The Impact of the COVID-19 Pandemic Lockdown Measures on the Prescribing Trends and Utilisation of Opioids in the English Primary Care Setting: segmented-liner regression analysis

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Abstract

Background: The COVID-19 lockdown has resulted in limited access to most of the conventional chronic pain management services. Subsequently, changes in opioids' utilisation could be expected. This study assessed the impact of the first COVID-19 lockdown on opioid utilisation using aggregated-level, community dispensing dataset covering the whole English population.

Method: A segmented-linear regression analysis was applied to monthly dispensed opioid prescriptions from March 2019-March 2021. Opioid utilisation was measured using the number of opioids' items dispensed/1000 inhabitants and Defined Daily Dose (DDD)/1000 inhabitants/day during 12-months pre/post the lockdown in March 2020 stratified by strong and weak opioids.

Results: For all opioids' classes, there were nonsignificant changes in the number of opioids' items dispensed/1000 inhabitants trend pre-lockdown, small increases in their level immediately post-lockdown, and a non-significant decline in the trend post-lockdown. Similarly, a non-significant reduction in the DDD/1000 inhabitant/day baseline trend pre-lockdown, nonsignificant immediate increases in the level post-lockdown, and declines in the trend post-lockdown for all opioids' classes were observed.

Conclusion: Unexpectedly, opioid utilisation does not appear to have been significantly affected by the lockdown measures during the study period. However, patient-level data is needed to determine more accurate estimates of any changes in the opioid prescribing including incident prescribing/use.

Keywords: Opioids; Utilisation trends; COVID-19; lockdown; England

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What is already known about this subject:

- The COVID-19 pandemic-related safety measures have resulted in limited access to healthcare services including chronic pain management, and a change in opioid prescriptions may be expected.
- Understanding the impact of lockdown measures on opioid use is important for promoting optimal opioid prescription practices.

What this study adds:

- The study highlights an unexpectedly non-significant impact of the first COVID-19 lockdown in England on opioid utilisation pattern which could be multi-factorial.
- However, further investigation is needed using patient-level data to confirm this finding to ensure effective chronic pain management during the pandemic including optimal opioid prescribing through understanding whether the pandemic has impacted on incident opioid prescriptions to continue promoting the safe and effective use of opioids given the ongoing concerns around the negative impact of the lockdown on other clinical areas.

1. Introduction

Following the outbreak of the Coronavirus disease (COVID-19), the WHO recognised COVID-19 as a global public health pandemic in March 2020 [1,2]. People across the world were affected by COVID-19 adversely in different ways. The COVID-19 pandemic exacerbated pre-existing physical or mental pain, which has created new issues and challenges that could exacerbate chronic pain and affect chronic pain patients, especially due to stressors extending over many months [3-5]. People living with pain may also experience co-morbidities, such as depression and anxiety, which may have been inadvertently aggravated by the government's response to the COVID-19 pandemic. This is because lockdown measures left many patients struggling with increased levels of loneliness, as well as fewer opportunities for distraction or physical exercise [6]. Additionally, it is necessary to comply with the recommendations on non-pharmacological strategies to manage chronic pain, which includes weight loss and exercise where pertinent. However, the UK government's quarantine and lockdown orders resulted in the cancellation and/or postponement of all pain management services, including elective pain-related surgical procedures and patient visits [7]. This has resulted in significant inactivity and deconditioning for patients who depended on exercise programs or physical therapy as part of their pain management programme [8]. A failure to access pain management services and elective surgery may lead to more patients commencing opioid therapy to manage their pain, and consequently may lead to more patients relying on opioid therapy.

The recent trend in opioid use has resulted in a considerable increase in the number of publications analysing opioid prescription patterns including different parts of the UK at different time periods [9-11]. However, as mentioned, the recent of COVID-19 and its associated major life stressors, exacerbated by lockdown and other measures, has appreciably impacted on health care and social life in the UK. In addition, the national safety measures, including a reduction in surgery and pain clinics, may have exacerbated the opioid problem, leaving people living with chronic pain restricted access to non-opioid interventional therapy services and therefore increasing their reliance on opioid therapy. Consequently, an increased prescription trend in opioid prescribing could have been expected. We aimed to assess this by analysing the impact of the COVID-19

outbreak and first national lockdown in England in March 2020 on trends in opioid prescriptions. Understanding the impact of the lockdown and the pandemic-related safety precautions on opioid use is important if we are to promote best practice regarding opioid prescription in the future including the role of community pharmacists. In view of this, the objectives of this paper were to analyse opioid prescription patterns in ambulatory care in England and examine whether opioid utilisation has been impacted by the COVID-19 lockdown. The findings can potentially be used to suggest possible ways forward if needed.

