Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study

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Introduction

Over 20% of adults in the UK present to primary care with a musculoskeletal (MSK) condition each year [21]. Guidance from the World Health Organisation and the UK National Institute for Health and Care Excellence (NICE) suggest using opioids as part of a stepped approach to controlling MSK pain [16,30]. This advice advocates incremental increases from analgesics such as paracetamol to stronger analgesics such as opioids. Previous studies suggest approximately 50% of patients consulting with MSK pain will be prescribed an analgesic at first consultation [10,27], of which 29% will be prescribed an opioid within 2 weeks [29].

There is evidence that opioid use often continues long-term (>3 months) [3,43]. In some patients with chronic pain opioids have been found to be beneficial [12,31], but their use has been associated with potential harms including dependence, addiction, self-poisoning and bone fractures [9,37]. Increases in prevalent long-term opioid use between 1997 and 2005 have been highlighted in the USA, doubling to approximately 46 per 1000 individuals [3]. In the USA the use of opioids is under increasing scrutiny, and governmental measures have been enacted to deal with what is seen as an increasing epidemic of opioid use and abuse [32]. However the trends in long-term opioid use seen in the USA may not be reflected in other westernised countries due to differences in health care systems and prescribing guidelines. Two studies have shown substantial increases in UK primary care prescribing of potent opioids from 2001–2010. One using a regional (North Staffordshire) general practice database (Consultations in Primary Care Archive, CiPCA) found a doubling of potent opioid use (from 545 to 1032 per 10,000 registered population)[1], whilst a study using the national Clinical Practice Research Datalink (CPRD), found an increase in prevalence of potent opioid use from 1.8 to

9.2 per thousand registered patients [46]. However, none of these studies examined the changing patterns of new primary care prescribing of long-term opioids, and it remains unclear whether the frequency of starting patients on long-term opioids is changing given the guidance available. In particular it is not known whether doctors are using more opioids of all types for longer periods of time, and whether, in those patients prescribed long-term opioids, there is a trend in the opioid formulations used towards increasingly potent types. Less potent, non-controlled opioids can be bought over-the-counter, and opioids are prescribed in secondary care settings such as pain clinics or specialist opioid addiction clinics, but the predominant source of opioid prescriptions is primary care [7,35]. Understanding what is happening with respect to the prescribing of long-term opioids in primary care is important due to the potential adverse effects and abuse that has been seen in the USA [26].

The objectives were to examine changes in the incidence and length of episodes of long-term opioid prescribing for musculoskeletal conditions in primary care from 2002–2013, and assess whether the strength of opioids prescribed to long-term users has changed over that time.

Methods

This was an observational database study performed in the Clinical Practice Research Datalink (CPRD), a high quality anonymised database of routinely recorded information from general practices trained and assessed in their recording of information. The data comprise approximately 14 million patients with around 5.4 million of these being currently active, and registered in 660 primary care practices spread throughout the UK [20,40]. In England, 98% of the population are registered with a general practice [18,33], and it is in primary care that 90% of all National Health Service (NHS) contacts occur [15]. The practices that constitute CPRD offer a

representative sample of the UK population providing a comprehensive database of primary care prescribing, consultations and diagnostic coding which has been validated in previous studies [20,45]. For the purposes of future analysis, practices included were required to have linked Office for National Statistics (ONS), deprivation, and Hospital Episode Statistics (HES) data. Practices with linkage have been shown to be similar to CPRD practices without linkage on age, deprivation, body mass index, years of follow-up and prescription of drugs [13]. We also restricted this analysis to the 190 practices who continuously contributed to CPRD between 2002 and 2013. The denominator population was taken from currently active patients aged 18 and over in these 190 practices.

We identified patients aged 18 years plus, starting a long-term opioid (defined below) at the time of a recorded non-inflammatory potentially painful musculoskeletal condition in primary care. Visits to the primary care physician for musculoskeletal conditions were identified using previously defined Read codes taken from Chapters 1 (History and symptoms), N (Musculoskeletal), R (Symptoms) and S (injury) [19,21]. Read codes are a commonly used method of recording morbidity in UK primary care. The codes used in this study are available from the authors. Patients were included if the musculoskeletal visit occurred within a period lasting from 14 days before the initial opioid prescription, and up to 90 days following it. This was done in order to link the musculoskeletal problem to the prescription, since the opioid prescriptions considered were long-term and a painful musculoskeletal problem occurring within that time frame will be affected by it. Each participant was required to have at least 12 months of records in the CPRD database prior to the initial opioid prescription and have no record of cancer prior to the initial opioid prescription and up to 6 months after the initial opioid prescription.

