

# **Opioid Prescribing Trends and Geographical Variation in England 1998-2018 - A Retrospective Database Study**

Helen J Curtis, DPhil<sup>1</sup>,  
Richard Croker, MSc<sup>1</sup>,  
Alex J Walker, PhD<sup>1</sup>,  
Georgia C Richards, BSc (Hons I)<sup>2</sup>,  
Jane Quinlan, FFPMRCA<sup>3</sup>,  
Ben Goldacre, MRCPsych<sup>\*1</sup>

<sup>1</sup> The DataLab, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK

<sup>2</sup> Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK

<sup>3</sup> Nuffield Department of Anaesthetics, Oxford University Hospitals NHS Foundation Trust, Oxford, OX3 9DU, UK.

\*Corresponding author:

[ben.goldacre@phc.ox.ac.uk](mailto:ben.goldacre@phc.ox.ac.uk),

+44 1865 289313

## Abstract

**Background:** There is a call for greater monitoring of opioid prescribing in the UK, particularly strong opioids in chronic pain, where benefits are limited. We set out to comprehensively assess trends and variation in opioid prescribing in English primary care, 1998-2018, and to assess factors associated with high-dose opioid prescribing behaviour in practices.

**Methods:** Retrospective database study using open data sources on prescribing for all general practices in England. For all standard opioids we calculated the number of items prescribed, costs, and oral morphine equivalency to account for variation in strength. We present long-term prescribing trends from 1998-2017, patterns of geographical variation for 2018, and investigate practice factors associated with higher opioid prescribing. We additionally conducted an analysis of prescriptions for long-acting opioids at high doses.

**Outcomes:** Nationally, opioid prescriptions per 1,000 patients increased over 1998-2016 by 34%. Correcting for total oral morphine equivalency, the increase was 127%. There was a decline from 2016-2017. If every practice prescribed high-dose opioids at the lowest decile rate, this could save 543k high-dose prescriptions over six months. Larger practice list size, ruralness and deprivation were associated with greater high-dose prescribing rates. The clinical commissioning group to which a practice belongs accounted for 11·7% of the variation.

**Interpretation:** Failing to account for opioid strength would substantially under-estimate the true increase in NHS opioid prescribing. All English primary care opioid prescribing data is openly shared down to individual practice level through our OpenPrescribing.net tool. Our findings support calls for greater action to promote best practice in chronic pain prescribing and reduce geographic variation. This study provides a model for routine monitoring of opioid prescribing to aid targeting of interventions to reduce opioid prescribing.

**Funding:** No specific funding was obtained for this study.

## **Research in context**

### **Evidence before this study**

Concerns have been raised around the use of strong opioids and high doses, especially in chronic pain; better monitoring and audit has been advocated. We reviewed the literature in English on PubMed on trends and variation in opioid prescribing for chronic non-cancer pain in the UK since 2010, screening abstracts for relevance after using combinations of search terms “opioid”/“opiate”, “prescribing”, “chronic pain” and “NHS”/“UK”. We also read relevant reports from public bodies. The consensus is for an increase in prescribing of opioids in primary care in England, but most data are several years out of date at publication, and very few correct for opioid strength or analyse high dose prescriptions separately. Few cover the entire country or perform robust statistical analyses. None provide detailed data or tools to allow readers to investigate detailed prescribing information for their local area.

### **Added value of this study**

There has been a very substantial increase in NHS opioid prescribing: failing to account for the different potencies of opioid being prescribed would underestimate this increase by a factor of 3.7. We provide long-term, detailed and up-to-date time trends on NHS primary care prescribing of opioids, and show that substantial increases have recently tailed off. We provide detailed information on geographical variation, seasonality, and factors associated with high prescribing. We provide detailed prescribing data at practice level openly to all through an interactive online tool at [OpenPrescribing.net](http://OpenPrescribing.net).

### **Implications of all the available evidence**

Our study provides a framework for monitoring of primary care opioid prescribing in routinely available data and provides a tool for live, ongoing monitoring across all practices in England. This tool is free for anyone to use for further research, such as local audits and improvement projects. Future work using patient-level data could reveal more detailed high-dose opioid prescribing patterns.

## INTRODUCTION

Opioids are commonly and appropriately prescribed to reduce the intensity of acute, end-of-life and cancer pain. However, they can cause harm, particularly at higher doses, including addiction and abuse <sup>1,2</sup>. The UK has seen a rising number of opioid-related deaths <sup>3</sup>; and the US has severely restricted access to prescribed opioids <sup>4</sup>. Concerns have particularly been raised around strong opioid use in chronic pain, where benefits are known to be limited <sup>5</sup>.

There has recently been a call for greater monitoring of opioid prescribing in the UK <sup>6</sup>. Guidelines released in 2010 promoted a cautious approach to any planned long-term prescribing of opioids <sup>7</sup>. The Opioids Aware resource, launched in 2016, was formed through collaborations among many of the UK's relevant major regulatory bodies, and gives guidance on the hazards around opioid prescribing <sup>8</sup>.

There have been a number of reports on trends in NHS non-cancer opioid prescribing, with research to date examining only a subset of treatments, practices, and conditions <sup>9,10</sup>. For example: a recent widely-reported paper explored prescribing trends in the Clinical Practice Research Datalink (CPRD) up to 2015 <sup>6</sup>; however, this study did not account for opioid strength, only analysed the five most commonly prescribed drug-dose pairs in detail, and is likely to be unrepresentative of the full picture. Another study from 2018 reported increased opioid prescribing for a limited period from 2010 to 2014 <sup>11</sup>.

We therefore set out to use the full NHS England primary care prescribing dataset to robustly and comprehensively assess trends and variation in prescribing of opioids in primary care from 1998 to 2018, and to assess factors associated with high-dose opioid prescribing behaviour in practices. We also provide an open tool at [openprescribing.net](https://openprescribing.net) where readers can find current data on opioid prescribing for each of England's practices and clinical commissioning groups (CCGs).

## METHODS

### Data Sources and Preparation

We used two sources of data: (A) monthly practice-level data covering October 2010 to August 2018; and (B) annual Prescription Cost Analysis (PCA) data, aggregated nationally, covering 1998-2017.

#### *A) Practice-level data*

The monthly prescribing datasets published by NHS Digital contain one row for each different medication and dose, in each prescribing organisation in NHS primary care in England, describing the number of prescriptions issued and the total cost. It is sourced from community pharmacy claims data, therefore contains all items which were dispensed. We extracted all available prescribing data, limited to institutions with setting code 4 - general practices (GPs), according to the NHS Digital dataset of practice characteristics <sup>12</sup>. We exclude all other organisations such as prisons and out-of-hours services as they are not represented fully or consistently in our dataset since many prescriptions would not be dispensed in community pharmacies. Practices were excluded for any month in which they had no registered patients or no prescribing. For analysis involving the latest six months, practices were also excluded if they had a current status of closed or dormant, as these practices are likely to have low and unusual patterns of prescribing. Number of patients registered at each practice were obtained from NHS Digital <sup>13</sup>.

#### *B) Annual PCA data*

The annual prescription cost analysis datasets contain one row for each different medication and dose, for all items dispensed in community settings in England,

describing the number of prescriptions and the total cost. PCA data was processed as previously described <sup>14</sup>. Briefly, data for each year between 1998 and 2017 were obtained from NHS Digital or archive locations, compiled and loaded into Google BigQuery. Full BNF codes were obtained from the latest British National Formulary (BNF) for each drug name where possible. Any remaining drugs were matched to a chemical in the current BNF by matching to the most similar item. Data were normalised by converting number of items prescribed and costs to relative figures per thousand population, using mid-year population estimates for England <sup>15</sup>. Costs were also corrected for inflation using the consumer price index compared to 2017 <sup>16</sup>. Full data processing details are available <sup>17</sup>.

### **Extraction and classification of prescribed opioids data**

We extracted prescribing data for all drugs in paragraph 4·7·2 (Opioid Analgesics), as well as opioid-containing combination drugs from paragraphs 4·7·1 (Non-Opioid Analgesics and Compound Preps) and 10·1·1 (Non-Steroidal Anti-Inflammatory Drugs) (Appendix A). We excluded preparations from section 4·10 (Drugs used for substance dependence) as these are less commonly used in pain; this section includes the formulations of methadone and buprenorphine which are normally used for treatment of opioid dependence. Drugs were each assigned to the appropriate class based on their chemical name (Appendix A). We calculated oral morphine equivalency (OME) for each drug using conversion tables available from a number of sources (conversion factors and sources listed in Appendix B).

Long-acting opioids are those used on a regular basis to control pain, as opposed to short acting preparations which act quickly and for a short duration. Long-acting formulations include modified release (MR) morphine and oxycodone tablets, and fentanyl and buprenorphine transdermal patches, but exclude preparations used for breakthrough pain,

e.g. Oramorph; and opioid injections, more commonly used in palliative care. Out of the long-acting opioids, high-dose opioids were taken as those with  $\geq 120\text{mg}$  morphine (or equivalent) per day based upon the estimated total daily dose. For example, for morphine sulfate MR tablets, usually taken as one tablet twice daily, we assumed 60mg tablets are high-dose (probable total daily dose 120mg), whereas 30mg tablets are not (probable total daily dose 60mg). See Appendix C for full list of opioids classed as high-dose.

### **Long-Term Time Trends**

We created stacked charts to display the number of items, OME and cost of all opioid-containing items (Appendix A) dispensed each year. We repeated this for opioids which were long-acting and those of which were high-dose (Appendix B and C).

### **Geographical Variation across England's practices and CCGs**

We used practice-level data, aggregated to CCGs, to create choropleth maps of current prescribing for all CCGs in England, for the latest available six months combined (Mar-Aug 2018). For each CCG we calculated: the total items, OME, and cost of all opioids prescribed per 1,000 registered patients; the percentage of long-acting OME prescribed which were high-dose; and the percentage of high-dose OME prescribed which were each of fentanyl, morphine, and oxycodone. We also calculated and plotted the change from 2016 to 2017 in total OME prescribed per 1,000 registered patients for each of England's CCGs.

We assessed variation in prescribing amongst England's practices by calculating deciles for each month (Oct 2010-Aug 2018) for: total OME per 1,000 registered patients, percentage of OME prescribed which were high-dose (out of all long-acting OME prescribed), and total cost of all opioids and high-dose opioids per 1,000 registered patients. We display these data as time trend charts.

We estimated potential savings which could be made in opioid prescribing by taking the total high-dose items per 1,000 patients for practices ranked at the 10th centile, for the latest available six months combined (Mar-Aug 2018), and applying this rate to every practice prescribing above this level. Similarly, we also calculated possible financial savings from more cost-effective prescribing, taking the 10th centile average cost-per-item (for high-dose items) and applying this to all items prescribed by practices with a higher cost-per-item.

### **Factors Associated With Prescribing High Dose Opioids and total OME volume**

In order to measure what factors are most associated with prescribing of high-dose opioids, we created a mixed effects logistic regression model, using publicly available demographic data to define a number of fixed effect variables, and included CCG as a random effect in order to assess its impact on prescribing variation. The fixed effect variables included were: proportion of patients registered aged over 65; proportion of patients with a long-term health condition; index of multiple deprivation; and Quality Outcomes Framework (QOF) score (each of which were obtained from Public Health England <sup>18</sup>); as well as practice list size (NHS Digital); and rural/urbanity of practice postcode <sup>19</sup>. Where possible, we tried to use variables that to some extent matched previous models of opioid prescribing <sup>6,11,20,21</sup>. Continuous variables were categorised *a priori* into quintiles in order to allow for nonlinearity of effects and to enhance the intelligibility of results.

The main outcome used was high-dose long-acting opioid prescriptions as a proportion of all long-acting opioid prescriptions. This proportion was transformed using a conditional logit transformation <sup>22</sup>. The model was used to calculate odds ratios and 95% confidence intervals (CI) for each of the fixed effect variables, as well as an R-squared value (along with the significance level) to describe the degree of variance associated with CCG membership.



A second model was also run, on the outcome of total OME prescribing per 1000 patients. This used mixed effects linear regression, and the same fixed and random effect variables, to determine the degree to which each variable was associated with the volume of opioid prescribing.

### **Data Sharing**

Data were extracted using SQL in Google BigQuery, including OME conversions. Further calculations and aggregations were carried out in Python, with regression analysis carried out using Stata v13.1. Charts and maps were produced using Python 'matplotlib.pyplot', 'seaborn' and 'geopandas' modules. Complete code are provided online at <https://figshare.com/s/787e8e94347c11a62762>.

### **Role of the funding source**

We receive funding for our work on prescribing data from various sources as detailed in the Acknowledgements. No specific funding was sought for this specific project and none of our funders took part in study design; collection, analysis, and interpretation of data; writing of report, nor in the decision to submit the paper for publication. The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## RESULTS

From the practice-level data between Oct 2010 and Aug 2018, 8,123 standard GP practices were included. For analysis relating to the latest six months (7,194 practices), we excluded those with a current status of closed (0) or dormant (166) according to NHS Digital organisation datasets, and those with non-standard CCG codes (1), leaving 7,026 practices included from all 195 CCGs. All PCA data were extracted successfully.

Between 1998 and 2016, there was a 34% increase in opioid items prescribed (568 to 761 per 1,000 population, Figure 1, Table S1). However, when correcting for OME, the total volume prescribed increased by 127% (190,000 to 431,000mg OME per 1,000 population). Failure to correct for strength and potency would therefore underestimate the increase in prescribing by a factor of 3·7. There was a decline in both items and OME from 2016 to 2017, largely accounted for by a reduction in morphine.

Morphine, fentanyl, oxycodone and buprenorphine made up relatively more of the total opioid prescribing by OME than by number of items, indicating they are subject to some high-dose prescribing (Figure 1). Among the lesser-prescribed opioids within the “Other” category, the use of tapentadol has been most rapidly increasing, since becoming available in 2011 (Figure S1); again more so by OME, indicating tendency towards high-dose prescribing. We have supplied information on the earliest prescribing date of each opioid for context (Table S2).

