What proportion of patients with chronic noncancer pain are prescribed an opioid medicine? Systematic review and meta-regression of observational studies (JIM-019-0665_R1)

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ABSTRACT

BACKGROUND: Guidelines now discourage opioid analgesics for chronic non-cancer pain because the benefits frequently do not outweigh the harms.

OBJECTIVES: To determine the proportion of patients with chronic non-cancer pain who are prescribed an opioid, the types prescribed, and factors associated with prescribing.

METHODS: Database searches were conducted from inception to 29th October 2018 without language restrictions. We included observational studies of adults with chronic non-cancer pain measuring opioid prescribing. Opioids were categorized as weak (e.g. codeine) or strong (e.g. oxycodone). Study quality was assessed using a risk of bias tool designed for observational studies measuring prevalence. Individual study results were pooled using a random-effects model. Meta-regression investigated study-level factors associated with prescribing (e.g. sampling year, geographic region as per World Health Organization). The overall evidence quality was assessed using Grading of Recommendations Assessment, Development and Evaluation criteria.

RESULTS: Of the 42 studies (5,059,098 participants) identified, majority (n = 28) from the United States of America. Eleven studies were at low risk of bias. The pooled estimate of the proportion of patients with chronic non-cancer pain prescribed opioids was 30.7% (95%CI 28.7% to 32.7%, 42 studies, moderate-quality evidence). Strong opioids were more frequently prescribed than weak (18.4% (95%CI 16.0% to 21.0%, n = 15 studies, low-quality evidence), versus 8.5% (95%CI 7.2% to 9.9%, n = 15 studies, low-quality evidence)). Meta-regression determined opioid prescribing was associated with year of sampling (more prescribing in recent years) (p = 0.014) and not geographic region (p = 0.056).

CONCLUSION: Opioid prescribing for patients with chronic non-cancer pain is common and has increased over time.

Key words: opioid analgesic, chronic pain, systematic review.

INTRODUCTION

Global opioid prescribing doubled between 2001–03 and 2011–13 [1]. Several developed countries have noted substantial increases in opioid prescriptions including the United States of America (USA) [2], Canada [3], United Kingdom (UK) [4], Scotland [5] and Australia [6], and also for some strong prescription opioids such as oxycodone [2, 5-10].

Chronic non-cancer pain is a common problem and can be due to a range of conditions including chronic low back pain and osteoarthritis. Estimates of the prevalence of chronic pain vary considerably according to the approach used [11]. Population-based studies report that one in five (20.4% (95% CI 19.7% to 21.0%) adults in the USA and nearly a half of UK adults (pooled estimate 43.5%, 95% CI 38.4% to 48.6%) have chronic non-cancer pain [12, 13]. Individuals with chronic pain have a poorer quality of life and report greater disability and depression than other people in the community [14]. Chronic pain costs billions of dollars each year in healthcare costs and lost work productivity [15].

Opioid analgesics are often used to manage chronic non-cancer pain [4]. Previously, opioids were considered an appropriate strategy to manage chronic non-cancer pain. Increases in opioid prescribing, particularly in the USA, came after campaigns promoting the safety of chronic opioid use. Opioid use was also encouraged by the initiative to consider pain as the 5th vital sign [16]. However, there is now greater appreciation of the harms associated with prescription opioid analgesics [17] and guidelines, such as those from The Centres for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain [17] now discourage the use of opioid analgesics. Furthermore, opioids are now not recommended for the management of some specific pain conductions such as chronic low back pain [18].

The proportion of patients with chronic non-cancer pain, including chronic low back pain, who are prescribed opioids is not well understood. Opioid prescribing data has been reported from individual health care settings [19-23]. However, there are no systematic

reviews that have synthesized these data in the chronic non-cancer pain population. Additionally, factors such as clinical setting or specialities which may be considered contributors to high opioid prescribing rates [24-27] have not been systematically evaluated within a chronic non-cancer pain population. Determining the proportion of patients with chronic non-cancer pain prescribed opioid analgesics provides a benchmark to help assess if prescription reduction strategies have been successful. Therefore, the aim of our systematic review was to determine how common opioid prescribing is for chronic non-cancer pain. Our secondary aims included examining the types of opioids prescribed; determining any factors associated with prescribing such as clinical setting, geographic location and the time period of the study; and determining how common opioid prescribing is, the types of opioids prescribed and factors associated with prescribing in the chronic low back pain population.

METHODS

This review was devised in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [28] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [29], and registered on PROSPERO (CRD42017063954; www.crd.york.ac.uk).

Eligibility

We included observational studies (cross-sectional, cohort or case-control studies) of adults (18+ years) with chronic non-cancer pain that were prescribed opioid analgesics for pain management. We included population-based studies (such as databases, including dispensing data), studies from clinical settings (i.e. primary (e.g. general practitioner), secondary (e.g. hospital, emergency department and medical specialists) or tertiary care settings (e.g. multidisciplinary pain treatment programs). We included studies that defined chronic non-cancer pain as pain in one or more body locations of non-cancerous origin for at least three months. We excluded studies that were not considered to be a representative

sample (i.e. not sampling consecutive cases or randomly sampled population), self-report of opioid use, and studies involving only pregnant women.

Search strategy

We searched PubMed **(**NLM® database), MEDLINE (OvidSP), EMBASE (OvidSP), Web of Science (Thomson Reuters), International Pharmaceutical Abstracts (via OvidSP) databases up to 29th October 2018 with no language restrictions using terms such as “opioid analgesic” and “chronic non-cancer pain”. The full search strategy is detailed in Appendix 1.
Additionally, we conducted backward and forward reference and author citation tracking, and communicated with content experts to identify any missing studies.

Screening

Two review authors (SM, GW) independently screened identified titles and abstracts to determine eligibility. Disagreements were resolved by discussion first, then arbitration by an independent third review author (CM) if needed. For articles written in languages that were unable to be read by the review authors, we asked colleagues to assist with reading and appraising the article. Individual review authors did not assess the eligibility of any studies to which they had contributed. We contacted study authors to confirm eligibility when necessary (five studies).

Data extraction and management

Two review authors from a panel of seven (SM, GW, CL, AM, RB, SP, MU) extracted data independently for each included study. Disagreements were resolved by discussion first, then arbitration by an independent third review author if necessary (CM). We contacted the authors of studies for clarification and additional data if relevant data were missing.
We used standardized and piloted data extraction forms. Information was extracted on bibliometric data, study characteristics (e.g. sampling dates, setting), participant characteristics (e.g. age, type and duration of chronic non-cancer pain), exposure (e.g.

number and type of opioids prescribed, if any medicines were co-prescribed with the opioid medicine) and data completeness (i.e. missing data).

Medicines were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [30]. Opioid analgesics (N02A) were simplified into (i) weak single ingredient opioid analgesics (e.g. codeine, tramadol), defined as < 50 morphine milligram equivalents (MME) per day; (ii) strong single ingredient opioid analgesics (e.g. tapentadol, oxycodone, morphine, pethidine, fentanyl, hydromorphone, buprenorphine), defined as ≥ 50 MME per day; and (iii) combination opioid analgesics. Medicines in the latter category were categorized based on the strongest medicine present in the combination, either as a weak combination opioid analgesic or strong combination opioid analgesic. Opioid classification is presented in Appendix 2. Opioid analgesic medicines were converted to MME dose to facilitate comparison and interpretability following conversion by Dowell 2016 [17].

Countries were grouped according to World Health Organisation (WHO) regions of Africa, Americas (Northern, Central and Southern), Europe, South-East Asia, Eastern Mediterranean and Western Pacific [31]. Low, middle and high-income countries were classified as per the World Bank [32]. High-income countries include Andorra, Australia, Austria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Israel, Italy, Japan, Lichtenstein, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK and USA. As we found no studies originating from South America, the region of Americas refers to North America only.

Risk of bias assessment

Two reviewers from a panel of seven (SM, GW, CL, AM, RB, SP, MU) independently assessed the risk of bias of eligible studies and disagreements were resolved by discussion first, then arbitration by an independent third review author if necessary (CM). Risk of bias

was assessed using the modified risk of bias tool developed by Hoy et al which assesses the risk of bias of observational studies measuring prevalence [33]. The tool comprises four questions assessing external validity and six questions on internal validity with each question scores “yes” (low risk of bias) or “no” (high risk of bias). An overall judgment of bias risk is then rated as low, moderate or high. The risk of bias assessment criteria and scores are presented in Appendix 3. This tool has been found to demonstrate high inter-rater reliability [33].

Data analysis

The flow of studies was summarized in a study flow diagram, following the PRISMA statement [28]. The results of the review were summarized both qualitatively as a narrative synthesis and quantitatively in a meta-analysis where possible. Study characteristics and participants were reported descriptively. Opioids prescribed and dichotomous variables are reported as proportions, n/N (%). Opioid prescribing was determined as the proportion of patients with chronic non-cancer pain that were prescribed opioids. Annual opioid prescribing data were used if available, and hence some studies have multiple, independent, opioid data presented per year. Opioid types were grouped as weak, strong, weak combination and strong combination opioids. Continuous outcomes were reported as means with 95% confidence interval (CI) (if to describe the precision of an estimate) or standard deviation (SD) (if to describe sample variability). Where possible, outcomes were converted to a common metric to facilitate comparison and interpretability e.g. opioid dose (MME/day).

Study results were combined in a meta-analysis using a random-effects model irrespective of setting. Statistical heterogeneity was assessed by visual inspection of the forest plot (e.g. P values and overlapping CIs) and the I^2 statistic. We followed the recommended guidance for interpretation of I^2 as: 0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; 75% to

100%, considerable heterogeneity. Where heterogeneity was present and the data could not be pooled, a narrative synthesis was conducted.

We used meta-regression to investigate heterogeneity and study-level factors associated with opioid prescribing. The study-level factors included (i) WHO region (North America (reference), Europe, Western Pacific, South East Asia); (ii) if study funding was disclosed (yes (reference)/no); (iii) setting (primary (reference), secondary, tertiary, multiple settings (i.e. primary and tertiary), database (population-based study (e.g. Veterans Affairs database or insurance claims database)); (iv) the duration of sampling period (in months); (v) mid-point of the study period (year) which the opioid prescribing estimate was sampled. We planned, but there was insufficient data to assess patient-level factors within studies such as age, gender. We used 2-sided p-value, Knapp-Hartung and maximum likelihood method. Analyses were conducted in Comprehensive Meta-Analysis Program version 3.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [34] to provide a summary of the overall quality of evidence. The GRADE assessment criteria and scores are presented in Appendix 4.

Subgroup analyses

Subgroup analyses of the review's aims were conducted confined to patients with chronic low back pain. Low back pain was defined as pain in the posterior aspect of the body from the lower margin of the twelfth ribs to the lower gluteal folds with or without pain referred into one or both lower limbs.

Sensitivity analysis

A sensitivity analysis was conducted with (i) high risk of bias studies removed, and (ii) tramadol classified as a 'strong opioid' rather than a 'weak opioid' to account for the

differences in scheduling between countries (e.g. tramadol is considered a ‘strong opioid’ in the United Kingdom [35] but a ‘weak opioid’ in other countries such as Australia [36]).

RESULTS

Search results

From 26,048 citations identified by the search, 269 full texts were screened, and 42 studies were eligible for inclusion (Figure 1).

