Role of Pharmacists in Optimising Opioid Therapy for Chronic Non-malignant Pain; a Systematic Review.

Abstract:

Background: Opioid optimisation is a global issue in Chronic Non-malignant Pain (CNMP) management.

Objective: This mixed-methods systematic review aims to assess the effectiveness of interventions delivered by pharmacists in outpatient clinical settings, community pharmacies and primary care services in optimising opioid therapy for people with CNMP and to explore stakeholders' opinions about role of pharmacists in optimising opioid therapy.

Methods: We conducted searches in PubMed, Cumulative Index to Nursing and Allied Health Literature, Psych Info, EMBASE, ISI Web of Science and Conference Proceedings and International Pharmaceutical Abstracts. All studies where pharmacists in outpatient clinical settings, community pharmacies and patient care services helped in optimisation of opioids in the treatment of CNMP as individuals or part of a team were included. We followed the 27-item Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the review was registered in PROSPERO. Studies not published in English language and participants with pain less than 3 months and cancer pain were excluded. All the included studies were descriptively synthesized.

Results: Fourteen studies were included in the final data synthesis of this review and the total number of participants in all studies was 1175. Interventions by pharmacists were successful in decreasing opioid dose in 4 studies and improved patient safety in 5 studies. Stakeholders considered that the role of pharmacists in optimisation of opioid therapy for people with CNMP can be promising and should be further developed.

Conclusion: This mixed-methods systematic review gives an overview of pharmacist intervention feasibility, stakeholders' opinions and possible benefits on opioid optimisation in people with CNMP in outpatient clinical settings, community pharmacies and primary care settings. However, further research is warranted, which can guide the development of new policies and guidelines to utilise the role of pharmacists to promote opioid safety in people using prescription opioids for CNMP management.

Keywords:

Chronic non-cancer pain, medication review, mixed-methods systematic review, prescription opioids, pain management, pharmacist

Introduction

Chronic non-malignant pain (CNMP) is one of the biggest challenges in healthcare. [1] In 2011, a World Health Organisation (WHO) report empirically reported that one-fifth of the global population have chronic pain. [2]

The use of prescription opioids in CNMP is common. [3-6] However, their long-term effectiveness for CNMP has not been beneficial. [7-12] A report by the Center for Disease Control (CDC) showed that opioid prescriptions quadrupled between 1990 and 2014 in the United States of America (USA) [13] [14] accounting for the death of 218,000 people.[15] In Canada over 20 million prescriptions for opioids were dispensed in 2016 [16] and between 2016 and 2018, 11,500 people died from an opioid related death. [17-19] There is also evidence of an increasing trend in prescribing the use of prescription opioids for chronic pain in many countries such as the UK, [20] France, [21] Italy, [22] Spain, [23] and Australia. [24] In developing countries, there is a lack of studies on opioid utilisation in CNMP, however two studies show that the prescribing of tramadol [25,26] has drastically increased for the treatment of CNMP in the last 2 decades. Potent opioid medicines are not easily available in the majority of developing countries due to weak opioid sale regulation, lack of pain management services and opioid misuse phobia. [27-30] Overdose with prescription opioids has been rising and can have fatal consequences. [31, 32] Inadequate knowledge of prescribing criteria for medicines as well as dispensing opioids without establishing individual patient needs, lack of, patient compliance, adherence to the therapeutic regimen and regular review for people with CNMP prescribed opioids have been mainly responsible for an increase in the prescription opioid overdose. [33, 34]

Medicines optimisation aims to ensure that patients get the most benefit from their medicines by making the process of use of medicine safe, effective and efficient. [35, 36]For the purpose of this review, the word optimising has been defined as “any pharmacist intervention in outpatient clinical settings, community pharmacies and primary care services that ensures people obtain

the best possible outcomes while using opioid medicines in the management of CNMP ". Every member of the health care team in a health care system has an integral role in optimising opioid use and reducing associated morbidity in people with CNMP using prescription opioids. With the improvement in pharmacy practice services, many studies have successfully evaluated patient centered roles of pharmacists in many health care settings and diseases such as hypertension, hyperlipidaemia, diabetes intensive care and their role in patient safety has been beneficial. [37-40] Pharmacist medication review can significantly reduce adverse drug events in many diseases. [41-43] The outpatient role of pharmacists has been beneficial in other diseases and conditions, it is therefore hypothesized that pharmacists in outpatient clinical settings, community pharmacies and primary care settings offering patient care services can improve and promote patient safety in people using prescription opioids for CNMP management. This review therefore focuses on evaluating the existing roles of pharmacists and effect of intervention(s) and exploring stakeholders' opinions about these roles and interventions. Exploring stakeholders' perceptions might help understanding the barriers and facilitators in optimising opioid use in people with CNMP in outpatient clinical settings, community pharmacies and primary care services.

Two similar systematic reviews on the role of the pharmacist in pain management have been reported. [44, 45] The evidence generated by the systematic review by Bennet et al [45] was inconclusive about the effect of pharmacist educational intervention in pain management even though the pharmacists were effective at reducing medicine related side effects in patients. In a meta-analysis Hadi et al [44] indicated that medication review by a pharmacist, as an intervention, reduced pain, and improved physical function. Although showing promising roles for pharmacists in reducing pain, Hadi et al [44] did not focus on the effect of pharmacist intervention on the use, dosage and frequency of prescription opioids and other analgesic medicines. Both reviews focused on pharmacist intervention with respect to pain management

but did not focus on opioid medicine optimisation. A further narrative review [46] discusses potential roles of community pharmacists in promoting opioid safe use but lacks information in context of optimisation in CNMP management. Thus, this mixed-methods systematic review aims to evaluate the effect of intervention(s) delivered by pharmacists in outpatient clinics, community pharmacy and primary care services and qualitatively explore the perceptions, feasibility, satisfaction, and possible barriers of pharmacists and people with CNMP to optimise opioid therapy in CNMP management.

Methods

We followed the 27-item Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [47] that evaluate health care interventions in conducting the present systematic review. The systematic review was prospectively registered with International Prospective Register of Systematic Reviews (PROSPERO)-2019 (Registration number: CRD42019154805). [48]

Eligibility criteria

Design

This study was a mixed-methods systematic review, so we included a range of study designs, including both quantitative and qualitative studies, and those using mixed methods. The review included a range of study designs, so no study specific filters were applied. The study aimed to assess all outpatient pharmaceutical care roles [16] of pharmacists in pain management of people using opioids, so all the studies between January 1990 and June 2020 were included in this systematic review.

Study selection

The study selection in this review followed a PICO framework, which is shown in Table 1.

Table 1

Framework for inclusion of studies in mixed-methods systematic review

PICO	Population, Intervention, Context, Outcomes
P: Population	People with pain originating from any origin except cancer pain and should be present for at least 3 months
I: Intervention	Any intervention by pharmacists, alone or in coordination with a health care team, which optimises opioid therapy in people with CNMP and improves patient medication experience in management of CNMP
C: Context	CNMP Pain originating from any origin except cancer pain and should be present for at least 3 months. Pharmacists May include either/or pharmacists in outpatient services, primary care services, secondary care services, community pharmacies, retail setup, clinical pharmacists, specialised pain clinics Settings All patient care settings such as outpatient clinical settings, community pharmacies and primary care services
O: Outcomes:	Outcome 1: Evaluation of pharmacist intervention that ensure people obtain the best possible outcomes while using opioid medicines in the management of CNMP Outcome 2: Perspectives and experiences of either people who received pharmacist intervention, pharmacists delivering the intervention or studies highlighting facilitators and barriers of intervention delivery by pharmacists to optimise opioid therapy in CNMP management

Exclusion criteria

All the studies where the people only had acute pain, chronic pain with duration less than 3 months, pain conditions treated without opioids, cost reduction related to pain medicines or healthcare utilisation, inpatients, palliative care patients or cancer diagnoses, participants with issues of opioid addiction and abuse, over the counter (OTC) opioids, and illicit opioid use

were excluded. Studies not published in English were excluded. Abstracts without a full-length article were excluded. Studies conducted with participants below age of 18 years were excluded. Editorials, commentary, reviews, clinical practice guidelines, policy documents, and professional society recommendations directing the role of pharmacists in optimising opioid therapy for people suffering from CNMP were excluded.

Information sources (Search engines)

The authors did a comprehensive database electronic search in PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL)**,** Psych Info**,** EMBASE**,** ISI Web of Science and Conference Proceedings and International Pharmaceutical Abstract (IPA). The authors also searched for similar reviews within the Cochrane Library, PROSPERO, and the Joanna Briggs Institute (JBI).

Search strategy

Databases were searched for publications using the search strategy (Appendix 1). The result was then subjected to language, adult age and year restrictions in all databases. Manual searches of selected bibliographies were also performed and the search similar citation feature was used to enhance the search bibliographies of retrieved articles for additional relevant articles. The bibliography of selected articles was also reviewed. The authors also did free word searches using Google Scholar and Science Watch to maximise the effort to include all published articles.

Data collection process

Data screening

The searches were performed in all databases by the author AI and reviewed independently by CA, RK, and LS. All the eligible studies were exported to Endnote X8 software (San Francisco, Clarivate Analytics). [49] Subgroups were maintained for different databases in the Endnote

software. All authors independently screened the titles and abstracts for inclusion in the full paper. Duplicates were removed using Endnote software. Full paper screening was done using a preliminary screening form (Appendix 2) by AI and was separately reviewed by all authors. Disagreements were resolved by discussion between all authors at all stages. The final inclusion of articles was based on mutual consensus. All included studies were given the format; "study number_ first author name_year of publication" as per PRISMA guidelines. The screening and selection processes is graphically represented via a PRISMA flow diagram (see Fig. 1).