2. Methods

2.1 Study Design and Data Sources

This analysis was based on a retrospective, cross-sectional study of the opioids dispensed in the primary care setting using England Prescription Cost Analysis (PCA) data, an aggregated, publicly available dataset. PCA datasets contain information about all prescribed medicines issued by GPs in the community in the UK, which includes medication's name, quantity, strength, and formulation [12]. Opioid utilisation was measured 12-months pre (March 2019-February 2020) and 12-months post the first national COVID-19 lockdown (April 2020-March 2021) including March 2020 when lockdown measures were enforced, equating to a total study duration of 25 months. This study included all of the opioid prescriptions that are indicated for pain management stratified into strong opioids (morphine, hydrophone, fentanyl, oxycodone, diamorphine, tramadol, tapentadol, methadone, buprenorphine, dipipanone, pentazocine, and pethidine) and weak opioids (codeine, dihydrocodeine, and meptazinol) based on the British National Formulary (BNF) classification [13]. Some methadone and buprenorphine preparations that are included in section 4.10 of the BNF are mostly used for opioids substitution therapy/opioid dependence [13]. Consequently, they were excluded as these preparations are unlikely to be prescribed for pain relief in the UK [15]. The study did not require ethical approval as we used publicly available datasets.

2.2 Study outcomes

The outcomes of the study were opioid utilisation trends pre and post the COVID-19 pandemic lockdown. Two utilisation metrics were used to measure the utilisation trends: the monthly number of opioids' items dispensed/1000 inhabitant and the monthly Defined Daily Doses (DDDs)/1000 inhabitant/day, stratified by total, strong, and weak opioids [14]. This was similar to the approach taken in previous research which highlighted distinct and different utilization patterns of strong and weak opioids giving differences in their use, efficacy and safety profile including issues of abuse, addiction, and dependence [15].

Firstly, the total number of opioids' items dispensed for England were calculated monthly during the study period using the PCA dataset. Subsequently, this figure was divided by the population size and then multiplied by 1000 in order to have a standard denominator to ensure that the demonstrated trends are not just an estimate of the annual variation in the population size. The UK Office of National Statistics was used to obtain a mid-year point population size estimate [16]. DDD/1000 inhabitant/day is an internationally well-recognised utilisation metric that seeks to overcome population variation when comparing and contrasting medicine use across countries [17]. DDDs is defined by the WHO as the assumed average maintenance dose of a drug per day

used for the drug's main indication in adults [18]. The DDD/1000 inhabitant/day was calculated by summing the monthly total dispensed amount (mg) for each opioid, adjusted by their assigned DDD value [19]. Subsequently, these values were divided by the estimated mid-year population size, multiplied by 1000 and divided by 30 days [16]. To calculate the total opioid amount in milligrams, each quantity of opioid dispensed was multiplied by its strength.

2.3 Data analysis

The utilisation trends were described using descriptive statistics. Absolute and relative percentage changes were used to present the changed in the utilisation trends over the study period. A segmented linear regression analysis of interrupted time series was performed to analyse the utilisation trends to obtain the average monthly changes in utilisation from March 2019 to March 2021 [20]. The regression coefficient results obtained from the analysis were presented, together with the p-value and 95% confidence intervals.

The baseline level (β0) and trend of utilisation during the pre-intervention period (β1), the level change immediately after the intervention (β2), and the change in the trend (β3) after the intervention were assessed and presented. The data analysis was conducted using Microsoft Excel (United States, California).

