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FULL TITLE: Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: A systematic review and meta-analysis

RUNNING TITLE: Incidence of iatrogenic opioid dependence or abuse

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Abstract

Background: The prevalence and incidence of chronic conditions, such as pain and opioid dependence, have implications for policy development, resource allocation and healthcare delivery. The primary objective of the current review was to estimate the incidence of iatrogenic opioid dependence or abuse following treatment with opioid analgesics.

Methods: Systematic electronic searches utilised six research databases (Embase, Medline, PubMed, Cinahl Plus, Web of Science, OpenGrey). A 'grey' literature search and a reference search of included articles were also undertaken. The PICOS framework was used to develop search strategies and the findings are reported in accordance with the PRISMA Statement.

Results: Following eligibility reviews of 6164 articles, 12 studies (involving 310,408 participants) were retained for inclusion in the meta-analyses. A random effects model (DerSimonian-Laird method) generated a pooled incidence of opioid dependence or abuse of 4.7%. There was little within-study risk of bias and no significant publication bias; however, substantial heterogeneity was found among study effects (99.78%). Sensitivity analyses indicated that the diagnostic criteria selected for identifying opioid dependence or abuse (DSM-IV versus ICD-9) accounted for 20% and duration of exposure to opioid analgesics accounted for 18% of variance in study effects. Longer-term opioid analgesic exposure, and prescription of strong rather than weak opioids, were associated with a significantly lower incidence of opioid dependence or abuse.

Conclusions: The incidence of iatrogenic opioid dependence or abuse was 4.7% of those prescribed opioids for pain. Further research is required to confirm the potential for our findings to inform prevention of this serious adverse event.

Keywords: Analgesics, opioid; Incidence; Opioid-related disorders; Pain.

Introduction

Rationale

The prevalence and incidence of chronic, relapsing conditions, such as chronic pain, have implications for policy development, resource allocation and healthcare delivery. Physical dependence and addiction are major clinical concerns that may deter adequate analgesic prescribing for patients whose previous treatment regimens have proven unsuccessful. Abuse and diversion of these drugs is an increasing problem that has been associated with increased prescribing rates[1]; however, there is little robust scientific evidence concerning the incidence of iatrogenic dependence disorders associated with opioid analgesic therapy. Indeed, there is growing interest[2] in the phenomenon of 'pseudoaddiction', an "iatrogenic syndrome that mimics the behavioural symptoms of addiction" in patients receiving inadequate analgesia[3]. This growing interested was highlighted in a systematic review examining the 'footprint' of pseudoaddiction in the literature[2]; however, it concluded that, to date, there is insufficient evidence to support or refute the existence of this phenomenon.

As the current review highlights, there is a dearth of prospective data examining *de novo* incidence of opioid misuse following analgesic prescribing; however this issue has been examined retrospectively[4 5]. These studies are limited, however, by an inability to establish the relative onset of chronic pain and opioid dependence. Patients are likely to seek analgesic treatment at an early stage in the development of pain, because it is perceived as problematic immediately following onset. Treatment for opioid dependence, however, is likely to be sought at a relatively later stage in disease development, because it is often not perceived as 'problematic' until symptoms become unmanageable. Additional issues arise due to the vague, and frequently changing, definitions associated with terms such as 'addiction' – a ubiquitous term in the literature which has been used synonymously with 'dependence' or with the wider definition of 'abuse', or, synonymously as an umbrella term, with 'aberrant drug-related behaviour'.

Several reviews have examined the relationship between opioid analgesic prescribing and opioid misuse[6 7 8 9 10]; however, many examined prevalence (existing cases) – rather than incidence (new cases) – and, in consequence, were unable to conclude that dependence or abuse was a direct function of opioid analgesic treatment. Furthermore, since studies included in many of these reviews were unable to control for pre-trial substance misuse, findings may reflect prevalence – rather than incidence – and, therefore, may not reflect a truly iatrogenic phenomenon.

Whilst the physiological characteristics of acute dependence are anticipated following prolonged exposure to opioids, clinical diagnoses of opioid dependence or abuse disorders are not. Acute tolerance is demonstrated to occur several minutes or hours following exposure[11]; however, dependence associated with prolonged exposure has not be characterised. Some studies have suggested that the proposed 7 days[12] has not been challenged adequately and remains a valid threshold[13] whilst other studies have used a more cautious approach to ensure that there is no controversy – for example, 2 weeks[14], 1 month[15] or 3 months[16].

The development of addiction-related problems is influenced by numerous factors and, as such, cannot be considered to be a direct function solely of opioid prescribing; however, the iatrogenic component is of key concern to both policy-makers and practitioners. Whilst it is important to acknowledge that a number of reviews have examined this topic, as recently as 2015, their translational value has been restricted by two important limitations. First, a wide range of addiction-related outcomes have been addressed without their having been defined clearly in these reviews and/or in included articles. This limits the potential for pooling homogenous study findings. Secondly, addressing prevalence (existing cases) – rather than incidence (new cases) – prevents control of pre-existing addiction-related problems. Such an examination of prevalence would, therefore, result in the inclusion of participants whose pre-existing drug-seeking behaviour led them to seek opioid analgesic treatment. Whilst information concerning the prevalence of addiction-related problems in patients in receipt of opioid analgesics is relevant, in terms of resource allocation, it does not permit elucidation on opioid dependence or abuse as an iatrogenic syndrome. The present review is distinguished from previous reviews in that it: (1) focuses on clinically-diagnostic opioid dependence or abuse

as the outcome, rather than on a poorly-defined range of addiction-related terminology; and (2) examines incidence (new cases) – rather than prevalence (existing cases) – of opioid dependence or abuse following analgesic treatment, thereby facilitating an understanding of the contributory role of opioid analgesic prescribing on the subsequent development of dependence and abuse disorders.