Data extraction

AI independently extracted the data using two predesigned data extraction forms. The Cochrane Collaboration data extraction form [50] was used for studies including Randomised Controlled Trials (RCTs) (with and without control groups), Non-randomised controlled study (NRS) and observational cohort studies. The data extraction tool for qualitative studies for mixed-methods systematic review was based on National Institute for Health and Clinical Excellence (NICE) data extraction guidelines. [51]

Risk of bias and applicability

For quality assessment, all articles were subjected to risk of bias assessment using standardized tools and were discussed amongst all authors. For RCTs, we used the Risk of Bias (RoB) tool from The Cochrane Collaboration Handbook. [52] Other quantitative studies were observational cohort studies, so we used the Newcastle Ottawa cohort scale (NOS) [53] for cross-sectional cohort studies . The risk of bias criteria was considered good, fair and poor respectively. [54,55] For risk of bias assessment in the qualitative studies, we used the Critical Appraisal Skills Programme (CASP) quality assessment tool. [56] The risk of bias was considered high, moderate and low. [57] As CASP lacks contextual details and has a positivist approach, we further used

the Standards for Reporting Qualitative Research (SRQR) tool [58] to analyse more theoretically rich perspectives when doing the qualitative assessment. The risk of bias across studies was assessed using Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) approach. [59]

Synthesis of results

The data were synthesised by separately analysing qualitative and quantitative studies. The intervention was assumed to have a positive effect if there was a statistically significant decrease in any primary or secondary outcomes listed in this review. Because of a lack of clinical trial studies, meta-analysis could not be conducted and the data were analysed descriptively. For the qualitative studies, experiences and perspectives of people with CNMP, physicians and pharmacists, as well as challenges and facilitators in context of intervention delivered by a pharmacist were summarised from the findings or results section of all studies. The extracted data from all studies are presented in Table 2 and 3.

Results

Study selection

Seven hundred and thirty papers were retrieved through database searches plus additional source searching via search similar function. De-duplication via EndNote software resulted in 595 papers considered for preliminary screening. The titles and bibliography were screened in preliminary screening. Out of them, 300 were found to be eligible and were subjected to abstract screening. Out of 300, 47 papers were found to be eligible and were subjected to full paper secondary screening. From other sources, 3 papers were found eligible to be included. The final inclusion was 14 papers (12 quantitative study designs and 2 qualitative studies for data synthesis).

Out of the total 14 studies included in this review, one was an RCT, [60] one had quasi-experimental study design, [61] two were uncontrolled trials, [62, 63] 6 were prospective cohort study designs, [64-69] 2 were retrospective chart reviews [70, 71] and 2 were qualitative studies. [72, 73]

The search process and screening are presented in a flowchart via PRISMA diagram Fig. 1.

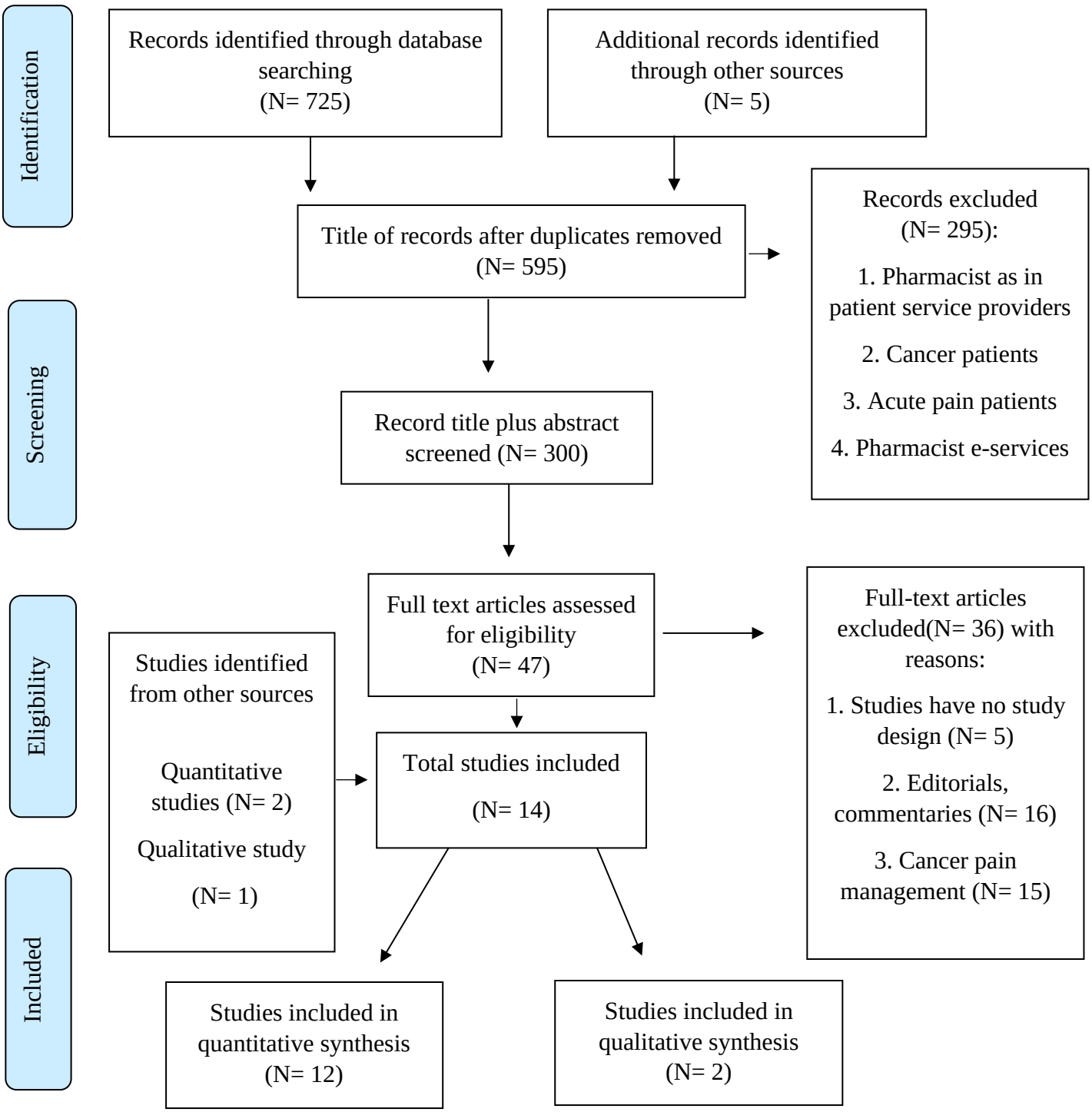

Fig. 1: PRISMA flow diagram [47]

Quantitative studies-data synthesis

Characteristic of studies and study participants

All of the study participants were receiving only opioid medicines except for 2 studies, [66, 70] where some people were receiving opioids as well as non-steroidal anti-inflammatory drugs (NSAIDs) and other pharmacological treatments for the management of chronic pain. One study [61] in this review did not mention whether the study participants with CNMP were using prescription opioids only or other analgesics as well. There were 1149 participants in total in all 12 quantitative studies. The majority of the participants in the studies were female [60, 61, 63, 65, 68-71] and mostly from white ethnic backgrounds. [60-63, 67, 71] Study characteristics such as location, invitation to participate in the studies, outcomes assessed in studies and comorbidities of participants (if any) to treat CNMP are shown in Table 2.

Table 2

Study description and characteristics

Study (location)	Design	Mean Age (range in years)	Setting	Participant recruitment	Total no. of study participants	Co-morbidities	Analgesics history (opioid plus if any)
1_Boren_ 2019 [71] (USA)	Retrospective chart review study	Age= 52.7 (40.2- 65.2)	People from Clinic outpatient clinic.	Physician referral from primary care clinic to service	Gender N= 383 (With pharmacist= 359) (Without pharmacist = 24) M=196 F=163	Anxiety N= 117 (32.6%) Depression N= 175 (48.7%) Insomnia N= 57 (15.9%)	None reported
2_Chelminski_2005 [62] (USA)	Uncontrolled trial	Age= 51 (27-76)	People attending an academic general medicine practice	Physician referral from primary care clinic	N= 85 M= 51 F= 34	Depression (51%)	None reported

3_Coffey_2019 [68] (USA)	Prospective cohort study	Age= 49.5 (none reported)	People attending unity Health Center clinic	Physician referral from primary care clinic to service	N= 39 M= 18 F= 21	None reported	None reported
4_ Cox_2018 [67] (USA)	Pilot study	Age= 57 (none reported)	People attending family medicine residency clinic	Self-selection from electronic medical records by pharmacists and recommendations provided	N= 45 M= 23 F= 22	Anxiety N= 27 (60%) Depression N= 25 (56%) Insomnia N= 20 (44%) Migraines N= 9 (20%) Bipolar N= 3 (7%) Other psychiatric condition N= 2 (4%)	Oxycodone (49%) hydrocodone (27%) Extended release morphine (20%) Tramadol (16%) Acetaminophen (64%) Oral NSAIDS (42%), Gabapentin/pregabalin (38%) TCA (31%) Topical NSAIDS (27%)

5_Hadi_2015 [61] (UK)	Mixed-methods Quasi-experimental study	Age= 46.5 (22-86)	Nurse-pharmacist managed pain clinic **(**secondary care clinic)	Physician referral from primary care clinic to service Screening eligible patients at the pain clinic by the nurse or pharmacist	N= 79 M= 26 F= 53 Pain (post) score available for N= 36	Unclear	None reported
6_ Tewell_2018 [64] (USA)	Prospective cohort study	None reported	Family medicine primary care clinic	Individual patient charts were reviewed by a pharmacist Eligible patients were contacted by telephone to meet a pharmacist for interview	N= 41 Gender not reported	None reported	None reported
7_Semerjian_2018 [70] (USA)	Retrospective chart review	Age= 52.2 (none reported)	Specialty pain clinic at an academic medical center	Physician referral from secondary pain clinic to clinical pharmacist	N= 67 M= 23 F= 44	Depression, anxiety, and insomnia	Medication Regimens of study participants including opioid and non-opioid analgesics

8_ Briggs_2008 [65] (UK)	Prospective cohort study	Age= 57 (27-86)	Secondary care clinic	A nurse and PCP referred patients to the NPLC	N= 65 Gender not reported	None reported	None reported
9_ Bruhn_2013 [60] (UK)	Exploratory RCT	Age= 65 (None reported)	6 primary care clinics	Screened against eligibility by computerised search and then reviewed by PCP Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff	N= 193 M= 73 F= 120	Excluded patients with mental problems	None reported

10_ McDermott_2005 [66] (UK)	Prospective cohort study	Two age groups: Age= 72 (29-64) Age= 68 (65-94)	Primary care clinic	Potential participants were sent: an information sheet describing the study; a form seeking signed consent to the three different parts of the study	N= 140 M= 53 F= 87	None reported	The most common prescription medicines used were paracetamol plus dextropropoxyphene, paracetamol plus dihydrocodeine, tramadol, paracetamol plus codeine, diclofenac, rofecoxib and topical NSAIDs