The following model was fitted for each individual outcome measure:

$$Y_t = \beta 0 + \beta 1 * \text{time} + \beta 2 * \text{COVID-19 lockdown intervention} + \beta 3 * \text{post the COVID-19 lockdown intervention} + et$$

Y_t is the outcome measure in months, and *time* here is a continuous variable indicating the time in months, starting from the observation period to the end of the study (from 1 to 25). The COVID-19 intervention is a binary variable indicating the time before and after the implementation of the COVID-19 lockdown, with a value of zero for all of the months pre-COVID-19, from 1 to 13, and a value of one for all of the months afterwards. The time after COVID-19 referring to the number of months after the occurrence of COVID-19, coded 0 before and (time-13) after COVID-19. et is the error term at time t, which indicates random variability that is not explained in the model.

3. Results

3.1 Monthly number of opioids' items dispensed per 1000 inhabitants

During the study period, 491.41 items of opioids were prescribed/1000 inhabitants, with strong opioids being the most frequently prescribed (340.2 prescriptions, 69.2%), followed by weak opioids (151.2 prescriptions, 30.8%).

Overall, there was a slight reduction in the trend in the number of opioids' items dispensed per 1000 inhabitants for total and strong opioids during the study period. However, a small increase in the trend was shown for weak opioids (Figure 1). The analysis indicated a slight reduction in the number of opioids' items dispensed per 1000 inhabitants for total opioids of -0.42 (2.12%) from 19.98 in March 2019 to 19.56 in March 2021, and for strong opioids of -0.44 (3.2%) from 13.9 to

13.45 at the same time points. For weak opioids, the analysis indicated a slight increase in the trend of 0.02 (0.33%). Nonetheless, the average monthly change in the number of opioids' items dispensed was nonsignificant for all three opioid types (total, strong, and weak opioids).

Prior to the first COVID-19 lockdown, there was an nonsignificant reduction in the baseline trend in the number of opioids' items dispensed for total (β1=-0.064, *p*=0.298) and strong opioids (β1=-.055, *p*=0.184), with a slight increase for weak opioids (β1=.009, p=0.667) (Table 1). Furthermore, there was an nonsignificant increase in the level immediately after the pandemic lockdown was implemented (β2), with an nonsignificant decline in the trend post the COVID-19 pandemic lockdown (β3) *(Figure 1, Table 1)*.

3.2 Number of DDDs per 1000 inhabitants per day

Over the study period, a decreasing trend in the DDD/1000 inhabitant /day for total and strong opioids was observed, with an increasing trend for weak opioids (Figure 1). For total opioids, the analysis indicated a significant reduction of -0.37 DDD/1000 inhabitant /day (-3.5%), from 10.34 in March 2019 to 10.03 (p=0.037) in March 2021. For strong opioids, there was a significant reduction of -0.4 DDD/1000 inhabitant /day (-6.18%), from 6.5 in March 2019 to 6.1 in March 2021 (p=0.006). There was a nonsignificant increase for weak opioids of 0.036% (0.92%).

Regarding the impact of the COVID-19 lockdown measures on the number of DDD/1000 inhabitants/day, there was an nonsignificant reduction in the baseline trend prior to the first lockdown (β1) for total opioids (β1=-0.028, *p*=0.363), strong opioids (β1=-0.027, *p*=0.186), and weak opioids (β1=-0.001, *p*=0.940). There was an nonsignificant increase in the level change immediately after COVID-19 lockdown measures were lifted (β2) for all opioid classes (β2=0.386, *p*=0.194), (β2=0.360, *p*=0.073), and (β2= 0.026, *p*=0.799) for the total, strong, and weak opioids, respectively. Moreover, there was an nonsignificant reduction in the trend post the first lockdown (β3) for total (β3=-.040) strong (β3=-0.029), and weak opioids (β3=-0.008) (*p*=>.05) *(Figure 1, Table 1).*

4. Discussion

4.1 Key findings

Unexpectedly, the study's findings showed an overall stable trend in the utilisation of opioids pre and post COVID-19 in England. There were decreasing trends in the number of opioids dispensed for all opioid classes; however, these were nonsignificant. In terms of the number of DDD/1000 inhabitants/day, there was a significant reduction in overall trends for total and strong opioids, and a nonsignificant increase for weak opioids. The findings suggest that, in both cases, there was a nonsignificant decline in the baseline trend, with an increase in the level immediately following the first COVID-19 shutdown. Subsequently, a return to the pre-pandemic trend after the initial disruption. The greatest changes were seen at months 12-13. We believe that this could potentially be due to patients' panic-ordering and stockpiling pain-relieving medicines due to concerns with the COVID-19 outbreak and its consequences including national lockdown. This could be clearly observed in published warning statements from several NHS health leaders in

