Risk of adverse events in patients prescribed long-term opioids: a cohort study in the UK Clinical Practice Research Datalink

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Significance: Long-term opioid use is associated with serious adverse events such as major trauma, addiction and overdose. The risk increases with higher opioid doses. Opioid prescribing should be reviewed before long-term use becomes established, and periodically thereafter to assess on-going effectiveness.

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Abstract

Background: Long-term opioid prescribing for musculoskeletal pain is controversial due to uncertainty regarding effectiveness and safety. This study examined the risks of a range of adverse events in a large cohort of patients prescribed long-term opioids using the UK Clinical Practice Research Datalink.

Methods: Patients with musculoskeletal conditions starting a new long-term opioid episode (defined as ≥3 opioid prescriptions within 90 days) between 2002-2012 were included. Primary outcomes: major trauma and intentional overdose (any). Secondary outcomes: addiction (any), falls, accidental poisoning, attempted suicide/self-harm, gastrointestinal pathology and bleeding, and iron deficiency anaemia. 'Control' outcomes (unrelated to opioid use): incident eczema and psoriasis.

Results: 98,140 new long-term opioids users (median age 61, 41% male) were followed for (median) 3.4 years. Major trauma risk increased from 285 per 10,000 person-years without long-term opioids to 369/10,000 for a long-term opioid episode (<20mg MED), 382/10,000 (20-50mg MED), and 424/10,000 (≥50mg MED). Adjusted hazard ratios were 1.09 (95% CI, 1.04, 1.14 for <20mg MED vs. not being in an episode of long-term prescribing), 1.24 (95% CI, 1.16, 1.32: 20-50mg MED) and 1.34 (95% CI, 1.20, 1.50: ≥50mg MED). Significant dose-dependent increases in the risk of overdose (any type), addiction, falls, accidental poisoning, gastrointestinal pathology, and iron-deficiency anaemia were also found.

Conclusions: Patients prescribed long-term opioids are vulnerable to dose-dependent serious adverse events. Opioid prescribing should be reviewed before long-term use becomes established, and periodically thereafter to ensure that patients are not being exposed to increased risk of harm, which is not balanced by therapeutic benefit.

Introduction

Internationally, the use of prescribed opioid analgesics has increased substantially (Manchikanti et al., 2010; Zin et al., 2014; Bedson et al., 2016; Foy et al., 2016; Farias et al., 2017). Most opioid prescribing is for non-cancer pain and painful chronic musculoskeletal conditions account for two-thirds of long-term opioid prescribing (Ray et al., 2016). In UK primary care, 20% of adults consult with a musculoskeletal problem annually (Jordan et al., 2010). There was a 41% increase in patients with musculoskeletal pain prescribed opioids long-term (≥90 days) in the UK between 2002-2011. The proportion of these patients who were prescribed stronger, long-acting opioids rose from 4% to 23% between 2002-2013 (Bedson et al., 2016).

Long-term opioid prescribing for musculoskeletal pain is controversial due to uncertainty regarding effectiveness and safety. Evidence for the long-term effectiveness of opioids from randomised placebo-controlled trials is lacking (Chou et al., 2015). A recent trial with 12 months follow-up found opioids were no more effective than non-opioid analgesics for chronic back pain and osteoarthritis (Krebs et al., 2017). However, limited evidence from open-label studies (Hauser et al., 2015), combined with clinical experience and expert consensus, suggests some patients may benefit from opioids in a multifaceted pain management strategy (O'Brien et al., 2017).

A Cochrane review reported significantly increased risks of a range of adverse events (including constipation, nausea, pruritus, dizziness, and drowsiness) with medium and long-term opioid use in chronic non-cancer pain (Els et al., 2017). Additionally, there was a paucity of follow-up data beyond 13 weeks and a lack of

important adverse events reporting, including overdose and addiction, and on their association with opioid dose. United States (US) observational studies report associations between long-term opioid use and serious adverse events including bone fractures and overdose (Dunn et al., 2009; Saunders et al., 2010). Solomon investigated adverse events in opioid users in the USA between 1996-2005 and found that some, including fractures and all-cause mortality were potentially related to the opioid agent (Solomon et al., 2010). A US study reported increased risk of all-cause mortality during the first 180 days of therapy in patients prescribed opioids versus anticonvulsants and low-dose tricyclic antidepressants for chronic pain (Ray et al., 2016). However, since these findings are restricted to subgroups of patients within the US healthcare system, their generalisability is uncertain.

We aimed to address the limitations of existing evidence by investigating a broad spectrum of adverse events potentially associated with prescribed long-term opioids in a large UK primary care electronic heath record database, and to determine how any increased risks varied by opioid dose prescribed.

One potential limitation of using observational data to investigate the risks of long-term opioids is confounding by indication. To reduce the risk of confounding we have set our study within a population of patients with painful musculoskeletal conditions and included only patients who have ever been prescribed opioids long-term. Our assumption is that these were all patients for whom their GP had considered that opioids were a potentially appropriate analgesic and not contraindicated for long-term use. We compared adverse events during episodes of long-term prescribing to adverse events during time periods where these patients were not prescribed long-term opioids, adjusting for important covariates and including ‘control’ outcomes.

Methods

Database

This was a cohort study performed in the Clinical Practice Research Datalink (CPRD), an anonymised database of routinely recorded information from UK general practices. The population included in CPRD is representative of the UK population on age, gender and ethnicity, and validation studies generally show high levels of positive predictive values of diagnosis codes (Herrett et al., 2010; Herrett et al., 2015). CPRD comprises information from over 20 million patients registered in more than 650 primary care practices spread throughout the UK (Williams et al., 2012; Tate et al., 2014). In the UK, the vast majority of the population are registered with a general practice, and it is here that 90% of all National Health Service (NHS) contacts occur (Gregory, 2009). Practices included in our analysis (n = 350, all from England) were required to have linked Office for National Statistics (ONS, for mortality information), Hospital Episode Statistics (HES), and Index of Multiple Deprivation (IMD, neighbourhood deprivation) data (Department for Communities and Local Government, 2010). Practices with and without linkage have been shown to be similar in respect of demographic data, years of follow-up, and prescribing (Gallagher et al., 2011).

Cohort identification

Cohort participants were those aged 18 years and over, starting a new long-term opioid episode at the time of a recorded non-inflammatory, potentially painful musculoskeletal condition between 2002 and 2012, as described previously (Bedson et al., 2016). Patients were included if a visit for a musculoskeletal condition occurred within a period starting 14 days before the initial opioid prescription, and up

to 90 days following it. This timeframe was chosen as it generated a temporal association between the musculoskeletal problem and the prescription, such that any painful musculoskeletal problem occurring within that time frame would potentially be affected by the opioid.

Musculoskeletal conditions were chosen because they are a common reason for patients consulting in primary care, are associated with chronic pain in the majority of cases (Woolf et al., 2004) and represent the commonest causes of chronic non-cancer pain (Breivik et al., 2006). Regular opioid use is more common in this group (Hudson et al., 2008) and chronic non-cancer pain accounts for the majority of the escalation in strong opioid prescribing (Zin et al., 2014).

Musculoskeletal conditions were identified using previously defined Read codes taken from Chapters 1 (History and symptoms), N (Musculoskeletal), R (Symptoms), and S (Injury) (Jordan et al., 2010). Read codes are a hierarchical coded thesaurus of clinical terms used for recording morbidity in UK primary care (NHS Digital, 2018). The codes used in the current study are available at www.keele.ac.uk/mrr/morbiditydefinitions/ . Each participant was also required to have at least 12 months of records in the CPRD database before the initial opioid prescription, and have no record of cancer diagnosis prior to the initial opioid prescription and up to 6 months after the initial prescription.

Long-term opioid use

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) (BNF, 2017). The start of an episode of opioid prescribing was defined as the date an opioid prescription was issued for a patient who had not received an opioid prescription

within the previous 6 months. Long-term opioid prescribing was defined as the issue of at least 2 further opioid prescriptions within the 90-day period following the date the new opioid prescription was issued (i.e. at least 3 opioid prescriptions in total within 90 days). An episode of long-term opioid prescribing ended if a period of 6 months elapsed without an opioid prescription. This definition is based on a classification of long-term opioid use that has been employed in previous studies (Von Korff et al., 2008; Dunn et al., 2010). The end date of a long-term opioid episode was defined as the date 28 days following the issue of the last opioid prescription, in keeping with local health authority guidance setting a maximum of 28 days supply of medication per prescription (Dowd, 2011). An individual patient may therefore have had multiple episodes of long-term opioid prescribing over the study period.

