Opioid medicines management in primary care settings: a scoping review of quantitative studies of pharmacists' activities

Authors and affiliations:
Margaret Jordan
School of Pharmacy
Faculty of Medicine and Health
University of Sydney
E: mjor5244@uni.sydney.edu.au
Orcid ID: https://orcid.org/0000-0002-3365-6650

Dr Asam Latif
Senior Research Fellow
Faculty of Medicine and Health Sciences
University of Nottingham, Nottingham, UK
E: Asam.Latif@nottingham.ac.uk
Orcid ID https://orcid.org/0000-0003-0730-7120

Associate Professor Judy Mullan
Academic Director: Centre for Health Research Illawarra Shoalhaven Population
Graduate Medicine | School of Medicine | Science, Medicine and Health Faculty |
University of Wollongong | Wollongong NSW 2522 |
Deputy Director: Illawarra & Southern Practice Research Network
Graduate Medicine | School of Medicine | Science, Medicine and Health Faculty |
University of Wollongong | Wollongong NSW 2522 |
E: jmullan@uow.edu.au
Orcid ID: https://orcid.org/0000-0003-3772-7986

Professor Timothy F Chen
Professor of Medication Management
Head of Pharmacy Practice and Health Services Research
School of Pharmacy | Faculty of Medicine and Health
E: timothy.chen@sydney.edu.au
Orcid ID: https://orcid.org/0000-0003-4189-8403

Corresponding author

Margaret Jordan
School of Pharmacy
Faculty of Medicine and Health
Pharmacy Building A15
The University of Sydney NSW 2006
mjor5244@uni.sydney.edu.au

Running head: PRIMARY CARE PHARMACISTS OPIOID ACTIVITY

Keywords: opioid, pharmacist, general practice, chronic non-cancer pain, stewardship, opioid use disorder, take-home naloxone, opioid agreement

Word count: 3491

Table count: 3

Figure count: 1

Abstract

Aim

To undertake a scoping review of pharmacists' activities in opioid medicines management in primary care settings, including those developed or led by pharmacists, or in which pharmacists were members of broader multi-disciplinary teams; and to collate the activities, models of care and settings, and reported outcomes.

Methods

The bibliographic databases MEDLINE, EMBASE, International Pharmaceutical Abstracts, CINAHL, SCOPUS and Web of Science were searched. Studies with quantitative evaluation and published in English were eligible. Participants were patients with any pain category or an opioid use disorder, and healthcare providers. Studies originating in hospitals or involving supply functions were not included. Screening of literature and data charting of results were undertaken by two researchers.

Results

The 47 studies included in the scooping review occurred in primary care settings collated into four categories: general practice or primary care clinics; healthcare organisations; community pharmacies and outreach services. Studies were primarily of opioid use in chronic, non-cancer pain. Other indications were opioid use disorder, cancer and dental pain. Pharmacist activities targeted risk-mitigation, patient and provider education and broader, strategic approaches. Patient-related outcomes included reduced opioid load, improved functionality and symptom management, enhanced access to services and medication-assisted treatments, and engagement in risk-mitigation strategies. Behaviour change of providers was demonstrated.

Conclusion

The review has identified the significant contribution that pharmacists working in primary care settings can make to minimise harm from opioids. Strategies implemented in isolation have the potential to further reduce adverse clinical outcomes with greater collaboration and coordination, such as opioid stewardship.

Introduction

The prescribing of opioids has increased internationally with up to four-fold increases in some countries such as Australia[1] and United States (US).[2] There have been sharp increases in prescribing of particular opioids; for example in France, where the prevalence of oxycodone use steadily increased over the ten-year period to 2015, when 10 times more people were supplied this opioid than in 2006.[3] The rise in the use of opioids has been attributed to increased prescribing for chronic non-cancer pain (CNCP) states,[4,5] despite limited evidence for benefit,[6] particularly for high doses.[7] In the United Kingdom (UK), the majority of prescriptions issued in a ten-year period was for non-cancer use, with 'strong' opioids predominating.[8] Chronic prescribing of medicines such as opioids has been noted to stem in part from continued prescribing of those commenced during acute episodes, at or after discharge from hospital.[9] Although initiated in hospital or pain clinic settings, the majority of ongoing prescribing of opioids occurs in primary care by family practice physicians and general practitioners (GPs).[10,11]

Associated with the significant rise in opioid prescribing is evidence of harm.[12-14] This can occur in the context of 'extramedical' (or 'non-medical') use, which refers to accessing prescription opioids outside the formal medical system or to use in a manner that is different to the prescriber's intention;[15] but also when opioids are used therapeutically, as intended. Harm can occur in the short-term or with chronic use, and includes emergency department presentations for overdose, altered mental status, gastrointestinal effects, increased health-service utilisation, aberrant drug behaviour, falls, trauma; tolerance and dependence, sleep disorders; hyperalgesia, endocrinopathies and depression.[16-21] While the contribution of illicit opioid derivatives to morbidity and mortality is rising,[13,14] prescription opioids remain a concern from their unintended consequences and extramedical use.[4,17] In 2017, prescribed opioids were implicated in almost a quarter of presentations to hospital emergency departments in Europe for acute drug-related harm in 2017.[14] In Australia in 2018, the primary drug group associated with unintentional drug-induced deaths was opioids, with over half of these due to prescription opioids.[22] A recent review concluded that, although lower than 'western' countries, such as the US, Australia and UK, the prevalence of prescription opioid misuse in countries within the Asia-Pacific region is significant and may strain their systems, especially in developing countries with healthcare infrastructure and resources already stretched or limited.[23]

To mitigate the risk of opioid-related harm in the community, several strategies have been recommended internationally, although variably implemented or evaluated. These include reducing the overall opioid load and use of higher potency formulations; restricting availability by legislation; employing prescription drug monitoring programs; negotiating boundaries and agreements with patients; improving access to specialty pain or addiction services, medication-assisted treatment of

opioid dependence and take-home naloxone (THN); and developing the clinical workforce, if necessary by outreach or academic detailing.[4,24-29]

Pharmacists' professional scope of practice in the community has evolved substantially in recent decades away from supply functions and into person-centred pharmaceutical care, with integration into general practice, family practice and other primary care settings.[30-32] Systematic reviews of outcomes achieved with pharmacists integrated into primary care have shown reduced medication-related problems, emergency department presentations and GP appointments; improved medicine adherence and health outcomes in patients with multiple medications and comorbidities; with some evidence of savings in overall health system and medication costs.[31-34] An under-researched area is the scope of pharmacists' activities in the management of opioids in primary care and how these complement recommended risk-mitigation strategies.

Despite the majority of opioid prescribing occurring in primary care, a search of the literature has not found any international systematic or scoping review of pharmacist activities in the management of opioids that occur outside of the hospital setting. The aim of this scoping review was to synthesise the literature on the role of pharmacists in the management of opioids in primary care settings, as this is an emerging professional practice for pharmacists. The objectives were to investigate the opioid medicine management activities of pharmacists, the settings in which these activities occurred, the reported outcomes and to use these to inform recommendations for future research and strategies.

Methods

The scoping review was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) framework.[35]

Eligibility criteria

Original, published studies which demonstrated the pharmacist's role in the management of opioids in primary care settings were included. Table 1 lists the eligibility criteria applied. Studies were excluded if they occurred in, or originated from hospitals, if the role of the pharmacist involved supply or dispensing of medicines or if the study design was primarily qualitative.

Information sources, search strategy and study selection

To identify relevant documents, the bibliographic databases of MEDLINE, EMBASE, International Pharmaceutical Abstracts (IPA) via OVIDSP; CINAHL, SCOPUS and Web of Science were searched. The search strategies were developed by all authors, assisted and reviewed by an experienced university medical librarian and conducted by one author (MJ).

The search was conducted in July 2020. Figure 1 shows a PRISMA flow diagram through from the search to the to the final inclusion of the studies, according to the PRISMA statement.[36] A full example of the search strategy used (MEDLINE) can be found in Appendix 1. The search results were exported into EndNote[x9], and duplicates removed. The results were supplemented by "snowballing" from reference lists of retrieved and relevant studies. Results reported only as conference abstracts were investigated for further publishing of the final studies that may have occurred. Grey literature was not included.

All the titles and if necessary, the abstracts of the results were screened in EndNote[X9] for eligibility by two reviewers, concurrently (MJ, AL). Studies were included for final analysis after agreement was reached.

Data extraction and synthesis of results

After piloting, key characteristics were compiled for each study: the country, design, context, nature and age of participants, phenomena of interest and reported outcomes. The studies were grouped by the primary care setting in which they occurred. The results of the scoping review were tabulated according to the review objectives: the context in which the studies occurred and reported outcomes (Table 2) and the nature of pharmacist activities in primary care settings (Table 3).

Results

In the 47 studies included in the scoping review, pharmacists developed or led,[37-49] and were part of interdisciplinary teams[47,50-65] and physician collaborative care models[45,48,66-71] in the management of opioids; whilst embedded in prescribers' location of practice[40-44,46,54-57,59,60,72], acting independently[73-75] or remotely[37,53,72,76-78]. The various primary care settings in which these occurred have been collated into four groups: general or family medicine practice and primary care clinics;[37-39,41-46,49-59,64-73,79,80] healthcare organisations with a range of primary care settings[47,48,60-63,76]; community pharmacy practice[74,75,81]; and outreach services.[77,78,82,83] The primary care settings, countries of origin and context of the studies are detailed in Table 2.

In the majority of studies, the outcome of interest for the patient cohorts was any change to opioid doses prescribed, in the context of reducing risk from high opioid doses in CNCP.[38,40,50,52,54,55,60,62,73] For comparative studies, the opioid load was most often estimated by converting it to the oral morphine equivalent daily dose, or oMED; a method to standardise the dose based on the knowledge that different opioids with varying potency may produce a similar analgesic effect.[84] Additional outcomes included the impact of any change to oMED or pharmacist involvement on symptom scores and functionality; [47,48,51,56,67] which were also outcomes for the four palliative care studies.[49,64,65,80] One study only investigated opioid specifically for acute pain and that was in a free dental clinic where the outcome was the change in rates of opioid prescribing.[71] Other quantitative outcomes were retention rates in pharmacist programs,[39,66,68] discontinuation of regular opioids,[74] initiation of pharmacist care plans,[40,50,85] procurement of take-home naloxone,[38,39,43,54,78] effect on overdose occurrence or premature deaths[39,61] and emergency department presentations.[54]

For medical and nurse prescriber participants, the outcomes were any impact as assessed by acceptance rates of pharmacists' or multidisciplinary committees' recommendations[37,40,42,47,53,58,59,62,70,72,75,77,81] as well as measures of prescriber behaviour change, such as adherence to pain management protocols; initiation of non-opioids; prescriptions for take-home naloxone; referrals to external providers; reduced concomitant prescribing with benzodiazepines; engagement of patients in prescriber-patient opioid agreements, prescription monitoring, urine toxicology screening and other measures to assess patient aberrant behaviours;[37,38,40,41,50,52-54,59,61,63,66,75-77,82,83] and electrocardiogram monitoring for patients prescribed long-term methadone for pain.[37,46] At the practice or organisational level, outcomes detailed the establishment of workflows and embedded protocols.[54,57,66] The study design, population sample and evaluation measures and outcomes are tabulated in Table 2

Pharmacists participated at the time of initial consideration of an opioid,[51,71] through to intervening to mitigate the harm of ongoing, high-dose or risky opioid use for specific patients[37,39,40,42-44,46,54-57,60,61,69,72,74-77,81]. Activities to reduce harm included targeting the opioid load and sedative

combinations; increasing uptake of take-home naloxone supply; assessing potential risks of opioids, either of use disorder or for adverse effects; enabling opioid agreements, urine screening and prescription monitoring programs and improving access to treatments. In many studies, pharmacists were actively involved in patient management and received direct referrals or prescribed independently.[39,45,50,61,70,73,79-81] In studies where pharmacists were not directly involved in patient care, recommendations for opioid management were provided based on patient records,[72] or with education of prescribers to encourage behaviour change.[82,83] Examples of pharmacists initiating, developing or having input into policies and protocols at the organisational level and effecting system-wide change were included in the results.[45,46,48,52,55,57,60-63]

The range and details of pharmacist activities and models of care in primary care settings are detailed in Table 3. The activities have been collated into foci or targets for risk-mitigation, with details of pharmacists' activities and roles described. The risk-mitigation strategies listed were not always implemented in isolation, but often occurred as a component of a multifaceted approach.

