Title

Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: a matched cohort study in the Clinical Practice Research Datalink

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Original Article

Funding

This research was funded by infrastructure support funds from North Staffordshire Primary Care Research Consortium, KD was supported by a Research Career Development Fellowship from the Wellcome Trust (083572). ER is supported by a National Institute for Health Research (NIHR) In-Practice Fellowship.

The funders played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The remaining authors have nothing to declare.

No conflicts of interest are declared

Significance: This is the first large scale cohort examining the relationship between long-term opioid use and reproductive dysfunction using a UK national primary care database. There is an increased risk of reproductive dysfunction associated with long-term opioid use.

Abstract

Background: One fifth of primary care attendees suffer chronic non-cancer pain, with musculoskeletal conditions the leading cause. 12% of patients with chronic non-cancer pain are prescribed strong opioids. Evidence suggests long-term opioid use is related to hypogonadism in men, but the relationship in women is unclear. Our aim was to investigate reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain.

Methods: We undertook a matched (matched 1:1; for year of birth, year of start of follow-up and practice) cohort study of women aged 18-55 years old, with musculoskeletal pain and an opioid prescription in the clinical practice research datalink (a primary care database) between 2002 and 2013. Long-term opioid users (≥90 days) were compared to short-term opioid users (<90 days) for four reproductive conditions (abnormal menstruation, low libido, infertility and menopause) using cox proportional hazards models.

Results: 44,260 women were included; the median cohort age at baseline was 43 years (Interquartile Range 36-49). Long-term opioid use was associated with an increased risk of altered menstruation (Hazard Ratio 1.13 95% CI 1.05 – 1.21); and with an increased risk of menopause (Hazard Ratio 1.16 95% CI 1.10 – 1.23). No significant association was found for libido (Hazard Ratio 1.19 95% CI 0.96 – 1.48) or infertility (Hazard Ratio 0.82 95% CI 0.64 – 1.06).

Conclusions: The risk of menopause and abnormal menstruation was increased in long-term opioid users. This has implications for clinicians as reproductive dysfunction will need to be considered when prescribing long-term opioids to women with musculoskeletal conditions.

Introduction

Chronic Non-Cancer Pain (CNCP) can be defined as any painful condition lasting for three months or more and not associated with neoplastic disease (cancer) (Chapman et al., 2010). Musculoskeletal (MSK) conditions are the leading cause of CNCP (Breivik et al., 2006). Over a fifth (22%) of patients attending primary care report CNCP, and women are more commonly affected than men (Gureje et al., 1998). ~~In 2002, the United Kingdom (UK) primary care workload for CNCP accounted for 4.6 million General Practitioner (GP) appointments costing the National Health Service (NHS) £69 million (Belsey, 2002). In 2008 the annual cost of CNCP in the United States was between $560 and $635 billion, an economic burden greater than for heart disease, diabetes or cancer (Gaskin and Richard, 2012).~~

Opioid prescribing has been increasing over the past 20 years and guidelines recommend their use as a second line treatment in MSK pain (Cheung et al., 2014; National Institute for Health and Care Excellence, 2014; World Health Organisation, 1990). A cross-sectional study in Europe found 12% of those with CNCP in the UK used strong opioids and 50% used weak opioids (Breivik et al., 2006). A ~~large American cohort found an annual increase in long-term opioid prescribing between 1997-2005 of 6%, and a more~~ recent British cohort found that the number of people starting a long-term opioid increased by 38% between 2002 and 2009 (Bedson et al., 2016). Evidence for opioids' effectiveness in CNCP is weak (Els et al., 2017a; Eriksen et al., 2006; Higgins and Green, 2011; Kissin, 2013; Noble et al., 2010), and there is a growing body of evidence that they can have significant side effects, including increased morbidity, mortality and overdose risk (Dunn et al., 2010; Els et al., 2017b; Saunders et al., 2009).

