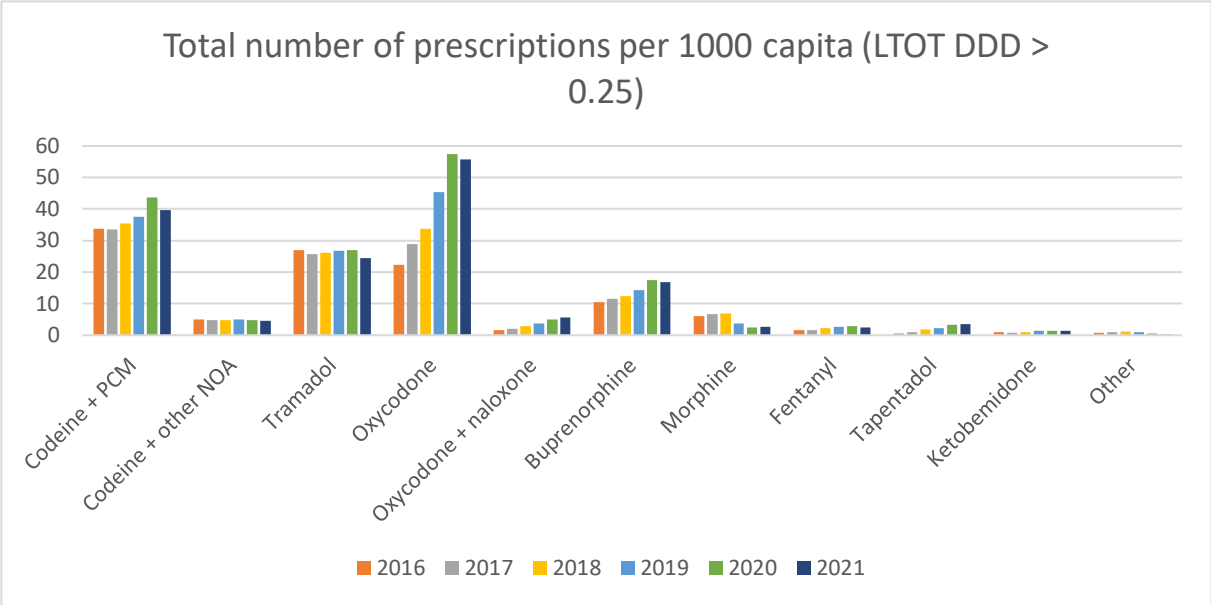


Figure 1: Total number of primary care opioid prescriptions per 1000 capita for LTOT (DDD > 0.25) patients, for each type of opioid from 2016 until 2021.

It can be observed that weaker opioids were more frequently prescribed than stronger opioids in 2016, whereas stronger opioids were more frequently prescribed in 2021 (figure 2). The prescription rate of weaker opioids remained more or less stable, whereas a substantial increase can be seen for the prescription rates of stronger opioids.

With the adoption of more strict definitions of LTOT, the same stable trend can be observed for the prescription rates of weaker opioids, whereas the increase of stronger opioid prescriptions seems to be less substantial (appendix 6).

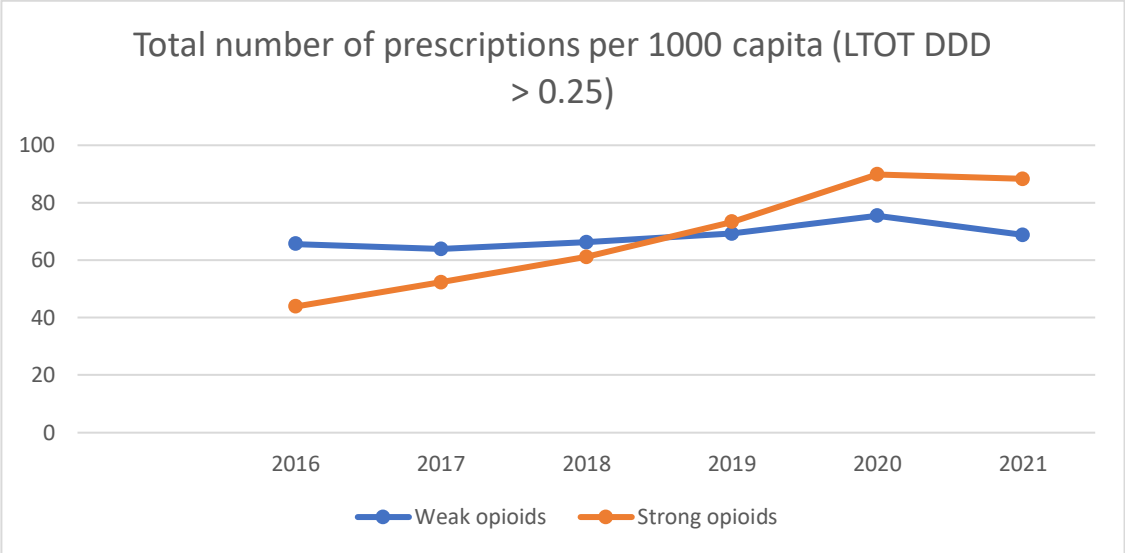


Figure 2: Total number of primary care opioid prescriptions per 1000 capita for LTOT (DDD > 0.25) patients, for weaker and stronger opioids combined from 2016 until 2021.

### 3.3.2 Total number of opioid users per year

Based on the national prescription data, codeine plus paracetamol was the opioid type with the most users per 1000 capita in 2016 (figure 3). This was still the case in 2021. However, oxycodone shows a substantial increase from 1.9 to 3.7 users per 1000 capita between 2016 and 2021.

Moreover, an increase in the total number of users is also visible for buprenorphine, whereas a decrease can be seen for tramadol. Fluctuation in the number of users for other opioid types is present, but less substantial. A similar trend can be observed when adopting a stricter definition for LTOT (appendix 7).

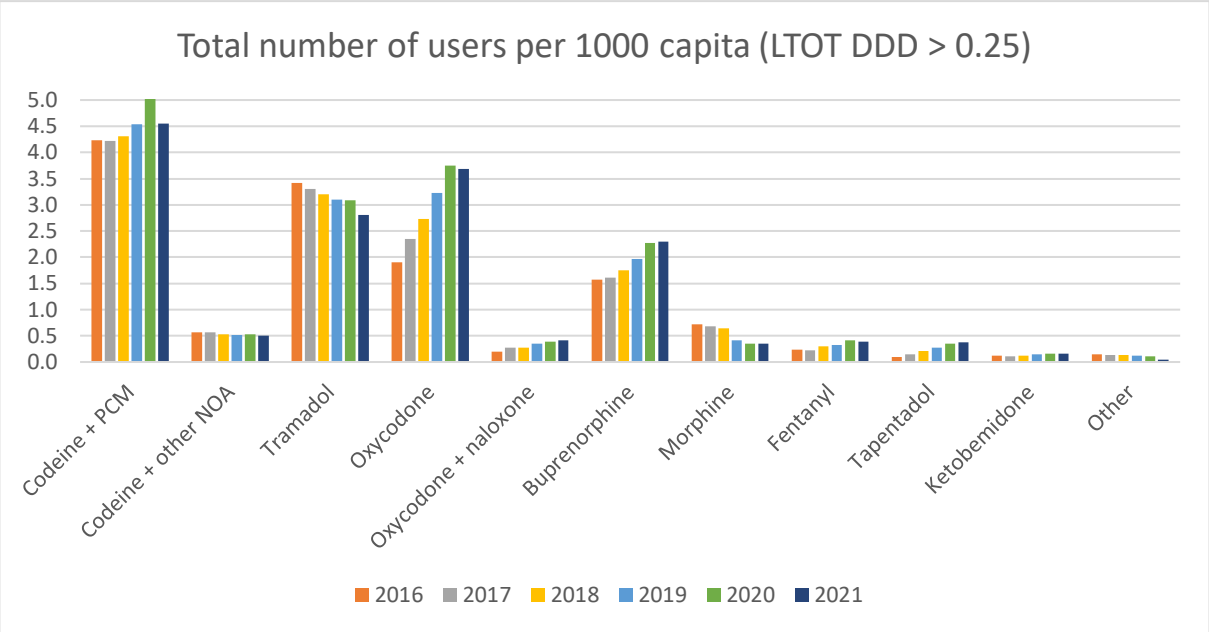


Figure 3: Total number of opioid users per 1000 capita for LTOT (DDD > 0.25) patients, for each type of opioid from 2016 until 2021.

In 2016, there were more users of weaker opioids per 1000 capita than for stronger opioids (figure 4). In 2021, the number of users is roughly the same, due to an increase in stronger opioid users and a more or less stable trend for weaker opioid users. The same trend can be seen when LTOT is defined as *DDD > 0.25 >= 3 quarters*, whereas the increase of stronger opioid users seems to be less evident when LTOT is defined as *DDD > 0.50* or *DDD > 0.50 >= 3 quarters* (appendix 8).

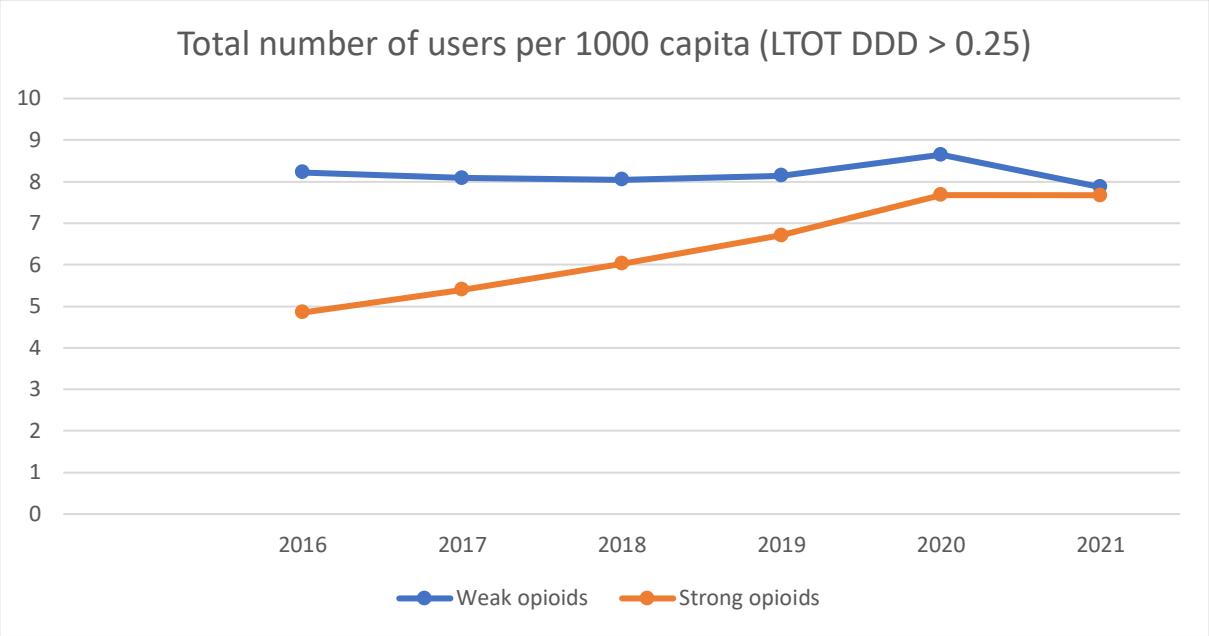


Figure 4: Total number of opioid users per 1000 capita for LTOT (DDD > 0.25) patients, for weaker and stronger opioids combined from 2016 until 2021.

### 3.3.3 Total sum of prescribed DDD per year

Codeine plus paracetamol was the opioid type with the most total prescribed DDD per 1000 capita in 2016 (figure 5). This was still the case in 2021. An increasing trend can be observed for codeine plus paracetamol, oxycodone and buprenorphine, whereas a decreasing trend can be seen for tramadol. Fluctuation in the number of users for other opioid types seems less evident. Similar trends can be seen when different definitions for LTOT are adopted (appendix 9).