Objective

The primary objective of the current review was to generate a pooled estimate of the incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy, based on a systematic review of published studies. It was hoped that data concerning dependence and abuse would be provided separately; however, it was anticipated that this distinction probably could not be made in studies. In the absence of distinct data for these two disorders, it was decided that data for these disorders would be pooled to provide an indication of a clinical dependence/abuse disorder. Should substantial heterogeneity be identified, sensitivity analyses would be undertaken in an effort to describe variance in study effects.

Methods

The established PICOS framework (**P**opulation, **I**nterventions, **C**omparators, **O**utcomes and **S**tudy design) was used to design the review and to develop an appropriate search strategy. The findings are reported in accordance with the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17 (Appendix 1)]. The structure of the current paper is based on the PRISMA 27-item checklist. The PRISMA four-phase flow diagram was used to show eligibility screening procedures (***Figure 1***).

Protocol and registration

The review protocol was registered on PROSPERO, the international database of prospectively registered systematic reviews in health and other related domains of study. The protocol registration number is CRD42017058445 and can be accessed at { HYPERLINK "https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058445" }.

Eligibility criteria

Populations were included if they were patients with pain in receipt of opioid analgesic treatment. Animal and *in vitro* models were excluded.

Interventions took the form of opioid analgesic treatment for a sufficient length of time for dependence to develop potentially. This is, of course, dependent upon a number of complex drug- and patient-related characteristics and the time between exposure and the development of dependence has not yet been characterised in humans. Data were, therefore, extracted from all studies where participants were exposed to opioid analgesics for 7 days or more and sensitivity analyses were undertaken based on the conservative exposure threshold of 3 months' exposure. Studies were excluded if they focused on opioid exposure in patients in receipt of opioid replacement therapy (ORT) for the treatment of opioid dependence.

Comparator populations were not applicable in the current review.

Outcomes comprised incidence from studies that specified a clinical diagnosis of opioid dependence or abuse disorder (established in studies by employing the use of DSM/ICD criteria or by clinician assessment). Studies

were excluded if they reported prevalence (existing cases) – rather than incidence (new cases) – to ensure that cases with pre-existing substance use disorders were not included in the pooled summary statistic. Studies were also excluded if they relied upon patient reports or proxy indicators of opioid misuse since it is impossible, using these methods of data collection, to distinguish between clinically-diagnostic dependence or abuse disorders and the wider concepts associated with 'addiction'. Articles using the terms 'addiction', 'misuse' and 'abuse' were included if these terms represented a clinical diagnosis of opioid dependence or abuse disorder, identified either using DSM/ICD criteria or by clinician assessment.

Study designs that were excluded were case reports (since 0% or 100% incidence would not be meaningful within the context of meta-analysis) or presenting secondary data (to avoid duplication of articles presenting primary data).

Information sources

Electronic searches were undertaken using: Embase; Medline; PubMed; Cinahl Plus; Web of Science and OpenGrey. A 'grey' literature search and a manual search of the references of included publications was also undertaken.

Search

The search term was constructed using the PICOS principles, shown below, and was run in each of the electronic databases. Searches were run on 1 April and no date restrictions were applied. The English language filter was applied in all databases and the participants filter (human only) was applied where available (Embase, Medline and PubMed).

Population: pain

Intervention: opioid* OR opiate* OR buprenorphine OR codeine OR diamorphine OR dihydrocodeine OR dipipanone OR fentanyl OR hydromorphone OR meptazinol OR methadone OR morphine OR oxycodone OR papaveretum OR pentazocine OR pethidine OR tramadol OR tapentadol OR levorphanol OR oxymorphone

OR meperidine OR butorphanol OR opium OR propoxyphene OR alfentanil OR levomethadyl OR sufentanil OR remifentanil OR dextropropoxyphene OR ketobemidone

Comparators: Not included in search strategy

Outcomes: (depend* OR toleran* OR withdraw*) AND (prevalence OR incidence OR rate* OR frequenc* OR proportion* OR percent*)

Study design: Not included in search strategy

Study selection

Initially, articles underwent title and abstract review. Where articles clearly did not meet inclusion criteria, they were excluded, and the reason for exclusion was recorded. Remaining articles underwent full text eligibility review, in light of careful consideration of the inclusion and exclusion criteria, and the reason for each article excluded at this stage was recorded. A random selection of 25% of included articles was assessed by a second reviewer who was blind to title, author, journal and year of publication.

Data collection process

A data extraction proforma was designed and piloted with 5 of the included articles. Where required, authors were contacted in an effort to seek clarification on the data presented in articles.

Data items

Data items were extracted and recorded on a pre-piloted proforma. The data items that were extracted for each study (where available) were: author(s); article title; date of publication; study design; number recruited and final number included in sample; pain type (malignant or non-malignant); nature of pain (nociceptive or neuropathic); name of opioid analgesic(s) (used to identify strong and weak opioids); length of exposure to opioid analgesic; method for diagnosing opioid dependence disorder (DSM, ICD or clinician assessment); event rate (total population under investigation and number of events reported); subgroup data (event rate

for all subgroups, as described in 'Additional Analyses'); and additional notes (free text box in which explanatory notes or issues for consideration were recorded).