Opioids were defined as analgesics used to relieve moderate to severe pain from sections 4.7.1 and 4.7.2 of the British National Formulary (BNF) [2]. The start of a long-term prescription of opioids was determined as the date of issue of an opioid prescription where the patient had not received any opioid prescription for at least a period of 6 months before this date. An episode of long-term use was defined as at least 3 opioid prescriptions issued within a 90 day period from the date of the new opioid prescription. An episode of long-term opioid use ended when there was a gap of six months or more without an opioid prescription. This definition is based on a classification of long-term opioid use that has been employed in previous studies [9,43]. The end date of a long-term opioid episode was set at 28 days following the issue of the last prescription for the opioid in keeping with local health authority guidance to set a maximum of a 28 day supply of medication per prescription and for schedule 2 and 3 opioids, no longer than 30 days [8,42]. In the UK, patients do not have to return to their primary care physician for every repeat prescription of their opioid, and can obtain them on a monthly basis from their medical practice using a doctor authorised repeat prescription service.

Opioids were grouped according to whether they were controlled or non-controlled drugs. The UK classification of controlled drugs, specifically schedule 2 and 3 of the misuse of drugs legislation [2,42], specifies which opioid analgesics are classified as controlled drugs and are subject to specific legal requirements when these drugs are prescribed. Opioids can be compared in potency by using their morphine equivalent dose (MED) which is the amount of morphine that achieves the same analgesic effect of the opioid in question. Controlled drugs are made up of the most potent opioid analgesics such oxycodone, where 1mg is equivalent to 1.5mg of morphine (i.e. 50% stronger than morphine). Non-controlled opioids include less potent opioids

such as codeine, where 1mg is equivalent to 0.15 mg of morphine. These opioids were then further stratified by determining if they were a short-acting analgesic (duration of effect 4 – 6 hours) or long-acting (minimum of 12 hours).

Statistical Analysis

The total number of patients receiving new episodes of long-term musculoskeletal-related opioid prescriptions from 2002 - 2013 was identified and the total number of such episodes as defined above determined for these patients.

Incident prescribing

Annual incidence of episodes of long-term opioid prescribing for musculoskeletal conditions was determined for each year from 2002 to 2013. The numerator was all patients starting a new episode of long-term opioids in that calendar year. The denominator population was person-years of all registered patients in a year not currently prescribed opioids. Annual incidence is reported per 10,000 person-years (with 95% confidence interval) stratified by age and gender. For the year 2013, the annual incidence is estimated from the data of the first 9 months as the data for 2014 required to determine new episodes of long-term prescribing for the fourth quarter of 2013 was not available at time of analysis. We also determined the percentage of episodes lasting more than 1 year, and the percentage lasting more than two years, stratified by year of start of episode.

We also determined annual incidence standardised to the age-gender distribution of the England 2013 population. Standardised figures were very similar to unstandardised figures, hence we only reported unstandardised figures here.

To determine points of change in trends, we determined the quarterly incidence of long-term opioid prescribing (per 10,000 person-quarters). The quarters were

defined on a seasonal basis from the first quarter of 2002 (comprising January, February and March) to the third quarter of 2013 (July, August and September). Quarterly incidence figures were seasonally adjusted (using multiplicative model, seasonal decomposition function, SPSS 21). Joinpoint regression was used to identify quarters where a statistically significant change (the 'joinpoint') in the underlying trend in opioid prescribing occurred [11,22,28]. The date of these joinpoints can then be matched to dates of external influences such as prescribing guidelines. This does not confirm that the change is linked to these influences but would suggest some influence on prescribing. If no joinpoints are identified, this would indicate no significant change in the underlying trend in prescribing between 2001 and 2013. Permutation tests using Monte Carlo methods were used to determine the minimum number of joinpoints required to provide an adequate fit to the data. The analysis started with the minimum number of joinpoints, and tested whether one or more joinpoints were statistically significant (p value < 0.05) and should be added to the model (up to five joinpoints). Models were fitted using the joinpoint regression program (version 4.1.1) [28] and the best-fitting model was chosen.

Subgroup prescribing

We determined the percentage of people prescribed each type of opioid (long or short-acting, controlled or non-controlled) at the initial opioid prescription and within 90 days of the start of the episode. Likewise we determined for those still in a long-term opioid episode, the percentage of patients prescribed each type of opioids 1 to 2 years, and more than 2 years after their episode start. If a patient was prescribed more than one type of opioid we used the highest ranking opioid based on the following order (highest to lowest): controlled long-acting opioid (group 4), controlled

short-acting opioid (group 3), non-controlled long-acting opioid (group 2), non-controlled short-acting opioid (group 1).

Sensitivity analysis

A sensitivity analysis was carried out also including practices which joined or left CPRD between 2002 and 2013 to determine if changes in the practice profiles influenced the findings.

Analysis was performed using STATA MP 13.1 and SPSS 21.