Average daily dose

Daily morphine equivalent dose (MED) is an accepted method of assigning a standard value for the dose of the many different opioids based on tables of their relative potency compared to morphine. The MED for each opioid medication was obtained by using a conversion factor for morphine equivalence shown in table 1, and detailed morphine equivalence sources are available at https://www.keele.ac.uk/mrr/morbiditydefinitions/ . The MED for a single prescription was calculated by multiplying the quantity of medication prescribed by the conversion factor. With respect of long-acting opioid patches (e.g. buprenorphine, fentanyl), the total MED for the patch was calculated by firstly determining the 24-hour MED using the appropriate conversion factor to determine the amount released per hour multiplying by 24, and then by the number of days the patch was prescribed

for use (e.g. 4 or 7 days). Total morphine equivalent dose (total MED) in a long-term opioid episode was calculated by adding the MEDs for each prescription dispensed during the episode. Average daily morphine equivalent dose (average daily MED) prescribed was the total MED for a long-term opioid episode divided by episode duration in days. In those participants, where an outcome of interest occurred within a long-term opioid episode, average MED was calculated only for the period before that outcome occurred, in order to minimise the influence from a potential prescribing change due to an outcome event.

Table 1 here

Average daily dose for each long-term opioid episode was grouped into 3 categories (< 20mg MED; ≥ 20 & < 50mg MED; ≥ 50mg MED) adapted from a previous study (Dunn et al., 2010).

Follow-up

Cohort participants were followed up from the date 90 days after the initial opioid prescription in their first long-term opioid episode until the study end date (10th January 2012) or the date the patient no longer contributed data (due to leaving the practice, the practice leaving CPRD, or patient death), whichever occurred earlier.

Outcome measures

As primary outcomes we examined two adverse events with some previous evidence of an association with long-term opioid use in studies within selected healthcare populations in the US: namely major trauma (Saunders et al., 2010) and intentional overdose (opioid or other) (Dunn et al., 2009)

We defined major trauma as a bone fracture, joint dislocation, ligament or tendon rupture, or head trauma (including subdural haemorrhage). Read code examples of opioid overdose included ‘self-poisoning with an opioid’, and non-opioid overdose ‘self-poisoning with a hypnotic’. It was not possible to determine if the codes used related to fatal or non-fatal overdoses.

Secondary outcomes were attempted suicide/self-harm (excluding overdose), incident addiction (opioids), incident addiction (other type), falls, accidental poisoning, newly diagnosed gastrointestinal pathology (inflammatory or erosive, e.g. ‘peptic ulcer’), gastrointestinal bleeding (gastric and non-gastric bleeding), and new diagnosis of iron deficiency anaemia (potentially occurring because of gastrointestinal bleeding). Accidental poisoning was coded per se, since all Read codes used to identify this type of outcome specifically state ‘accidental’ e.g. accidental poisoning by other tranquillisers (Code T83yz). All other self-poisonings or overdoses were then classified as intentional, since CPRD GPs are trained to use appropriate codes for the problem being documented, and where self-poisoning was ‘accidental’, this would be labelled as such, leaving other codes inherently as intentional. This list includes adverse events where limited evidence of an association with long-term opioid use currently exists (Els et al., 2017), and where recognised side effects of opioids such as delayed gastrointestinal motility, confusion, dependence, drowsiness, dysphoria, postural hypotension, vertigo and visual disturbances, make an association feasible (BNF, 2017). Additionally, abdominal pain is a reported adverse effect from using the opioid codeine phosphate (BNF, 2017), and reports of anaemia have been recorded by the US FDA Adverse Events Recording System in users of opioids such as codeine (eHealthMe, 2017).

We therefore included gastrointestinal pathologies which can cause both abdominal pain and anaemia to investigate any association with opioid use.

We also included two dermatological control outcomes, new diagnosis of eczema or psoriasis, that theoretically should have no relationship with long-term prescribed opioids. These act as 'negative controls' to identify possible sources of bias (e.g. due to unmeasured confounding) (Lipsitch et al., 2010, Arnold et al., 2016). Our hypothesis was that failure to identify an association of long-term opioid prescribing with these control outcomes would increase confidence that any associations found for the primary and secondary outcomes are less likely to be due to possible sources of bias.

Outcomes of interest were the first recording of these adverse events within the follow-up period. Outcomes were analysed separately so an individual patient could have multiple different adverse events. All potential adverse events were identified through Read Codes in CPRD and Read Codes mapped to ICD-10 codes in the linked HES dataset, or where relevant through the linked ONS dataset for events ending in mortality. All relevant adverse event codes (available from https://www.keele.ac.uk/mrr/morbiditydefinitions/) appropriate for the analysis were identified through a consensus exercise by two academic primary care physicians (JB and RAH), experienced in identifying database codes. An incident event or new diagnosis was defined as a record made during the follow-up period with no such record during the 15 months prior to start of follow-up (365 days prior to initial opioid prescription to 90 days after).

Covariates

Possible confounding covariates were identified. Prior occurrence of adverse events, except for those where the outcome was defined as an incident event or new diagnosis, were identified in the 15-month period prior to start of follow-up.

Smoking and alcohol information were classified as ever, never or missing based on data prior to start of follow-up date. The missing category was included to maximise numbers in analysis. BMI value used was the record at the closest date before the start of follow-up, and was grouped into <25 kg/m2, ≥25 kg/m2 (overweight) or missing.

Geographical region was grouped as London, South of England, Midlands and East of England, and North of England. Deprivation level, based on the Index of Multiple Deprivation 2010 [Department for Communities and Local Government], was categorised based on quintile score (1 least, 5 most deprived). The deprivation measure is an ecological indicator based on area of residence, covering seven aspects of neighbourhood deprivation including income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime, and living environment.

Depression has been linked to use of opioids in studies from the US (Scherrer et al., 2013; Scherrer et al., 2015; Scherrer, et al., 2015a,). We identified prior recorded depression in the 15 months prior to start of follow-up.

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of gastrointestinal adverse events (Lanza et al., 2009), therefore co-prescribing of a NSAID was identified using prescription data for the 4 months prior to follow-up start (to ensure any potential clinical NSAID-related adverse events that might

manifest themselves for up to 90 days after finishing a prescription of NSAID, usually issued for 28 days, could be taken into account).

The total number of prescriptions for drugs recorded under different BNF sections in the 15-month period prior to start of follow-up was used as a surrogate measure of the number of co-morbid conditions at baseline (Perkins et al., 2004).

Statistical analysis

The rate of each of the adverse events per 10,000 person-years at risk were determined during follow-up, stratified by whether or not they occurred during an episode of long-term opioid prescribing, and by average daily dose during a long-term opioid episode.

Patients were followed up from 90 days after their initial opioid prescription in their first long term episode. For subsequent new opioid prescribing episodes, the first 90 days was used to determine long-term opioid prescribing status according to our definition of ≥3 prescriptions in the first 90 days and this 90-day period was therefore excluded from the analysis of adverse events. Patients with an adverse event in that 90 days were censored at time of initial opioid prescription for that episode. Proportional-hazards modelling was used to compare the risk of adverse events occurring during episodes of long-term opioid prescribing with the risk of adverse events occurring during episodes when long-term opioids were not being prescribed. Long-term opioid prescribing and average daily dose were treated as time-dependent exposures. Patients were categorised as either currently being in a long-term opioid episode or not currently being prescribed opioids. In those within a long-term episode, patients were further categorised based on average daily dose (< 20mg MED; ≥ 20 & < 50mg MED; ≥ 50mg MED). Separate models were performed

for each adverse event and for each of the two exposures (long-term episode status and average daily dose).

Cox regression was used to produce both unadjusted and adjusted hazard ratios (HRs) for each outcome separately, estimating the excess risk of each adverse event associated with long-term opioid prescribing. The validity of the proportional-hazards assumption was tested using Schoenfeld residuals and deemed adequate for the exposure variables of long-term opioid prescribing and average daily dose. Age at baseline, gender, year of start of follow-up, ever smoking, ever alcohol drinking, overweight (BMI ≥25kg/m^2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID, and total number of co-morbid conditions were included as baseline covariates in the final model. For the outcomes of major trauma, falls, intentional overdose (opioids and non-opioids separately) and accidental poisoning, baseline previous events were also included in the final model. For the outcomes of incident gastrointestinal conditions and bleeding, iron deficiency anaemia, addiction (opioids and non-opioids separately), eczema and psoriasis, patients with a previous event in their records were excluded from the analysis. We further stratified analysis by gender.

A sensitivity analysis excluded patients with missing data on covariates. Analysis used Stata14.1.