Recently, concerns surrounding opioids and their effects on the endocrine system have arisen. ~~Guidelines from the~~The British Pain Society highlight the likelihood of endocrine side effects

from opioids (including reproductive dysfunction), but they conclude that there still remains insufficient data to be able to quantify the risk, ~~associated with long-term opioids~~and a recent Cochrane review found no current evidence for hypogonadism or sexual dysfunction (Els et al., 2017b; The British Pain Society, 2010). Current literature suggests that long-term opioid therapy has an ~~strong~~ impact on the male reproductive system, for which the primary mechanism is thought to be through suppression of the hypothalamic-pituitary-gonadal (HPG) axis which leads to low testosterone levels and reproductive and sexual dysfunction (Abs et al., 2000; Aloisi et al., 2009; Benyamin et al., 2008; Daniell, 2002; Katz and Mazer, 2009; Smith and Elliott, 2012). Potentially, opioids may have similar biochemical and clinical effects in women, with the addition of altered menstrual cycles and possibly galactorrhoea (Ballantyne and Mao, 2003; Brennan, 2013; Brown and Zueldorff, 2007; Colameco and Coren, 2009; Katz and Mazer, 2009; Schmittner et al., 2005; The British Pain Society, 2010). A systematic review examining reproductive dysfunction and prescribed long-term opioids in women found 12 relevant papers, and although they were small studies, the majority suggested a link between long-term opioid use and reproductive dysfunction, both biochemically (decreased sex hormones) and clinically (decreased libido and altered menstrual cycle) (Wersocki et al., 2017).

The aim of this study was to assess if long-term opioid use for MSK pain, compared to short-term use is associated with reproductive dysfunction in women.

Methods

Study setting and population

This study used data from the Clinical Practice Research Datalink (CPRD). CPRD is a high-quality, anonymised, large UK primary care database containing information on over 11 million patients from over 600 primary care practices; there are currently between 4 and 5 million active patients (Herrett et al., 2015; Williams et al., 2012). UK primary care databases

provide almost complete population coverage, as over 98% of the population are registered with GPs, who are the gatekeepers to secondary care (Garci-a Rodri-guez and Perez Gutthann, 1997; Herrett et al., 2015; Williams et al., 2012). CPRD has been compared with the UK census and was shown to be broadly representative of the UK population in terms of age, ethnicity and sex (Herrett et al., 2010). CPRD includes data on patients' clinical conditions and prescribed medications. For the purpose of analysis, the practices included (n = 350, all from English regions) were those linked to the Office for National Statistics (ONS) neighbourhood deprivation data (the Index of Multiple Deprivation) and Hospital Episode Statistics (HES) (Department for Communities and Local Government, 2011). Practices with linked data have been shown to be similar to practices without linkage in respect of demographic data, years of follow-up and prescribing of medication (Gallagher et al., 2011). All doctors in practices contributing to CPRD are trained in their recording of consultations and diagnostic codes and CPRD has been validated in previous studies (Herrett et al., 2010, 2015).

Study participants

This study represents secondary data analysis of an established cohort (Bedson et al., 2016). We identified women aged 18 to 55 years old from within the cohort, starting a long-term opioid (defined below) and with a coded non-inflammatory potentially painful MSK condition from 2002-2012. The following factors were used as exclusion criteria: a cancer diagnosis at any time prior to the first day of opioid use or within the following six month and less than one year of records within CPRD prior to the first day of opioid prescription. MSK conditions were identified from the database using a previously defined list of Read codes (a clinical coded dictionary used for recording consultations in UK primary care IT systems; list available online at www.keele.ac.uk/mrr) (Health and Social Care Information Centre, 2015; Jordan et al., 2010). Opioids were defined as analgesics used to relieve moderate or severe