Discussion

Pharmacists were found to be involved in a range of opioid-related activities in primary care settings, with significant contributions for both patients and their providers of care. The primary care settings, although varied, could be collated into four comparable groups: general or family medicine practice and primary care clinics, healthcare organisation with range of primary care settings, community pharmacy practices and outreach services. Activities spanned the full range of those accepted in medication management, described as the delivery of patient-centred care to optimise the safe, effective and appropriate therapy,[86] including that of prescribing independently or collaboratively but excluding, for the purpose of this review, the supply function. The indications for opioids in the studies included all pain states, although only one study in acute pain was identified, in this case, dental.[71] Conversely, the impact of pharmacists' involvement in management of acute pain and the appropriate use of opioids in the hospital setting has been well described. Activities initiated in hospitals have included prescriber education, 'de-escalation' of opioids following surgery, and embedding systemic changes to improve prescribing at the time of handover from hospital and transitions of care.[87-91]

For patients with CNCP, significant findings were realised in reducing the burden of opioid prescribing, using the oMED[40,47,48,50,52,54-56,60,62,64,73] and prescribing rates[37,53,57,61,63,77] as measures, but also for the patient-reported outcomes of pain and functionality. Outcomes from pharmacist consultations included assessments of pain, depression, disability, function, potential risks of opioids and development of care plans.[40,45,47,48,51,64,67,73,81] These concur with the recommendation from the Centers for Disease Control and Prevention (CDC) 2016 guidelines for prescribing opioids for chronic pain,

which is to establish patient and prescriber goals for functional (physical, social and emotional) improvement, and not purely for pain.[29] The outcome for three studies in the review was a reduction in opioid use without significant change in the patient-reported outcomes of pain, depression or disability,[48,56,67] thus potentially reducing harm from opioids without adversely or otherwise affecting function. On the other hand, some studies with pharmacist input demonstrated improvements in measures of patient-reported outcome by rationalising other therapies, either with[48,64] or without[47] significant reductions in opioid load. The finding that reducing opioids can be of benefit to patients agree with those of a 2017 systematic review of studies examining patient outcomes after dose reduction of long-term opioid therapy, in which improvement was reported in pain severity (8 fair-quality studies), function (5 fair-quality studies), and quality of life (3 fair-quality studies).[92] A later systematic review investigated the effects of opioid tapering on pain only.[93] The conclusion from consistent type 3 and 4 study evidence of the review (as defined by the Agency for Health Care Policy and Research) was that opioid tapering reduces pain or maintains the same level of pain, but with the caveat that these represent lower levels of evidence. The variance in patient-reported outcomes found in studies of the scoping review reflects the heterogeneity in their design, as well as in the patient population with CNCP that is prescribed opioids.[94]

Apart from the focus on reducing overall opioid load, pharmacist activities included implementing or participating in many of the recommended harm minimisation strategies, applied broadly in primary care organisations or directly, in patient management. Engagement of patients in opioid or 'Controlled Substance' agreements, or informed consents is an example of such a strategy identified in the scoping review, employed directly[50,57,69] or enabled by pharmacists after input into organisational commitment.[37,52,60-63] It has been proposed that pharmacists have a part in these agreements, which presents a role aside from that of the 'gate-keeper' of opioid supply.[95] Such patient-provider agreements can function as tools for shared decision-making, to provide education, facilitate conversations and mitigate misuse. Common elements include medication review, any testing requirements, clinician and pharmacy restrictions, consequences of deviation from the agreement and importantly, agreed goals of therapy.[96] Although agreements have become standard practice in some outpatient pain clinics, they are not universally accepted by all providers and patients.[95] 'Structural iatrogenesis' has been attributed to these, as a potential cause of patient harm.[97] A systematic review concluded that there was weak evidence to support the effectiveness of patient-prescriber agreements in the reduction and mitigation of opioid misuse and abuse.[96] However, only one study included in that review provided details of additional, universal strategies along with agreements to reduce aberrant behaviours. In our scoping review of pharmacist input, the study in which agreements were implemented as only one of many opioid harm-mitigation strategies presented evidence of beneficial clinical outcomes with a reduction in premature deaths.[61] This provides a context for the use of agreements; that is, as one of many possible strategies and of questionable benefit if used in isolation.

A further major activity in risk-mitigation was the active involvement of pharmacists in promoting take-home naloxone (THN). Activities ranged from education of providers[41,75,82] and patients and their community,[39,41,43,54,74] in some instances via outreach;[38,78,82] systematic identification of people at-risk of opioid-induced respiratory failure due to opioid dose, concomitant medicines or comorbidities using electronic records and algorithms;[39,41,43,44,54,78] and additionally, by its prescribing.[38] These activities complement the traditional supply and education roles that pharmacists within the community have for take-home naloxone, especially given its increased availability by down-scheduling or standing orders in many countries, and the availability of intranasal formulations.[98] Identification of people at-risk of respiratory depression and eligible for naloxone has been recognised as a barrier to prescribing[99] and supply by pharmacists[100,101] in primary care. There is limited recognition of the many patient and medication factors that contribute to risk of overdose, including by the patients themselves.[102] In a large cohort of Australian patients with CNCP and prescribed opioids, it was estimated that 78% had at least one risk factor for overdose and 42% had at least two,[103] according to Centers for Disease Control and Prevention criteria.[29] The systematic approaches to patient identification and upskilling of prescribers described in this scoping review, directly target those gaps in behaviour and knowledge. Along with explicit patient education, the review revealed the range of strategies that have enhanced the uptake of naloxone prescribing and supply, many of which could be applied in wider contexts.

Increasing access in primary care to pain management specialist services, as well as medication-assisted therapies for opioid use disorder or those using opioids non-medically are further strategies that have been recommended to reduce harm from long-term opioids.[4,27,29] The scoping review provides evidence of pharmacists' contribution in both domains. Increased access to pain physicians[50] and pain management services for CNCP was demonstrated,[45,47,48,54,59,67,73] by utilising collaborative models of care, previously applied to other chronic conditions such as atrial fibrillation, diabetes, hypertension and depression.[67] Three studies provided evidence of pharmacists expanding treatment options for patients in the community requiring medication-assisted treatment, under collaborative care models of management.[66-68] For the buprenorphine maintenance practice, additional evaluation realised a cost-benefit compared to the usual model of care.[66] Co-prescribing of opioid substitution treatment with an accredited physician, is a further expansion of scope of practice proposed for pharmacists in Australia, to alleviate the demand for services.[104] Qualitative analysis of patients' responses to this proposed model were all positive, with enhanced access, availability and continuity of care as perceived benefits along with reduced costs. Evaluation of pharmacists' responses was mostly positive, although it was recognised that enhanced skills and competencies would be required.[104]

Most of the studies of the review detailed pharmacists' involvement in chronic non-cancer pain, cancer-related pain or opioid use disorder, reflecting the bulk of indications for opioids prescribed in primary care.[10,11] However, only one study in acute pain was identified, in this case, dental.[71] Opioid prescribing for dental indications has been recognised as contributing to persistence of use after the acute event, opioid dependence and as a target for 'doctor shopping'.[105] The dental clinic study included in the scoping review[71] demonstrated significant reductions in opioid prescribing with greater active pharmacist collaboration, so that with full pharmacist integration, prescribing rates were a fifth of those for when there was no pharmacist involvement. Conversely, in a recent pilot intervention study into dental practices without direct pharmacist involvement, although an on-line prescribing tool reduced codeine combinations, the result was not significant.[106]

Based on the successes of antimicrobial stewardship, a stewardship program has been proposed as a model to mitigate preventable opioid adverse events in the hospital setting, and also to reduce the risk of long-term opioid use by rationalising duration and supply at discharge.[107-109] The US National Quality Forum, with its release of the *Opioid Stewardship Playbook,*™[110,111] proposed seven fundamentals to support stewardship for healthcare organisations and clinicians which are applicable to any healthcare organisation or setting. Several primary care studies in the scoping review directly referred to opioid, or controlled substances stewardship models,[40,60-63] demonstrating many of the recommended fundamentals. Although some of these studies involved coordinated activities in well-resourced, larger healthcare organisations, the review also demonstrated that it is possible to integrate stewardship fundamentals and a practice-wide approach into smaller and single-site practice settings with embedded pharmacists. One recommendation from the Victorian Government, Australia, in response to an inquiry into drug law reform, was to develop and promote a sector-wide stewardship for the medical profession, including for hospitals, specialist services and general practitioners.[112]

Strength and weaknesses

This is the first scoping review of pharmacists' involvement on opioid medication management in primary care settings, which is a major strength. The limitations are that only papers involving studies with quantitative outcomes and conducted in English were included and that few had comparative cohorts. Only original, published literature was analysed. As this is an emerging area of professional practice for pharmacists, abstracts were found of results presented at recent conferences and symposia, which implies that evidence may be accumulating and a future review of would yield more definitive evidence.

The inclusion criteria were broad and identified studies in a diverse range of settings and with varied methodologies. The inclusion criteria were such that the focus of the review was on opioids, and so

extended roles for pharmacists which concentrate on non-opioids, non-pharmacological pain management or medicine management in general may not have been included in the results.

The scoping review is of a new topic so comparisons with other studies was not possible. As a scoping review, the quality and rigor of the included studies was not formally evaluated.

Conclusions

This scoping review has demonstrated the many ways in which pharmacists working in general practice settings contribute to strategies designed to reduce opioid-related harm. Evidence was provided from studies with extended scope of practice for pharmacists, with interprofessional collaboration to drive change and in independent activities such as prescribing and delivering education. For those studies which detailed patient-reported outcomes, there was evidence of benefit in opioid reduction, symptom management and improved service access. Further qualitative research or collation of existing studies into a scoping review, has the potential to expand on the perspectives of patients,

The findings of the review raise awareness of the benefits possible from embedding pharmacists into models of care, for primary care prescribers such as GPs and for leaders in primary care organisations, to utilise their expertise in opioid medicine management. Fundamental actions to support opioid stewardship are to promote leadership commitment, implement policies, advance knowledge and practice, enhance patient engagement, monitor performance data, establish accountability, and support community collaboration.[110,111] Several strategies identified in the review, although individually successful, were implemented in isolation, suggesting that further reductions in adverse clinical outcomes could be realised with collaborative or coordinated efforts, such as opioid stewardship.