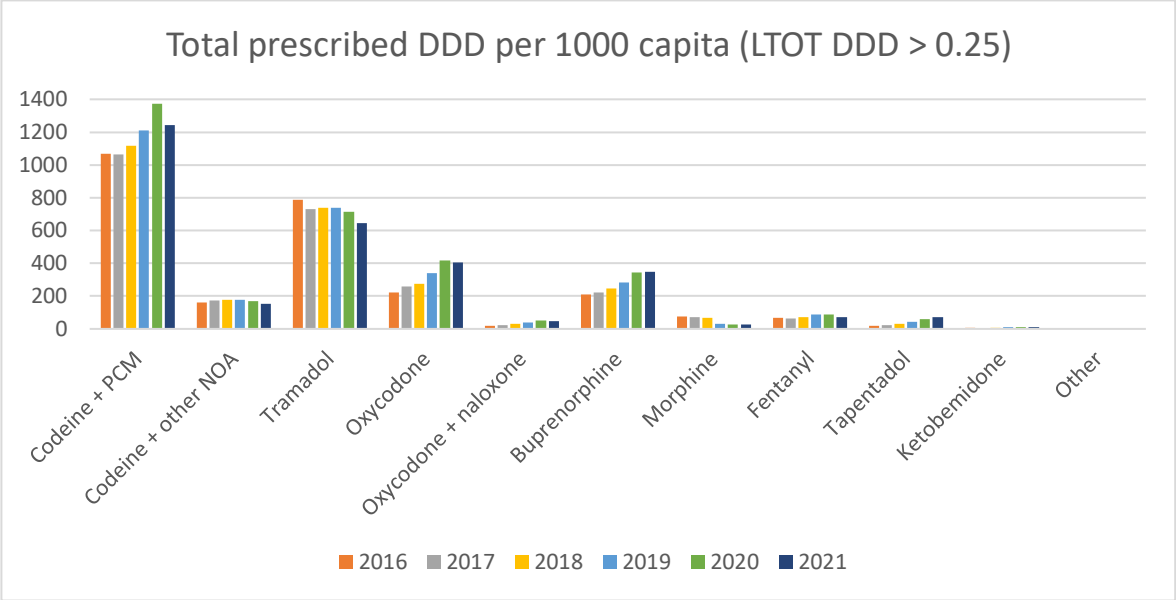


Figure 5: Total sum of prescribed DDD per 1000 capita for LTOT (DDD > 0.25) patients, for each type of opioid from 2016 until 2021.

Between 2016 and 2021, the total prescribed DDD is higher for weaker opioids than for stronger opioids (figure 6). A more or less stable trend can be seen for weaker opioids, whereas the total prescribed DDD per 1000 capita for stronger opioids has almost doubled from 592 in 2016 to 970 in 2021. Nonetheless, the line for weaker opioids is still substantially higher in 2021, with 1981 total prescribed DDD per 1000 capita. Similar trends can be seen when different definitions for LTOT are adopted (appendix 10).

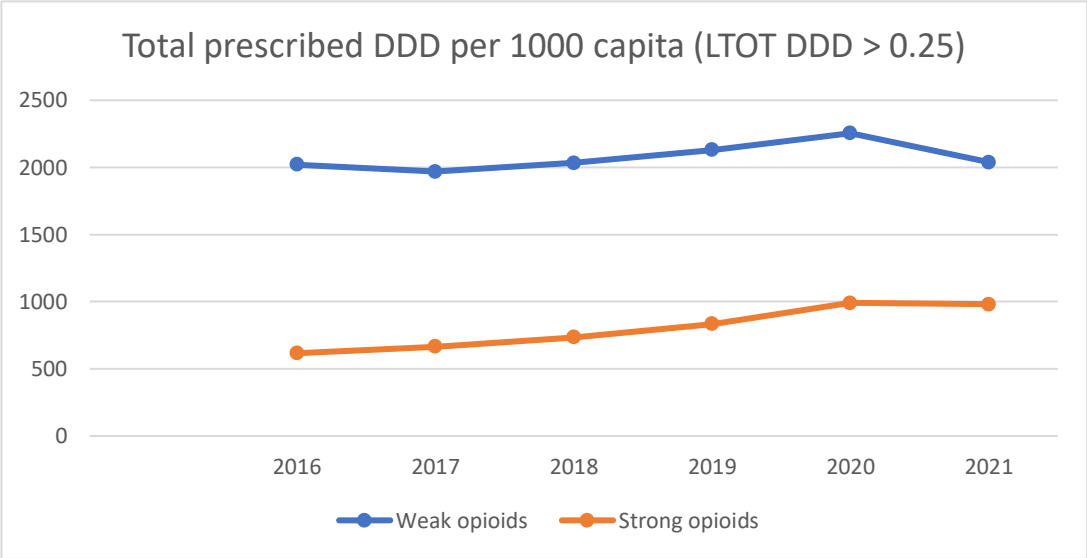


Figure 6: Total sum of prescribed DDD per 1000 capita for LTOT (DDD > 0.25) patients, for weaker and stronger opioids combined from 2016 until 2021.

### 3.3.4 Mean DDD per prescription and per user

With 0.14, fentanyl was the opioid type with the highest mean DDD per prescription per 1000 capita in 2016 (appendix 11). Due to the decreasing trend for fentanyl, codeine plus other NOA accounted for the highest mean DDD per prescription per 1000 capita in 2021, with 0.11. Besides fentanyl, it can be observed that tapentadol shows a decreasing trend in the mean DDD per prescription over time as well, whereas fluctuation for the other opioid types remains more or less stable. These trends are similar when different definitions for LTOT are adopted.

Codeine plus other NOA and fentanyl were the opioid types with the highest mean DDD per user per 1000 capita in 2016 (appendix 12). In 2021, it was only codeine plus other NOA, due to the decrease for fentanyl from 0.97 in 2016 to 0.60.

Other opioid types that show a decreasing trend are tapentadol, and to a lesser extent morphine. For the other opioid types, the fluctuation over time seems less prominent. When adopting different definitions for LTOT, similar trends can be seen for most opioid types. For oxycodone plus naloxone and ketobemidone, an increasing trend can be observed.

### 3.3.5 Lorenz curve

The Lorenz curve is different from the equality line (blue line), which indicates that opioid prescriptions are not equally distributed among LTOT patients (figure 7). The Gini coefficient of 0.72 supports this result, as the value is closer to one than zero.

The Lorenz curve and Gini coefficient did not seem to change substantially when adopting different definitions for LTOT (appendix 13).

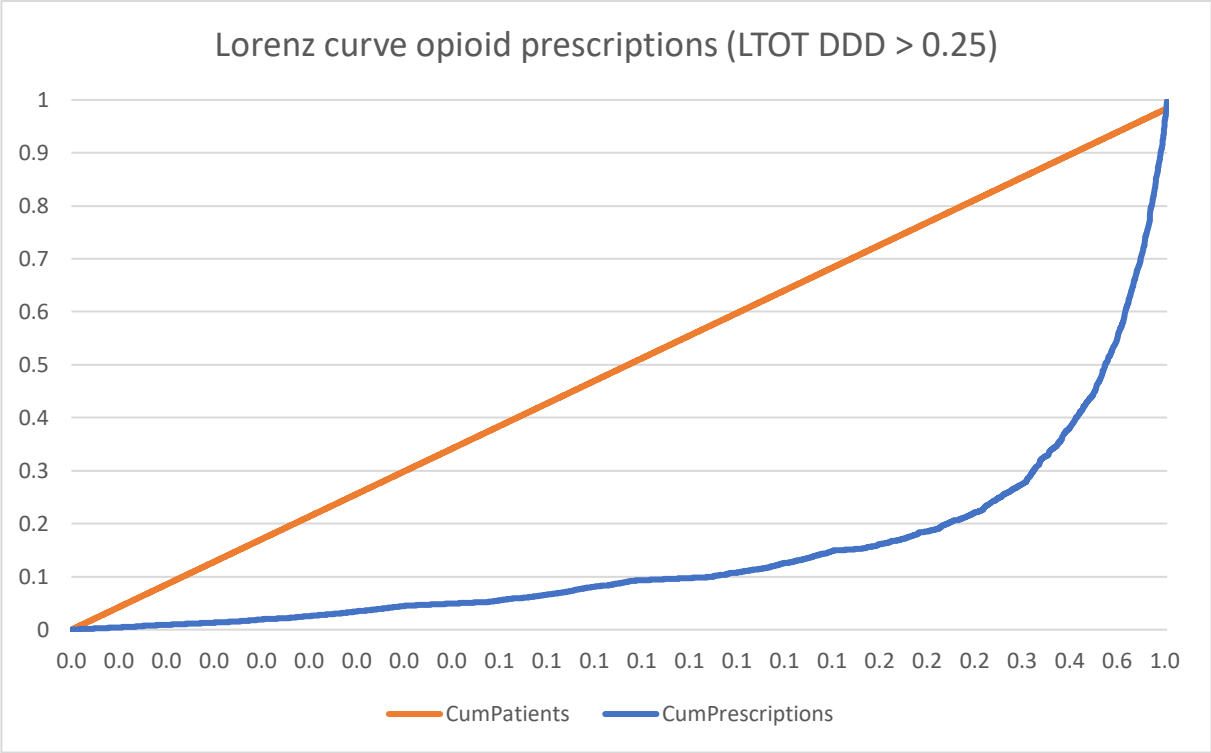

Figure 7: Lorenz curve of all opioid prescriptions for LTOT (DDD > 0.25) patients. Data from 01-01-2016 until 01-09-2022.

# 4. Discussion

In this retrospective study of opioid prescriptions of adult patients primary care in Uppsala county, LTOT (*DDD > 0.25*) prevalence rates of 0.77% (regional dataset) and 1.13% (national dataset) were reported for the period 01-06-2021 until 31-05-2022. LTOT prevalence rates decreased when adopting stricter definitions of LTOT, which is in line with clinical expectations. Moreover, the individual primary care practices differed in terms of LTOT prevalence.

The characteristics of both datasets are likely to contribute to the differences in the LTOT prevalence rates that were reported. First, the regional dataset contained information on written opioid prescriptions, whereas the national dataset contained information on dispensed prescriptions. Second, only opioid prescriptions from public primary care practices were included in the regional dataset, whereas both public and private primary care prescriptions were included in the national dataset.

Codeine plus paracetamol was the opioid type with the most prescriptions, users and highest total prescribed DDD among LTOT patients (*DDD > 0.25*) in 2016. However, it seems that oxycodone has surpassed codeine plus paracetamol in the number of prescriptions since 2019. Furthermore, the results showed an increasing trend in the number of prescriptions, users and total prescribed DDD for stronger opioids between 2016 and 2021, whereas these variables remain roughly the same for weaker opioids. The most pronounced increases were found for oxycodone and buprenorphine, whereas only tramadol showed a decreasing trend in prescriptions, users and total prescribed DDD. The adoption of different definitions for LTOT showed no substantial difference in the outcomes.

In line with our results, other studies have observed similar increasing trends in the use of stronger opioids [20,35,36]. In The Netherlands, the number of dispensed oxycodone prescriptions almost quadrupled between 2008 and 2017 [35], whereas other studies reported a six-fold and ten-fold increase in oxycodone prescriptions between 2006 and 2018 in Sweden [20,36]. Moreover, they report that Sweden's high oxycodone prescribing rate is tempered by lower doses, which results in a decreasing trend in the mean DDD per oxycodone

prescription. This is in line with our findings. The decreasing trend in tramadol use in our results has been reported in other studies as well [36,37].

The combination of an increase in stronger opioid use and a decrease in weaker opioid use is reason for concern. Even though the slight decrease in weaker opioid use in our results is mainly caused by tramadol, it may be an indication for a shifting trend from the prescription of weaker opioids to stronger opioids. This is in line with recent Swedish studies [16,20].

Important to note is that some caution is needed when interpreting and comparing opioid prescription rates and trends, as studies may have used different definitions and time periods.

