Systematic Review

A Systematic Review of Interventions and Programs Targeting Appropriate Prescribing of Opioids

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Background: Canada and the United States have the highest levels of prescription opioid consumption in the world. In an attempt to curb the opioid epidemic, a variety of interventions have been implemented. Thus far, evidence regarding their effectiveness has not been consolidated.

Objectives: The objectives of this study were to: 1) identify interventions that target opioid prescribing; 2) assess and compare the effectiveness of interventions on opioid prescription and related harms; 3) determine the methodological quality of evaluation studies.

Study Design: The study involved a systematic review of the literature including bibliographical databases and gray literature sources.

Setting: Systematic review including bibliographical databases and gray literature sources.

Methods: We searched MEDLINE, Embase, and LILACS databases from January 1, 2005 to September 23, 2016 for any intervention that targeted the prescription of opioids. We also examined websites of relevant organizations and scanned bibliographies of included articles and reviews for additional references. The target population was that of all health care providers (HCPs) or users of opioids with no restriction on indication. Endpoints were those related to process (implementation), outcomes (effectiveness), or impact. Sources were screened independently by 2 reviewers using pre-defined eligibility criteria. Synthesis of findings was qualitative; no pooling of results was conducted.

Results: Literature search yielded 12,278 unique sources. Of these, 142 were retained. During full-text review, 75 were further excluded. Searches of the gray literature and bibliographies yielded 49 additional sources. Thus, a total of 95 distinct interventions were identified. Over half consisted of prescription monitoring programs (PMPs) and mainly targeted HCPs. Evaluation studies addressed mainly opioid prescription rate (30.6%), opioid use (19.4%), or doctor shopping or diversion (9.7%). Fewer studies considered overdose death (9.7%), abuse (9.7%), misuse (4.2%), or diversion (5.6%). Study designs consisted of cross-sectional surveys (23.3%), pre-post intervention (26.7%), or time series without a comparison group (13.3%), which limit the robustness of the evidence. Although PMPs and policies have been associated with a reduction in opioid prescription, their impact on appropriateness of use according to clinical guidelines and restriction of access to patients in need is inconsistent. Continuing medical education (CME) and pain management programs were found effective in improving chronic pain management, but studies were conducted in specific settings. The impact of interventions on abuse and overdose-death is conflicting.

Limitations: Due to the very large number of publications and programs found, it was difficult to compare interventions owing to the heterogeneity of the programs and to the methodologies of evaluation studies. No assessment of publication bias was done in the review.

Conclusions: Evidence of effectiveness of interventions targeting the prescription of opioids is scarce in the literature. Although PMPs have been associated with a reduction in the overall prescription rates of Schedule II opioids, their impact on the appropriateness of use taking into consideration benefits, misuse, legal and illegal use remains elusive. Our review suggests that existing interventions have not addressed all determinants of inappropriate opioid prescribing and usage. A well-described theoretical framework would be the backdrop against which targeted interventions or policies may be developed.

Key words: Opioid, prescription, abuse, misuse, diversion, interventions, prescription monitoring programs

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North America has the highest levels of prescription opioid consumption in the world. Associated opioid use disorders include abuse, addiction, misuse, diversion, overdose, and death (1). The Centers for Disease Control, as well as other organizations, have shown that the opioid overdose epidemic is continuing in the United States, with an increase in the age-adjusted opioid-related death rate of 15.6% from 2014 to 2015 (2). In Canada, the same trend has been observed with an increase in the opioid-related death rate of 285% over the past 25 years in Ontario (3) and an increase of 14.4% from 2014 to 2015 in the province of Quebec (4). In the United States, a risk evaluation and mitigation strategy (REMS) applicable to all extended-release (ER) and long-acting (LA) opioids has been in effect since 2012, and an updated Blueprint for Prescriber Education of ER-LA opioids was issued in June 2018 by the United States Food and Drug Administration (FDA) (5,6). In 2017, Health Canada released a draft guidance for industry on targeted opioids risk management plans (RMPs) (7).