England urging members of the public not to stockpile medicines with many pharmacies reporting being inundated by over-ordering of prescriptions [21]. The stable trends observed in our study could be due to multiple factors. Firstly, patient level data and information about the specific indication were unavailable in the PCA datasets. Consequently, we were unable to examine the trend between the existing and new (incident) patients to obtain more accurate data for opioid utilisation. Moreover, the guidelines and strategies that have been implemented with regard to opioid prescription in the UK to help regulate and minimize the harm from their use in chronic pain management may have had an impact [22-24]. Similar to our results, a published study in the USA showed no change in the prescribing of psychotropic medication during the early months of the COVID-19 [25].

Having said this, many countries during the pandemic, including the UK, introduced temporary measures such as relaxing the regulation on controlled substance prescription to avoid delays in accessing pain medication [26-28]. This enabled registered pharmacists to supply some controlled medications without a prescription as well as extend or vary the frequency of a dispensed drug [28,29]. Furthermore, similar to the US and Canada, the UK relaxed the regulations around telemedicine to promote its use as a first approach to initiating, evaluating and continue opioid prescription [30,31].In view of these relaxed regulations, along with the suspension of services including primary care and non-pharmacological pain management for existing opioid patients, an increase in opioid prescription might have been expected, although this may have been counterbalanced by fewer opioid-naïve patients receiving opioid prescription. The latter may have influenced the patterns we saw in our study.

Alongside this, since only emergency services were in operation during the pandemic, patients might have been reluctant to visit the emergency department for pain relief especially if worried about contracting COVID-19 in hospital and emergency attendances have declined since the start of the COVID-19 pandemic [32,33]. This may have led to fewer diagnoses of chronic pain and a subsequent reduction in the number of patients embarking on new opioid treatment resulting in the patterns we saw in our study. One study that analysed the opioid prescription trends in the US using patient level data reported a decline in total opioid prescription at the peak of the lockdown (late April 2020) followed by a return to the trend in opioid prescription at the pre-COVID-19 level [34]. The study also reported that 44% fewer patients initiated new opioid therapy during the COVID-19 period. Another study suggested that changes in prescribing behaviour and in the quantity of the drugs prescribed for anticipatory purposes for management of end-of-life symptoms were also made in order to reserve stock during COVID-19 [35]. However, the database we used only contains aggregated level data, and we were unable to specify the actual indications or distinguish between existing and new patients receiving opioid analgesics since patient level data is required for this.

The observed significant reduction in the number of DDD/1000 inhabitant/day compared with the nonsignificant change in number of opioids' items indicates a reduction in the dispensed quantity and/or strength despite a stable number of prescriptions. This might be due to prescribers' concerns over patients' safety from opioids' adverse events due to the limited/restricted access to the normal opioid monitoring practices imposed by the COVID-19 lockdown measures; however, the nonsignificant impact of COVID-19 lockdown, as indicated by the segmented regression analysis results, would suggest that the observed overall reduction in the number of DDD/1000

inhabitant/day is unlikely to be due to COVID-19 and associated lockdown measures but rather could be, at least partly, due to the impact of various strategies implemented the UK to optimise opioid use over the recent years; however, further research is needed to confirm this

In fact, with all these restrictions and challenges, patients on opioid prescriptions may have experienced a reduction in their pain medication supply, with possible negative outcomes for pain control, so switched to over-the-counter codeine preparations, high doses of the NSAID, or even illicit drug use, which may increase addictive behaviour, thus aggravating the opioid epidemic [36-39]. It might prove helpful to analyse the impact of COVID-19 on opioid-related deaths, as monthly data on drug-related deaths were unavailable when this study was performed [40]. We will be looking at this further along with the growing role of pharmacists to assist with healthcare building on their increasing role during the pandemic. This includes not only advice during the pandemic but also a greater role in the supply and use of medicines as well as vaccinations.