Risk of bias in individual studies

Assessment of risk of bias in individual studies was undertaken at study level. Study design was identified using Agency for Healthcare Research and Quality AHRQ (US DoH) criteria[18]. Risk of bias assessment was achieved using instruments designed by the National Institutes of Health (NIH). Two instruments were required for use in the current review:

1. Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (**URL: {** HYPERLINK "https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after" **}**)
2. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies **(URL: {** HYPERLINK "https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort" **}**)

These instruments are not intended to be summed to provide a total score, since assigning scores may be considered to be misleading[19]. Instead, these instruments are designed to prompt consideration of the key concepts relating to internal validity and potential risk of bias in individual study designs. As such, study quality was rated as: 'poor'; 'fair'; or 'good'.

Summary measures

The principal measure used was event rate – i.e. the proportion of total population developing dependence or abuse. The raw event rate was shown in forest plots and reported as percentages in the main body of the text.

Synthesis of results

Pooled incidence estimates were generated using the random effects (DerSimonian-Laird method) model. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance. Several measures of heterogeneity have been reported (Cochran's Q; Tau^2; and I^2); however, the preferred I^2 statistic[20] was discussed in the text. Definitive heterogeneity thresholds can be misleading; however, as per guidance in the Cochrane Handbook (section 9.5.2) we accepted that ≥50% may represent substantial heterogeneity.

Risk of bias across studies

Publication bias was assessed using the Egger regression intercept and the Begg-Mazumdar rank correlation test. The use of imputational strategies in meta-analyses remain controversial and, furthermore, are unlikely to alter the conclusions in over 90% of secondary data analyses[21]. In consequence, imputational strategies were not used in the current review.

Additional analyses

Sensitivity analyses were undertaken in an effort to explain substantial heterogeneity and to test the robustness of findings in light of process decisions. Subgroup analyses were planned based on socio-demographics, clinical characteristics concerning psychiatric health and characteristics associated with pain, opioid analgesic prescribing and vulnerability to opioid dependence. Where sufficient data were available these analyses were undertaken. Moderator variables were based on study design and risk of bias in individual studies. Subgroups and moderator variables were entered into a meta-regression model (DerSimonian-Laird method). Within the scope of the current review there were insufficient studies to undertake meta-regression with more than one subgroup/moderator variable in each analysis.

Results

Study selection

Electronic searches identified 6088 articles and a further 76 were identified through manual searches. A total of 2721 duplicates were identified resulting in a total of 3443 articles retained for eligibility review. ***Figure 1*** shows the total number of articles that underwent eligibility review, reasons for exclusions on full text review and the total number of articles retained for inclusion. Data were extracted from 12 articles, involving a total of 310,408 participants.

[INSERT FIGURE 1 AROUND HERE]

As shown in ***Figure 1***, following abstract screening, 3347 articles were excluded. They were identified as ineligible for the following reasons: systematic reviews/no primary data (n=434); *in vitro*/animal models (n=524); focus on addicted populations (n=364); drug efficacy studies (n=828); and focus on pain-related outcomes only (n=1197).

Study characteristics

The characteristics of included studies are shown in ***Table 1***. Where incidence of opioid dependence or abuse was not the primary objective, or was not the sole primary objective, the study design was reported for the method used to obtain incidence data rather than the method used in the overall study. One of the included studies[26] included 16 participants and had an event rate of zero; however, this study was retained in the meta-analysis since our selected meta-analysis method has the capacity to apply an adjustment, known as a 'continuity correction', to facilitate inclusion of zero-count studies. A continuity correction involves adding a constant value to each of the cells in the contingency table. In consequence, the event rate for this study was 0.029 (i.e. 2.9%) rather than zero. This does, however, necessarily impact on the confidence interval, widening it substantially, and this can be seen in the main forest plot in ***Figure 2***.

[INSERT TABLE 1 AROUND HERE]

Risk of bias within studies

Risk of bias within studies were undertaken at study level, rather than outcome level, and assessed using instruments designed by the National Institutes of Health (NIH). All studies were identified as being of either 'good' or 'fair' quality; none were excluded due to being of 'poor' quality.

Synthesis of results

Figure 2 shows the overall study effects and summary effect. The study effect symbol sizes are representative of the weighted contribution of each study (i.e. the precision of each study).

[INSERT FIGURE 2 AROUND HERE]

The summary effect, the weighted mean of all studies using a random effects model, was 0.047 (95% CI = 0.021-0.104), indicating that 4.7% of patients prescribed opioid analgesic therapy were associated with *de novo* diagnostic status for opioid dependence or abuse during the follow-up observation period. The confidence interval suggests that the 'true' value of the pooled effect size lies within the range 2.1% to 10.4%. The included studies are listed in **Figure 2** in chronological order of date of publication and there was no pattern associated with findings over time. Substantial heterogeneity was identified in study effects (I^2=99.78) [Q=4973 (df=11); p<0.001; Tau^2=2.146 (SE=1.394; Variance=1.942; Tau=1.465)]. Heterogeneity was anticipated, and was examined further.