Appropriate opioid prescribing focuses on providing care to patients in need. To this end, guidelines, such as those released by the Medical Board of California for prescribing controlled substances for pain, aim at creating a reference document for physicians and clinicians (8). Guidance on indications for the initiation of opioids as well as on treatment modalities (dosage, duration, monitoring) is provided. In parallel, public health initiatives and policies have also been implemented locally and nationally, but an evaluation of the best strategy remains elusive. To our knowledge, a review of interventions beyond the guidelines that target the prescription of opioids has not yet been conducted.

Opioids are mainly indicated to treat moderate to severe pain and should only be considered as second-line therapy for patients who do not respond to non-opioid analgesics (8,9). Prescription of opioids is considered appropriate for acute pain management, cancer-related pain, as well as end-of-life pain (8). An opioid treatment for patients with chronic non-cancer pain is less well-defined as it needs to be driven by patient characteristics, such as comorbid mental illnesses and the potential risk of abuse (8,9). The long-term use of opioids is one of the strongest risk factors for abuse (10). Hence, all patients receiving opioids in the long term should be closely monitored to continuously reassess the benefit-risk of treatment (11). In practice, however, there are 2 distinct populations of long-term opioid users: those who have apparent substance use disorder and those who experience chronic pain uncontrolled by non-opioid analgesics and other interventions. Both are currently merged into the opioid epidemic or crisis, which makes the study of appropriate usage challenging. Furthermore, opioid use disorder, which is characterized by problematic usage, such as increased tolerance and withdrawal symptoms (1), should be distinguished from inappropriate use of opioids. The disorder may develop even when opioids are prescribed and used as recommended (10).

According to a previous systematic review that we conducted on therapeutic risk minimization interventions, not focused on opioids (12), there exist important methodological gaps in evaluation methods of interventions designed to improve prescribing practices and drug usage. Identification of gaps in interventions specific to opioids will inform the development of future interventions or policies.

We conducted a systematic review to identify interventions that target the prescribing of opioids. Furthermore, this study aimed to review the methods and outcome measures that have been used to evaluate the effect of interventions, and to compare the effects of the various interventions.

Methods

Data Sources

We conducted a systematic review using the method proposed by the Cochrane group (13) and the Institute of Medicine of the National Academy (14). We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (15) for the reporting of results, and the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) items for quality control (16). We developed the literature search strategy in the following electronic bibliographical databases: MEDLINE, Embase, and LILACS/Bireme from January 1, 2005 to September 23, 2016 (last date searched). We derived the search terms from the PICOS (participants, intervention and exposure, comparator, outcomes, and study design) approach, using the appropriate MeSH and Emtree terms, respectively, for MEDLINE and Embase, as well as free-text keywords for LILACS/Bireme.

We searched the gray literature in English and French using Google and Google Scholar. In addition, we examined the following websites: FDA, European Medicines Agency (EMA), National Institutes of Health, ClinicalTrials.gov, Health Canada, Institut

national d'excellence en santé et en services sociaux" (INESSS in Quebec), and Canadian Agency for Drugs and Technologies in Health (CADTH). We also reviewed the references of published literature reviews in order to identify interventions that are not indexed in the bibliographical search engines ("snowballing"). Due to the large amount of information, search of the gray literature targeted programs or interventions, not opioid prescribing in general.

Study Selection

We screened search outputs using titles and abstracts in order to identify potentially relevant articles. We examined the full-text articles of retained records to confirm eligibility and extract relevant data. Both processes were independently conducted by 2 assessors and any conflict resolved by a third.

Eligibility Criteria

Literature search strategy and eligibility criteria (listed in Table 1) were based on the PICOS model:

Populations

We considered the following 2 categories of population: the target population of the interventions (e.g., physicians, pharmacists, nurses, dentists) and the at-risk population of opioid users indirectly targeted by the interventions (e.g., chronic pain patients, pregnant women, prisoners).

Intervention(s)

We considered all interventions/programs targeting the prescription of opioids, with no restriction on indication (i.e., non-cancer chronic pain, cancer pain, etc.) or setting (outpatient or inpatient). We excluded publications related to the development of clinical guidelines on opioid prescribing or treatment of chronic pain but retained those on interventions designed to enhance the use of such guidelines.

Comparison

We did not pre-specify any comparator group, which may include absence of intervention, usual care, or no comparator.