Results

The denominator population varied from 1,253,300 in 2002 to 1,379,217 in 2011, but the age and gender structure remained largely consistent (Appendix 1). Between 2002 and 2013, 76,416 patients with a potentially painful musculoskeletal consultation were identified as starting at least one episode of a long-term opioid. In total, 84,184 episodes were identified, with 57,171 (67.9%) being completed episodes by the end of 2013. Uncompleted episodes were either due to end of patient's registration or end of study follow-up. The median episode length was 227 (IQR 98, 673) days. This will be an under-estimate as it includes the 32% of episodes that were not completed. The annual incidence of long-term opioids for patients with musculoskeletal conditions increased by 38% from 2002 (incidence 42.4 per 10,000 person-years) to 2009 (58.3/10,000) and then remained approximately stable until decreasing slightly in 2012 and 2013 to levels which were just below those in 2009 (55.8/10,000) (Table 1). Joinpoint regression analysis indicated the levelling out of the increasing trend started in the fourth quarter of 2008 and the slight decrease in incidence started from the third quarter of 2011 (Figure 1).

Females and those in the older age group (≥ 65 yrs) were more likely to start new episodes of long-term opioids but trends over time were similar across gender and age groups (Table 1). 42.3% of those starting a new long-term opioid prescription in 2002 were in that episode for more than a year, decreasing to 38.8% by 2012, and 28.6% for more than 2 years which remained consistent over time (Table 2).

Subgroup prescribing

In 2002, 96.9% of all first prescribed opioids at the start of a long-term opioid episode were short-acting less potent non-controlled opioids. This decreased slightly to 95.7% by 2013 with the percentage prescribed long-acting more potent controlled opioids at their initial prescription increasing from 0.7% to 2.8% (Table 3). Between 2002 and 2013, the percentage of people who received a controlled long-term opioid within the first 90 days of their long-term episode increased from 2.3% to 9.9%. By 2013, 14.7% of people who had been in an episode between one and two years were receiving long-acting more potent controlled opioids, compared to only 4.0% in 2003. 22.6% of patients in a long-term episode for more than two years were being prescribed long-acting more potent controlled opioids in 2013, compared to 3.5% in 2004. Females aged 65 and over were prescribed more long-acting potent controlled opioids within 90 days of initial start of a new episode (Figure 2), but there was little variation by age if episodes lasted more than 1 year (Figure 2).

Sensitivity analysis

Including practices which joined or left CPRD during the study period (*n*=360) in the analysis gave similar trends to the analysis restricted to those practices continuously contributing to CPRD.

Discussion

To our knowledge, this is the first study outside of the USA to demonstrate an increase specifically in the prescribing of long-term opioids from 2002 to 2009. However, uniquely, we also observed a smaller gradual decrease between 2011 and 2013 to levels similar to those in 2009. Over the 11 years of the study there was increased prescribing of the more potent controlled and long-acting, long-term opioids. Additionally, for the first time, we have found that there was also an increase in use of more potent controlled and longer-acting opioids early on in a patient's long-term episode, and over a fifth of patients who had been on opioids for more than 2 years were being prescribed more potent controlled long-acting opioids by 2013.

The increase in incidence of long-term opioids between 2000 and 2009 matches the increasing trend in the prevalence of opioid use among chronic non-cancer pain patients in the USA between 1997 and 2006 [3,34], and in more potent controlled opioids in the UK [46], although these studies were not restricted to patients with potentially painful musculoskeletal conditions. Chevalier et al. showed that from 2006 - 2011, 1 in 5 UK opioid users were prescribed them chronically (>183 days of continuous use), and that over the period of their chronic use the amount they used decreased, but they did not examine in detail trends over time in prescribing and looked at the whole population rather than specifically patients with painful MSK conditions as in this study [5]. The increased use of long-term opioids may reflect beneficial effects in terms of helping patients with their long-term painful condition, for there is some evidence that they can help in some patients [12,31]. Indeed guidelines suggest using opioids if alternative prescribing strategies have failed which might prompt doctors to use opioids in patients where pain has been difficult to control [16,30]. However, the increasing incidence of long-term opioids prescribing

started slowing down shortly after the introduction of the NICE guidance on management of osteoarthritis (February 2008) when the recommendation was to use opioids only after weaker analgesia had been tried. Shortly after the USA Government's Office of National Drug Control Policy guidance (April 2011) [32], the incidence of long-term opioid prescribing in the UK started to gradually decline to the same levels as those in 2009. The increased use of opioids over the previous decade in the USA and an apparent increase in abuse of long-acting opioids had led to this USA initiative [26]. Whilst any direct connection of the USA guidance to prescribing in UK cannot be determined here, it is possible its message and the well documented increase in opioid prescribing in the US [26] may have had some 'spill over' effect through the medical media into the UK.