11_ Lagisetty_2020[63] (USA)	Pilot study	Age= 55.8 (None reported)	2 primary care clinics	All eligible candidates were mailed an introduction letter, an outline of the study and contact information Most eligible participants were recruited in person by the research team by identifying upcoming visits. Referral by PCPs were phoned to schedule an appointment	N= 47 M= 21 F= 26	90% of patients had moderate to severe disability	Nondrug pain therapies N= 7 (15%) Opiates N= 42 (89%) Gabapentinoids N= 22 (47%) TCA and/or SNRI N= 15 (32%) Adjuvant therapies N= 27 (57%) Buprenorphine N= 9 (19%) Other N= 5 (11%) Naloxone prescribed or recommended N= 7 (15%)

12_ Tilli _2020 [69] (Canada)	Prospective cohort study	Age control= 60 (None reported) Age Intervention = 57 (None reported)	Three primary care clinics (one was control)	All participants after EMR review and then screened manually by PI if fulfilled inclusion criteria	N= 35 (intervention) M= 11 F= 24 N= 20 (control) M= 7 F= 13	Psychiatric comorbidity Depression Anxiety Substance use disorder Post-traumatic stress disorder or history of trauma Bipolar disorder or schizophrenia	None reported

13_Hartung_2017 [72] (USA)	Exploratory study	Age Pharmacists = 39 (26-57) Age patients= 60.1 (30-77)	Urban and rural Pharmacists urban (47%) rural (26%) Patients urban (29%) rural (71%)	Purposive sampling via invitation using emails and flyers	Pharmacists N= 19 M= 8 F= 11 Patients N= 18 M= 6 F= 12	None reported	Patients using prescription opioids like oxycodone, hydrocodone, morphine
14_Tabeefar_2020 [73] (Canada)	Exploratory study	Age= 46 (27-63)	Urban	Purposive sampling via invitation using emails and flyers	N= 12 M= 4 F= 8	None reported	None reported

Non-Steroidal Anti-inflammatory Drugs=NSAIDS, Tricyclic Antidepressant =TCA and/or serotonin-norepinephrine reuptake inhibitor= SNRI, Electronic Medical Record = EMR, PI= Principal investigator, M= male, F= female

Synthesis of results

The major results for pharmacist interventions in outpatient clinical settings and primary care services in quantitative studies were changes in, dose of opioid medicines, effect on CNMP management, opioid medicine knowledge, Quality of Life (QOL), adherence to standard treatment guidelines, alteration in the number of prescription medicines, type of analgesic medicine and doses, number of visits for inadequate pain management or referral, patient and physician acceptance and satisfaction , and decreased frequency of medication related problems (MRPs). There was no evaluation of pharmacist interventions in community pharmacy settings for optimising opioid therapy in people with CNMP.

Effect of pharmacist intervention on opioid dose(s)

Five studies [63, 67-69, 71] showed that the overall opioid dose was decreased after pharmacist intervention. One study [69] also showed that with pharmacist intervention, there was a fourfold increase in the number of people with an active opioid taper, however, in the control clinic, there were no active opioid tapers. However, opioid dose increased in one study [62] where, 48% participants had their opioid dose increased over 3 months and the overall mean opioid equivalent increased (Table 3).

Effect of pharmacist intervention on chronic pain

Five studies [60-62, 65, 68] showed that pharmacist intervention was statistically significant in pain reduction. In 3 studies [63, 67 66] the pharmacist intervention was not significant in decreasing the pain scores (Table 3).

Effect on opioid medicine knowledge

One study [64] reported the effect of pharmacist intervention on increasing opioid knowledge and awareness, where after pharmacist education and counselling to detect opioid overdose, 83%

(N= 41) participants' bought naloxone. Another study [68] also shows improved patient opioid medicine knowledge after pharmacist intervention. Lagisetty et al [63] also showed that pharmacist intervention improved patients' knowledge about buprenorphine.

Effect on Quality of life

One study [60] used the Short Form (SF)-12 PCS/MSC (Physical Component Summary and Mental Component Summary) and no significant difference between intervention arms was observed after pharmacist intervention. Another study [61] measuring the QOL using SF-36, also found no statistically significant differences in the mean PCS or MCS scores but the difference within individual domains were found to be significant after pharmacist intervention (Table 3).

Effect on adherence to standard treatment guidelines

Two studies [67, 71] showed overall adherence to treatment guidelines for patient safety increased after pharmacist intervention. Annual urine screening was found to increase in both studies after pharmacist intervention as shown in Table 3. Adherence to prescription drug monitoring programs was also seen in Cox et al's study [67] where an increase was seen in performing detailed medication reviews and in 45 people, it increased from 12 people to 26 (P= .001).

Effect on prescribing medicines

Cox et al [67] showed that the pharmacist intervention was not significant in reducing mean number of opioid analgesics prescribed but the prescribing of non-opioid analgesics increased (P= .002). The pharmacist intervention also resulted in increased naloxone prescribing by Primary Care Physicians (PCPs) to improve patient safety.

Effect on patient primary care visits

Boren et al [71] showed that there was an increase in access to a physician due to the pharmacist's availability to review pain patients. The decrease in number of visits by pain patients to primary care was also seen in Lagisetty et al's study [63] where the number of people with CNMP visits decreased following the pharmacist intervention (Table 3).

Referral to secondary care

Cox et al [67] indicated that pharmacist intervention resulted in increased referrals from PCPS to pain specialists and physical therapists. Briggs et al [65] used the referral parameter in a different context as compared to Cox et al's study [67] where they showed, that overall few referrals were needed and indicated ability of pharmacist –nurse clinic to manage chronic pain patients and a reduced need of further review by specialised care physicians.

Acceptance of pharmacist recommendation

Six studies [60, 61, 63, 66, 68, 69] showed high acceptance of pharmacist management plan and recommendations and high implementation rate by physicians for opioid medicines.

Satisfaction of people with pharmacist intervention

Most of the people were satisfied with the pharmacist intervention in 5 studies [60, 63, 65, 68, 69] . In one study [68] majority of patients (70%, N= 39) remained overall satisfied with the pharmacist intervention except they were dissatisfied with the pain relief although their pain score had improved (P= < 0.0001).

Medication related problems

Semerjian et al [70] showed that more than one MRP was identified in the majority of participants visiting the pharmacists during the study duration. A total of 820 MRPs were identified by pharmacists and only 125 were referred to other primary care members showing that clinical

pharmacist was able to intervene and directly respond to the majority of MRPs arising in people using prescription opioids.

Table 3

Nature of intervention, primary and secondary outcomes, follow-up, risk of bias

Study	Type of Intervention	Person measuring/ reporting outcome	Intervention delivered by	Follow-up	Primary outcomes results	Secondary outcome results	Risk of bias
1_Boren_ 2019 [71]	Medication reviews	Pharmacist (part of intervention)	Multi-disciplinary team	0 to 24 months (1-20 visits)	After five visits with the pharmacist an average decrease of MED 270 mg/day was observed between initial and final visit	Annual urine toxicological screen increased from mean 54% to 84% Signed medication agreement increased from mean 27% to 67% Physician access was increased by 1197 additional visits	Fair quality [a]

2_Chelminski_2005 [62]	Medication reviews Modified or titrated a patient's pain medications Consultation with the primary care physician.	Research assistant (independent of intervention)	Multi- disciplinary team	0 and 3 months	Pain (BPI) scores improved on an average of 12 to 15% Baseline average pain (NRS-11) improved from 6.5 to 5.5 (P= 0.003) Mean daily opioid dose in MME increased from 72 mg per day to 91 mg per day 48 % of patients had their opioid dose increased over 3 months. People receiving opioid medicines increased from 93% (baseline)	Mean PDI score improved from 47 to 39.3 (P < 0.001) Average CESD score improved from 24.0 to 18.0 (P < 0.001) Proportion of depressed patients decreased from 79% to 54% (P= 0.003)	Poor quality [a]

					to 97% (follow-up)		
3_Coffey_2019 [68]	Educational video by student pharmacist Knowledge assessment Referral to secondary care 1 hour direct MTM session (3-14 days later) with pharmacist plus opioid misuse risk assessment Management plan discussed with patients and sent to doctors electronically	Unclear	Multi- disciplinary team	0 and 12 months	Average pain scores (NRS-11) decreased from 8.3 to 5.6 P= 0.0001 Average MED decreased from 19.7 to 11.8 mg/day P= 0.001 Overall total MEDD/ patient decreased from 20.5 to 18.1 mg/day P= 0.3	Physician acceptance: 88% (29 of 33) of recommendations for narcotic medications were implemented High patient satisfaction(N= 33) Improved patient knowledge= Correct responses to questions were given on an average of 76% to 94%	Poor quality [a]

4_ Cox_2018 [67]	Dose calculation Retrospective medication review	unclear	Physician plus pharmacist	0 and 4 months	Average pain (1-10 scale) scores increased from 5.3 to 5.5 (P= .783) Mean MME/day decreased by 14% (P= .001) Average MMEs/day: Based on prescription directions decreased from 151 to 125 mg/day Based on number of pills prescribed per month: 135 to 116 mg/day	Urine drug screening increased from mean of 15 people to 27 (P= .001) Adherence to PDMP increased from 12 people to 26 (P= .001). Referrals by PCPs to: a. Pain specialists increased from 17 to 21 (P= .046) b. Physical therapist from 33 to 34 (P= .317) Prescribing of opioid analgesics mean= 1.6 to 1.5 (P= .219) Prescribing of non-opioid analgesics mean=	Poor quality [a]

2.1 to 2.4 (P= .002)

Prescribing of naloxone increased= 6 to 22 (P= .009).