Risk of bias across studies

Assessment of risk of publication bias showed a fairly symmetrical distribution suggesting no significant publication bias. This was confirmed by the Egger regression intercept (t=0.64; df=10; p=0.536) and the Begg-Mazumdar rank correlation test (Tau=0.15; p=0.493).

Additional analyses

Sensitivity analyses for overall heterogeneity of study effects

Sensitivity analyses were undertaken with two moderator variables (study design; and risk of bias in individual studies) and three subgroup variables (diagnostic criteria for identifying dependence or abuse; strength of analgesic opioid; and duration of opioid exposure). Moderator and subgroup variables were entered into regression models, in an effort to explain the overall variance in study effects, and the results of significant models were reported in tables.

Pooled effect estimates of incidence of iatrogenic opioid dependence or abuse did not differ significantly by study design (p=0.432). Cross-sectional study designs generated a pooled effect of 4.7%; pre-post study designs generated a pooled effect of 10.7%; and prospective cohort study designs generated a pooled effect of 1.7%. Meta-regression generated a non-significant model.

Pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by risk of bias within studies (p=0.024). Studies identified as being of 'fair' quality generated a pooled effect of 15.1% whilst studies identified as being of 'good' quality generated a pooled effect of 3.1%. Meta-regression generated a non-significant model.

Pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by diagnostic criteria for identifying dependence or abuse (p<0.001). There were, however, two single-sample groups – one study using both DSV-IV and ICD-9 criteria generated an effect of 2.9% and one study using clinician assessment generated an effect of 34.2%. These two single-sample groups were removed and the data were reanalysed. Findings are shown in ***Figure 3***.

[INSERT FIGURE 3 AROUND HERE]

As ***Figure 3*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by DSM-IV and ICD-9 diagnostic criteria for identifying dependence or abuse (p=0.002). Studies which used ICD-9 criteria generated a pooled effect of 1.3% whilst studies which used DSM-IV criteria generated a pooled effect of 11.3%. The meta-regression model was statistically significant (Q=7.77; df=1; p=0.005) and the results are shown in the supplementary material (Table 2). The coefficient for the moderator variable was positive (+2.30), indicating that the use of DSM-IV diagnostic criteria was associated with more than twice the mean effect size of that of the reference category (i.e. ICD-9 criteria). The meta-regression showed that the inclusion of this moderator variable in the regression model explained 20% of the overall variance in study effects (R^2=0.20).

Pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by whether participants were in receipt of strong opioids, weak opioids or a mix of strong and weak opioids within individual study samples (p<0.001). Studies where participants were prescribed strong opioids generated a pooled effect of 0.7%, studies where participants were prescribed weak opioids generated a pooled effect of 5.5% and studies where participants were prescribed a mix of strong and weak opioids generated a pooled effect of 6.1%. Findings are shown in ***Figure 4***. Meta-regression generated a non-significant model.

[INSERT FIGURE 4 AROUND HERE]

Pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by duration of exposure to opioid analgesics (p=0.020). Studies where participants were prescribed opioids for 3 months or more generated a pooled effect of 2.3% whilst studies where participants were prescribed opioids for a varied period of time generated a pooled effect of 10.7%. Findings are shown in ***Figure 5***. The meta-regression model was statistically significant (Q=3.98; df=1; p<0.005) and the results are shown in the supplementary material (Table 3).

[INSERT FIGURE 5 AROUND HERE]

The coefficient for the moderator variable was negative (-1.57), indicating that studies where participants were exposed to opioid analgesics for ≥3 months were associated with a mean effect size 1.57 times smaller (with the inverse of 1.57 being 0.66) than studies where participants underwent a mix of acute and chronic exposure. The meta-regression showed that the inclusion of this moderator variable in the regression model explained 18% of the overall variance in study effects (R^2=0.18).

Discussion

Summary of evidence

The current review is novel in examining the incidence (assumed to be new cases) – rather than prevalence (existing cases) – of iatrogenic opioid dependence or abuse following exposure to prescribed opioid analgesics. Furthermore, the outcome measure focused on diagnostic status of dependence or abuse disorders, ensuring examination of debilitating problematic opioid use rather than focusing on aberrant drug-related behaviour indiscriminately, which may include recreational use and other forms of non-problematic use. Twelve studies were identified for inclusion in the meta-analysis, including 310,408 participants, and were of either 'good' or 'fair' quality. The pooled incidence estimate was 4.7%, but substantial heterogeneity in study effect sizes was found with incidence ranging from 0.2% to 34.2%. In an effort to explain the substantial heterogeneity, a number of sensitivity analyses were undertaken. Studies rated as being of 'good' quality were associated with a significantly lower incidence (3.1%) than 'fair' quality studies (15.1%). ICD-9 diagnostic criteria were associated with a significantly lower incidence (1.3%) than DSM-IV criteria (11.3%) and this explained 20% of the heterogeneity in study effects. Strong opioids were associated with a significantly lower incidence (0.7%) than either weak opioids (5.5%) or studies utilising a mix or strong and weak opioids (6.1%). Studies in which participants were prescribed opioids for 3 months or more were associated with a significantly lower incidence (2.3%) than studies in which participants were prescribed opioids for a varied period of time (10.7%) and this explained 18% of heterogeneity in study effects. Indicators of potential publication bias were negative.