Included studies

The majority of studies were from USA (n = 28) [37-64], followed by UK (n = 4 studies) [65-68], Spain (n = 3 studies) [69-71] and Canada (n = 3 studies) [72-74], with single studies from Norway [22], Denmark [75], Australia [76] and India [77]. There were no studies that compared data from multiple countries. Other than the study from India [77], classed as a lower middle-income country, there were no studies from low or middle-income countries. Study sample sizes ranged from 143 patients [39] to a database of 4,175,765 patients [42]. Studies reported prescription data from 1991 to 2015 and were all published in English. Thirty-one studies (74%) were retrospective reviews of medical records across a range of settings (Table 1).

There were 5,059,098 patients with chronic non-cancer pain across the forty-two studies. Twenty-seven studies (64%) included specific subgroups of chronic non-cancer pain such as chronic low back pain [44, 46, 47, 49, 53, 66], osteoarthritis [47, 54, 57, 58, 70, 72] rheumatoid arthritis [59, 60] and fibromyalgia [61-64, 73]. The mean age of participants was 58.6 years (SD 13.1, n = 29 studies). The mean age of those prescribed an opioid analgesic was slightly younger at 55.7 years (SD 13.3, n = 11 studies). The mean pain intensity in patients with chronic non-cancer pain who were taking opioid analgesics was infrequently reported (6.0 out of 10 on a Numerical Pain Rating Scale, SD 1.8, n = 5 studies). Only four

studies reported when other analgesic medicines were co-prescribed with other analgesics at the time of opioid prescribing [22, 52, 59, 66].

Risk of bias

Eleven studies were found to have low risk of bias (26%). The majority of studies were considered to have moderate risk of bias (62%, n = 26 studies) with a small proportion of studies with high risk of bias (12%, n = 5 studies) (Appendix 3). The domain covering the reliability and validity of questionnaires used to measure prevalence was frequently at high risk of bias as most studies retrospectively reviewed site-specific medical records rather than using validated measures.

Opioid analgesic prescribing estimates

Proportion of patients with chronic non-cancer pain prescribed opioid analgesics

The pooled estimate of opioid analgesic prescription for those with chronic non-cancer pain was 30.7% (95%CI 28.7% to 32.7%, n = 42 studies; moderate quality evidence) (Figure 2).

Types of opioid analgesics prescribed to patients with chronic non-cancer pain

Seventeen studies provided data on the type of opioid analgesics prescribed to patients with chronic non-cancer pain [38, 39, 41, 43, 44, 46, 54, 59, 60, 64, 68-70, 72, 73, 75, 76]. The pooled estimate of prescribing a weak opioid was 8.5% (95%CI 7.2% to 9.9%, n = 15 studies; low quality evidence) [38, 39, 43, 44, 46, 54, 59, 60, 64, 69, 70, 72, 73, 75, 76], a strong opioid 18.4% (95%CI 16.0% to 21.0%, n = 15 studies; low quality evidence) [38, 39, 41, 43, 46, 54, 59, 60, 68-70, 72, 73, 75, 76], a weak combination opioid 11.0% (95% CI 6.6% to 17.8%, n = 4 studies; moderate quality evidence) [54, 69, 70, 76] and a strong combination opioid 24.1% (95%CI 7.8% to 54.4%, n= 2 studies; low quality evidence) [54, 69] (Appendix 5.1).

Proportion of patients with chronic low back pain prescribed and opioid analgesics and their types

Twelve studies [41, 42, 44, 46, 47, 49, 52, 53, 56, 66, 71, 76] provided data on 758,248 patients with chronic low back pain. Nine (75%) were from North America with single studies from UK [66], Australia [76], Spain [71]. The pooled estimate of opioid prescribing was 41.5% (95%CI 28.9% to 55.4%, n = 12 studies; low quality evidence) (Appendix 5.2). A post-hoc analysis of opioid prescribing was conducted stratified by condition (chronic pain, chronic back pain, fibromyalgia, chronic headache, inflammatory arthritides, neuropathic pain, osteoarthritis, chronic pain from spinal cord injury) and is presented in Appendix 5.3. Conditions of inflammatory arthridites (29.5% (95%CI 25.5% to 33.9%)) and osteoarthritis (27.3% (95%CI 24.3% to 30.5%)) had a similar estimate of opioid prescribing compared to all chronic non-cancer pain conditions.

The specific types of opioids prescribed to patients with chronic low back pain was infrequently reported. We could determine that weak opioid analgesics were prescribed for 11.0% of patients (95% CI 7.5% to 12.6%; moderate quality evidence) from one study [44] over the decade of 2000 to 2010. No studies provided data related to the number of participants taking strong opioid analgesics or combination opioid analgesics in patients with chronic low back pain.

Factors associated with opioid analgesic prescribing

Our meta-regression model explained 28% of the variance in the proportion of patients with chronic non-cancer pain prescribed an opioid ($R^2 = 0.28$). The prescribing estimates were associated with the year of sampling (increasing over time, p = 0.014), no disclosure of funding (p = 0.047; higher opioid prescribing if a study did not provide a funding statement compared to studies that reported a funding statement), but not by WHO region (p = 0.056), setting (secondary, tertiary, database or multiple settings compared to primary care) (p =

0.955) or the duration of the sampling period in months (p = 0.103) (Appendix 6.1). The adjusted estimates of opioid prescribing over time are presented in Figure 3.

A separate meta-regression model restricted to studies of chronic low back pain (n = 12 studies) explained 82% of the variance in prescribing (R^2 = 0.82). The prescribing estimates were affected by year of sampling (increasing over time, p = 0.001) but not WHO region (p = 0.503), disclosure of funding (p = 0.365) or setting (p = 0.228) (Appendix 6.2). The adjusted estimates of opioid prescribing over time are presented in Appendix 6.3.

Sensitivity analysis

Removing the five studies at high risk of bias did not influence opioid prescribing estimates (30.4% (95%CI 28.3% to 32.6%, n = 37 studies) versus 30.7% (95%CI 28.7% to 32.7%, n = 42 studies)). When tramadol was considered a 'strong opioid', there were small changes in the prescribing estimates: weak opioids reduced from 8.5% (95%CI 7.2% to 9.9%; n = 15 studies) to 5.9% (95%CI 3.9% to 8.7%; n = 11 studies); strong opioids increased from 18.4% (95%CI 16.0% to 21.0%; n = 15) to 19.2% (95%CI 17.9% to 20.6%; n = 17 studies); weak combination opioids decreased from 11.0% (95%CI 6.6% to 17.8%; n = 4 studies) to 9.9% (95%CI 5.3% to 17.5%; n = 3 studies); and strong combination opioids decreased from 24.1% (95%CI 7.8% to 54.4%; n = 2 studies) to 20.7% (95%CI 11.9% to 33.5%; n = 3 studies). Post-hoc analyses explored if limiting data to the most recent available affected opioid estimates. Our approach of using all available data was more conservative. When the analysis only used data from recent years of all studies, the opioid prescribing estimate increased to 34.3% (95%CI 30.0% to 38.8%).

DISCUSSION

Our review established, primarily from published reports stemming from the USA, that almost one third of patients with chronic non-cancer pain are prescribed an opioid (31%). This estimate was even higher (42%) for patients with chronic low back pain. For chronic

non-cancer pain, stronger opioids are more commonly prescribed than weaker opioids, while the type of opioid was infrequently reported for patients with chronic low back pain. The year of prescribing (more recent) and the lack of funding statement was associated with prescribing to patients with chronic non-cancer pain but not influenced by WHO region, setting and study risk of bias. Time (more recent) was significantly associated with opioid prescribing for patients with chronic low back pain.

Our review is the first to examine the frequency of prescribing of opioid analgesic to patients with chronic non-cancer pain across countries and potential factors associated with prescribing. An additional strength of our review is that we identified studies by a sensitive literature search, including using backwards and forward reference and author citation tracking. Of the included studies, some studies were of single-site clinics. However, sample representativeness was a specific eligibility criterion and evaluated in the risk of bias assessment. We acknowledge a weakness of the review is the range of chronic pain conditions and clinical settings included, which we addressed by using meta-regression to explore heterogeneity. We note the reporting of opioid prescriptions rarely included data related to dose and duration of treatment prescribed, and hence, we were unable to determine if the dosing regimens have changed over time. Understanding the types of opioids (i.e. weak versus strong) prescribed to patients with chronic low back pain remains unclear as only one study reported such detail. Additionally, our review can only summarize available data, and the availability and access to opioids varies between health care systems and countries [78].

The prescription of opioids across the globe differs. The high-income WHO regions of North America, Europe (western and central) and Oceania account for 95.7% of global opioid use but only represents approximately 15% of the world's population [1]. We found from our studies that the prescription of opioids for chronic non-cancer pain is more commonly reported in these regions, but no studies compared data from multiple countries. However,

there is some uncertainty as only 11 of the 42 studies were from countries other than North America. Although our results show that opioids are being increasingly prescribed for chronic non-cancer pain over time, this is at odds with the pattern of general opioid use in some countries. For instance, reports from Scandinavian countries suggest stable opioid dispensing in Demark, Sweden and Norway between 2006 and 2014 [79], whereas in the UK, the prescribing of opioids in general practice doubled between 2000 and 2012 [80] then began to decline from 2016 to 2017 [19]. In the USA following reports in 2017 that the prescription of opioids is now a contributor to reduced life expectancy in the USA and their life expectancy is lower than most high-income countries [81], opioid mitigation strategies may have reduced opioid prescribing. A 2019 study noted a halving in the monthly incidence of initial opioid analgesics prescribed to opioid naïve enrolees of a USA health insurer from 1.63% of enrolees in July 2012 to 0.75% of enrolees in December 2017 [82]. The differences across health care systems such as government regulations regarding access to opioids, reimbursements and views on the role opioids play in chronic non-cancer pain management may contribute to the variation of opioid use across countries.

The access to opioid analgesics in low to middle income countries, which account for 80% of the world's population [83] is often limited, and pain is frequently undertreated [84]. Although recent population growth in low income and middle income regions has been the highest in Africa, Asia, and Latin America [85], we found only one study examining opioid prescribing for chronic non-cancer pain in a low or middle income country (India [77]). Although South-East Asia being home to one-quarter of the world's population [84], the consumption of opioids is low, partly due to tight government drug regulations restricting opioid access [84]. The prescription of opioids to patients with chronic non-cancer pain in other low- and middle-income countries remains unclear.

Meta-regression assessed potential study factors associated with opioid prescribing for patients with chronic non-cancer pain. One factor that did not influence opioid prescribing in

our review was setting, despite some reports suggesting that particular settings such as hospital discharge [86] and the surgical area contribute to the “opioid crisis” because of the absence of chronic non-cancer pain management in training curricula and the unnecessary prescription post-surgery [25, 87]. In pharmacy dispensing data from the USA, high volume opioid prescribers have been noted within the specialities of family medicine, internal medicine and orthopaedics [88] and payments from pharmaceutical companies influenced a higher volume of prescribing and of more expensive opioid analgesics [89]. We had insufficient data to assess sub-specialities and only forty percent of studies detailed the types of opioids prescribed (i.e. strong or weak). The prescription of some types of opioids such as oxycodone has increased over time [3, 5, 8, 9, 90], but our meta-regression analysis determined that year was not associated with the prevalence of weak, strong or combination opioid analgesics in patients with chronic non-cancer pain. The prescribing of opioids to patients with chronic low back pain significantly increased over time but other study level factors were unable to explain any associations of opioid prescribing in this population.

