

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prescribed opioids in primary care: cross sectional and longitudinal analyses of influence of patient and practice characteristics
AUTHORS	Foy, Robbie; Leaman, Ben; McCrorie, Carolyn; Petty, Duncan; House, AO; Bennett, Mike; Carder, Paul; Faulkner, Simon; Glidewell, Liz; West, Robert

VERSION 1 - REVIEW

REVIEWER	Catherine Stannard Pain Clinic Gloucester House Southmead Hospital Bristol BS10 5ND UK
REVIEW RETURNED	16-Nov-2015

GENERAL COMMENTS	This is an important and timely study. It is clear from the introduction, methodology and discussion that the authors have a very detailed knowledge of the complexity of influences around opioid prescribing informed by an accurate and insightful review of current literature. The important associations revealed in the results add much needed detail to the picture of increasing opioid prescribing for non-cancer pain in the face of clear evidence that this is more likely to be harmful than helpful. What we do know in practice is that the influences on prescribing are shaped by a number of prescriber factors and influences that extend beyond the immediate clinical interaction, including the role of medicines management teams, local formularies, commissioning influences, political imperatives, influence of carers and friends and messages from the media. This study retains a rational focus given the data available for analysis. I think the paper adds value to the current opioid debate but could be enhanced a little further by acknowledgement in the introduction and discussion about the importance of the myriad other influences on opioid prescribing including the very important dynamic of the patient-prescriber relationship, which, while very difficult to quantify and analyse, may well be contributing to some of the unexplained variances identified in this rich paper.
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REVIEWER	Roger Knaggs University of Nottingham and Nottingham University Hospitals NHS Trust
REVIEW RETURNED	07-Dec-2015

GENERAL COMMENTS	This manuscript describes several studies analysing routinely collected data to identify patient and practice characteristics associated with changes in opioid prescribing. Abstract In the section describing the participants it would be helpful to describe the purpose of the cross-sectional and longitudinal analyses. Rather than use the phrase 'referrals for pain management' in the results section, I would use the phrase 'to specialist pain management services' Background The last paragraph describes a current 'opioid epidemic'. This is certainly the case in the US but whether there are similar issues in the UK and other European countries is unclear. Methods Variables Tramadol and tapentadol have been classified as weak opioids, however both are classed strong opioids in the BNF. Please justify. Were different formulations How were smoking status and BMI defined. Results Page 9 Para 3 Line 3 Sentence is missing 'for' between 'unavailable' and 'one' Page 10 Para 8 Line 2 Unclear where the odds quoted for stepping up an stepping down have come from - the figures quoted do not appear in table 5 Tables 2-5 contain large amounts of data. Greater use of bold sub-heading would be helpful for the reader Table 2 Several of the variables (e.g. Practice Index of Multiple Deprivation and proportion of salaried GP) have identical end and start boundaries The format of references should be reviewed and amended in line with format required.
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REVIEWER	Areti Boulieri Department of Epidemiology and Biostatistics Imperial College London, UK
REVIEW RETURNED	16-Feb-2016

