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. In 2011, a World Health Organisation (WHO) report empirically reported that one-fifth of the global population have chronic pain. The use of prescription opioids in CNMP is common. However, their long-term effectiveness for CNMP has not been beneficial. 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) accounting for the death of 218,000 people. In Canada over 20 million prescriptions for opioids were dispensed in 2016 and between 2016 and 2018, 11,500 people died from an opioid related death. 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, France, Italy, Spain, and Australia. In developing countries, there is a lack of studies on opioid utilisation in CNMP, however two studies show that the prescribing of tramadol 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. Overdose with prescription opioids has been rising and can have fatal consequences. 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. 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. 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 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 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).

**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 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

<table>
<thead>
<tr>
<th>PICO</th>
<th>Population, Intervention, Context, Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>P: Population</td>
<td>People with pain originating from any origin except cancer pain and should be present for at least 3 months</td>
</tr>
<tr>
<td>I: Intervention</td>
<td>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</td>
</tr>
</tbody>
</table>
| 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). 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, one had quasi-experimental study design, two were uncontrolled trials, 6 were prospective cohort study designs, 2 were retrospective chart reviews and 2 were qualitative studies.

The search process and screening are presented in a flowchart via PRISMA diagram Fig. 1.
Records identified through database searching (N= 725)

Additional records identified through other sources (N= 5)

Title of records after duplicates removed (N= 595)

Record title plus abstract screened (N= 300)

Records excluded (N= 295):
1. Pharmacist as in patient service providers
2. Cancer patients
3. Acute pain patients
4. Pharmacist e-services

Full text articles assessed for eligibility (N= 47)

Full-text articles excluded (N= 36) with reasons:
1. Studies have no study design (N= 5)
2. Editorials, commentaries (N= 16)
3. Cancer pain management (N= 15)

Total studies included (N= 14)

Studies identified from other sources
Quantitative studies (N= 2)
Qualitative study (N= 1)

Studies included in quantitative synthesis (N= 12)

Studies included in qualitative synthesis (N= 2)