Total recommendations provided= 301 out of which 114 were implemented

Most common recommendations Provided:
a. Initiate/change non-opioid analgesic therapy= 100%
b. Opioid taper = 96%
c. Refer the patient to a pain specialist= 93%
d. Offer an outpatient naloxone prescription= 82%

PCP acceptance:
a. Offer an outpatient naloxone prescription= 54%
b. Complete a urine drug screen= 52%
c. Taper opioid therapy= 51%
d. Initiate/change non-opioid analgesic therapy= 49%

5_Hadi_2015 [61]	Medication review by pharmacist Patient education by nurse Recommendation to primary care physicians Referrals to secondary care	Pharmacist and nurse (part of the intervention)	Nurse and pharmacist	0 and 3 months	Reduction in mean BPI pain interference= 7.1 to 6.1 (P= 0.02) BPI pain intensity: a. Worst pain= 8 to 7.5 (P= 0.02) b. Least pain= 5 to 4 (P= 0.12) c. Average pain= 7 to 6 (P = 0.02) CPG: a. Median pain intensity score= 76.66 to 73.33 (P= 0.02) b. Median disability score= 70 to 73.33 (P= 0.89) No improvement in CPG score was observed in	No statistically significant differences were found in the PCS overall mean scores= 28.8 to 30.8 (P= 0.15) or the MCS overall mean scores of 36.3 to 41.2 (P= 0.08) In individual domains scores, statistically significant improvements were found in physical role (P= 0.01), bodily pain (P= 0.01) and social functioning (SF) (P= 0.03)	Poor quality [a]

					majority of the patients= 21 (61.7%)		
6_ Tewell_2018 [64]	Medication review by pharmacist Patient education To give Naloxone prescription	Unclear	Pharmacist	Follow up unclear.	Pharmacist educated all 41 participants and 83% procured naloxone (69% of all candidates who received a prescription for the medication)	NA	Poor quality [a]

7_Semerjian_2018 [70]	Medication review Identification of Medication drug related problems Referral to secondary care Drug safety testing Patient counselling	Pharmacist (part of the intervention)	Pharmacist	No follow-up-chart review	The pharmacist was able to discontinue opioid therapy completely in 2 long-term opioid users Intervention: Dose adjustment= 84% Medication counselling= 47% of the time Non-pharmacologic counselling= 13% new medication for countering side effect of ADR= 70%	At least 1 MRP was identified in 98.7% of the 380 visits included in this study. In 27.1% of visits, only one MRP was identified One MRP= 71.6% 2-3 MRPs= 60.5% More than 3 MRPs= 11.1% The mean number of MRPs per visit was 2 Categories of MRPS: a. Medication refills needed= 43% b. Medication appropriateness/effectiveness= 18% c. Miscellaneous= 17% d. Safety= 16%	Poor quality [a]

8_ Briggs_2008 [65]	Pharmacist medication review Nurse role unclear	Unclear	Nurse plus pharmacist	0 and 6 months	Average pain scores (NRS-11) improved from 8 to 6.3 (P= 0.0001)	e. Non-adherence/patient variables= 6% 92% of patients were either satisfied or very satisfied with their overall care Referrals by pharmacists to specialised care units= 13/120 patients	Poor quality [a]

9_ Bruhn_2013 [60]	Prescribing arm: Pharmacist as independent prescriber and medication review Review arm: Patient medication review only and recommendation communicated to PCP Control arm- no pharmacist review only PCP	Research team by follow-up questionnaires	Physician plus pharmacist	0, 3, and 6 months	Within-arm improvement in pain (CPG) in the prescribing (P= 0.003) and review arm (P= 0.001), but not in the control arm	SF-12 PCS/MSC : PCS domain showed a statistically significant improvement in control arm (P= 0.02) and MCS domain showed statistically significant deterioration in the control arm (P= 0.002) however no significant effect was observed in the scores in both the trial arms The non-categorised HADS scores showed a statistically significant improvement within the prescribing arm for Depression	Poor quality b

(P= 0.022) and
Anxiety
(P= 0.007) only

Patient who were
satisfied: 39/46
(85%)

10_ McDermott_2005 [66]	Two methods: a. Pharmacist medication review (medical charts) and questionnaires, recommendations made to primary care providers b. Pharmacist medication review via medical charts and interview with the patients and recommendations made to PCPs	Unclear	Physician plus pharmacist	6 months	As compared to baseline, 18 people progressed to higher CPG, 29 maintained the same CPG, and 20 progressed to a lower CPG Incomplete responses to the CPG questionnaire= 14 In 81 recommendations the change in mean score for current general health was -0.06 and for current psychological health +0.04	a. Review plus questionnaires: 192 recommendations (N= 113, 85.6%) of all patients reviewed, out of which 107 (55.7%) were related directly to analgesic use Physician acceptance: Recommendations had fully been carried out in 77.0% of patients (87/113), partially completed in 8.8% (10/113), and not implemented at all in 14.2% (16/113) b. Review plus interview: 11 recommendations were made, for 9/23 individuals	Good quality [a]

Physician acceptance: Recommendations had fully been carried out in 9/11 people

11_ Lagisetty_2020 [74]	60 minute meeting where pharmacist reviewed pain history, medication history, response to prior medicine and risk factors pharmacist discussed recommendation with the patient and if agreed by the patient the pharmacist then contacted the patient's PCP Pharmacist provided additional support to PCPs with patient follow- up, education, and dose	Unclear	Physician plus pharmacist	4-month follow-up	No significant improvement in reducing pain (PEG) 6.2 to 6.1 (P= 0.84) Mean opioid dose reduced from 36 to 29.1 mg/day (P= 0.23) Before intervention, the OME mean was 36.0. After intervention participants had an average opioid dose reduction of 7 OME (19%) without worsening pain (P= 0.23)	Improved patient knowledge about buprenorphine: a. Heard of buprenorphine,= 22 to 30 (P= 0.021) b. Believe buprenorphine is used for detox and/or OUD treatment= 17 to 13 (P= 0.013) c. Believe buprenorphine is used to treat pain= 14 to 20 (P= 0.06) Pharmacist recommendation: a. Add or change non-opioid pain medication= 30 (64%) b. Switch to buprenorphine= 20 (43%) c. Add non-pharmacological	Poor quality [a]

measures= 8 (17%)
d. Switch to other opioid formulation= 6 (13%)
e. Pharmacist agreement with or support for current plan= 4(8%)
f. Opioid taper= 3 (6%)
g. Refer to specialist for pain, mental health disorders, or substance use disorder= 2 (4%)

Switch to buprenorphine at follow-up was 2/20

Physicians acceptance:

a. PCP acknowledged recommendations = 35/46 (76%)

b. PCP accepted/followed at least 1 part of recommendations = 34/46 (74%)

Decreased mean clinic visits= 10.4 to 8.9 (P= 0.06)

Both stakeholders generally satisfied with intervention

12_ Tilli _2020 [69]	Patient identification through medical record queries Developing care plans Discussing recommendations with physicians Discussing implementing recommendations	Pharmacists	Physician plus pharmacist	6 months	Change in pain unremarkable Intervention clinic= mean opioid MME decreased by 11% , from 50.5 to 44.7 mg/day Control clinic= mean opioid MME increased by 15% from 62.3 to 71.4 mg/day	Physician acceptance 24/32 (75%) Patient acceptance rate 13/24(54%) Opioid taper increased from 14 to 66% in intervention clinic (increased 4 times) Control clinic, the active opioid tapers remained zero	Good quality [a]

13_Hartung_2017 [72]	Two focus groups methods used. Face-to-face and online Crystallisation-immersion approach	Unclear	Not applicable	Not applicable	Community pharmacist role in opioid medication safety was perceived essential by stakeholders Both the stakeholders were unclear about the role and extent of pharmacist services in community pharmacy setup in opioid optimisation	Challenges and barriers : a. Faced by pharmacists included difficult communicating with PCPs, attitude of people who were prescribed high doses of opioid medicines, lack of access to patient records b. Faced by people included pharmacists overstepping their professional roles, time consuming, lack of awareness of pharmacist roles, uncomfortable	Low quality [c]

14_ Tabeefar_2020 [73]	Interviews conducted via 2 methods. Face-to-face and telephone Thematic analysis approach influenced by grounded theory	Not applicable	Not applicable	Development of expanded role of pharmacists in opioid safety was perceived to be beneficial by pharmacists.	Barriers included lack of training and confidence, high volume of workload, gaps in communications with PCPs, inadequate monitoring, lack of patient medical information and unrealistic patient expectations about recovery from pain	Moderate quality [c]

a= NOS scale criteria, b RoB tool of the Cochrane Collaboration Handbook, c= CASP criteria, Morphine equivalent dose = MED, Brief Pain Inventory= BPI, Medication therapy management= MTM, Morphine equivalent daily dose= MEDD, Morphine milligram equivalent = MME, Quality of Life = QOL, Hospital Anxiety and Depression Scale= HADS A and D, Medication related problems= MRPs, Chronic pain grade= CPG, primary care physicians= PCPs, milligrams diazepam equivalent= MDE, Numeric Rating Scale-11= NRS-11, Patient Satisfaction Questionnaire Short Form= PSQ-18**,** Pain, Enjoyment, General Activity= PEG, Chronic Pain Grade= CPG, Physical and Mental Health Composite= PCS/MCS, Randomised Controlled trial= RCT, Nurse-pharmacist led-clinic= NPLC, Quality of Life Short form= QOL SF, Prescription drug monitoring program= PDMP, Pain Disability Index= PDI, Morphine equivalent dose= MED, Oral Morphine Equivalents= OME, Pain, Enjoyment, General Activity= PEG, NA= Not applicable

Qualitative data synthesis

Two qualitative studies were included in this systematic review, Hartung et al [72] studied 18 people with CNMP and 19 community pharmacists, whereas Tabeefar et al [73] studied 9 community pharmacists (Table 2)

Hartung et al [72] show that both the stakeholders perceived the role of pharmacists in opioid medication safety was integral. People widely accepted and were satisfied with the pharmacist role in delivering opioid medicine safety education and advice, which is consistent with the quantitative results of this systematic review. [60, 65, 69] However, the stakeholders perceived there is a lack of clarity about the role and extent to which a pharmacist can intervene to optimise prescription opioid use. People with CNMP considered that there might be ambiguity in the role of community pharmacists because they were concerned that pharmacists sometimes overstep their job responsibilities by meddling with prescribers' clinical judgment in altering the dose or refusing opioid prescription medicines. People also considered that pharmacists discussing their medications with the PCPs is time consuming and felt uncomfortable and scared when they had to wait for the opioid medicines to be dispensed or refused. People also considered it unfair and unsatisfactory, that the pharmacists and PCPs would decide on a therapeutic regimen remotely, without involving them, which resulted in confusion and mistrust in pharmacists.

Community pharmacists generally found it difficult dealing with people who were prescribed high opioid doses or were refilling their prescription before due time. Rejecting the prescription or communicating and discussing their concern with the PCPs was, in general, a difficult process for pharmacists. Pharmacists also mentioned lack of access to patient records as a major barrier to optimise patients' opioid therapy according to peoples' individual needs in the community pharmacy setting. The authors provided 3 recommendations to utilise pharmacists

to improve medication safety in people using opioids. Pharmacist access to patient medication records should be improved, new services in the community pharmacy setting should be introduced which utilises pharmacists in opioid medication safety, and education of pharmacists and prescribers on safe and effective opioid prescribing and dispensing in management of CNMP should be improved.