GENERAL COMMENTS	The authors present an observational study of patient data from general practices in Leeds and Bradford over the period April 2005 - March 2012. The analysis is split into 3 parts: i) descriptive temporal trends of opioid prescribing, ii) a cross sectional study which considers the last year of data aiming to assess patient- and practice-characteristics associated with long-term and strong opioid prescribing, and iii) a longitudinal study which considers the last 4 years of the data aiming to assess patient- and practice-characteristics associated with stepping up to and down from opioid prescribing. Overall, this is an interesting study with an appropriate study design and statistical approach. However, I found that it lacks
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	clarity on some crucial aspects and that sometimes the level of details is not appropriate to allow the reader to fully understand it. My detailed comments are described below: Abstract 1) The setting of the study is 111 practices only for the last year. Previous years consider fewer practices. Please delete the number or amend accordingly. Background 1) It is not crystal clear what the novelty of the manuscript is. The authors should be more explicit as to how this study furthers existing knowledge about opioid prescribing within primary care populations. 2) Pg 5, paragraph 4: high risk prescribing is not previously stated. The corresponding definition is provided in the referenced paper however here it is not clear. Methods 1) Pg 5, paragraph 6: The temporal coverage for the cross sectional and longitudinal studies is not specified. It is implied here that all data (April 2005 to Mar 2012) are used which is not the case. 2) Pg 6, paragraph 1: Some more information is needed about the SystmOne platform. When was it introduced? Did the authors consider that there might be systematic differences between the practices that use SystmOne and those that don't? 3) Pg7, paragraph 5: The authors acknowledge that the data collection within each 12-month period restricts the study to the incident cases. However, a more important consequence of this is the misclassification issue: it seems reasonable to me that patients who suffer from a chronic mental condition or alcohol problems are not recorded as such every single year. Isn't there a way to account for this, for instance to include data on patient-level characteristics from previous years? 4) The classification of variables (long-term prescribing, drinker group, GP consultations and missing appointments) into categories needs references. Is it based on specific guidelines? Also, what do BL, AH.. represent for the illness variable? 5) Pg 7, paragraph 4: The part with the IMD variable is a bit confusing. What information was originally available? (ie IMD of LSOA where each patient lives?) The authors need to explain why they chose to include it as a practice-level variable and not as a patient-level one. Furthermore, did they eventually use the mean value of all IMDs? Perhaps the median value would be more appropriate here. 6) The authors properly account for the hierarchical structure of the data through the random effects model. Not enough information is provided though about the model implementation. For instance, how are the variables introduced into the model? Is there performed a model selection? This is an important aspect of the analysis, as it might introduce bias in the results. Also, it seems that a large number of variables are included in the model, and some of them are likely to be highly correlated (ie overweight, underweight). Collinearity might be also apparent between a patient-level predictor and a practice-level predictor and consequently introduce confounding into the model. Did the authors check for this? They should at least provide a correlation matrix. 7) How were the 17165 patients chosen for the longitudinal study? Are the ones with missing variables excluded? Is the missingness systematic? 8) How were the person-years calculated?
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	9) What software was used for the analysis? Results 1) The authors need to provide additional information in Table 1 – apart from the number of practices included in the study, it is also important to know the total number of all practices in each year and the corresponding number of practices using SystmOne. They should also provide information on the exclusion criteria for each year (if other than non-enrolment to SystmOne). 2) The results section lacks some pieces of information for allowing appropriate interpretation. How are the ORs for the stronger opioid outcome estimated? I find it a bit confusing that the authors present in Table 1 the nb of patients prescribed weak opioid at least once (96959), and the nb of those prescribed strong opioid at least once (6605), while in Table 2 they classify patients as 'weaker only' (93242) and 'stronger' (6605). What is taken as a baseline here? Additionally, wouldn't it make more sense to classify patients as 'weak only', 'weak and strong', and 'strong only' in order to observe patterns for all three groups? Please clarify. 3) The tables need some improvement. First, it is not mentioned what the numbers in parentheses indicate. Second, the headings could be more informative – for instance, 'long-term versus short-term opioid prescriptions'. Third, the level of significance of the results is not provided (ie p-values *, **, or ***?). I would also suggest that a column is added with the sign of the coefficient (+) or (-) to increase readability. 4) Pg 9, last paragraph, first sentence: Where can we find this info in Table 4? I presume this is the random effect component which is not shown here.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

This is an important and timely study. It is clear from the introduction, methodology and discussion that the authors have a very detailed knowledge of the complexity of influences around opioid prescribing informed by an accurate and insightful review of current literature. The important associations revealed in the results add much needed detail to the picture of increasing opioid prescribing for non-cancer pain in the face of clear evidence that this is more likely to be harmful than helpful.