pain and were identified from sections 4.7.1. and 4.7.2. of the British National Formulary (BNF) (BNF, 2014). This definition includes weak opioids such as codeine, and potent opioids such as morphine, both in long-acting (duration of action 12 hours or longer) and short-acting (duration of action 4-6 hours) forms (Fallon et al., 2006). Long-term opioid use was defined as the issue of least three opioid prescriptions within 90 days from and including the first date of a new prescription for opioids. A new episode of opioid use starts on the date of an opioid prescription if there had been no opioids prescribed within the previous six months. This definition is in line with classification of long-term opioid use in previous studies and the definition was developed by Von Korff et al (2008) following exploratory analyses (Bedson et al., 2016; Dunn et al., 2010; Von Korff et al., 2008). Any opioid prescription not fitting this definition at any point during 2002-2012 was defined as short-term opioid use (i.e. a maximum of two prescriptions within a 90 day period). The end of a period of opioid use was defined by a gap of more than six months from last use of opioids, which was taken to be 28 days after the issue of the last prescription (prescribing guidelines for controlled drugs from the NHS Business Services Authority state that no more than a 28 day supply should be given except in exceptional circumstances)(N H S Business Services Authority, 2014).

MSK conditions were identified from between 14 days before and 90 days after the start of a new episode of opioid use in order to create a temporal association between a new opioid prescription and an MSK condition. MSK conditions were chosen as they represent a large proportion of CNCP patients, with arthritis being identified as the cause for CNCP is 40% of UK patients. MSK conditions are a homogenous group and limit confounding by indication (Breivik et al., 2006). ~~Inclusion and exclusion criteria are detailed in Table 1.~~

Study design

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We conducted a matched cohort study consisting of women starting a long-term opioid (exposed population) at the time of a MSK condition, matched to women starting a short-term opioid (non-exposed population) at the time of a MSK condition. We matched for year of birth (up to ±5 years), general practice and first year of opioid use (up to ±2 years).

Follow-up

Follow-up started from 90 days after the initial opioid prescription (in both short-term and long-term opioid users) until the study outcome occurred, or for a maximum of 5 years. Censoring occurred if the patient no longer contributed data (death, practice leaving CPRD or patient leaving a CPRD practice) or if the study end date was reached (10th January 2012) prior to the end of the 5 year follow-up period.

Outcome Measures

The primary outcomes of interest were defined following a systematic review by the authors, these were altered menstruation, amenorrhoea (absent menstruation) or oligomenorrhoea (less frequent menstruation, either less than 9 menstrual periods a year or at least 35 days in between menstrual periods), decreased libido, menopause and infertility (Impey and Child, 2012; Norwitz and Schorge, 2013; The Practice Committee of the American Society for Reproductive Medicine, 2008; Wersocki et al., 2017). These outcomes were identified through searching the database for relevant Read codes from 90 days after commencing opioids until end of follow-up. The read code list for each outcome was developed by EW and then reviewed by JB who is experienced in developing read code lists and a consensus decision was reached; both are academic GPs in the UK (lists available online at www.keele.ac.uk/mrr). Outcomes were analysed separately so each participant could have more than one outcome.

Covariate data

Data on comorbidities was collected over a 15-month time period, from 12 months before initial opioid prescription until 3 months after (when follow-up began). Three types of comorbidity data were identified. The outcomes of interest were considered comorbidities if they occurred prior to the start of follow-up, and they were identified in the same way as described for outcome measures. The following covariates were also identified: thyroid conditions, low BMI <18 (as a coded condition), adrenal conditions, obesity (as a coded condition), and BMI (categorised as <25 kg/m2, ≥25 kg/m2 (overweight) or missing) was recorded at the date closest to the start of follow-up, structural gynaecology condition and illegal opioid misuse. These conditions were chosen following a literature search for common conditions that could be associated with the outcomes of interest. Finally the total number of prescriptions were mapped to BNF sections and used as a surrogate measure for the number of comorbid conditions (Perkins et al., 2004).

