



Opioids in the United Kingdom: safety and surveillance during COVID-19

Vicki Osborne^{a,b}

Purpose of review

Opioid use is prevalent in the United Kingdom and prior to the COVID-19 pandemic it had been recognized that the safety of opioids was an important issue to be monitored by the UK medicines regulatory agency. With the emergence of COVID-19, this requirement has been even greater. This review was undertaken to determine the impact of the pandemic on safety and surveillance of opioids in the United Kingdom.

Recent findings

During the COVID-19 pandemic, the surveillance of opioids in the United Kingdom continued, although primary research was often conducted with data prior to the pandemic. Of those studies that were conducted while the pandemic was ongoing, access to opioids (or opioid substitution therapy) and the subsequent effect on patient safety was the main theme.

Summary

In the United Kingdom, changes in accessibility to the healthcare system and how healthcare providers operated during the COVID-19 pandemic may have had unintended consequences on use and safety of opioids, due to the shift in focus to preventing COVID-19 from overwhelming the healthcare system. The findings from this review support the need to continue surveillance in the United Kingdom, including the impact of the COVID-19 pandemic on opioid utilization and safety.

Keywords

COVID-19, opioids, safety, surveillance, United Kingdom

INTRODUCTION

The opioid crisis in the United States is ongoing and well publicized, with overdoses involving opioids contributing to over two-thirds (67.8%) of overdose deaths in the United States in 2017 alone (47 600 deaths in total) [1,2]. The United Kingdom has not seen the same levels of use as in the United States, though this does not mean safety of opioids is not an issue or should not be monitored. In 2017/2018, 12.8% of the adult population in England were prescribed opioids [3]. While this is a decrease in prescriptions from 2016, opioid use in general requires ongoing surveillance to ensure frequency of adverse events is not greater than anticipated and does not result in a negative risk–benefit profile [3]. This figure from the National Health Service (NHS) Business Services Authority also only accounts for prescribed opioids and does not consider use of opioids obtained without a prescription or illicit opioids such as heroin. In England, 1829 opioid-related deaths (including illicit opioids) were reported in 2017, with 815 opioid-related deaths

reported in Scotland the same year [4]. This represented a doubling on 2007 figures in Scotland and a 40% increase from 2007 in England [4]. Scotland has the highest drug-related death rate in Europe (17 per 100 000 in 2017) [5] and opioid deaths have increased further since 2017 (1021 deaths in 2018 [6] and 1092 deaths in 2019 [7]). In addition, codeine use increased five-fold between 2006 and 2017 in the United Kingdom, to 2456 prescriptions per 10 000 persons/year. Other opioid prescribing rates also increased during this period and following initiation, 14.6% of patients progressed to long-term use (defined as at least three opioid prescriptions issued within a 90-day period, or ≥ 1 opioid prescription lasting at least 90

^aDrug Safety Research Unit, Southampton and ^bSchool of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK

Correspondence to Vicki Osborne, PhD, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK.
Tel: +44 0 2380 408600; e-mail: vicki.osborne@dsrcu.org

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KEY POINTS

- Surveillance of opioids and their safety continued in the United Kingdom during the COVID-19 pandemic.
- Changes in health care during the COVID-19 pandemic may have had unintended consequences on use and safety of opioids.

days) in the first year [8]. It is acknowledged that this is a high proportion progressing to long-term use, though definitions of long-term use vary and other studies have focused on diagnostic outcomes such as opioid dependence instead [9].

The UK Medicines and Healthcare Regulatory Agency (MHRA) has recognized the importance of assessing the benefits and risks of opioid medications, with the launch of an Opioid Expert Working Group [10]. This group has already recommended that the labelling for opioid medicines must carry a warning that informs patients about the risk of addiction, which was accepted by the MHRA in April 2019 [11]. The MHRA also announced in September 2020 that additional, strengthened warnings were to be added to the patient information leaflets of all opioids about the risk of dependence and addiction [12].