Acknowledgment

The authors acknowledge the assistance and guidance of Dr Yulia Ulyannikova, University of Sydney Academic Liaison Librarian of Sydney Pharmacy School, for assistance in formulation of the database search strategy.

Conflicts of Interest

The authors have no conflicts of interest to report.

Funding

The primary author is a recipient of a University of Sydney Research Training Program Stipend.

References

1. Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty−five years of prescription opioid use in Australia: a whole−of−population analysis using pharmaceutical claims. *Br J Clin Pharmacol.* 2016;82(1):255-267.
2. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. *Pain.* Dec 2013;154 Suppl 1:S94-100. doi: 10.1016/j.pain.2013.09.009.
3. Daveluy A, Micallef J, Sanchez-Pena P, et al. Ten-year trend of opioid and nonopioid analgesic use in the French adult population. *Br J Clin Pharmacol.* Jun 4 2020. doi: 10.1111/bcp.14415.
4. Campbell G, Lintzeris N, Gisev N, Larance B, Pearson S, Degenhardt L. Regulatory and other responses to the pharmaceutical opioid problem. *Med J Aust.* Jan 2019;210(1):6-8 e1. doi: 10.5694/mja2.12047.
5. Mathieson S, Wertheimer G, Maher C, 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(5):458-474.
6. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA.* Dec 18 2018;320(23):2448-2460. doi: 10.1001/jama.2018.18472.
7. Els C, Jackson TD, Hagtvedt R, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* Oct 30 2017;10(10):CD012299. doi: 10.1002/14651858.CD012299.pub2.
8. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *European Journal of Pain.* 2014;18(9):1343-1351. doi: 10.1002/j.1532-2149.2014.496.x.
9. Bennett F, Ferner R, Sofat R. Overprescribing and rational therapeutics: Barriers to change and opportunities to improve. *Br J Clin Pharmacol.* Mar 26 2020. doi: 10.1111/bcp.14291.
10. Lalic S, Ilomäki J, Bell JS, Korhonen MJ, Gisev N. Prevalence and incidence of prescription opioid analgesic use in Australia. *Br J Clin Pharmacol.* 2019;85(1):202-215.
11. Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of Opioids by Different Types of Medicare Prescribers. *JAMA Intern Med.* Feb 2016;176(2):259-261. doi: 10.1001/jamainternmed.2015.6662.
12. Kimber J, Hickman M, Strang J, Thomas K, Hutchinson S. Rising opioid-related deaths in England and Scotland must be recognised as a public health crisis. *The lancet Psychiatry.* 2019;6(8):639.
13. Ayoo K, Mikhaeil J, Huang A, Wasowicz M. The opioid crisis in North America: facts and future lessons for Europe. *Anaesthesiol Intensive Ther.* 2020;52(2):139-147. doi: 10.5114/ait.2020.94756.
14. European Monitoring Centre for Drugs and Drug Addiction (2019). European drug report 2019: trends and developments. Luxembourg: Publications Office of the European Union; 2019.
15. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: Extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug Alcohol Rev.* 2011;30(3):236-245. doi: 10.1111/j.1465-3362.2010.00283.x.

16. Lovegrove MC, Dowell D, Geller AI, et al. US emergency department visits for acute harms from prescription opioid use, 2016–2017. *American journal of public health*. 2019;109(5):784-791.

17. Lalic S, Jokanovic N, Ilomäki J, et al. Harms associated with extramedical use of prescription opioid analgesics in Australia: A scoping review. *Research in social and administrative pharmacy*. 2019;15(8):925-935.

18. Harned M, Sloan P. Safety concerns with long-term opioid use. *Expert Opinion on Drug Safety*. 2016;15(7):955-962.

19. Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. May 2019;23(5):908-922. doi: 10.1002/ejp.1357.

20. Bialas P, Maier C, Klose P, Häuser W. Efficacy and harms of long–term opioid therapy in chronic non–cancer pain: Systematic review and meta–analysis of open–label extension trials with a study duration≥ 26 weeks. *European Journal of Pain*. 2020;24(2):265-278.

21. Higgins C, Smith BH, Matthews K. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. *Br J Anaesth*. Jun 2019;122(6):e114-e126. doi: 10.1016/j.bja.2018.09.019.

22. Penington Institute (2020). *Australia's Annual Overdose Report 2020*. Melbourne Penington Institute.

23. Chan WL, Wood DM, Dargan PI. Prescription medicine misuse in the Asia-Pacific Region: an evolving issue? *Br J Clin Pharmacol*. Nov 3 2020. doi: 10.1111/bcp.14638.

24. Cairns R, Schaffer AL, Brown JA, Pearson SA, Buckley NA. Codeine use and harms in Australia: evaluating the effects of re–scheduling. *Addiction*. 2020;115(3):451-459.

25. Harris K, Jiang A, Knoeckel R, Isoardi KZ. Rescheduling codeine-containing analgesics reduced codeine-related hospital presentations. *Med J Aust*. Apr 2020;212(7):328. doi: 10.5694/mja2.50400.

26. Finley EP, Garcia A, Rosen K, McGeary D, Pugh MJ, Potter JS. Evaluating the impact of prescription drug monitoring program implementation: a scoping review. *BMC Health Serv Res*. Jun 20 2017;17(1):420. doi: 10.1186/s12913-017-2354-5.

27. Vojtila L, Pang M, Goldman B, Kurdyak P, Fischer B. Non-medical opioid use, harms, and interventions in Canada–a 10-year update on an unprecedented substance use-related public health crisis. *Drugs: Education, Prevention and Policy*. 2020;27(2):118-122.

28. Davis MT, Bateman B, Avorn J. Educational outreach to opioid prescribers: the case for academic detailing. *Pain Physician*. 2017;20(2s):S147-Ss151.

29. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624-1645.

30. Williams R, Keers R, Gude WT, et al. SMASH! The Salford medication safety dashboard. *J Innov Health Inform*. Oct 18 2018;25(3):183-193. doi: 10.14236/jhi.v25i3.1015.

31. Anderson C, Zhan K, Boyd M, Mann C. The role of pharmacists in general practice: A realist review. *Res Social Adm Pharm*. Apr 2019;15(4):338-345. doi: 10.1016/j.sapharm.2018.06.001.

32. Tan EC, Stewart K, Elliott RA, George J. Pharmacist services provided in general practice clinics: a systematic review and meta-analysis. *Res Social Adm Pharm*. Jul-Aug 2014;10(4):608-622. doi: 10.1016/j.sapharm.2013.08.006.

33. Hayhoe B, Cespedes JA, Foley K, Majeed A, Ruzangi J, Greenfield G. Impact of integrating pharmacists into primary care teams on health systems indicators: a systematic review. *Br J Gen Pract*. Oct 2019;69(687):e665-e674. doi: 10.3399/bjgp19X705461.

34. Hazen ACM, de Bont AA, Boelman L, et al. The degree of integration of non-dispensing pharmacists in primary care practice and the impact on health outcomes: A systematic review. *Res Social Adm Pharm*. Mar 2018;14(3):228-240. doi: 10.1016/j.sapharm.2017.04.014.

35. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. Oct 2 2018;169(7):467-473. doi: 10.7326/M18-0850.

36. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med*. 2009;6(7):e1000097.

37. Jacobs SC, Son EK, Tat C, Chiao P, Dulay M, Ludwig A. Implementing an opioid risk assessment telephone clinic: Outcomes from a pharmacist-led initiative in a large Veterans Health Administration primary care clinic, December 15, 2014-March 31, 2015. *Subst Abus*. 2016;37(1):15-19. doi: 10.1080/08897077.2015.1129527.

38. Jensen AN, Beam CM, Douglass AR, Brabson JE, Colvard M, Bean J. Description of a pharmacist-led clinical video telehealth group clinic for opioid overdose prevention and naloxone education. *Ment Health Clin*. Jul 2019;9(4):294-297. doi: 10.9740/mhc.2019.07.294.

39. Pauly J, Vartan C, Brooks A. Implementation and evaluation of an opioid overdose education and naloxone distribution (OEND) program at a Veterans Affairs Medical Center. *Subst Abus*. 2018;39(2):206-210. doi: 10.1080/08897077.2018.1449174.

40. 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 Qual*. Apr 2020;9(2). doi: 10.1136/bmjoq-2019-000635.

41. Cariveau D, Fay AE, Baker D, Fagan EB, Wilson CG. Evaluation of a pharmacist-led naloxone coprescribing program in primary care. *J Am Pharm Assoc (2003)*. Nov - Dec 2019;59(6):867-871. doi: 10.1016/j.japh.2019.07.012.

42. 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*. February 2006;23(1):46-52.

43. Tewell R, Edgerton L, Kyle E. Establishment of a pharmacist-led service for patients at high risk for opioid overdose. *Am J Health Syst Pharm*. Mar 15 2018;75(6):376-383. doi: 10.2146/ajhp170294.

44. Wilson CG, Rodriguez F, Carrington AC, Fagan EB. Development of a targeted naloxone coprescribing program in a primary care practice. *J Am Pharm Assoc (2003)*. Mar - Apr 2017;57(2S):S130-S134. doi: 10.1016/j.japh.2016.12.076.

45. Norman JL, Kroehl ME, Lam HM, et al. Implementation of a pharmacist-managed clinic for patients with chronic nonmalignant pain. *Am J Health Syst Pharm*. Aug 15 2017;74(16):1229-1235. doi: 10.2146/ajhp160294.

46. Weidman-Evans E, Jacobs TF, Isherwood P, Evans JD, Jenkins T. Impact of a pharmacist-developed protocol on the cardiac monitoring of methadone in chronic noncancer pain management. *J Am Pharm Assoc (2003)*. Jul 21 2009:e102-e109. doi: 10.1331/JAPhA.2009.08149.

47. Coffey CP, Ulbrich TR, Baughman K, Awad MH. The effect of an interprofessional pain service on nonmalignant pain control. *Am J Health Syst Pharm*. May 17 2019;76(Supplement_2):S49-S54. doi: 10.1093/ajhp/zxy084.

48. Harden P, Ahmed S, Ang K, Wiedemer N. Clinical Implications of Tapering Chronic Opioids in a Veteran Population. *Pain Med*. Oct 2015;16(10):1975-1981. doi: 10.1111/pme.12812.

49. Valgus J, Jarr S, Schwartz R, Rice M, Bernard SA. Pharmacist-led, interdisciplinary model for delivery of supportive care in the ambulatory cancer clinic setting. *J Oncol Pract*. Nov 2010;6(6):e1-4. doi: 10.1200/JOP.2010.000033.

50. 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(11):1170-1177.

51. 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 Serv Res*. Jan 13 2005;5(1):3. doi: 10.1186/1472-6963-5-3.