Fentanyl, oxycodone and buprenorphine contribute a greater proportion of overall prescribing costs relative to the number of items prescribed. Prescribing of co-proxamol (a

previously popular opioid), reduced dramatically following its withdrawal,<sup>23</sup> but spend remained stable as it continued to be prescribed as a “special” at extremely high unit cost.

Figure 2 shows trends in high-dose (>120mg OME), long-acting opioids between 1998 and 2017 (with long-acting opioids of all doses and non-high-doses shown in Figures S2 and S3 respectively). There was a rapid and very large increase in the volume of high-dose long-acting prescribing, seen in both the crude and OME data (Figure 2a-b). The number of prescriptions per 1,000 population increased from 3 in 1998 to 23 in 2016 (581%, or 457% by OME). The greatest contributors in 2016 were fentanyl, morphine and oxycodone, together accounting for over 90% of high-dose long-acting prescribing (Table S3). Oxycodone has increased the most, since becoming available in 2000. The number of long-acting opioids not at high doses has also increased dramatically but shows a similar decline from 2016 to 2017, largely in morphine use (Figure S3). The overall spend on high-dose preparations has reduced since 2010, mainly due to decreased spend on fentanyl and, more recently, oxycodone (Figure 2c).

Maps indicate the range of prescribing behaviour across England’s CCGs over the latest six-month period (Figure 3). Total OME differed almost eight-fold (from 52,700 to 416,000mg per 1,000 registered patients, Figure 3a), whereas total items prescribed varied 6·1-fold (119-727 items per 1,000, Table S4). Total spend on opioids closely reflected the total OME prescribed, with a 5·9-fold variation (£859-5,050 per 1,000, Figure 3b). High-dose items prescribed varied 15-fold (1·73 to 26·4 per 1,000, Figure 3c). The lowest prescribers of opioid OME and high-dose items were focused around the Greater London regions, with high prescribers in northern and coastal areas. However, the CCGs with the greatest percentage of items prescribed as high-dose were more distributed across England (Figure

3d). For OME prescribed in high-dose formulations, there was wide variation between CCGs on which opioid group were the most frequently prescribed (Figure 3e-g). We also show the change in total opioid prescribing between 2016 and 2017 for each of England's CCGs (Figure S4), which ranges from a decrease of almost 60,000 OME per 1,000 (-10·5%) to an increase of 20,000 (3·5%).

Figure 4 shows the range and time-course of variation in prescribing behaviour across England's practices since 2010. Although there is wide variation, there has been relatively little change in the extent of this variation during the time period available. The range (10-90th percentiles) of total OME prescribed per patient has increased, mostly due to an increase amongst the highest prescribers. The increasing trend appears to have stabilised since 2015. The percentage of long-acting opioid items prescribed in high-dose preparations has reduced in range, with the highest decile decreasing (68% to 60%), while the lower deciles increased. The overall cost of opioid prescribing per 1,000 patients ranged from £150 to £700 in August 2018, having declined since 2015; for high-dose preparations it was £10-£120.

If every practice in the country prescribed high-dose opioids at the same rate as the lowest decile (0·17 items, or £6·56, per 1,000 patients per month) over the latest six months, overall 543k fewer high-dose prescriptions could have been issued out of a total of 601k; or a cost saving of £24·8m out of a total £27·0m. If each practice prescribed at the lowest decile cost-per-item for high-dose opioids over the latest six months (£25·64 per item), without reducing the number of items prescribed, in total they could have saved £12·0m out of £27·0m (44·4%).

We modelled the practice factors associated with the proportion of long-acting opioids prescribed as high-dose (Table 1). Practice list size had the strongest and most consistent effect size, with larger practices being more likely to prescribe high-dose opioids

(multivariable odds ratio for smallest vs largest: 1.53, 95% CI 1.44-1.64). Greater ruralness and deprivation scores were both associated with more high-dose prescribing, with practices in the 'Urban with major conurbation' category less likely to prescribe high-dose opioids than those in 'Mainly rural' areas (multivariable odds ratio 0.77, 95% CI 0.68-0.86), and practices in the most deprived areas more likely to prescribe high-dose than those in the least deprived areas (multivariable odds ratio: 1.24, 95% CI 1.13-1.36). Practices having a higher proportion of patients with a long term health condition had slightly higher odds of prescribing high-dose opioids (multivariable odds ratio for lowest vs highest: 1.19, 95% CI 1.11-1.28). The proportion of patients over 65 registered at a practice was not associated with prescribing high-dose opioids in multivariable modelling, though there was some effect in univariable analysis. Practice QOF score was only marginally associated with high-dose opioid prescribing, with much of the observed effect in the univariable analysis absent in the multivariable analysis. The CCG to which a practice belongs (as a random effect) was significantly associated with high-dose prescribing ( $p < 0.0001$ ) and accounted for 11.7% of the variation in high-dose opioid prescribing.

We also modelled the factors associated with total OME prescribing rate per 1000 patients (Table S5). These results are broadly similar to the first model in terms of which factors are associated with prescribing, but cannot be directly compared in magnitude of association.

## DISCUSSION

### Summary

We found a substantial increase in opioid prescribing. We also found that measuring opioid prescribing in terms of number of items, without correcting for oral morphine equivalency, would underestimate the true increase in prescribing between 1998 and 2016 by a factor of 3·7 (34% vs 127%). We also report wide variation in opioid prescribing across England's practices and CCGs, particularly in costs, but with relatively little change in variation over time. If every practice prescribed high-dose opioids at the lowest decile rate, this could have saved 543k high-dose prescriptions over six months. Larger list size, ruralness and higher deprivation scores were associated with greater rates of high-dose prescribing. The CCG to which a practice belongs accounted for 11·7% of the variation in high-dose opioid prescribing behaviour.

### Strengths and Weaknesses

Our data covers the complete prescribing data for all practices in England, not a sample. Our work could be complemented by analysis of patient-level data to determine the number of different recipients per practice; the total combined dose, course length and continual prescribing period for each individual; and to separate indications by identifying patients with cancer diagnoses <sup>24</sup>. However, these datasets currently cover only a subset of all NHS prescribers, and do not identify individual CCGs and practices; furthermore, data on diagnosis and indication for each individual prescription in datasets such as CPRD are commonly very incomplete <sup>25</sup>.

We accounted for variation in opioid strength, and listed our sources of conversion figures. These will not apply equally to all patients and prescriptions due to variation in drug formulations, patient tolerability, and type of pain <sup>26</sup>. However, they are appropriate for calculation of totals, long-term trends and comparison of overall prescribing behaviours. We

made general assumptions on common dosing schedules in order to classify high-dose prescriptions, but some low-dose formulations could also represent high doses if taken more frequently, or in combination with short acting formulations.

We included all opioids likely to be prescribed for chronic pain. Although the majority of prescriptions are probably non-cancer <sup>24</sup>, we may include some used in cancer, short-term or end-of-life pain (e.g. patches for patients unable to swallow <sup>27</sup>). The gradually increasing need for end-of-life pain relief may contribute slightly to the increases in prescribing we show <sup>28</sup>. Secondary care prescribing is not included; however, ongoing care is largely managed in primary care. Our data originates from pharmacy claims, and therefore does not include prescriptions which are issued but never presented to a pharmacist.

Our savings estimates indicate the possible extent of savings if all practices were able to reduce their high-dose opioid prescribing to the level of the lowest 10% of prescribers or match the 10% most cost-effective prescribers on cost-per-item. However, a more detailed analysis would be required to fully adjust for the extent of patient need in each practice.

## **Findings in Context of Other Research**

Our results are consistent with another study in CPRD which reported a large increase in prescribing of four strong opioids in the UK between 2000 and 2010 <sup>24</sup>. The results of this previous study indicate that the increase in high-dose opioids is largely attributable to prescribing for non-cancer patients, both through increasing numbers of recipients as well as prescriptions per patient. We show a levelling off of the increase in national opioid prescribing from 2014; and similarly the report commissioned by the National Institute for Health Research (NIHR) Policy Research Programme showed that the proportion of patients prescribed opioids began to decline since 2012, with the mean duration of opioid prescribing periods levelling off in 2014 <sup>6</sup>.

Another study, looking at musculoskeletal conditions, also showed a trend towards opioids being prescribed sooner and in longer-acting forms between 2002 and 2013, but a decline in prescribing overall after 2011 <sup>9</sup>.

Our study also builds upon a recent 2018 publication showing increasing opioid prescribing up to February 2014 <sup>11</sup>. We include all classes of opioid and also much more recent data, importantly showing that the increase is now slowing. We detail high-dose prescribing, present time trends for the most-prescribed opioids and include our full data and code. We also report wide variation across practices and CCGs, with CCG membership accounting for 11·7% of practice-level variation in high-dose prescribing. A similar CCG-level pattern (for total OME, 2010-2014) was previously reported, with highest prescribers in northern areas <sup>11</sup>, but that study did not have access to practice-level data. The NIHR report based geographic patterns on a single presentation (Tramadol 50mg), which is unlikely to represent the full extent of variation <sup>6</sup>. We also show that the decreases in opioid prescribing rates between 2016 and 2017 are not evenly distributed across CCGs, with some having increased prescribing.

Greater practice list size, rurality and deprivation were associated with high-dose prescribing. Less optimal opioid prescribing has previously been associated with deprivation in England <sup>6,11</sup> and in Scotland <sup>29</sup>; with rurality in Australia and the USA <sup>20,21</sup>; and with age, but not including adults over 65 <sup>20</sup>. However, a previous cohort study in one English region (Leeds and Bradford) found no practice-level factors associated with opioid prescribing behaviour <sup>10</sup>. The limited geographic area may fail to capture the level of variation we found across the country.

## **Policy Implications**

It is important to interpret data on opioid prescribing thoughtfully and cautiously. A large increase in opioid prescribing may represent better pain management for patients with acute



or palliative pain, or unwarranted and dangerous prescribing in chronic pain. The prolonged prescribing periods reported elsewhere <sup>9</sup> suggest the latter. Currently, there is no evidence to support the routine prescription of high-dose opioid analgesics <sup>2</sup>, and there are clear guidelines to limit opioid prescribing for chronic pain <sup>7</sup>. Thus, our findings support calls for greater action to promote best practice: lower doses, for shorter durations, and ceasing opioids if non-beneficial <sup>10</sup>. This may reduce adverse events <sup>2</sup>, prescribing costs, and the costs of managing dependency.

The geographical variation highlights where interventions can best be targeted, for example rural areas, and conversely where there are examples of chronic pain prescribing guidelines being effectively implemented. Our map of changes in CCG-level prescribing between 2016 and 2017 indicate that some regions are substantially reducing their opioid prescribing, presumably through concerted efforts to address this issue. Reviewing patients on high doses can lead to improved prescribing: a recent study in 41 English practices led to modification of the treatment for 23% of the 363 non-cancer patients prescribed high-dose opioids <sup>30</sup>. Some geographical variation may be driven by the availability and quality of clear chronic pain pathways using multidisciplinary services involving pain psychologists, which are recommended to help patients manage chronic pain <sup>31</sup>. For patients requiring specialist help with prescribed opioid addiction, most publicly funded addiction services generally address illicit drug use and so may not be well equipped to help patients with pain. Local guidelines and formularies can also influence prescribing patterns <sup>32</sup>, and the complex decision-making processes in opioid prescribing <sup>33</sup> may also contribute to variation between individual clinicians. In addition, some GPs may lack understanding of the strength of the widely-used fentanyl and buprenorphine patches <sup>34</sup>. The best methods to reduce inappropriate opioid prescribing in chronic pain warrant further study, particularly those which have led to the greatest reductions in CCG-level prescribing.

Better access to comparative data can play a valuable role in monitoring and improving clinical practice <sup>35</sup>. Importantly, qualitative studies suggest there is scope to prevent dose escalation within primary care <sup>36</sup> and that educational interventions can improve clinical decision-making <sup>33</sup>. Therefore, routine monitoring and feedback on opioid prescribing at practice level is likely to be beneficial. Previous systematic review data on audit and feedback across a range of targeted clinical behaviours shows a modest impact <sup>35</sup>, and when clinicians in the USA were informed of a death of one of their patients from an opioid overdose, their opioid prescribing subsequently reduced <sup>37</sup>. The measures used in our study provide easy and accessible tools to routinely monitor opioid prescribing. Three measures presented in this paper are also displayed on our OpenPrescribing.net site, an openly accessible data tool displaying the latest five years of NHS England prescribing data. For every practice in England, the site displays the number of high-dose opioid ( $\geq 120\text{mg}$  daily) items prescribed, both per 1,000 population and as a proportion of all opioids prescribed, as well as the total Oral Morphine Equivalency (OME, mg) prescribed per 1,000 population. We will maintain these live charts for all practices and CCGs as long as our team has funding and they remain relevant to patient care.

## **Conclusions**

Overall levels of opioid prescribing have increased dramatically since 1998, but despite a slowing of this trend, wide geographic variation exists across England. Our study and OpenPrescribing.net tool provide a current picture of opioid prescribing. Monitoring the data nationally and locally for potentially problematic prescribing may help to highlight areas where action is most required.

## **ACKNOWLEDGEMENTS:**

**Author contributions:** RC and BG conceived the project, with input from JQ, HC and AW. RC, HC BG and AW designed the methods and interpreted the findings, with input from JQ and GR. HC extracted and processed the data with input from RC. HC conducted analyses in Python and AW conducted analyses in Stata. GR and HC performed the literature search. HC wrote the first draft. All authors contributed to and approved the final manuscript. BG obtained funding, supervised the project and is guarantor. We are also grateful to Seb Bacon and Peter Inglesby for obtaining and managing the data and OpenPrescribing.net website.

**Funding:** BG receives funding from the Health Foundation, the National Institute for Health Research School of Primary Care Research, the NIHR Biomedical Research Centre Oxford, and NHS England for work on UK prescribing data, including this study. HC, AW and RC are employed on these grants. GR is financially supported by the NIHR School for Primary Care Research, the Naji Foundation and the Rotary Foundation to study for a Doctor of Philosophy. The funders had no involvement in the study design or the decision to submit.