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

<table>
<thead>
<tr>
<th>Study (location)</th>
<th>Design</th>
<th>Mean Age (range in years)</th>
<th>Setting</th>
<th>Participant recruitment</th>
<th>Total no. of study participants</th>
<th>Co-morbidities</th>
<th>Analgesics history (opioid plus if any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1_Boren_ 2019</td>
<td>Retrospective chart review study</td>
<td>Age= 52.7 (40.2-65.2)</td>
<td>People from Clinic outpatient clinic.</td>
<td>Physician referral from primary care clinic to service</td>
<td>383 (With pharmacist= 359) (Without pharmacist = 24) M=196 F=163 N= 85</td>
<td>Anxiety N= 117 (32.6%)</td>
<td>None reported</td>
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<td>(USA)</td>
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<tr>
<td>2_Chelminski_2005</td>
<td>Uncontrolled trial</td>
<td>Age= 51 (27-76)</td>
<td>People attending an academic general medicine practice</td>
<td>Physician referral from primary care clinic</td>
<td>175 (51%)</td>
<td>Depression N= 175 (48.7%)</td>
<td>None reported</td>
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<tr>
<td>(USA)</td>
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<tr>
<td>Study</td>
<td>Study Type</td>
<td>Age</td>
<td>Referral Site</td>
<td>N</td>
<td>Sex</td>
<td>Main Findings</td>
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<tr>
<td>3_Coffey_2019</td>
<td>Prospective</td>
<td>49.5</td>
<td>People attending Unity Health Center clinic</td>
<td>39</td>
<td>18</td>
<td>None reported</td>
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</tr>
<tr>
<td>(USA)</td>
<td>cohort study</td>
<td>(none</td>
<td>Physician referral from primary care clinic to service</td>
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<td>None reported</td>
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<td></td>
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<td>reported)</td>
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<tr>
<td>4_Cox_2018</td>
<td>Pilot study</td>
<td>57</td>
<td>People attending Family Medicine Residency clinic</td>
<td>45</td>
<td>23</td>
<td>Anxiety N= 27 (60%)</td>
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<td>(USA)</td>
<td></td>
<td>(none</td>
<td>Self-selection from electronic medical records by pharmacists and</td>
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<td>22</td>
<td>Oxycodone (49%)</td>
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<td></td>
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<td>reported)</td>
<td>recommendation provided</td>
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<td>hydrocodone (27%)</td>
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<td>Extended release morphine (20%)</td>
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<td>Insomnia N= 20 (44%)</td>
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<td>Tramadol (16%)</td>
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<td>Migraines N= 9 (20%)</td>
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<td></td>
<td>Acetaminophen (64%)</td>
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<td>Oral NSAIDS (42%), Gabapentin/pregabalin (38%)</td>
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<td>Bipolar N= 3 (7%)</td>
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<td>TCA (31%)</td>
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<td>Other psychiatric condition N= 2 (4%)</td>
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<td></td>
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<td></td>
<td></td>
<td>Topical NSAIDS (27%)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Study Team Characteristics</td>
<td>Methods</td>
<td>Sample Size</td>
<td>Outcomes</td>
<td></td>
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</tr>
</tbody>
</table>
| 5_Hadi_2015 | Mixed-methods Quasi-experimental study | Nurse-pharmacist managed pain clinic (secondary care clinic) | Physician referral from primary care clinic to service | N=79  
M= 26  
F= 53 | Unclear | None reported |
| 6_Tewell_2018 | Prospective cohort study | Family medicine primary care clinic | Screening eligible patients at the pain clinic by the nurse or pharmacist | Pain (post) score available for N= 36  
N= 41 | Gender not reported | None reported |
| 7_Semerjian_2018 | Retrospective chart review | 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 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Age Range</th>
<th>Setting</th>
<th>Recruitment Method</th>
<th>Sample Size</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>8_ Briggs_2008 65 (UK)</td>
<td>Prospective cohort study</td>
<td>Age= 57 (27-86)</td>
<td>Secondary care clinic</td>
<td>A nurse and PCP referred patients to the NPLC</td>
<td>N= 65</td>
<td>Gender not reported</td>
</tr>
<tr>
<td>9_ Bruhn_2013 60 (UK)</td>
<td>Exploratory RCT</td>
<td>Age= 65 (None reported)</td>
<td>6 primary care clinics</td>
<td>Screened against eligibility by computerised search and then reviewed by PCP</td>
<td>N= 193</td>
<td>Excluded patients with mental problems</td>
</tr>
</tbody>
</table>

Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff.
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Type of Study</th>
<th>Study Details</th>
<th>Sample Size</th>
<th>Adverse Events</th>
<th>Medicines Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>10_McDermott_2005</td>
<td>Prospective cohort study</td>
<td>Two age groups: Age=72 (29-64)</td>
<td>Primary care clinic</td>
<td>Potential participants were sent: an information sheet describing the study; a form seeking signed consent to the three different parts of the study</td>
<td>N=140 M=53 F=87</td>
</tr>
<tr>
<td>(UK)</td>
<td></td>
<td>Age=68 (65-94)</td>
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<td></td>
<td>The most common prescription medicines used were paracetamol plus dextropropoxyphene, paracetamol plus dihydrocodeine, tramadol, paracetamol plus codeine, diclofenac, rofecoxib and topical NSAIDs</td>
</tr>
</tbody>
</table>
Pilot study

Age = 55.8 (None reported)