52. Downes JM, Klepser DG, Foster J, Nelson M. Development of a standardized approach for managing opioids in adults with chronic noncancer pain. *Am J Health Syst Pharm*. Mar 1 2018;75(5):321-326. doi: 10.2146/ajhp161012.

53. Miller DM, Harvey TL. Pharmacist pain e-consults that result in a therapy change. *Federal Practitioner*. 2015;32(7):14.

54. Seal KH, Rife T, Li Y, Gibson C, Tighe J. Opioid Reduction and Risk Mitigation in VA Primary Care: Outcomes from the Integrated Pain Team Initiative. *J Gen Intern Med*. Apr 2020;35(4):1238-1244. doi: 10.1007/s11606-019-05572-9.

55. Westanmo A, Marshall P, Jones E, Burns K, Krebs EE. Opioid Dose Reduction in a VA Health Care System--Implementation of a Primary Care Population-Level Initiative. *Pain Med*. May 2015;16(5):1019-1026. doi: 10.1111/pme.12699.

56. Cox N, Tak CR, Cochella SE, Leishman E, Gunning K. Impact of Pharmacist Previsit Input to Providers on Chronic Opioid Prescribing Safety. *J Am Board Fam Med*. Jan-Feb 2018;31(1):105-112. doi: 10.3122/jabfm.2018.01.170210.

57. Shah NR, Haddad-Lacle J, Hogan T. Successful interventions in decreasing oxycodone CR prescriptions within an underserved population. *J Opioid Manag*. Nov-Dec 2015;11(6):481-488. doi: 10.5055/jom.2015.0301.

58. Bauters TG, Devulder J, Robays H. Clinical pharmacy in a multidisciplinar team for chronic pain in adults. *Acta Clin Belg*. Jul-Aug 2008;63(4):247-250. doi: 10.1179/acb.2008.045.

59. Semerjian M, Durham MJ, Mirzaian E, Lou M, Richeimer SH. Clinical Pharmacy Services in a Multidisciplinary Specialty Pain Clinic. *Pain Pract*. Mar 2019;19(3):303-309. doi: 10.1111/papr.12745.

60. Bourgeois HC, Proteau RC, Vielma CV, Hartung DM, Irwin AN. Evaluation of an Interdisciplinary Controlled Substance Review Committee on Opioid Prescribing in a Community Health Center. *Pain Med*. Sep 1 2020;21(9):1840-1846. doi: 10.1093/pm/pnaa075.

61. Homsted FAE, Magee CE, Nesin N. Population health management in a small health system: Impact of controlled substance stewardship in a patient-centered medical home. *Am J Health Syst Pharm*. Sep 15 2017;74(18):1468-1475. doi: 10.2146/ajhp161032.

62. Gernant SA, Bastien R, Lai A. Development and evaluation of a multidisciplinary controlled substances committee within a patient-centered medical home. *J Am Pharm Assoc (2003)*. Nov-Dec 2015;55(6):656-663. doi: 10.1331/JAPhA.2015.14257.

63. Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. *J Eval Clin Pract*. Dec 2017;23(6):1173-1179. doi: 10.1111/jep.12756.

64. Gagnon L, Fairchild A, Pituskin E, Dutka J, Chambers C. Optimizing pain relief in a specialized outpatient palliative radiotherapy clinic: contributions of a clinical pharmacist. *J Oncol Pharm Pract*. Mar 2012;18(1):76-83. doi: 10.1177/1078155211402104.

65. Ma JD, Tran V, Chan C, Mitchell WM, Atayee RS. Retrospective analysis of pharmacist interventions in an ambulatory palliative care practice. *J Oncol Pharm Pract*. Dec 2016;22(6):757-765. doi: 10.1177/1078155215607089.

66. DiPaula BA, Menachery E. Physician-pharmacist collaborative care model for buprenorphine-maintained opioid-dependent patients. *J Am Pharm Assoc (2003)*. Mar-Apr 2015;55(2):187-192. doi: 10.1331/JAPhA.2015.14177.

67. Lagisetty P, Smith A, Antoku D, et al. A physician-pharmacist collaborative care model to prevent opioid misuse. *Am J Health Syst Pharm*. May 7 2020;77(10):771-780. doi: 10.1093/ajhp/zxaa060.

68. Suzuki J, Matthews ML, Brick D, et al. Implementation of a collaborative care management program with buprenorphine in primary care: A comparison between opioid-dependent patients and patients with chronic pain using opioids nonmedically. *Journal of Opioid Management*. May-June 2014;10(3):159-168.

69. Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med*. Oct-Nov 2007;8(7):573-584. doi: 10.1111/j.1526-4637.2006.00254.x.

70. Atayee RS, Best BM, Daniels CE. Development of an ambulatory palliative care pharmacist practice. *J Palliat Med*. Oct 2008;11(8):1077-1082. doi: 10.1089/jpm.2008.0023.

71. Stewart A, Zborovancik KJ, Stiely KL. The impact of pharmacy services on opioid prescribing in dental practice. *J Am Pharm Assoc (2003)*. Mar - Apr 2017;57(2S):S78-S82. doi: 10.1016/j.japh.2017.01.010.

72. Shayegani R, Pugh MJ, Kazanis W, Wilkening GL. Reducing coprescriptions of benzodiazepines and opioids in a veteran population. *Am J Manag Care*. Aug 1 2018;24(8):e265-e269.

73. Bhimji H, Landry E, Jorgenson D. Impact of pharmacist-led medication assessments on opioid utilization. *Can Pharm J (Ott)*. May-Jun 2020;153(3):148-152. doi: 10.1177/1715163520908285.

74. Cochran G, Chen Q, Field C, et al. A community pharmacy-led intervention for opioid medication misuse: A small-scale randomized clinical trial. *Drug Alcohol Depend*. Dec 1 2019;205:107570. doi: 10.1016/j.drugalcdep.2019.107570.

75. Luchen GG, Prohaska ES, Ruisinger JF, Melton BL. Impact of community pharmacist intervention on concurrent benzodiazepine and opioid prescribing patterns. *J Am Pharm Assoc (2003)*. Mar - Apr 2019;59(2):238-242. doi: 10.1016/j.japh.2018.10.010.

76. Qureshi N, Wesolowicz LA, Liu CM, Tungol Lin A. Effectiveness of a Retrospective Drug Utilization Review on Potentially Unsafe Opioid and Central Nervous System Combination

Therapy. *J Manag Care Spec Pharm*. Oct 2015;21(10):938-944. doi: 10.18553/jmcp.2015.21.10.938.

77. Bingham JM, Taylor AM, Boesen KP, Axon DR. Preliminary Investigation of Pharmacist-Delivered, Direct-to-Provider Interventions to Reduce Co-Prescribing of Opioids and Benzodiazepines among a Medicare Population. *Pharmacy*. 2020;8(1):25.
78. Watson A, Guay K, Ribis D. Assessing the impact of clinical pharmacists on naloxone coprescribing in the primary care setting. *Am J Health Syst Pharm*. Mar 24 2020;77(7):568-573. doi: 10.1093/ajhp/zxaa007.
79. Hill D, Marr E, Smith C. Development of Pharmacist Independent Prescribing Clinics to Treat Opioid Analgesic Dependence in NHS Lanarkshire. *Pharmacy (Basel)*. Aug 22 2019;7(3):22. doi: 10.3390/pharmacy7030119.
80. Patel JN, Boselli D, Hamadeh IS, et al. Pain Management Using Clinical Pharmacy Assessments With and Without Pharmacogenomics in an Oncology Palliative Medicine Clinic. *JCO Oncol Pract*. Feb 2020;16(2):e166-e174. doi: 10.1200/JOP.19.00206.
81. Manzur V, Mirzaian E, Huynh T, et al. Implementation and assessment of a pilot, community pharmacy-based, opioid pain medication management program. *J Am Pharm Assoc (2003)*. May - Jun 2020;60(3):497-502. doi: 10.1016/j.japh.2019.11.029.
82. Bounthavong M, Devine EB, Christopher MLD, Harvey MA, Veenstra DL, Basu A. Implementation evaluation of academic detailing on naloxone prescribing trends at the United States Veterans Health Administration. *Health Serv Res*. Oct 2019;54(5):1055-1064. doi: 10.1111/1475-6773.13194.
83. Larson MJ, Browne C, Nikitin RV, et al. Physicians report adopting safer opioid prescribing behaviors after academic detailing intervention. *Subst Abus*. 2018;39(2):218-224. doi: 10.1080/08897077.2018.1449175.
84. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf*. Jun 2016;25(6):733-737. doi: 10.1002/pds.3945.
85. Kuntz JL, Schneider JL, Firemark AJ, et al. A Pharmacist-Led Program to Taper Opioid Use at Kaiser Permanente Northwest: Rationale, Design, and Evaluation. *The Permanente Journal*. 2020;24.
86. Institute of Safe Medication Practices Canada. Definition of terms. https://www.ismp-canada.org/definitions.htm#:~:text=Medication%20Management%3A,and%20their%20health%20care%20teams. Published 2012. Accessed 25th November, 2020.
87. Stevens J, Trimboli A, Samios P, et al. A sustainable method to reduce postoperative oxycodone discharge prescribing in a metropolitan tertiary referral hospital. *Anaesthesia*. Mar 2019;74(3):292-299. doi: 10.1111/anae.14570.
88. Hopkins RE, Bui T, Magliano D, Arnold C, Dooley M. Prescriber Education Interventions to Optimize Opioid Prescribing in Acute Care: A Systematic Review. *Pain Physician*. Nov 2019;22(6):E551-E562.
89. Bui T, Grygiel R, Konstantatos A, et al. The impact of an innovative pharmacist-led inpatient opioid de-escalation intervention in post-operative orthopedic patients. *J Opioid Manag*. May/Jun 2020;16(3):167-176. doi: 10.5055/jom.2020.0565.
90. Poirier RH, Brown CS, Baggenstos YT, et al. Impact of a pharmacist-directed pain management service on inpatient opioid use, pain control, and patient safety. *Am J Health Syst Pharm*. Jan 1 2019;76(1):17-25. doi: 10.1093/ajhp/zxy003.

91. Hopkins RE, Bui T, Konstantatos AH, et al. Educating junior doctors and pharmacists to reduce discharge prescribing of opioids for surgical patients: a cluster randomised controlled trial. *Med J Aust*. Nov 2020;213(9):417-423. doi: 10.5694/mja2.50812.

92. Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. *Ann Intern Med*. 2017;167(3):181-191.

93. Fishbain DA, Pulikal A. Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review. *Pain Medicine*. 2018;20(11):2179-2197. doi: 10.1093/pm/pny231.

94. Eccleston C, Fisher E, Thomas KH, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database of Systematic Reviews*. 2017. doi: 10.1002/14651858.cd010323.pub3.

95. Craig DS. The pharmacists' role in patient–provider pain management treatment agreements. *J Pharm Pract*. 2012;25(5):510-516.

96. McAuliffe Staehler TM, Palombi LC. Beneficial opioid management strategies: A review of the evidence for the use of opioid treatment agreements. *Substance Abuse*. 2020;41(2):208-215. doi: 10.1080/08897077.2019.1692122.

97. Stonington S, Coffa D. Structural Iatrogenesis—A 43-Year-Old Man with "Opioid Misuse". *New England Journal of Medicine*. 2019;380(8):701-704.