Alcohol and smoking were categorised as never, ever or missing and was identified prior to the start of follow-up. Age was included within analysis as a continuous variable.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with anovulation, therefore we specifically identified co-prescribing with NSAIDs for 4 months prior to the start of follow-up (Salman et al., 2015).

Statistical Analysis

The baseline demographics of the two groups were first described and compared using appropriate simple statistical tests (Wilcoxon-Mann-Whitney or Chi squared test).

The rates of adverse events per 10,000 person-years at risk in short-term and long-term opioid user groups were determined. Cox proportional hazards models were used to produce both unadjusted and adjusted hazard ratios (HRs), estimating the effects of association between opioid use and reproductive dysfunction. The validity of the proportional hazards

assumption was tested using Schoenfeld residuals, where the proportional hazards assumption was violated those covariates were included as time varying covariates (see Table 34) (Bellera et al., 2010). HRs were adjusted for the covariates described above. Sensitivity analyses were undertaken using first a complete case approach, secondly removing those with pre-existing outcome conditions and finally removing all those women with reported menopausal symptoms (a proxy for analysis of those not receiving Hormone Replacement Therapy (HRT)). Data was analysed using STATA 14.0 (StataCorp, 2017).

Ethics committee approval

Approved by the CPRD Independent Scientific Advisory committee (reference number ISAC, Protocol No. 13_135).

Results

The study cohort included 44,260 women (22,130 long-term opioid users and 22,130 short-term users). Table 12 shows the baseline characteristics of the two groups. The median age in both groups was 43. Long-term opioid users were more likely to use NSAIDs, have a higher BMI, have more comorbidities and to be smokers when compared with short-term opioid users (see Table 12). Median follow-up was 39 months, the total number of years under follow-up for each outcome is shown in table 23.

The incidence of abnormal menstruation was higher for long-term opioid users (209.5 per 10,000 person-years (95% CI 199.0 – 220.7)) than for short-term opioid users (186.2 per 10,000 person-years (95% CI 176.4 - 196.7)). The adjusted HR showed an increased risk of abnormal menstruation 1.13 (95% CI 1.05 – 1.21) for long-term opioid users compared to short-term opioid users over the five year follow-up.

The incidence of menopausal symptoms was higher in long-term opioid users (383.7 per 10,000 person years (95% CI 369.1 – 398.8)) than in short-term opioid users (330.9 (95% CI

317.5 – 344.8)). The adjusted HR was 1.16 (95% CI 1.10 – 1.23) for long-term users compared with short-term users.

Low libido had an incidence in long-term opioid users of 27.7 per 10,000 person years (95% CI 24.0 – 31.8) and in short-term users of 22.6 (95% CI 19.4 – 26.4). The adjusted hazard ratio did not find a statistically significant difference in risk of low libido between long-term and short-term opioid users (adjusted HR 1.19, 95% CI 0.96-1.48).

Infertility had an incidence in short-term opioid users of 19.0 per 10,000 person years (95% CI 16.0 – 22.5) and a lower incidence in long-term opioid users of 16.4 (95% CI 13.7 – 19.7). However, there was no statistically significant difference in risk of infertility seen with the adjusted Cox regression between short-term and long-term opioid users (adjusted HR 0.82, 95% CI 0.64 – 1.06).

Sensitivity analysis using only complete cases, removing those with menopausal symptoms and also for those without pre-existing reproductive dysfunction gave similar results (see Table 4~~5~~).

Discussion

To our knowledge, this study of over 40,000 opioid users in primary care is the first to demonstrate an increased risk of abnormal menstruation and of menopausal symptoms in women aged 18-55 years prescribed long-term opioids compared with short-term opioids. The relationship between opioid use and low libido and infertility was not so clear. These results are consistent with the limited current literature, where a recent systematic review found a possible relationship between opioid use and female reproductive dysfunction (Wersocki et al., 2017).