Outcomes

We considered all studies describing the effect of a program/intervention on the prescription of opioids or on the prevention of opioid-related harms. We considered all types of evaluation: process/implementation, outcome/effectiveness, and impact. An evaluation targeting process/implementation determines whether program components have been implemented as intended. This type of evaluation describes the usage of interventions, barriers to and/or facilitators of the adoption of interventions by target users. Outcome/effectiveness evaluations measure program effects in the target population by assessing progress in the outcomes or the program's targeted objectives. For example, for the evaluation of effectiveness of a prescription monitoring program (PMP), the outcome would consist of a change in opioid prescription behavior. Attitude, knowledge, and understanding of the intervention were categorized as a process/implementation outcome. However, attitude, knowledge, and understanding of opioid prescription were considered as an effectiveness outcome, mainly used to assess the effectiveness of communication strategies. Lastly, an impact evaluation assesses program effectiveness in achieving its ultimate goals, such as an overall reduction of abuse, misuse, overdose, and death.

Table 1. *Eligibility criteria for the selection of studies.*

Inclusion criteria	Exclusion criteria
Study written in English or French	Opinions or editorials
Topic: Intervention to reduce or avoid opioid abuse/misuse/diversion/overdose (e.g., Prescription Monitoring Programs, Methadone Maintenance Program, Continued Medical Education (CME), Risk Evaluation and Mitigation Strategy (REMS), Guidelines, Policies)	Guidelines without program/intervention designed to enhance the use of guidelines
Patient population: Any opioid user, adolescents, adults, chronic pain (cancer or non-cancer), pregnant women, prisoners, or opioid/substance abusers, etc.	Literature reviews*
Target of interventions: Primary-care physicians, medical or surgical specialists, pharmacists, nurses, dentists and other HCP (e.g., paramedics, nurse practitioner), patients	
Descriptive studies or evaluative studies (interventional or non-interventional)	
Studies conducted in or which used data sources originating from one or more of the OECD countries	

* Literature reviews were however retained for snowballing of references

Study Types

We considered both interventional and noninterventional studies. Hence, randomized controlled trials (RCTs), pragmatic trials, quasi-experimental studies, time series, pre- and post- intervention studies (with or without comparison group), prospective and retrospective cohort studies (with or without comparison group), case-control studies, cross-sectional studies, and qualitative assessments were included. Descriptive studies, such as case series and individual case reports, were also considered only to address the objective of describing the various types of interventions, but not for the assessment of effectiveness.

Data Extraction and Quality Assessment

We extracted data from retained sources into a standardized data extraction form, constructed in an Excel spreadsheet. For each study retained, the data were extracted by 2 independent assessors using publicly available information. We sought the following characteristics of the intervention/program: funding sources, geographical scope, publication year, target of intervention (doctors, pharmacists, patients, etc.), at-risk population (opioid users, cancer pain, non-cancer pain, pregnant women, etc.), description of intervention, opioid-related harm targeted by intervention (abuse, addiction, misuse, diversion, overdose, death), presence of an evaluation assessment, type of evaluation (implementation, effectiveness, impact), method of evaluation (design, study population, data source(s), outcome(s), follow-up, and sample size), and results of the evaluation. The extraction form was validated by consensus before an official broad list of interventions was developed.

The strength of evidence regarding the effectiveness of interventions was assessed using the Shadish et al (17) ranking scale of designs for causal inference, which range from strong designs (e.g., RCTs) to weaker designs (e.g., observational studies without a comparison group). The hierarchy of study designs having a good rating to a poor rating is as follows: RCTs, interrupted time-series analysis (with and without comparison), pre/post intervention (with and without comparison), cohort studies or registries (with and without comparison), case-control studies, cross-sectional studies or surveys, and finally qualitative assessments.

Data Handling

No attempt was made to combine results through a meta-analysis. We summarized findings qualitatively. Based on the extracted data, descriptive analyses were made regarding the type of intervention, type of program, target populations, effectiveness outcomes, and effectiveness results. The type of intervention was also cross-referenced with the robustness of the designs used to evaluate effectiveness.