One of our goals was to establish a baseline of how commonly opioids are prescribed for chronic non-cancer pain which may help determine the success of future opioid mitigation strategies. While we have sufficient data for this purpose for the USA, we have sparse or no data for other countries. Additionally, there were insufficient data on the dose and duration of opioids prescribed to patients with chronic non-cancer pain. Future research could begin to close these evidence gaps and evaluate if patients with chronic non-cancer pain receive low-value pharmaceutical care. The ‘deprescribing’ of opioids needs to address reducing the initial prescription of opioids, but also how to support the cessation of opioids while still providing access to appropriate pain management. Opioid mitigation strategies have begun, for example, national initiatives [91], opioid stewardship programs[92, 93], and up-scheduling of codeine in Australia [94] and Italy [95]. However, research on opioid mitigation strategies specific to the needs of patients with chronic non-cancer pain is needed. The overuse of

opioid analgesics is a public health issue and solutions to reduce overuse are likely to be multi-faceted.

CONCLUSION

Opioid prescribing for patients with chronic non-cancer pain is common and has increased over time, with stronger opioids more frequently prescribed than weaker opioids.

Conflicts of interests

SM, GW, CL and SP declare no conflicts of interest. CM has received research grant funding from NHMRC; research grants from New South Wales Health, Medibank Health Research Fund, Sydney Health Partners, Sydney University, Arthritis Australia, Defence Health Foundation, WorkCover NSW, FAPESP (Sao Paulo Research Foundation); has had his travel expenses covered when presenting at scientific conferences; has received small gifts (e.g. bottle of wine) for giving lectures and talks and received Flexeze heat wraps for use in the SHaPED clinical trial. AM has received GSK untied research funding to the Sydney Pharmacy School for a postgraduate student scholarship under his supervision. RB has received research grant funding from NHMRC, Arthritis Australia, Cabrini Foundation, Australian Department of Health, Royal Australian College of General Practitioners, HCF, Therapeutic Guidelines Ltd, Monash University and the US-based Patient-Centered Outcomes Research Institute. She has had her travel expenses covered when invited to speak at conferences hosted by professional organizations. She is a member of the Australian Medical Services Advisory Committee (MSAC) and the National Prescribing Service (NPS) MedicineWise Clinical Intervention Advisory Group. MU was Chair of the NICE accreditation advisory committee until March 2017 for which he received a fee. He is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a co-investigator on grants funded by the Australian NHMRC. He is an NIHR Senior Investigator. He has received travel expenses for speaking at conferences from the professional organisations

hosting the conferences. He is a director and shareholder of Clinvivo Ltd that provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd related to return to work initiatives. He is a co-investigator on a study receiving support in kind from Stryker Ltd. He has accepted honoraria for teaching/lecturing from CARTA & Sterling Events. He is an editor of the NIHR journal series, and a member of the NIHR Journal Editors Group, for which he receives a fee. He is co-investigator on an NIHR funded trial of opioid withdrawal ISRCTN49470934.

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Figure legends

Figure 1: Study flow diagram.

Figure 2: The proportion of patients with chronic non-cancer pain prescribed opioid analgesics.

Figure 3: Adjusted estimates of opioid analgesics prescribed over time.

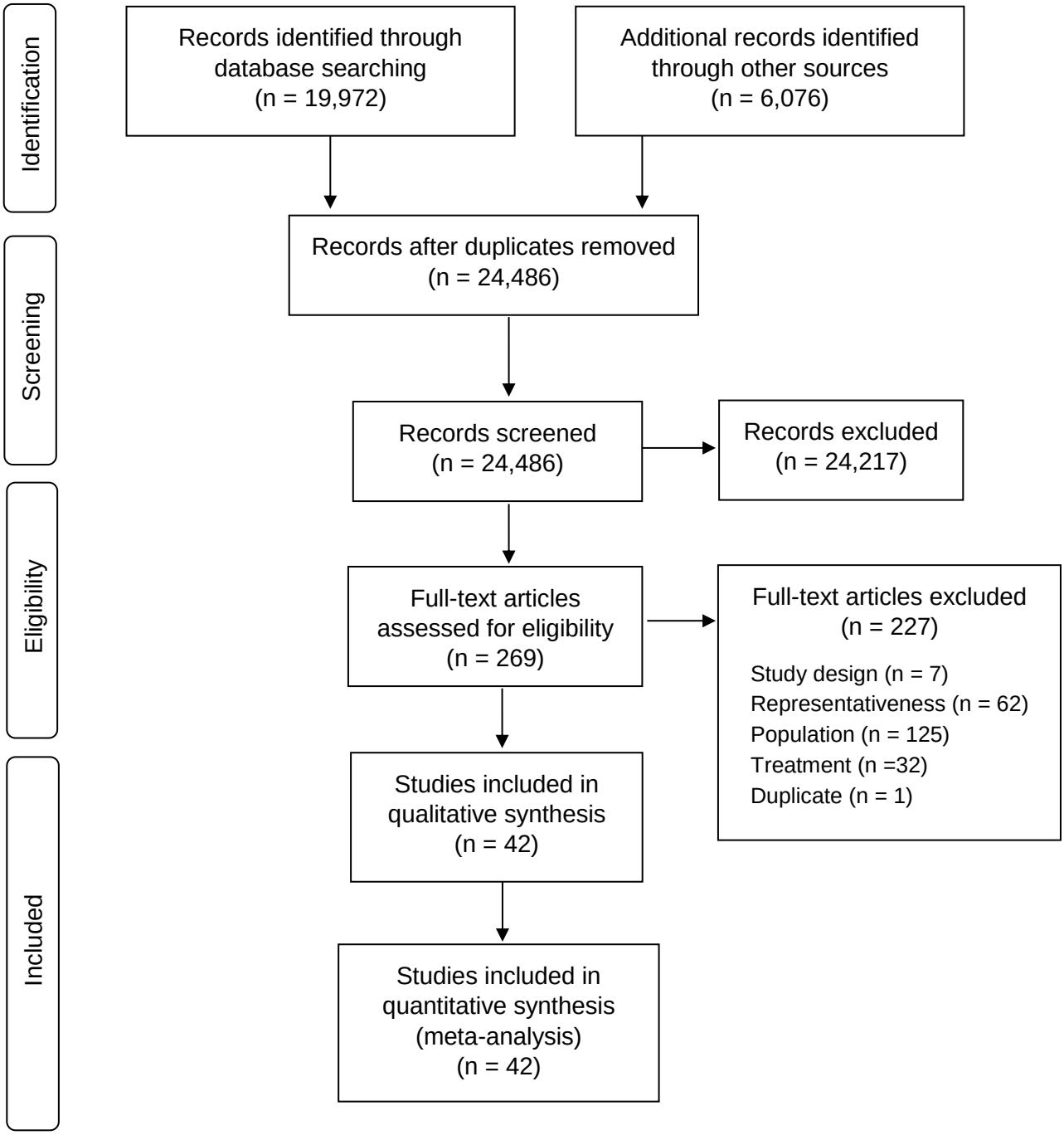


Figure 1: Study flow diagram.

Study name	Events/Total	Statistics for each study				Weight (random)	Event rate and 95%CI	Risk of bias	Sampling year	Region
	Total	Event rate	Lower limit	Upper limit	p-Value	Relative weight				
Jensen 200	64/160	0.400	0.327	0.478	0.012	1.32		Moderate	1991	Europe
Castillo 2016	96/569	0.169	0.140	0.202	0.000	1.42		Moderate	1995	North America
Mahowald 200	152/230	0.661	0.597	0.719	0.000	1.37		Moderate	1997	North America
Turk 1997	81/191	0.424	0.356	0.495	0.037	1.35		Moderate	1997	North America
AlMakadma 2013	526/1500	0.351	0.327	0.375	0.000	1.51		High	1998	Europe
Cowan 2003	104/1392	0.075	0.062	0.090	0.000	1.44		Moderate	1999	Europe
Dominick 2004	1248/3061	0.408	0.390	0.425	0.000	1.52		High	1999	North America
Mafi 2013	144/572	0.252	0.218	0.289	0.000	1.45		Moderate	1999	North America
Mafi 2015	68/352	0.193	0.155	0.238	0.000	1.38		Low	1999	North America
Clarke 2002	47/143	0.329	0.257	0.410	0.000	1.28		Moderate	2000	North America
Mapel 2004	16581/188452	0.088	0.087	0.089	0.000	1.53		Low	2000	North America
Steinman 2015	269/6559	0.041	0.036	0.046	0.000	1.50		Moderate	2000	North America
Gore 2007	3464/30999	0.112	0.108	0.115	0.000	1.53		Moderate	2001	North America
Mafi 2013	212/725	0.292	0.260	0.327	0.000	1.47		Moderate	2001	North America
Mafi 2015	98/585	0.168	0.139	0.200	0.000	1.42		Low	2001	North America
Mafi 2013	227/831	0.273	0.244	0.304	0.000	1.48		Moderate	2003	North America
Mafi 2015	134/577	0.232	0.200	0.268	0.000	1.45		Low	2003	North America
Rolita 2013	61/3731	0.016	0.013	0.021	0.000	1.39		Moderate	2003	North America
Wright 2013	151/488	0.309	0.270	0.352	0.000	1.45		High	2003	North America
Richter 2017	60/244	0.246	0.196	0.304	0.000	1.35		Moderate	2004	North America
Ashworth 2013	234/715	0.327	0.294	0.363	0.000	1.48		Low	2005	Europe
Carbone 2013	5106/7447	0.686	0.675	0.696	0.000	1.53		Moderate	2005	North America
Mafi 2013	245/816	0.300	0.270	0.333	0.000	1.48		Moderate	2005	North America
Mafi 2015	86/504	0.171	0.140	0.206	0.000	1.41		Low	2005	North America
Richter 2017	67/244	0.275	0.222	0.334	0.000	1.36		Moderate	2005	North America
Beehler 2013	524/792	0.662	0.628	0.694	0.000	1.48		Moderate	2006	North America
Berger 2012	15444/31688	0.487	0.482	0.493	0.000	1.53		Moderate	2006	Europe
Podichetty 2008	283/486	0.582	0.538	0.625	0.000	1.46		Moderate	2006	North America
Richter 2017	67/244	0.275	0.222	0.334	0.000	1.36		Moderate	2006	North America
Wright 2013	186/477	0.390	0.347	0.434	0.000	1.45		High	2006	North America
Fredheim 2014	2204/14477	0.152	0.146	0.158	0.000	1.53		Low	2007	Europe
Mafi 2013	508/979	0.519	0.488	0.550	0.237	1.50		Moderate	2007	North America
Mafi 2015	101/522	0.193	0.162	0.230	0.000	1.42		Low	2007	North America
Mohanty 2016	2419/8208	0.295	0.285	0.305	0.000	1.53		Moderate	2007	North America
Richter 2017	68/244	0.279	0.226	0.338	0.000	1.36		Moderate	2007	North America
Rolita 2013	3329/11012	0.302	0.294	0.311	0.000	1.53		Moderate	2007	North America
Sule 2008	17/467	0.036	0.023	0.058	0.000	1.11		High	2007	South East Asia
Vincent 2015	423/1111	0.381	0.353	0.410	0.000	1.50		Moderate	2007	North America
Dobscha 2013	2040/5961	0.342	0.330	0.354	0.000	1.53		Low	2008	North America
Fitzcharles 2011	144/457	0.315	0.274	0.359	0.000	1.44		Moderate	2008	North America
Henderson 2013	356/1088	0.327	0.300	0.356	0.000	1.50		Low	2008	Western Pacific
Richter 2017	71/244	0.291	0.237	0.351	0.000	1.36		Moderate	2008	North America
Shadd 2015	543/1219	0.445	0.418	0.473	0.000	1.50		Moderate	2008	North America
Wilson 2015	76495/238536	0.321	0.319	0.323	0.000	1.53		Moderate	2008	Europe
Edlund 2014	662090/1332810	0.497	0.496	0.498	0.000	1.54		Low	2009	North America
Mafi 2013	295/700	0.421	0.385	0.458	0.000	1.48		Moderate	2009	North America
Mafi 2015	93/594	0.157	0.130	0.188	0.000	1.42		Low	2009	North America
Richter 2017	73/244	0.299	0.245	0.360	0.000	1.37		Moderate	2009	North America
Robinson 2012	672/1700	0.395	0.372	0.419	0.000	1.51		Moderate	2009	North America
Steinman 2015	597/6559	0.091	0.084	0.098	0.000	1.52		Moderate	2009	North America
Wright 2013	168/422	0.398	0.352	0.446	0.000	1.44		High	2009	North America
Zamora-Legoff 2016	155/501	0.309	0.270	0.351	0.000	1.45		Moderate	2009	North America
Curtis 2017	97859/240750	0.406	0.405	0.408	0.000	1.53		Moderate	2010	North America
Edlund 2014	700140/1405563	0.498	0.497	0.499	0.000	1.54		Low	2010	North America
Margolis 2016	28368/64038	0.443	0.439	0.447	0.000	1.53		Moderate	2010	North America
Park 2016	4707/12165	0.387	0.378	0.396	0.000	1.53		Low	2010	North America
Richter 2017	73/244	0.299	0.245	0.360	0.000	1.37		Moderate	2010	North America
Young 2011	210/360	0.583	0.532	0.633	0.002	1.43		High	2010	North America
Birtwhistle 2015	9761/29562	0.330	0.325	0.336	0.000	1.53		Low	2011	North America
Edlund 2014	720287/1437392	0.501	0.500	0.502	0.008	1.54		Low	2011	North America
Perez 2013	4847/8579	0.565	0.554	0.575	0.000	1.53		Moderate	2011	Europe
Richter 2017	73/244	0.299	0.245	0.360	0.000	1.37		Moderate	2011	North America
Tian 2013	3231/7491	0.431	0.420	0.443	0.000	1.53		Low	2011	North America
Richter 2017	72/244	0.295	0.241	0.355	0.000	1.36		Moderate	2012	North America
Romanelli 2017	69935/120481	0.580	0.578	0.583	0.000	1.53		Low	2012	North America
Videla 2017	126/269	0.468	0.409	0.528	0.300	1.40		Moderate	2012	Europe
Richter 2017	65/244	0.266	0.215	0.325	0.000	1.35		Moderate	2013	North America
Richter 2017	68/244	0.279	0.226	0.338	0.000	1.36		Moderate	2014	North America
Richter 2017	75/244	0.307	0.253	0.368	0.000	1.37		Moderate	2015	North America
Pooled estimate		0.307	0.287	0.327	0.000					
							0.00 0.50 1.00			