What we do know in practice is that the influences on prescribing are shaped by a number of prescriber factors and influences that extend beyond the immediate clinical interaction, including the role of medicines management teams, local formularies, commissioning influences, political imperatives, influence of carers and friends and messages from the media. This study retains a rational focus given the data available for analysis. I think the paper adds value to the current opioid debate but could be enhanced a little further by acknowledgement in the introduction and discussion about the importance of the myriad other influences on opioid prescribing including the very important dynamic of the patient-prescriber relationship, which, while very difficult to quantify and analyse, may well be contributing to some of the unexplained variances identified in this rich paper.

Thank you for this suggestion. We agree that that much of the variation we observed, and could not explain using routinely collected data. We also acknowledge the likely influence of wider system and social factors on prescribing. We have added a comment to this effect in the Discussion.

Reviewer 2

Abstract

In the section describing the participants it would be helpful to describe the purpose of the cross-sectional and longitudinal analyses.

We now delineate the three objectives of the study at the start of the Abstract, and have edited the Abstract further to keep within the 300 word limit.

Rather than use the phrase 'referrals for pain management' in the results section, I would use the phrase 'to specialist pain management services'

We have changed this phrasing in the abstract and throughout the manuscript.

Background

The last paragraph describes a current 'opioid epidemic'. This is certainly the case in the US but whether there are similar issues in the UK and other European countries is unclear.

We jumped the gun here with this piece of rhetoric; indeed, one purpose of our study was to describe opioid trends in a sample of UK general practices. We have therefore applied this term earlier and specifically to the US context.

Methods

Variables

Tramadol and tapentadol have been classified as weak opioids, however both are classed strong opioids in the BNF. Please justify.

We accept that there is a discrepancy between the categorisation we applied (from: Leppert W. Pain management in patients with cancer: focus on opioid analgesics. Current pain and headache reports 2011;15(4):271-9) and that in the BNF. Our categorisations will still allow readers to interpretation our findings.

Were different formulations

This appears to be an incomplete comment.

How were smoking status and BMI defined?

We used the most recently recorded codes for smoking, as well as other patient variables, recognising that clinical recording is of limited reliability (acknowledged under our study limitations) We used the most recently recorded BMI in each year and assigned patients accordingly as underweight (BMI under 18.5), normal (18.5 to 25), overweight (25 to 30); and obese (over 30). We have now clarified this in the manuscript.

Results

Page 9 Para 3 Line 3

Sentence is missing 'for' between 'unavailable' and 'one'

Corrected – thank you.

Page 10 Para 8 Line 2

Unclear where the odds quoted for stepping up an stepping down have come from - the figures

quoted do not appear in table 5

This was an oversight; these odds were only intended for the text and do not appear in Table 5. We have changed the position of the reference to Table 5 accordingly.

Tables 2-5 contain large amounts of data. Greater use of bold sub-heading would be helpful for the reader

We agree that the Tables contain large amounts of data (in accordance with reporting requirements). Given that we have already used a number of bold sub-headings, we have used italics for further sub-sections.

Table 2. Several of the variables (e.g. Practice Index of Multiple Deprivation and proportion of salaried GP) have identical end and start boundaries

This is because we divided the data into thirds for a number of variables. For example, For Practice Index of multiple deprivation in Table 2, the values for the middle third of the practices lie between 26.7 and 39.5 whilst the values for the highest third lie between 39.5 and 57.5.

The format of references should be reviewed and amended in line with format required.

We used the BMJ style for references in Endnote. We have checked and this appears correct: <http://journals.bmj.com/site/authors/preparing-manuscript.xhtml>

Reviewer 3

The authors present an observational study of patient data from general practices in Leeds and Bradford over the period April 2005 - March 2012. The analysis is split into 3 parts: i) descriptive temporal trends of opioid prescribing, ii) a cross sectional study which considers the last year of data aiming to assess patient- and practice-characteristics associated with long-term and strong opioid prescribing, and iii) a longitudinal study which considers the last 4 years of the data aiming to assess patient- and practice-characteristics associated with stepping up to and down from opioid prescribing. Overall, this is an interesting study with an appropriate study design and statistical approach. However, I found that it lacks clarity on some crucial aspects and that sometimes the level of details is not appropriate to allow the reader to fully understand it. My detailed comments are described below:

Abstract

The setting of the study is 111 practices only for the last year. Previous years consider fewer practices. Please delete the number or amend accordingly.