Limitations

Searches were restricted to English language text only. The search term was broad; however, an exhaustive list of drug-related terminology was not included. Whilst unlikely, it is possible that articles referring to, for example, 'aberrant drug-related behaviour', could have identified clinical status in samples or subgroups. Although studies were each of reasonable quality, there was substantial heterogeneity found in study effects. A range of study designs and settings were used,

population characteristics varied between studies and very few studies provided evidence of sufficient statistical power to detect significant effects. Furthermore, most of the included studies provided insufficient homogenous data to facilitate appropriate subgroup analyses. Ideally, future studies will utilise rigorous study designs that may be pooled to generate summary effects in future meta-analyses. Furthermore, the importance of subgroup data should be recognised and future studies should include, if possible, subgroup analyses of the most pertinent socio-demographic and clinical characteristics.

All required data for all included studies were obtained and no publication bias was identified, demonstrated by study effects being relatively symmetrically-distributed around the mean and non-significant findings of statistical tests of publication bias. As a result of the relatively small number of studies included, and the established observations to predictors ratio of 10:1, it was not possible to enter more than one explanatory variable into each meta-regression model and, therefore, it was not possible to derive complete models explaining heterogeneity. Further studies are required to facilitate a robust evidence base that can effectively inform policy and practice in this important domain of health research.

Comparison with other reviews

The pooled incidence estimate of 4.7% is similar to the 3.3% incidence reported by Fishbain and colleagues[8]. They undertook a 'structured evidence-based' review of the incidence of opioid abuse/addiction. They used a wider outcome definition (including addiction) than that of the current review; however, this finding shows that, irrespective of whether or not patients were associated with a clinical diagnosis of a dependence disorder, estimated incidence was similar.

The incidence reported by Noble and colleagues[7] was considerably lower than the current finding; they reported signs of opioid addiction in 0.27% of pooled participants (and 0.14% in studies that did not refer to any previous history of substance misuse); however, due to the inclusion solely of case series in this part of their review, they were unable to compute a statistical pooled estimate of effect size using meta-analytical techniques. Minozzi and colleagues[9] undertook a qualitative synthesis of incidence of opioid dependence and reported an incidence range of 0 to 24% (with a median of 0.5%). They did not, however, compute a pooled estimate of effect sizes. Similarly, in a qualitative synthesis, Littlejohn and colleagues[6] identified prevalence, as opposed to incidence, rates of up to 24% dependence and 41% abuse. Furthermore, in the studies included by Littlejohn and colleagues, it was not made clear how the authors of included studies defined the varied terms that they used (dependence, withdrawal, addiction and abuse) and which, if any, indicated a clinical diagnosis. Despite examination of a similar question, the findings of these three reviews are not comparable to the current review in terms of outcome measures and statistical techniques. The calculation of averages and total percentages cannot take account of within-study variance in pooling methods and, in consequence, will generate relatively unreliable event rates.

In the remaining review[10], some of the included studies provided a single rate of misuse or addiction whilst others reported a range. To ensure synthesis of the full complement of studies, the authors of this review calculated both a minimum and a maximum rate and, where a single value was reported in studies, this value was used to represent both the minimum and the maximum. Whilst the reported prevalence rates of addiction are similar to the summary effect reported in the current review (4.3% and 4.7%, respectively), the reported prevalence rates of misuse were dramatically higher (69.4% and 69.5%, respectively). One explanation may be that Vowles and colleagues defined ‘misuse’ as opioid use contrary to directions irrespective of the presence of harm or adverse effects. This definition could include a substantial proportion of people engaging in non-problematic substance use and patients seeking or obtaining effective pain relief. One additional potential reason for elevated rates may be that, similar to Littlejohn and colleagues, Vowles and colleagues examined prevalence (existing cases) – rather than incidence (new cases) – of non-medical or illicit substance use. This would necessarily result in elevated rates, since this would include people whose

substance misuse preceded analgesic prescribing. Additionally, from a translational perspective, examination of prevalence rates cannot contribute effectively to an understanding of the development of dependence disorders following analgesic prescribing.

Sensitivity analyses indicated a significantly lower incidence in studies that diagnosed dependence disorders in accordance with ICD-9 criteria as compared with DSM-IV criteria. It is generally accepted that ICD criteria are typically somewhat more stringent than respective DSM criteria in producing a clinical diagnosis of many mental and behavioural disorders; it is, therefore, not surprising that a significantly lower incidence is associated with ICD-9 diagnostic criteria. Subgroup analyses also indicated a significantly lower incidence associated with strong opioids and longer-term analgesic prescribing. If the development of opioid dependence disorders is less likely in patients prescribed strong opioids in the longer term, this may suggest a mediatory role of pseudoaddiction, whereby patients in receipt of inadequate analgesia (weak opioids prescribed over short-term periods) exhibit addiction-like behaviour in an effort to achieve successful pain management. We note that there may be other potential explanations of these counter-intuitive findings, such as differences in aetiology, pain severity or the nature of the pain; however, examination of these potential explanations goes beyond the scope of the present review.