98. Jauncey ME, Nielsen S. Community use of naloxone for opioid overdose. *Australian Prescriber*. 2017;40(4):137.

99. Behar E, Bagnulo R, Coffin PO. Acceptability and feasibility of naloxone prescribing in primary care settings: A systematic review. *Prev Med*. 2018;114:79-87. doi: 10.1016/j.ypmed.2018.06.005.

100. Rudolph SE, Branham AR, Rhodes LA, Hayes HH, Moose JS, Marciniak MW. Identifying barriers to dispensing naloxone: A survey of community pharmacists in North Carolina. *J Am Pharm Assoc (2003)*. 2018;58(4):S55-S58.e53. doi: 10.1016/j.japh.2018.04.025.

101. Nielsen S, Olson A. Using the Behaviour Change Wheel to understand and address barriers to pharmacy naloxone supply in Australia. *Int J Drug Policy*. 2020;in press.

102. Nielsen S, Peacock A, Lintzeris N, Bruno R, Larance B, Degenhardt L. Knowledge of opioid overdose and attitudes to supply of take-home naloxone among people with chronic noncancer pain prescribed opioids. *Pain Medicine*. 2018;19(3):533-540.

103. Lintzeris N, Santo Jr T, Nielsen S, Degenhardt L, Campbell G. Estimating Centre for Disease Control and Prevention-defined overdose risk in people prescribed opioids for chronic non-cancer pain: implications for take-home naloxone provision. *Intern Med J*. 2019;49(8):1054-1055. doi: 10.1111/imj.14386.

104. Le P-P, Braunack-Mayer A, Laurence C. Collaborative pharmacist prescribing within the opioid substitution treatment program in South Australia: Patient and pharmacist views. *Research in Social and Administrative Pharmacy*. 2018;14(2):187-195. doi: 10.1016/j.sapharm.2017.02.017.

105. Teoh L. Editorial: Opioid prescribing in dentistry – is there a problem? *Australian Prescriber*. 2020;43(5):144-145. doi: 10.18773/austprescr.2020.056.

106. Teoh L, Stewart K, Marino RJ, McCullough MJ. Improvement of dental prescribing practices using education and a prescribing tool: A pilot intervention study. *Br J Clin Pharmacol*. May 20 2020. doi: 10.1111/bcp.14373.

107. Ardeljan LD, Waldfogel JM, Bicket MC, et al. Current state of opioid stewardship. *Am J Health Syst Pharm*. Apr 1 2020;77(8):636-643. doi: 10.1093/ajhp/zxaa027.

108. Perrone J, Weiner SG, Nelson LS. Stewarding recovery from the opioid crisis through health system initiatives. *Western Journal of Emergency Medicine*. 2019;20(2):198.

109. Schug SA. Opioid stewardship can reduce inappropriate prescribing of opioids at hospital discharge. *The Medical Journal of Australia*. 2020;213(9):409-410.

110. National Quality Forum. National Quality Partners. https://www.qualityforum.org/National_Quality_Partners.aspx. Published 2020. Accessed 18th September 2020.

111. Sandbrink F, Uppal R. The time for opioid stewardship is now. *Jt Comm J Qual Patient Saf*. 2019;45(1):1-2.

112. Parliament of Victoria. Law Reform Road and Community Safety Committee: Inquiry into drug law reform. https://www.parliament.vic.gov.au/file_uploads/LRRCSC_58-03_Full_Report_Text_WEB_XQB31XDL.pdf. Published 2018.

113. *Australian Medicines Handbook 2020 (online)*. Adelaide: Australian Medicines Handbook Pty Ltd; ; 2020 July.

114. Joint Formulary Committee (2019). *BNF 74: September 2017-March 2018*. London: Pharmaceutical Press.

Table 1: Eligibility criteria for study inclusion

Date of publication	January 2001 until July, 2020
Language of publication	English
Age of participants	No age restriction
Indication for opioid	Opioids prescribed for any pain, such as cancer or malignancy-related, chronic non-cancer (malignant) pain (CNCP), end-of-life and palliative care, and acute or post-trauma pain were included, as were opioids for opioid use disorder.
Opioids included	All opioids listed in the Australian Medicines Handbook 2020[113] and the British National Formulary 2019[114] were included as text-words
Primary care settings	Ambulatory outpatient, primary care or general practice locations, including residential, aged or long-term care facilities; that is, any location in which the care was not provided to hospital inpatients.
Study participants	Patients of primary care settings; healthcare professionals
Study designs	Quantitative (experimental, quasi-experimental, observational) and those with a quantitative component of a mixed-methods study.

Table 2:Study characteristics and outcomes

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
A. General or family medicine practice and primary care clinics				
Atayee RS et al,[70] 2008 US	Establishment of a model for ambulatory care palliative care pharmacist; prospective.	Outpatient adult palliative care clinic with collaborative practice model of care in opioid dose titration and symptom management	n = 29 mean age = 49 (range, 20–78).	1. 114 pharmacist consultations for 29 patients; 93% referrals were for pain management; 98% (112/114) recommendations accepted 2. >80% physicians found pharmacist management of pain and symptoms useful
Bauters TG et al,[58] 2008 Belgium	Prospective, single site;	Adults with CNCP referred to multidisciplinary outpatient centre for chronic pain	n=93	1. Interventions involving analgesics by team pharmacist: increase, decrease dose; commenced or cease 2. Acceptance by physicians: 55%
Boren LL et al,[50] 2019 US	Retrospective chart review; controlled study	Adults with CNCP; outpatient physical medicine and rehabilitation clinic with team-based model of care with collaborative drug therapy agreement (≥2 pharmacist visits/year); control group prior to pharmacist access	n = 383 (1072 pharmacist visits) mean age = 52.7 ±12.5	1. Clinically significant changes in oMED - oMED decreased after patients had ≥5 pharmacist visits: average decrease of 270 mg; - for patient cohort with oMED > 500 mg, decrease in mean oMED to 925 mg compared to 1250 mg for control, 2. non-opioids initiated in 209 (20%) visits 3. urine drug screening compliance increased (54% v 84%) p < 0.001 4. signed patient-agreements increased (27% v 67%) p < 0.001 5. physician availability for patients increased as 2 patient visits/year was transitioned to pharmacist
Chelminski PR et al,[51] 2005 US	Pre-test/ post-test	Adults with CNCP either receiving or being considered for opioid therapy referred to multidisciplinary pain management program in primary care clinic	n = 85 mean age = 51 60% = male 93% receiving opioids 32% identified with substance misuse	Pain, function and mood assessed at baseline compared to 3 months, for63 (73%) patients, by Brief Pain Inventory, Pain Disability Index (PDI), Center for Epidemiological Studies-Depression (CESD) scale Baseline mean scores / 3-month follow-up mean scores pain = 6.5 / pain = 5.5 (p = 0.003) PDI = 47 / PDI 39.3 (p < 0.001) CESD = 24 / CESD = 18.0 (p < 0.001) Proportion depression: 79% / Proportion depression: 54% (p = 0.003)
Cariveau D et al,[41] 2019 US	Single site pre- and post-intervention study	Adults with CNCP identified by embedded practice pharmacist as at risk of opioid overdose	n = 234	After provider and patient education: 1. THN prescribing increased from 3.4% at baseline to 37.2% (p = 0.0001) 2. 31% THN prescriptions filled
Cox N et al,[56] 2018 US	Pre-intervention/ post-intervention comparison	Family medicine multidisciplinary clinic; Pharmacist review of medication regimens of adults with CNCP prescribed opioids, prior to appointment with PCP	n = 45 female 49%	Comparison of baseline and 4-month data: 1. Significant reduction in mean oMED (SD) calculated from prescription directions (151 mg (110) v 125 mg (114) p<0.001; 17% reduction) and of amount prescribed amount prescribed (135 mg (100) v 116 mg (106) p< 0.001; 14% reduction) 2. Mean (SD) pain scores for 27 with documentation: 5.3 (2.6) v 5.5 (2.5) p=0.783

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
A. General or family medicine practice and primary care clinics (continued)				
DiPaula BA et al,[66] 2015 US	Retrospective review of quantitative results for patients enrolled and remaining at 1 year	Suburban health clinic; physician and pharmacist buprenorphine/naloxone maintenance collaborative care model practice; uninsured adults with opioid use disorder	n =12 patients mean age = 30 years range, 22–41 Male: 92%	1. Patients attended mean of 11 appointments (range, 2–25); 91% routine appointment attendance 2. Percentage retention in pilot at 12 months: 73% retention 3. Urine toxicology: 88% urine negative for opioids, positive for buprenorphine 4. 50% patients progressed from weekly to monthly screening 5. Estimated cost savings of program compared to previous care (provided by contracted physicians): $22,000 6. Pilot data used to develop permanent physician–pharmacist program and the first state-approved opioid use disorder drug therapy management protocol
Downes JM et al,[52] 2018 US	Quantitative evaluation of system changes; comparison pre/post-intervention (CNCP protocol)	Primary care, multidisciplinary clinic; included nurse practitioners, pharmacists Patients with CNCP receiving opioid/s > 3 months, identified by pharmacists using electronic extraction of records	n = 220 (in 2015) n = 123 (in 2016)	Comparison of before (2015) and after (2016): 1. Adherence to chronic pain protocol updated by pharmacist and physician - 23% increase in pain agreements ($p < 0.001$), - Patients who had a urine drug screen during 12- month period increased by 18.3% ($p = 0.0016$). - Percentage of patients above oMED threshold (according to prescriber status): 6% decreased to 5% (NS) 2. Percentage of patients prescribed long-term opioids: 97 fewer in 2016; 88% reduction by nurse practitioners
Gagnon L et al,[64] 2012 Canada	Prospective analysis; pre-intervention/ post-intervention comparison	Adult patients in outpatient palliative radiotherapy clinic; introduction of pharmacist-patient appointments on opioid and symptom management	n = 114 Median age = 68.3 years, 68% were male	1. Pharmacist contributions to management over 2 years: initial pain and symptom assessment tools; medication history; opioid toxicity screen; oMED calculation; therapeutic interventions; communication with community resources; referrals recommendations; telephone follow-up 2. Median baseline pain score was 6/10 (SD 2.6); and 2.1/10 (SD 2.4) by week 4 3. Mean oMED baseline = 76.8 mg; 44.5 mg at week 4.
Hill D et al,[79] 2019 Scotland	Description of development and implementation of service model; pharmacist recommendations; quantitative analysis of case series results	Two Pharmacist Independent Prescribers (PIP) in 2 general practices Adults with opioid CNCP prescribed long-term opioids and with opioid dependence: referred by GPs or identified by risk-assessment tool.	n = 240 (PIP 1) n = 225 (PIP2)	1. Service model development and implementation described, 2. Narrative of pharmacist recommendations and rationale 3. Graphical depiction of reduction in longitudinal prescribing patterns for targeted opioids and other opioids, at local population level.