## 4.1 Strengths and limitations

This is the first in-depth analysis of primary care prescription data of opioids in the adult population of Uppsala county, Sweden. A major strength of this study is the use of two different datasets containing different information on individual prescriptions (e.g. written or dispensed prescriptions), patient characteristics and specific primary care practices. Especially the national dataset can be regarded as very comprehensive, as it is derived from a national registry that contains information on all dispensed opioid prescriptions in community pharmacies in Sweden [21].

Furthermore, different definitions for LTOT were adopted to be able to assess the potential impact on the outcomes. Last, the use of DDD as part of the definitions for LTOT enables a better comparison between all different opioid types.

Besides these strengths, we should also take into account inherent limitations. First, the regional dataset only contained information on written prescriptions from the public electronic health record system. Therefore, prescriptions for patients with automated dose dispensing and prescriptions from private practices were not included. However, comprehensive information on all dispensed opioid prescriptions was available from the national dataset. But the national dataset, in turn, lacks information on patient characteristics and individual primary care practices.

Second, several analyses (e.g. full descriptive statistics and Lorenz curves) could not be performed due to fact that the regional dataset contained aggregated data. However, this was unavoidable due to ethical and data protection reasons.

Third, the definitions for LTOT can also identify false negative patients, e.g., those who use occasional low-dose opioids all year long but do not meet the minimum of DDD > 0.25 or > 0.50. When relying exclusively on data from a prescription database, it is not possible to pinpoint the exact use. Nevertheless, it appears from our findings that the patients identified by the included definitions are likely to be long-term opioid users. Moreover, there is no guarantee that the dispensed drugs in our data have actually been consumed. However, this is considered to be an unavoidable limitation of the use of prescription databases.

Last, our analysis was limited to outpatient opioid prescriptions. The fact that only adult prescription data was included in our analysis, could contribute to a slight underestimation of the LTOT prevalence. However, based on the results of the regional dataset where the minimum age of LTOT patients is above 20 years for most primary care practices, it is likely that there are nearly no LTOT patients under the age of 18 in primary care.

## 4.2 Implications for research and clinical practice

The results of this study can be used to fill the gap in terms of the general understanding about LTOT prevalence and opioid use in Uppsala county, Sweden. Our results provide an in-depth insight and could be used as a starting and reference point for further research. The evidence on effectivity and safety of long-term opioid use remains highly questionable. Still, chronic pain patients in Sweden make up a population that is seriously exposed to opioids. Based on our study, a substantial group of patients in Uppsala county are possibly unjustly on LTOT.

The appropriateness of prescribing opioids must be critically reconsidered. One of the proposed initiatives is a novel multidisciplinary team-based approach, including a pharmacist, in primary care practices to improve pain treatment outcomes in chronic non-cancer pain patients, for which an intervention trial is currently planned. Data from this observational study may support the planned trial to select intervention practices and matched control practices based on number of LTOT patients and LTOT prevalence per practice.

Our results report that to date, pharmacists are present at 6 out of the 23 included primary care practices. Due to their assumably important role in healthcare teams and their regular interactions with patients, pharmacists may take up a more prominent role in the encouragement and implementation of appropriate opioid use.

## 4.3 Conclusion

In conclusion, the LTOT (defined as *DDD > 0.25*) prevalence rates among adult patients in primary care in Uppsala county varied between 0.77% and 1.13% and LTOT patients were not equally distributed among public primary practices.

Codeine plus paracetamol was the opioid with the highest number of prescriptions, users and total prescribed DDD among LTOT (*DDD > 0.*25) patients in 2016. Since 2019, however, oxycodone accounts for the highest number prescriptions. Between 2016 and 2021, an increasing trend in the number of prescriptions, users and total prescribed DDD was found for stronger opioid types, whereas fluctuation for weaker opioids was not substantial. Oxycodone and buprenorphine showed the most pronounced increases, whereas only tramadol showed a decreasing trend.

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# Appendix

## Appendix 1 – Different types of opioids and their corresponding ATC-code

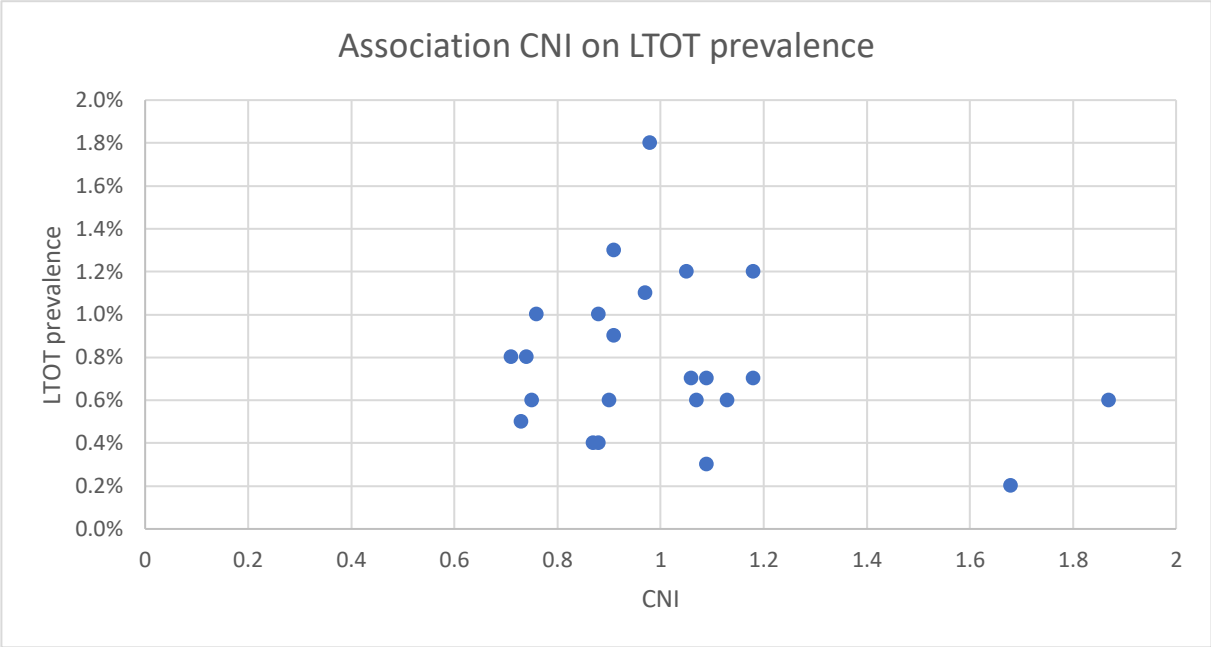
| | ATC-code | Drug name |
|---|---|---|
| **Weaker** | N02AJ06 | Codeine + PCM |
| | N02AJ09 | Codeine + other NOA |
| | N02AX02 | Tramadol |
| | | |
| **Stronger** | N02AA05 | Oxycodone |
| | N02AA55 | Oxycodone + naloxone |
| | N02AE01 | Buprenorphine |
| | N02AA01 | Morphine |
| | N02AB03 | Fentanyl |
| | N02AX06 | Tapentadol |
| | N02AB01 | Ketobemidone |
| | N02A | Other |

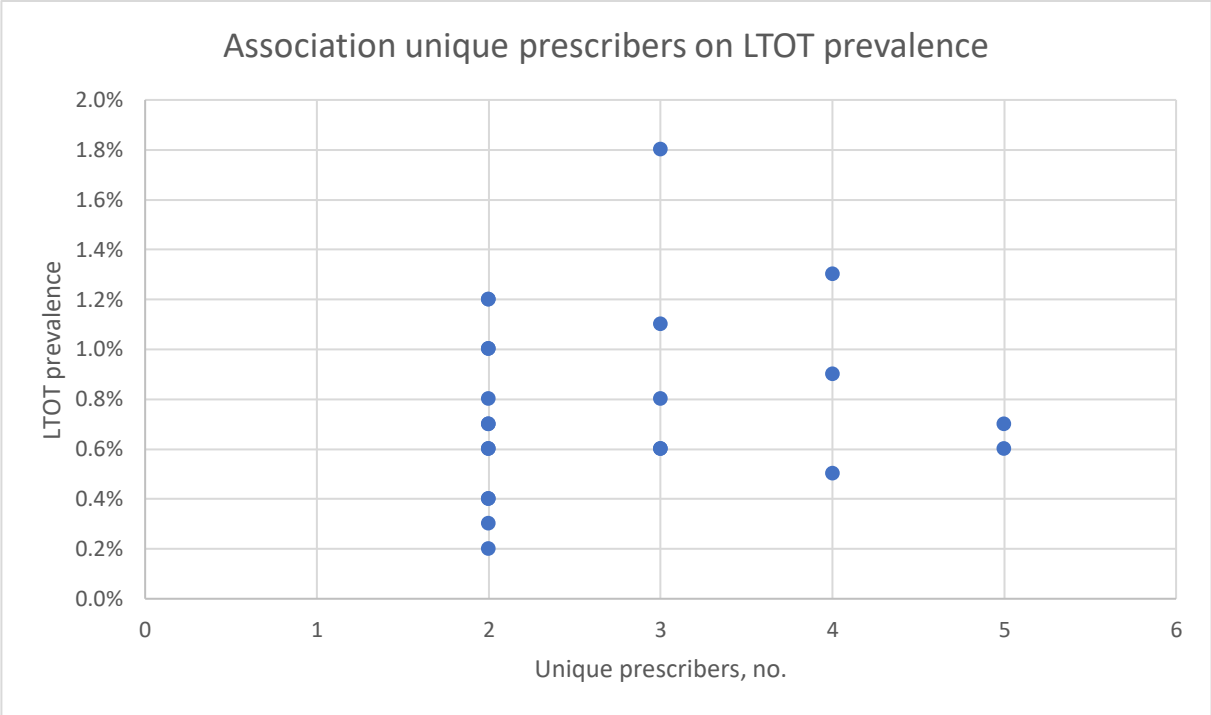
[27,28]

## Appendix 2 – Total number of citizens registered within Uppsala county per year

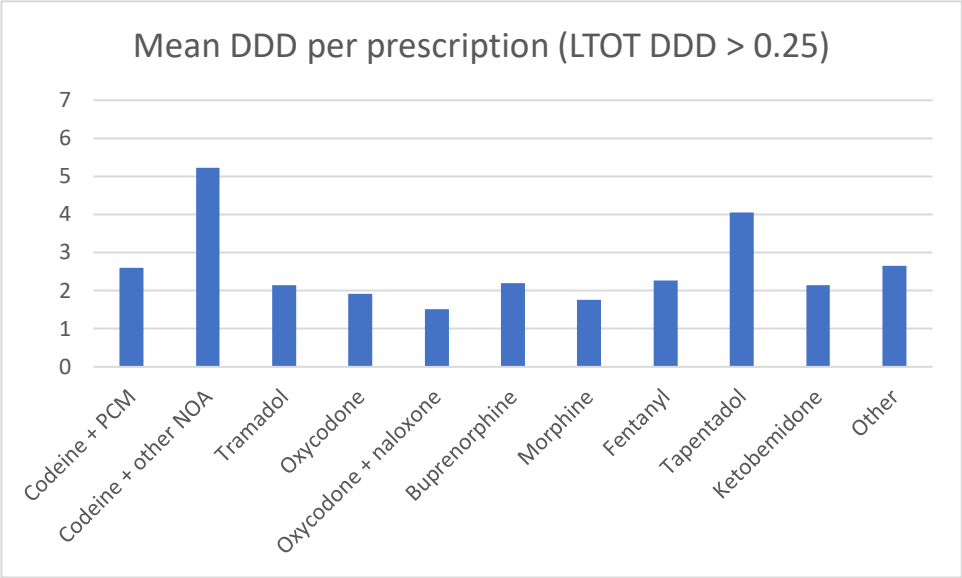
| Year | Population |
|---|---|
| **2016** | 286294 |
| **2017** | 291433 |
| **2018** | 296823 |
| **2019** | 302488 |
| **2020** | 306321 |
| **2021** | 311766 |