Women aged 18-55 years old with painful MSK conditions and prescribed opioids were identified for this study. We used MSK pain to define the cohort rather than all cause CNCP

as MSK conditions represent a large proportion of CNCP cases and are a more homogenous group of conditions, in order to address some elements of indication bias (Breivik et al., 2006). However, residual confounding cannot be ruled out as one explanation for the findings, particularly where severity and longevity of the MSK condition is not taken into account. We also cannot be completely confident that the opioid was prescribed for an MSK condition, since if the indication was a different type of pain this may introduce additional confounding. As our cohort included only participants with MSK pain this may mean the results are not generalizable to other types of CNCP. It is also important to note that the MSK conditions include all joints and all MSK conditions that would not be considered inflammatory. Accordingly, this still represents a broad group of conditions.

The women in the long-term opioid use group also had a higher number of comorbidities than the short-term opioid use group which may indicate that they may experience poorer health in general. Additionally the increased stress levels that may be associated with increased comorbidity can be associated with some of the outcomes of interest; however, this was adjusted for during Cox regression (The Practice Committee of the American Society for Reproductive Medicine, 2008). Long-term opioid users were also more likely to be smokers and there is some evidence that smoking can be associated with premature ovarian failure (POF), however we were able to include smoking within the analysis in order to account for this (Luborsky et al., 2003). There was a significant difference seen for alcohol use as well with long-term opioid users appearing to drink less alcohol. There is evidence that alcohol use can be associated with low libido and this was also adjusted for within the analysis (Arunakumari and Walker, 2009). The groups were also significantly different in statistical terms with respect to ethnicity where there was also a large amount of missing data, due to the missing data. As a consequence we were unable to adjust for ethnicity and this is a

potential limitation as there is some evidence that distinct ethnic groups enter the menopause at different ages and experience variation in rates of POF (Luborsky et al., 2003).

Everyone in the cohort was considered suitable to receive prescribed opioids and this decreases potential systematic differences between the comparison groups. However, the groups may still be different in terms of the severity or nature of the underlying condition. We have also not assessed the impact of daily morphine equivalent opioid dose and it may be that long-term users were receiving higher daily doses, although there is evidence in the UK that the majority of long-term opioid users are receiving less potent opioids such as codeine 15mg, this would be an important area for future research (Bedson et al., 2016). The identification of women as either long-term or short-term opioid users was based on issued prescriptions, although we cannot definitely establish how or if the patient used the medication. It is also important to note that opioid exposure was only identified at baseline and participants did not move in and out of opioid exposure groups, whereas in real life opioid exposure is time-varying so this may have an impact on the generalisability of the results. The study is unable to report on the risk associated with opioid use compared to no opioid use for the adverse effects studied (as the comparison was between opioid duration), this is a limitation of the study. However it was felt that comparing duration of opioid use reduced the likelihood of confounding by indication and this was an important consideration when designing the study. It also removed the possibility of contraindications to opioid prescribing affecting the prescription of opioids in either group. Further attempts were made to control for confounding through statistical adjustment for important factors including: age, BMI, smoking status, NSAID use and medical conditions associated with the outcomes of interest. The study did not identify women receiving HRT or hormonal contraception and these may have affected results, but there is no reason to suspect usage is different between the short-term and long-term opioid users. We undertook a sensitivity analysis where women

with a diagnosis of menopause were removed and there was no difference seen in the results for the other outcomes (see Table 4). We were unable to include hormonal contraception within the analysis as CPRD does not capture all the relevant information, in the period from April 2012 to March 2013 1.2 million women attended family planning clinics and of these 47% received oral contraception and this information would not be routinely recorded within CPRD (Health and Social Care Information Centre, 2013). Given the different routes through which women can access oral contraception we were unable to confidently include this within the analysis.