Figure 2: The proportion of patients with chronic non-cancer pain prescribed opioid analgesics.

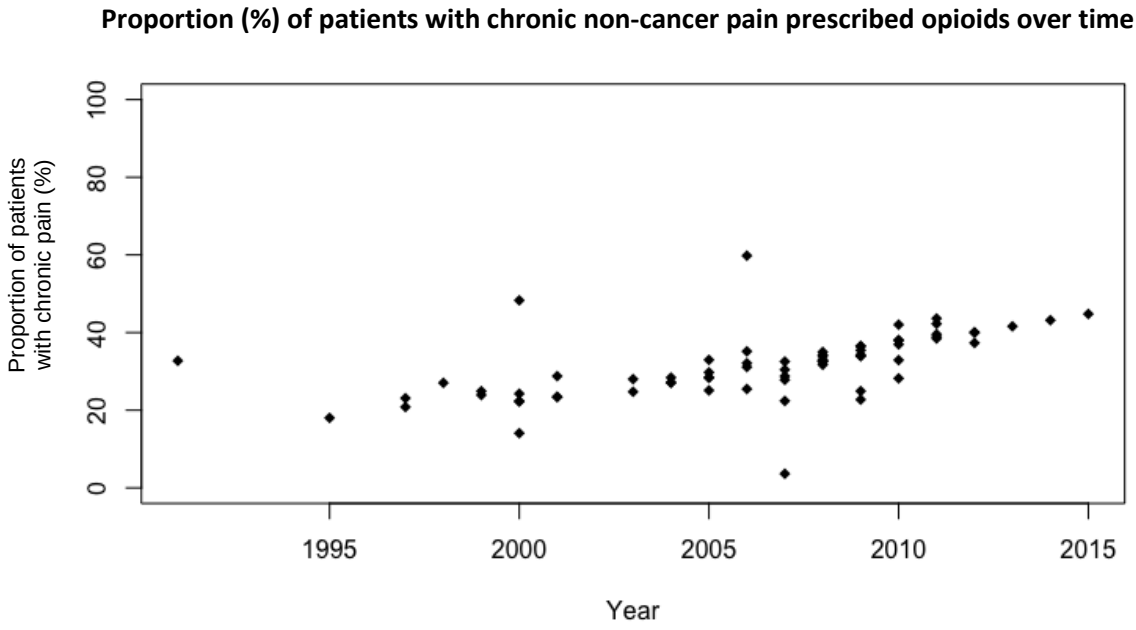


Figure 3: Adjusted estimates of opioid analgesics prescribed over time.

Meta-regression model was calculated in logit space, adjusted for WHO region, the disclosure of funding, setting, duration of the sampling period and year of study sampling. Adjusted estimates for each study were back transformed from logit scale to percentages and presented over time.

Study	Country	Sampling dates	Setting	Data source	Number of participants	Diagnosis
Almakadma 2013	UK	1990-2006	Tertiary	Retrospective cross-sectional review of medical records	1,500	Chronic pain
Ashworth 2013	UK	2004-2006	Primary	Prospective cohort questionnaire	715	Chronic low back pain
Beehler 2013	USA	2003-2009	Primary, secondary (specialist)	Retrospective case control review of medical records	792	Chronic musculoskeletal pain
Berger 2012	UK	2006	Primary	Retrospective cohort record review (The Health Improvement Network)	31,688	Painful neuropathic disorders
Birtwhistle 2015	Canada	2010-2012	Primary	Retrospective cohort review of medical records (Canadian Primary Care Sentinel Surveillance Network)	29,562	Osteoarthritis and spondylosis
Carbone 2013	USA	2002-2007	Population-based (Veterans Affairs database)	Retrospective review of Veterans Affairs Healthcare System records	7447	Chronic pain and spinal cord injury
Castillo 2006	USA	1994-1997	Tertiary	Prospective cohort from Lower Extremity Assessment Project	569	Chronic pain post fracture
Clarke 2002	USA	2000	Population-based (Veterans Affairs database)	Retrospective cross-sectional review of medical records	143	Chronic pain
Cowan 2003	UK	1999-2009	Tertiary	Retrospective cross-sectional review of medical records	1,393	Chronic pain
Curtis 2017	USA	2007-2014	Secondary (specialist)	Retrospective cohort review of medical records	240,750	Rheumatoid arthritis
Dobscha 2013	USA	2008	Population-based (Veterans Affairs database)	Prospective case control review (Veterans Integrated Service Network)	17,126	Chronic pain
Dominick 2004	USA	1998-1999	Population-based (Veterans Affairs database)	Retrospective cohort review of medical records (Durham Veterans Affairs Medical Centre)	3 061	Osteoarthritis
Edlund 2014	USA	2009-2011	Population-based (Veterans Affairs database)	Retrospective cohort review from claims databases	4,175,765	Chronic pain
Fitzcharles 2011	Canada	2005-2010	Tertiary	Retrospective cross-sectional review of medical records	457	Fibromyalgia
Fredheim 2014	Norway	2006-2008	Population-based (dispensing database)	Cross sectional random sample of 3 surveys/databases	14,477	Chronic pain
Gore 2007	USA	2001	Primary	Retrospective cross-sectional database of medical records	30,999	Peripheral neuropathies

				(General Practice Research Database)		
Henderson 2013	Australia	2008-2009	Primary	Retrospective cross-sectional survey (Bettering the Evaluation And Care of Health program)	1,113	Chronic pain
Jensen 2006	Denmark	1989-1992	Tertiary	Retrospective cross-sectional review of medical records	160	Chronic pain
Mafi 2013	USA	1999-2010	Secondary (outpatient, ED)	Retrospective cohort database of medical records (NAMCS and NHAMCS)	4,623	Chronic low back and neck pain
Mafi 2015	USA	1999-2010	Secondary (outpatient)	Retrospective cohort database of medical records (NAMCS and NHAMCS)	3134	Chronic headache
Mahowald 2005	USA	1997	Secondary (specialist)	Retrospective cohort of medical records (Spine Clinic of the Minneapolis Veterans Affairs Medical Center)	230	Chronic low back pain
Mapel 2004	USA	2000-2001	Population-based (claims database)	Retrospective cohort database of medical records (Lovelace Health Plan)	8,993	Chronic low back pain, osteoarthritis
Margolis 2016	USA	2008-2012	Population-based (private data company)	Retrospective cross-sectional database of medical records (Humedica)	64,038	Fibromyalgia
Mohanty 2016	USA	2002-2012	Population-based (Veterans Affairs database)	Retrospective cross-sectional medical chart review of veterans	8,208	Fibromyalgia
Park 2016	USA	2010	Population-based (claims database)	Retrospective cross-sectional review of medical records (Henry Ford Health System)	12,165	Chronic pain
Perez 2013	Spain	2011	Primary, secondary (specialist)	Retrospective cross-sectional review of medical records	8,695	Chronic pain
Podichetty 2008	USA	2005-2007	Tertiary	Prospective cohort	486	Chronic low back pain
Ritcher 2017	USA	2005-2015	Secondary (outpatient), tertiary	Retrospective cohort of medical records (Rochester Epidemiology Project)	244	Polymyalgia rheumatica
Robinson 2012	USA	2008-2010	Primary, secondary (specialist)	Prospective cohort (RELECTIONS study)	1,700	Fibromyalgia

Rolita 2013	USA	2001-2009	Population-based (claims database)	Retrospective case-control of medical records (Geisinger Health System)	13,354	Osteoarthritis
Romanelli 2017	USA	2012	Primary, secondary (specialist)	Sutter Health electronic health record data	120,481	Chronic pain
Shadd 2015	Canada	2005-2010	Primary	Retrospective cohort of medical records (Deliver Primary Healthcare Information)	1219	Neuropathic pain
Steinman 2015	USA	1999-2010	Secondary (outpatient)	Retrospective cohort database of medical records (NAMCS and NHAMCS)	6,559	Chronic pain
Sule 2008	India	NR	Secondary (specialist)	Prospective cohort	467	Neuropathic pain
Tian 2013	USA	2011-2012	Primary	Retrospective cohort of medical records (eClinicalWorks)	7,491	Chronic pain
Turk 1997	USA	NR	Tertiary	Prospective cohort	191	Chronic pain
Videla 2017	Spain	2011-2014	Secondary (specialist)	Prospective cohort	269	Chronic pain
Vincent 2015	USA	2005-2009	Secondary, tertiary	Retrospective cohort of medical records (Rochester Epidemiology Project)	1,111	Fibromyalgia
Wilson 2013	Spain	2006	Primary	Retrospective review medical records (Sistema d'Informacio´ per al Desenvolupament de l'Investigacio´ en Atencio´ Prima` ria (SIDIAP) database)	238,536	Osteoarthritis
Wright 2013	USA	2003, 2006, 2009	Population-based (claims database)	Retrospective cross-sectional review from claims database (MCBS & Medicare)	1,387	Knee osteoarthritis
Young 2011	USA	NR	Primary	Prospective cohort	360	Chronic low back pain
Zamora-Legoff 2016	USA	2005-2014	Secondary outpatient), tertiary	Retrospective cohort of medical records (Rochester Epidemiology Project)	501	Rheumatoid arthritis

Table 1: Description of included studies.