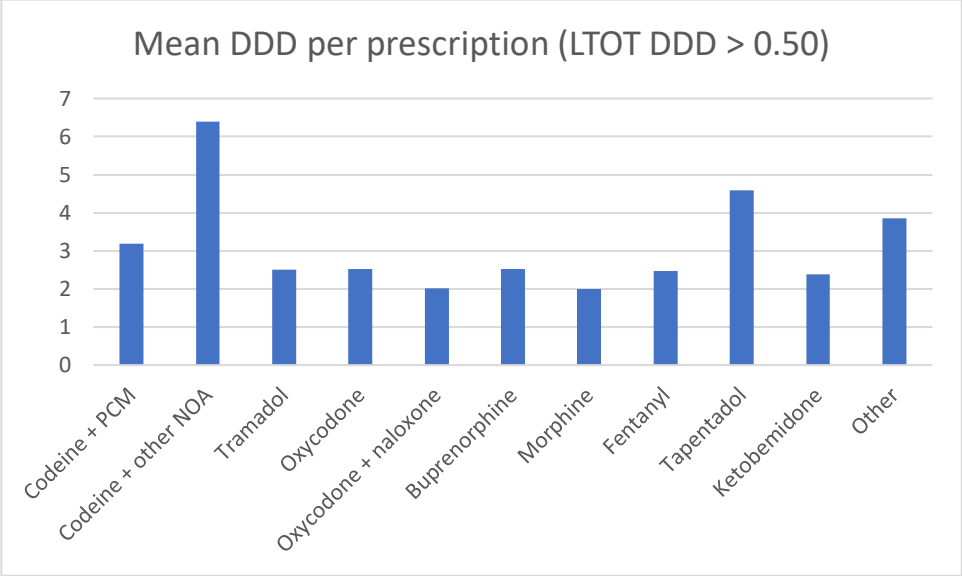
## Appendix 3 – Plots on potential association between CNI, unique prescribers and LTOT prevalence

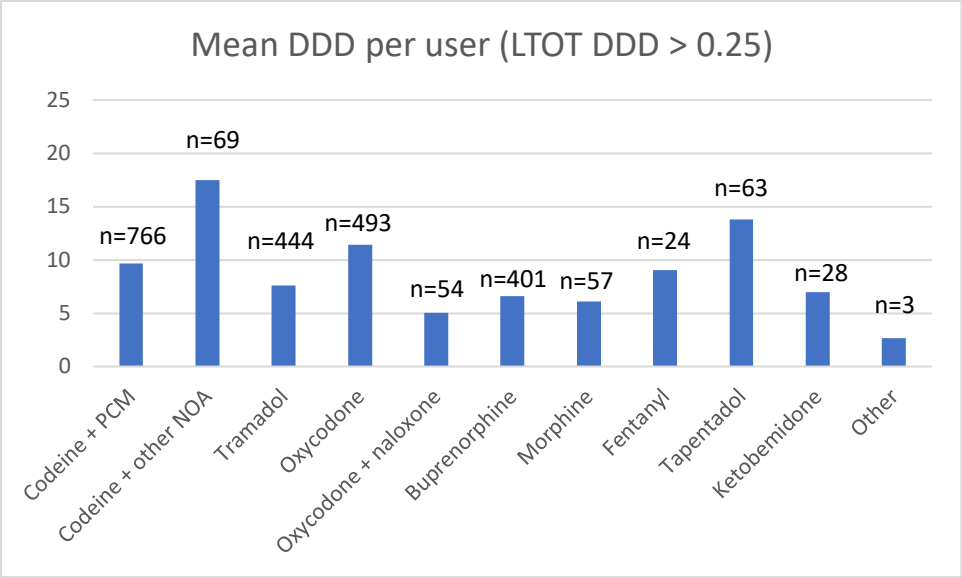


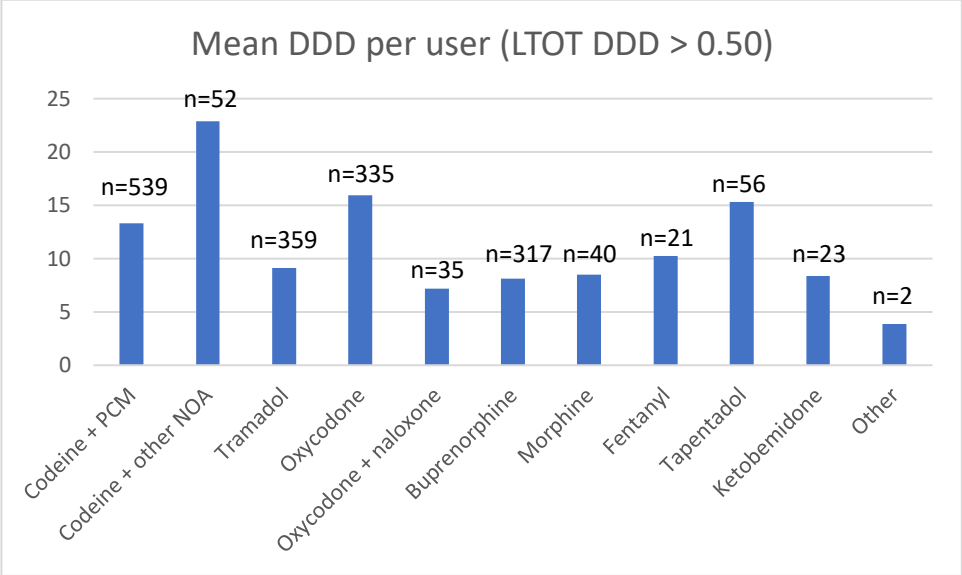



## Appendix 4 – Mean DDD per prescription and per user for different definitions of LTOT

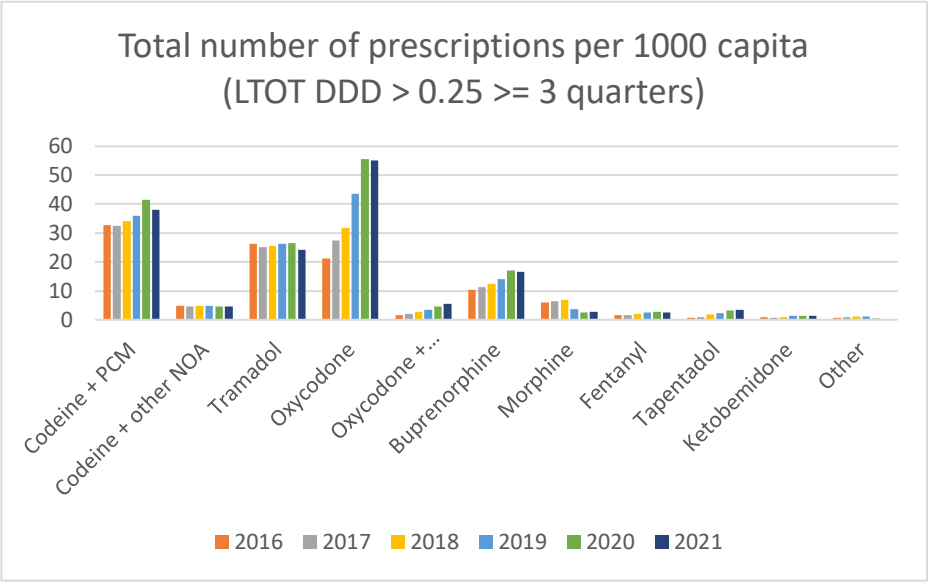


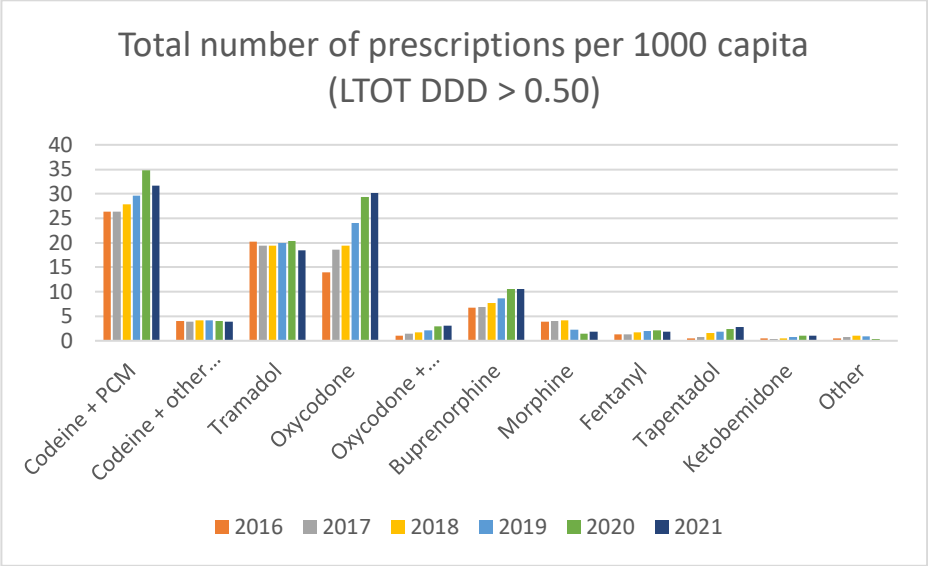



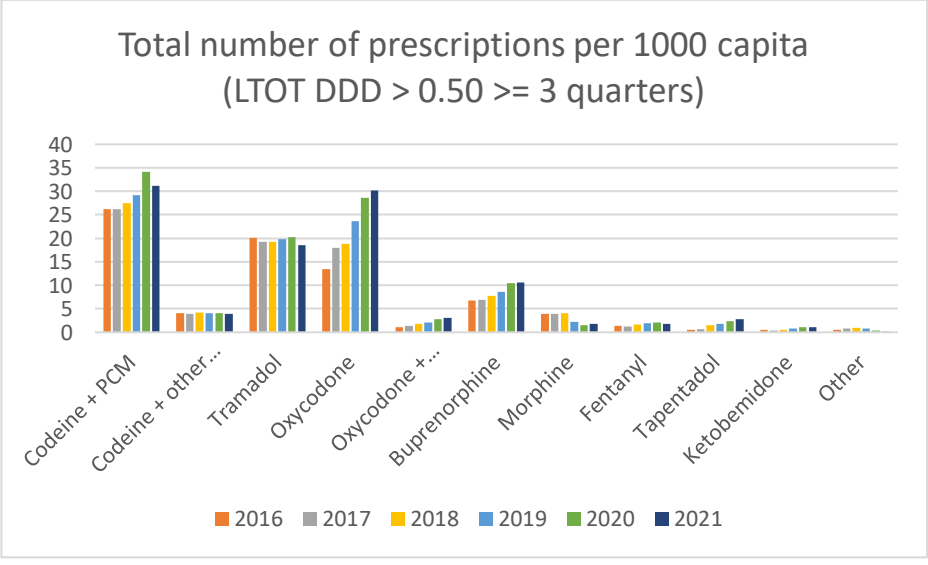

Mean DDD per user (LTOT DDD > 0.25)
25
20
15
10
5
0
n=766
n=69
n=444
n=493
n=54
n=401
n=57
n=24
n=63
n=28
n=3
Codeine + PCM
Codeine + other NOA
Tramadol
Oxycodone
Oxycodone + naloxone
Buprenorphine
Morphine
Fentanyl
Tapentadol
Ketobemidone
Other


Mean DDD per user (LTOT DDD > 0.50)
25
20
15
10
5
0
n=539
n=52
n=359
n=335
n=35
n=317
n=40
n=21
n=56
n=23
n=2
Codeine + PCM
Codeine + other NOA
Tramadol
Oxycodone
Oxycodone + naloxone
Buprenorphine
Morphine
Fentanyl
Tapentadol
Ketobemidone
Other