The use of CPRD was a strength, as it allowed us access to a large sample of opioid users which provided enough statistical power to undertake the appropriate analysis. A particular strength of this study when compared to the current body of evidence which is mainly set in secondary care is its generalisability to primary care, as CPRD is broadly representative of the UK population (Herrett et al., 2010). Only 23% of pain patients are seen by a pain specialist, so these secondary care studies may represent a subset of patients with more severe pain conditions (Breivik et al., 2006). There will be little missing data, as in the UK prescriptions are recorded automatically in the electronic records on issue and CPRD practices must code a condition when prescribing; this will also have helped reduce missing data when identifying outcomes of interest (Lawson et al., 1998). In the UK the only opioids available without a prescription are low dose codeine and dihydrocodeine and then they are only recommended for a maximum of three days for acute painful injuries and come in a maximum pack size of 32 tablets, so any long-term opioid use should be via prescription (Medicines and Healthcare products Regulatory Agency, 2009). CPRD has previously been shown to be valid for identifying patients with MSK conditions (Jordan et al., 2006). A review of CPRD studies found a median proportion of confirmed diagnoses of 89% over 357 validation studies examining 183 diagnoses (Herrett et al., 2010).

The number of women with low libido within the cohort was lower than would be expected, with only 0.8% of the cohort having a coded diagnosis compared to population estimates of between 25 and 50% (Dunn et al., 1998; Laumann et al., 2005). This is likely to have affected the possibility of finding a statistically significant relationship. This also raises the question as to why there were such low numbers. Sexual dysfunction is more subjective condition in women when compared to men and they may worry about their privacy in relation to presenting clinically (Montgomery, 2008). Treatment options for sexual dysfunction in women is poor. Consequently women with sexual dysfunction infrequently present in primary care creating a clinical iceberg (Last, 1963). Investigation of low libido might be better undertaken in other ways, for instance a cross-sectional study.

In conclusion, this large cohort study has uniquely found that women aged 18-55 years receiving long-term opioids for painful MSK conditions were at increased risk of menopause and abnormal menstruation when compared with women receiving short-term opioids. This is an important finding against the background of increasing long-term opioid use (Bedson et al., 2016). This should be considered when clinicians are prescribing opioids and discussed with patients. If a patient is receiving opioids, ~~it should also~~ this should be considered ~~as a possible causative factor~~ when investigating women presenting with reproductive dysfunction. It is recommended that clinicians undertake regular reviews of patients prescribed long-term opioids and to assess the effectiveness of the medication but also to raise the possibility of adverse effects including reproductive adverse effects as patients may not volunteer these symptoms. The study was unable to find a definite link for low libido, and further research is required, potentially using direct patient data collection. Further research may also be needed to identify whether there is a daily dosage level where risk becomes more significant.

Acknowledgements

This research was funded by infrastructure support funds from North Staffordshire Primary Care Research Consortium, KD was supported by a Research Career Development Fellowship from the Wellcome Trust (083572). ER is supported by a National Institute for Health Research (NIHR) In-Practice Fellowship.

The funders played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The remaining authors have nothing to declare.

Author Contributions

JB, YC, ER and KD were involved in the development of the research question and methods.

ER and YC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

All authors discussed and interpreted the results, commented on the manuscript and approved the final draft.

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Table 1. Characteristics of study participants on short- and long-term opioids (n=44260).

Table 1 footnote: Data is either presented as n,% or median (interquartile range). P value was obtained from Wilcoxon-Mann-Whitney or Chi-squared tests where appropriate.

Table 2. Hazard Ratios for the relationship between length of opioid exposure and each reproductive dysfunction outcome.

Table 2 footnote: [a] adjusted for the outcome of interest (if pre-existing), thyroid conditions, structural gynaecological conditions, illegal opioid use, NSAID use, BMI (<25kg/m^2, ≥25kg/m^2 or missing), smoking status, alcohol use and age

Table 3 Proportional-hazards assumption test and time-varying covariates entered into each Cox regression model.

Table 4 Sensitivity Analysis for complete cases only, excluding women with menopausal symptoms (both pre-existing and new) and if outcome is present prior to start of follow-up