Opioid surveillance varies among countries; the majority of countries have systems in place to monitor prescription and over the counter opioids, as with all licensed medications. Monitoring often examines prescriptions issued, adverse drug reactions and deaths due to overdose. Spontaneous reporting is the most frequently used method for monitoring adverse drug reactions, which relies on physician and patient reporting and is known to be subject to under-reporting [13]. In the United Kingdom, the yellow card system is used for capturing spontaneous reports, while in Europe these are reported to EudraVigilance [14,15]. Illicit opioid use is monitored primarily through surveys, such as the Crime Survey for England and Wales or the National Survey on Drug Use and Health in the United States [16,17]; however, routine surveillance may not be in place in all countries. Despite encouraging steps in recognizing the importance of opioid surveillance in the United Kingdom, the arrival COVID-19 in 2020 may have impacted monitoring plans. For several months, the NHS cancelled non-urgent services in an attempt to avoid overwhelming the health service, due to the rapid increase in COVID-19 cases. While a return to some services occurred later in the year, it is unclear how those using opioids (illicit or prescribed) were affected. In addition, with such an intense focus on COVID-19,

there remains a risk that opioid surveillance has been put to one side during the pandemic. Consequently, the aim of this review was to determine the impact of the COVID-19 pandemic on safety and surveillance of opioids in the United Kingdom.

SEARCH STRATEGY

A literature search was conducted in PubMed using the following search strategy:

[(Opioid) AND (UK OR United Kingdom OR England OR Scotland OR Wales OR Northern Ireland)] AND (Safety OR surveillance OR monitoring)

The search was restricted to publications between 1 August 2019 and 1 January 2021. In total, 307 articles were identified from this search. After screening titles and abstracts, 24 articles were reviewed for potential inclusion in the review, with a final focus on 10 original research articles as references of special interest. Other online resources were also used as references where appropriate.

SUMMARY OF ARTICLES PUBLISHED DURING THE REVIEW PERIOD

The review identified relatively few research studies that were conducted during the COVID-19 pandemic; several studies were conducted and published prior to the pandemic. One such study examined drugs associated with intentional overdose and found that risk of death was 12 times higher for opioids compared with nonopioid analgesics [18]. This study was conducted in the Republic of Ireland, rather than the United Kingdom, but provides useful statistics which inform on opioid safety in general. Another study examined the epidemiology of opioid use in the United Kingdom and the association with mortality [19], informing on opioid utilization and safety. A further study examined the benefit–risk profile of the buprenorphine implant for treatment of opioid dependence, conducted as part of the licensing application in Europe [20]. A favourable benefit–risk profile was observed [20] and the buprenorphine implant was approved for use in Europe in 2019 [21].

Other studies identified in the review were conducted prior to the pandemic and published during the pandemic time period. Several of these articles were not focussed primarily on opioids, but recognized the high prevalence of co-use with other drugs (e.g. gabapentinoids) and the importance of monitoring co-use [22]. Surveillance of treatment for substance use disorders (including opioid use disorder) and coprescription of other drugs was also examined [23], as were long-term outcomes for mothers of infants with neonatal abstinence syndrome [24].

Further articles were not specifically focused on surveillance in the United Kingdom but included UK data; for example, Layne *et al.* [25] examined nonmedical use of tramadol in several European countries.

Several opinion pieces and reviews were published during the COVID-19 time frame and specifically focused on the potential impact of the pandemic on opioid prescribing, safety and surveillance. While these articles do not contribute original research data, they provide useful insights in to the desire to continue opioid research during COVID-19. Some articles focused on opioids, substance use disorder and patient care during the COVID-19 pandemic [26–28], recognizing that services could be impacted by pressure on, or changes in, the healthcare system [29,30]. Since opioids are often used in end-of-life and palliative care, ensuring continued availability and effective use is vital given known morbidity and mortality with COVID-19. Further to these articles, 10 original research articles of special interest were selected for further detailed discussion in this review.