Tabeefar et al [73] also explored in depth perceptions of pharmacists about the role of community pharmacists in opioid safety in CNMP management. Similar to Hartung et al, [72] the role of pharmacists was perceived to be beneficial by the participants, by providing patient education and monitoring the appropriate use of opioids for medicine optimisation and CNMP management. However, pharmacists anticipated barriers in implementing the opioid safety roles, which included lack of training and confidence in opioid medicine safety. According to participants opinions, other barriers that hinder the role of community pharmacists in opioid safety is high workload, gaps in communications with PCPs, inadequate monitoring, lack of patient medical information, unrealistic patient expectations, inadequate access to alternative treatments for opioids and the lack of policies in utilizing all members of health care team.

Pharmacists in Tabeefar et al's study [73] suggested developing skills to perform opioid optimisation roles, by getting specialized training and education in opioid safety and CNMP management, which is consistent with Hartung et al. [72] Additionally, educating people about their pain and defining the treatment outcomes as improved physical functions might also help in possible management of pain and avoiding diversion and opioid overdose. The participants in the study also suggested that documenting and monitoring of opioid prescriptions should be remunerated as pharmacy services. The stakeholders expressed that clear policies and guidelines should be developed which can facilitate and motivate the pharmacists to practice their expanded roles in opioid safety and pain management. Neither study used theory to influence the study design or analysis. Both Hartung et al. [72] and Tabeefar et al's study [73]

explored the perception of stakeholders within existing community pharmacy services delivered as part of routine service provision.

Three quantitative studies [60, 61, 63] included in this systematic review also explored stakeholders' opinion about the pharmacist intervention using qualitative methods and the extracted data is included in this section of this review. Lagisetty et al [63] explored the PCPs opinion about the intervention delivered by pharmacists via qualitative interviews. The PCPs expressed that the intervention delivered by the pharmacists was effective in primary care settings and easy to comprehend by both PCPs and people with CNMP. However, PCPs provided suggestions to improve the intervention, by increasing communication with patients and increased use of protocols and algorithms to simplify the intervention. The PCPs were also concerned that although the intervention by pharmacists was beneficial, however there was shortage of specialised pharmacists in existing primary care service models.

Hadi et al [61] and Bruhn et al [60] explored perceptions, experience and satisfaction of people with CNMP with the pharmacist intervention. The participants in both studies were mostly satisfied with the pharmacist intervention because of ample consultation time, specialised knowledge regarding opioid medicines and individual need based assessments done by the pharmacists. Bruhn et al [60] also assessed the stakeholders' satisfaction via interviews, and PCPs and pharmacists were in general satisfied with the intervention outcomes. However, some PCPs expressed that the interventions were of minor nature and shared some concerns about the cost effectiveness of including pharmacists in primary care.

Perception of stakeholders [60, 61, 72-74] shows that pharmacists can be beneficial in optimizing opioid use in CNMP management in outpatient care settings, primary care or community pharmacies, which resonates with the findings from the quantitative studies in this review, however clear guidelines and trainings should be developed which can facilitate pharmacists

in performing these roles.

Risk of bias

Of the 14 studies included in this review, 2 studies were assessed to be good quality, [66, 69] 2 studies were graded as fair, [71, 73] whilst the remainder were categorised as poor [60-65, 67, 68, 70, 72] (Table 3).

In most of the studies in this review, pharmacists assessed outcomes and were involved in the direct and indirect selection of participants. The assessment of outcomes was undertaken by the pharmacist as part of the intervention in 4 studies [61, 68, 70, 71] while in 3 other studies [67 60, 62] the outcome assessment was done by an independent research assistant. In the studies where the pharmacists assessed the outcomes, a risk of confirmation bias was introduced hence; the actual effect of intervention might have been influenced. In the studies,[69 63-66, 69] information about who did the outcome assessments was missing and was responsible for bias in those studies. There was no information on allocation concealment in any of the studies neither from the team delivering the intervention nor the participants, however Bruhn et al [60] and McDermott et al [66] described that participants were divided into different arms randomly; but the method of allocation remains unclear.

Tabeefar et al [73] failed to provide any demographic information about participants and the criteria used to purposely sample among willing participants, which introduces bias. Overall, Tabeefar et al's study [73] was considered to have moderate credibility according to CASP criteria and indicates moderate quality in the SRQR assessment tool for reporting qualitative work because the authors' made efforts to neutralize their own influences and potential bias by including a non-technical neutral person, who had no background information about the study area. In Hartung et al's study [72] the authors failed to discuss their interpretation and presentation of their study findings. The study also lacks in author reflections and do not address any

techniques to enhance the trustworthiness of data e.g. no audit trail was provided and no triangulation of data with existing literature. Overall, the study lacks credibility using CASP criteria and indicates poor quality in the SRQR assessment tool for reporting qualitative work.

Discussion

This mixed-methods systematic review integrates evidence from 14 studies where the main intervention delivered by pharmacists was medication review in people with CNMP using opioid medicines for pain management. The impact of pharmacist intervention in reducing the dose of opioid medicines was considered in 5 studies, out of which, the dose of opioids increased only in one study. [62] The increase in dose could be attributed to the fact that pharmacists were managing other comorbidities like depression, anxiety, and sleep disturbances in addition to pain, where dose of prescribed opioids can significantly increase. [75] The pharmacist intervention effect on pain was assessed in 8 studies and pain improved in all except 3 studies. [66, 67, 69] In all of the studies, the pain outcome results were self-reported by the participants however, this is considered normal in pain studies as pain is a subjective experience. [76, 77]

This review shows that patient safety can be improved by identifying MRPs while using opioids for CNMP management by a pharmacist review. [64,72] This is also in accordance with the findings of other studies, where the pharmacist role has been documented in improving medication safety in patients by identifying MRPs in other diseases. [78-80] Study participants in the studies in this review were overall satisfied with the education, counselling and services provided to them by the pharmacist for optimising opioid medicines in CNMP management, which is consistent with the findings of other studies in other diseases. [79-85]

This systematic review provides evidence that the recommendations by pharmacists after medication review of people using prescription opioids were generally well accepted by the PCPs, which is also supported by the findings of other studies. Moreno et al's [85] study show

that PCPs highlighted that the contribution of clinical pharmacists are necessary, and their roles should be expanded in medication management in primary care. Karleen et al [86] show the PCPs perception about role of clinical pharmacists in opioid management, patient education, and promoting adherence to standard guidelines, which is similar to findings from this review. Study findings in this review show that pharmacists reviewing people with pain helped to reduce the number of their visits to PCPs. The pharmacists also successfully managed people with CNMP and the need for referral to specialised care or PCPs was less. [78, 87]

This review highlights certain barriers perceived by stakeholders to hinder the role of pharmacists in community pharmacies in optimisation of opioids in CNMP management. These include gaps in communications with PCPs, inadequate monitoring due to lack of access to patient medical information, the lack of a comprehensive approach by utilizing skillset of all members of healthcare team and service remuneration which have been found consistent with the results of a survey conducted in a UK study for developing community pharmacy services. [88] Other perceived barriers highlighted in this systematic review in different settings show that the pharmacists feel less confident due to lack of specialised education and training in CNMP management especially with opioids. [89,90] Additionally, the PCPs in primary care settings perceive that the current nature of interventions although is feasible and contributes towards better patient outcomes, yet pharmacists should use specified protocols and algorithms to simplify the intervention. PCPs also expressed their general concerns over the cost effectiveness of these interventions and sustainability due to lack of specialised pharmacists currently in primary care settings.

This review shows the perception of people with CNMP to be involved in deciding therapeutic regimes in order to facilitate better patient outcomes. This is similar to other studies where participants wanted to be part of the decision making for a treatment plan so it is important that

when discussing new models of care in opioid safety in CNMP management, people should be aware and involved to improve individual health outcomes and satisfaction. [85, 91-93]

The participants in the studies included in this review considered that providing opioid optimisation services in community pharmacies might increase workload, which is consistent with the findings of other studies in literature. [94, 95] However, the impact of pharmacist workload on patient health outcomes and optimisation of opioids have not yet been explored. Despite the perceived barriers, the studies in this review, demonstrate the possibilities, stakeholders' opinions, satisfaction, and the impact of a pharmacist review in improving patient outcomes and optimising opioid therapy in people with CNMP, which is consistent with the findings from other studies. [80-82, 96, 97]

It is interesting to note that there are many articles, editorials and commentaries, [46, 89, 93, 98, 99] that suggest and recommend that pharmacists can have a promising role in reducing opioid related harm when they encounter people with CNMP in outpatient settings and their role should be further developed. However, this review identified a lack of research studies especially in community pharmacies. Two pilot trials are currently in progress, [100, 101] that are evaluating the role of community pharmacists in opioid safety.

Overall, there is a lack of research studies and trials in the developed countries and no studies in developing countries evaluating outcomes, impact and stakeholder opinions about the role of pharmacists in opioid optimisation in people with CNMP in outpatient, primary care and community pharmacy settings. The lack of studies from developing nations might be due to lack of potent opioids and patient-centered pharmacist roles in developing countries. [27-30] Therefore, further research is needed to explore pharmacist roles in developing countries, which may help with the availability, controlled sale regulations and optimisation of opioid therapy in people with CNMP.

The results of studies included in this systematic review show beneficial roles of pharmacists in respective settings in optimisation of opioids in CNMP management; however, it should be noted, that there is high risk of bias in majority of the studies and further research should be conducted.

Strengths and limitations

The main strength of this mixed-methods systematic review comes from combining qualitative and quantitative mixed study paradigms, which helped search available literature for the objectives of this review in dimensions and depth that would not have been possible to achieve by including studies of single research design. This review provides an extensive up to date overview of pharmaceutical care services provided by pharmacists in outpatient, primary care and community pharmacy settings and the perception of stakeholders about the role of pharmacists in optimising opioids in the management of CNMP.

One of the limitations of this systematic review was the inclusion of studies published only in the English language and as full text publications however, the extent of the effect on the findings of systematic reviews is debatable. [102] This review focused only on people with CNMP pain and hence the results might not apply to pharmacist intervention in cancer pain management. The majority of studies included in this review showed promising roles of clinics and services involving pharmacists as team members, but the identification of the contribution of a pharmacist only was not possible because of team intervention. In many studies, due to the small sample size, the statistically significant intervention effect on study outcomes might be a false positive result. [103] The studies included in this review are all from the USA, UK and Canada, so the findings of this review may not be representative of other countries.