Conclusions

The incidence of opioid dependence or abuse associated with analgesic prescribing identified in the current review was 4.7%. Rates were lower among those with longer-term prescribing (>3 months) and those receiving strong rather than weak opioids. This suggests a more modest direct effect of opioid analgesic prescribing, even in the longer term, than is generally perceived on the development of dependence or abuse. It is beyond the scope of the present review to examine potential explanations of this finding. It remains important to note, and aim to prevent, this serious adverse effect, and we have identified and quantified some key relevant factors. There is a need for well-designed, rigorously-controlled, adequately-powered, prospective experimental studies

examining the incidence – rather than prevalence – of iatrogenic opioid dependence and abuse following analgesic prescribing. Consideration should be given to the commissioning of a prospective registry with robust follow-up, which would enable careful oversight of incidence rates and facilitate the development of preventative strategies. Furthermore, funders and commissioners should consider the potential for future meta-analyses when reviewing the study design, terminology definitions, outcome measures and statistical power of proposed future studies.

Details of authors' contributions

Conception and design was undertaken by all three authors (CH, BHS, KM). Data acquisition and analysis were undertaken by CH. All three authors (CH, BHS, KM) contributed to interpretation of data, critical evaluation of intellectual content and final approval of the published version.

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Declaration of interests

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Figure legends

Figure 1: *Eligibility screening procedures and the total number of articles included in the review, shown on the PRISMA four-phase flow diagram*

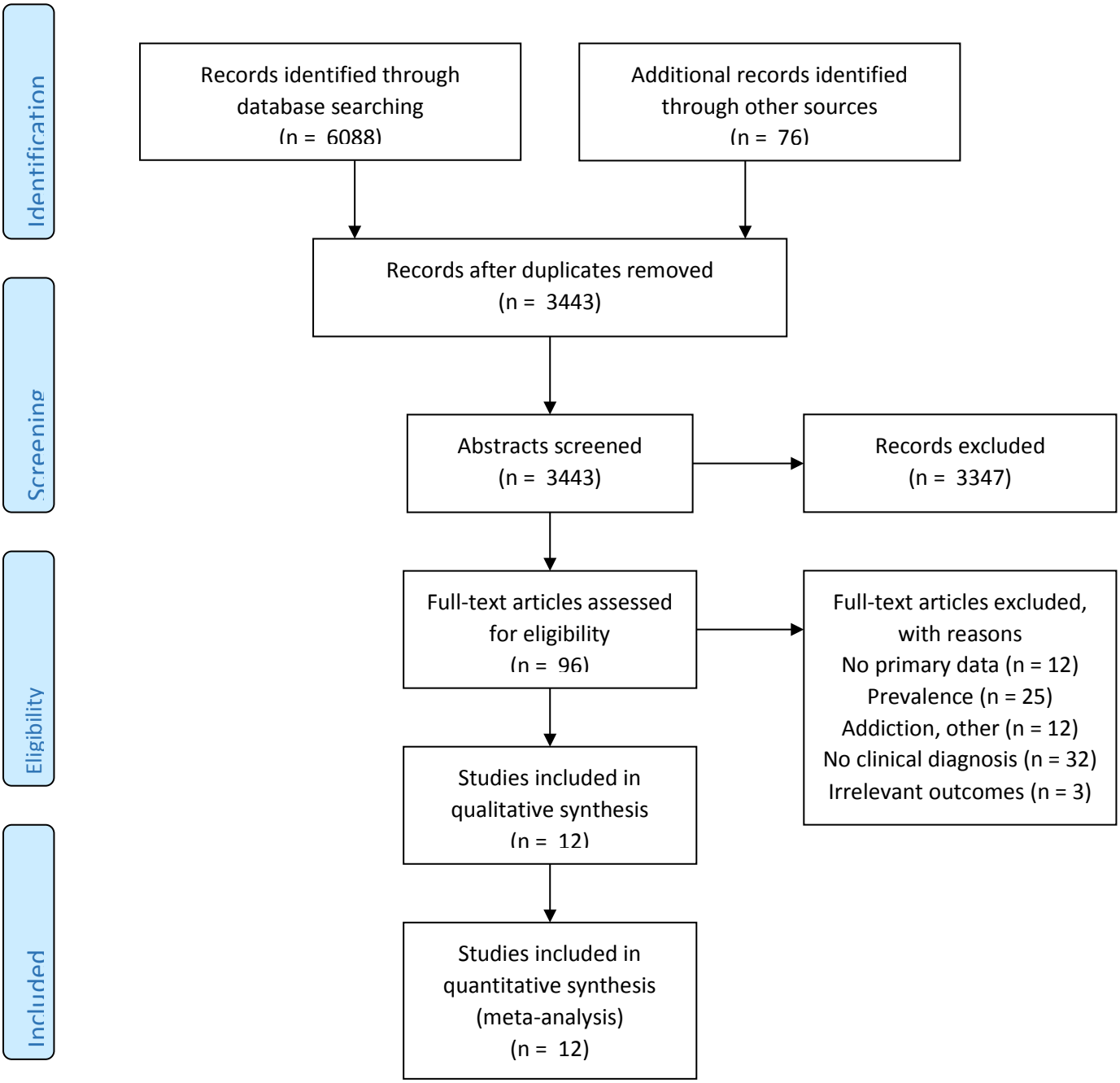
Figure 2: *Meta-analysis (random effects model) of overall study findings of the incidence of iatrogenic opioid dependence or abuse. Studies are reported by ascending year of publication*

Note: It is recognised that incidence cannot fall below zero; however, the company providing the CMA software (Biostat Inc.) confirmed that it is not possible to generate a scale that is not symmetrical around zero.