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%)
<table>
<thead>
<tr>
<th>12_ Tili _2020</th>
<th>Prospective cohort study</th>
<th>Age control= 60 (None reported)</th>
<th>Three primary care clinics (one was control)</th>
<th>All participants after EMR review and then screened manually by PI if fulfilled inclusion criteria</th>
<th>N= 35 (intervention)</th>
<th>M= 11 F= 24</th>
<th>N= 20 (control)</th>
<th>M= 7 F= 13</th>
<th>None reported</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Age Intervention = 57 (None reported)</td>
<td></td>
<td></td>
<td>Psychiatric comorbidity</td>
<td>Depression</td>
<td>Anxiety</td>
<td>Substance use disorder</td>
<td>Post-traumatic stress disorder or history of trauma</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Type</td>
<td>Age</td>
<td>Gender</td>
<td>Patients</td>
<td>Prescription Opioids</td>
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<tr>
<td>13_Hartung_2017</td>
<td>USA</td>
<td>Exploratory study</td>
<td>Age Pharmacists = 39 (26-57)</td>
<td>M= 8 F= 11</td>
<td>None reported</td>
<td>None reported</td>
<td></td>
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<tr>
<td>(USA)</td>
<td></td>
<td></td>
<td>Age patients= 60.1 (30-77)</td>
<td></td>
<td></td>
<td>Patients using prescription opioids like oxycodone, hydrocodone, morphine</td>
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<tr>
<td>14_Tabeefar_2020</td>
<td>Canada</td>
<td>Exploratory study</td>
<td>Age= 46 (27-63)</td>
<td>M= 4 F= 8</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>(Canada)</td>
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</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Intervention</th>
<th>Person measuring/reporting</th>
<th>Intervention delivered by</th>
<th>Follow-up</th>
<th>Primary outcomes results</th>
<th>Secondary outcome results</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1_Boren_ 2019</td>
<td>Medication reviews</td>
<td>Pharmacist (part of intervention)</td>
<td>Multi-disciplinary team</td>
<td>0 to 24 months (1-20 visits)</td>
<td>After five visits with the pharmacist an average decrease of MED 270 mg/day was observed between initial and final visit</td>
<td>Annual urine toxicological screen increased from mean 54% to 84%</td>
<td>Fair quality</td>
</tr>
</tbody>
</table>

Signed medication agreement increased from mean 27% to 67%
Physician access was increased by 1197 additional visits
Modified or titrated a patient's pain medications
Consultation with the primary care physician.

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
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Setting</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffey et al. (2019)</td>
<td>Educational video by student pharmacist</td>
<td>Unclear</td>
<td>Multi-disciplinary team, 0 and 12 months</td>
<td>1 hour direct MTM session (3-14 days later) with pharmacist plus opioid misuse risk assessment</td>
</tr>
<tr>
<td></td>
<td>Knowledge assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referral to secondary care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Management plan discussed with patients and sent to doctors electronically</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- 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%

Overall, total MEDD/patient decreased from 20.5 to 18.1 mg/day, *P* = 0.3

Poor quality

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
<table>
<thead>
<tr>
<th>4_Cox_2018 67</th>
<th>Dose calculation unclear</th>
<th>Physician 0 and 4 months plus pharmacist</th>
<th>Average pain (1-10 scale) scores increased from 5.3 to 5.5 (P= .783)</th>
<th>Urine drug screening increased from mean of 15 people to 27 (P=.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective medication review</td>
<td>Mean MME/day decreased by 14% (P=.001)</td>
<td>Average MMEs/day:</td>
<td></td>
<td>Adherence to PDMP increased from 12 people to 26 (P=.001).</td>
</tr>
<tr>
<td></td>
<td>Average MMEs/day:</td>
<td>Based on prescription directions decreased from 151 to 125 mg/day</td>
<td></td>
<td>Referrals by PCPs to:</td>
</tr>
<tr>
<td></td>
<td>Based on number of pills prescribed per month: 135 to 116 mg/day</td>
<td></td>
<td></td>
<td>a. Pain specialists increased from 17 to 21 (P=.046)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b. Physical therapist from 33 to 34 (P=.317)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prescribing of opioid analgesics mean= 1.6 to 1.5 (P=.219)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prescribing of non-opioid analgesics mean=</td>
</tr>
</tbody>
</table>
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%
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reduction in mean BPI pain interference= 7.1 to 6.1 (P = 0.02)</th>
</tr>
</thead>
</table>