Conclusions

This mixed-methods systematic review provides an overview of outcome assessments, acceptance, satisfaction and key stakeholders' opinions about current role of pharmacists in outpatient, primary care and community pharmacy settings in opioid optimisation in CNMP management. The pharmacist provided patient education, counselling and medication reviews to help optimise opioid therapy and improve adherence to existing guidelines in the management of CNMP but further evidence from research studies is warranted. [46, 82, 96, 104, 105] This mixed-methods systematic review further suggests a need for more studies focusing on, utilising pharmacists in opioid optimisation services, evaluating the impact of pharmacists, exploring the perceptions of key stakeholders and the cost evaluation of these services in outpatient, primary care and community pharmacy settings. This systematic review also provides an overview of the feasibility, extent and barriers of conventional pharmacist roles and its possible impact on opioid optimisation in CNMP management in outpatient, primary care and community pharmacy settings, which can help revise and develop new policies and guidelines utilising the role of pharmacists in optimising prescription opioid use. Opioid optimisation is a global issue, and the findings of this review will be of interest to policy makers and practitioners across the world, especially where new pharmacy practice services are in development phase and when looking to expand the roles of pharmacists in optimisation of opioid therapy in CNMP management.

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Conflict of interest

The authors have no conflict of interest.

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References

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018;392:1789-1858.
2. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *The Lancet* 2011;377:2226-2235.
3. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. *Canadian Family Physician* 2011;57:1257-1266.
4. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians'(ASIPP) Guidelines. *Pain physician* 2008;11:S5-S62.
5. Lipman AG. Managing pain in the era of substance abuse. *Journal of pain & palliative care pharmacotherapy* 2015;29:100-101.
6. Mathieson S, Wertheimer G, Maher CG, et al. What proportion of patients with chronic noncancer pain are prescribed an opioid medicine? Systematic review and meta-regression of observational studies. *Journal of Internal Medicine* 2020;287:458-474.
7. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Experimental and Clinical Psychopharmacology* 2008;16:405.
8. The Pharmaceutical Journal. A crisis hidden in plain sight? Prescription opioid misuse in the UK.November 2017. https://www.pharmaceutical-journal.com/news-and-analysis/a-crisis-hidden-in-plain-sight-prescription-opioid-misuse-in-the-uk/20203928.article. Accessed
9. Reinecke H, Weber C, Lange K, Simon M, Stein C, Sorgatz H. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. *British Journal of Pharmacology* 2015;172:324-333.
10. Laxmaiah Manchikanti M, Hary Ailinani M, Dhanalakshmi Koyyalagunta M, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain physician* 2011;14:91-121.
11. Bailey RW, Vowles KE. Chronic noncancer pain and opioids: Risks, benefits, and the public health debate. *Professional Psychology: Research and Practice* 2015;46:340.
12. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *New England Journal of Medicine* 2003;349:1943-1953.
13. Center For Disease Control. Prescription opioid data.2018. https://www.cdc.gov/drugoverdose/data/prescribing.html. Accessed 11/06/2019
14. Ahmad FB RL, Sutton P. National Center for Health Statistics. Provisional drug overdose death counts.2020. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed 10/09/2020
15. Centers for Disease Control and Prevention USDoHaHS. Centers for Disease Control and Prevention. 2019 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States Surveillance Special Report. .Published November 1, 2019. . https://www.

cdc.gov/drugoverdose/pdf/ pubs/2019-cdc-drug-surveillancereport.pdf. . Accessed 10/09/2020

16. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *American journal of hospital pharmacy* 1990;47:533-543.
17. Orpana HM, Lang JJ, Baxi M, et al. Canadian trends in opioid-related mortality and disability from opioid use disorder from 1990 to 2014 through the lens of the Global Burden of Disease Study. *Health Promotion and Chronic Disease Prevention in Canada : Research, Policy and Practice* 2018;38:234-243.
18. Belzak L, Halverson J. The opioid crisis in Canada: a national perspective. *Health Promotion and Chronic Disease Prevention in Canada : Research, Policy and Practice* 2018;38:224-233.
19. Government of Canada. National Report: Apparent Opioid-related Deaths in Canada.2019. https://health-infobase.canada.ca/datalab/national-surveillance-opioid-mo. Accessed 21/06/2019
20. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. *British journal of clinical pharmacology* 2013;76:823-824.
21. Hider-Mlynarz K, Cavalié P, Maison P. Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe. *British Journal of Clinical Pharmacology* 2018;84:1324-1334.
22. Caraceni A, Brunelli C, Rocco P, Minghetti P. Trends in opioid analgesics sales to community pharmacies and hospitals in Italy (2000-2010). *Minerva Anestesiologica* 2013;79:906-914.
23. Del Pozo JG, Carvajal A, Viloria JM, Velasco A, Del Pozo VG. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *European Journal of Clinical Pharmacology* 2008;64:411-415.
24. Berecki-Gisolf J, Hassani-Mahmooei B, Clapperton A, McClure R. Prescription opioid dispensing and prescription opioid poisoning: population data from Victoria, Australia 2006 to 2013. *Australian and New Zealand Journal of Public Health* 2017;41:85-91.
25. Vijayan R, Afshan G, Bashir K, et al. Tramadol: a valuable treatment for pain in Southeast Asian countries. *J Pain Res* 2018;11:2567-2575.
26. Yorke E, Oyebola FO, Otene SA, Klein A. Tramadol: a valuable treatment for pain in Ghana and Nigeria. *Current medical research and opinion* 2019;35:777-784.
27. Johnson MI, Elzahaf RA, Tashani OA. The prevalence of chronic pain in developing countries. *Pain Management* 2013;3:83-86.
28. Krakauer EL, Cham NTP, Husain SA, et al. Toward safe accessibility of opioid pain medicines in Vietnam and other developing countries: a balanced policy method. *Journal of Pain and Symptom Management* 2015;49:916-922.
29. Bond M. Availability and accessibility of opioids in developing countries, with special reference to Eastern Europe. *Eur Oncology* 2009;5:17-18.
30. Bond M. Pain education issues in developing countries and responses to them by the International Association for the Study of Pain. *Pain Res Manag* 2011;16:404-406.
31. Häuser W, Tölle T. Problematic use of prescribed opioids for chronic noncancer pain—no scarcity of data outside the United States. *Pain* 2017;158:2277.
32. Lipman A. Managing pain in the era of substance abuse2015.
33. Weiss RD, Potter JS, Griffin ML, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *Journal of substance abuse treatment* 2014;47:140-145.
34. Vissers KCP, Besse K, Hans G, Devulder J, Morlion B. Opioid Rotation in the Management of Chronic Pain: Where Is the Evidence? *Pain Practice* 2010;10:85-93.
35. Faria R, Barbieri M, Light K, Elliott RA, Sculpher M. The economics of medicines optimization: policy developments, remaining challenges and research priorities. *Br Med Bull* 2014;111:45-61.

36. De Simoni A, Mullis R, Clyne W, Blenkinsopp A. Medicines optimisation in primary care: can community pharmacies deliver? *Br J Gen Pract* 2012;62:398-399.

37. Casteel C, Blalock SJ, Ferreri S, Roth MT, Demby KB. Implementation of a community pharmacy–based falls prevention program. *American Journal of Geriatric Pharmacotherapy* 2011;9:310-319. e312.

38. Bucci C, Jackevicius C, McFarlane K, Liu P. Pharmacist's contribution in a heart function clinic: patient perception and medication appropriateness. *Canadian journal of cardiology* 2003;19:391-396.

39. Sczupak CA, Conrad WF. Relationship between patient-oriented pharmaceutical services and therapeutic outcomes of ambulatory patients with diabetes mellitus. *American Journal of Health-System Pharmacy* 1977;34:1238-1242.

40. Tsuyuki RT, Johnson JA, Teo KK, et al. A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). *Archives of internal medicine* 2002;162:1149-1155.

41. JohnsonJA B. Drug-related morbidity and mortality A cost-ofillness model. *Arch Intern Med* 1995;155:1949-1956.

42. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman Med J* 2011;26:155-159.

43. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Archives of internal medicine* 2009;169:894-900.

44. Hadi MA, Alldred DP, Briggs M, Munyombwe T, Closs SJ. Effectiveness of pharmacist-led medication review in chronic pain management: systematic review and meta-analysis. *The Clinical journal of pain* 2014;30:1006-1014.

45. Bennett MI, Bagnall AM, Raine G, et al. Educational interventions by pharmacists to patients with chronic pain: systematic review and meta-analysis. *The Clinical journal of pain* 2011;27:623-630.

46. Bach P, Hartung D. Leveraging the role of community pharmacists in the prevention, surveillance, and treatment of opioid use disorders. *Addiction Science and Clinical Practice* 2019;14:30.

47. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of Internal Medicine* 2009;151:W-65-W-94.

48. PROSPERO. Registration for systematic review.2019. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019154805. Accessed 04/04/2020

49. Analytics C. EndNote version X8. *San Francisco, CA: Clarivate Analytics* 2018.

50. Cochrane. Cochrane Collaboration data extraction form. https://dplp.cochrane.org/data-extraction-forms. Accessed 20/11/2019

51. S. NJL. *Chapter 5: Extracting qualitative evidence.*: Cochrane Collaboration Qualitative Methods Group; 2011.

52. Handbook TCC. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials. Accessed 20/11/2019

53. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell,. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 20/11/2019

54. Presley B, Groot W, Pavlova M. Pharmacy-led interventions to improve medication adherence among adults with diabetes: A systematic review and meta-analysis. *Research in Social and Administrative Pharmacy* 2019;15:1057-1067.

55. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa: Ottawa Hospital Research Institute* 2011.

56. UK C. Critical Appraisal Skills Programme (CASP) quality assessment tool https://casp-uk.net/casp-tools-checklists/. Accessed 15/08/2019

57. Wells G, Shea B. Newcastle-Ottawa quality assessment scale cohort studies.

58. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Academic Medicine* 2014;89:1245-1251.

59. Schünemann H. *The GRADE handbook*: Cochrane Collaboration; 2013.

60. Bruhn H, Bond CM, Elliott AM, et al. Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial. *BMJ open* 2013;3:e002361.

61. Hadi MA, Alldred DP, Briggs M, Marczewski K, Closs SJ. Effectiveness of a community based nurse-pharmacist managed pain clinic: a mixed-methods study. *International Journal of Nursing Studies* 2016;53:219-227.

62. Chelminski PR, Ives TJ, Felix KM, et al. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. *BMC Health Services Research* 2005;5:3.