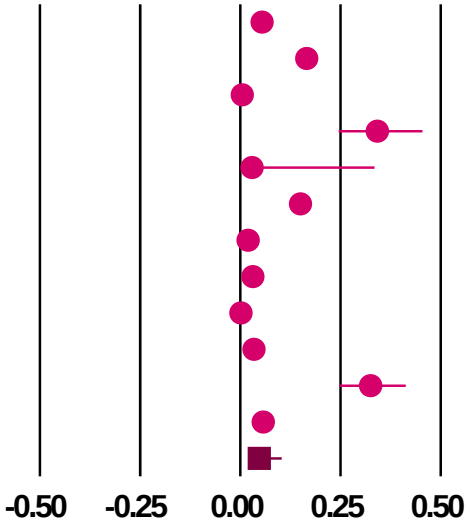
Figure 3: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by DSM-IV and ICD-9 diagnostic criteria for identifying dependence or abuse*

Figure 4*: Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by strength of prescription opioid analgesics*

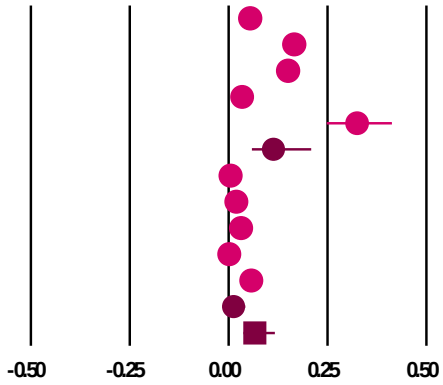
Figure 5: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by length of exposure to opioid analgesics*


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 6088)
Additional records identified through other sources (n = 76)
Records after duplicates removed (n = 3443)
Abstracts screened (n = 3443)
Records excluded (n = 3347)
Full-text articles assessed for eligibility (n = 96)
Full-text articles excluded, with reasons
No primary data (n = 12)
Prevalence (n = 25)
Addiction, other (n = 12)
No clinical diagnosis (n = 32)
Irrelevant outcomes (n = 3)
Studies included in qualitative synthesis (n = 12)
Studies included in quantitative synthesis (meta-analysis) (n = 12)

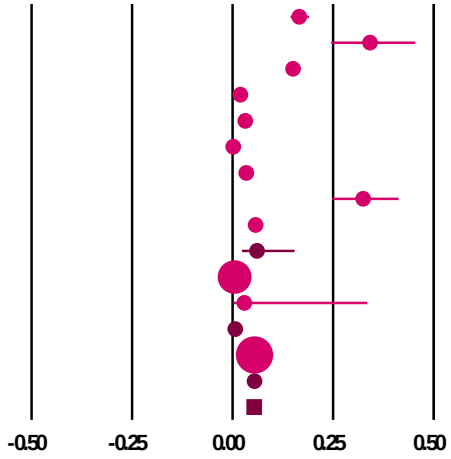
Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Adams (2006)	0.055	0.049	0.061	-51.192	0.000
Buse (2012)	0.166	0.143	0.191	-18.240	0.000
Cepeda (2013)	0.005	0.004	0.006	-74.328	0.000
Chabal (1997)	0.342	0.245	0.455	-2.705	0.007
Cowan (2002)	0.029	0.002	0.336	-2.436	0.015
Dersh (2008)	0.150	0.132	0.171	-22.512	0.000
Edlund (2007)	0.020	0.018	0.022	-66.821	0.000
Edlund (2010)	0.032	0.030	0.033	-128.818	0.000
Edlund (2014)	0.002	0.002	0.002	-118.020	0.000
Flemming (2008)	0.034	0.024	0.048	-18.263	0.000
Huffman (2013)	0.325	0.247	0.414	-3.750	0.000
Hylan (2015)	0.057	0.049	0.067	-34.150	0.000
	0.047	0.021	0.104	-6.929	0.000



Group by Diagnostic criteria	Studyname	Event rate	Lover limit	Upper limit	Z-Value	p-Value
DSM-IV	Adams (2006)	0.055	0.049	0.061	-51.192	0.000
DSM-IV	Buse (2012)	0.166	0.143	0.191	-18.240	0.000
DSM-IV	Dersh (2008)	0.150	0.132	0.171	-22.512	0.000
DSM-IV	Flemming (2008)	0.034	0.024	0.048	-18.263	0.000
DSM-IV	Huffman (2013)	0.325	0.247	0.414	-3.750	0.000
DSM-IV		0.113	0.058	0.210	-5.528	0.000
ICD-9	Cepeda (2013)	0.005	0.004	0.006	-74.328	0.000
ICD-9	Edlund (2007)	0.020	0.018	0.022	-66.821	0.000
ICD-9	Edlund (2010)	0.032	0.030	0.033	-128.818	0.000
ICD-9	Edlund (2014)	0.002	0.002	0.002	-118.020	0.000
ICD-9	Hylan (2015)	0.057	0.049	0.067	-34.150	0.000
ICD-9		0.013	0.004	0.043	-6.870	0.000
Overall		0.066	0.037	0.118	-8.246	0.000