Abbreviations: NR = Not Reported; ED = Emergency Department; NAMCS = The National Ambulatory Medical Care Survey; NHAMCS = The National Hospital Ambulatory Medical Care Survey; MCBS = Medicare Beneficiary Survey.

Appendix

APPENDIX

Appendix 1: Search strategies

PubMed (NLM® database)
(epidemiologic studies OR cohort studies OR cross sectional studies OR (epidemiologic adj (study or studies)) OR (follow up adj (study or studies)) OR retrospective* OR longitudinal OR prospective* OR (observ* adj (study or studies))) AND (prevalence OR occurrence OR burden) AND ((chronic pain) OR (chronic non-cancer pain or chronic non cancer pain or chronic noncancer pain) OR (chronic non-malignant pain or chronic non malignant pain or chronic nonmalignant pain) OR (pain adj (long-term or long term or longterm or persistent)) OR human) AND (NO2A* OR (opioid* adj3 analges*) OR opioid* OR (opioid* adj3 medicine) OR (opioid* adj3 drug*) OR narcotic* OR (narcotic* adj3 drug*) OR (narcotic* adj3 analges*) OR morphine OR ordine OR hydromorphone OR dilaudid OR oxycodone OR endone OR targin OR oxymorphone OR OPANA* OR codeine OR dihydrocodeine OR (opioid* adj3 alkaloid*) OR ketobemidone OR (phenylpiperidine adj3 deriv*) OR pethidine OR fentanyl OR durogesic OR diphenylpropylamine OR dextromoramide OR piritramide OR dextropropoxyphene OR di-gesic OR capodex OR bezitramide OR methadone OR physeptone OR (benzomorphan adj3 deriv*) OR pentazocine OR phenazocine OR (oripavine adj3 deriv*) OR buprenorphine OR norspan OR suboxone OR subutex OR etorphine OR (morphinan adj3 deriv*) OR tilidine OR trama* or tramadol OR dezocine OR tapendatol OR meptazinol OR nicomorphine OR butorphanol OR nalbuphine))

MEDLINE, EMBASE and International Pharmaceutical Abstracts (OvidSP)
((epidemiologic studies or cohort studies or cross sectional studies or (epidemiologic adj (study or studies)) or (follow up adj (study or studies)) or retrospective* or prospective* or (observ* adj (study or studies))) and (prevalence or occurrence or burden) and ((chronic pain) or (chronic non-cancer pain or chronic non cancer pain or chronic noncancer pain) or (chronic non-malignant pain or chronic non malignant pain or chronic nonmalignant pain) or (pain adj (long-term or long term or longterm or persistent)) or human) and (NO2A* or (opioid* adj25 analges*) or opioid* or (opioid* adj25 med*) or (opioid* adj25 drug*) or narcotic* or (narcotic* adj25 drug*) or (narcotic* adj25 analges*) or morphine or (morphine adj25 sul*) or ordine or hydromorphone or dilaudid or oxy* or oxycodone or endone or targin or oxymorphone or OPANA* or codeine or dihydrocodeine or (opi* adj25 alkaloid*) or ketobemidone or (phenylpiperidine adj25 deriv*) or pethidine or fentanyl or durogesic or diphenylpropylamine or dextromoramide or piritramide or dextropropoxyphene or di-gesic or capodex or bezitramide or methadone or physeptone or (benzomorphan adj25 deriv*) or pentazocine or phenazocine or (oripavine adj25 deriv*) or buprenorphine or norspan or suboxone or subutex or etorphine or (morphinan adj25 deriv*) or tilidine or trama* or tramadol or dezocine or tapendatol or meptazinol or nicomorphine or butorphanol or nalbuphine))

Web of Science (Thomson Reuters)
((((((((((((epidemiologic studies OR cohort studies) OR cross sectional studies) OR (epidemiologic NEAR study)) OR (epidemiologic NEAR studies)) OR (follow up NEAR study)) OR (follow up NEAR studies)) OR retrospective$) OR prospective$) OR (observ$ NEAR study)) OR (observ$ NEAR studies))) AND ((prevalence OR occurrence) OR burden)) AND ((((chronic pain OR ((chronic non-cancer pain OR chronic non cancer pain) OR chronic noncancer pain)) OR ((chronic non-malignant pain OR chronic non malignant pain) OR chronic nonmalignant pain)) OR ((((pain NEAR long-term) OR (pain NEAR long term)) OR (pain NEAR longerterm)) OR (pain NEAR persistent))) OR human)) AND ((NO2A$ OR opioid$ ada3 analges$) OR opioid$) OR opioid$ ada3 medicine) OR opioid$ ada3 drug$) OR narcotic$) OR narcotic$ ada3 drug$) OR narcotic$ ada3 analges$) OR morphine) OR ondine) OR hydromorphone) OR diclaudio) OR oxycodone) OR enzone) OR targis) OR oxymorphone) OR OPANA$) OR codeine) OR dihydrocodeine) OR opioid$ ada3 alkaloid$) OR ketobemidon) OR phenylpiperidino ada3 deriv$) OR pethidine) OR fentanyl) OR duragesic) OR diphenylpropylamino) OR dextromoramide) OR piritramid) OR dextropropoxyphene) OR di-gesic) OR casodex) OR bezitramide) OR methadone) OR physetine) OR benzomorphans ada3 deriv$) OR pentazocine) OR pentazocine) OR oripavines ada3 deriv$) OR buprenorphine) OR norstar) OR subclone) OR suratex) OR exorphins) OR morphinans ada3 deriv$) OR tolidine) OR trama$) OR tramadol) OR diazocine) OR tapentadol) OR meptazinol) OR nicomorphine) OR butorphanol) OR nalbuphine))

Appendix 2: Opioid classification and conversion

N02A Opioids	Category
N02AA Natural opium alkaloids	
N02AA01 Morphine	Strong
N02AA02 Opium	Strong
N02AA03 Hydromorphone	Strong
N02AA04 Nicomorphine	Strong
N02AA05 Oxycodone	Strong
N02AA08 Dihydrocodeine	Weak
N02AA10 Papaveretum	Strong
N02AA51 Morphine, combinations	Strong
N02AA55 Oxycodone and naloxone	Strong
N02AA58 Dihydrocodeine, combinations	Combination – weak
N02AA59 Codeine, combinations excluding psycholeptics	Combination – weak
N02AA79 Codeine, combinations with psycholeptics	Combination – weak
N02AB Phenylpiperidine derivatives	
N02AB01 Ketobemidone	Strong
N02AB02 Pethidine	Strong
N02AB03 Fentanyl	Strong
N02AB52 Pethidine, combinations excluding psycholeptics	Combination – strong
QN02AB53 Fentanyl, combinations excluding psycholeptics	Combination – strong
N02AB72 Pethidine, combinations with psycholeptics	Combination – strong
QN02AB73 Fentanyl, combinations with psycholeptics	Combination – strong
N02AC Diphenylpropylamine derivatives	
N02AC01 Dextromoramide	Strong
N02AC03 Piritramide	Strong
N02AC04 Dextropropoxyphene	Weak
N02AC05 Bezitramide	Strong
N02AC52 Methadone, combinations excluding psycholeptics	Combination – strong
N02AC54 Dextropropoxyphene, combinations excluding psycholeptics	Combination – weak
N02AC74 Dextropropoxyphene, combinations with psycholeptics	Combination – strong
N02AD Benzomorphan derivatives	
N02AD01 Pentazocine	Strong
N02AD02 Phenazocine	Strong
N02AE Oripavine derivatives	
N02AE01 Buprenorphine	Strong
N02AF Morphinan derivatives	
N02AF01 Butorphanol	Strong
N02AF02 Nalbuphine	Strong
N02AG Opioids in combination with antispasmodics	
N02AG01 Morphine and antispasmodics	Combination – strong
N02AG02 Ketobemidone and antispasmodics	Combination – strong
N02AG03 Pethidine and antispasmodics	Combination – strong
N02AG04 Hydromorphone and antispasmodics	Combination – strong
N02AJ Opioids in combination with non-opioid analgesics	
N02AJ01 Dihydrocodeine and paracetamol (acetaminophen)	Combination – weak
N02AJ02 Dihydrocodeine and acetylsalicylic acid	Combination – weak
N02AJ03 Dihydrocodeine and other non-opioid analgesics	Combination – weak
N02AJ06 Codeine and paracetamol (acetaminophen)	Combination – weak
N02AJ07 Codeine and acetylsalicylic acid	Combination – weak
N02AJ08 Codeine and ibuprofen	Combination – weak
N02AJ09 Codeine and other non-opioid analgesics	Combination – weak
N02AJ13 Tramadol and paracetamol (acetaminophen)	Combination – weak
N02AJ14 Tramadol and dexketoprofen	Combination – weak
N02AJ15 Tramadol and other non-opioid analgesics	Combination – weak
N02AJ17 Oxycodone and paracetamol (acetaminophen)	Combination – strong
N02AJ18 Oxycodone and acetylsalicylic acid	Combination – strong

N02AJ19 Oxycodone and ibuprofen	Combination – strong
N02AX Other opioids	
N02AX01 Tilidine	Weak
N02AX02 Tramadol	Weak
N02AX03 Dezocine	Strong
N02AX05 Meptazinol	Strong
N02AX06 Tapentadol	Strong

Morphine milligram equivalents (MME) was calculated as per Dowell et al.

Appendix 3: Risk of bias scores and assessment criteria

Study	1. Study population representative	2. Sampling frame representative	3. Random selection or census	4. Minimal non-response bias	5. Data collected from subjects?	6. Acceptable case definition	7. Reliable and valid study instrument	8. Same mode of data collection	9. Prevalence period appropriate	10. Appropriate numerator/ denominator	Summary risk of bias
AlMakadma 2013	High	Low	High	High	High	High	High	Low	High	Low	High
Ashworth 2013	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Beehler 2013	High	Low	Low	Low	Low	High	High	Low	Low	Low	Moderate
Berger 2012	Low	High	Low	High	Low	High	High	Low	Low	Low	Moderate
Birtwhistle 2015	Low	High	Low	Low	Low	High	Low	Low	Low	Low	Low
Carbone 2013	Low	High	High	High	High	Low	Low	High	High	High	Moderate
Castillo 2016	High	High	High	High	Low	Low	High	Low	Low	Low	Moderate
Clarke 2002	High	Low	Low	Low	Low	High	High	Low	Low	High	Moderate
Cowan 2003	High	Low	Low	Low	Low	High	High	Low	Low	Low	Moderate
Curtis 2017	Low	High	Low	High	Low	Low	High	Low	Low	Low	Moderate
Dobscha 2013	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Dominick 2004	High	High	High	High	Low	High	High	Low	Low	Low	High
Edlund 2014	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low
Fitzcharles 2011	High	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Fredheim 2014	Low	Low	Low	High	Low	Low	High	Low	Low	Low	Low
Gore 2007	Low	High	High	Low	Low	High	Low	Low	Low	Low	Moderate
Henderson 2013	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Jensen 2006	High	Low	Low	Low	Low	High	High	Low	High	Low	Moderate
Mafi 2013	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Mafi 2015	Low	High	Low	Low	Low	Low	High	Low	Low	Low	Low
Mahowald	High	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Mapel 2004	Low	High	Low	Low	Low	High	Low	Low	Low	Low	Low
Margolis 2004	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Mohanty 2016	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Park 2016	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low
Perez 2013	High	Low	High	High	Low	Low	High	Low	Low	Low	Moderate
Podichetty 2008	High	High	Low	High	Low	Low	High	Low	High	Low	Moderate
Richter 2017	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Robinson 2012	High	High	High	Low	Low	Low	High	Low	Low	Low	Moderate
Rolita 2013	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Romanelli 2017	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low

Shadd 2015	High	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Steinman 2015	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Sule 2008	High	High	High	High	Low	Low	High	Low	Low	High	High
Tian 2013	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Turk 1997	High	Low	Low	Low	Low	High	High	Low	Low	Low	Moderate
Videla 2017	High	Low	High	High	Low	High	High	Low	Low	Low	Moderate
Vincent 2015	High	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Wilson 2015	High	Low	High	High	High	Low	Low	High	High	High	Moderate
Wright 2013	High	High	High	High	Low	High	High	Low	Low	Low	High
Young 2011	High	High	High	High	Low	Low	High	Low	Low	Low	High
Zamora-Legoff 2016	High	High	Low	Low	Low	High	High	Low	Low	Low	Moderate

Risk of bias questions modified from Hoy et al 2012.