**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 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).
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methodology</th>
<th>Follow up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>6_Tewell_2018</td>
<td>Medication review by pharmacist</td>
<td>Unclear</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>To give Naloxone prescription</td>
<td>Pharmacist</td>
<td>Follow up</td>
<td>Pharmacist educated all 41 participants and 83% procured naloxone (69% of all candidates who received a prescription for the medication)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pharmacist</td>
<td>unclear.</td>
<td></td>
</tr>
</tbody>
</table>

Majority of the patients = 21 (61.7%)
Medication review
Identification of Medication drug related problems
Referral to secondary care
Drug safety testing
Patient counselling

Pharmacist (part of the intervention)

Pharmacist

No

The pharmacist was able to discontinue opioid therapy completely in 2 long-term opioid users

follow-up chart review

In 27.1% of visits, only one MRP was identified

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.

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%
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Follow-Up</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briggs 2008</td>
<td>Pharmacist medication review</td>
<td>Nurse plus pharmacist</td>
<td>0 and 6 months</td>
<td>Average pain scores (NRS-11) improved from 8 to 6.3 (P= 0.0001)</td>
</tr>
</tbody>
</table>

92% of patients were either satisfied or very satisfied with their overall care.

Referrals by pharmacists to specialised care units= 13/120 patients

e. Non-adherence/patient variables= 6%

Poor quality a
<table>
<thead>
<tr>
<th>Prescribing arm: Pharmacist as independent prescriber and medication review</th>
<th>Research team by follow-up questionnaires</th>
<th>Physician plus 6 months</th>
<th>Within-arm improvement in pain (CPG) in the prescribing arm (P= 0.003) and review arm (P= 0.001), but not in the control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review arm: Patient medication review only and recommendation communicated to PCP</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control arm- no pharmacist review only PCP</td>
<td></td>
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</table>

SF-12 PCS/MCS: Poor quality b

Physician plus 0, 3, and 6 months within-arm improvement in pain (CPG) in the prescribing arm (P= 0.003) and review arm (P= 0.001), but not in the control arm

The non-categorised HADS scores showed a statistically significant improvement within the prescribing arm for Depression.
(P= 0.022) and Anxiety (P= 0.007) only

Patient who were satisfied: 39/46 (85%)
Two methods: Unclear Physician 6 months

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

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
Physician acceptance: Recommendations had fully been carried out in 9/11 people.
### 11._Lagisetty_2020

<table>
<thead>
<tr>
<th>60 minute meeting where pharmacist reviewed pain history, medication history, response to prior medicine and risk factors</th>
<th>Physician 4-month follow-up pharmacist recommendation</th>
<th>Improving patient knowledge about buprenorphine:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>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)</td>
<td>a. Heard of buprenorphine, = 22 to 30 (P = 0.021)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Believe buprenorphine is used for detox and/or OUD treatment = 17 to 13 (P = 0.013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Believe buprenorphine is used to treat pain = 14 to 20 (P = 0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor quality a</td>
</tr>
</tbody>
</table>

**Pharmacist recommendation:**

a. Add or change non-opioid pain medication = 30 (64%)
b. Switch to buprenorphine = 20 (43%)
c. Add non-pharmacological
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
<table>
<thead>
<tr>
<th>12_ Tilli _2020 69</th>
<th>Patient identification through medical record queries</th>
<th>Pharmacists</th>
<th>Physician plus pharmacist</th>
<th>6 months</th>
<th>Change in pain unremarkable</th>
<th>Physician acceptance 24/32 (75%)</th>
<th>Good quality a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Developing care plans</td>
<td></td>
<td></td>
<td></td>
<td>Intervention clinic= mean opioid MME decreased by 11% , from 50.5 to 44.7 mg/day</td>
<td>Patient acceptance rate 13/24(54%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussing recommendations with physicians</td>
<td></td>
<td></td>
<td></td>
<td>Control clinic= mean opioid MME increased by 15% from 62.3 to 71.4 mg/day</td>
<td>Opioid taper increased from 14 to 66% in intervention clinic (increased 4 times)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discussing implementing recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control clinic, the active opioid tapers remained zero</td>
<td></td>
</tr>
<tr>
<td>13_Hartung_2017</td>
<td>Two focus groups methods used. Face-to-face and online Crystallisation-immersion approach</td>
<td>Unclear</td>
<td>Not applicable</td>
<td>Community pharmacist role in opioid medication safety was perceived essential by stakeholders</td>
<td>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</td>
<td>Low quality</td>
<td></td>
</tr>
<tr>
<td>Interviews conducted via 2 methods. Face-to-face and telephone</td>
<td>Not applicable</td>
<td>Development of expanded role of pharmacists in opioid safety was perceived to be beneficial by pharmacists.</td>
<td>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</td>
<td>Moderate quality c</td>
<td></td>
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</tbody>
</table>