Results

Study Selection

Findings of the literature and pragmatic searches are summarized in the QUORUM flow chart presented in Fig. 1 (18). Our literature search identified a total of 17,674 sources. Of these, we removed 5,396 duplicates, yielding a total of 12,278 unique sources that were screened for eligibility using titles and abstracts. Following the screening process, we retained 142 references for full-text review. At this point, we excluded another 75 articles for the following reasons: not being related to opioids (n = 31), editorials/opinions (n = 11), guidelines only (n = 9), alcohol/heroin/other substance addicts (n = 9), systematic reviews (n = 8), FDA guidance documents (n = 2), language barrier (n = 1), recommendations (n = 3), and unavailable article (n = 1). Therefore, we retained a total of 67 published articles for the review, corresponding to 58 distinct interventions. We identified another 124 sources through the gray literature search and snowballing process, of which we retained 49, corresponding to 37 distinct interventions. Since most interventions designed to prevent and reduce opioid abuse/misuse originated from the United States or Canada, we went back to excluded reports and searched specific Web sites of major European countries. No other studies or sources met the eligibility criteria.

Overall, we included in the review a total of 116 publications corresponding to 95 distinct interventions. Of these, 111 were studies evaluating the effects of the programs/interventions. The remaining 5, mainly Web sites uncovered during the gray literature search, were descriptive studies.

Types of Interventions

Of the 95 distinct interventions identified, 57 aimed at preventing opioid-related harms, 31 aimed at treating and managing patients with addiction, while 7 aimed at both prevention and treatment. The great majority of preventive (96.9%) and treatment (92.2%) interventions originated from the United States or Canada, with a greater representation of United States