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
A. General or family medicine practice and primary care clinics (continued)				
Jacobs SC et al,[37] 2016 US	Retrospective review of pilot study data; statistical comparison of pre- and post-study data	Clinical pharmacist telephone risk-assessment clinic and consultative service; 5 pilot primary care clinic providers; adults with CNCP receiving opioids > 90days	n = 148 patients assigned to pilot; mean age = 64 years; 146 (98%) male	1. 447 pharmacist assessments of 148 patients with recommendations (communication between pain pharmacists and providers via telephone, medical record alerts, e-mail, instant messaging) for opioid and pain management: - 61 of 66 individual recommendations accepted (92%) for opioids; additional 30 recommendations for pain management; chronic opioid therapy discontinued in 14 (9.5%) patients during pilot 2. Significant increases in rates of annual urine testing, opioid informed consents, prescription monitoring. 3. Non-significant increase in cardiac monitoring (methadone patients)
Jensen AN et al,[38] 2019 US	Single-centre, prospective descriptive analysis	Adults at high-risk of overdose; pharmacist-led clinical video telehealth (CVT) clinics for remote or on-site attendance; pharmacists embedded in central community-based outpatient clinics	n = 84 (CVT clinic) n = 313 (non-CVT clinic) mean age = 57 94% male	1. Clinic pharmacist generated 21% of total THN prescriptions for primary clinic patients (CVT clinic and on-site patients), during 6 months of analysis. Total number of THN prescribers = 82. 2. Patient risk factors identified and THN prescribed by CVT clinic pharmacist: patients with concomitant BZDs more likely to be prescribed THN (69% v 34%, $p < 0.0001$) than those with oMED > 100mg
Lagisetty P et al,[67] 2020 US	Cohort study, mixed methods; quantitative analysis medical record	Adults with CNCP Primary care physicians and medical assistants Two primary care clinics Pharmacist collaborative care model	n = 46 patients mean age = 55.8 years	1. Feasibility and acceptability of pharmacist-based collaborative care model applied to chronic pain amongst primary care providers (PCPs): 74% of pharmacist recommendations had action by PCP (adding or switching pain medication; changing to buprenorphine for complex persistent opioid dependence) 2. Non-significant mean reduction of 7mg oMED (19%) between pre- and post-intervention at 4-month follow-up, without worsening pain ($p = 0.23$) 3. Patients initiated fewer overall health provider visits
Ma JD et al,[65] 2016 US	Retrospective data analysis of model described in [70]	Pharmacist-led outpatient adult palliative care practice in transdisciplinary clinic	n = 84 new patients n = 135 follow-up patients	1. Pharmacist interventions: change in opioid dose; timing, formulation and adjuvant analgesics 2. Patient outcomes (impact on pain score): statistically significant changes in pain score at third visit, but not second or 4th
McDermott ME et al,[42] 2006 Scotland	Quantitative; Prospective; cohort study, single site; pre-test, post-test descriptive statistics	Adults with CNCP in one general practice	n = 132 medication reviews of patient records after completion of pain questionnaire Age-groups: 29–64: 51.4% 65–94: 48.6%; n = 23 subset had face-to-face pharmacist consultation	Feasibility testing of pharmacist-led medication review of patients receiving analgesics, using data extraction from practice records, patient questionnaires and consultations for sub-set 1. 77% of pharmacist recommendations were completely carried out by 6 months review; majority for analgesics 2. No change to patient general or psychological health scores at baseline and 6-month follow-up

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
A. General or family medicine practice and primary care clinics (continued)				
Norman JL et al,[45] 2017 US	Narrative description of development and activities of pharmacist-managed clinic; processes described	Adults with CNCP prescribed opioids ≥ 3 months. Pharmacist-managed chronic pain outpatient clinic integrated into primary care; pharmacists manage patients through collaborative drug therapy management protocol	n = 487 referred; 38% accepted; 53% waiting review	1. Process outcomes: pain referrals & pharmacist activities 2. Patient data collection for 69 patients with initial pharmacist consultations: pain scores, adverse effects, patient-reported functionality, oMED mg, non-opioid changes, recommendations for opioid management, assessments of opioid risk, pain management plans developed
Patel JN et al,[80] 2020 US	Two studies 1.Prospective, observational 2. Subset of study 1: prospective interventional (pharmacogenomic)	Adult oncology patients with uncontrolled pain referred to pharmacy services in outpatient palliative care; pharmacogenomic analysis and analgesic management of subset	Study 1: n = 142 median age = 58 range, 20 to 90; 57% female 85% stage 111-IV 92% ECOG status of 0–2 Study 2: n = 43 (subset)	Study 1 1. proportion of patients achieving clinically significant pain improvement by final visit at 30 days: 53% compared to 30% for historical controls (p = 0.001) 2. proportion of patients with pain score 0 - 3 at baseline, visit 1, 2 and final visit: 14%, 30%, 29%, and 45% (p = 0.001) Study 2 1. No difference in pain improvement between those who did (n = 43) and did not (n = 99) receive pharmacogenomic testing: 56% v 52%; (p = 0.72) 2. Patients with actionable genotype for therapy modification: 15 had actionable genotype - most common actionable gene was CYP2D6 (n = 13 of 15; 87%) resulting in change of opioids 3. pain improvement rate in subset = 73% v 46% of remaining (p = 0.12)
Pauly JB et al,[39] 2018 US	Single site prospective observational study	Adults identified by primary care physicians at high-risk of opioid respiratory depression; pharmacist-led primary care THN education and prescribing clinic	n =243 referrals	1. Patient and caregiver attendances at pharmacist clinic and post-attendance evaluation: education was presented in a way that could be understood (97%) 2. No opioid overdoses during study in sample population 3. 98% THN prescription fills; 14 refills

Semerjian M et al,[59] 2019
US
	Retrospective chart review	Adults with CNCP referred to pharmacists for management in a primary care, multidisciplinary specialty pain clinic	n = 67;
			mean age = 52.2 years;
			66% female
				Pharmacists' data collected:
				1. mean = 5.7 pharmacist appointments /patient
				2. ≥1 problem medication-related problems detected in 99% appointments
				3. Pharmacist interventions: referral to appropriate providers; medication counselling; medication initiation, dose adjustment, discontinuation

Shah NR et al,[57] 2015 US	Prospective interventional study	Underserved, uninsured adults with CNCP at family medicine clinic; pharmacist and physician collaboration in implementation of a pain management protocol and Controlled Substance agreements	Target population > 11,000 (Numbers included in analysis not specified)	3 months after implementation compared to baseline: 1. Number of prescriptions for oxycodone controlled release prescriptions and tablets reduced from 40 to 10/month 2. Number of oxycodone controlled release tablets reduced from 2,500 to 600/month 3. No increase in other opioids analysed

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
A. General or family medicine practice and primary care clinics (continued)				
Shayegani R et al,[72] 2018 US	Retrospective chart review post intervention	Veterans with CNCP receiving combination opioid and BZDs for > 90days from prescribers at any of 5 outpatient suburban community clinics; co-located pharmacist assessment and passive review of electronic records.	n = 61 90% male 79% age > 55 years mean [SD] age = 61 [9] years n = 14 PCPs n = 7 mental health practitioners	1. By 30 days, prescribers': - 48% (n = 29) acknowledgement of pharmacist review - commitment to recommended interventions by initiating taper schedule: 11% (n = 7) prescriptions tapered; 11% (7) reported plans to taper at future visits 2. Mental health providers less likely to provide acknowledgment (p = 0.0215) or initiate taper schedules (p = 0.0410) compared with PCPs
Stewart A et al,[71] 2017 US	Retrospective chart review, comparisons between zero, partial and full pharmacist integration	Adult patients with acute dental pain Free, urban dental clinic with introduction of pharmacy service	n = 89 mean age = 44 years range = 20-69 62% female	1. Opioid prescribing rates with no pharmacist integration (1.8 prescriptions/ 100 dental visits) were significantly reduced with partial integration (0.43 /100 visits), p < 0.001; and full integration (0.34 /100 visits), p < 0.001 2. Dentists were 81% less likely to prescribe opioids during full integration (odds ratio [OR] 0.19, 95% confidence interval [CI] 0.124-0.293; P <0.001) compared to no integration
Suzuki J et al,[68] 2014 US	Prospective, observational comparative study	Opioid-dependent adult patients or chronic pain patients using opioids non-medically referred for buprenorphine; new collaborative care model offered in a primary care clinic; pharmacist as patient's care manager	n = 45	1. At 6 months, 55% remained in treatment 2. Proportion of aberrant urine toxicology decreased significantly from baseline (69.2% vs 31.8%, p<0.01) 3. opioid craving scores significantly decreased (4.1 vs 0.9, p<0.01) 4. Opioid-dependent patients were significantly more likely to complete 6 months of treatment compared to chronic pain patients using opioids nonmedically (70.8% vs 38.0%, p<0.05) 5. Primary care physician's confidence in treating opioid use disorders increased significantly from baseline to 18 months (p<0.01)
Tewell R et al,[43] 2018 US	Single site pre- and post-intervention study; descriptive report of systematic approach to identification of target population	Adults at high risk of opioid-related adverse event in family medicine practice with embedded pharmacist	n = 41	Procurement of THN by patients at high-risk, after identification by pharmacists and counselling increased to 83% post-intervention from 17% prior to the intervention

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
A. General or family medicine practice and primary care clinics (continued)				
Tilli T et al,[40] 2020 Canada	Case control study; Quantitative analysis using descriptive statistics Pre-test post-test	Three primary care clinics with pharmacists embedded: (2 intervention, 1 control); Pharmacists without specialised training in pain or psychiatry. Patients prescribed long-term opioids and co-prescribed BZDs	Intervention: n = 35; mean age 57 (±12.3) Control: n= 20 mean age 60 (±8.4)	1. Pharmacist recommendations acceptance: physicians' (75%); patients' (54%) 2. Intervention cohort: impact of pharmacist-led opioid stewardship, from baseline compared to control Intervention cohort: / Control cohort: 11% reduction in mean oMED mg / 15% increase in mean oMED 8% reduction in mean daily BZD dose / 4% decrease in mean daily BZD dose 66% patients with pharmacist-developed care plans, increased from 20% / Pharmacist care plans < 20% 4-fold increase in active opioid taper / 0% active opioid taper
Valgus J et al,[49] 2010 US	Prospective database review; retrospective chart review	Pharmacist-led, supportive care interdisciplinary outpatient adult palliative cancer care clinic; patients referred from oncology clinics	n = 89 <44 years - 21% 44-59years - 34% ≥60 - 45%	1. Pharmacist reviews: patients seen average 3 visits; 2. 85% patients had a change in opioid choice/ formulation / dose. 3. Patient symptom scores (pain, nausea, constipation): all scores reduced and maintained by third visit
Weidman-Evans E et al,[46] 2009 US	Comparative study, pre-test/post-test	Mainly uninsured adults with CNCP receiving methadone in primary care clinics; pharmacist developed protocol for recognition and cardiac monitoring of patients at high risk of QT prolongation; Pharmacists responsible for implementation on pain management clinic	n = 96 high-risk patients (pre-intervention) n = 100 high-risk patients (post-intervention mean age = 51 years	Overall increase in absolute proportion of electrocardiogram (ECG) monitoring pre- and post-protocol in high-risk patients, by 19%, p = 0.02 (relative increase 136%). No significant change occurred in other clinics
Wiedemer NL et al[69], 2007 US	Naturalistic prospective outcome study; mixed-method evaluation	Adults with CNCP in primary care clinic; implementation of collaborative pharmacist-run prescription management clinic, with nurse practitioner	n = 335 patients referred; 171 for aberrant behaviours 164 – no aberrant behaviours identified n = 35 primary care physicians	1. PCP behavioural change from baseline: - Opioid agreements: 63 at baseline (2001); 144 in 2002; 214 in 2003 - Urine testing increased to average of 200 per month during last 6 months of data collection 2. 171 patients with identified aberrant behaviours: - 45% adhered to agreements; 38% self-discharged; 13% referred for specialist addition treatment; 4% weaned from opioids 3. 164 (without identifed aberrant behaviours): - 100% adhered to opioid agreement
Wilson CG et al,[44] 2017 US	Retrospective, observational	Adults with CNCP at risk of opioid overdose; primary care, family medicine practice with embedded pharmacists	n = 350	1. Implementation of pharmacist-led, targeted THN prescribing program to patients receiving opioids>3 months. Pharmacist education of prescribers, patients and development and implementation of at-risk identification process through algorithm and electronic medical record review 2. 350 patients identified at-risk (oMED > 50mg, 62%; concomitant BZDs, 37%); THN on current regimen