Assessment	Additional notes and examples#
External validity	
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	
• Yes (LOW RISK): The study's target population was a close representation of the national population. • No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	The target population refers to the group of people with chronic pain or entities to which the results of the study will be generalized. Examples: • The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: Yes (LOW RISK). • The study was conducted in one province or village or one clinic only, and it is not clear if this was representative of the national population. The answer is: No (HIGH RISK).
2. Was the sampling frame a true or close representation of the target population?	
• Yes (LOW RISK): The sampling frame was a true or close representation of the target population. • No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: • The sampling frame was a list of almost every individual within the target population (i.e. all types of chronic pain). The answer is: Yes (LOW RISK). • The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: Yes (LOW RISK). • The sampling frame was a list of just one particular ethnic group within the overall target population, or city, which comprised many groups (i.e. only a subgroup of chronic pain patients i.e. chronic back pain only). The answer is: No (HIGH RISK).
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	
• Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimize study bias. Examples: • The sample was selected using simple random sampling. The answer is: Yes (LOW RISK). • The target population was the village and every person in the village was sampled. The answer is: Yes (LOW RISK). • The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: No (HIGH RISK).

4. Was the likelihood of non-response bias minimal?

- Yes (LOW RISK): The response rate for the study was ≥ 75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders, or entire database.
- No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.

Examples:

- The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socioeconomic status. The answer is: Yes (LOW RISK).
- The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders. The answer is: No (HIGH RISK).
- The response rate was 69% and the researchers did an analysis and found a significant difference in age, sex and socio-economic status between responders and non-responders. The answer is: No (HIGH RISK).

Internal validity

5. Were data collected directly from the subjects (as opposed to a proxy)?

- Yes (LOW RISK): All data were collected directly from the subjects.
- No (HIGH RISK): In some instances, data were collected from a proxy.

A proxy is a representative of the subject. Examples:

- All eligible subjects in the household were interviewed separately. The answer is: Yes (LOW RISK).
- A representative of the household was interviewed and questioned about the presence of low back pain in each household member. The answer is: No (HIGH RISK).

6. Was an acceptable case definition used in the study?

- Yes (LOW RISK): An acceptable case definition was used. Duration of chronic pain must be stated and followed appropriate standard/guideline.
- No (HIGH RISK): An acceptable case definition was NOT used.

Example:

- For a study on low back pain, the following case definition was used: “Low back pain is defined as activity-limiting pain lasting more than one day in the area on the posterior aspect of the body from the bottom of the 12th rib to the lower gluteal folds”. The answer is: Yes (LOW RISK).
- For a study on back pain, there was no description of the specific anatomical location “back“ referred to. The answer is: No (HIGH RISK).
- For a study on osteoarthritis, the following case definition was used: “Symptomatic osteoarthritis of the hip or knee, radiologically confirmed as Kellgren-Lawrence grade 2-4”. The answer is: Yes (LOW RISK).

7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?

- Yes (LOW RISK): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.

Example:

- The authors used a questionnaire which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: Yes (LOW RISK).

• No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	• The authors developed their own questionnaire (or medical chart review) and did not test this for validity or reliability. The answer is: No (HIGH RISK).
8. Was the same mode of data collection used for all subjects?	
• Yes (LOW RISK): The same mode of data collection was used for all subjects. • No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to-face interviews, telephone interviews and self-administered questionnaires. Examples: • All eligible subjects had a face-to-face interview. The answer is: Yes (LOW RISK). • Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: No (HIGH RISK).
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	
• Yes (LOW RISK): The shortest prevalence period for the parameter of interest was appropriate (e.g. point prevalence). • No (HIGH RISK): The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence)	The prevalence period is the period that the subject is asked about e.g. "Have you experienced low back pain over the previous year?" In this example, the prevalence period is one year. The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest (e.g. low back pain). Examples: • Subjects were asked about medicine use over the past week or no recall bias likely (i.e. medical chart review). The answer is: Yes (LOW RISK). • Subjects were asked about medicine use for the last month or longer (i.e. subjective recall with no objective measure). The answer is: No (HIGH RISK).
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	
• Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain). • No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: Yes (LOW RISK). • In reporting the overall prevalence of low back pain (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: No (HIGH RISK).

If there is insufficient information = No (HIGH RISK) for that particular item.

A study's overall risk of bias was considered:

- 'Low' if further research was very unlikely to change our confidence in the estimate;
- 'Moderate' if further research was likely to have an important impact on our confidence in the estimate and may change the estimate; or
- 'High' if further research was very likely to have an important impact on our confidence in the estimate and was likely to change the estimate.

Appendix 4: GRADE criteria and scoring

The overall quality of evidence may be:

- High: further research is very unlikely to change the confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact in the confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low: any estimate of effect is very uncertain.

Reasons for downgrade:
Each domain were assessed, and points downgraded or upgraded accordingly from “high” quality evidence.

Factors that downgrade the quality of evidence:

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
4. Imprecision of results (wide confidence intervals).
5. High probability of publication bias.

Assessment criteria

Domain	Assessment criteria
1. Study design	No randomised controlled trials were included in this review. We did not downgrade for studies being observational in design as this the appropriate method of measuring prevalence. Only observational studies containing a representative sample were included in this review. This included representativeness from the population which participants were sampled, participants were representative of the disease/condition of interest etc.
2. Risk of bias	Risk was bias was assessed using the criteria by Hoy et al. No downgrade given if all studies had "low" overall risk of bias score. Downgrade by one level if an overall risk of bias score of "moderate" or "high" was found across studies.
3. Inconsistency	Statistical heterogeneity was considered present if the I_2 value suggested substantial heterogeneity was present and there were widely differing estimates of effect. Clinical heterogeneity was considered in the domain of indirectness. No downgrade given if no statistical heterogeneity was present or only one study was present. Downgraded by one level if statistical heterogeneity was present.
4. Indirectness	Indirectness refers to how well the evidence included in the review answers the review question. Indirectness may come from indirect: • Population: mean age, gender bias, ethnicity, pain mechanism. • Intervention: opioid dosing. • Comparator: not applicable • Outcome: missing data No downgrade if indirectness was not present. Downgraded by one level if indirectness was present in either population, intervention or outcomes.
5. Imprecision	Results are imprecise there is variation in the effect. No downgrade if there were narrow confidence intervals around the prescribing estimate. Downgraded by one level if there were wide confidence intervals around the prescribing estimate.
6. Publication bias	Publication bias is a systematic under or over estimation of the underlying effect, due to the selective publication of studies or availability of their data. We did not assess publication bias because of uncertainty in assessing for missing observational studies and applying funnel plots for observational studies is not well established.

b) Factors that can upgrade the quality of evidence:

Nil.

GRADE Scoring

Opioid prescribing estimate	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall score
Chronic non-cancer pain							
All opioids	0	-1	0#	0	0	NA	Moderate
Weak opioids	0	-1	-1 (I_2 = 72.3%)	0	0	NA	Low
Strong opioids	0	-1	-1 (I_2 = 84.3%)	0	0	NA	Low
Weak combination opioids	0	-1	0 (I_2 = 0%)	0	0	NA	Moderate
Strong combination opioids	0	-1	0 (I_2 = 0%)	0	-1	NA	Low
Chronic low back pain							
All opioids	0	-1	0#	0	-1	NA	Low
Weak opioids	0	-1	0 (I_2 = 0%)	0	0	NA	Moderate
Strong opioids							NA
Weak combination opioids							NA
Strong combination opioids							NA

Statistical heterogeneity was explored in meta-regression.

Abbreviations: NA = no subgroup analysis conducted.