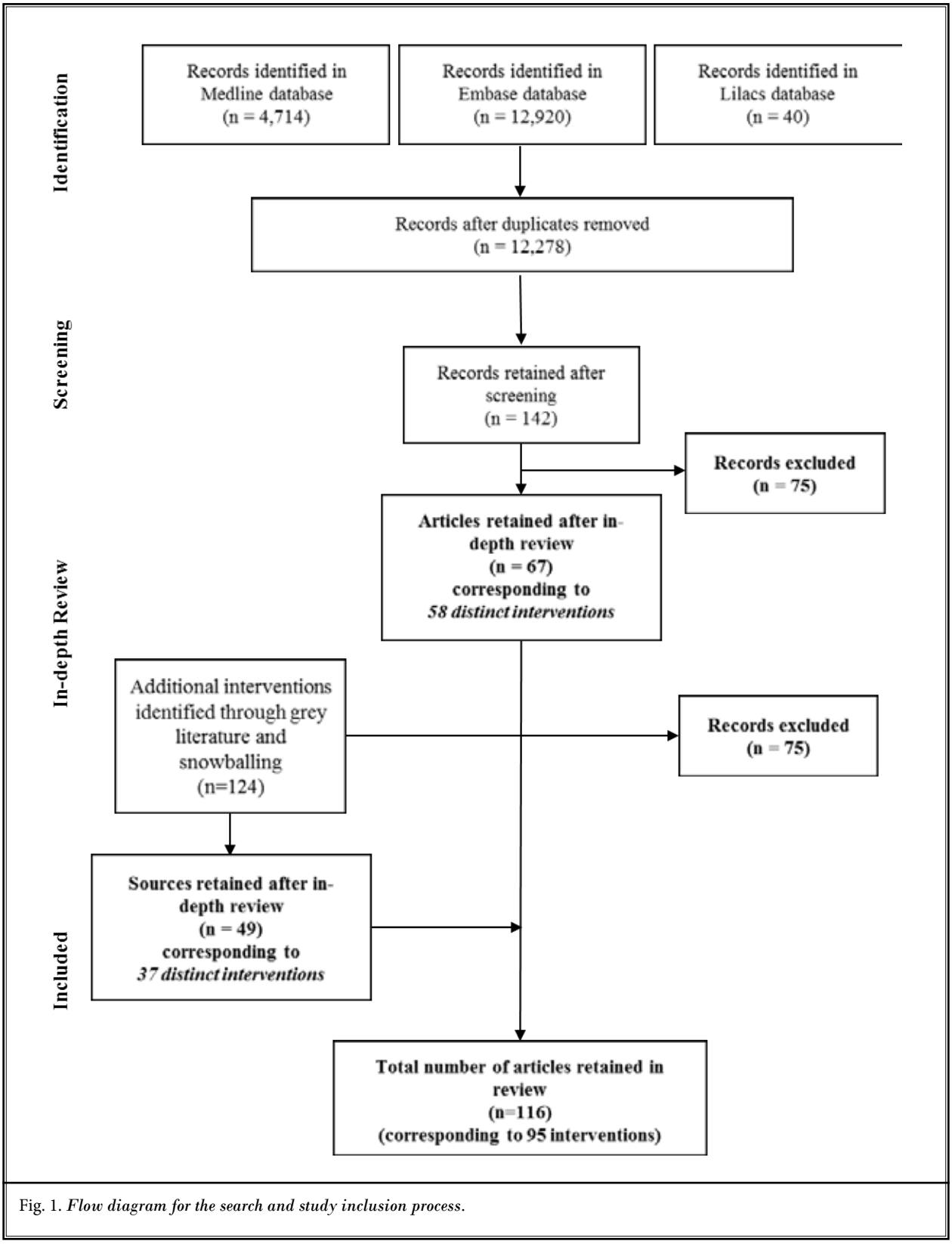

Fig. 1. *Flow diagram for the search and study inclusion process.*

programs (71.1%). Other programs were identified in Europe, Switzerland, and Israel. Since our search strategy was not specifically designed to identify interventions aiming at treating patients with addiction, we decided to focus our description on the 64 prevention interventions (57 prevention as well as the 7 that included both prevention and treatment).

Over half (n = 33; 51.6%) of the interventions consisted of PMPs, a tool that is used to address prescription drug diversion and abuse through a prescription database accessible by all health care providers (HCPs) (19). PMPs have been implemented in the majority of states in the United States, with some variations in program characteristics such as interface characteristics (electronic or paper-based queries) and legislation (i.e., in several states, PMP usage is enforced by law). For example, the California PMP, known as CURES (Controlled substance Utilization and Review Evaluation System), is enforced by law and supported by the Medical Board of California (8). Although PMPs are present in all Canadian provinces, not all have been implemented (19) and evaluation data remain scarce (20,21).

There were 7 continuing medical education (CME) programs (n = 7; 10.9%) identified in the review (22,23,24,25,26,27,28), one of which is the REMS for ER-LA opioids (28). A total of 4 pain management programs (n = 4; 6.3%) were found, which consist of a multidisciplinary pain care approach that is used for analgesic medications, encouraging the use of non-opioid analgesics such as antidepressants and anticonvulsants (23,29-31). Several United States policies (n = 3; 4.7%) were also identified including the following: a case study from Oregon of the National Governor's Association State Policy Academy on Reducing Prescription Drug Abuse; the Texas Triplicate Prescription Law; The Florida Pill Mill Law, which essentially involves mandatory PMP and duplicate prescriptions; medication schedule; and formulary restrictions (32-34).

Target Populations and At-Risk Populations

The target populations for the interventions are described in Table 2. Most (n = 59; 92.2%) targeted HCPs, including dentists, prescribers, and nurses, mainly due to the majority of interventions consisting of PMPs. The majority of the programs (n = 44; 68.8%) aimed at preventing opioid-related harms in any type of patient using opioids, whereas 8 (12.5%) and 7 (10.9%) targeted chronic non-cancer pain patients and chronic pain patients, respectively. A very small portion of programs targeted specific at-risk populations, such as emergency (35) and urgent dental patients (36). Only 3 interventions targeted the patients themselves instead of HCPs (37-39).

Types of Evaluation

The 64 preventive interventions accounted for 82 of the identified sources; evaluation studies were conducted for 72 of those. As presented in Table 3, study designs generally consisted of cross-sectional surveys (n = 14; 23.3%), pre-post intervention (n = 16; 26.7%), or time series without a comparison group (n = 8; 13.3%). Data sources were mainly surveys (n = 17; 28.3%), followed by electronic medical records (EMRs) (n = 11; 18.3%) or PMP databases (n = 4; 6.7%).

Studies either evaluated process/implementation (n = 12; 16.7%), outcomes/effectiveness or impact (n = 36; 50.0%), or both process and outcomes (n = 24; 33.3%). The majority of the studies obtained positive results for the interventions with 91.6% for implementation, 88.5% for outcome/effectiveness, and 82.6% for impact.