63. Lagisetty Pooja SA, Antoku Derek,Winter Suzanne, Smith Michael, Jannausch Mary, Mi Choe Hae, Bohnert Amy SB, Heisler Michele A physician–pharmacist collaborative care model to prevent opioid misuse. *American Journal of Health-System Pharmacy* 2020.

64. Tewell R, Edgerton L, Kyle E. Establishment of a pharmacist-led service for patients at high risk for opioid overdose. *The Bulletin of the American Society of Hospital Pharmacists* 2018;75:376-383.

65. Briggs M, Closs SJ, Marczewski K, Barratt J. A feasibility study of a combined nurse/pharmacist-led chronic pain clinic in primary care. *Quality in primary care* 2008;16:91-94.

66. McDermott ME, Smith BH, Elliott AM, Bond CM, Hannaford PC, Chambers WA. The use of medication for chronic pain in primary care, and the potential for intervention by a practice-based pharmacist. *Family practice* 2006;23:46-52.

67. Cox N, Tak CR, Cochella SE, Leishman E, Gunning K. Impact of pharmacist previsit input to providers on chronic opioid prescribing safety. *The Journal of the American Board of Family Medicine* 2018;31:105-112.

68. Coffey CP, Ulbrich TR, Baughman K, Awad MH. The effect of an interprofessional pain service on nonmalignant pain control. *Am J Health Syst Pharm* 2019;76:S49-S54.

69. Tilli T, Hunchuck J, Dewhurst N, Kiran T. Opioid stewardship: implementing a proactive, pharmacist-led intervention for patients coprescribed opioids and benzodiazepines at an urban academic primary care centre. *BMJ open quality* 2020;9:e000635.

70. Semerjian M, Durham MJ, Mirzaian E, Lou M, Richeimer SH. Clinical Pharmacy Services in a Multidisciplinary Specialty Pain Clinic. *Pain Practice* 2019;19:303-309.

71. Boren LL, Locke AM, Friedman AS, Blackmore CC, Woolf R. Team-Based Medicine: Incorporating a Clinical Pharmacist into Pain and Opioid Practice Management. *PM&R* 2019;11:1170-1177.

72. Hartung DM, Hall J, Haverly SN, et al. Pharmacists' role in opioid safety: a focus group investigation. *Pain Medicine* 2018;19:1799-1806.

73. Tabeefar H, Chang F, Cooke M, Patel T. Community Pharmacists and Chronic Pain: A Qualitative Study of Experience, Perception, and Challenges. *Canadian Journal of Pain* 2020.

74. Lagisetty P, Smith A, Antoku D, et al. A physician–pharmacist collaborative care model to prevent opioid misuse. *Am J Health Syst Pharm* 2020.

75. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use. *Archives of Internal Medicine* 2006;166:2087-2093.

76. Dansie EJ, Turk DC. Assessment of patients with chronic pain. *Br J Anaesth* 2013;111:19-25.

77. Caraceni A, Cherny N, Fainsinger R, et al. Pain Measurement Tools and Methods in Clinical Research in Palliative Care: Recommendations of an Expert Working Group of the European Association of Palliative Care. *Journal of Pain and Symptom Management* 2002;23:239-255.

78. Boorman S, Cairns C. Another way forward for pharmaceutical care: a team-based clinical pharmacy service. *Pharmaceutical Journal* 2000;264:343-346.

79. Manolakis PG, Skelton JB. Pharmacists' contributions to primary care in the United States collaborating to address unmet patient care needs: the emerging role for pharmacists to address the shortage of primary care providers. *Am J Pharm Educ* 2010;74:S7-S7.

80. Blondal AB, Jonsson JS, Sporrong SK, Almarsdottir AB. General practitioners' perceptions of the current status and pharmacists' contribution to primary care in Iceland. *International journal of clinical pharmacy* 2017;39:945-952.

81. Patwardhan A, Duncan I, Murphy P, Pegus C. The value of pharmacists in health care. *Population health management* 2012;15:157-162.

82. Hohmann L. An untapped potential in addressing the opioid epidemic. *Journal of the American Pharmacists Association* 2019;59:625-627.

83. Hussain S, Hussain AAS, Hussain K, et al. Pharmacist–patient counselling in Dubai: assessment and reflection on patient satisfaction. *European Journal of Hospital Pharmacy: Science and Practice* 2013;20:241.

84. AlShayban DM, Naqvi AA, Islam MA, et al. Patient Satisfaction and Their Willingness to Pay for a Pharmacist Counseling Session in Hospital and Community Pharmacies in Saudi Healthcare Settings. *Frontiers in Pharmacology* 2020;11.

85. Moreno G, Lonowski S, Fu J, et al. Physician experiences with clinical pharmacists in primary care teams. *Journal of the American Pharmacists Association : JAPhA* 2017;57:686-691.

86. Giannitrapani KF, Glassman PA, Vang D, et al. Expanding the role of clinical pharmacists on interdisciplinary primary care teams for chronic pain and opioid management. *BMC Family Pract* 2018;19:107.

87. Medeconomics. The benefits of employing pharmacists in GP practices.2014. https://www.medeconomics.co.uk/article/1286630/benefits-employing-pharmacists-gp-practices. Accessed 08/04/2020

88. Agomo CO, Ogunleye J, Portlock J. A survey to identify barriers in the public health role of community pharmacists. *Journal of pharmaceutical health services research* 2016;7:253-261.

89. Thakur T, Frey M, Chewning B. Pharmacist Services in the Opioid Crisis: Current Practices and Scope in the United States. *Pharmacy (Basel)* 2019;7:60.

90. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *Cmaj* 2017;189:E659-E666.

91. England N. Involving people in their own health and care.2013. https://www.england.nhs.uk/wp-content/uploads/2017/04/ppp-involving-people-health-care-guidance.pdf. Accessed 08/04/2020

92. Informing And Involving Patients To Improve The Quality Of Medical Decisions. *Health Affairs* 2011;30:699-706.

93. Marlowe KF, Geiler R. Pharmacist's role in dispensing opioids for acute and chronic pain. *Journal of Pharmacy Practice* 2012;25:497-502.

94. Hassell K, Seston EM, Schafheutle EI, Wagner A, Eden M. Workload in community pharmacies in the UK and its impact on patient safety and pharmacists' well-being: a review of the evidence. *Health Soc Care Community* 2011;19:561-575.

95. Chui MA, Mott DA. Community pharmacists' subjective workload and perceived task performance: a human factors approach. *Journal of the American Pharmacists Association* 2012;52:e153-e160.

96. Bratberg JP, Smothers ZPW, Collins K, Erstad B, Ruiz Veve J, Muzyk AJ. Pharmacists and the opioid crisis: A narrative review of pharmacists' practice roles. *J Am Coll Clin Pharm* 2020;3:478-484.
97. Hoppe D, Ristevski E, Khalil H. The attitudes and practice strategies of community pharmacists towards drug misuse management: A scoping review. *Journal of Clinical Pharmacy and Therapeutics* 2020;45:430-452.
98. Jouini G, Choinière M, Martin E, et al. Pharmacotherapeutic management of chronic noncancer pain in primary care: lessons for pharmacists. *J Pain Res* 2014;7:163.
99. Pringle JL, Cochran J, Aruru M. Role of pharmacists in the Opioid Use Disorder (OUD) crisis. *Research in Social and Administrative Pharmacy* 2019;15:228-229.
100. Cochran G, Field C, Karp J, et al. A community pharmacy intervention for opioid medication misuse: a pilot randomized clinical trial. *Journal of the American Pharmacists Association* 2018;58:395-403.
101. Nielsen S, Kowalski M, Wood P, et al. Routine opioid outcome monitoring in community pharmacy: Pilot implementation study protocol. *Research in Social And Administrative Pharmacy* 2019;15:1047-1055.
102. Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health technology assessment (Winchester, England)* 2003;7:1-90.
103. Vadillo MA, Konstantinidis E, Shanks DR. Underpowered samples, false negatives, and unconscious learning. *Psychon Bull Rev* 2016;23:87-102.
104. Mishriky J, Stupans I, Chan V. Expanding the role of Australian pharmacists in community pharmacies in chronic pain management - a narrative review. *Pharm Pract (Granada)* 2019;17:1410-1410.
105. Chisholm-Burns MA, Spivey CA, Sherwin E, Wheeler J, Hohmeier K. The opioid crisis: Origins, trends, policies, and the roles of pharmacists. *American Journal of Health-System Pharmacy* 2019;76:424-435.

Supplementary data

The following is the supplementary data to this article:

Appendix 1: Search strategy

The authors first created a preliminary search strategy using free text terms in 4 main domains (pharmacists, opioids, chronic pain and management/intervention). The initial search items as free text terms and medical subject headings (MeSH) headings for MEDLINE are attached as Table 4. Vocabulary and alternate spellings (UK and American) were adjusted and were used interchangeably across databases. Synonyms were identified by performing a basic search. An advanced search using truncation and wild card were also used to maximise the search. Subject headings (if applicable) were used according to each respective database. Where applicable the explode option was also used. After all the basic searches (having free terms and MeSH headings) were combined into an individual search, they were intersected using AND/OR as applicable.