**Conflict of interest:** BG has additionally received funding from the Laura and John Arnold Foundation, the Wellcome Trust, and the World Health Organisation to work on better use of data in medicine; and receives personal income from speaking and writing for lay audiences on the misuse of science. RC is employed by a CCG to optimise prescribing, and has received (over 3 years ago) income as a paid member of advisory boards for Martindale Pharma, Menarini Farmaceutica Internazionale SRL and Stirling Anglian Pharmaceuticals Ltd. HC, AW, GR and JQ have nothing to disclose.

**Ethics committee approval:** not required.

## **SUPPLEMENTARY MATERIALS:**

Supplementary results tables and figures.

Appendix: Code and reference tables.

## REFERENCES

- 1 Chou R, Turner JA, Devine EB, *et al.* The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015; **162**: 276–86.
- 2 Els C, Jackson TD, Hagtvedt R, *et al.* High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2017; **10**: CD012299.
- 3 ONS. Deaths related to drug poisoning in England and Wales. 2017; published online Aug 2.  
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations> (accessed Feb 22, 2018).
- 4 DEA. DEA Reduces Amount Of Opioid Controlled Substances To Be Manufactured In 2017. 2016; published online Oct 4.  
<https://www.dea.gov/divisions/hq/2016/hq100416.shtml> (accessed Sept 10, 2018).
- 5 Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. *BMJ* 2016; **352**: i20.
- 6 Cartagena Farias J, Porter L, McManus S, *et al.* Prescribing patterns in dependence forming medicines. *London: NatCen* 2017; published online Sept.  
<http://www.natcen.ac.uk/our-research/research/prescribing-patterns-in-dependence-forming-medicines-2000-2015/> (accessed Sept 11, 2017).
- 7 British Pain Society. Opioids for persistent pain: summary of guidance on good practice from the British Pain Society. *Br J Pain* 2012; **6**: 9–10.
- 8 Royal College of Anaesthetists. Opioids Aware. A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. 2016.  
<http://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware> (accessed Sept 7, 2017).
- 9 Bedson J, Chen Y, Hayward RA, *et al.* Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. *Pain* 2016; **157**: 1525–31.
- 10 Foy R, Leaman B, McCrorie C, *et al.* Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. *BMJ Open* 2016; **6**: e010276.
- 11 Mordecai L, Reynolds C, Donaldson LJ, de C Williams AC. Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. *Br J Gen Pract* 2018; : bjgp18X695057.
- 12 NHS Digital. GP and GP practice related data. 2018.  
<https://digital.nhs.uk/services/organisation-data-service/data-downloads/gp-and-gp-practice-related-data> (accessed Dec 7, 2018).
- 13 NHS Digital. Number of Patients Registered at a GP Practice. 2018; published online Nov. <http://content.digital.nhs.uk/gppatientsregistered> (accessed Nov 20, 2018).

- 14 Curtis HJ, Goldacre B. OpenPrescribing: normalised data and software tool to research trends in English NHS primary care prescribing 1998-2016. *BMJ Open* 2018; **8**: e019921.
- 15 Office for National Statistics. Population Estimates. ONS Statistical bulletin. 2018; published online June 28.  
<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2017> (accessed Nov 20, 2018).
- 16 Office for National Statistics. CPI All Items Index. ONS Time Series Data. 2017; published online Sept 12.  
<https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bt/mm23> (accessed Sept 20, 2017).
- 17 Curtis HJ. Prescription Cost Analysis 1998-2016 data processing and normalisation. 2017; published online Sept 28.  
<https://gist.github.com/HelenCEBM/192307b3c671a391f5ad6b44a3676880> (accessed Sept 28, 2017).
- 18 Public Health England. Public Health England - Public Health Profiles. 2017.  
<https://fingertips.phe.org.uk/profile/general-practice/data> (accessed July 31, 2017).
- 19 Department for Environment, Food & Rural Affairs. 2011 Rural-Urban Classification of Local Authorities and other geographies - GOV.UK. 2011.  
<https://www.gov.uk/government/statistics/2011-rural-urban-classification-of-local-authority-and-other-higher-level-geographies-for-statistical-purposes> (accessed Feb 5, 2018).
- 20 Heins SE, Sorbero MJ, Jones CM, Dick AW, Stein BD. High-Risk Prescribing to Medicaid Enrollees Receiving Opioid Analgesics: Individual- and County-Level Factors. *Subst Use Misuse* 2018; : 1–11.
- 21 Degenhardt L, Gisev N, Cama E, Nielsen S, Larance B, Bruno R. The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. *Pharmacoepidemiol Drug Saf* 2016; **25**: 521–38.
- 22 Stevens S, Valderas JM, Doran T, Perera R, Kontopantelis E. Analysing indicators of performance, satisfaction, or safety using empirical logit transformation. *BMJ* 2016; **352**: i1114.
- 23 Hawton K, Bergen H, Simkin S, *et al*. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. *BMJ* 2009; **338**: b2270.
- 24 Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain* 2014; **18**: 1343–51.
- 25 Chevalier P, Smulders M, Chavoshi S, Sostek M, LoCasale R. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. *Pain Manag* 2014; **4**: 267–76.
- 26 Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: are they all equally dangerous? *J Pain Symptom Manage* 2009; **38**: 409–17.

- 27 NICE. Prescribing in palliative care. 2014.  
<https://bnf.nice.org.uk/guidance/prescribing-in-palliative-care.html> (accessed April 19, 2018).
- 28 Etkind SN, Bone AE, Gomes B, *et al.* How many people will need palliative care in 2040? Past trends, future projections and implications for services. *BMC Med* 2017; **15**: 102.
- 29 Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain* 2015; **19**: 59–66.
- 30 Ponton R, Sawyer R. Opioid prescribing in general practice: use of a two-stage review tool to identify and assess high-dose prescribing. *Br J Pain* 2018; **12**: 171–82.
- 31 BMA. Analgesic use. 2017; published online March 17.  
<https://www.bma.org.uk/collective-voice/policy-and-research/public-and-population-health/analgesics-use> (accessed Sept 7, 2017).
- 32 Croker R, Walker AJ, Goldacre B. Why did some practices not implement new antibiotic prescribing guidelines on urinary tract infection? A cohort study and survey in NHS England primary care. *bioRxiv*. 2018; : 355289.
- 33 Toye F, Seers K, Tierney S, Barker KL. A qualitative evidence synthesis to explore healthcare professionals' experience of prescribing opioids to adults with chronic non-malignant pain. *BMC Fam Pract* 2017; **18**: 94.
- 34 Botterman J, Criel N. Inappropriate use of high doses of transdermal fentanyl at admission to a palliative care unit. *Palliat Med* 2011; **25**: 111–6.
- 35 Ivers N, Jamtvedt G, Flottorp S, *et al.* Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012; : CD000259.
- 36 McCrorie C, Closs SJ, House A, *et al.* Understanding long-term opioid prescribing for non-cancer pain in primary care: a qualitative study. *BMC Fam Pract* 2015; **16**: 121.
- 37 Doctor JN, Nguyen A, Lev R, *et al.* Opioid prescribing decreases after learning of a patient's fatal overdose. *Science* 2018; **361**: 588–90.

## FIGURE LEGENDS

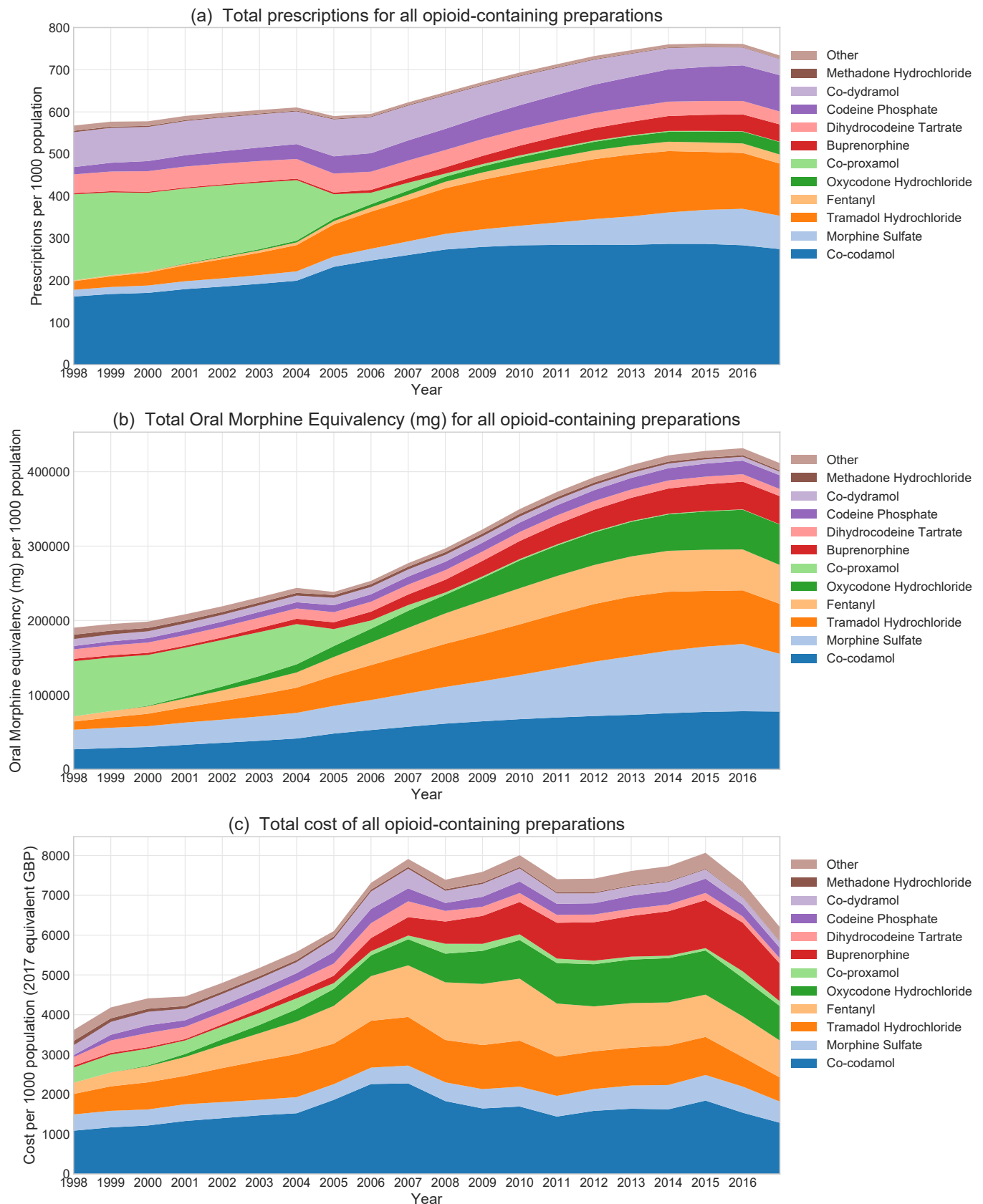
**Figure 1.** Trends in all opioid-containing products dispensed in in England, 1998-2017. (a) Total items per 1,000 population. (b) Total OME per 1,000 population. (c) Total cost per 1,000 population (2017 equivalent GBP). Summary data are presented in Tables S1-2; the “Other” group is expanded in Figure S1.

**Figure 2.** Trends in high-dose ( $\geq 120$ mg OME/day), long-acting opioid prescribing in England, 1998-2017. (a) Total items dispensed per 1,000 population. (b) Total mg OME dispensed per 1,000 population. (c) Total cost per 1,000 population (2017 equivalent GBP). OME data are shown in Table S3.

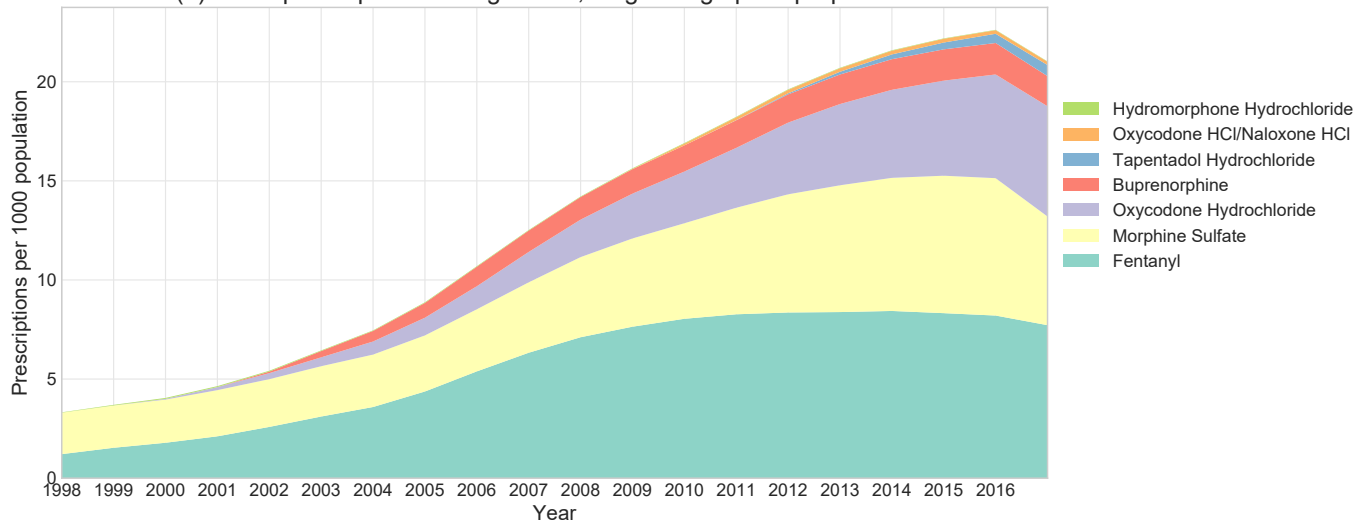
**Figure 3.** Variation in opioid prescribing by England’s CCGs, Mar-Aug 2018. (a) Total OME for all opioid-containing preparations per 1,000 registered patients. (b) Total cost of opioid prescribing per 1,000 registered patients. (c) Total opioid items prescribed as high-dose per 1,000 registered patients. (d) Percentage of long-acting opioid items prescribed as high-dose ( $\geq 120$ mg OME per day). (e-g) Percentage of high-dose OME prescribed as fentanyl, morphine, and oxycodone, respectively. Figures are summarised in Table S4.