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**Abbreviations:**
- NOS scale criteria
- RoB tool of the Cochrane Collaboration Handbook
- 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 = MRP
- 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.\textsuperscript{72} studied 18 people with CNMP and 19 community pharmacists, whereas Tabeefar et al.\textsuperscript{73} studied 9 community pharmacists (Table 2).

Hartung et al.\textsuperscript{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.\textsuperscript{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
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. 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. The pharmacist intervention effect on pain was assessed in 8 studies and pain improved in all except 3 studies. 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.

This review shows that patient safety can be improved by identifying MRPs while using opioids for CNMP management by a pharmacist review. 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. 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.

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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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.

**Funding**

Work by AI was supported by the Schlumberger Foundation Faculty for the Future program (partially) and Vice Chancellor scholarship for research excellence by the University of Nottingham (partially) for the completion of a PhD degree.

**Conflict of interest**

The authors have no conflict of interest.
Acknowledgement

The authors would like to acknowledge the contribution of Dr Douglas Grindlay, Information Specialist in Centre of Evidence Based Dermatology, the University of Nottingham for his guidance in building and reviewing the search strategy.

References


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

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<th>Chronic pain</th>
<th>Management/intervention</th>
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<td>Analgesics, Opioid</td>
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<td>pharmacy</td>
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<td>Community health services</td>
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<td>Pain measurement</td>
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<td>Chronic non-cancer pain</td>
<td>Delivery of health care</td>
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<td>Chronic non-cancer pain</td>
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Database: Ovid MEDLINE(R) ALL <1946 to November 01, 2019>

Search Strategy:

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)
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39 out patient pharmacy.mp. (12)
out patient pharmacies.mp. (2)
ambulatory care pharmacy.mp. (87)
ambulatory care pharmacies.mp. (8)
pharmacy service.mp. (11909)
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Community Pharmacy Services/ (4372)
primary health care.mp. (87847)
Primary Health Care/ (74241)
primary health care service.mp. (224)
primary health care services.mp. (1116)
ambulatory health care.mp. (361)
ambulatory health care service.mp. (2)
ambulatory health care services.mp. (33)
ambulatory care.mp. (65281)
Ambulatory Care/ (42014)
pharmacy health care.mp. (11)
community health service.mp. (388)
community health services.mp. (31667)
Community Health Services/ (30983)
community health care service.mp. (17)
community health care services.mp. (52)
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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
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(547047)
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Analgesics, Opioid/ (41624)
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narcotic analgesic.mp. (615)
narcotic analgesics.mp. (1395)
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narcotics.mp. (20616)
Narcotics/ (16241)
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fentanyl.mp. (21984)
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methadone.mp. (16417)
exp Methadone/ (12144)
buprenorphine.mp. or Buprenorphine/ (7271)
exp Buprenorphine/ (5052)
codeine.mp. (6809)
exp Codeine/ (6819)
opioid disorder.mp. (10)
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opioid related disorder.mp. (5)
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OUD.mp. (660)
prescription opioid misuse.mp. (258)
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drug overdose.mp. (11924)
Drug Overdose/ (10771)
Opioid medication safety.mp. (2)
opia*.mp. (27257)
opiate.mp. (21543)
exp Opiate Alkaloids/ (84739)
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)
pain.mp. (686125)
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chronic non-cancer pain.mp. (564)
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repetitive pain.mp. (35)
untreatable pain.mp. (21)
idiosyncratic pain.mp. (2)
incurable pain.mp. (13)
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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

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