Results

98,140 patients were prescribed long-term opioids during the study period. The median age (at start of follow-up) was 61 years, and 41% were males. Baseline characteristics are given in Table 2. Patients were followed for a median of 3.4 years (IQR 1.6, 5.8).

Risk of adverse events in long-term opioid users

Table 2 here

106,818 long-term opioid episodes were identified during the study period. The median length of long-term opioid episodes was 237 days (IQR 103, 658). This may be an underestimate as it includes the 27.4% of episodes that were not completed by the end of follow-up. Within long-term opioid episodes, the median average daily dose of opioid prescribed to patients was 12.3 mg MED (IQR 7.1, 20.3 mg MED) (Table 3).

Table 3 here

Increased risks for major trauma and overdose (of both non-opioids and opioids) were found during episodes of long-term opioid prescribing, compared to periods when long-term opioids were not prescribed. Furthermore, higher risks were associated with a higher average daily MED. For example, risk of major trauma increased from 285/10,000 person-years at risk in periods when long-term opioids were not prescribed to 369/10,000 (average daily dose of <20mg MED), 382/10,000 (20-50mg MED) and 424/10,000 (≥50mg MED) in periods of long-term opioid prescribing. Adjusted hazard ratios for the increase in risk were 1.09 (95% CI, 1.04, 1.14 compared to not being in an episode of long-term use; <20mg MED), 1.24 (95% CI, 1.16, 1.32; 20-50mg MED) and 1.34 (95% CI, 1.20, 1.50; ≥ 50mg MED) (Table 4).

Table 4 here

Dose-response relationships (i.e. increased risk in periods of stronger long-term opioid prescribing) were also identified for the secondary outcomes of falls, iron deficiency anaemia, gastrointestinal events, addiction, and accidental poisoning. The

number of attempted suicide/self-harm events was small, with no statistically significant relationship with long-term opioids observed (Table 5).

Table 5 here

Prescriptions of long-term opioids were not associated with increased risks of eczema or psoriasis, regardless of average daily dose (Table 6).

Table 6 here

Adjusted risks of adverse events were similar between females and males (Supplementary Tables 1-4).

Sensitivity analysis using complete case analysis gave very similar results.

Discussion and conclusions

This study of nearly 100,000 patients in UK primary care has shown a dose-dependent increase in the risk of overdose and major trauma when patients were prescribed long-term opioids for chronic musculoskeletal pain. Intentional opioid overdose was nearly 4 times more likely in patients prescribed long-term opioids at the highest doses (≥50mg) compared to periods when they were not receiving long-term opioids, Similarly, patients prescribed the highest doses also had a 71% higher risk of intentional non-opioid overdose and a 34% higher major trauma risk, compared to time periods when they were not prescribed long-term opioids. Dose-dependent increases in the risk of addiction, falls, accidental poisoning, incident gastrointestinal pathology, gastrointestinal bleeding, and iron deficiency anaemia with current long-term opioid, compared to periods of no long-term use were also identified.

The median average daily dose of prescribed opioids during long-term opioid episodes was 12.3mg (IQR 7.1, 20.3 mg MED). This is consistent with an earlier dosage study of opioid prescribing (Von Korff et al., 2008) and another indicating that 95% of initially prescribed opioids in long-term episodes were for low dose short-acting non-controlled opioids (Bedson et al., 2016).

Our study findings are consistent with smaller long-term opioid use observational studies in the US which demonstrated dose-dependent, increases in the risk of bone fractures (Saunders et al., 2010), opioid overdose (Dunn et al., 2009) and addiction (Edlund et al., 2014). Our finding of a dose-dependent increased risk of falls seems consistent with the increased risk of major trauma identified. In contrast, one large prospective longitudinal study found no significant association of opioids with falls or fractures in an all-male cohort (Krebs et al., 2016). However, this discrepancy may relate to the absence of data on opioid dose or duration, thereby potentially reducing the study's power to detect a dose-dependent association if most events occur at higher doses. Adverse events in opioids might be related to the preparation. One systematic review found that transdermal buprenorphine was less likely to be related to adverse effects than other opioids (Richardson et al., 2018), and Solomon found that fractures were less likely in those who were prescribed tramadol compared to hydrocodone (Solomon et al., 2010). However, since our study considers MED as the main variable, we are unable to examine this phenomenon and therefore potentially some outcomes may be related more to the type of opioid than the MED.

A higher risk of erosive gastrointestinal pathology, gastrointestinal bleeding, and iron deficiency anaemia has not previously been identified in relation to long-term opioids. Opioids may impair oesophageal motility and delay gastric emptying,

potentially worsening gastroesophageal reflux (Ratuapli et al., 2015), however, its clinical relevance is uncertain. Opioids are used as an alternative to NSAIDs for patients at risk of peptic ulcers and we cannot rule out residual confounding. Long-term use of paracetamol (>13 weeks) has been associated with gastrointestinal blood loss (Doherty et al., 2011), and a systematic review reported higher rates of upper gastrointestinal bleeding in paracetamol users (Roberts et al., 2016). Paracetamol is frequently used in combination with opioids. Potentially, long-term opioid prescribing increases the likelihood of regular, long-term paracetamol use and that this is the risk factor associated with increased risk of gastrointestinal events, rather than the use of opioids per se. Although the analysis adjusted for prescribed NSAIDs, it did not adjust for paracetamol which may be purchased over the counter. Further exploration of this phenomenon is needed.

A Cochrane review highlighted the lack of reporting on several important adverse events, such as addiction and overdose, and recommended longer follow-up to detect adverse events which this study has now examined. (Els et al., 2017).

Reproductive and sexual dysfunction in occurs in male long-term opioid users. No such association has been identified in females (Daniell, 2002; Smith and Elliott, 2012; Katz and Mazer, 2009). Therefore, other gender related differences in adverse events might exist. No studies have examined this area (Els et al., 2017) and we did not identify any differences in the rates of adverse events between males and females either. Patients moved from long-term opioid use to periods of no use. This would be consistent with previous work examining the trajectories of pain which people experience. For example, in back pain, one of the commonest causes of chronic non-cancer pain, pain trajectories are very variable and depend to some

extent on the original presentation. Backpain sufferers can be grouped according to those with persistent severe pain, fluctuating pain, persistent mild pain and occasional pain. However, all groups vary around their mean pain trajectory (Dunn et al., 2017, Tamcan et al., Pain 2010) which would be consistent with our findings of patients moving from periods of long-term opioid use to no use.

Key strengths of this study relate to the use of CPRD, allowing analysis of a large cohort of primary care patients linked to secondary care and mortality data. All prescribing is recorded electronically in UK primary care at the point of medication issue and there is automatic recording of repeat opioid prescriptions. The likelihood of missing opioid prescribing data in CPRD is therefore low. Another factor facilitating the collection of outcome data and which makes our results more generalisable is the fact that primary care physicians in CPRD practices were historically requested to ensure recording of a diagnostic code for any new problem or when a new treatment is given (Lawson et al., 1998). CPRD data is not limited to particular healthcare populations, for example it is not based on medical insurance schemes as many USA healthcare databases are, thereby making the results more generalisable. Additionally, this population was restricted to patients with painful musculoskeletal conditions who had all been prescribed long-term opioids. This reduces the likelihood of cofounding by indication.

We adjusted for previous occurrence of the adverse events, except for outcomes defined as incident events (where patients with a previous event were excluded), and for potential confounders. Depression and overdose during the past year are strong predictors of overdose and suicide in patients taking long-term opioids (Oliva et al., 2017). By adjusting for depression and previous overdose, we have controlled

for important confounders in relation to our primary outcome of overdose and increased confidence in the study findings. However, we were unable to adjust for a previous history of substance misuse which may influence some outcomes.

We also included ‘control’ outcomes (Lipsitch et al., 2010; Arnold et al., 2016) which hypothetically should not be associated with long-term opioid prescribing to detect potential bias. The absence of any dose-dependent increased risk of either control outcome (incident eczema or psoriasis) further increases our confidence in the study findings.

Our study was observational and therefore the results should be viewed as associations, and not necessarily causal. Our study population is restricted to patients with painful musculoskeletal conditions and, whilst this reflects the majority of patients with chronic pain, it is possible the findings may not be generalisable to those prescribed long-term opioids for non-musculoskeletal chronic pain. However, despite chronic musculoskeletal pain representing a broad range of heterogenous conditions, in light of recent research, (Artus et al., 2017; Green et al., 2018) which has demonstrated strong evidence that prognosis and prognostic factors are similar across multiple pain sites, we have assumed that the relationship of long-term opioid use with adverse events is consistent across musculoskeletal conditions, but future research should assess this further.