Table 4

Free text terms and MeSH headings; example of Medline database

Pharmacist	Opioids	Chronic pain	Management/intervention
Pharmacists	Analgesics, opioid	Chronic pain	Prescription drug misuse
Community pharmacy services	Analgesics, Opioid	Pain measurement	Pain management
Patient care team	morphine	Pain management	Patient compliance
Professional role	meperidine	Chronic disease	Counselling
Primary health care	methadone	Pain	Community health services
	buprenorphine	Chronic non-cancer pain	Patient care management
	fentanyl		Delivery of health care
	hydrocodone		Health care costs
	oxycodone		Outcome and Process Assessment (Health Care)
	codeine		Health services research
	narcotics		Quality of life
	Opiate		Health Knowledge, Attitudes, Practice
			Patient medication knowledge
			Patient Education handout
			Patient education
			Early intervention
			Pharmacy service hospital
			Education, pharmacy
			Drug monitoring
			Pharmaceutical services
			Prescription drug monitoring program
			Patient compliance
			Medication adherence
			Reduc*

	Raper
	Stop
	Terminat*
	Remove
	Substitu*

*truncation

Database: Ovid MEDLINE(R) ALL <1946 to November 01, 2019>

Search Strategy:

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1 pharmacist.mp. (14861)
2 pharmacists.mp. (30168)
3 Pharmacists/ (15938)
4 clinical pharmacist.mp. (1543)
5 clinical pharmacists.mp. (1505)
6 hospital pharmacist.mp. (413)
7 hospital pharmacists.mp. (1115)
8 community pharmacist.mp. (754)
9 community pharmacists.mp. (2503)
10 ambulatory care pharmacist.mp. (17)
11 ambulatory care pharmacists.mp. (30)
12 druggist.mp. (56)
13 druggists.mp. (99)
14 retail pharmacist.mp. (20)
15 retail pharmacists.mp. (53)
16 patient care team.mp. (63895)
17 patient care teams.mp. (91)
18 Patient Care Team/ (63650)
19 health professional.mp. (8673)
20 health professionals.mp. (44976)
21 health personnel.mp. (168330)
22 health personnels.mp. (49)
23 Health Personnel/ (39090)
24 professional role.mp. (14344)
25 professional roles.mp. (975)
26 Professional Role/ (13022)
27 pharmacy.mp. (61045)
28 exp Pharmacy/ (8267)
29 pharmacies.mp. (15711)
30 Pharmacies/ (7691)
31 community pharmacy.mp. (5967)
32 community pharmacies.mp. (3073)
33 clinical pharmacy.mp. (3401)
34 clinical pharmacies.mp. (2)
35 retail pharmacy.mp. (236)
36 retail pharmacies.mp. (341)
37 commercial pharmacy.mp. (17)
38 commercial pharmacies.mp. (17)
39 out patient pharmacy.mp. (12)

40 out patient pharmacies.mp. (2)
41 ambulatory care pharmacy.mp. (87)
42 ambulatory care pharmacies.mp. (8)
43 pharmacy service.mp. (11909)
44 pharmacy services.mp. (6227)
45 pharmaceutical service.mp. (177)
46 pharmaceutical services.mp. (12704)
47 exp Pharmaceutical Services/ (67235)
48 community pharmacy service.mp. (49)
49 community pharmacy services.mp. (4541)
50 Community Pharmacy Services/ (4372)
51 primary health care.mp. (87847)
52 Primary Health Care/ (74241)
53 primary health care service.mp. (224)
54 primary health care services.mp. (1116)
55 ambulatory health care.mp. (361)
56 ambulatory health care service.mp. (2)
57 ambulatory health care services.mp. (33)
58 ambulatory care.mp. (65281)
59 Ambulatory Care/ (42014)
60 pharmacy health care.mp. (11)
61 community health service.mp. (388)
62 community health services.mp. (31667)
63 Community Health Services/ (30983)
64 community health care service.mp. (17)
65 community health care services.mp. (52)
66 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (547047)
67 opioid analgesic.mp. (1884)
68 opioid analgesics.mp. (3453)
69 Analgesics, Opioid/ (41624)
70 opiate analgesic.mp. (146)
71 opiate analgesics.mp. (269)
72 narcotic analgesic.mp. (615)
73 narcotic analgesics.mp. (1395)
74 narcotic.mp. (44288)
75 narcotics.mp. (20616)
76 Narcotics/ (16241)
77 opioid pain killer.mp. (0)
78 opioid painkiller.mp. (9)
79 opioid pain killers.mp. (4)
80 opioid painkillers.mp. (16)
81 opiate pain killers.mp. (2)
82 opiate painkillers.mp. (2)
83 narcotic pain killer.mp. (2)
84 narcotic painkiller.mp. (0)
85 narcotic pain killers.mp. (3)

86 narcotic painkillers.mp. (5)
87 morphine.mp. (57397)
88 exp Morphine/ (37700)
89 fentanyl.mp. (21984)
90 exp Fentanyl/ (15453)
91 methadone.mp. (16417)
92 exp Methadone/ (12144)
93 buprenorphine.mp. or Buprenorphine/ (7271)
94 exp Buprenorphine/ (5052)
95 codeine.mp. (6809)
96 exp Codeine/ (6819)
97 opioid disorder.mp. (10)
98 opioid disorders.mp. (13)
99 opioid related disorder.mp. (5)
100 opioid related disorders.mp. (13677)
101 exp Opioid-Related Disorders/ (25157)
102 OUD.mp. (660)
103 prescription opioid misuse.mp. (258)
104 prescription drug misuse.mp. (1810)
105 exp Prescription Drug Misuse/ (12457)
106 opioid misuse.mp. (891)
107 opioid overdose.mp. (1317)
108 drug overdose.mp. (11924)
109 Drug Overdose/ (10771)
110 Opioid medication safety.mp. (2)
111 opia*.mp. (27257)
112 opiate.mp. (21543)
113 exp Opiate Alkaloids/ (84739)
114 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 (208412)
115 pain.mp. (686125)
116 exp Pain/ (383255)
117 chronic pain.mp. (41227)
118 exp Chronic Pain/ (12995)
119 chronic non-cancer pain.mp. (564)
120 chronic non-malignant pain.mp. (280)
121 non-cancer pain.mp. (771)
122 non-malignant pain.mp. (379)
123 chronic pain condition.mp. (384)
124 chronic pain conditions.mp. (1560)
125 chronic pain disease.mp. (28)
126 chronic pain diseases.mp. (26)
127 persistent pain.mp. (4955)
128 recurring pain.mp. (78)
129 repetitive pain.mp. (35)
130 untreatable pain.mp. (21)
131 idiosyncratic pain.mp. (2)
132 incurable pain.mp. (13)

133 pain scale.mp. (5540)
134 pain scales.mp. (1048)
135 pain measurement.mp. (83579)
136 Pain Measurement/ (83159)
137 measuring pain.mp. (429)
138 pain service.mp. (555)
139 pain services.mp. (247)
140 pain clinic.mp. (1757)
141 pain clinics.mp. (1885)
142 exp Pain Clinics/ (1448)
143 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 (764300)
144 managing pain.mp. (906)
145 pain management.mp. (48698)
146 Pain Management/ (31862)
147 pain education.mp. (457)
148 counseling.mp. (97067)
149 Counseling/ (34767)
150 counselling.mp. (25848)
151 patient counseling.mp. (2403)
152 patient counselling.mp. (663)
153 pain counseling.mp. (10)
154 pain counselling.mp. (3)
155 patient compliance.mp. (63145)
156 exp Patient Compliance/ (73503)
157 medicine adherence.mp. (52)
158 medication adherence.mp. (22903)
159 Medication Adherence/ (17535)
160 Patient care management.mp. (4169)
161 exp Patient Care Management/ (751351)
162 delivery of health care.mp. (105332)
163 exp "Delivery of Health Care"/ (1039383)
164 Risk assessment.mp. (282979)
165 exp Risk Assessment/ (253905)
166 Health care cost.mp. (2075)
167 health care costs.mp. (47412)
168 Health Care Costs/ (37935)
169 Pharmaco-economics.mp. (72)
170 patient Safety.mp. (40485)
171 Patient Safety/ (18195)
172 Prescription drug diversion.mp. (256)
173 Prescription Drug Diversion/ (210)
174 quality of life.mp. (323711)
175 "Quality of Life"/ (183790)
176 Quality of health care.mp. (139731)
177 exp "Quality of Health Care"/ (6676872)
178 Acceptance of illness.mp. (170)
179 Patient medication knowledge.mp. (198)
180 Patient Medication Knowledge/ (160)

181 patient education.mp. (97894)
182 Patient Education as Topic/ (83289)
183 Patient Education handout.mp. (5076)
184 Patient Education Handout/ (5035)
185 pharmacist education.mp. (79)
186 Education, Pharmacy, Continuing/ (891)
187 intervention.mp. (579918)
188 pharmacist intervention.mp. (577)
189 interventions.mp. (426043)
190 pharmacist interventions.mp. (514)
191 pharmacy intervention.mp. (119)
192 pharmacy interventions.mp. (136)
193 Early Medical Intervention/ (2736)
194 pharmacist consultation.mp. (82)
195 pharmacist consultations.mp. (34)
196 pharmacy consultation.mp. (31)
197 pharmacy consultations.mp. (25)
198 exp "Referral and Consultation"/ (72393)
199 Drug monitoring.mp. (25927)
200 Drug Monitoring/ (20125)
201 monitoring prescription.mp. (28)
202 monitoring prescriptions.mp. (15)
203 Prescription Drug Monitoring Programs/ (139)
204 drug information service.mp. (213)
205 drug information services.mp. (3886)
206 exp Drug Information Services/ (12195)
207 drug screening.mp. (35244)
208 Drug utilization review.mp. (3884)
209 Drug utilisation review.mp. (20)
210 "Drug Utilization Review"/ (3681)
211 Prescription screening.mp. (16)
212 medicine review.mp. (206)
213 medication review.mp. (1165)
214 MUR.mp. (486)
215 Medication therapy management.mp. (2323)
216 Medication Therapy Management/ (1901)
217 Medication therapy management service.mp. (14)
218 Medication therapy management services.mp. (141)
219 clinical pharmacy service.mp. (141)
220 clinical pharmacy services.mp. (645)
221 prescription drug monitoring program.mp. (240)
222 prescription drug monitoring programs.mp. (319)
223 Prescription Drug Monitoring Programs/ (139)
224 medication error.mp. (1579)
225 medication errors.mp. (14681)
226 exp Medication Errors/ (16433)
227 patient advice.mp. (82)
228 patient satisfaction.mp. (95989)
229 exp Patient Satisfaction/ (86017)

230 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 (7954067)
231 66 and 114 and 143 and 230 (2807)
232 66 and 114 and 143 (3153)
233 limit 232 to (english language and yr="1990 - 2020" and "all adult (19 plus years)") (1313)

Search strategy for other databases can be provided on demand from the corresponding author.

Appendix 2: Preliminary screening tool

	Title	Yes (relevant)					No (next search)		
	Abstract	Yes (relevant)					No (next search)		
	Design of study	Quantitative	RCT	NRS	Observational	descriptive			
		Mixed methods							
		Qualitative	Focus groups	Interviews	Narratives	Ethnography	Case study/s		
	Study population	Chronic non-Malignant pain					Yes	no	unclear
		Prescription Opioids					Yes	no	unclear
	Pharmacist	Community							
		Out patient							
		Clinical							
		Hospital							
		Healthcare team member							
		Primacy care team							
	Intervention	Yes							
		Maybe (indirectly)							
		No							

	Comparison	Yes	
		Maybe (indirectly)	
		No	
	Outcomes	Yes	
		Maybe (indirectly)	
		No	
	Seems to qualify inclusion criteria so retrieve	Yes	
		Maybe (indirectly)	
		No	
	Move towards step 2	Yes	
		No	