**Figure 4.** Trends over time in opioid prescribing by England’s practices, Oct 2010 - Aug 2018. Solid line shows median, dotted lines are deciles. (a) Total OME for all opioid-containing preparations per 1,000 registered patients. (b) Total opioid items prescribed as high-dose per 1,000 registered patients. (c) Percentage of long-acting opioid items prescribed as high-dose ( $\geq 120$ mg OME per day). (d) Percentage of long-acting opioid OME prescribed as high-dose. (e) Total cost of all opioids per 1,000 registered patients. (f) Total cost of high-dose opioids per 1,000 registered patients.

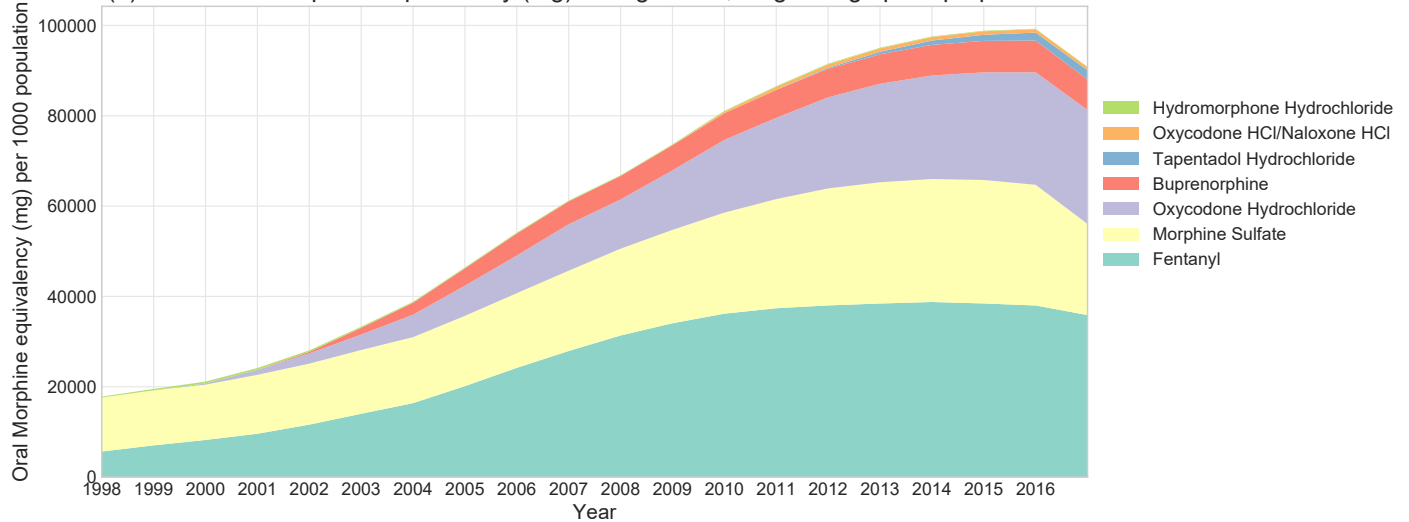




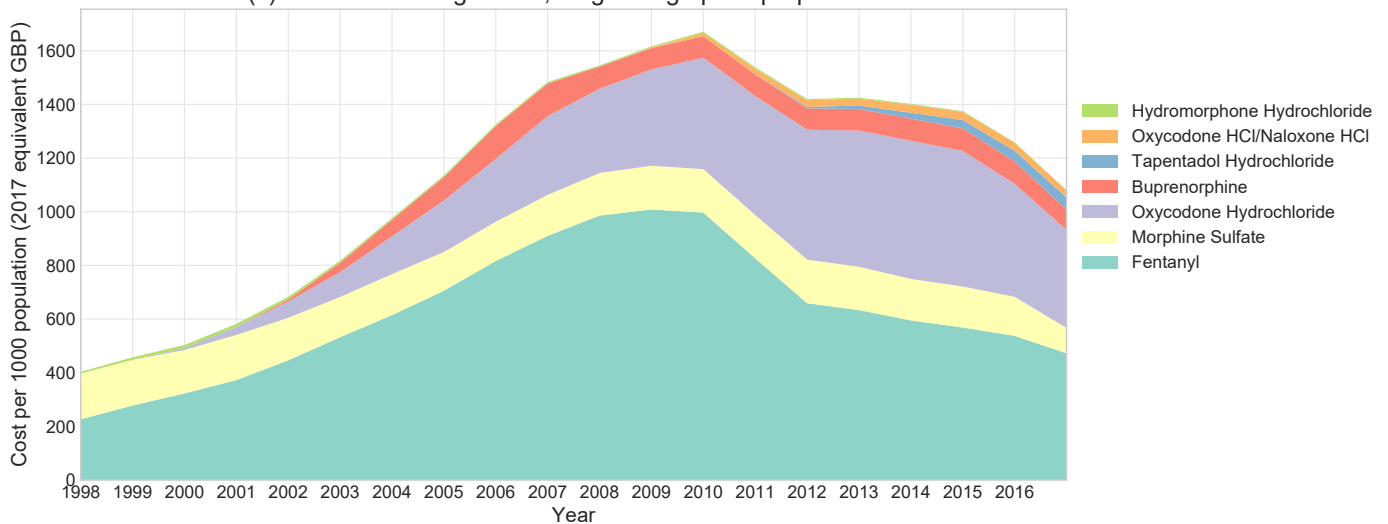
(a) Total prescriptions for high-dose, long-acting opioid preparations

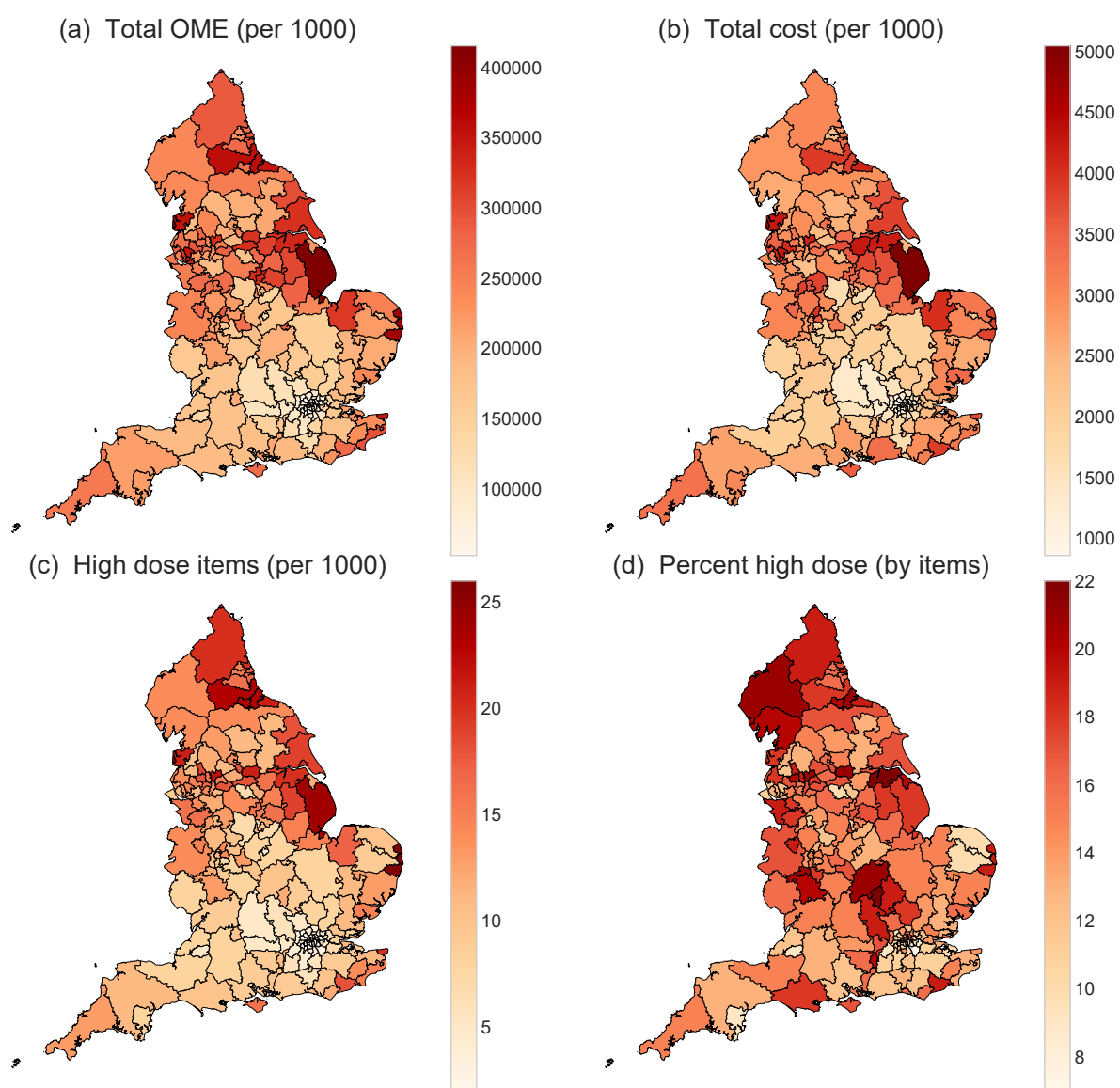


(b) Total Oral Morphine Equivalency (mg) for high-dose, long-acting opioid preparations



(c) Total cost of high-dose, long-acting opioid preparations



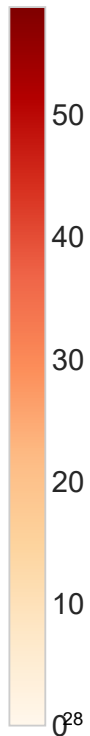
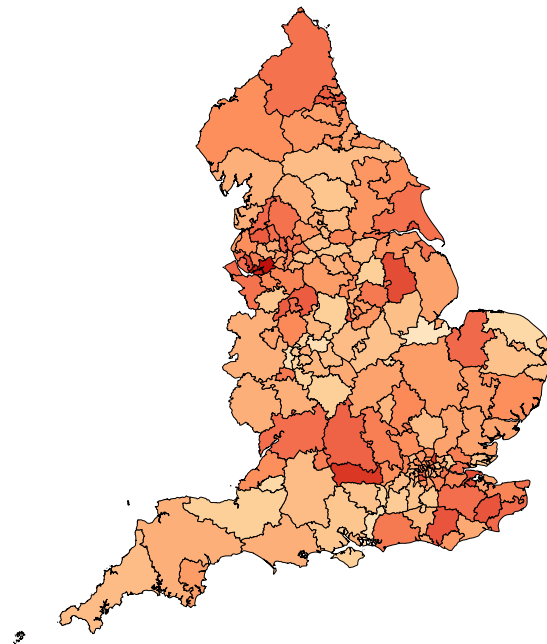
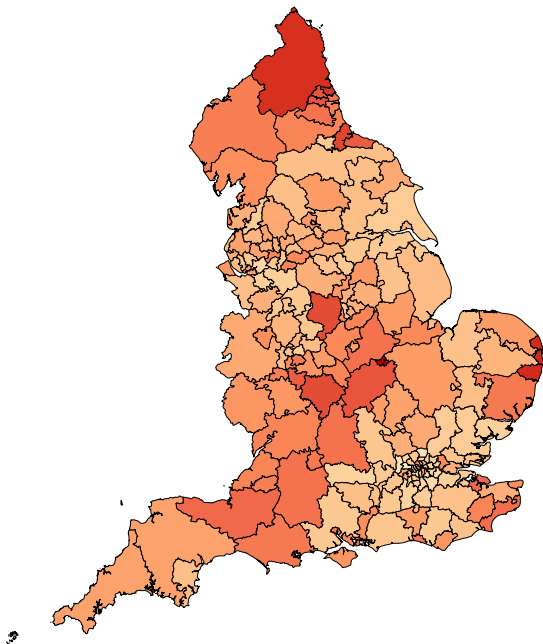
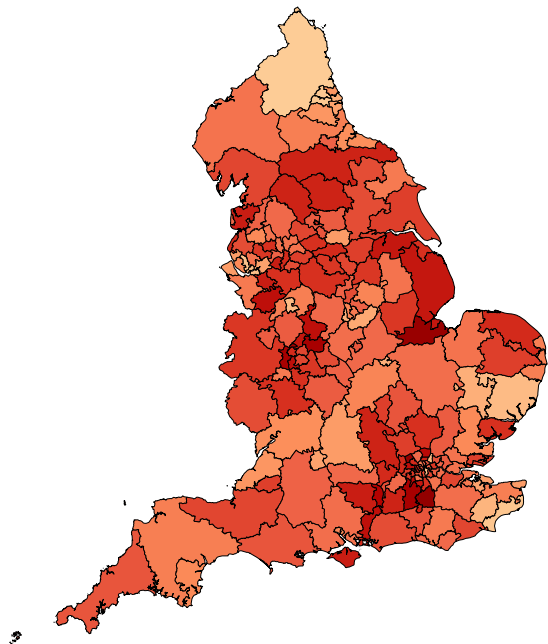