EFFECTIVENESS OF NOVEL OPIOID AND PAIN REVIEW SERVICES

An article published in February 2020 by Scott *et al.* [31[■]] evaluated a primary care-based opioid and pain review service using a mixed methods approach. In the United Kingdom, primary care refers to the management of patients with a general practice setting, which is where the majority of patients are managed unless they require specialist treatment. This study was conducted in two general practice practices in England between 2016 and 2017. In total, 34 patients enrolled in the novel service and a decrease in median prescribed opioid dose was observed from baseline ($P < 0.0001$). Improvements in health, wellbeing and quality of life were also observed [31[■]]. The authors concluded that the service was well received overall and appeared to have potential benefits, warranting further exploration of this care pathway through a randomized controlled trial. A further article published in February 2020 by Kesten *et al.* [32[■]] provided further results from the same general practice practices for 2017–2018. The findings from this article supported the conclusions from 2016 to 2017 [32[■]]. Appropriate pain management and support of patients prescribed opioids is critical to ensure effective treatment. The development of novel services within primary care, where most UK patients will be managed, is not only an important advancement but could potentially improve patient outcomes.

SURVEILLANCE OF OPIOID SUBSTITUTION THERAPY

A mixed methods analysis was conducted by Gibson *et al.* [33[■]] to examine safety incidents with methadone or buprenorphine as opioid substitution therapy in England and Wales, published in March 2020. The study itself was conducted between 2005 and 2015 and concluded that most risks from opioid substitution treatments arose from failures in care delivery processes [33[■]]. Specifically, these failures included insufficient or lack of patient supervision during dispensing, insufficient monitoring or communication with patients, and incomplete or inaccurate prescribing. Failures were reported to have occurred due to both attentional slips by staff members and poor working conditions (including overloading staff) [33[■]]. This evidence highlights the importance of well managed care to ensure patient safety during opioid substitution treatment, emphasizing that patient outcomes are not only dependent on the treatment prescribed but also the supportive care provided. A further article by Jones *et al.* [34[■]] was published in May 2020 and estimated the prevalence of opioid use disorder in England from drug-related mortality data in 2008/2009. This article outlined a method for linking drug treatment and administrative data to mortality registers, to estimate prevalence of opioid use disorder [34[■]]. Overall prevalence of opioid dependence was estimated to be 0.82%, similar to previously published data [34[■]]. Record linkage was also examined by Roberts *et al.* [35[■]] in an article published in November 2020. The authors sought to evaluate record linkage between treatment for substance misuse and inpatient hospitalizations in England [35[■]]. The study was conducted using data on substance misuse treatment from 2018 to 2019. Overall, the authors found that linkage to inpatient hospitalization records was possible for nearly 80% of the sample (total sample size = 268 251) [35[■]]. It was noted that both error and bias could affect results; however, the ability to conduct such linkage is important for studying associations between treatment and substance-related harm. Overall, the use of these novel methods for monitoring substance use disorder and patient outcomes can help identify the magnitude of these conditions in the United Kingdom. In addition, using pre-existing data is often more cost-effective than other surveillance methods.

SURVEILLANCE OF NONPRESCRIPTION CODEINE USE

In England, codeine containing products can be sold without a prescription in pharmacies (over the counter), though it is a requirement to consult with a pharmacist before purchase. In a qualitative study