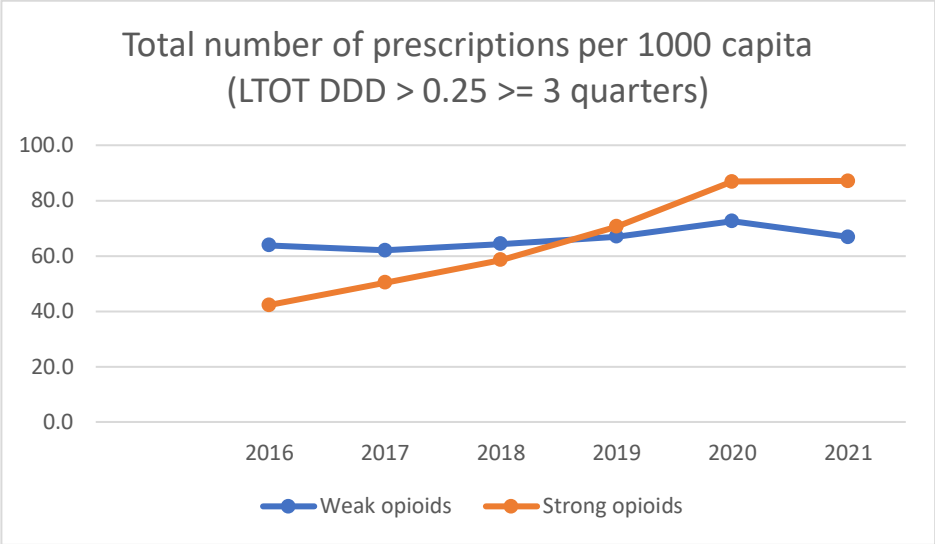
## Appendix 5 – Total number of opioid prescriptions for different definitions of LTOT

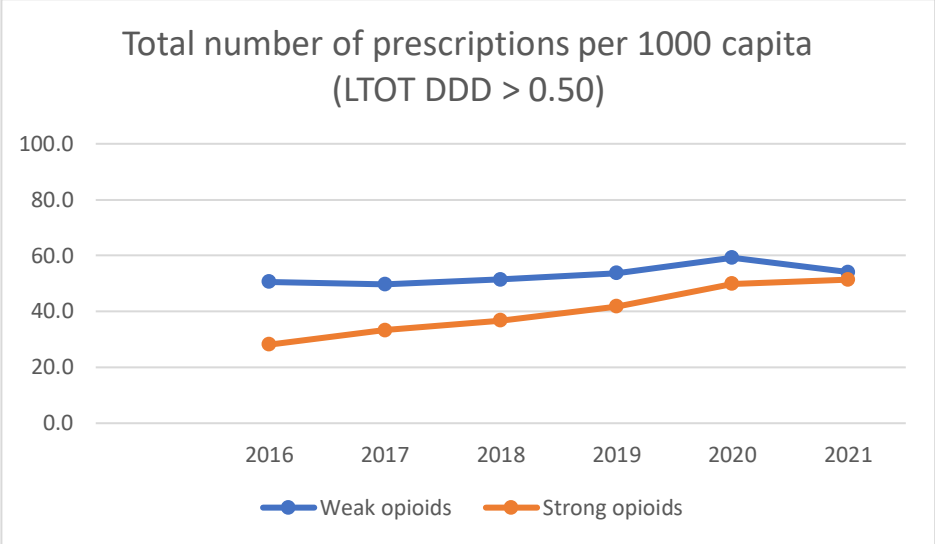


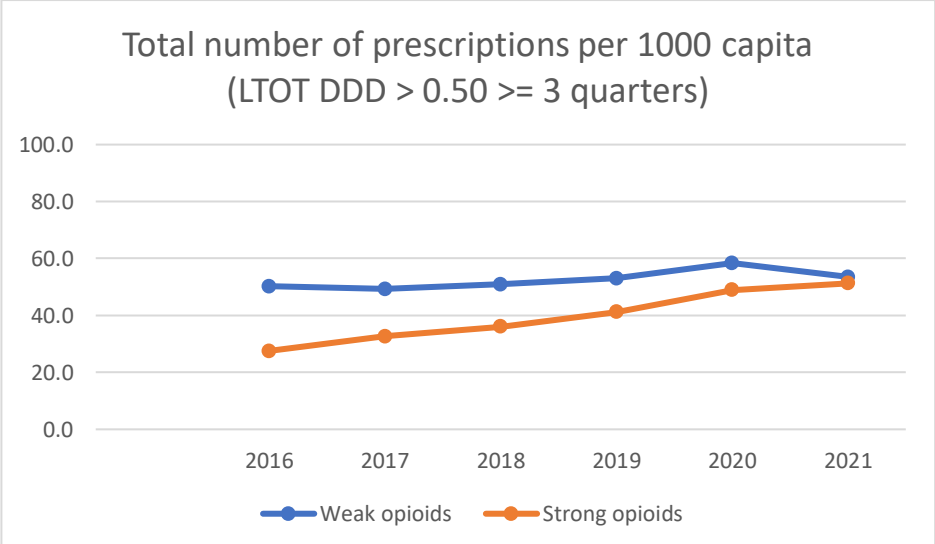



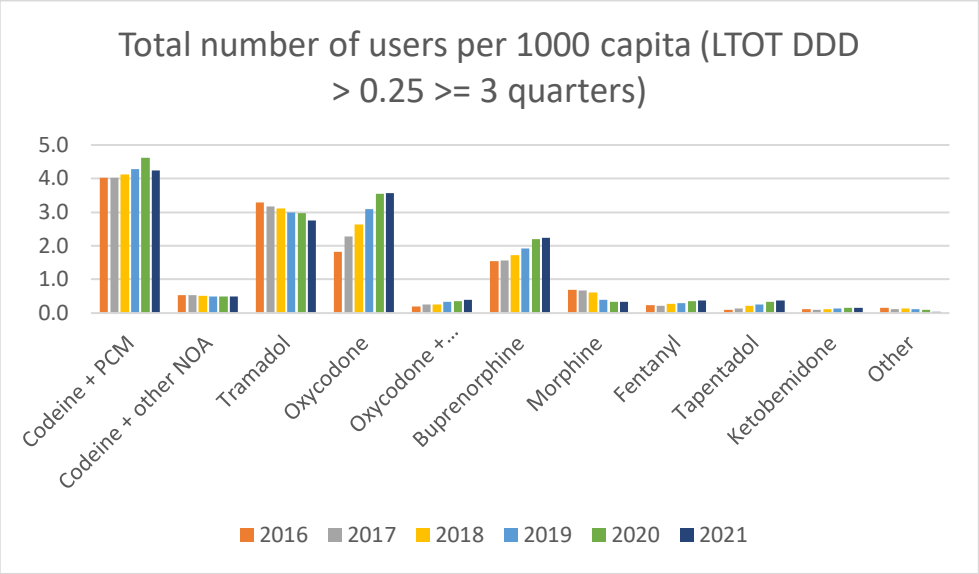
## Appendix 6 – Total number of weaker and stronger opioid prescriptions for different definitions of LTOT

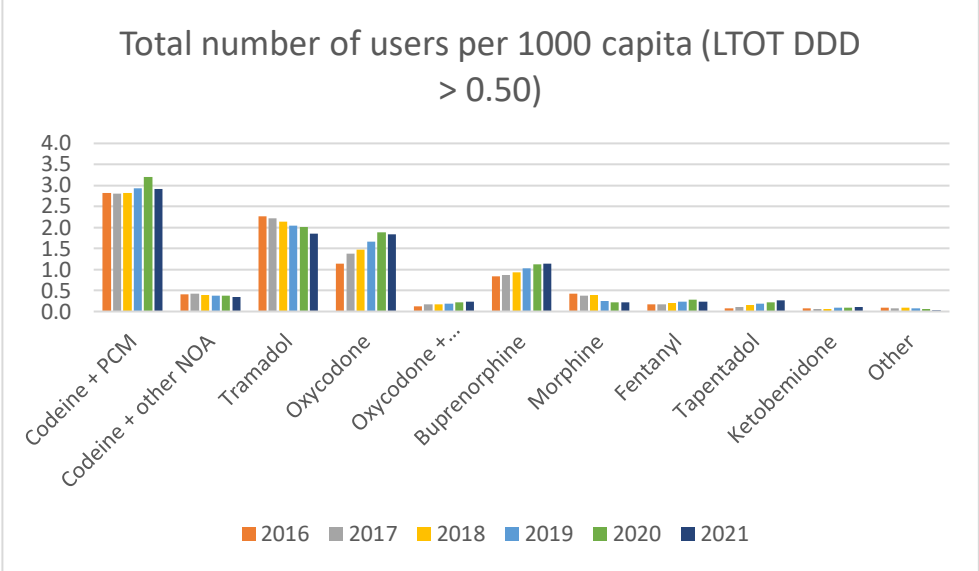


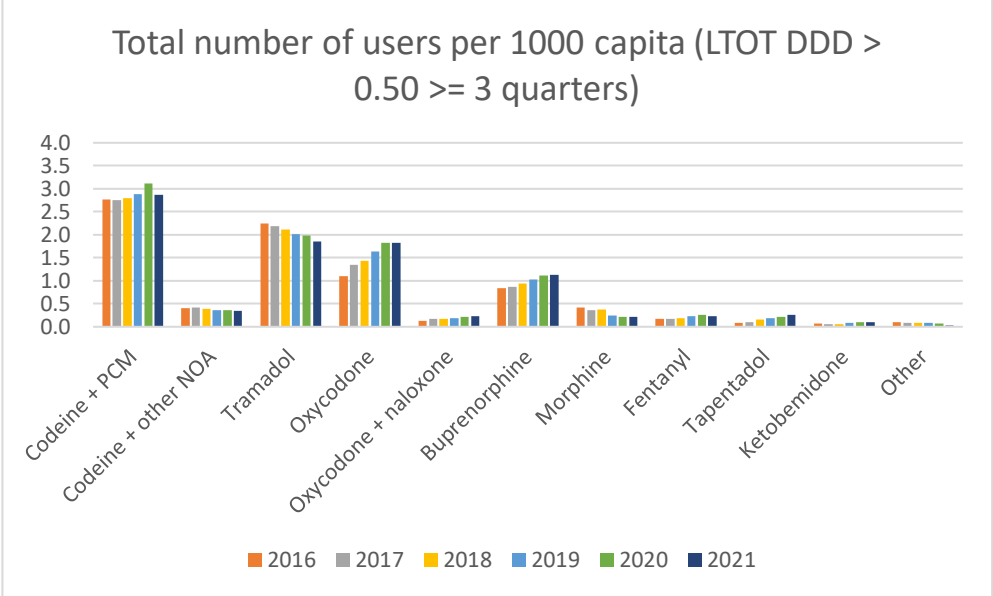



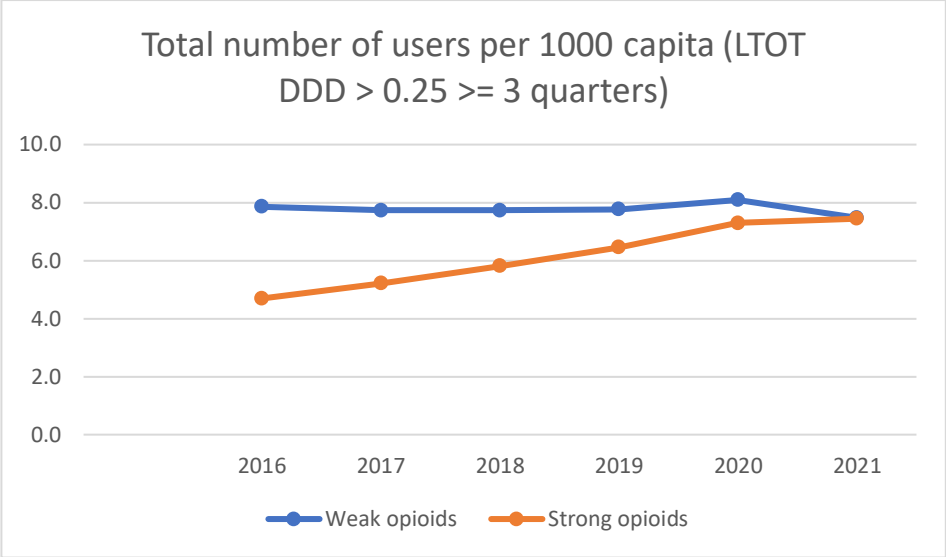
## Appendix 7 – Total number of opioid users for different definitions of LTOT