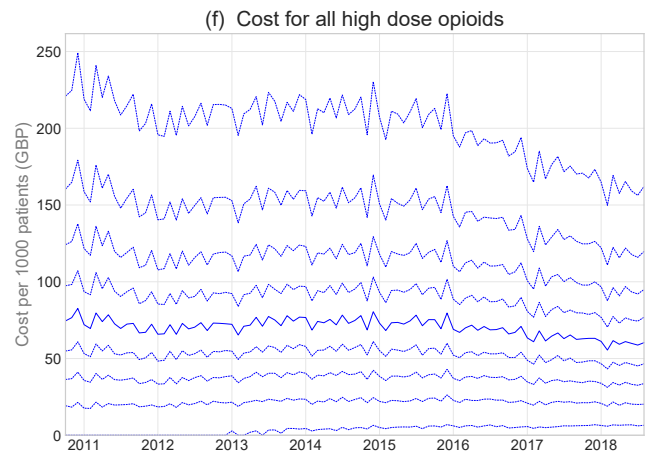
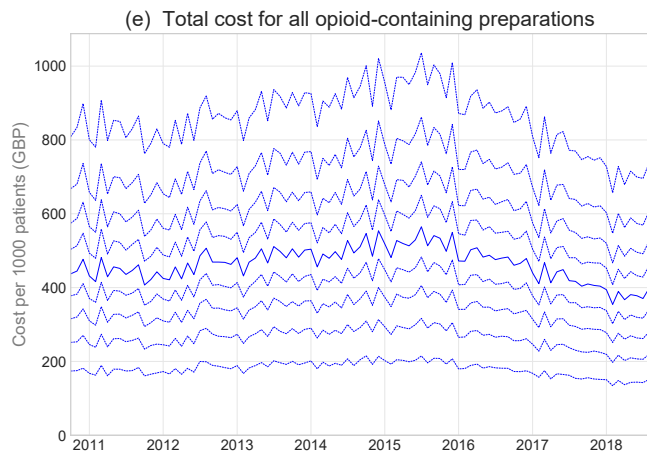
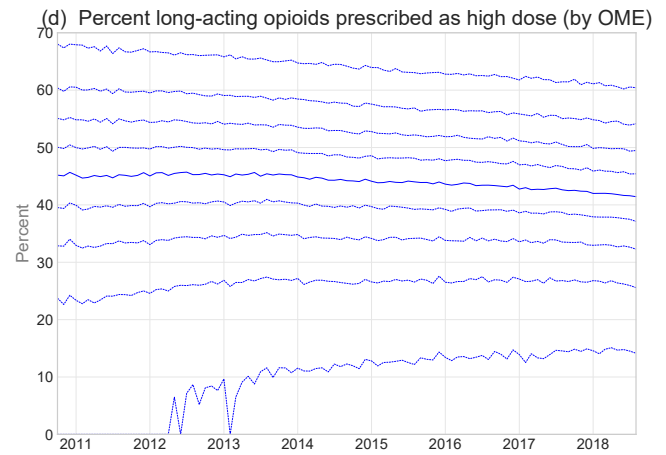
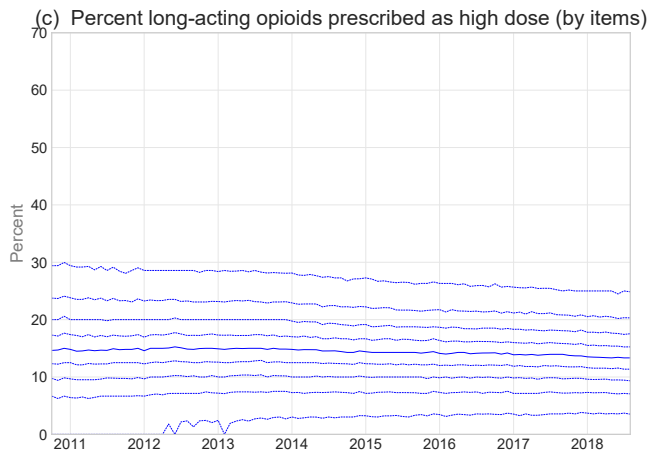
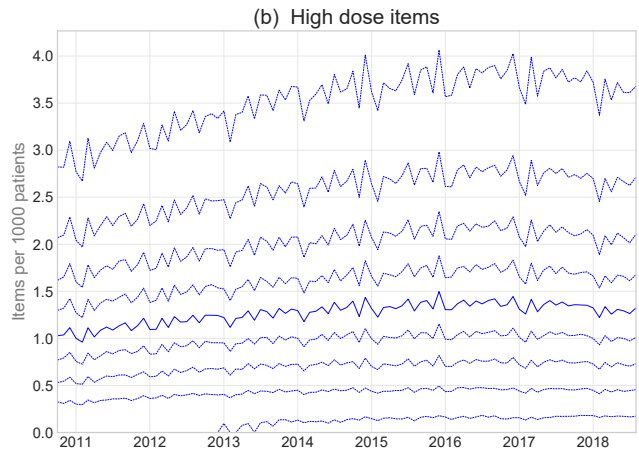
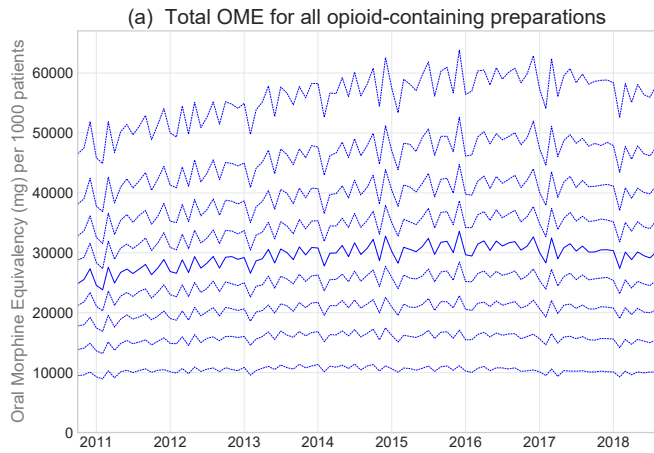
(e) % Fentanyl of high dose OME

(f) % Morphine of high dose OME

(g) % Oxycodone of high dose OME

opioids\_Figure3eg\_revised





# **Opioid Prescribing Trends and Geographical Variation in England 1998-2017**

## **Supplementary Information**

### **Supplementary Results Figures and Tables**

**Figure S1:** Trends in opioid prescribing in England 1998-2017, for lesser-prescribed opioids, presented in Figure 1 grouped into the “Other” category.

**Figure S2:** Trends in long-acting opioids prescribed in England, 1998-2017.

**Figure S3:** Trends in long-acting opioids not classed as high-dose, prescribed in England, 1998-2017.

**Figure S4:** Change in total annual OME prescribed per 1,000 registered patients from 2016 to 2017 across England’s CCGs.

**Table S1:** Summary of opioids prescribed in England by year, relative to mid-year population.

**Table S2:** First year of appearance in prescribing data for each opioid type, split by formulation.

**Table S3:** Opioids prescribed in England per year in morphine equivalent mg, per thousand mid-year population, 1998-2017.

**Table S4:** Summary of opioid prescribing across England’s CCGs, Mar-Aug 2018.

**Table S5:** Factors associated with the total rate of opioid prescribing (OME per 1000 patients), using mixed effects linear regression.

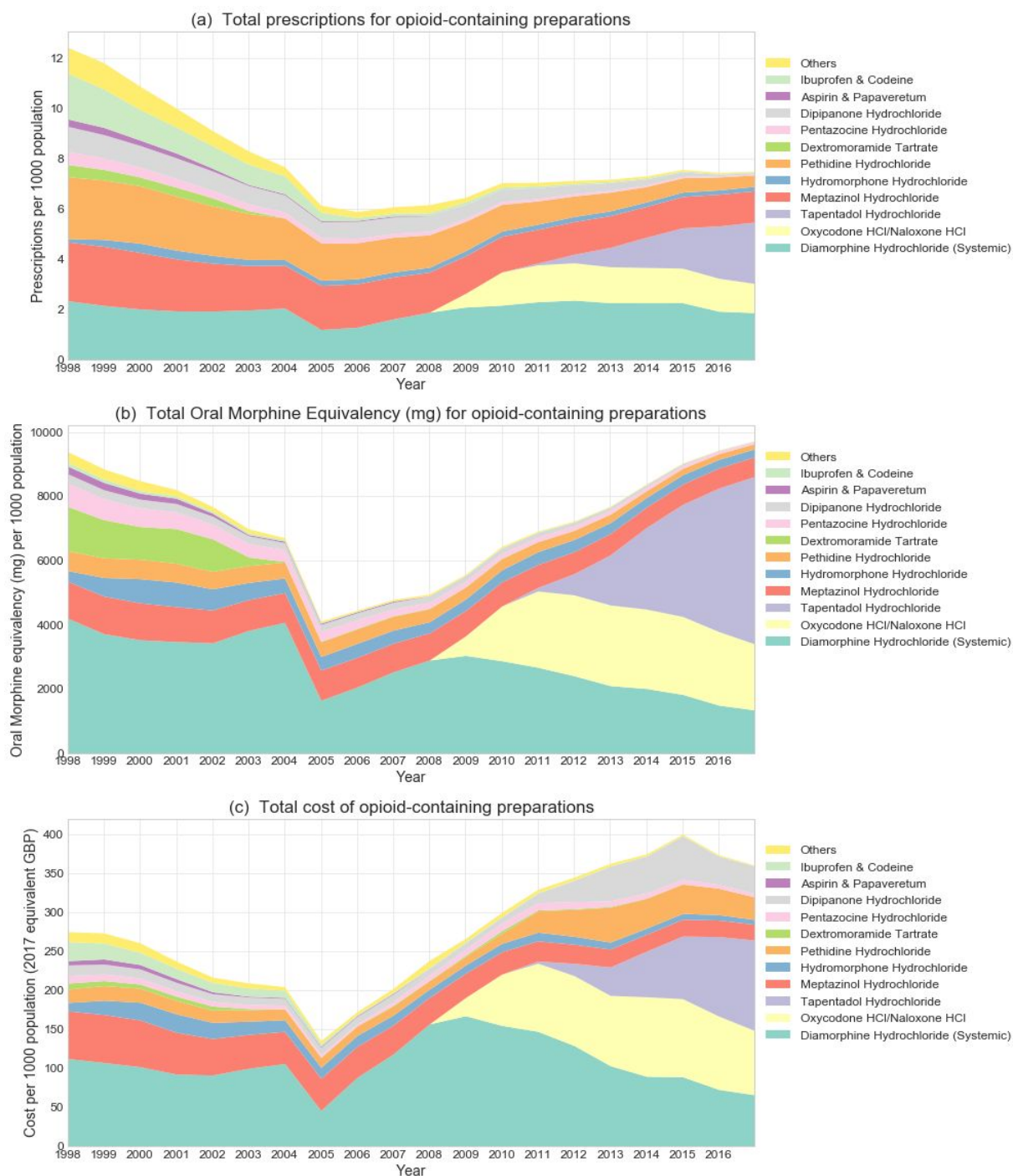
### **Appendix: Code and reference tables**

**A:** SQL code for classifying opioids

**B.** Conversion to OME for each opioid type included

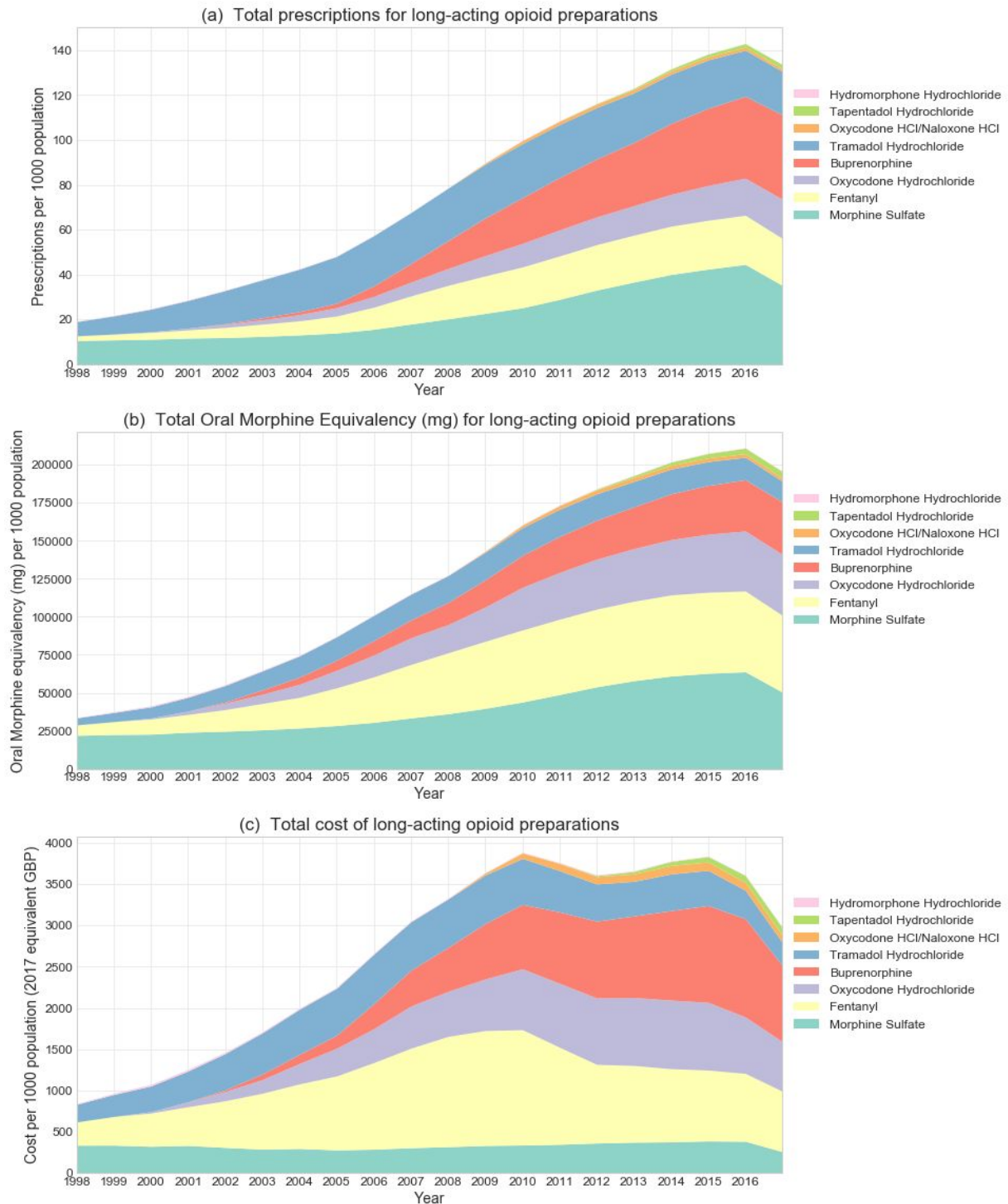
**C.** Summary of opioids classed as high-dose

## Appendix 1 - Supplementary Figures and Tables



**Figure S1. Trends in opioid prescribing in England 1998-2017, for lesser-prescribed opioids, presented in Figure 1 grouped into the “Other” category.** (a) Total items prescribed per 1,000 population. (b) Total OME prescribed per 1,000 population. (c) Total cost of opioids per 1,000 population (2017 equivalent GBP).