Our study uses opioid prescribing data from a healthcare database and cannot account for patients not taking the prescribed medication as directed. In addition, we were unable to adjust for the use of over-the-counter analgesics. Long-term opioid use for musculoskeletal conditions is highly likely to be by prescription and therefore captured within the CPRD data, given that low dose codeine (8-12mg maximum

pack size of 32 tablets for short-term use) is the only opioid available over the counter in the UK (Medicines and Healthcare Products Regulatory Agency, 2009). However, it is possible that over the counter paracetamol or NSAID use may be implicated in the finding of higher risk of erosive gastrointestinal events. Additionally, though our definition of long-term opioid use is dependent on the use of three consecutive prescriptions for opioids within 90 days, we cannot be certain that patients used them consistently in that period, and that every prescription was intended to last more or less than a four-week period. Though GPs are advised to use at least 2 – 4 weeks of an opioid before changing or stopping (NICE, 2017), and that at least 28 days of medication should be given (Dowd, 2016), this might lead to some patients being erroneously classed as long-term users, though within the framework that GPs work, the vast majority are likely to have been classified correctly. Ultimately, however, the issue of a prescription for an opioid does not necessarily mean a patient has taken the medication. Accordingly, we cannot be certain whether a patient has used their prescribed opioids or not, though the fact that repeat prescriptions for opioids are issued in each long-term case would suggest that patients are likely to be using them. Although we adjusted for prescribed NSAID use, we did not adjust for any other prescribed medications used for chronic pain or other medications that might have impacted mental health such as antidepressants or benzodiazepines. However, we did adjust for total number of prescribed medications as a surrogate marker for comorbidity, but no specific co-morbidities other than depression were investigated such as substance misuse or osteoporosis which may impact overdose and bone fractures. Polypharmacy and the use of other medications for pain will be reflected to some extent by that. However, we are unable

to account for the specific effects of other potentially sedating medications on adverse event outcomes.

We did not include adverse events occurring during the first 90 days of opioid prescribing as outcomes due to the likelihood of these being related to patients being opioid naïve. This study aimed to look at adverse events associated with long-term opioid use, and events after 90 days are more likely to be specifically associated with long-term use. However, events within 90 days were either adjusted for, or for incident outcomes, patients with such events were excluded.

This study has shown dose-dependent associations between prescribed long-term opioids and increased risks of a range of serious adverse events. Whilst in absolute terms, the increased number of events may be relatively small, this must be viewed in the context of both the seriousness of the events and the long-term efficacy of opioids for chronic pain. Whilst some patients may benefit from moderate doses of opioids for chronic pain, many do not (Moore et al., 2013). However, they may continue to be prescribed opioids because of a perceived lack of other treatment options (Moore et al., 2013; Stannard, 2013). It seems self-evident that patients should not be exposed to increased risk of harm, when this is not balanced by therapeutic benefit (Stannard, 2013; Faculty of Pain Medicine, 2013). Our findings reinforce the message that doctors need to be vigilant when prescribing opioids for chronic pain, and to give due consideration to the dose prescribed and the appropriateness of continuing opioids long-term. These clinical decisions must be made on an individual patient basis, taking into account any benefits observed in terms of pain relief, the impact on functioning, side-effects and the potential risks of long-term use. Opioid prescribing should be reviewed before long-term use becomes

established, and periodically thereafter to assess on-going effectiveness. Unfortunately, the challenges facing UK Primary Care, including rising GP workload, present a major barrier to this becoming routine practice (Primary Care Workforce Commission, 2015). Further research is needed to develop and test strategies and interventions to reduce inappropriate opioid prescribing. Given that most long-term opioid prescribing occurs in primary care, it is recommended that future research focusses on the role of multidisciplinary primary care teams, including clinical pharmacists, in reviewing patients prescribed long-term opioids.

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Contributors

JB conceived and developed the study and is guarantor of the paper. YC was responsible for analysis. JB and YC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and had equal contribution to the paper. All authors collaborated on design of the study, and contributed to the interpretation, and writing and final draft of the article. All authors have read and approved the paper.

References

Arnold BF, Ercumen A, Benjamin-Chung J, Colford JM. (2016). Brief Report: Negative Controls to Detect Selection Bias and Measurement Bias in Epidemiologic Studies. Epidemiology ;27,637-641.

Artus M, Campbell P, Mallen CD, Dunn KM, van der Windt DA. (2017) Generic prognostic factors for musculoskeletal pain in primary care: a systematic review. BMJ Open ;doi: 10.1136/bmjopen-2016-012901.

Bedson J, Chen Y, Ashworth J, Hayward RA, et al. (2016). Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. Pain ;doi: 10.1097/j.pain.0000000000000557.

BNF. (2017). *British National Formulary* (London: BMJ Group).

Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain ;10,287-333.

Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, et al. (2015). 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 ;162,276-286.

Daniell HW. (2002). Hypogonadism in men consuming sustained-action oral opioids. J Pain ;3,377-384.

Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, et al. (2011). A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of

ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis ;70,1534-1541.

Dowd A. (2011). Some PCTs recommend GPs limit prescriptions to 28 days. BMJ ;342,d2410.

Dunn KM, Jordan K P, Croft PR. (2006). Characterizing the Course of Low Back Pain: A Latent Class Analysis. Am J Epidemiol;63, 754-761.

Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, et al. (2010). Opioid Prescriptions for Chronic Pain and Overdose. Ann Intern Med ;152,85-92.

Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, et al. (2014). The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals With Chronic Noncancer Pain : The Role of Opioid Prescription. Clin J Pain ;30,557-564.

Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, et al. (2017). Adverse events associated with medium and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews ;doi: 10.1002/14651858.CD012509.pub2.

Farias JC, Porter L, McManus S, Strang J, Hickman M, et al. (2017). Independent research commissioned and funded by the National Institute for Health Research (NIHR) Policy Research Programme (PHPEHF50/14). Prescribing Patterns in Dependence Forming Medicines. Public Health Research Consortium.

Foy R, Leaman B, McCrorie C, Petty D, House A, et al. (2016)). Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. BMJ Open ;6:e010276. doi:10.1136/bmjopen-2015- 010276.

Gallagher AM, Puri S, Van Staa T. (2011). Linkage of the General Practice Research Database (GPRD) with other data sources. Pharmacoepidemiol Drug Saf ;20,S230-231.

Green DJ, Lewis M, Mansell G, Artus M, Dziedzic KS, Hay EM, et al. (2018) Clinical course and prognostic factors across different musculoskeletal pain sites: A secondary analysis of individual patient data from randomised clinical trials. Eur J Pain ;doi: 10.1002/ejp.

Hauser W, Bernardy K, Maier C. (2015). Long-term opioid therapy in chronic noncancer pain. A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. Shcmerz ;29(1),96-108.

Herrett E, Thomas SL, Schoonen WM. (2010). Validation and validity of diagnoses in the general practice research database: a systematic review. Br J Clin Pharmacol, ;69,4-14.

Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol ;44,827-836.

Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD. (2008). Epidemiology of regular prescribed opioid use: results from a national, population-based survey. J Pain Symptom Manage ;36,280-288.

Jordan K, Kadam U, Hayward R, Porcheret M, Young C, et al. (2010). Annual consultation prevalence of regional musculoskeletal problems in primary care. BMC Musculoskelet Disord ;11,144.

Katz N, Mazer NA. (2009). The Impact of Opioids on the Endocrine System. Clin J Pain ;25,170-175.

Krebs EE, Jensen AC, Nugent S, DeRonne B, Rutks I, et al. (2017). Design, recruitment outcomes, and sample characteristics of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial. Contemp Clin Trials ;62,130-139.

Krebs EE, Paudel M, Taylor BC, Bauer DC, Fink HA, et al., for the Osteoporotic Fractures in Men (MrOS) Study,Research Group. (2016). Association of Opioids with Falls, Fractures, and Physical Performance among Older Men with Persistent Musculoskeletal Pain. J Gen Intern Med ;31,463-469.

Lanza F, Chan F, Quigley E. (2009). Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol ;104,728-738.

Lawson D, Sherman V, Hollowell J. (1998). The General Practice Research Database. Q J Med ;91,445-452.

Lipsitch M, Tchetgen ET, Cohen T. (2010). Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies. Epidemiology ;21,383-388.

Manchikanti L, Fellows B, Ailinani H, Pamapti P. (2010). Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. Pain Physician ;13,401-435.

Moore A, Derry S, Eccleston C, Kalso E. (2013). Expect analgesic failure; pursue analgesic success. BMJ, ;346:f2690.