Appendix 5: Forest plots

5.1 The types of opioid analgesics prescribed to patients with chronic non-cancer pain

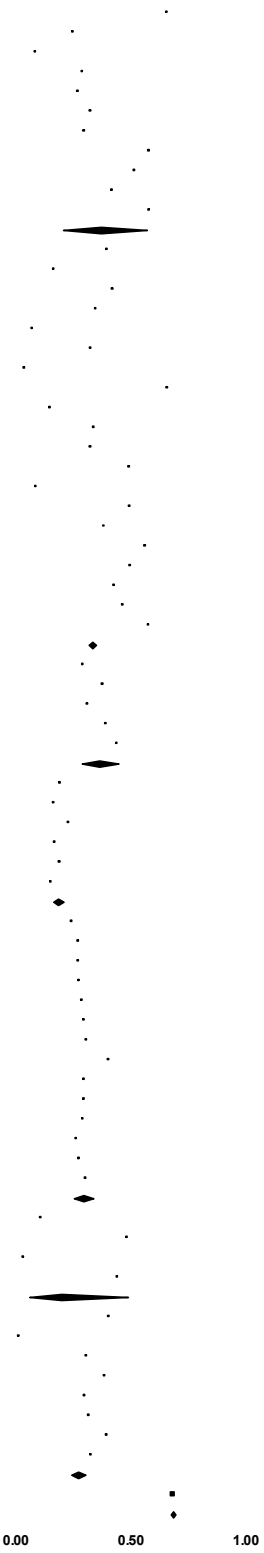
Study name	Opioid type	Sampling year	Events		Statistics for each study				Weight (Random)	Event rate and 95%CI
			Total	Total	Event rate	Lower limit	Upper limit	p-Value	Relative weight	
Jensen 2006	Strong	1991	64	160	0.400	0.327	0.478	0.012	4.02	
Mahowald 2005	Strong	1997	56	230	0.243	0.192	0.303	0.000	4.08	
Cowan 2003	Strong	1999	341	1393	0.245	0.223	0.268	0.000	4.61	
Dominick 2004	Strong	1999	54	3061	0.018	0.014	0.023	0.000	4.20	
Clarke 2002	Strong	2000	27	143	0.189	0.133	0.261	0.000	3.61	
Gore 2007	Strong	2001	3464	30999	0.112	0.108	0.115	0.000	4.73	
Carbone 2013	Strong	2005	5907	7447	0.793	0.784	0.802	0.000	4.71	
Curtis 2017	Strong	2007	34740	240750	0.144	0.143	0.146	0.000	4.73	
Dobscha 2013	Strong	2008	2040	5961	0.342	0.330	0.354	0.000	4.71	
Fitzcharles 2011	Strong	2008	105	457	0.230	0.193	0.271	0.000	4.37	
Henderson 2013	Strong	2008	160	1088	0.147	0.127	0.169	0.000	4.51	
Wilson 2015	Strong	2008	9822	238536	0.041	0.040	0.042	0.000	4.73	
Zamora-Legoff 2016	Strong	2008	112	501	0.224	0.189	0.262	0.000	4.39	
Curtis 20178	Strong	2008	35719	240750	0.148	0.147	0.150	0.000	4.73	
Curtis 2017	Strong	2009	37676	240750	0.156	0.155	0.158	0.000	4.73	
Curtis 2017	Strong	2010	39633	240750	0.165	0.163	0.166	0.000	4.73	
Curtis 2017	Strong	2011	41101	240750	0.171	0.169	0.172	0.000	4.73	
Birtwhistle 2015	Strong	2011	3898	29562	0.132	0.128	0.136	0.000	4.73	
Perez 2013	Strong	2011	2564	8695	0.295	0.285	0.305	0.000	4.72	
Curtis 2017	Strong	2012	41590	240750	0.173	0.171	0.174	0.000	4.73	
Curtis 2017	Strong	2013	41101	240750	0.171	0.169	0.172	0.000	4.73	
Curtis 2017	Strong	2014	40122	240750	0.167	0.165	0.168	0.000	4.73	
Pooled estimate					0.184	0.160	0.210	0.000		
Dominick 2004	Strong combination	1999	1176	3061	0.384	0.367	0.402	0.000	49.99	
Perez 2013	Strong combination	2011	1210	8695	0.139	0.132	0.147	0.000	50.01	
Pooled estimate					0.241	0.078	0.544	0.089		
Jensen 2006	Weak	1991	0	160	0.003	0.000	0.048	0.000	0.36	
Mahowald 2005	Weak	1997	109	230	0.474	0.410	0.539	0.429	3.77	
Dominick 2004	Weak	1999	116	3061	0.038	0.032	0.045	0.000	3.93	
Mafi 2013	Weak	1999	16	572	0.028	0.017	0.045	0.000	3.09	
Clarke 2002	Weak	2000	19	143	0.133	0.086	0.199	0.000	3.13	
Gore 2007	Weak	2001	1900	30999	0.061	0.059	0.064	0.000	4.10	
Mafi 2013	Weak	2001	32	725	0.044	0.031	0.062	0.000	3.52	
Mafi 2013	Weak	2003	15	831	0.018	0.011	0.030	0.000	3.04	
Carbone 2013	Weak	2005	2687	7447	0.361	0.350	0.372	0.000	4.10	
Mafi 2013	Weak	2005	37	816	0.045	0.033	0.062	0.000	3.59	
Curtis 2017	Weak	2007	19572	240750	0.081	0.080	0.082	0.000	4.11	
Vincent 2015	Weak	2007	174	1111	0.157	0.136	0.179	0.000	3.97	
Fitzcharles 2011	Weak	2008	39	457	0.085	0.063	0.115	0.000	3.59	
Henderson 2013	Weak	2008	96	1088	0.088	0.073	0.107	0.000	3.88	
Wilson 2015	Weak	2009	30811	238536	0.129	0.128	0.131	0.000	4.11	
Zamora-Legoff 2016	Weak	2008	44	501	0.088	0.066	0.116	0.000	3.64	
Curtis 2017	Weak	2008	20550	240750	0.085	0.084	0.086	0.000	4.11	
Mafi 2013	Weak	2007	38	979	0.039	0.028	0.053	0.000	3.60	
Curtis 2017	Weak	2009	21040	240750	0.087	0.086	0.089	0.000	4.11	
Curtis 2017	Weak	2010	20061	240750	0.083	0.082	0.084	0.000	4.11	
Mafi 2013	Weak	2009	33	700	0.047	0.034	0.066	0.000	3.53	
Curtis 2017	Weak	2011	16147	240750	0.067	0.066	0.068	0.000	4.11	
Birtwhistle 2015	Weak	2011	9180	29562	0.311	0.305	0.316	0.000	4.11	
Perez 2013	Weak	2011	593	8695	0.068	0.063	0.074	0.000	4.07	
Curtis 2017	Weak	2012	16636	240750	0.069	0.068	0.070	0.000	4.11	
Curtis 2017	Weak	2013	17125	240750	0.071	0.070	0.072	0.000	4.11	
Curtis 2017	Weak	2014	17125	240750	0.071	0.070	0.072	0.000	4.11	
Pooled estimate					0.085	0.072	0.099	0.000		
Dominick 2004	Weak combination	1999	342	3061	0.112	0.101	0.123	0.000	24.99	
Henderson 2013	Weak combination	2008	166	1088	0.153	0.132	0.175	0.000	24.70	
Wilson 2015	Weak combination	2009	35862	238536	0.150	0.149	0.152	0.000	25.24	
Perez 2013	Weak combination	2011	480	8695	0.055	0.051	0.060	0.000	25.07	
Pooled estimate					0.110	0.066	0.178	0.000		
					0.129	0.117	0.143	0.000		

5.2 The proportion of opioid analgesics prescribed to patients with chronic low back pain

Study name	Sampling year	Events		Statistics for each study				Weight (Random)	Event rate and 95%CI
		Total	Total	Event rate	Lower limit	Upper limit	p-Value	Relative weight	
Turk 1997	1997	17	42	0.405	0.269	0.557	0.220	5.54	
Mafi 2013	1999	144	572	0.252	0.218	0.289	0.000	5.90	
Mapel 2004	2000	8801	84912	0.104	0.102	0.106	0.000	5.94	
Mafi 2013	2001	212	725	0.292	0.260	0.327	0.000	5.91	
Mafi 2013	2003	227	831	0.273	0.244	0.304	0.000	5.91	
Ashworth 2013	2005	234	715	0.327	0.294	0.363	0.000	5.91	
Mafi 2013	2005	245	816	0.300	0.270	0.333	0.000	5.91	
Podichetty 2008	2006	283	486	0.582	0.538	0.625	0.000	5.90	
Dobscha 2013	2008	864	2431	0.355	0.337	0.375	0.000	5.93	
Henderson 2013	2008	122	313	0.390	0.337	0.445	0.000	5.88	
Mafi 2013	2007	508	979	0.519	0.488	0.550	0.237	5.92	
Edlund 2014	2009	374753	605084	0.619	0.618	0.621	0.000	5.94	
Mafi 2013	2009	295	700	0.421	0.385	0.458	0.000	5.91	
Mahowald 2005	2010	152	230	0.661	0.597	0.719	0.000	5.86	
Young 2011	2010	210	360	0.583	0.532	0.633	0.002	5.89	
Romanelli 2017	2012	40062	58925	0.680	0.676	0.684	0.000	5.94	
Videla 2017	2012	62	127	0.488	0.402	0.575	0.790	5.80	
Pooled estimate				0.415	0.289	0.554	0.228		

5.3 The proportion of opioid analgesics prescribed to patients across all diagnoses

Group by Diagnosis	Study name	Sampling year	Events/Total	Statistics for each study				Weight (random)	Event rate and 95%CI
			Total	Event rate	Lower limit	Upper limit	p-Value	Relative weight	
Chronic back pain	Mahowald 2005	1997	152/230	0.661	0.597	0.719	0.000	9.04	
Chronic back pain	Mafi 2013	1999	144/572	0.252	0.218	0.289	0.000	9.08	
Chronic back pain	Mapel 2004	2000	16581/188452	0.088	0.087	0.089	0.000	9.13	
Chronic back pain	Mafi 2013	2001	212/725	0.292	0.260	0.327	0.000	9.10	
Chronic back pain	Mafi 2013	2003	227/831	0.273	0.244	0.304	0.000	9.10	
Chronic back pain	Ashworth 2013	2005	234/715	0.327	0.294	0.363	0.000	9.10	
Chronic back pain	Mafi 2013	2005	245/816	0.300	0.270	0.333	0.000	9.10	
Chronic back pain	Podichetty 2008	2006	283/486	0.582	0.538	0.625	0.000	9.09	
Chronic back pain	Mafi 2013	2007	508/979	0.519	0.488	0.550	0.237	9.11	
Chronic back pain	Mafi 2013	2009	295/700	0.421	0.385	0.458	0.000	9.10	
Chronic back pain	Young 2011	2010	210/360	0.583	0.532	0.633	0.002	9.07	
Chronic back pain				0.372	0.207	0.573	0.208		
Chronic pain	Jensen 2006	1991	64/160	0.400	0.327	0.478	0.012	2.80	
Chronic pain	Castillo 2016	1995	96/569	0.169	0.140	0.202	0.000	3.88	
Chronic pain	Turk 1997	1997	81/191	0.424	0.356	0.495	0.037	3.09	
Chronic pain	AlMakadma 2013	1998	526/1500	0.351	0.327	0.375	0.000	5.36	
Chronic pain	Cowan 2003	1999	104/1392	0.075	0.062	0.090	0.000	4.14	
Chronic pain	Clarke 2002	2000	47/143	0.329	0.257	0.410	0.000	2.51	
Chronic pain	Steinman 2015	2000	269/6559	0.041	0.036	0.046	0.000	5.17	
Chronic pain	Beehler 2013	2006	524/792	0.662	0.628	0.694	0.000	4.84	
Chronic pain	Fredheim 2014	2007	2204/14477	0.152	0.146	0.158	0.000	5.92	
Chronic pain	Dobscha 2013	2008	2040/5961	0.342	0.330	0.354	0.000	5.87	
Chronic pain	Henderson 2013	2008	356/1088	0.327	0.300	0.356	0.000	5.11	
Chronic pain	Edlund 2014	2009	662090/1332810	0.497	0.496	0.498	0.000	6.06	
Chronic pain	Steinman 2015	2009	597/6559	0.091	0.084	0.098	0.000	5.60	
Chronic pain	Edlund 2014	2010	700140/1405563	0.498	0.497	0.499	0.000	6.06	
Chronic pain	Park 2016	2010	4707/12165	0.387	0.378	0.396	0.000	5.97	
Chronic pain	Perez 2013	2011	4847/8579	0.565	0.554	0.575	0.000	5.94	
Chronic pain	Edlund 2014	2011	720287/1437392	0.501	0.500	0.502	0.008	6.06	
Chronic pain	Tian 2013	2011	3231/7491	0.431	0.420	0.443	0.000	5.92	
Chronic pain	Videla 2017	2012	126/269	0.468	0.409	0.528	0.300	3.63	
Chronic pain	Romanelli 2017	2012	69935/120481	0.580	0.578	0.583	0.000	6.05	
Chronic pain				0.334	0.319	0.351	0.000		
Fibromyalgia	Mohanty 2016	2007	2419/8208	0.295	0.285	0.305	0.000	20.36	
Fibromyalgia	Vincent 2015	2007	423/1111	0.381	0.353	0.410	0.000	19.94	
Fibromyalgia	Fitzcharles 2011	2008	144/457	0.315	0.274	0.359	0.000	19.16	
Fibromyalgia	Robinson 2012	2009	672/1700	0.395	0.372	0.419	0.000	20.11	
Fibromyalgia	Margolis 2016	2010	28368/64038	0.443	0.439	0.447	0.000	20.43	
Fibromyalgia				0.365	0.289	0.448	0.002		
Headache	Mafi 2015	1999	68/352	0.193	0.158	0.241	0.000	14.59	
Headache	Mafi 2015	2001	98/585	0.168	0.139	0.200	0.000	17.02	
Headache	Mafi 2015	2003	134/577	0.232	0.200	0.268	0.000	18.35	
Headache	Mafi 2015	2005	86/504	0.171	0.142	0.208	0.000	16.25	
Headache	Mafi 2015	2007	101/522	0.193	0.162	0.230	0.000	17.01	
Headache	Mafi 2015	2009	93/594	0.157	0.130	0.188	0.000	16.78	
Headache				0.186	0.164	0.210	0.000		
Inflammatory arthridities	Richter 2017	2004	60/244	0.246	0.196	0.304	0.000	6.94	
Inflammatory arthridities	Richter 2017	2005	67/244	0.275	0.222	0.334	0.000	7.01	
Inflammatory arthridities	Richter 2017	2006	67/244	0.275	0.222	0.334	0.000	7.01	
Inflammatory arthridities	Richter 2017	2007	68/244	0.279	0.226	0.338	0.000	7.02	
Inflammatory arthridities	Richter 2017	2008	71/244	0.291	0.237	0.351	0.000	7.04	
Inflammatory arthridities	Richter 2017	2009	73/244	0.299	0.245	0.360	0.000	7.06	
Inflammatory arthridities	Zamora-Legoff 2016	2009	155/501	0.309	0.270	0.351	0.000	7.57	
Inflammatory arthridities	Curtis 2017	2010	97859/240750	0.406	0.405	0.408	0.000	8.10	
Inflammatory arthridities	Richter 2017	2010	73/244	0.299	0.245	0.360	0.000	7.06	
Inflammatory arthridities	Richter 2017	2011	73/244	0.299	0.245	0.360	0.000	7.06	
Inflammatory arthridities	Richter 2017	2012	72/244	0.295	0.241	0.355	0.000	7.05	
Inflammatory arthridities	Richter 2017	2013	65/244	0.266	0.215	0.325	0.000	6.99	
Inflammatory arthridities	Richter 2017	2014	68/244	0.279	0.226	0.338	0.000	7.02	
Inflammatory arthridities	Richter 2017	2015	75/244	0.307	0.253	0.368	0.000	7.07	
Inflammatory arthridities				0.295	0.255	0.339	0.000		
Neuropathic pain	Gore 2007	2001	3464/30999	0.112	0.108	0.115	0.000	25.21	
Neuropathic pain	Berger 2012	2006	15444/31688	0.487	0.482	0.493	0.000	25.21	
Neuropathic pain	Sule 2008	2007	17/467	0.036	0.023	0.058	0.000	24.42	
Neuropathic pain	Shadd 2015	2008	543/1219	0.445	0.418	0.473	0.000	25.17	
Neuropathic pain				0.199	0.061	0.489	0.043		
Osteoarthritis	Dominick 2004	1999	1248/3061	0.408	0.390	0.425	0.000	13.51	
Osteoarthritis	Rolita 2013	2003	61/3731	0.016	0.013	0.021	0.000	10.25	
Osteoarthritis	Wright 2013	2003	151/488	0.309	0.270	0.352	0.000	11.54	
Osteoarthritis	Wright 2013	2006	186/477	0.390	0.347	0.434	0.000	11.70	
Osteoarthritis	Rolita 2013	2007	3329/11012	0.302	0.294	0.311	0.000	13.78	
Osteoarthritis	Wilson 2015	2008	76495/238536	0.321	0.319	0.323	0.000	13.90	
Osteoarthritis	Wright 2013	2009	168/422	0.398	0.352	0.446	0.000	11.47	
Osteoarthritis	Birtwhistle 2015	2011	9761/29562	0.330	0.325	0.336	0.000	13.86	
Osteoarthritis				0.273	0.243	0.305	0.000		
Spinal cord injury	Carbone 2013	2005	5106/7447	0.686	0.675	0.696	0.000	100.00	
Spinal cord injury				0.686	0.675	0.696	0.000		