Individual endpoints used for the evaluation are presented in Table 5, with a total of 38 different outcome measures identified. For process/implementation outcomes, the use and/or exposure to the intervention (30.6%) was the most commonly used. Barriers and facilitators of program use (13.9%), attitude towards program (12.5%), and knowledge and awareness of program (8.3%) followed. Outcomes/effectiveness was mostly evaluated using opioid prescription rate (30.6%), opioid utilization (19.4%), and opioid prescription behavior (13.9%) as outcomes. Abuse and overdose death were equally used (each 9.7%) for evaluating impact, followed by diversion (5.6%) and misuse (4.2%).

Effectiveness and Impact of Interventions

The following section qualitatively synthesizes results of evaluation studies for the most frequent interventions, i.e., PMPs, CME, pain management programs, and policies.

Success of the implementation of PMPs was shown to vary and more research is needed to determine factors that may be associated with their use by HCPs. According to a survey, more than 84% of prescribers are aware of the Ohio PMP, but fewer than 59% of those who are aware have ever used it (40). Barriers to use PMPs include difficulty in registering, complex user interface, and lack of interstate compatibility (41-43). Use of PMP also varies according to medical specialty; PMP is less frequently used by pediatricians and most frequently

used by emergency physicians (40). Compared to paper/fax PMPs (e.g., Rhode Island), an electronic platform (e.g., Connecticut) increases screening for drug abuse and doctor shopping (44,45). Among Oregon PMP users, 95% reported accessing it when abuse or diversion was suspected, but fewer than half would check it for every new patient or every time a controlled drug was prescribed (46). In law enforcement-governed PMPs, utilization by HCPs was lower than that by PMPs under health/pharmacy boards, and the number of requests by pharmacists was lower than the rate of requests by prescribers (45).

The impact of interventions on opioid prescription seemed variable, as decreases as well as increases were observed. Across 20 states, PMPs have been shown to reduce the per capita prescription of pain relievers and stimulants (47). A decrease of 78% in opioid prescriptions by dentists was observed following the implementation of the New York PMP (36), while a small positive relationship between the growth in the utilization of the PMP and the number of prescriptions filled for opioid analgesics was observed in North Carolina (48). In Kentucky, where a PMP known as KASPER has been implemented since 1999, analysis of Medicaid data showed that the rate of use of oxycodone and hydrocodone increased between 2002 and 2005 and plateaued since (49). Overall, fewer morphine milligram equivalents (MMEs) were dispensed in states with a PMP than in those without (50). Although a decrease in MMEs of 66% was observed in Colorado following the implementation of the PMP, an increase of 61% occurred in Connecticut. The addition of policy and legislation appears to have more effect on opioid prescription than PMP alone. In Florida, the implementation of the pill mill law resulted in a decrease in opioid volume and in MMEs per transaction, but no change in days' supply was observed (51). PMPs coupled with multiple prescription programs such as Triplicate Prescription Programs (TPPs) or PMPs with media campaign (e.g., Utah) have greater effects on opioid prescription than a PMP alone (52).

Difficulty in access to a controlled substance by patients in need has also been reported following the implementation of PMPs. For example, with CURES, Schedule II-IV substances are now listed and hydrocodone, formerly a Schedule III, is now a Schedule II. In Kentucky, patients diagnosed with chronic non-cancer pain conditions and those living in an urban setting were more likely to report difficulty in obtaining a prescription (53). A channeling effect appears to be present, as shown by a parallel relation between the decrease in Schedule II opioid usage and the increase in Schedule III opioid analgesics, which are less scrutinized (43,54). Requiring a security form in California resulted in an increase in short-acting opioid prescriptions such

Table 2. *Populations targeted by the interventions to prevent opioid-related harms.*

Intervention Target Population	No. of Interventions n (%)
Healthcare providers	59 (92.2)
All Health Care Providers (HCPs)	28
Physicians & Pharmacists	2
Physicians	4
Primary Care Providers	2
General Practitioner	1
Emergency Department Physicians	2
Internal Medicine Residents	1
Medical toxicologists	1
Dentists	1
Primary Care Nurse Managers	1
Nurses	1
Opioid Prescribers	15
Patients- opioid users	3 (4.7)
All opioid users	2
Chronic non-cancer pain patients	1
HCPs + Patients/Public	2 (3.1)
Patients & Physicians	1
HCPs, Patients, Insurers and the Public	1
Total	64 (100)