O'Brien T, Christrup LL, Drewes AM, Fallon MT, Kress HG, et al. (2017). European Pain Federation position paper on appropriate opioid use in chronic pain management. Eur J Pain ;21,3-19.

Oliva EM, Bowe T, Tavakoli S, Martins S, Lewis E,T., et al. (2017). Development and applications of the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM) to improve opioid safety and prevent overdose and suicide. Psychol Serv ;14,34-49.

Perkins AJ, Kroenke K, Untzer J, Katon W, Williams JW, et al. (2004). Common comorbidity scales were similar in their ability to predict health care costs and mortality. J Clin Epidemiol ;57,1040-1048.

Ratuapli SK, Crowell MD, DiBaise JK, Vela MF, Ramirez FC, et al. (2015). Opioid-Induced Esophageal Dysfunction (OIED) in Patients on Chronic Opioids. Am J Gastroenterol ;110,979.

Ray WA, Chung CP, Murray KT, Hall K, Stein C. (2016). Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA ;315,2415-2423.

Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, et al. (2016). Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis ;75,552-559.

Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, et al. (2010). Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med ;25,310-315.

Scherrer JF, Salas J, Copeland LA, Stock EM, Ahmedani BK, et al. (2015). Prescription Opioid Duration, Dose, and Increased Risk of Depression in 3 Large Patient Populations. Ann Fam Med ;14,54-62.

Scherrer JF, Salas J, Lustman PJ, Burge S, Schneider FD, For the Residency Research Network of Texas. (2015a). Change in Opioid Dose and Change in Depression in a Longitudinal Primary Care Patient Cohort. Pain ;156,348-355.

Scherrer JF, Svrakic DM, Freedland KE, Chrusciel T, Balasubramanian S, et al. (2013). Prescription Opioid Analgesics Increase the Risk of Depression. J Gen Intern Med ;29,491-499.

Stannard C. (2013). Opioids in the UK: what's the problem? BMJ ;347:f5108.

Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, et al. (2010) The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med ;170, 1979-1986.

Tamcan O, Mannion AF, Eisenring C, Horisberger B, Elfering A, Müller U. (2010). The course of chronic and recurrent low back pain in the general population. Pain ;150, 451-457.

Tate AR, Beloff N, Al-Radwan B, Wickson J, Puri S, et al. (2014). Exploiting the potential of large databases of electronic health records for research using rapid

search algorithms and an intuitive query interface. J Am Med Inform Assoc ;21,292-298.

Von Korff M, Saunders K, Thomas Ray G, Boudreau D, Campbell C, et al. (2008). De facto long-term opioid therapy for noncancer pain. Clin J Pain ;24,521-527.

Williams T, van Staa T, Puri S, Eaton S. (2012). Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf ;3,89-99.

Woolf AD, Zeidler H, Haglund U, Carr AJ, Chaussade S, et al. (2004). Musculoskeletal pain in Europe: its impact and a comparison of population and medical perceptions of treatment in eight European countries. Ann Rheum Dis ;63,342-347.

Zin CS, Chen LC, Knaggs RD. (2014). Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain ;18,1343-1351.

Web References

Department for Communities and Local Government. (2010). The English Indices of Deprivation 2010. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf

eHealthMe. (2017). Codeine and Anaemia - from FDA reports, 2018. https://www.ehealthme.com/ds/codeine/anaemia/

Faculty of Pain Medicine. Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. 2017. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

Gregory S. (2009). The King's Fund. General practice in England: an overview. https://www.kingsfund.org.uk/sites/default/files/general-practice-in-england-overview-sarah-gregory-kings-fund-september-2009.pdf

Medicines and Healthcare Products Regulatory Agency. (2009). Over-the-counter painkillers containing codeine or dihydrocodeine, 2009. https://www.gov.uk/drug-safety-update/over-the-counter-painkillers-containing-codeine-or-dihydrocodeine

NHS Digital. (2018). Read Codes. https://digital.nhs.uk/article/1104/Read-Codes

Primary Care Workforce Commission. (2015). The future of primary care: Creating teams for tomorrow. 2015. https://hee.nhs.uk/sites/default/files/documents/WES_The-future-of-primary-care.pdf

Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD), 2012. http://www.painphysicianjournal.com/current/pdf?article=MTcxMg%3D%3D&journal=68

Table legends

Table 1. Morphine equivalent dose (MED) in mg, per 1 mg of opioid analgesic

Table 2 - Participant characteristics at baseline

Table 3 Average daily dose of prescribed opioids during the long-term opioid episodes

Table 4 - Risks of major trauma and overdose in musculoskeletal patients newly prescribed long-term opioids

Table 5 - Risks of falls, iron deficiency anaemia, gastrointestinal pathology, addiction, accidental poisoning and attempted suicide/self-harm in musculoskeletal patients newly prescribed long-term opioids

Table 6 - Risks of eczema and psoriasis in musculoskeletal patients newly prescribed long-term opioids

Supplementary Table 1 - Risks of major trauma and overdose in musculoskeletal patients newly prescribed long-term opioids in males

Supplementary Table 2 - Risks of major trauma and overdose in musculoskeletal patients newly prescribed long-term opioids in females

Supplementary Table 3 - Risks of falls, iron deficiency anaemia, gastrointestinal pathology, addiction, accidental poisoning and attempted suicide/self-harm in musculoskeletal patients newly prescribed long-term opioids in males

Supplementary Table 4 - Risks of falls, iron deficiency anaemia, gastrointestinal pathology, addiction, accidental poisoning and attempted suicide/self-harm in musculoskeletal patients newly prescribed long-term opioids in females

Supplementary Table 1. Risks of major trauma and overdose in musculoskeletal patients newly prescribed long-term opioids in males

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Major trauma					
Periods not on long-term opioids	2,296	96,708.6	237.4	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	1,480	46,622.5	317.4	1.20 (1.12, 1.28)	1.13 (1.06, 1.21)
Periods on long-term opioids (daily MED < 20mg)	976	32,219.7	302.9	1.12 (1.04, 1.21)	1.08 (1.0, 1.17)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	403	11,210.2	359.5	1.39 (1.25, 1.55)	1.29 (1.15, 1.43)
Periods on long-term opioids (ADD ≥ 50mg MED)	101	3,192.6	316.4	1.25 (1.03, 1.53)	1.09 (0.89, 1.33)
Overdose (non-opioids)					
Periods not on long-term opioids	189	103,155.5	18.3	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	153	48,983.0	31.2	1.39 (1.11, 1.74)	1.25 (1.0, 1.58)
Periods on long-term opioids (ADD < 20mg MED)	70	33,667.8	20.8	0.88 (0.66, 1.17)	0.92 (0.69, 1.23)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	58	11,938.3	48.6	2.24 (1.66, 3.02)	1.67 (1.23, 2.26)
Periods on long-term opioids (ADD ≥ 50mg MED)	25	3,377.0	74.0	3.58 (2.35, 5.44)	1.95 (1.27, 2.98)
Overdose (opioids)					
Periods not on long-term opioids	53	103,499.2	5.1	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	63	49,168.6	12.8	2.34 (1.60, 3.43)	2.40 (1.62, 3.57)
Periods on long-term opioids (ADD < 20mg MED)	30	33,733.5	8.9	1.56 (0.98, 2.49)	1.89 (1.17, 3.06)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	19	12,029.3	15.8	2.88 (1.70, 4.90)	2.43 (1.42, 4.18)
Periods on long-term opioids (ADD ≥ 50mg MED)	14	3,405.8	41.1	7.66 (4.24, 13.9)	4.70 (2.56, 8.64)

ADD, average daily dose; MED, morphine equivalent dose; [a] Adjusted for age, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, co-prescribing of non-steroidal anti-inflammatory drug, and for prior occurrence of adverse event.

