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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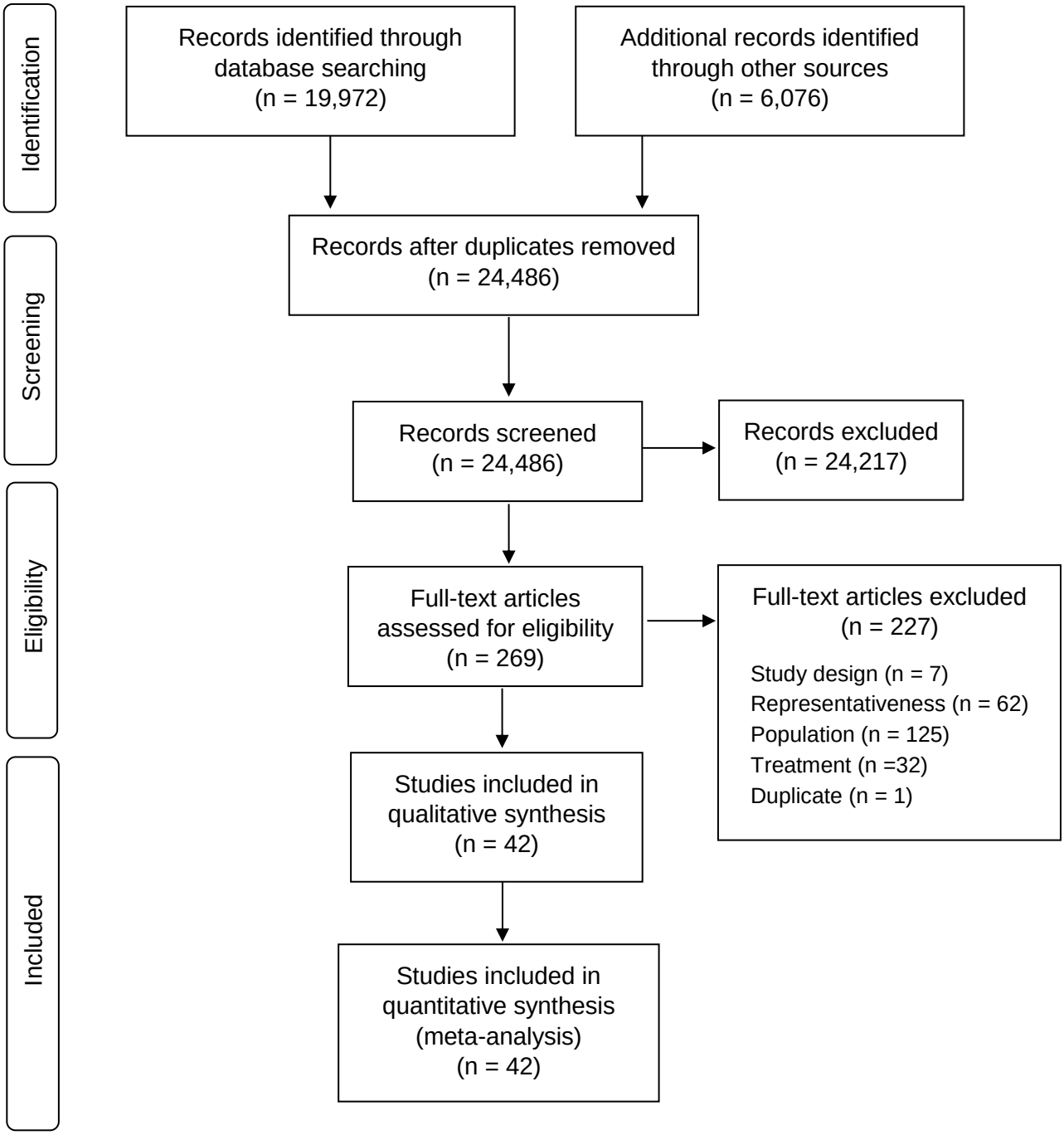
Figure legends

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.