				for 3%

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
B. Healthcare organisation with range of primary care settings				
Bourgeois, HC et al, [60] 2020 US	Retrospective cohort study	Adults with CNCP receiving long-term opioids (1 – 3 formulations), with oMED > 120 mg for at least 3 months Community health centre with interdisciplinary controlled substance committee; recommendations to primary care prescribers at 6 sites. Clinical pharmacists embedded into teams.	n = 94 age = 47 (12)	1. Committee recommendations implemented by PCPs: median: 3 (IQR 2– 5, range 1–8) at 8 months; 50% accepted at 8 months. 2. Patient cohort (n=78) oMED at baseline and at 8 months after review: significant reduction in oMED = 60mg (IQR = 27.5–135 mg, range 5–1,260 mg) at baseline to oMED = 40 mg (IQR = 15–105 mg, range 0–1,260 mg); p < 0.001.
Coffey C et al,[47] 2019 US	Retrospective analysis pre- and post-intervention study Post-study provider acceptance and patient satisfaction	Adults with CNCP prescribed opioids > 3 months in community health centre; Pharmacy-led comprehensive interprofessional non-malignant pain management service	n = 39 Mean age 49.5 years	After pharmacist education session and consultations for medication review 1. Improvement in mean pain score from pre intervention = 8.3/10; post-intervention: 5.6/10 (p < 0.0001). 2. Decrease in mean oMED per patient from 20.5 to 18.1, [NS, (p = 0.3)]. 3. 88% acceptance of pharmacists' opioid recommendations by referring providers 4. Patient satisfaction on follow-up telephone survey (Likert) presented graphically for 7 questions
Homsted FAE et al[61] 2017 US	Narrative and retrospective review of stewardship establishment and activities	Patient-centred medical home in community health centre; implementation of population health management process; i.e., controlled substance stewardship (defined as 'a coordinated effort to promote the appropriate use of controlled substances, improve patient outcomes, reduce misuse and abuse, and decrease patient morbidity and mortality')	N > 1300 prescribed long-term opioids	Impact of multidisciplinary committee: 1. All patients prescribed controlled substances provide informed consent, sign an annual agreement, have random urine screening 2. > 1,300 high-risk patients (>100 mg oMED) referrals and reviews: patients receiving long-term opioids decreased by 67%; 66% decrease in number of patients receiving BZDs; premature deaths decreased by 50%
Gernant SA et al,[62] 2015 US	Narrative and retrospective review of committee establishment and activities	The Controlled Substances Initiative Committee (pharmacists and prescribers) in a patient-centred medical home and accountable care organisation; adults prescribed opioids	n = 93	1. Workflow processes established & described 2. Prescribers implemented 76% of 78 committee's recommended dose reductions at 3 months; 3. Opioids completely ceased for 32% patients; oMED for patients with recommended dose reductions was 175.5 ± 344.3 mg at 3 months compared to baseline 292.7 ± 466.5 mg; p < 0.05; 4% patients had increased oMED, mean = 26.5 ± 14.0 mg per day 4. NS difference in premature mortality rates pre- and post-intervention
Harden P et al[48] 2015 US	Retrospective and prospective chart review.	Adults with CNCP prescribed opioids > 90 days with agreed plans to collaboratively taper opioids; collated patients from primary care, pain service or pharmacist-run pain management clinics	n = 50 mean age = 54 Range: 25–71	1. Opioid doses reduced on average by 46% at 12 months; 13% patients tapered completely at 12 months; unsuccessful taper 6% 2. 70% patients reported less or no change to pain at 12 months; 30% reported more pain 3. Fewer adjuvants 22%; no change 39%; more adjuvants 39% at 12 months.

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	Context	Sample	Evaluation measures
B. Healthcare organisation with range of primary care settings (continued)				
Losby JL et al[63] 2017 US	Retrospective pre–post evaluation	Adults prescribed opioids; comprehensive system-level strategy in large healthcare organisation; Safe and Appropriate Opioid Prescribing (SAOP) program led by primary care, pain and addiction medicine physicians and pharmacists; prescribers of opioids.	n = 3,203,880	Indicators of SAOP (primary care outcomes not separated from tertiary care) after establishment of systems, education, audit and feedback: - 30% reduction in prescribing high-dose opioids; 98% reduction in supply > 200 pills; 90% decrease opioid combinations with benzodiazepines or carisoprodol; 72% reduction in long acting opioid formulations; no increase in methadone prescribing
Qureshi N et al,[76] 2015 US	Pre-post study after retrospective drug utilisation review and intervention	Adults commercially insured and enrolled in health plan and concurrently prescribed high-dose opioid plus BZD or antidepressant; prescriber-directed intervention developed and reviewed by pharmacists and physicians	n = 980 patients identified n = 734 patient data analysed. n = 671 prescribers (26% family medicine)	1. 528 patients (post-intervention) v 734 pre-intervention prescribed opioid/CNS combinations (28% reduction at 120 days after intervention 2. Prescriber survey response rate 24%; 25% family medicine physicians; 23% responded changes were made to opioid± combination; 71% responded no changes were made
Seal K et al,[54] 2020 US	Multi-site prospective matched cohort study	Veterans with CNCP prescribed opioids in 6 primary care community-based clinics with embedded pharmacists referred to Integrated Pain Team (IPT) for face-to-face or telehealth appointments: interdisciplinary, primary care team (included pain pharmacist) compared to usual primary care.	IPT care: n= 47 mean age = 62.1 (12.4) years Usual care: n = 147 mean age = 62.9 (11.4) years	For IPT patients compared to usual care: 1. Mean oMED at baseline was significantly reduced in the IPT versus usual care by 6 months ($p < 0.03$); 2. All variables of opioid risk mitigation strategies employed (urine screening, THN distribution, BZD co-prescribing) improved compared to usual care; 3. Emergency department (ED) visits reduced compared to usual care
Westanmo A et al,[55] 2015 US	Pre/post intervention comparison of data and survey responses	Adults with CNCP; community based outpatient clinics with embedded pharmacists; prescribers of high-dose opioids (>200mg oMED); population-level opioid safety initiative with pharmacist input.	n = 50,749 unique pharmacy patients	1. Prescribing of all oMEDs at 3 years reduced compared to 3 months prior to intervention 2. Relative percentage reductions in prescribing methadone (47%), long acting formulations of oxycodone (99%), morphine (14%)

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
C. Community pharmacy practice				
Cochran G, et al,[74] 2019 US	Randomised control trial	Adults identified with prescription opioid misuse in point-of-service community pharmacies. Randomised to intervention (pharmacy-based integrated care model with medication counselling/brief motivational interviewing and 8 patient navigation sessions) or standard counselling	n = 34	1. Participants who received intervention reported high level of satisfaction 2. Continued opioid misuse at 3 months: 6.7% (intervention) v 43.8% (standard care), p = 0.02 3. NS improvement in pain scores 2 and 3 months; NS improvement in depression scores; NS changes in cannabis toxicology; NS difference in naloxone prescription fills
Luchen GG et al, [75] 2019 US	Prospective study	Adults with concurrent prescriptions for opioids and benzodiazepines; Community pharmacist-generated communication to primary care providers	n = 13 pharmacies n = 121 patients mean age = 62 (IQR = 52 - 69.5) years 67% female 137 prescribers	1. Communication from prescribers at 4 weeks: 25% responses from prescribers; 59% declined all recommendations; 21% to taper or discontinue opioid/BZD; 6% prescribers discontinued care 2. Changes to regimens at 3 months: 63% opioid/BZD agent tapers/ discontinuation; 26% opioid/BZD dose increases; 6% naloxone prescriptions
Manzur Y et al,[81] 2020 US	Pilot study, descriptive	Adult rheumatology outpatient clinic patients identified at high-risk of opioid adverse event; referred for community pharmacy on-site consultations	n = 11 age range 36 - > 65 91% female	1. Pharmacist assessments: Opioid Risk Tool; prescription monitoring review; mood assessment; pain assessment; Pain, Enjoyment, General Activity (PEG) assessment 2. Recommendations to providers: establish patient-provider opioid agreements; addition of adjuvant therapy (for pain, depression, anxiety, or insomnia); adverse effect management; multidisciplinary engagement; opioid dose de-escalation, and more frequent follow-up

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
D. Outreach service				
Bhimji H et al,[73] 2020 Canada	Retrospective chart audit	Adults with CNCP or migraine taking an opioid referred to pharmacist-run teaching clinic; Clinic not co-located with referring physicians	n = 36 mean age 59.8 years	After pharmacist assessments and follow-up appointments: mean oMED dose reduced by 16.6%, from 129.8 mg/day to 108.2 mg/day (p = 0.043)
Bingham JM et al,[77] 2020 US	Retrospective analysis of prescription claims pre and post intervention, at 1 year	Medication management therapy sponsored program; claims data identified adults co-prescribed opioids and BZDs; pharmacist remote review and recommendations to patients' primary care prescribers via facsimile	n = 57,748 patients < 65 years old = 33% ≥65 years 67% n = 57,746 prescribers	1. Prescriber acceptance of pharmacist recommendations 66%; total reduction in medicines 37,990 (opioids 60%, BZDs 40%) 2. significantly greater percentage of older patients discontinued compared to younger
Bounthavong M et al,[82] 2019 US	Retrospective cohort design; multi-site; one healthcare organisation	VA medical centres and outpatient clinics Academic detailing by clinical pharmacists targeted to prescribers of opioids to at least one veteran at high risk of opioid overdose, to promote THN prescribing	n = 5452 primary care providers in 179 medical centres and 1061 outpatient clinics; mean age = 54.4 (9.5) years	1. increase of THN prescriptions from baseline average of 0.03 per 1000 population at-risk to 5.12 per 1000; increase of THN prescriptions from baseline average of 0.06 per 1000 population at 'high-risk' to 6.31 per 1000 2. 0 to 94 % of providers per site exposed to academic detailing; 27% sites had no exposure 3. Monthly number of THN prescriptions prescribed in the site with 100 % providers received academic detailing had significantly 5.52 times higher incidence rate (95% CI: 1.87, 16.27) compared to a site with 0 % providers exposed.
Larson MJ et al,[83] 2018 US	Single group, pre-post comparison (at 3 months). Quantitative evaluation using web-based survey of academic detailing of 3 key messages by pharmacists delivered in practices.	Veterans Administration community practices Primary care physicians who reported prescribing opioids for CNCP	n = 87 academic detailing sessions n = 68 volunteers followed up	1. 83% adoption of prescription monitoring program 2. significant increase in assessments of patients using a standardised scale to monitor pain intensity and interference with daily functioning; significant increase in urine toxicology screens for patients maintained long-term on opioids.