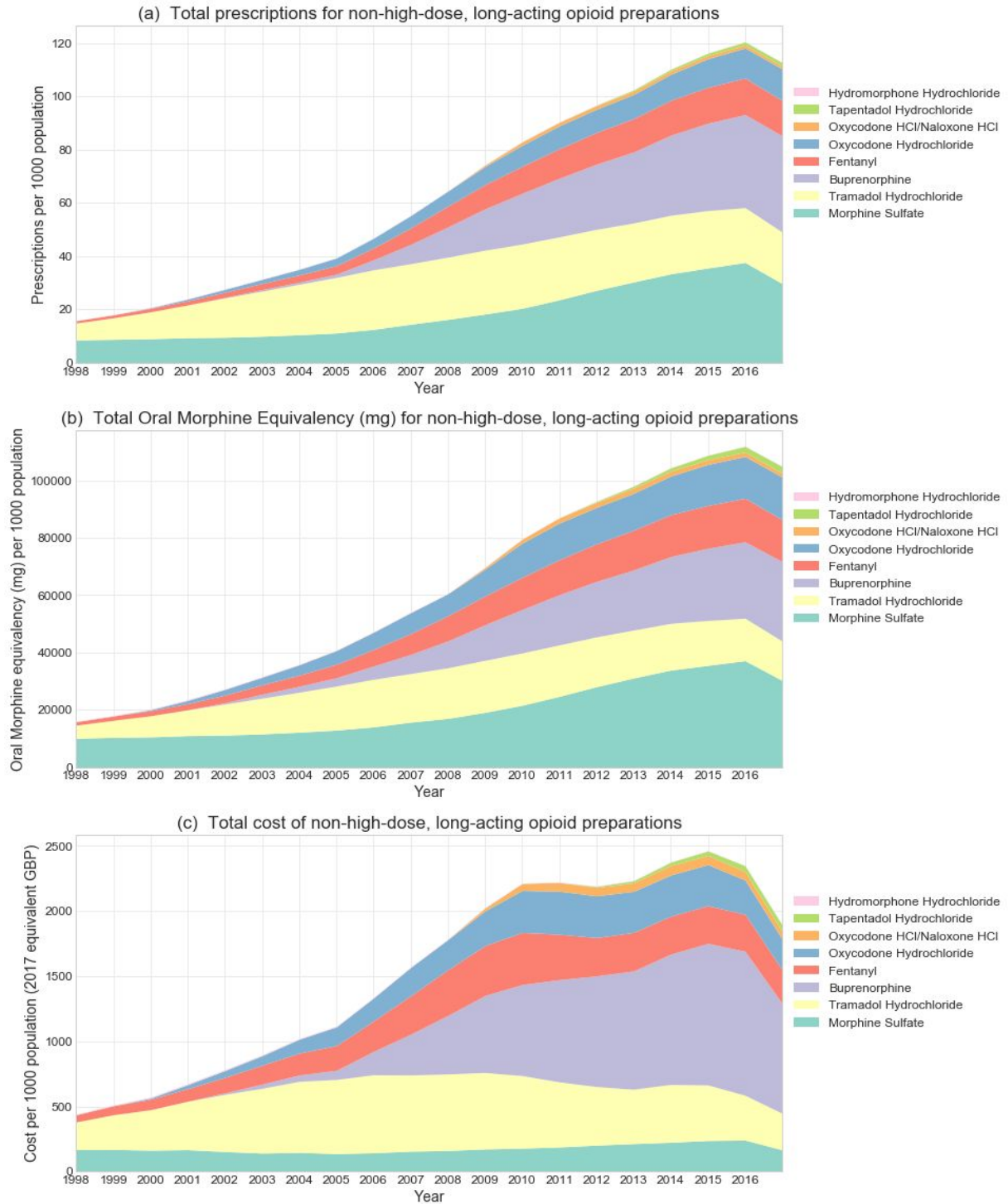




**Figure S2. Trends in long-acting opioids prescribed in England, 1998-2017.**

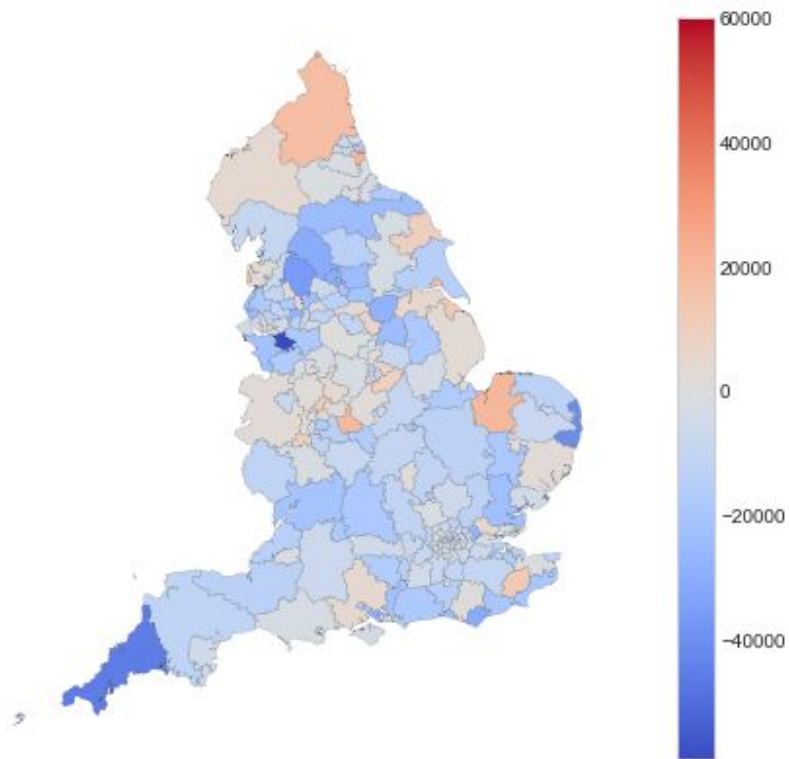
(a) Total items prescribed per 1,000 population. (b) Total OME prescribed per 1,000 population. (c) Total cost per 1,000 population (2017 equivalent GBP).





**Figure S3. Trends in long-acting opioids not classed as high-dose, prescribed in England, 1998-2017.**

(a) Total items prescribed per 1,000 population. (b) Total OME prescribed per 1,000 population. (c) Total cost per 1,000 population (2017 equivalent GBP).



**Figure S4:** Change in total annual OME prescribed per 1,000 registered patients from 2016 to 2017 across England's CCGs.

**Table S1. Summary of opioids prescribed in England by year, relative to mid-year population.**

High-dose opioids are the subset of long-acting opioids prescribed in doses  $\geq 120$ mg OME per day, and the percentage high-dose figures are also calculated as such. “% change” figures compare 2016 with 1998. OME, Oral Morphine Equivalency (mg).

year	OME per 1000				Items per 1000				Cost per 1000			
	Total	Long Acting	High Dose	% High Dose	Total	Long Acting	High Dose	% High Dose	Total	Long Acting	High Dose	% High Dose
1998	190,341	33,764	17,817	52.8	568	19	3.3	17.3	£3,616	£843	£403	47.8
1999	195,274	37,527	19,514	52.0	577	22	3.7	17.0	£4,183	£969	£457	47.2
2000	198,519	41,403	21,144	51.1	578	25	4.0	16.3	£4,412	£1,076	£503	46.8
2001	208,351	47,672	24,149	50.7	590	29	4.6	16.2	£4,458	£1,257	£582	46.3
2002	219,125	55,375	28,053	50.7	598	33	5.4	16.4	£4,801	£1,466	£683	46.6
2003	231,226	64,847	33,298	51.3	604	38	6.4	17.0	£5,178	£1,714	£817	47.7
2004	243,831	74,701	38,811	52.0	611	43	7.5	17.5	£5,581	£1,999	£976	48.8
2005	238,391	87,232	46,405	53.2	590	48	8.9	18.4	£6,103	£2,252	£1,135	50.4
2006	253,305	101,332	54,127	53.4	595	58	10.7	18.6	£7,314	£2,664	£1,325	49.8
2007	277,079	115,244	61,221	53.1	623	68	12.5	18.5	£7,914	£3,056	£1,483	48.5
2008	296,867	127,423	66,828	52.4	647	79	14.2	18.1	£7,392	£3,331	£1,546	46.4
2009	322,459	143,447	73,678	51.4	671	90	15.6	17.4	£7,590	£3,644	£1,616	44.4
2010	349,771	160,741	81,083	50.4	693	100	16.9	16.9	£8,009	£3,887	£1,671	43.0
2011	372,736	173,672	86,558	49.8	713	109	18.2	16.8	£7,406	£3,763	£1,538	40.9
2012	392,604	184,346	91,529	49.7	733	116	19.6	16.9	£7,419	£3,613	£1,420	39.3
2013	408,791	193,190	95,067	49.2	747	123	20.7	16.8	£7,612	£3,662	£1,425	38.9
2014	421,983	202,073	97,553	48.3	760	132	21.6	16.4	£7,731	£3,781	£1,402	37.1
2015	428,015	207,728	98,834	47.6	762	138	22.2	16.0	£8,069	£3,841	£1,375	35.8
2016	431,623	211,262	99,271	47.0	761	143	22.6	15.8	£7,331	£3,611	£1,259	34.9
2017	411,502	195,830	90,854	46.4	734	134	21.0	15.7	£6,198	£2,976	£1,081	36.3
% Change	127%	526%	457%		34%	647%	581%		103%	328%	212%	

**Table S2. First year of appearance in England's prescribing data for each opioid type, split by formulation.**  
1998 is the first year of data available, hence any drug available in 1998 may have been available before this.

chem_substance	min_year	formulation
Aspirin & Papaveretum	1998	Lozenge/Sublingual tab
Buprenorphine	1998	Injectible, Lozenge/Sublingual tab
	2002	Patch
Co-codamol	1998	Soluble Tab/Powder, Tab/Cap
	2010	Liquid
Co-codaprin	1998	Tab/Cap
Co-dydramol	1998	Tab/Cap, Soluble Tab/Powder
	2003	Liquid
Co-proxamol	1998	Tab/Cap, Liquid
Codeine Phosphate	1998	Tab/Cap, Injectible, Liquid
	2011	Suppository
Dextromoramide Tartrate	1998	Suppository, Tab/Cap
Dextropropoxyphene	1998	Tab/Cap
Diamorphine Hydrochloride (Systemic)	1998	Inhalation, Tab/Cap, Injectible
	2003	Liquid
	2012	Suppository
Dihydrocodeine Tartrate	1998	Liquid, Tab/Cap, Injectible
Dipipanone Hydrochloride	1998	Tab/Cap, Liquid
Fentanyl	1998	Patch
	2001	Lozenge/Sublingual tab
	2010	Inhalation
Hydromorphone Hydrochloride	1998	Tab/Cap
	2005	Injectible
Ibuprofen & Codeine	1998	Tab/Cap
Meptazinol Hydrochloride	1998	Tab/Cap, Injectible
Methadone Hydrochloride	1998	Inhalation, Injectible, Tab/Cap
Morphine Hydrochloride	1998	Liquid, Injectible
	2010	Suppository
Morphine Sulfate	1998	Soluble Tab/Powder, Liquid, Tab/Cap, Injectible, Suppository
	2010	Cream/Gel
Morphine Tartrate & Cyclizine Tartrate	1998	Injectible
Nalbuphine Hydrochloride	1998	Injectible
Oxycodone	1998	Suppository
Oxycodone HCl/Naloxone HCl	2009	Tab/Cap
	2015	Liquid
Oxycodone Hydrochloride	2000	Liquid, Tab/Cap
	2003	Injectible
Papaveretum	1998	Injectible
Pentazocine Hydrochloride	1998	Tab/Cap
Pentazocine Lactate	1998	Suppository, Injectible
Pethidine Hydrochloride	1998	Injectible, Tab/Cap
	2010	Liquid
Phenazocine Hydrobromide	1998	Tab/Cap
Powdered Opium	1998	Liquid
Tapentadol Hydrochloride	2011	Tab/Cap
	2014	Liquid
Tramadol Hydrochloride	1998	Injectible, Tab/Cap, Soluble Tab/Powder
	2003	Lozenge/Sublingual tab
	2011	Liquid

**Table S3. Opioids prescribed in England per year in morphine equivalent mg, per thousand mid-year population, 1998-2017.**

High-dose opioids are the subset of long-acting opioids prescribed in doses  $\geq 120$ mg OME per day. OME, Oral Morphine Equivalency (mg).