Supplementary Table 2. Risks of major trauma and overdose in musculoskeletal patients newly prescribed long-term opioids in females

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Major trauma					
Periods not on long-term opioids	4,158	129,431.8	321.3	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	3,107	75,482.6	411.6	1.20 (1.14, 1.26)	1.14 (1.08, 1.19)
Periods on long-term opioids (daily MED < 20mg)	2,174	53,103.6	409.4	1.18 (1.12, 1.25)	1.10 (1.04, 1.16)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	693	17,519.4	395.6	1.18 (1.08, 1.28)	1.19 (1.09, 1.29)
Periods on long-term opioids (ADD ≥ 50mg MED)	240	4,859.6	493.9	1.48 (1.30, 1.69)	1.43 (1.26, 1.63)
Overdose (non-opioids)					
Periods not on long-term opioids	289	140,800.6	20.5	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	254	80,887.4	31.4	1.28 (1.07, 1.52)	1.21 (1.0, 1.44)
Periods on long-term opioids (ADD < 20mg MED)	119	56,720.8	21.0	0.81 (0.65, 1.02)	0.91 (0.72, 1.14)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	100	18,814.8	53.1	2.25 (1.78, 2.83)	1.70 (1.34, 2.15)
Periods on long-term opioids (ADD ≥ 50mg MED)	35	5,351.8	65.4	2.85 (2.0, 4.0)	1.54 (1.08, 2.21)
Overdose (opioids)					
Periods not on long-term opioids	65	141,502.1	4.6	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	88	81,217.9	10.8	2.06 (1.47, 2.88)	2.18 (1.55, 3.06)
Periods on long-term opioids (ADD < 20mg MED)	37	56,876.2	6.5	1.17 (0.77, 1.78)	1.42 (0.92, 2.18)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	37	18,923.3	19.6	3.79 (2.52, 5.71)	3.24 (2.14, 4.91)
Periods on long-term opioids (ADD ≥ 50mg MED)	14	5,418.3	25.8	5.15 (2.89, 9.21)	3.38 (1.88, 6.08)

ADD, average daily dose; MED, morphine equivalent dose; [a] Adjusted for age, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, co-prescribing of non-steroidal anti-inflammatory drug, and for prior occurrence of adverse event.

Supplementary Table 3. Risks of falls, iron deficiency anaemia, gastrointestinal pathology, addiction, accidental poisoning and attempted suicide/self-harm in musculoskeletal patients newly prescribed long-term opioids in males

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Falls[b]					
Periods not on long-term opioids	2,530	96,939.4	261.0	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	1,785	46,202.8	386.3	1.41 (1.33, 1.51)	1.28 (1.20, 1.36)
Periods on long-term opioids (ADD < 20mg MED)	1,216	31,882.6	381.4	1.38 (1.29, 1.49)	1.18 (1.10, 1.27)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	421	11,206.7	375.7	1.39 (1.25, 1.54)	1.41 (1.27, 1.57)
Periods on long-term opioids (ADD ≥ 50mg MED)	148	3,113.5	475.3	1.78 (1.50, 2.10)	1.99 (1.68, 2.35)
Incident iron deficiency anaemia[c]					
Periods not on long-term opioids	813	100,603.4	80.8	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	620	47,495.1	130.5	1.62 (1.45, 1.81)	1.42 (1.27, 1.59)
Periods on long-term opioids (ADD < 20mg MED)	390	32,686.4	119.3	1.47 (1.30, 1.67)	1.21 (1.06, 1.37)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	171	11,547.2	148.1	1.83 (1.55, 2.16)	1.83 (1.55, 2.17)
Periods on long-term opioids (ADD ≥ 50mg MED)	59	3,261.6	180.9	2.24 (1.72, 2.92)	2.46 (1.88, 3.22)
Incident gastrointestinal pathology[c]					
Periods not on long-term opioids	1,051	99,000.0	106.2	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	714	46,745.2	152.7	1.40 (1.26, 1.54)	1.26 (1.14, 1.40)
Periods on long-term opioids (ADD < 20mg MED)	469	32,278.9	145.3	1.32 (1.18, 1.48)	1.17 (1.04, 1.32)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	168	11,324.0	148.4	1.36 (1.16, 1.61)	1.27 (1.08, 1.50)
Periods on long-term opioids (ADD ≥ 50mg MED)	77	3,142.3	245.0	2.27 (1.80, 2.86)	2.12 (1.68, 2.69)
Incident gastrointestinal bleeding[c]					
Periods not on long-term opioids	489	101,682.4	48.1	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	312	48,144.2	64.8	1.25 (1.08, 1.46)	1.11 (0.95, 1.29)
Periods on long-term opioids (ADD < 20mg MED)	202	33,083.3	61.1	1.16 (0.98, 1.38)	1.01 (0.85, 1.20)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	77	11,741.6	65.6	1.29 (1.01, 1.64)	1.18 (0.92, 1.50)
Periods on long-term opioids (ADD ≥ 50mg MED)	33	3,319.3	99.4	1.99 (1.39, 2.83)	1.80 (1.26, 2.58)
Incident addiction (non-opioids) [c]					
Periods not on long-term opioids	353	101,834.6	34.7	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	317	48,005.0	66.0	1.70 (1.45, 2.0)	1.59 (1.35, 1.87)
Periods on long-term opioids (ADD < 20mg MED)	161	33,192.4	48.5	1.21 (0.99, 1.47)	1.22 (1.0, 1.49)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	110	11,618.5	94.7	2.49 (2.0, 3.09)	2.03 (1.63, 2.52)
Periods on long-term opioids (ADD ≥ 50mg MED)	46	3,194.1	144.0	3.88 (2.85, 5.28)	2.75 (2.01, 3.76)
Incident addiction (opioids) [c]					

Periods not on long-term opioids	54	103,164.3	5.2	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	77	48,978.3	15.7	2.45 (1.70, 3.53)	2.63 (1.81, 3.84)
Periods on long-term opioids (ADD < 20mg MED)	18	33,698.3	5.3	0.76 (0.44, 1.31)	0.96 (0.55, 1.68)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	32	11,964.3	26.7	4.19 (2.68, 6.55)	3.47 (2.20, 5.45)
Periods on long-term opioids (ADD ≥ 50mg MED)	27	3,315.8	81.4	13.44 (8.43, 21.44)	8.10 (5.01, 13.09)
Accidental poisoning[b]					
Periods not on long-term opioids	21	103,622.2	2.0	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	17	49,225.0	3.5	1.77 (0.90, 3.48)	1.48 (0.74, 2.94)
Periods on long-term opioids (ADD < 20mg MED)	8	33,751.9	2.4	1.19 (0.50, 2.79)	1.01 (0.43, 2.41)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	6	12,044.9	5.0	2.46 (0.98, 6.19)	2.06 (0.81, 5.28)
Periods on long-term opioids (ADD ≥ 50mg MED)	3	3,428.2	8.8	4.38 (1.30, 14.78)	3.21 (0.93, 11.13)
Attempted suicide/self-harm[b]					
Periods not on long-term opioids	7	103,666.6	0.7	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	6	49,242.0	1.2	1.89 (0.61, 5.80)	1.72 (0.55, 5.43)
Periods on long-term opioids (ADD < 20mg MED)	3	33,758.9	0.9	1.36 (0.34, 5.46)	1.49 (0.36, 6.15)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	2	12,051.1	1.7	2.53 (0.52, 12.32)	1.88 (0.38, 9.39)
Periods on long-term opioids (ADD ≥ 50mg MED)	1	3,432.0	2.9	4.43 (0.54, 36.17)	2.39 (0.27, 20.73)

ADD, average daily dose; MED, morphine equivalent dose; [a]Adjusted for age, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, and co-prescribing of non-steroidal anti-inflammatory drug ; [b]Also adjusted for prior occurrence of adverse event; [c]Excluded patients with previous record of event.

Supplementary Table 4. Risks of falls, iron deficiency anaemia, gastrointestinal pathology, addiction, accidental poisoning and attempted suicide/self-harm in musculoskeletal patients newly prescribed long-term opioids in females