by Kimergård *et al.* [36[■]], a sample of 27 participants from an addiction treatment service and an online survey in England were interviewed about experiences of tampering with codeine containing medicines. A total of 14 participants reported such tampering by cold water extraction to separate the codeine from other analgesic agents [36[■]]. Motivations for such behaviour included concerns about paracetamol (acetaminophen) overdose from excessive use [36[■]]. For those who also used heroin, reduced local heroin availability influenced tampering with codeine containing medicines to avoid opioid withdrawal. Restrictions on codeine sourcing in pharmacies also played an influential role [36[■]]. Overall, the study results support the assertion that such tampering should be considered in risk assessments for opioids. A study by Zhao *et al.* [37[■]] published in July 2020, examined designing effective warnings about addiction for the patient information leaflet provided with the packaging for nonprescription codeine products. Their efforts were specifically focused on targeting these warnings to university students and they gained feedback from participants. The study identified that 47% of 30 participating students felt there should be tight restrictions on regulation due to the addiction potential of codeine [37[■]]. Useful feedback on the design of these information leaflets was also obtained. Nonprescription codeine safety was also explored by Mody *et al.* [38[■]] within the context of developing a new educational safety card to be handed out at pharmacies. Twenty four pharmacies were involved in distributing this card between June and July 2020, during the COVID-19 pandemic, and recorded data on the impact of interactions with customers using the card [38[■]]. Specific to the COVID-19 pandemic, the authors noted that customer numbers in pharmacies may have been reduced during the study period and that pharmacies were selected taking into account the operational impact of COVID-19. Of 3993 interactions recorded, 5.5% of customers who were known to staff and frequently bought codeine products chose not to purchase any pain relief products, compared with 1.1% of unknown customers ($P < 0.0001$) [38[■]]. The card was found to be easy to use by staff and the majority of patients accepted the card when offered. The results of the study suggest that community pharmacists can be involved in behavioural change regarding purchasing codeine, which could assist in decreasing misuse [38[■]]. These studies highlight the potential risks of codeine containing products which are available to purchase without a prescription. They also highlight risk mitigation measures which could have valuable impact, such as new or revised educational materials and further educational intervention by pharmacists.

PRESCRIBING IN PALLIATIVE AND END-OF-LIFE CARE

Opioids are frequently prescribed in the United Kingdom as part of palliative and end-of-life care, to relieve pain and suffering. Research into the effect of the COVID-19 pandemic on these services is important to understand any changes in opioid use during this period, which could in turn influence patient comfort or safety. Antunes *et al.* [39[■]] conducted a survey in the United Kingdom and Ireland in April 2020 to investigate clinician experiences of changes in anticipatory prescribing during the COVID-19 pandemic and their recommendations for changes in process. Anticipatory prescribing occurs in advance of clinical need for symptom management at the end of life. April 2020 was a challenging period in the United Kingdom for health care, when the country was under lockdown and many nonessential health services had been suspended due to a surge in COVID-19 cases. There was a concern that the NHS would become overwhelmed unless COVID-19 cases decreased. Of 261 replies to the survey, 47% reported changes in route of administration during the pandemic [39[■]]. For example, it was noted that oral/buccal routes provide more control to the patient without the need for a healthcare professional (to administer injections) [39[■]]. Other findings included changes in the drugs prescribed (38%), with one participant noting an increase in off-label use, in addition to changes in the quantities of drugs prescribed (35%) [39[■]]. A specific comment was made that smaller quantities were being prescribed to preserve stocks [39[■]]. Overall, the results from this survey highlight changes in prescribing behaviour for opioids in the United Kingdom during the COVID-19 pandemic which may in turn have influenced both patient care and safety. The authors concluded that the effectiveness of such approaches needs to be researched, in addition to whether they would persist beyond the pandemic [39[■]]. Similar to the previous study, Alderman *et al.* [40[■]] examined end-of-life symptom control in COVID-19 patients in the United Kingdom. The audit was conducted in a hospital in England, over 8 weeks from March to May 2020, with a final sample size of 81 patients [40[■]]. They concluded that patients who die with COVID-19 have similar end of life needs to other end-of-life patients [40[■]]. Morphine was required in 34.5% of cases to manage shortness of breath [40[■]]. Both of these studies indicate that demand for opioids not only persisted but may have increased during the COVID-19 pandemic, due to use in end-of-life care. These findings further support the need for ongoing surveillance, to ensure both adequate supply and appropriate patient care.

CONCLUSION

During the COVID-19 pandemic, the surveillance of opioids in the United Kingdom continued, although primary research was often conducted with data prior to the pandemic. Of those studies that were conducted while the pandemic was ongoing, access to opioids (or opioid substitution therapy) and the subsequent effect on patient safety was the main theme. In the United Kingdom, changes in accessibility to the healthcare system and how healthcare providers operated during the COVID-19 pandemic may have had unintended consequences on use and safety of opioids, due to the shift in focus to preventing COVID-19 from overwhelming the healthcare system. The findings from this review support the need to continue surveillance in the United Kingdom, including the impact of the COVID-19 pandemic on opioid utilization and safety.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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