Since 2013, initiatives in the UK have recommended action to underpin regulations designed to improve monitoring and use of controlled drugs such as strong opioids [4,6]. However it would appear from this study that nationally from 2011 primary care physicians had already acted to reduce their use of new opioids, but where opioids were being prescribed, the shift towards using the more potent controlled and long-acting opioids continued. The increased use of controlled opioids is in keeping with the findings of other European studies [17,36,46]. Whilst less potent non-controlled opioid prescriptions still make up the majority of initial prescriptions for opioids, it was evident that primary care physicians did change to the more potent controlled opioids even within the first 90 days of a long-term episode. Those on more potent controlled opioids, either short-acting or long-acting, are of the greatest concern in relation to prescription opioid drug abuse. Our results show that a quarter of patients starting long-term opioids will still be on them more than 2 years later, and over a fifth of these will be on long-acting controlled prescriptions, raising concerns about the

potential for abuse and addiction amongst this group of users. Guidelines that are now being incorporated into normal practice [4,6] need to ensure clear messages around appropriate use of opioids, including the correct dosage and indications for continued use. Regular review would also ensure that opioid use is only continued when necessary reducing the potential for addiction and side effects.

Those in the older age groups had higher rates of long-term opioid prescribing and of stronger opioids early on in these episodes. A higher rate of opioid use in older age groups has also been found in other studies [14,36,46]. This group pose a dilemma for clinicians, as they are at increased risk of side effects [9,37], and hence the clinically rational approach would be to use less potent opioids in these patients. However they are more likely to be affected by severely painful musculoskeletal conditions [21], and are more likely to have adverse effects from alternatives, such as NSAIDs [23]. Females had higher rates of new prescriptions for long-term opioids compared with males. This is also consistent with other work [3,34,36], and may reflect the higher prevalence of painful musculoskeletal conditions amongst females [21].

This study used a novel method to identify opioid subgroups using the classification according to the UK Misuse of Drugs Act schedule of controlled drugs [41]. We did not use morphine equivalent dose (MED) or daily defined dose (DDD) [44] as has been used in previous studies [17,46], but this classification allows direct comparison of less potent (non-controlled) opioids with the more potent controlled opioids of schedule 2 and 3 that are of major concern for prescribers and regulating bodies in terms of the potential for abuse of long-acting opioid medications [4,6]. Opioids cannot be directly marketed to patients in the UK, unlike in the USA where marketing may have influenced increases in use of long-term opioids [39]. Management of

established abuse and addiction is included in UK guidelines which clearly define the prescribing of pharmacological interventions to treat addiction [7]. These strict criteria, which often require the use of specialist services, predetermine opioid use and will have some bearing on the opioid prescribing we have described. However, within the opioids examined here, methadone (an opioid primarily used in the UK as a substitute in opioid withdrawal) was not included as one of the opioids we examined for this reason.

An advantage of our study was that all prescribing is recorded in CPRD at the point of medication issue in the visit to the primary care physicians, and all repeat prescriptions of these drugs are recorded automatically so there is unlikely to be any missing opioid data. We examined only patients who had potentially painful musculoskeletal conditions and our findings may not be generalisable to opioids prescribed for other conditions, such as pain in cancer, or neuropathic pain. However amongst patients reporting chronic pain, there are comparatively few with neuropathic pain [38]. Some error in under-recording or coding of musculoskeletal conditions might have occurred leading to an underestimation of opioid use. However, historically GPs in practices contributing to CPRD have been required to enter morbidity codes at a minimum for a new diagnosis or when treatment has changed, therefore the majority of new prescribing of opioids in consulters should have been identified [24]. It is possible not all the opioids within an episode were prescribed for the initial musculoskeletal condition.

This analysis relates to information on all patients prescribed opioids, and not just those with health insurance as in studies from the USA, thereby making the results more generalisable to westernised populations outside of the USA. Accordingly, the increasing use of long-acting stronger opioids in patients on long-term opioids

indicates the continuing need to promote vigilance regarding the ongoing use of opioids amongst patients with MSK conditions in Europe and further afield. While the overall prescribing of opioids for musculoskeletal conditions has reduced in the most recent years, in the light of recent evidence suggesting lack of effectiveness of paracetamol for knee and back pain [25], doctors may in the future change their prescribing habits again in an attempt to help their patients' MSK pain, possibly driving a further increase in the prescribing of opioids. Monitoring with regular review and assessment of analgesic needs in the patients receiving opiates might reduce the potential for their abuse as well as helping to determine their effectiveness in controlling chronic pain. Further research to determine if such changes are being implemented will be required in the future.

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Figure captions

Figure 1. Quarterly incident prescribing of long-term musculoskeletal-related opioids

Figure 2. Percentage of patients receiving long-acting controlled opioid prescription by age, gender and length of time in episode