measure	year	Buprenorphine	Fentanyl	Morphine Sulfate	Other	Oxycodone Hydrochloride	Tapentadol Hydrochloride	Tramadol Hydrochloride	Total
<b>OME per 1000 High Dose</b>	<b>1998</b>	0	5,656	11,964	196	0	0	0	<b>17,817</b>
	<b>1999</b>	0	7,023	12,180	312	0	0	0	<b>19,514</b>
	<b>2000</b>	0	8,223	12,250	395	276	0	0	<b>21,144</b>
	<b>2001</b>	0	9,595	13,048	395	1,111	0	0	<b>24,149</b>
	<b>2002</b>	336	11,616	13,501	322	2,279	0	0	<b>28,053</b>
	<b>2003</b>	1,484	14,019	14,117	254	3,424	0	0	<b>33,298</b>
	<b>2004</b>	2,662	16,378	14,607	201	4,963	0	0	<b>38,811</b>
	<b>2005</b>	3,839	20,141	15,556	185	6,684	0	0	<b>46,405</b>
	<b>2006</b>	4,882	24,188	16,540	191	8,326	0	0	<b>54,127</b>
	<b>2007</b>	5,056	27,920	17,779	180	10,287	0	0	<b>61,221</b>
	<b>2008</b>	5,214	31,346	19,223	150	10,895	0	0	<b>66,828</b>
	<b>2009</b>	5,563	34,064	20,673	202	13,176	0	0	<b>73,678</b>
	<b>2010</b>	5,902	36,182	22,367	520	16,113	0	0	<b>81,083</b>
	<b>2011</b>	6,180	37,383	24,168	806	17,990	31	0	<b>86,558</b>
	<b>2012</b>	6,315	38,011	25,904	907	20,172	220	0	<b>91,529</b>
	<b>2013</b>	6,513	38,429	26,850	910	21,807	558	0	<b>95,067</b>
	<b>2014</b>	6,784	38,764	27,231	898	22,918	959	0	<b>97,553</b>
	<b>2015</b>	6,971	38,443	27,339	897	23,829	1,355	0	<b>98,834</b>
	<b>2016</b>	7,036	37,993	26,721	857	24,912	1,752	0	<b>99,271</b>
	<b>2017</b>	6,754	35,870	20,173	768	25,246	2,043	0	<b>90,854</b>
<b>OME per 1000 (Long Acting)</b>	<b>1998</b>	0	6,839	22,013	290	0	0	4,621	<b>33,764</b>
	<b>1999</b>	0	8,516	22,546	487	0	0	5,978	<b>37,527</b>
	<b>2000</b>	0	9,975	22,796	630	620	0	7,382	<b>41,403</b>
	<b>2001</b>	0	11,727	24,045	640	2,240	0	9,020	<b>47,672</b>
	<b>2002</b>	795	14,282	24,675	541	4,236	0	10,846	<b>55,375</b>
	<b>2003</b>	2,853	17,312	25,688	439	6,059	0	12,496	<b>64,847</b>
	<b>2004</b>	4,753	20,240	26,796	376	8,586	0	13,950	<b>74,701</b>
	<b>2005</b>	6,734	24,823	28,479	340	11,483	0	15,372	<b>87,232</b>
	<b>2006</b>	9,518	29,955	30,577	329	14,341	0	16,612	<b>101,332</b>
	<b>2007</b>	11,712	35,212	33,477	309	17,572	0	16,960	<b>115,244</b>
	<b>2008</b>	14,574	40,131	36,223	260	18,554	0	17,682	<b>127,423</b>
	<b>2009</b>	17,966	44,148	39,788	878	22,517	0	18,149	<b>143,447</b>
	<b>2010</b>	21,048	47,422	43,955	1,994	28,053	0	18,269	<b>160,741</b>
	<b>2011</b>	23,714	49,587	48,870	2,693	30,783	79	17,946	<b>173,672</b>
	<b>2012</b>	25,648	51,131	53,979	2,812	32,889	516	17,371	<b>184,346</b>
	<b>2013</b>	27,475	52,314	57,950	2,781	34,670	1,265	16,737	<b>193,190</b>
	<b>2014</b>	30,087	53,372	61,084	2,711	36,405	2,091	16,322	<b>202,073</b>

<b>OME per 1000 (Total)</b>	<b>2015</b>	32,156	53,363	62,842	2,652	38,158	2,878	15,679	<b>207,728</b>
	<b>2016</b>	33,710	53,177	63,862	2,500	39,498	3,705	14,809	<b>211,262</b>
	<b>2017</b>	34,472	50,483	50,414	2,242	40,142	4,349	13,728	<b>195,830</b>
	<b>1998</b>	3,195	6,839	26,260	142,500	0	0	11,073	<b>189,867</b>
	<b>1999</b>	3,020	8,516	27,272	142,137	0	0	13,881	<b>194,824</b>
	<b>2000</b>	2,782	9,975	27,976	139,866	742	0	16,769	<b>198,110</b>
	<b>2001</b>	2,624	11,745	29,887	140,387	2,783	0	20,630	<b>208,055</b>
	<b>2002</b>	3,360	14,374	31,067	139,943	5,296	0	24,904	<b>218,943</b>
	<b>2003</b>	5,400	17,408	32,662	138,729	7,676	0	29,239	<b>231,115</b>
	<b>2004</b>	7,204	20,455	34,443	136,902	10,869	0	33,898	<b>243,771</b>
	<b>2005</b>	9,149	25,154	37,220	111,604	14,665	0	40,556	<b>238,349</b>
	<b>2006</b>	11,905	30,431	40,349	105,204	18,411	0	46,973	<b>253,273</b>
	<b>2007</b>	14,220	35,796	44,780	106,987	22,940	0	52,323	<b>277,046</b>
	<b>2008</b>	17,119	40,900	49,264	106,601	24,977	0	58,002	<b>296,863</b>
	<b>2009</b>	20,907	45,144	53,823	109,069	30,396	0	63,120	<b>322,459</b>
	<b>2010</b>	24,212	48,571	59,300	112,194	37,356	0	68,129	<b>349,763</b>
	<b>2011</b>	27,154	50,821	65,939	114,474	40,897	114	73,330	<b>372,728</b>
	<b>2012</b>	29,269	52,420	72,967	115,950	43,813	659	77,518	<b>392,597</b>
	<b>2013</b>	31,185	53,859	78,824	116,615	46,532	1,560	80,213	<b>408,789</b>
	<b>2014</b>	33,880	55,052	83,968	118,349	48,951	2,542	79,241	<b>421,983</b>
	<b>2015</b>	35,796	55,297	87,698	119,409	51,420	3,489	74,906	<b>428,015</b>
	<b>2016</b>	37,258	55,004	90,402	119,041	53,388	4,468	72,062	<b>431,623</b>
	<b>2017</b>	37,869	52,309	77,520	117,098	54,377	5,221	67,108	<b>411,502</b>

**Table S4. Summary of opioid prescribing across England's CCGs, Mar-Aug 2018.**

High-dose opioids are the subset of long-acting opioids prescribed in doses  $\geq 120$ mg OME per day, and percent high dose is calculated as such. Other measures are items/OME/cost per 1,000 registered patients. OME, Oral Morphine Equivalency (mg).

	min	median	max	fold-difference
<b>Total items (per 1000)</b>	118.6	342.9	726.9	6.1
<b>Total OME (per 1000)</b>	52,711.6	205,480.2	415,635.0	7.9
<b>High dose items (per 1000)</b>	1.7	10.7	26.4	15.3
<b>Percent high dose (by items)</b>	7.1	15.0	22.2	3.1
<b>Percent high dose (by OME)</b>	28.4	44.9	56.2	2.0
<b>Total cost (per 1000)</b>	859.3	2,695.1	5,051.1	5.9
<b>% Fentanyl of high dose OME</b>	17.5	38.5	55.9	
<b>% Morphine of high dose OME</b>	6.8	23.8	52.9	
<b>% Oxycodone of high dose OME</b>	8.7	26.6	49.5	

**Table S5: Factors associated with the total rate of opioid prescribing (OME per 1000 patients),** using mixed effects linear regression, stratified by various practice factors, along with odds ratios from a univariable and multivariable logistic regression model. IMD, Index of Multiple Deprivation; QOF, Quality Outcomes Framework

			Univariable logistic regression			Multivariable logistic regression		
		Mean OME per 1000	Change in OME per 1000			Change in OME per 1000		
			95% CI			95% CI		
% of patients over 65	0-11.0	105305	Ref			Ref		
	11.0-15.5	187222	81916	74437	89396	57764	51997	63531
	15.5-18.9	216358	111053	103573	118533	77926	71429	84424
	18.9-22.5	227347	122042	114562	129522	89512	82404	96619
	22.5-92.2	228361	123056	115576	130536	95761	87656	103867
% with a long term health condition	16.5-47.0	110882	Ref			Ref		
	47.0-51.4	160342	49460	42306	56614	14364	8948	19780
	51.4-55.3	196791	85909	78755	93063	24155	18537	29773
	55.3-59.6	225274	114393	107239	121547	31566	25720	37412
	59.6-96.0	271719	160838	153684	167992	52726	46581	58872
Practice list size (thousands)	0-3.9	197939	Ref			Ref		
	3.9-5.9	190453	-7486	-19458	4486	14104	8839	19369
	5.9-8.1	197701	-238	-12212	11737	21296	15964	26628
	8.1-11.3	201590	3651	-8321	15623	24458	19031	29884
	11.3-60.6	188887	-9051	-21026	2923	21808	16245	27370
Urban/rural	Mainly rural	221125	Ref			Ref		
	Largely rural	229076	7951	-9680	25581	-581	-10851	9689
	Urban with significant rural	219702	-1423	-18743	15896	-5686	-15821	4449
	Urban with city and town	210055	-11070	-26326	4186	-17596	-26723	-8468
	Urban with minor conurbation	236570	15445	-7211	38102	-10572	-36266	15122
	Urban with major conurbation	163000	-58125	-72542	-43708	-49121	-63246	-34996
IMD	Least deprived	143339	Ref			Ref		
		183571	40231	32266	48197	36196	30547	41844
		202394	59055	51089	67020	70048	63800	76297
		211257	67918	59952	75883	97137	90189	104085
	Most deprived	224005	80666	72700	88632	125228	117295	133161
QOF	14-523	179987	Ref			Ref		
	523-541	189218	9231	962	17500	5944	642	11246
	541-550	194032	14045	5772	22318	2762	-2591	8115
	550-557	198923	18935	10666	27204	5757	334	11180
	557-559	204448	24461	16187	32734	361	-5235	5957



## Appendix 2 - Code and reference tables

### A. SQL code for categorising opioids and formulations

List of all opioid chemical codes included in this study, and their classification:

```
WHEN chemical_code_current = '0407010A0' THEN 'Combination'
WHEN chemical_code_current = '0407010F0' THEN 'Combination'
WHEN chemical_code_current = '0407010M0' THEN 'Combination'
WHEN chemical_code_current = '0407010M0' THEN 'Combination'
WHEN chemical_code_current = '0407010N0' THEN 'Combination'
WHEN chemical_code_current = '0407010N0' THEN 'Combination'
WHEN chemical_code_current = '0407010Q0' THEN 'Combination'
WHEN chemical_code_current = '0407010W0' THEN 'Combination'
WHEN chemical_code_current = '0407010X0' THEN 'Combination'
WHEN chemical_code_current = '040702020' THEN 'Morphine'
WHEN chemical_code_current = '040702040' THEN 'Tramadol'
WHEN chemical_code_current = '040702050' THEN 'Hydromorphone'
WHEN chemical_code_current = '0407020A0' THEN 'Fentanyl'
WHEN chemical_code_current = '0407020AB' THEN 'Papaveretum'
WHEN chemical_code_current = '0407020AD' THEN 'Oxycodone'
WHEN chemical_code_current = '0407020AF' THEN 'Combination'
WHEN chemical_code_current = '0407020AG' THEN 'Tapentadol'
WHEN chemical_code_current = '0407020B0' THEN 'Buprenorphine'
WHEN chemical_code_current = '0407020C0' THEN 'Codeine'
WHEN chemical_code_current = '0407020D0' THEN 'Dextromoramide '
WHEN chemical_code_current = '0407020E0' THEN 'Dextropropoxyphene'
WHEN chemical_code_current = '0407020G0' THEN 'Dihydrocodeine '
WHEN chemical_code_current = '0407020H0' THEN 'Dipipanone '
WHEN chemical_code_current = '0407020K0' THEN 'Diamorphine '
WHEN chemical_code_current = '0407020L0' THEN 'Meptazinol '
WHEN chemical_code_current = '0407020M0' THEN 'Methadone '
WHEN chemical_code_current = '0407020P0' THEN 'Morphine '
WHEN chemical_code_current = '0407020Q0' THEN 'Morphine '
WHEN chemical_code_current = '0407020T0' THEN 'Pentazocine '
WHEN chemical_code_current = '0407020U0' THEN 'Pentazocine '
WHEN chemical_code_current = '0407020V0' THEN 'Pethidine '
WHEN chemical_code_current = '0407020W0' THEN 'Opium'
WHEN chemical_code_current = '0407020X0' THEN 'Phenazocine '
WHEN chemical_code_current = '0407020Y0' THEN 'Nalbuphine '
WHEN chemical_code_current = '0407020Z0' THEN 'Oxycodone'
WHEN chemical_code_current = '1001010J0' THEN 'Combination'
```

Formulations (mid-string field is obtained from the Drug name and represents the formulation):

```
WHEN RTRIM(mid_string) IN ('Vag Crm','Vag Gel','Oily Crm','Crm','Gel','Lot','Gel','Soln','Gel
Sach','Oint','Intrasite Gel') THEN 'Cream/Gel'
WHEN RTRIM(mid_string) IN ('Tab Buccal','Buccal Film','Tab Subling','Disper
Tab','Orodisper Tab','Loz','Tab Sublingual','Oral Lyophilisate') THEN 'Lozenge/Sublingual tab'
WHEN RTRIM(mid_string) IN ('Tab Solb','Eff Tab','Solb Tab','Tab Eff','Pdr Sach','Eff
Pdr Sach','Susp Gran Sach') THEN 'Soluble Tab/Powder'
WHEN RTRIM(mid_string) LIKE '%Tab' OR RTRIM(mid_string) LIKE '%Cap' OR
RTRIM(mid_string) IN ('Cap','Cap E/C','Capl') THEN 'Tab/Cap'
WHEN RTRIM(mid_string) LIKE '%Susp%' OR
RTRIM(mid_string) IN ('Liq Spec','Oral Soln','Sod Oral Soln','Elix','Liq','Oral
Susp','Tinct','Liq Conc','Oral Dps','Oral Soln Conc','Oral Conc','Mix','Elix BPC Inc
Duty','Methadone HCl Mix') THEN 'Liquid'
WHEN RTRIM(mid_string) LIKE '%Inj' OR RTRIM(mid_string) IN ('I/V
Inf','Syr','Inj','(S)','Lact Inj','P','Morph Sulf','Morph Sulph','Implant') THEN 'Injectible'
WHEN RTRIM(mid_string) IN ('Patch','Patches','TransdermalPatch','Transdermal
Patch','T/Derm Patch') THEN 'Patch'
WHEN RTRIM(mid_string) IN ('Lact Suppos','Suppos') THEN 'Suppository'
```