We considered deleting the number of practices as suggested. In that case, readers would be unable to judge the scale of our study from the Abstract. We considered other amendments but incorporating these would have resulted in leaving other critical detail out of the abstract.

Background

It is not crystal clear what the novelty of the manuscript is. The authors should be more explicit as to how this study furthers existing knowledge about opioid prescribing within primary care populations.

Whilst number of studies have examined associations with long-term or strong opioid prescribing, these have often related to selected or largely US-based patient groups. Studies in more typical primary populations have examined associations with prescribing but generally not attempted to tease out risk factors associated with increases or duration or strength of opioid prescribing. We have clarified our aim at the end of the Background: "We aimed to improve understanding of patient

trajectories towards long-term and stronger opioid prescribing in a UK primary care population.”

Pg 5, paragraph 4: high risk prescribing is not previously stated. The corresponding definition is provided in the referenced paper however here it is not clear.

We have now incorporated the definition in our text.

Methods

Pg 5, paragraph 6: The temporal coverage for the cross sectional and longitudinal studies is not specified. It is implied here that all data (April 2005 to Mar 2012) are used which is not the case.

We have now specified the data coverage periods for all three studies.

Pg 6, paragraph 1: Some more information is needed about the SystmOne platform. When was it introduced? Did the authors consider that there might be systematic differences between the practices that use SystmOne and those that don't?

Table 1 gives an indication of the growth in coverage of SystmOne from 2005, and hence inclusion in our sample. We do not hold data comparing characteristics of practices that use SystmOne in Leeds and Bradford with those of practices that use other systems. However, over 80% of practices in Leeds and Bradford used SystmOne at the time of our study and our sample is therefore likely to represent a typical range of practices. Nationally, however, use of SystmOne is associated with higher QOF achievement (Kontopantelis et al, 2013), raising the question of whether particular system characteristics facilitate higher quality of care, better data recording or both. This may be of limited relevance to our study as our dependent variables are not directly related to QOF targets. We have now highlighted that we used data from only one practiced computerised record system under study limitations.

Pg7, paragraph 5: The authors acknowledge that the data collection within each 12-month period restricts the study to the incident cases. However, a more important consequence of this is the misclassification issue: it seems reasonable to me that patients who suffer from a chronic mental condition or alcohol problems are not recorded as such every single year. Isn't there a way to account for this, for instance to include data on patient-level characteristics from previous years?

We were unable to identify such diagnoses from previous years from our dataset; we already acknowledge this under limitations.

The classification of variables (long-term prescribing, drinker group, GP consultations and missing appointments) into categories needs references. Is it based on specific guidelines? Also, what do BL, AH.. represent for the illness variable?

We describe in the text how we derived our categories, adding some additional detail suggested by Reviewer 2. We have also added references, including to support our operational definition of long-term opioid prescribing. However, our categorisation of GP consultations, missed appointments and other independent variables was data driven.

Under illness variables, 'BL, AH, RF and DP' are the initials of the authors.

Pg 7, paragraph 4: The part with the IMD variable is a bit confusing. What information was originally available? (ie IMD of LSOA where each patient lives?) The authors need to explain why they chose to include it as a practice-level variable and not as a patient-level one. Furthermore, did they eventually use the mean value of all IMDs? Perhaps the median value would be more appropriate here.

We were unable to obtain patient-level deprivation data because of concerns about potential identification of individuals in our dataset. We categorised practice IMD into thirds and hence used tertiles rather than the median.

The authors properly account for the hierarchical structure of the data through the random effects model. Not enough information is provided though about the model implementation. For instance, how are the variables introduced into the model? Is there performed a model selection? This is an important aspect of the analysis, as it might introduce bias in the results. Also, it seems that a large number of variables are included in the model, and some of them are likely to be highly correlated (ie overweight, underweight). Collinearity might be also apparent between a patient-level predictor and a practice-level predictor and consequently introduce confounding into the model. Did the authors check for this? They should at least provide a correlation matrix.