Table 2: Study characteristics and outcomes (continued)

Citation, year and country	STUDY CHARACTERISTICS			
	Design	**Context**	**Sample**	**Evaluation measures**
D. Outreach service (continued)				
Miller DM et al,[53] 2015 US	Retrospective review	Primary care prescribers in community-based outpatient clinics; patients with CNCP prescribed (or potentially prescribed) opioids; e-pain consults provided by external team including pain pharmacists	n = 122 patients 95% male	1. Recommendations made by pharmacist in pain e-consults during 3-month study period: - discontinue or reduce opioids and BZDs; add and/or change adjunctive analgesics (pharmacological) - laboratory tests, referral to physical and specialty therapies (non-pharmacological) 2. Acceptance rate by physicians that resulted in a change in therapy (50%). Most common accepted: • addition and/or change in anti-epileptic drug therapy and topical therapy; decrease opioid dose.
Watson A et al,[78] 2020 US	Descriptive; Implementation of electronic tool to identify patients at risk of opioid-related adverse event and targeting by pharmacist	Clinical pharmacists in primary care organisation across 7 practice sites. Pharmacist outreach to patients prescribed long-term opioids and at high-risk via telephone, according to pharmacist-implemented algorithm and review	n = 144 determined suitable for pharmacist telephone advice re THN	1. 63 (44%) elligible patients consented to conversation re THN 2. 48 (33%) collected THN after prescribed by pharmacist

Legend

BZD = benzodiazepine
CI = confidence interval
CNCP = chronic, non-cancer pain
GP = General Practitioner
IPT = integrated pain team
IQR = interquartile range
NS = not significant;
NSAID = non-steroidal anti-inflammatory drug
oMED = oral morphine (mg) equivalent, daily dose
PCP = primary care provider
SAOP = safe and appropriate opioid prescribing
THN = take-home naloxone
VA = Veteran Affairs (US)
US = United States

Table 3: Pharmacist activities and models of care in the management of opioids in primary care settings

Focus of activity	Description of pharmacist activity
Opioid load targeted	• Development and implementation of safety initiatives and stewardship models in collaborative interdisciplinary teams[55,60-63] with provision of support for prescribers of high doses[48] • Collaborative development of pain management protocols[52,57] and Controlled Substance agreements[57] • Face-to-face and remote medication review and risk assessment[37,56] care plans and recommendations for risk reduction[40,56] • Opioid dependence targeted through implementation of pharmacist independent prescriber clinics[79] • Provision of direct patient care in collaborative care models[45,50,67]and collaborative prescribing[71] • Initiation of electronic alerts to prescribers in patient records[72] • Supervision of individualised opioid tapers as member of integrated pain management team[54] • Review after prescriber referrals in specialised pain service[47] and pharmacist teaching clinic[73] • Review, risk screening and change to opioid doses, formulations and recommended analgesics for palliative care clinic outpatients[49,64,65]
Symptom management	• Pharmacists as member of population-level opioid safety and pain management initiative, incorporating education, training, and implementation;[55] and controlled substance committee[60] • Review and recommendations in palliative care clinics for management of pain and adverse medication effects, in person [49,64,65] or via phone;[80] including via collaborative practice model of care[70] • Direct patient care in collaborative models of pain management[45,47,59,67] • Medication review and recommendations from community pharmacy practice[81] and non-specialist settings,[56] using data extraction from practice records,[42] and via remote electronic record access[37] • Review and recommendations as pain management pharmacist in specialised pain services;[47,58] including via telehealth,[54] or via electronic consultation[53]
Opioid agreements; urine screening; prescription monitoring programs promoted	• Pharmacists as members of controlled substance committees and safety initiatives, with policy, education and recommendations for uptake[60,62,63] • Facilitated uptake in specialised pain and rehabilitation teams,[50,54] and collaborative pharmacist/ nurse practitioner prescription clinic[69] • Recommendations for uptake after remote review of electronic records[37] or clinic patients[81] • Academic detailing of key messages to promote behaviour changes of prescribers[83]
Take-home naloxone (THN) uptake	• THN targeted as one risk-mitigation measure, as member of integrated pain team, face-to-face or via telehealth[54] • Education of patients identified at-risk and their carers[39] and THN prescribing;[39] including via telephone and CTV outreach[38,78] and from community pharmacy practice[74] • Developed, implemented programs to identify at-risk patients; improved co-prescribing of naloxone[41,43,44,61,81] • Included as a key message of academic detailing to prescribers[82]
Co-prescribing of opioid/ sedatives targeted	• Recommendation from specialist pain services face-to-face or via telehealth,[54] or after electronic consult[53] • Developed care plans and risk reduction recommendations for high-risk patients, as embedded pharmacist[40] • Alerts added to patient records for prescribers after electronic review by co-located pharmacist[72] • Pharmacists as members of controlled substance committees and safety initiatives, with policy, education and recommendations to target combination[60,62,63] • Prescribers of high doses or risky combinations supported to taper doses, through organisation opioid safety initiative[48] • Developed drug utilisation review activity with correspondence to combination prescribers as the intervention[76] • Correspondence to combination prescribers in health systems, via email or facsimile, with recommendations[61,77] • Correspondence to prescribers of combinations from community pharmacy practice[75] • Review and recommendations for high-risk patients identified in community pharmacy practice[81]
Medication-assisted treatment	• Manage patents under collaborative care models in primary care clinics[66-68]

Table 4: Pharmacist activities and models of care in the management of opioids in primary care settings (continued)

Focus of activity	Description of pharmacist activity
Assessment of risk of Opioid Use Disorder or adverse effects	• Pharmacist-led medication review[42] • Pharmacist-led interprofessional non-malignant pain management service[47] • Identification of risk via electronic records and communication to prescribers in team [37,52] or via fascimile[77] • Review by pharmacist independent prescribers after identification by risk-assessment tool and GP referral[79] • Risk-assessment in outpatient palliative care radiotherapy clinic[64] • Developed and implemented protocols and recommendations for cardiac monitoring of high-risk patients receiving methadone[37,46] • Managed patients under collaborative care models and drug therapy management protocols[45,67] • Developed and implemented programs to identify at-risk patients and to improve THN prescribing[38,39,41,43,44,61] including calculation of overdose risk scores[39] • Interdisciplinary controlled substance committee recommendations[60] • Intensive intervention of outpatients identified with prescription opioid misuse[74] • Communicated to prescribers of risky combinations after review of electronic records[77] • Outreach education via telephone to patients identified at-risk by algorithm assessment of records[78]
Education and skills development	• Opioid safety initiatives designed and implemented throughout organisations, including prescriber education and training supported by policies, protocols, follow-up and feedback and patient clinical review[55,61-63] • Pain, analgesic and risk-mitigation education to PCPs and patients of pain service in underserved practice setting[47] • Training in use of opioid risk-mitigation strategies to PCPs in pharmacist-run prescription management clinic[69] • Correspondence with relevant clinical practice guidelines to prescribers of opioid/BZD combinations for patients of community pharmacy practice[75] • Behaviour change promoted via academic detailing to prescribers in integrated healthcare system[82,83] • Education of risk-assessment strategies to providers; patient and carer THN counselling from embedded pharmacists,[39,41] and in pharmacist-run service[43] • THN education to providers and patients from community pharmacy practice adjacent to rheumatology clinic[81] • Pain management education for patients in clinic managed by pharmacists, with collaborative care model[45] • Identification of medication-related problems and medication counselling to patients in specialist pain clinic[59] • Intensive intervention (counselling/brief motivational interviewing) for outpatients identified with prescription opioid misuse in community pharmacy practice[74] • THN education to providers and patients from community pharmacy practice adjacent to rheumatology clinic[81] • Outreach by telephone to patients to provide education around THN and promote procurement[78]
Protocol and policy; strategic approach and systems-level change	• Input into population-level safety initiative, supported by pharmacists involvement in patient management[55] • With physicians, designed and implemented a Safe and Appropriate Opioid Prescribing program with prescribing and dispensing policies, monitoring, follow-up and clinical coordination[63] • Implemented policies, education and recommendations for patient care with physicians in Controlled Substances Initiative Committee[62] • Led interdisciplinary controlled substance stewardship across a community health care system as population health management strategy[61] • Policy development and recommendations to PCPs for patient care, as members of an interdisciplinary controlled substance committee in community health centre[60] • Led controlled substance stewardship across a community health care system; recommendations for patient care emailed to PCPs[61] • Development of standardised approach to opioid management in primary care clinic[52] • Development of structured, step-wise pain management protocol for patient-centred medical home with pharmacist and physician collaboration in patient carec[57] • Implementation of controlled substance policy in pharmacy-managed chronic pain clinic with collaborative care[45] • Participation in locally implemented Opioid Safety Initiative with support provided for prescribers to taper opioid doses[48] • Development and implementation of cardiac monitoring protocol of high-risk patients receiving methadone[46]

Legend: CNCP = chronic non-cancer pain CTV = clinical video telehealth GP = General Practitioner PCP = primary care provider THN = take-home naloxone

Appendix 1: MEDLINE search strategy; performed 260720

1	exp family practice
2	exp Physicians, Family
3	exp Community Health Services
4	exp general practice/
5	(general adj2 practi*).mp.
6	(gps or gp).mp.
7	(prim* adj2 (care or health)).mp
8	exp primary health care/
9	family adj2 (doctor* or medic* or practi* or physician*).mp
10	exp palliative therapy/
11	exp terminal care/
12	(palliat* adj1 care).mp.
13	exp nursing home/
14	exp long term care/
15	exp ambulatory care/
16	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
17	exp pharmacist/
18	pharmacist*.mp.
19	pharmacy.mp.
20	(pharmaceutical adj1 care).mp.
21	17 or 18 or 18 or 20
22	buprenorphine.mp. or codeine.mp or dihydrocodeine.mp or diamorphine.mp or dipipanone.mp or dextropropoxyphene.mp. or fentanyl.mp. or hydrocodone.mp. or hydromorphone.mp. or meperidine.mp. or meptazinol.mp or methadone.mp or morphine.mp. or naloxone.mp or oxycodone.mp. or oxymorphone.mp. or papaveretum.mp or pentazocine.mp or pethidine.mp. or sufentanil.mp or tapentadol.mp or tramadol.mp.
23	exp Analgesics, Opioid/
24	exp Opiate Alkaloids
25	(opi* adj1 analgesi*).mp
26	(narcotic* adj1 analgesi*).mp
27	22 or 23 or 24 or 25 or 26
28	16 and 21 and 27
29	Limit English; 2001 – current (July 2020)