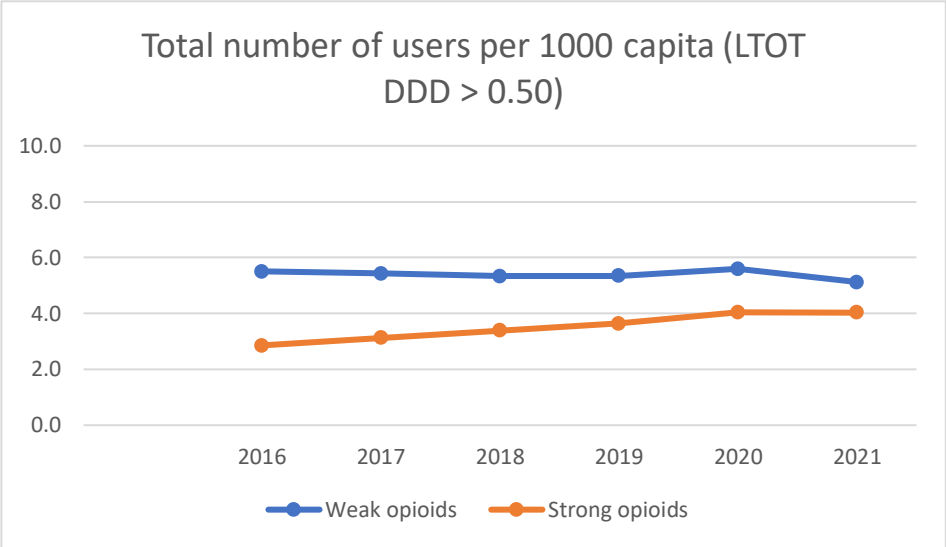


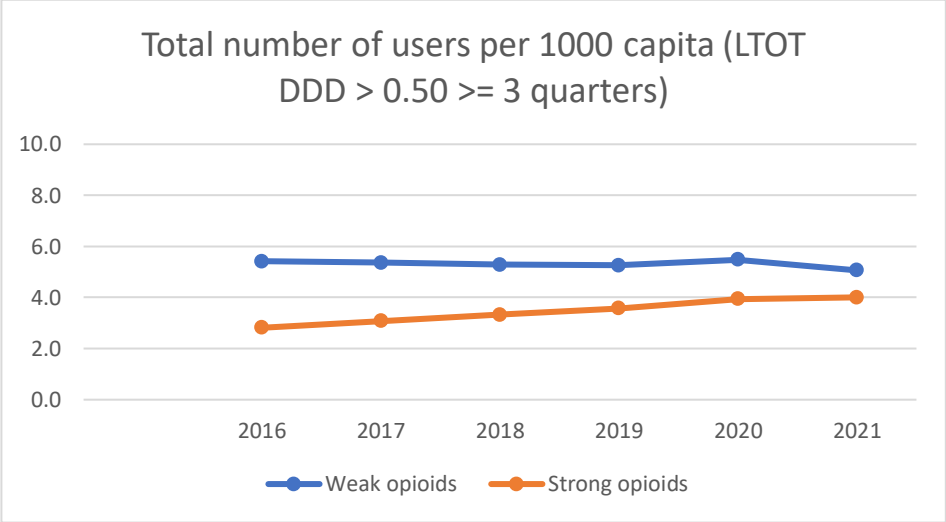



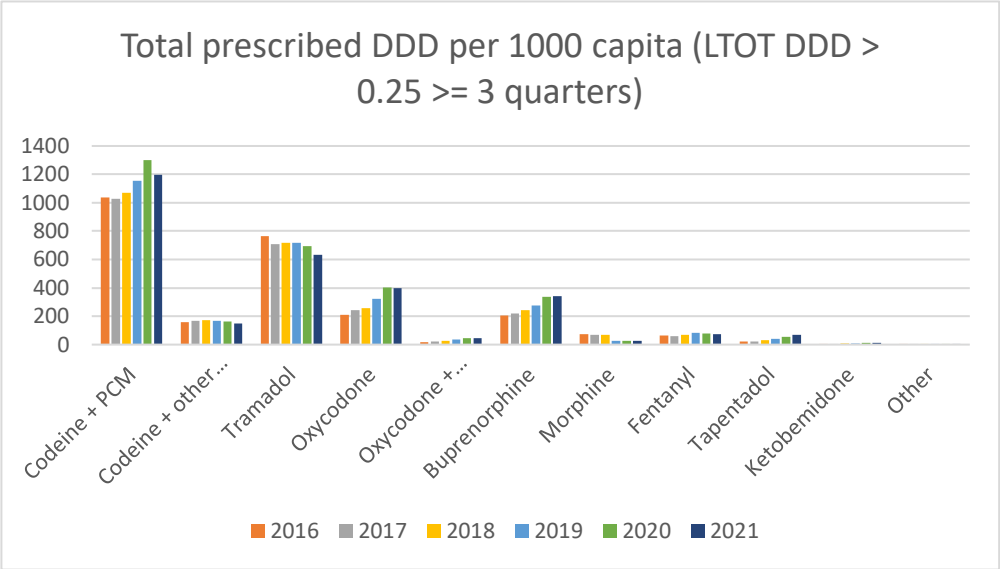
## Appendix 8 – Total number of weaker and stronger opioid users for different definitions of LTOT

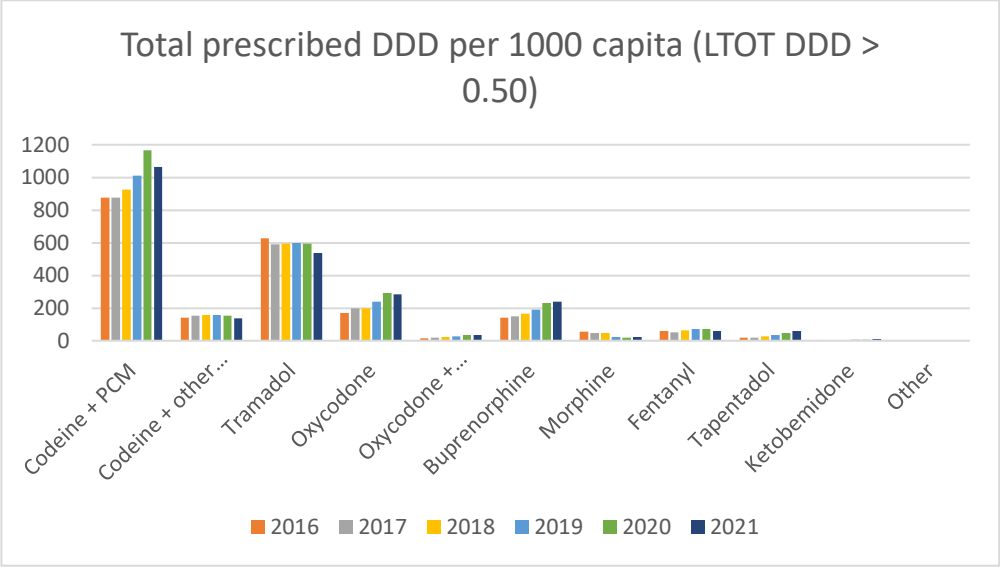


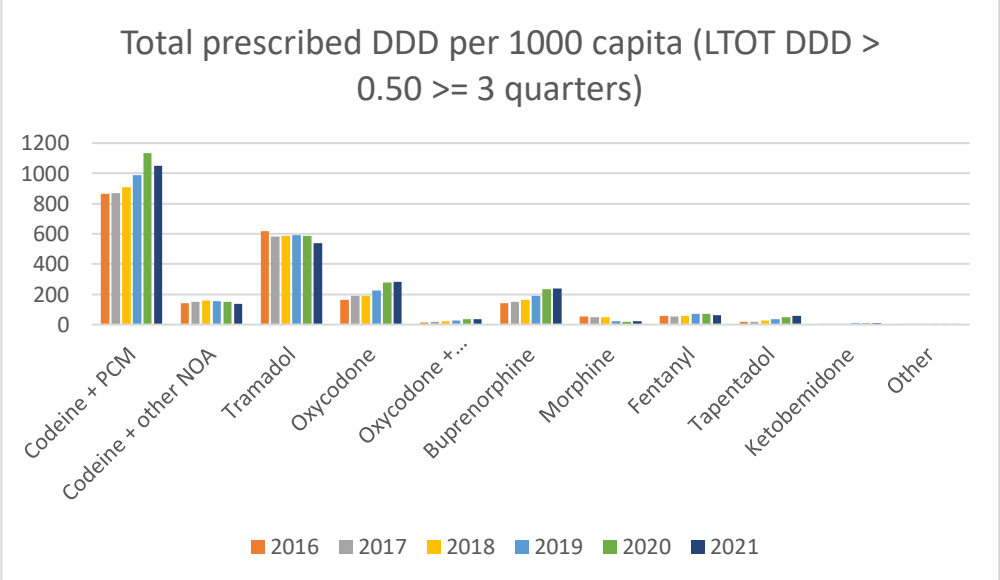



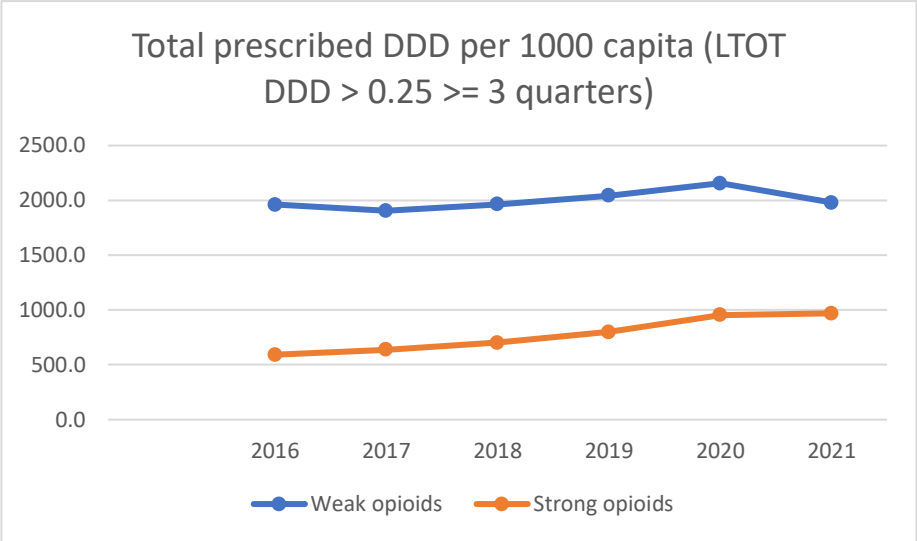
## Appendix 9 – Total sum of prescribed DDD for different definitions of LTOT