We recognise that the manuscript is already lengthy with detailed tables. We only described model fitting briefly once in order to focus on the findings. We included a random intercept term for practices and for ethnicity and these points are explained in the manuscript. Model selection was driven by hypothesised or evidenced associations as explained in the text. Terms for which the effect size was small and for which statistical significance at the 5% level was not reached were dropped from the model for reasons of parsimony. This is stated in the manuscript. This may have led to bias and we have added a comment to the discussion.

How were the 17165 patients chosen for the longitudinal study? Are the ones with missing variables excluded? Is the missingness systematic?

These were the 17165 patients prescribed any opioid in each of the four years considered for the longitudinal study. Our models excluded patients with missing covariates; patients with missing data may systematically differ from those with complete data. We earlier acknowledged these issues as limitations in the Discussion.

How were the person-years calculated?

The number of patient years was calculated by multiplying the number of patients included in all four years of the longitudinal study by four.

What software was used for the analysis?

Thank you – we have now specified this and added relevant citations. All analyses conducted used R statistical software, specifically Revolution R Open 3.2.0, with the lme4 library version 1.1.7.

Results

The authors need to provide additional information in Table 1 – apart from the number of practices included in the study, it is also important to know the total number of all practices in each year and the corresponding number of practices using SystmOne. They should also provide information on the exclusion criteria for each year (if other than non-enrolment to SystmOne).

Data on the total number of practices for previous years are not routinely available. We are uncertain about the added value of pursuing such data and suggest that the practice participation data we provide at the start of the Results allows readers to judge the sufficiency of our sample. There were no exclusion criteria applied to each year other than non-enrolment to SystmOne.

The results section lacks some pieces of information for allowing appropriate interpretation. How are the ORs for the stronger opioid outcome estimated? I find it a bit confusing that the authors present in

Table 1 the nb of patients prescribed weak opioid at least once (96959), and the nb of those prescribed strong opioid at least once (6605), while in Table 2 they classify patients as 'weaker only' (93242) and 'stronger' (6605). What is taken as a baseline here? Additionally, wouldn't it make more sense to classify patients as 'weak only', 'weak and strong', and 'strong only' in order to observe patterns for all three groups? Please clarify.

Table 1 is intended to describe the basic prescribing patterns over 2005-12. We judged that it made sense to present the numbers prescribed any opioid at least once, a weaker opioid at least once and a stronger opioid at least once to allow readers to see how many prescriptions each group received on average per year. Table 1 is not intended to provide a baseline for subsequent tables.

The tables need some improvement. First, it is not mentioned what the numbers in parentheses indicate. Second, the headings could be more informative – for instance, 'long-term versus short-term opioid prescriptions'. Third, the level of significance of the results is not provided (ie p-values *, **, or ***?). I would also suggest that a column is added with the sign of the coefficient (+) or (-) to increase readability.

The numbers in parentheses in Tables 2 and 3 are percentages; we have now clarified this. We suggest that our table headings provide efficient descriptions within the confines of space (but would be happy to accept a further, editorial steer on this and other aspects of presentation). We have not included significance levels as we suggest that the confidence intervals provide sufficient information. We disagree with the suggestion of adding a column to indicate the sign of the coefficient as this is also indicated by the confidence intervals. However, realising that we are presenting readers with a lot of information, we therefore provided Table 6 to provide an overview of our findings.

Pg 9, last paragraph, first sentence: Where can we find this info in Table 4? I presume this is the random effect component which is not shown here.

This was an oversight; these odds were only intended for the text and do not appear in Table 4. We have changed the position of the reference to Table 4 accordingly.

VERSION 2 – REVIEW

REVIEWER	Areti Boulieri Imperial College London, UK
REVIEW RETURNED	18-Mar-2016

GENERAL COMMENTS	The authors have addressed most comments adequately.
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