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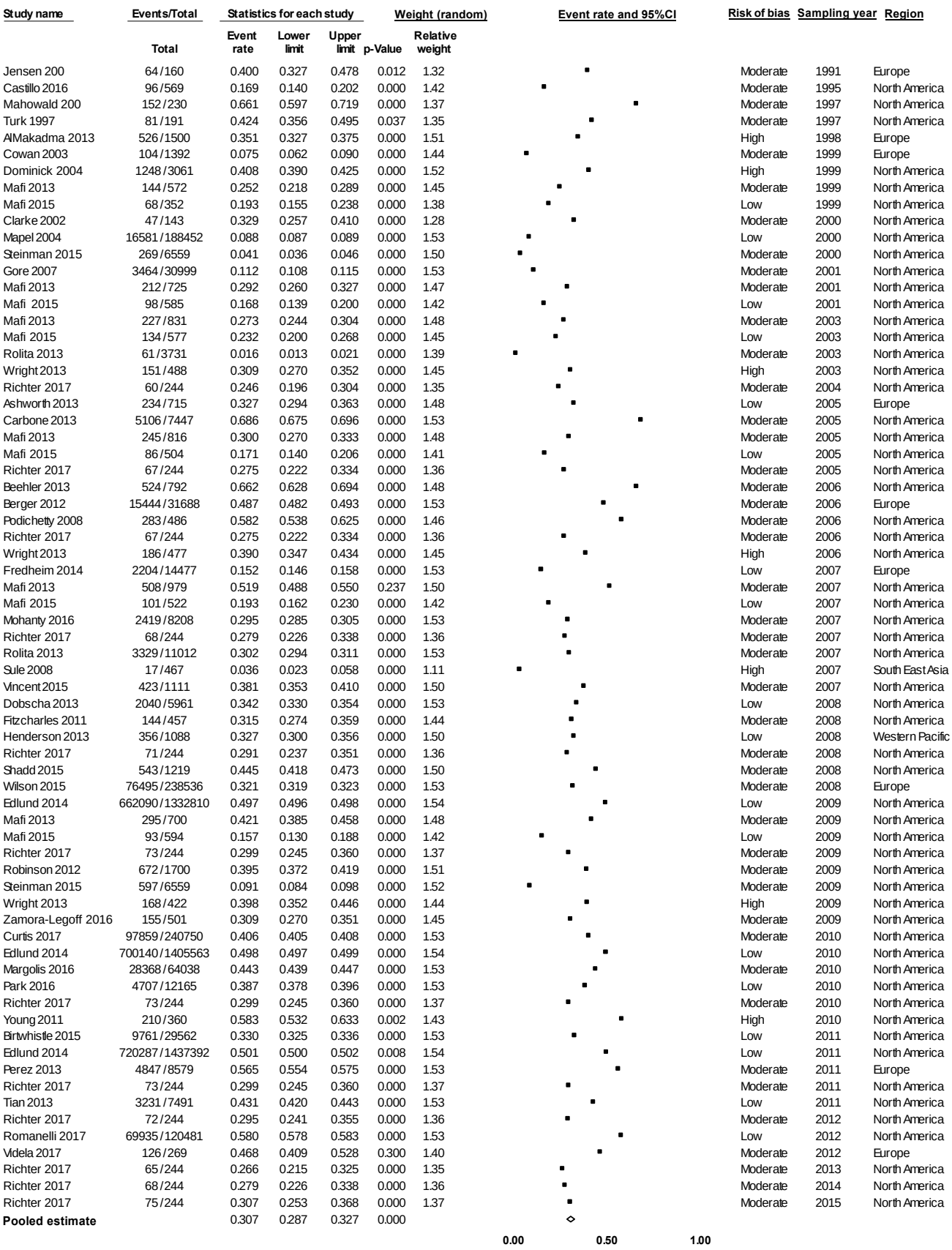

Figure 2: The proportion of patients with chronic non-cancer pain prescribed opioid analgesics.

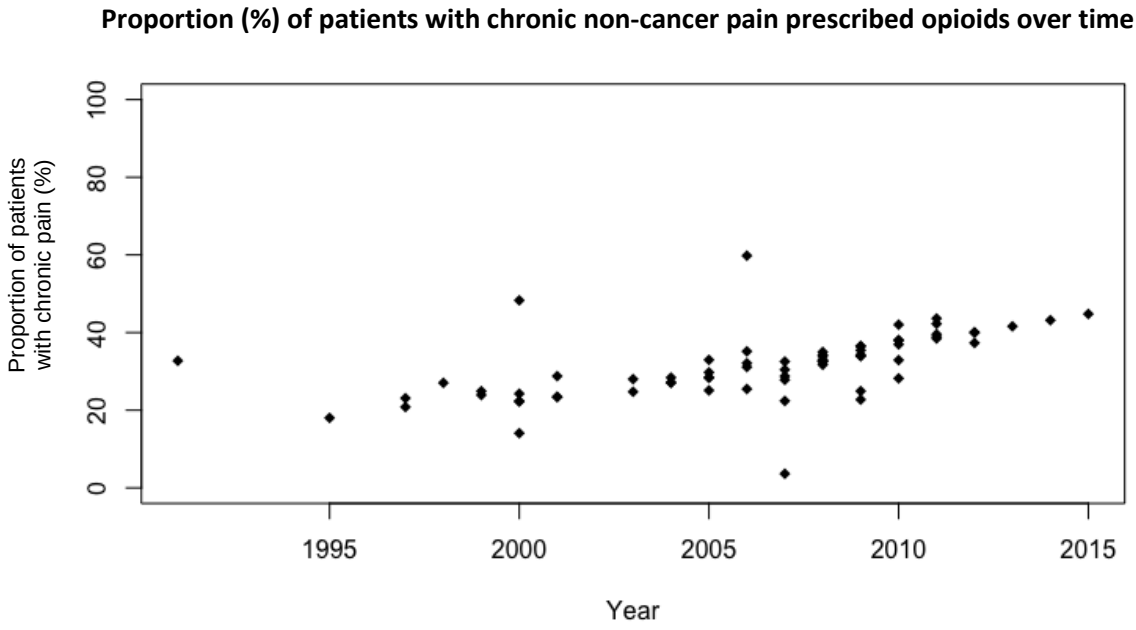

Figure 3: Adjusted estimates of opioid analgesics prescribed over time.

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