Group by Opioid strength	Studyname	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Mixed	Buse (2012)	0.166	0.143	0.191	-18.240	0.000
Mixed	Chabal (1997)	0.342	0.245	0.455	-2.705	0.007
Mixed	Dersh (2008)	0.150	0.132	0.171	-22.512	0.000
Mixed	Edlund (2007)	0.020	0.018	0.022	-66.821	0.000
Mixed	Edlund (2010)	0.032	0.030	0.033	-128.818	0.000
Mixed	Edlund (2014)	0.002	0.002	0.002	-118.020	0.000
Mixed	Flemming (2008)	0.034	0.024	0.048	-18.263	0.000
Mixed	Huffman (2013)	0.325	0.247	0.414	-3.750	0.000
Mixed	Hylan (2015)	0.057	0.049	0.067	-34.150	0.000
Mixed		0.061	0.023	0.155	-5.168	0.000
Strong	Cepeda (2013)	0.005	0.004	0.006	-74.328	0.000
Strong	Cowan (2002)	0.029	0.002	0.336	-2.436	0.015
Strong		0.007	0.002	0.026	-7.273	0.000
Weak	Adams (2006)	0.055	0.049	0.061	-51.192	0.000
Weak		0.055	0.049	0.061	-51.192	0.000
Overall		0.054	0.049	0.060	-51.871	0.000



Group by 3 months or more on opioids	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
3 months or more	Cepeda (2013)	0.005	0.004	0.006	-74.328	0.000
3 months or more	Chabal (1997)	0.342	0.245	0.455	-2.705	0.007
3 months or more	Edlund (2007)	0.020	0.018	0.022	-66.821	0.000
3 months or more	Edlund (2010)	0.032	0.030	0.033	-128.818	0.000
3 months or more	Edlund (2014)	0.002	0.002	0.002	-118.020	0.000
3 months or more	Hylan (2015)	0.057	0.049	0.067	-34.150	0.000
3 months or more		0.023	0.007	0.070	-6.318	0.000
Varied	Adams (2006)	0.055	0.049	0.061	-51.192	0.000
Varied	Buse (2012)	0.166	0.143	0.191	-18.240	0.000
Varied	Cowan (2002)	0.029	0.002	0.336	-2.436	0.015
Varied	Dersh (2008)	0.150	0.132	0.171	-22.512	0.000
Varied	Flemming (2008)	0.034	0.024	0.048	-18.263	0.000
Varied	Huffman (2013)	0.325	0.247	0.414	-3.750	0.000
Varied		0.107	0.055	0.195	-5.863	0.000
Overall		0.071	0.040	0.123	-8.298	0.000

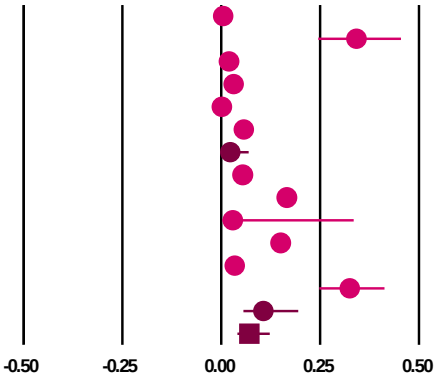


Table 1: *Characteristics of included studies*

Author (year)	Study design (location)	Malignant/non-malignant pain (N)	Prescription opioid (minimum length of exposure)	Event rate (%)
Adams (2006)[22]	Prospective cohort (USA)	Non-malignant (6243)	Hydrocodone; tramadol (varied)	5.5
Buse (2012)[23]	Cross-sectional (USA)	Non-malignant (922)	Any (varied)	16.6
Cepeda (2013)[24]	Prospective cohort (USA)	Mixed (39,367)	Any (12 months)	0.5
Chabal (1997)[25]	Cross-sectional (USA)	Non-malignant (76)	Any (6 months)	34.2
Cowan (2002)[26]	Pre-post (UK)	Non-malignant (16)	Any (varied)	2.9
Dersh (2008)[27]	Cross-sectional (USA)	Non-malignant (1323)	Any (not known)	15.0
Edlund (2007)[28]	Cross-sectional	Non-malignant (15,160)	Any (3 months)	2.0
Edlund (2010)[29]	Cross-sectional (USA)	Non-malignant (46,256)	Any (3 months)	3.2
Edlund (2014)[30]	Cross-sectional	Non-malignant (197,269)	Any (3 months)	0.2
Flemming (2008)[31]	Cross-sectional (USA)	Mixed (904)	Any (varied)	3.4
Huffman (2013)[32]	Pre-post (USA)	Non-malignant (120)	Any (not known)	32.5
Hylan (2015)[33]	Pre-post (USA)	Non-malignant (2752)	Any (6 months)	5.7

Table 2: *Random effects (DerSimonian-Laird) meta-regression of duration of logit event rate on the criteria used to diagnose dependence or abuse (DMS-IV compared with ICD-9) using a Z-distribution*

Covariate	**Coefficient**	**SE**	**95% lower**	**95% upper**	**Z value**	**p value**
Intercept	-4.3506	0.5815	-5.4902	-3.2109	-7.48	<0.0001
DSM-IV	2.2962	0.8240	0.6812	3.9111	2.79	0.0053

Table 3: *Random effects (DerSimonian-Laird) meta-regression of duration of logit event rate on opioid analgesic exposure (≥3 months compared with varied duration of exposure) using a Z-distribution*

Covariate	**Coefficient**	**SE**	**95% lower**	**95% upper**	**Z value**	**p value**
Intercept	-2.1772	0.5709	-3.2962	-1.0582	-3.81	0.0001
≥3 months	-1.5727	0.7887	-3.1186	-0.0268	-1.99	0.0462