WHEN RTRIM(mid\_string) LIKE '%Nsl Spy%' or RTRIM(mid\_string) = 'Reefer' THEN  
'Inhalation'

**B. Conversion to OME for each opioid type included. Reference sources are listed in the second table.**

Opioid	OME conversion (mg)	Reference Source
Aspirin & Papaveretum	1	OA
Buprenorphine (Sublingual)	60	MIMS
Buprenorphine (Injection, transdermal patch)	100	OA
Co-codamol	0.1	GPN
Co-codaprin	0.1	GPN
Codeine Phosphate	0.1	GPN
Co-dydramol	0.1	GPN
Co-proxamol	0.1	GPN
Dextromoramide Tartrate	4	GPN
Dextropropoxyphene	0.1	GPN
Diamorphine Hydrochloride (Systemic) (Oral)	1	GPN
Diamorphine Hydrochloride (Systemic) (Injection)	3	GPN
Dihydrocodeine Tartrate	0.1	GPN
Dipipanone Hydrochloride	0.5	ABHB
Fentanyl (Transdermal patch, transmucosal lozenge)	100	CMS
Fentanyl (Buccal and sublingual tablet)	130	CMS
Fentanyl (Nasal Spray)	160	CMS
Fentanyl (Buccal film)	180	CMS
Hydromorphone Hydrochloride	5	BNF
Ibuprofen & Codeine	0.1	GPN
Meptazinol Hydrochloride	0.03	ABHB
Methadone Hydrochloride	3	CMS
Morphine Hydrochloride (Oral)	1	GPN
Morphine Hydrochloride (Injection)	2	GPN
Morphine Sulfate (Oral)	1	GPN
Morphine Sulfate (Injection)	2	GPN
Morphine Tartrate & Cyclizine Tartrate	2	GPN
Nalbuphine Hydrochloride	1	CMS
Oxycodone	2	GPN
Oxycodone HCl/Naloxone HCl	2	GPN
Oxycodone Hydrochloride	2	GPN
Papaveretum	1	GPN
Pentazocine Hydrochloride	0.37	CMS
Pentazocine Lactate	0.37	CMS
Pethidine Hydrochloride (Oral)	0.1	ABHB
Pethidine Hydrochloride (Injection)	0.24	ABHB
Phenazocine Hydrobromide	4	GPN
Tapentadol Hydrochloride	0.4	CMS
Tramadol Hydrochloride	0.1	GPN

Reference	Reference Name	Reference Link
-----------	----------------	----------------

BNF	British National Formulary	<a href="https://www.bnf.org/products/bnf-online/">https://www.bnf.org/products/bnf-online/</a>
CMS	Centers for Medicare & Medicaid Services	<a href="https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf">https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf</a>
GPN	GP Notebook	<a href="https://www.gpnotebook.co.uk/">https://www.gpnotebook.co.uk/</a>
MIMS	Monthly Index of Medical Specialities	<a href="https://www.mims.co.uk/">https://www.mims.co.uk/</a>
OA	Opioids Aware	<a href="https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware">https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware</a>
ABHB	Aneurin Bevan Health Board	<a href="https://www.wales.nhs.uk/sites3/Documents/814/OpiateConversionDoses%5BFinal%5DNov2010.pdf">https://www.wales.nhs.uk/sites3/Documents/814/OpiateConversionDoses%5BFinal%5DNov2010.pdf</a>

**C. Summary of opioids classed as high-dose.** See Appendix B for source of OME multipliers.

Chemical substance	bnf_code	drug_name	Total_dose Per_unit (mg)	Duration (hrs)	Daily dose	OME multiplier	Daily OME
Buprenorphine	0407020B0AAAGAG	Buprenorphine_Patch 70mcg/hr (96hr)	6.72	96	1.68	100	168
Buprenorphine	0407020B0BDACAG	Transtec_T/Derm Patch 70mcg/hr (40mg)	6.72	96	1.68	100	168
Buprenorphine	0407020B0BIACAG	Bupeaze_Transdermal Patch 70mcg/hr(96hr)	6.72	96	1.68	100	168
Buprenorphine	0407020B0BGACAG	Hapoctasin_Patch 70mcg/hr	6.72	96	1.68	100	168
Buprenorphine	0407020B0BPACAG	Relevtec_Transdermal Patch 70mcg/hr	6.72	96	1.68	100	168
Buprenorphine	0407020B0BNACAG	Buplast_Transdermal Patch 70mcg/hr	6.72	96	1.68	100	168
Buprenorphine	0407020B0BJACAG	Prenotrix_T/Derm Patch 70mcg/hr	6.72	96	1.68	100	168
Buprenorphine	0407020B0AAAF	Buprenorphine_Patch 52.5mcg/hr (96hr)	5.04	96	1.26	100	126
Buprenorphine	0407020B0BDABAF	Transtec_T/Derm Patch 52.5mcg/hr (30mg)	5.04	96	1.26	100	126
Buprenorphine	0407020B0BIABAF	Bupeaze_TransdermalPatch52.5mcg/hr(96hr)	5.04	96	1.26	100	126
Buprenorphine	0407020B0BGABAF	Hapoctasin_Patch 52.5mcg/hr	5.04	96	1.26	100	126
Buprenorphine	0407020B0BPABAF	Relevtec_Transdermal Patch 52.5mcg/hr	5.04	96	1.26	100	126
Buprenorphine	0407020B0BJABAF	Prenotrix_T/Derm Patch 52.5mcg/hr	5.04	96	1.26	100	126
Buprenorphine	0407020B0BNABAF	Buplast_Transdermal Patch 52.5mcg/hr	5.04	96	1.26	100	126
Fentanyl	0407020A0BEAEAH	Matrifen_Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BBALAH	Durogesic DTrans_T/Derm Patch 100mcg	7.2	72	2.4	100	240
Fentanyl	0407020A0BQAEAH	Fencino_Transdermal Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0AAHAH	Fentanyl_Transdermal Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BFAEAH	Mezolar Matrix_TransdermalPatch100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BVAEAH	Yemex_Transdermal Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BMADAH	Victanyl_Transdermal Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BGADAH	Fentalis Reservoir_T/Derm Patch100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BLADAH	Osmanil_Transdermal Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BUAEAH	Mylafent_Transdermal Patch 100mcg/hr	7.2	72	2.4	100	240

Fentanyl	0407020A0BBADAH	Durogesic_Transdermal Patch 100mcg	7.2	72	2.4	100	240
Fentanyl	0407020A0BDADAH	Tilofyl_Patch 100mcg/hr	7.2	72	2.4	100	240
Fentanyl	0407020A0BEADAG	Matrifen_Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0AAAGAG	Fentanyl_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BQADAG	Fencino_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BBAKAG	Durogesic DTrans_T/Derm Patch 75mcg	5.4	72	1.8	100	180
Fentanyl	0407020A0BFADAG	Mezolar Matrix_TransdermalPatch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BGACAG	Fentalis Reservoir_T/Derm Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BVADAG	Yemex_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BMACAG	Victanyl_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BLACAG	Osmanil_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BDACAG	Tilofyl_Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BHACAG	Osmach_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BUADAG	Mylafent_Transdermal Patch 75mcg/hr	5.4	72	1.8	100	180
Fentanyl	0407020A0BEACAF	Matrifen_Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0AAAF	Fentanyl_Transdermal Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BQACAF	Fencino_Transdermal Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BBAJAF	Durogesic DTrans_T/Derm Patch 50mcg	3.6	72	1.2	100	120
Fentanyl	0407020A0BFACAF	Mezolar Matrix_TransdermalPatch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BGABAF	Fentalis Reservoir_T/Derm Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BVACAF	Yemex_Transdermal Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BMABAF	Victanyl_Transdermal Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BUACAF	Mylafent_Transdermal Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BLABAF	Osmanil_Transdermal Patch 50mcg/hr	3.6	72	1.2	100	120
Fentanyl	0407020A0BBABAF	Durogesic_Transdermal Patch 50mcg	3.6	72	1.2	100	120
Hydromorphone Hydrochloride	040702050BBAGAB	Palladone-SR_Cap 24mg	24	12	48	5	240
Hydromorphone Hydrochloride	040702050BBAFAA	Palladone-SR_Cap 16mg	16	12	32	5	160
Morphine Sulfate	0407020Q0BKAEI	Zomorph_Cap 200mg	200	12	400	1	400
Morphine Sulfate	0407020Q0BIAFEI	MXL_Cap 200mg	200	12	400	1	400
Morphine Sulfate	0407020Q0AAAGAG	Morph Sulf_Tab 200mg M/R	200	12	400	1	400
Morphine Sulfate	0407020Q0BIAEDW	MXL_Cap 150mg	150	12	300	1	300
Morphine Sulfate	0407020Q0BIADDV	MXL_Cap 120mg	120	12	240	1	240
Morphine Sulfate	0407020Q0BKADEB	Zomorph_Cap 100mg	100	12	200	1	200
Morphine Sulfate	0407020Q0AAHAH	Morph Sulf_Tab 100mg M/R	100	12	200	1	200

Morphine Sulfate	0407020Q0BNADAH	Morphgesic SR_Tab 100mg	100	12	200	1	200
Morphine Sulfate	0407020Q0BJACEB	Morcap SR_Cap 100mg	100	12	200	1	200
Morphine Sulfate	0407020Q0BIACDU	MXL_Cap 90mg	90	12	180	1	180
Morphine Sulfate	0407020Q0BKACEH	Zomorph_Cap 60mg	60	12	120	1	120
Morphine Sulfate	0407020Q0AAAI	Morph Sulf_Tab 60mg M/R	60	12	120	1	120
Morphine Sulfate	0407020Q0BNACAI	Morphgesic SR_Tab 60mg	60	12	120	1	120
Morphine Sulfate	0407020Q0BIABEH	MXL_Cap 60mg	60	12	120	1	120
Oxycodone HCl/Naloxone HCl	0407020AFBBADAD	Targinact_Tab 40mg/20mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBEAFAP	Longtec_Tab 120mg M/R	120	12	240	2	480
Oxycodone Hydrochloride	0407020ADBCAFAP	OxyContin_Tab 120mg M/R	120	12	240	2	480
Oxycodone Hydrochloride	0407020ADBEAEAI	Longtec_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADAAIAI	Oxycodone HCl_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBCADAI	OxyContin_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBKAIEAI	Reltebon_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBMAHAI	Abtard_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBF AEAI	Oxylan_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBNAAAI	Zomestine_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBPAGAI	Leveraxo_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBQADAI	Onexila_XL_Tab 80mg	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBDAEAI	Carexil_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBLABAI	Oxeltra_Tab 80mg M/R	80	12	160	2	320
Oxycodone Hydrochloride	0407020ADBEAIAQ	Longtec_Tab 60mg M/R	60	12	120	2	240
Oxycodone Hydrochloride	0407020ADAAAQAQ	Oxycodone HCl_Tab 60mg M/R	60	12	120	2	240
Oxycodone Hydrochloride	0407020ADBCAGAQ	OxyContin_Tab 60mg M/R	60	12	120	2	240
Oxycodone Hydrochloride	0407020ADBKAHAQ	Reltebon_Tab 60mg M/R	60	12	120	2	240

Oxycodone Hydrochloride	0407020ADBMAQAQ	Abtard_Tab 60mg M/R	60	12	120	2	240
Oxycodone Hydrochloride	0407020ADBLADAQ	Oxeltra_Tab 60mg M/R	60	12	120	2	240
Oxycodone Hydrochloride	0407020ADBPAFAQ	Leveraxo_Tab 60mg M/R	60	12	120	2	240
Oxycodone Hydrochloride	0407020ADBEADAH	Longtec_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADAAHAH	Oxycodone HCl_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBCACAH	OxyContin_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBKADAH	Reltebon_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBMAEAH	Abtard_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBFADAH	Oxylan_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBNABAH	Zomestine_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBQACAH	Onexila_XL_Tab 40mg	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBPAAEH	Leveraxo_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBDADAH	Carexil_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBLAEAH	Oxeltra_Tab 40mg M/R	40	12	80	2	160
Oxycodone Hydrochloride	0407020ADBEAHAR	Longtec_Tab 30mg M/R	30	12	60	2	120
Oxycodone Hydrochloride	0407020ADAAARAR	Oxycodone HCl_Tab 30mg M/R	30	12	60	2	120
Oxycodone Hydrochloride	0407020ADBCAHAR	OxyContin_Tab 30mg M/R	30	12	60	2	120
Oxycodone Hydrochloride	0407020ADBKAGAR	Reltebon_Tab 30mg M/R	30	12	60	2	120
Oxycodone Hydrochloride	0407020ADBMAFAR	Abtard_Tab 30mg M/R	30	12	60	2	120
Oxycodone Hydrochloride	0407020ADBPADAR	Leveraxo_Tab 30mg M/R	30	12	60	2	120
Tapentadol Hydrochloride	0407020AGBBAGAG	Palexia_SR Tab 250mg	250	12	500	0.4	200
Tapentadol Hydrochloride	0407020AGBBAFAF	Palexia_SR Tab 200mg	200	12	400	0.4	160
Tapentadol Hydrochloride	0407020AGBBAAEAE	Palexia_SR Tab 150mg	150	12	300	0.4	120