Appendix 6: Meta-regression results

6.1 Meta-regression to determine study-level factors associated with opioid prescribing to patients with chronic non-cancer pain

Main results for Model 1, Random effects (ML), Knapp Hartung, Logit event rate

Set	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	t-value df = 58	2-sided P-value	VIF	
	Intercept	-133.3279	52.4218	-238.2616	-28.3942	-2.54	0.0137	280701.096	
WHO Region Reference: North America	**WHO Region: Europe**	-0.0245	0.3284	-0.6818	0.6328	-0.07	0.9408	1.255	F=2.66, df=3, dfErr=58, p=0.0563
	WHO Region: South East Asia	-2.4922	0.8873	-4.2683	-0.7160	-2.81	0.0068	1.055	
	WHO Region: Western Pacific	-0.3021	0.8777	-2.0590	1.4548	-0.34	0.7320	1.135	
	FundingDisclosed: No	1.0691	0.5274	0.0133	2.1249	2.03	0.0473	1.533	
Setting Reference: Primary care	**Setting: Database**	-0.1647	0.3697	-0.9048	0.5754	-0.45	0.6576	2.608	F=0.16, df=4, dfErr=58, p=0.9553
	Setting: Multiple	-0.2130	0.3665	-0.9466	0.5206	-0.58	0.5633	2.631	
	Setting: Secondary	-0.2627	0.3776	-1.0185	0.4931	-0.70	0.4893	2.801	
	Setting: Tertiary	-0.0306	0.5168	-1.0650	1.0038	-0.06	0.9530	2.474	
	Sample Duration (months)	-0.0045	0.0027	-0.0100	0.0009	-1.66	0.1028	1.141	
	Year	0.0662	0.0261	0.0139	0.1185	2.53	0.0140	1.612	

Statistics for Model 1

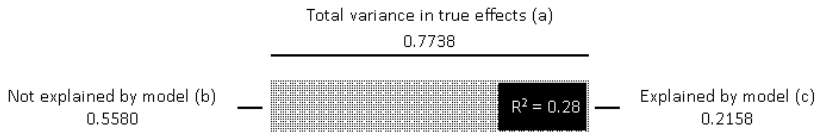
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
F = 2.23, df = 10, 58, p = 0.0285
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.5580, Tau = 0.7470, I^2 = 99.87%, Q = 45026.46, df = 58, p = 0.0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.7738, Tau = 0.8797, I^2 = 99.95%, Q = 150585.02, df = 68, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.28

Number of studies in the analysis 69

R^2 for Model 1, Random effects (ML), Knapp Hartung, Logit event rate



$$R^2 = \frac{\text{Explained (c)}}{\text{Total (a)}} = \frac{0.2158}{0.7738} = 0.28$$

(a) To compute the total variance (of all studies about the grand mean) we run the regression with no covariates.
(b) To compute the variance not explained by the model (of all studies about the regression line) we run the regression with the covariates.
(c) The difference between these values gives us the variance explained by the model.

6.2 Meta-regression to determine study-level factors associated with opioid prescribing to patients with chronic low back pain

Main results for Model 1, Random effects (ML), Knapp Hartung, Logit event rate

Set	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	t-value df = 8	2-sided P-value	VIF	
	Intercept	-341.3394	69.3905	-501.3542	-181.3246	-4.92	0.0012	370328.165	
WHO Region Reference: North America	**WHO Region: Europe**	-0.4569	0.4233	-1.4330	0.5191	-1.08	0.3118	1.355	F=0.75, df=2, dfErr=8, p=0.5026
	WHO Region: Western Pacific	-0.5727	0.6197	-2.0016	0.8563	-0.92	0.3824	1.596	
	FundingDisclosed: No	-0.8126	0.8441	-2.7591	1.1340	-0.96	0.3639	3.091	
Setting Reference: Primary care	**Setting: Database**	-0.4813	0.4718	-1.5693	0.6067	-1.02	0.3375	2.678	F=1.77, df=4, dfErr=8, p=0.2278
	Setting: PrimaryTertiary	-0.0514	0.6246	-1.4917	1.3889	-0.08	0.9365	1.825	
	Setting: Secondary	-0.2436	0.4069	-1.1819	0.6947	-0.60	0.5659	3.173	
	Setting: Tertiary	1.3605	0.8140	-0.5165	3.2375	1.67	0.1332	4.281	
	Year	0.1701	0.0346	0.0903	0.2498	4.92	0.0012	1.509	

Statistics for Model 1

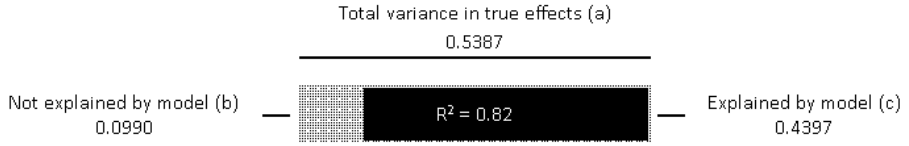
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
F = 4.45, df = 8, 8, p = 0.0247
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.0990, Tau = 0.3146, I^2 = 99.04%, Q = 830.62, df = 8, p = 0.0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.5387, Tau = 0.7340, I^2 = 99.97%, Q = 56109.30, df = 16, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.82

Number of studies in the analysis 17

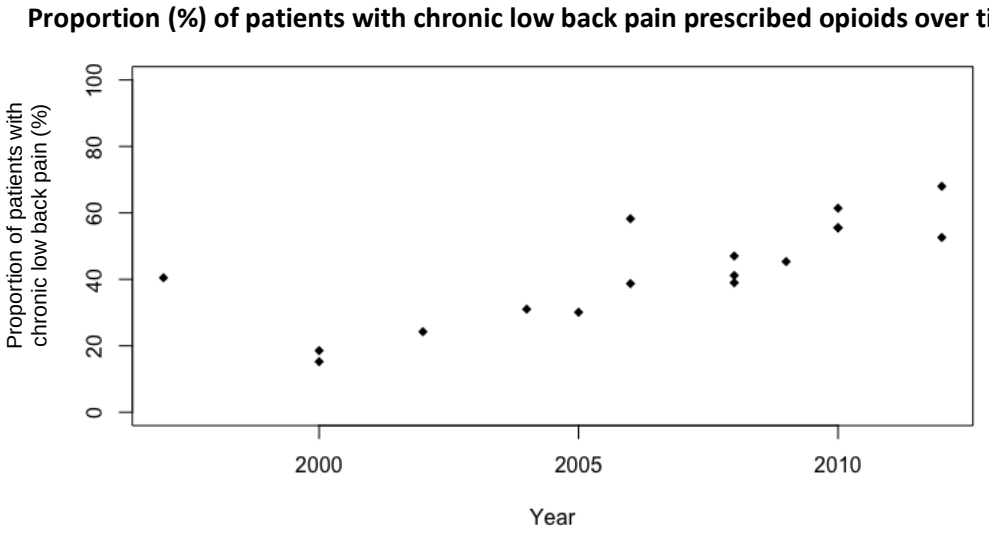
R^2 for Model 1, Random effects (ML), Knapp Hartung, Logit event rate



$$R^2 = \frac{\text{Explained (c)}}{\text{Total (a)}} = \frac{0.4397}{0.5387} = 0.82$$

(a) To compute the total variance (of all studies about the grand mean) we run the regression with no covariates.
(b) To compute the variance not explained by the model (of all studies about the regression line) we run the regression with the covariates.
(c) The difference between these values gives us the variance explained by the model.

Appendix 6.3 Adjusted estimates of opioid analgesics prescribed to patients with chronic low back pain over time



Meta-regression model was calculated in logit space, adjusted for WHO region, the disclosure of funding, setting and year of study sampling. Adjusted mean estimates for each study were back transformed from logit scale to percentages and presented over time.