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Falls[b]					
Periods not on long-term opioids	5,656	124,594.3	454.0	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	4,722	72,351.6	652.6	1.34 (1.29, 1.40)	1.21 (1.16, 1.26)
Periods on long-term opioids (ADD < 20mg MED)	3,318	50,985.4	650.8	1.32 (1.27, 1.38)	1.16 (1.11, 1.21)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	1,040	16,795.9	619.2	1.30 (1.21, 1.39)	1.31 (1.22, 1.40)
Periods on long-term opioids (ADD ≥ 50mg MED)	364	4,570.3	796.4	1.68 (1.51, 1.87)	1.54 (1.39, 1.72)
Incident iron deficiency anaemia[c]					
Periods not on long-term opioids	1,688	133,904.0	126.1	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	1,465	76,854.3	190.6	1.48 (1.38, 1.59)	1.37 (1.27, 1.47)
Periods on long-term opioids (ADD < 20mg MED)	966	54,009.5	178.9	1.38 (1.27, 1.50)	1.26 (1.16, 1.37)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	364	17,842.8	204.0	1.59 (1.42, 1.78)	1.54 (1.37, 1.73)
Periods on long-term opioids (ADD ≥ 50mg MED)	135	5,002.0	269.9	2.11 (1.77, 2.52)	1.87 (1.57, 2.24)
Incident gastrointestinal pathology[c]					
Periods not on long-term opioids	1,368	135,393.1	101.0	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	1,098	77,473.1	141.7	1.33 (1.22, 1.44)	1.24 (1.14, 1.35)
Periods on long-term opioids (ADD < 20mg MED)	707	54,534.9	129.6	1.20 (1.09, 1.32)	1.12 (1.01, 1.23)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	286	17,885.8	159.9	1.52 (1.33, 1.72)	1.44 (1.27, 1.64)
Periods on long-term opioids (ADD ≥ 50mg MED)	105	5,052.3	207.8	1.99 (1.63, 2.43)	1.77 (1.45, 2.17)
Incident gastrointestinal bleeding[c]					
Periods not on long-term opioids	550	139,535.3	39.4	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	462	79,912.1	57.8	1.37 (1.20, 1.56)	1.24 (1.09, 1.41)
Periods on long-term opioids (ADD < 20mg MED)	307	56,012.5	54.8	1.28 (1.10, 1.48)	1.14 (0.99, 1.33)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	108	18,618.5	58.0	1.39 (1.13, 1.72)	1.33 (1.08, 1.64)
Periods on long-term opioids (ADD ≥ 50mg MED)	47	5,281.2	89.0	2.17 (1.61, 2.93)	1.94 (1.43, 2.62)
Incident addiction (non-opioids) [c]					
Periods not on long-term opioids	208	140,443.4	14.8	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	245	80,101.6	30.6	1.85 (1.53, 2.25)	1.82 (1.50, 2.21)
Periods on long-term opioids (ADD < 20mg MED)	119	56,356.1	21.1	1.23 (0.97, 1.56)	1.31 (1.03, 1.66)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	88	18,522.8	47.5	2.93 (2.27, 3.77)	2.49 (1.93, 3.21)
Periods on long-term opioids (ADD ≥ 50mg MED)	38	5,222.6	72.8	4.57 (3.23, 6.46)	3.35 (2.36, 4.76)
Incident addiction (opioids) [c]					

Periods not on long-term opioids	36	141,459.6	2.5	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	65	81,214.7	8.0	2.79 (1.83, 4.26)	3.07 (1.99, 4.72)
Periods on long-term opioids (ADD < 20mg MED)	17	56,882.0	3.0	0.96 (0.53, 1.74)	1.20 (0.66, 2.20)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	24	18,951.6	12.7	4.38 (2.60, 7.41)	3.73 (2.19, 6.33)
Periods on long-term opioids (ADD ≥ 50mg MED)	24	5,381.0	44.6	15.87 (9.43, 26.72)	10.65 (6.27, 18.12)
Accidental poisoning[b]					
Periods not on long-term opioids	26	141,627.5	1.8	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	44	81,333.2	5.4	2.93 (1.77, 4.83)	2.50 (1.51, 4.14)
Periods on long-term opioids (ADD < 20mg MED)	23	56,898.4	4.0	2.14 (1.20, 3.83)	1.88 (1.05, 3.38)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	13	18,993.8	6.8	3.64 (1.86, 7.13)	3.01 (1.53, 5.94)
Periods on long-term opioids (ADD ≥ 50mg MED)	8	5,441.1	14.7	7.78 (3.51, 17.24)	5.84 (2.60, 3.11)
Attempted suicide/self-harm[b]					
Periods not on long-term opioids	7	141,694.1	0.5	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	3	81,407.6	0.4	0.52 (0.13, 2.08)	0.51 (0.12, 2.13)
Periods on long-term opioids (ADD < 20mg MED)	1	56,927.6	0.2	0.23 (0.03, 1.94)	0.29 (0.03, 2.52)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	1	19,020.4	0.5	0.81 (0.10, 6.65)	0.67 (0.08, 5.62)
Periods on long-term opioids (ADD ≥ 50mg MED)	1	5,459.6	1.8	2.96 (0.36, 24.3)	1.12 (0.11, 11.38)

ADD, average daily dose; MED, morphine equivalent dose; [a]Adjusted for age, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, and co-prescribing of non-steroidal anti-inflammatory drug ; [b]Also adjusted for prior occurrence of adverse event; [c]Excluded patients with previous record of event.

Table 1. Morphine equivalent dose (MED) in mg, per 1 mg of opioid analgesic

Opioid Analgesic (1mg)	**Morphine Equivalent Dose (mg)**
Non-controlled opioids	
Codeine	0.15
Co-proxamol	0.23
Dihydrocodeine	0.25
Meptazinol	0.04
Tramadol (Controlled since 06/2014)	0.1
Controlled opioids	
Alfentanil Hydrochloride	30
Buprenoprhine Sublingual Tablets	80
Buprenorphine Transdermal Patches	75
Dextromoramide/Palfium	3
Diamorphine	3
Dipipanone hydrochloride/Diconal	0.5
Fentanyl mcg/hr patch (for 24 hours)	2.4
Fentanyl Lozenge	130
Fentanyl Nasal Spray	160
Hydromorphone	4
Levorphanol	6
Morphine	1
Methadone	3
Oxycodone	1.5
Papaveretum/Omnopon	0.75
Pentazocine	0.12
Pethidine	0.1
Tapentadol	0.4

Table 2 - Participant characteristics at baseline

Participants, n	98,140
Age at start of follow-up, median (IQR)	61 (47, 73)
Male, n (%)	40,203 (41.0)
Year of start of follow-up, median (IQR)	2007 (2005, 2009)
Geographical region, n (%)	
London	8,375 (8.5)
South	34,051 (34.7)
Midlands and East	27,457 (28.0)
North	28,257 (28.8)
Smoking, n (%)	
Non smoker	48,223 (49.1)
Ever smoker	37,634 (38.4)
Unknown	12,283 (12.5)
Alcohol drinking, n (%)	
Non drinker	12,643 (12.9)
Ever drinker	72,646 (74.0)
Unknown	12,851 (13.1)
Body mass index, n (%)	
< 25 kg/m2	26,748 (27.3)
≥ 25 kg/m2	60,054 (61.2)
Unknown	11,338 (11.6)
Neighbourhood Deprivation level, n (%)	
1 (least)	17,882 (18.2)
2	21,398 (21.8)
3	19,067 (19.4)
4	19,612 (20.0)
5 (most)	19,582 (20.0)
Unknown	599 (0.6)
Depression consultationa, n (%)	6,615 (6.7)
Co-prescribing NSAID[b], n (%)	
None	52,734 (53.7)
Basic oral NSAID only	38,698 (39.4)
COX-2	6,708 (6.8)
Comorbidity (total number of prescriptions)[a], median (IQR)	9 (6, 14)

[a] in 15 months prior to start of follow-up; [b] in 4 months prior to start of follow-up; IQR, interquartile range; NSAID, Non-steroidal anti-inflammatory drug; COX-2, selective cyclooxygenase-2 inhibitor

Table 3 Average daily dose of prescribed opioids during the long-term opioid episodes

Percentiles	Average daily dose in morphine equivalents, all patients	Average daily dose in morphine equivalents, males	Average daily dose in morphine equivalents, females
5%	3.1 mg	3.3 mg	3.0 mg
25%	7.1 mg	7.7 mg	6.7 mg
50% (median)	12.3 mg	13.2 mg	11.7 mg
75%	20.3 mg	21.4 mg	19.5 mg
95%	42.8 mg	44.0 mg	42.0 mg

Table 4 - Risks of major trauma and overdose in musculoskeletal patients newly prescribed long-term opioids

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Major trauma					
Periods not on long-term opioids	6,454	226,140.4	285.4	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	4,587	122,105.1	375.7	1.22 (1.17, 1.27)	1.14 (1.10, 1.19)
Periods on long-term opioids (daily MED < 20mg)	3,150	85,323.3	369.2	1.18 (1.13, 1.23)	1.09 (1.04, 1.14)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	1,096	28,729.5	381.5	1.26 (1.18, 1.35)	1.24 (1.16, 1.32)
Periods on long-term opioids (ADD ≥ 50mg MED)	341	8,052.2	423.5	1.42 (1.27, 1.58)	1.34 (1.20, 1.50)
Overdose (non-opioids)					
Periods not on long-term opioids	478	243,956.2	19.6	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	407	129,870.4	31.3	1.32 (1.15, 1.52)	1.23 (1.07, 1.42)
Periods on long-term opioids (ADD < 20mg MED)	189	90,388.6	20.9	0.84 (0.71, 1.01)	0.91 (0.77, 1.09)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	158	30,753.0	51.4	2.25 (1.88, 2.71)	1.71 (1.42, 2.06)
Periods on long-term opioids (ADD ≥ 50mg MED)	60	8,728.8	68.7	3.13 (2.39, 4.10)	1.71 (1.30, 2.25)
Overdose (opioids)					
Periods not on long-term opioids	118	245,001.3	4.8	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	151	130,386.5	11.6	2.16 (1.68, 2.78)	2.24 (1.73, 2.89)
Periods on long-term opioids (ADD < 20mg MED)	67	90,609.7	7.4	1.31 (0.96, 1.79)	1.59 (1.16, 2.19)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	56	30,952.7	18.1	3.41 (2.47, 4.71)	2.83 (2.04, 3.92)
Periods on long-term opioids (ADD ≥ 50mg MED)	28	8,824.1	31.7	6.15 (4.06, 9.30)	3.81 (2.50, 5.80)

ADD, average daily dose; MED, morphine equivalent dose; [a] Adjusted for age, gender, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, co-prescribing of non-steroidal anti-inflammatory drug, and for prior occurrence of adverse event.