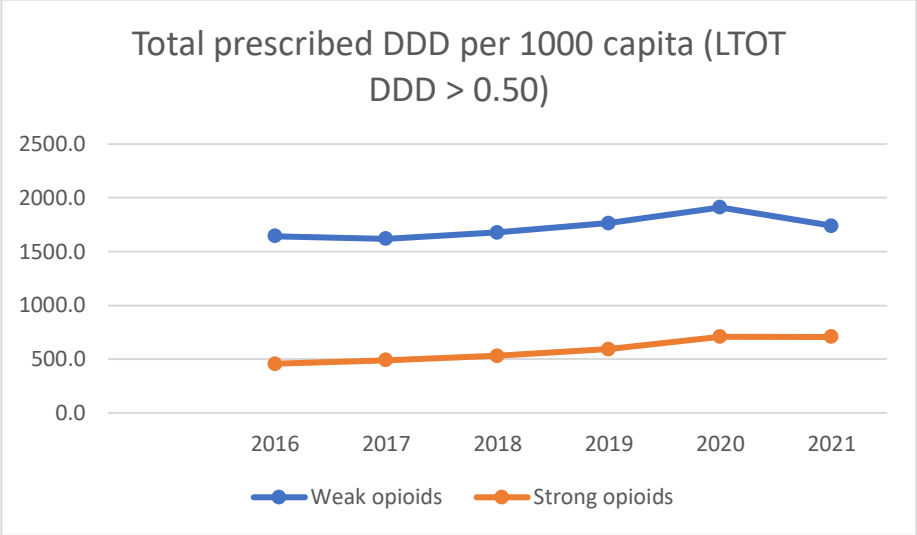


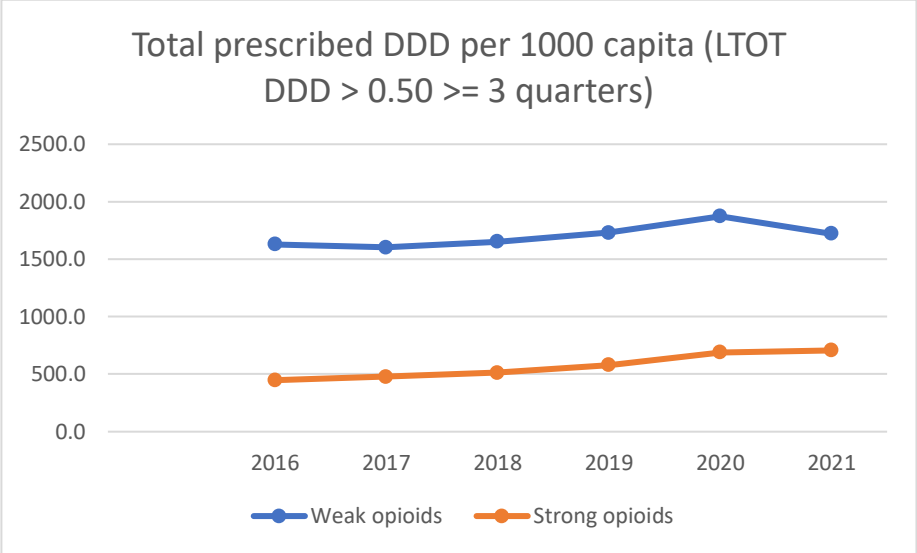



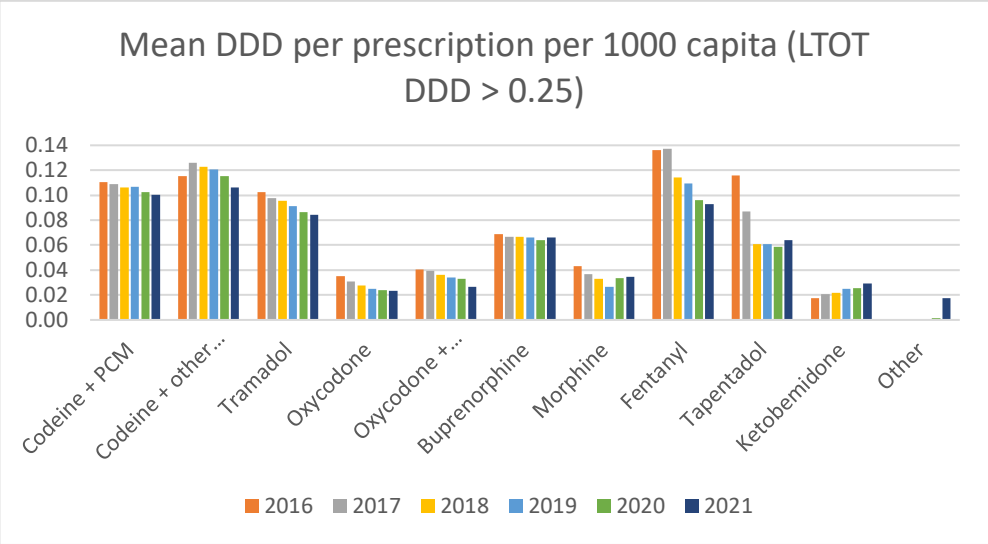
## Appendix 10 – Total sum of prescribed DDD for weaker and stronger opioids for different definitions of LTOT