4.2 Implications

Our findings indicate important implications for future research. There is an opportunity to reinforce the surveillance system and appropriate monitoring measures to track opioid prescriptions involving patient data and detailed indications information in order to understand whether the COVID-19 pandemic has impacted on the opioid prescription trends or not, and so indicate areas for improvement. Further investigation of the opioid prescription trends related to both new and existing patients is needed to reconcile the findings and identify the patterns and trends among these two groups. Further studies could also expand the analysis to include regional variations and the remaining UK countries (Scotland, Wales, and Northern Ireland) to evaluate the impact on the UK as a whole, as each country has a different prescription pattern.

4.3 Strength and limitations

To the best of our knowledge, we believe this is the first study to estimate and quantify the impact of the COVID-19 pandemic on opioid utilisation using a segmented regression analysis. This was facilitated by the study focusing on opioid prescriptions over a 25-month period, i.e. 12 months either side of the pandemic, to predict a trend line for opioid prescription. This duration was beneficial as it gave us adequate time to investigate if COVID-19 and associated lockdown and other measures had affected prescribing volumes. However, we acknowledge that the study has limitations. Due to the lack of patient level information, it was impossible to establish whether the observed trends have been affected by changes in opioid prescription to new patients or not. Moreover, specific indications for prescribing opioids were lacking. Consequently, we could not specify if opioids were prescribed for non-cancer chronic pain vs. cancer pain. In addition, over-the-counter codeine products were not included in the study as the datasets we used included only prescription medicines in ambulatory care. Ideally, to separate the effect of the COVID-19 from other confounders that might have affected the opioid prescription pattern at the same time, the

impact of COVID-19 on the opioid prescription trends should be compared to a control group (the COVID-19-free group). However, COVID-19 has affected the whole world as well as all other type of medications and conditions. Consequently, it was impossible to choose a suitable control group.

We also acknowledge that we did not study regional variations because just showing geographic variation alone, without being able to assess the impact of all the patient-level factors that have been reported to influence prescribing pattern of opioids, would we believe be of limited value because based on the evidence from the literature and our previous research in this area, we do believe that there would be geographical variations in patient-level factors that could influence prescribing of opioids [15]. However, unfortunately, due to the lack of information on key patient-level factors in the PCA datasets used in our current study due to its aggregated-level nature, we could not perform further analysis to assess these factors in more detail as well as looking at continuation vs. new prescriptions. Other factors along with geographical variations could include i) population demographics such as proportion of elderly patients (>65 years old), female gender, smokers, obesity and socioeconomic status; ii) prevalence of pain-related comorbidities such as depression; iii) rural vs. urban geography; iv) variations in the accessibility, availability and quality of pain management services; v) variation in local pain treatment guidelines, formularies and extent of uptake/implementation of opioid-related strategies; vi) variations in COVID-19 spread and infection rates and the subsequent impact on accessing healthcare services [15]. Finally, It is worth highlighting that DDDs is only a unit of utilisation and does not necessarily correspond to the recommended therapeutic dose or the actual prescribed dose because the latter will be based on characteristics of individual patients such as age, body weight, ethnicity, and disease severity etc; hence the difference from DDDs. However, DDDs are a well-recognised standard international utilisation metric providing a rough estimate of drug use independent of price, strength and pack sizes enabling comparisons within different regions of a country or across countries [18]. Furthermore, due to the aggregated nature of the dataset and lack of information on patient-level daily doses, it was not possible to examine daily morphine milligram equivalent either."

5. Conclusion

The utilisation trend for all opioid classes has not changed significantly following the first COVID-19 lockdown in England. Our findings support the further monitoring and investigation of patient level data to explore the impact of the pandemic on opioid prescription and to continue promoting the safe and effective use of opioids.

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7. Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

8. Author' contribution

All authors have substantially contributed to the conception and design of the review article and interpreting the relevant literature and been involved in writing the review article or revised it for intellectual content.

Study conception and design: all authors; data collection and management: OS, AK, FA; data analysis and interpretation: ON, AK, BG ; manuscript writing and drafting: ON, AK; manuscript reviewing and revising as well as providing constrictive criticism and final approval: all authors

9. Ethics statement

Ethical approval and informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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