Table 5 - Risks of falls, iron deficiency anaemia, gastrointestinal pathology, addiction, accidental poisoning and attempted suicide/self-harm in musculoskeletal patients newly prescribed long-term opioids

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Falls[b]					
Periods not on long-term opioids	8,186	221,533.7	369.5	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	6,507	118,554.4	548.9	1.39 (1.35, 1.44)	1.23 (1.19, 1.28)
Periods on long-term opioids (ADD < 20mg MED)	4,534	82,868.0	547.1	1.38 (1.33, 1.43)	1.17 (1.12, 1.21)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	1,461	28,002.6	521.7	1.35 (1.28, 1.43)	1.34 (1.27, 1.42)
Periods on long-term opioids (ADD ≥ 50mg MED)	512	7,683.8	666.3	1.74 (1.59, 1.90)	1.64 (1.50, 1.80)
Incident iron deficiency anaemia[c]					
Periods not on long-term opioids	2,501	234,507.3	106.6	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	2,085	124,349.5	167.7	1.55 (1.46, 1.65)	1.38 (1.29, 1.46)
Periods on long-term opioids (ADD < 20mg MED)	1,356	86,696.0	156.4	1.44 (1.34, 1.54)	1.24 (1.16, 1.33)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	535	29,389.9	182.0	1.69 (1.53, 1.85)	1.61 (1.46, 1.77)
Periods on long-term opioids (ADD ≥ 50mg MED)	194	8,263.6	234.8	2.18 (1.89, 2.53)	1.97 (1.70, 2.28)
Incident gastrointestinal pathology[c]					
Periods not on long-term opioids	2,419	234,393.5	103.2	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	1,812	124,218.2	145.9	1.35 (1.27, 1.44)	1.25 (1.17, 1.33)
Periods on long-term opioids (ADD < 20mg MED)	1,176	86,813.8	135.5	1.24 (1.15, 1.33)	1.14 (1.06, 1.22)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	454	29,209.8	155.4	1.45 (1.31, 1.61)	1.37 (1.24, 1.52)
Periods on long-term opioids (ADD ≥ 50mg MED)	182	8,194.6	222.1	2.10 (1.80, 2.44)	1.90 (1.63, 2.21)
Incident gastrointestinal bleeding[c]					
Periods not on long-term opioids	1,039	241,217.7	43.1	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	774	128,056.4	60.4	1.31 (1.18, 1.44)	1.18 (1.07, 1.31)
Periods on long-term opioids (ADD < 20mg MED)	509	89,095.8	57.1	1.22 (1.09, 1.36)	1.09 (0.97, 1.22)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	185	30,360.1	60.9	1.34 (1.14, 1.57)	1.26 (1.08, 1.48)
Periods on long-term opioids (ADD ≥ 50mg MED)	80	8,600.5	93.0	2.07 (1.65, 2.60)	1.88 (1.49, 2.37)
Incident addiction (non-opioids) [c]					
Periods not on long-term opioids	561	242,278.0	23.2	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	562	128,106.6	43.9	1.69 (1.50, 1.91)	1.68 (1.49, 1.91)
Periods on long-term opioids (ADD < 20mg MED)	280	89,548.5	31.3	1.16 (1.0, 1.35)	1.25 (1.08, 1.46)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	198	30,141.4	65.7	2.58 (2.19, 3.04)	2.22 (1.88, 2.62)
Periods on long-term opioids (ADD ≥ 50mg MED)	84	8,416.7	99.8	4.01 (3.18, 5.05)	2.99 (2.37, 3.78)

Incident addiction (opioids) [c]					
Periods not on long-term opioids	90	244,623.9	3.7	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	142	130,193.0	10.9	2.51 (1.90, 3.30)	2.83 (2.13, 3.76)
Periods on long-term opioids (ADD < 20mg MED)	35	90,580.3	3.9	0.81 (0.54, 1.21)	1.06 (0.71, 1.60)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	56	30,915.9	18.1	4.17 (2.97, 5.86)	3.59 (2.55, 5.06)
Periods on long-term opioids (ADD ≥ 50mg MED)	51	8,696.8	58.6	14.05 (9.93, 19.88)	9.33 (6.55, 13.29)
Accidental poisoning[b]					
Periods not on long-term opioids	47	245,249.7	1.9	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	61	130,558.2	4.7	2.47 (1.66, 3.68)	2.09 (1.40, 3.12)
Periods on long-term opioids (ADD < 20mg MED)	31	90,650.3	3.4	1.77 (1.10, 2.84)	1.53 (0.95, 2.47)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	19	31,038.7	6.1	3.17 (1.85, 5.43)	2.64 (1.53, 4.56)
Periods on long-term opioids (ADD ≥ 50mg MED)	11	8,869.3	12.4	6.43 (3.32, 12.42)	4.76 (2.43, 9.32)
Attempted suicide/self-harm[b]					
Periods not on long-term opioids	14	245,360.7	0.6	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	9	130,649.6	0.7	1.05 (0.44, 2.49)	1.01 (0.42, 2.45)
Periods on long-term opioids (ADD < 20mg MED)	4	90,686.5	0.4	0.65 (0.21, 2.02)	0.74 (0.23, 2.35)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	3	31,071.6	1.0	1.52 (0.43, 5.35)	1.24 (0.35, 4.40)
Periods on long-term opioids (ADD ≥ 50mg MED)	2	8,891.5	2.2	3.63 (0.82, 16.05)	1.87 (0.40, 8.74)

ADD, average daily dose; MED, morphine equivalent dose; [a]Adjusted for age, gender, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, and co-prescribing of non-steroidal anti-inflammatory drug ; [b]Also adjusted for prior occurrence of adverse event; [c]Excluded patients with previous record of event.

Table 6 - Risks of eczema and psoriasis in musculoskeletal patients newly prescribed long-term opioids

Adverse event	Number of events	Time at risk (person-years)	Absolute risk (per 10,000 person-years)	Crude hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Incident eczema[b]					
Periods not on long-term opioids	2,443	232,337.7	105.1	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	1,522	124,982.2	121.8	1.11 (1.04, 1.18)	1.07 (0.99, 1.13)
Periods on long-term opioids (ADD < 20mg MED)	1,025	87,031.0	117.8	1.06 (0.98, 1.15)	1.04 (0.97, 1.13)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	383	29,534.1	129.7	1.19 (1.07, 1.33)	1.13 (1.00, 1.26)
Periods on long-term opioids (ADD ≥ 50mg MED)	114	8,417.1	135.4	1.26 (1.04, 1.52)	1.10 (0.91, 1.33)
Incident psoriasis[b]					
Periods not on long-term opioids	919	239,887.8	38.3	1.0 (referent)	1.0 (referent)
Periods on long-term opioids (combined)	559	127,960.4	43.7	1.02 (0.92, 1.14)	0.98 (0.88, 1.10)
Periods on long-term opioids (ADD < 20mg MED)	389	88,855.5	43.8	1.01 (0.89, 1.14)	1.0 (0.88, 1.13)
Periods on long-term opioids (20 ≤ ADD < 50mg MED)	130	30,461.4	42.7	1.03 (0.86, 1.24)	0.94 (0.78, 1.12)
Periods on long-term opioids (ADD ≥ 50mg MED)	40	8,643.5	46.3	1.14 (0.83, 1.56)	0.96 (0.70, 1.32)

ADD, average daily dose; MED, morphine equivalent dose; [a]Adjusted for age, gender, index year, geographical region, smoking and alcohol status, body mass index, deprivation, depression consultation, comorbidity, and co-prescribing of non-steroidal anti-inflammatory drug; [b]Excluded patients with previous record of event