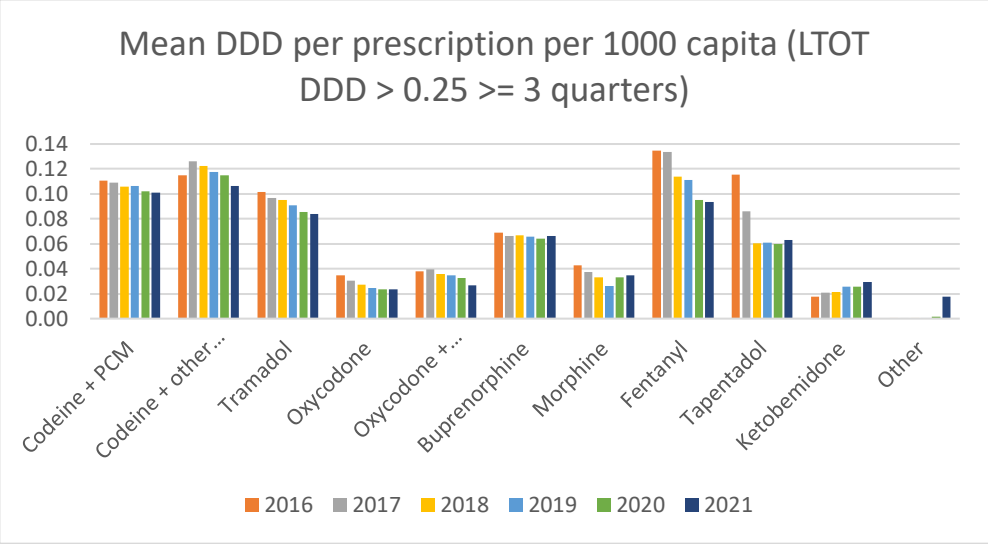


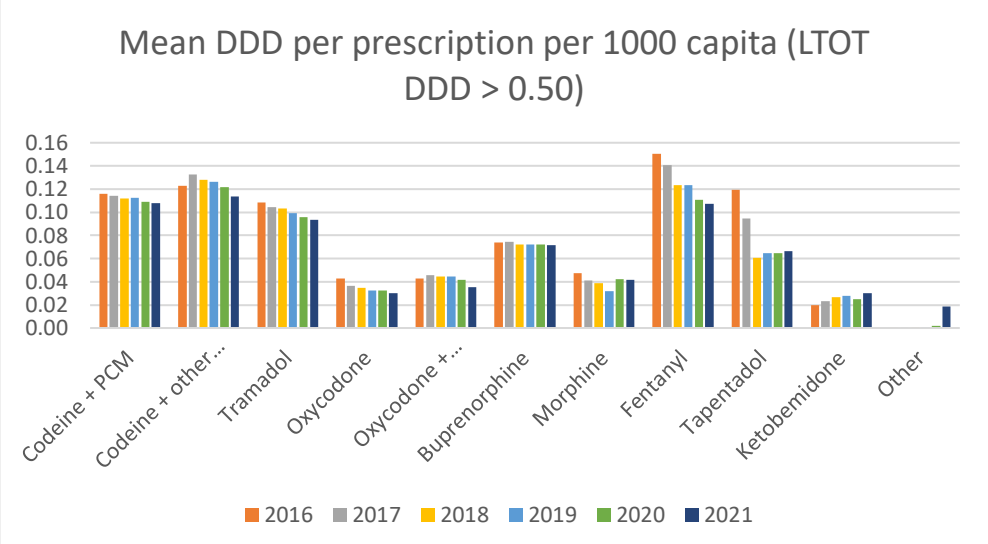



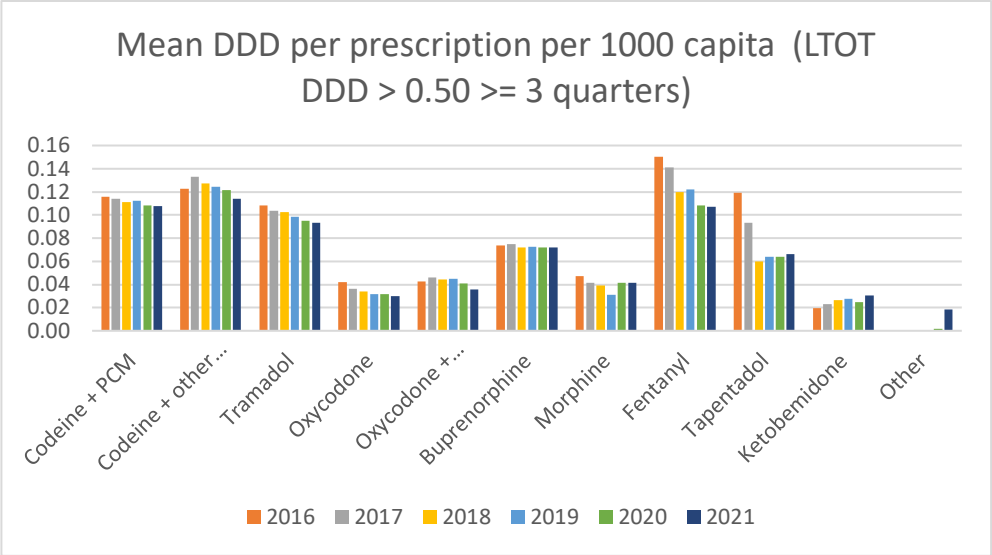



## Appendix 11 – Mean DDD per prescription for different definitions of LTOT

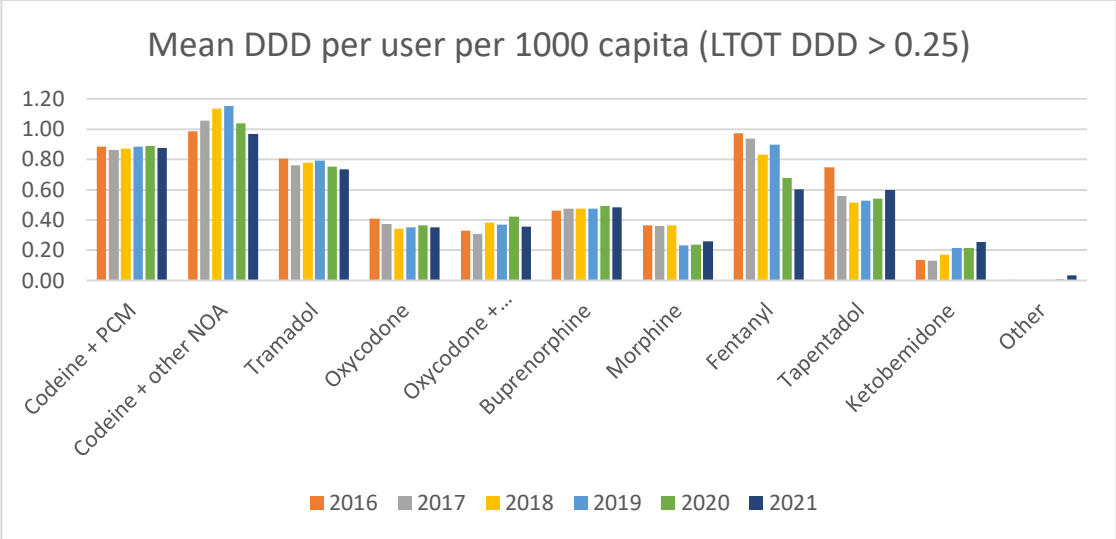


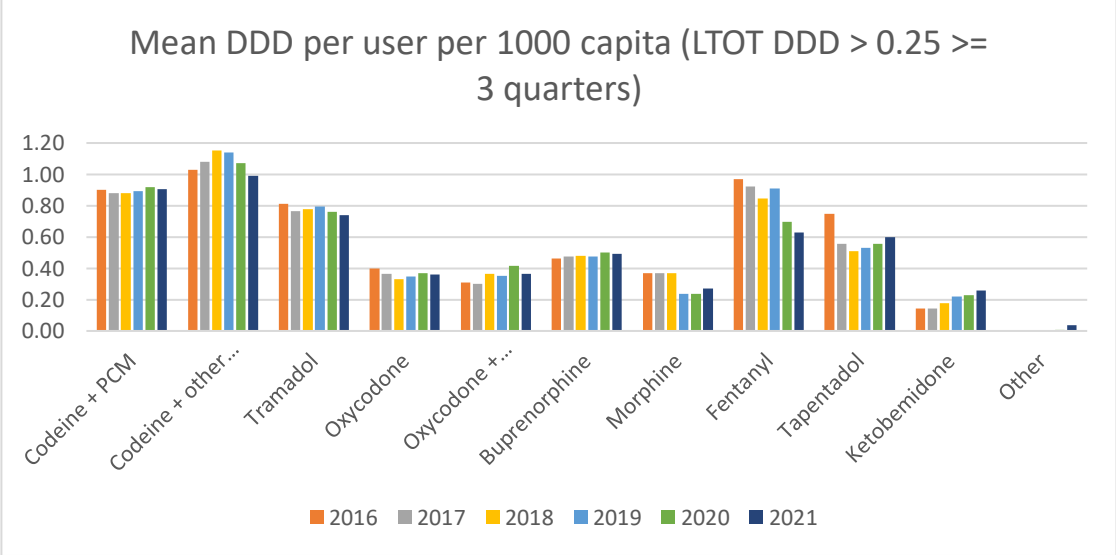



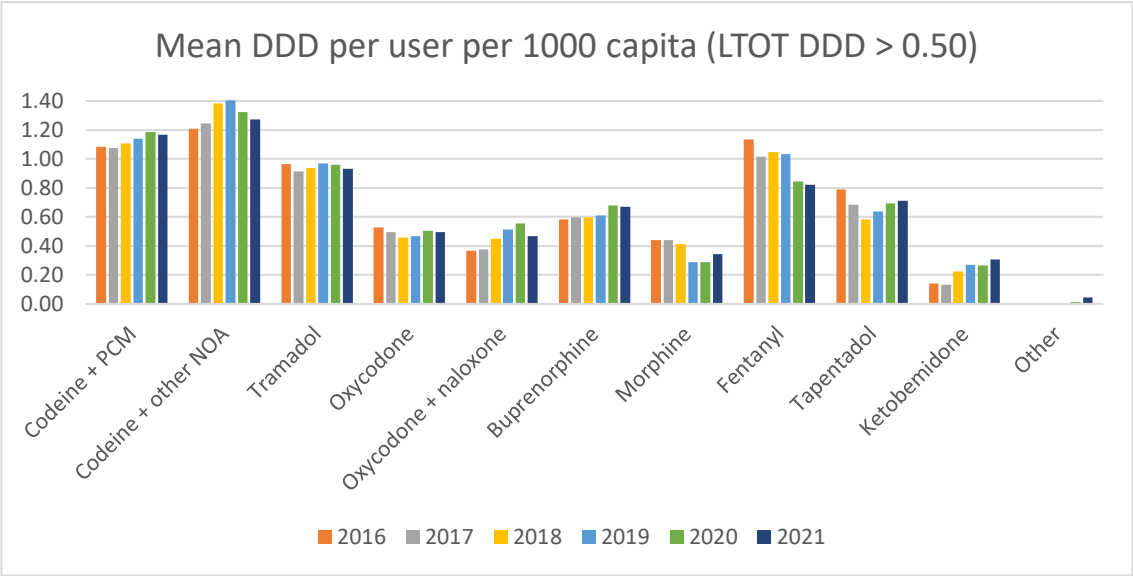



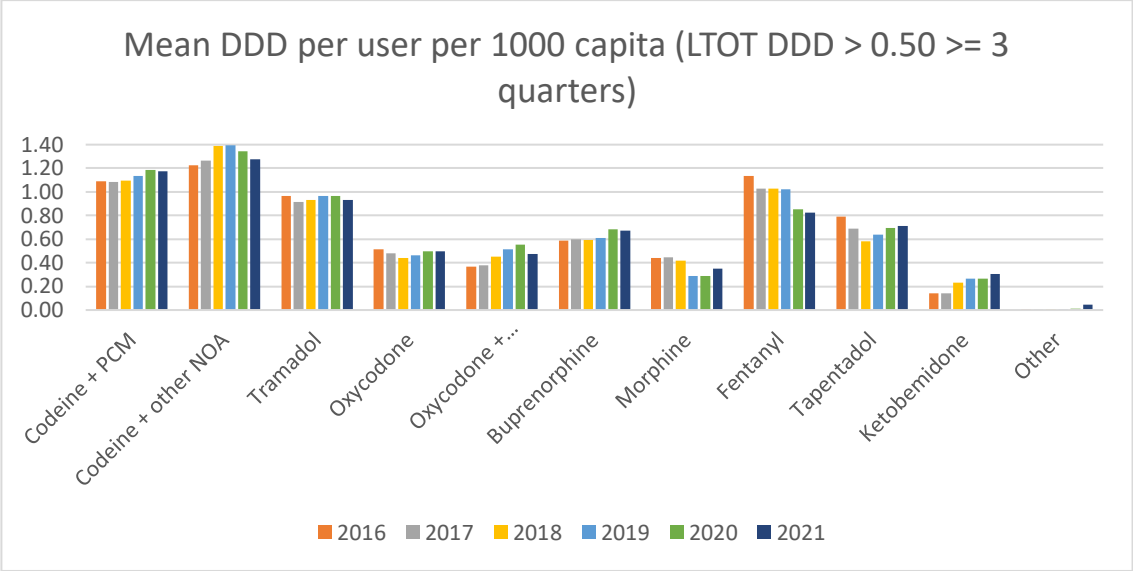



## Appendix 12 – Mean DDD per user for different definitions of LTOT

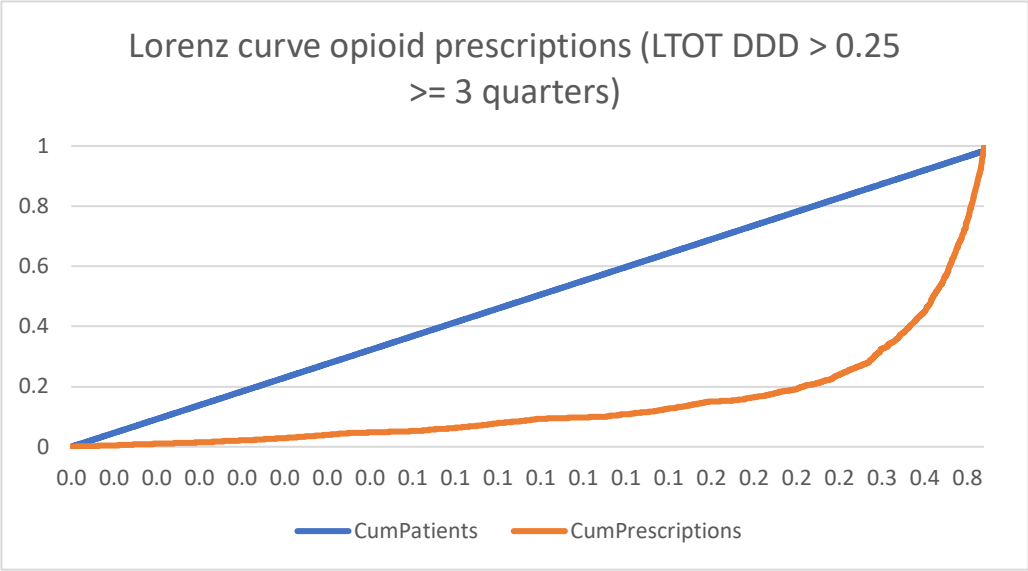


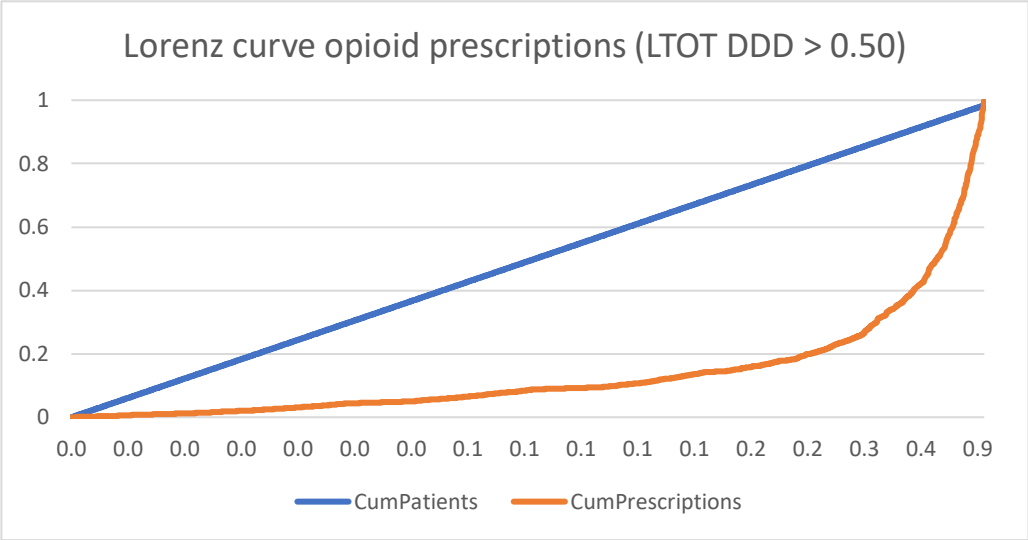

Mean DDD per user per 1000 capita (LTOT DDD > 0.50)
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Codeine + PCM
Codeine + other NOA
Tramadol
Oxycodone
Oxycodone + naloxone
Buprenorphine
Morphine
Fentanyl
Tapentadol
Ketobemidone
Other
2016
2017
2018
2019
2020
2021


Mean DDD per user per 1000 capita (LTOT DDD > 0.50 >= 3 quarters)
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Codeine + PCM
Codeine + other NOA
Tramadol
Oxycodone
Oxycodone +...
Buprenorphine
Morphine
Fentanyl
Tapentadol
Ketobemidone
Other
2016
2017
2018
2019
2020
2021

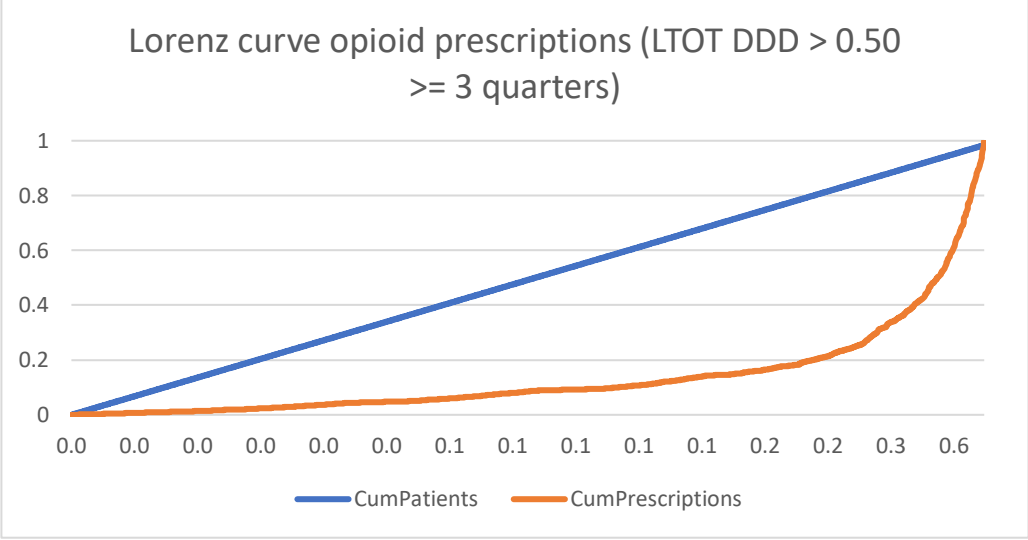
## Appendix 13 – Lorenz curves for different definitions of LTOT




Gini = 0.726




Gini = 0.733




Gini = 0.734