Table 3. *Designs of the included studies on the evaluation of interventions to prevent opioid-related harms.*

Types of Designs	n (%)
Randomized controlled trial	5 (8.3)
Quasi-Experimental	0 (0.0)
Time series (Comparison +)*	3 (5.0)
Time series (Comparison -)*	8 (13.3)
Pre/Post (Comparison +)*	2 (3.3)
Pre/Post (Comparison -)*	16 (26.7)
Cohort (Comparison +)*	5 (8.3)
Cohort (Comparison -)*	6 (10.0)
Cross-Sectional	14 (23.3)
Qualitative	1 (1.7)
Total	60 (100.0)

*Comparison +/-: with/without a comparison group

as hydromorphone, meperidine, and oxycodone; but no effect for fentanyl, methadone, morphine, or LA opioids (55).

For the most part, the clinical impact of PMPs has not been observed, as the vast majority of the studies found no significant association between program implementation and the rates of drug overdose or opioid mortality. Some studies did, however, show a beneficial effect of PMPs on diversion or abuse of specific opioids, such as oxycodone in Florida, and product-specific mortality. In France, after a 4-year increase in diversion through doctor-shopping for buprenorphine, implementation of a regional PMP was concomitant with a marked decrease in doctor-shopping indicators without notable impact on access to treatment (56). In Florida, the PMP and the pill mill law reduced the use of oxycodone and product-specific mortality (57). PMPs aim at reducing the supply and prescription of opioids, which in turn should result in a decrease in abuse. In practice, however, the rate of abuse was found to be higher in states with a PMP than in those without; these findings, however, are largely explained by confounding, whereby states without PMP have a lower rate of abuse to begin with (47). In California, out of the 254 unintentional prescription-related deaths, 186 (73%) had PMP data 12 months before death. Although opioids were responsible for the majority (70.6%) of single medication deaths, 40% of unintentional deaths were due to the ingestion of prescription medications along with illicit drugs, alcohol, and/or over-the-counter medications (58). Very few community interventions were identified. The Lazarus project, for example, coordinates community efforts (including face-to-face meetings on safe prescribing, community activation building, PMP, prevention of overdose through academic detailing, and use of rescue medication for reversing overdose by community members) leading to a reduction in overdose deaths (59). These results, although local, indicate that interventions that only limit the use of prescription opioids are not sufficient to curb the opioid epidemic.

Overall, most of the CME programs were evaluated using pre-post intervention studies without comparison groups. This type of design is prone to confounding by external factors that are unrelated to the programs. Nevertheless, an improvement in knowledge and attitude towards safe opioid prescribing was shown. HCPs reported an intent to modify their prescription practices following various CME programs. A single study, conducted in the emergency department (ED), examined prescription practices, where it was found that the number of opioid discharge packs decreased, especially for patients at high risk for dependence (26). Furthermore, according to a robust randomized controlled trial (RCT), web-based interactive training was more effective than clinical guidelines in improving chronic pain management (60). Similarly, knowledge and attitude improved with CME on overdose and its treatment (27).

The pain management programs (23,29,30,61) resulted in a decrease in opioid usage overall (especially LA opioids) and an increase in non-opioid treatment alternatives for the treatment of chronic non-cancer pain (30). However, the long-term effect of these interventions remains unclear. Of note, study designs that have been used to evaluate the effectiveness of pain management programs are limited by the absence of parallel comparison groups.

Studies showed that multiple copy prescription program (MCPPs) were associated with a decrease in the prescription of Schedule II medications; this decrease was due to inconvenience rather than an increased awareness of appropriate prescribing (34). These patterns suggest that less potent drugs are substituted for Schedule II analgesics in MCPP states (36). Therefore, MCPPs tend to alter analgesic utilization patterns, which has implications for physician practice patterns and patient access to analgesic therapies (62). Similarly, formulary restrictions for a specific opioid were shown to decrease the prescription of that opioid, but resulted in an increase in the use of non-restricted opioids, also indicative of a channeling effect (63).

Discussion

The majority of the interventions and studies targeting the prescription of opioids originate from the United States, and to a lesser extent, Canada. Although the regional difference may be due to publication bias, it was also apparent in the gray literature and pragmatic search. Of the 64 preventive interventions identified, over half were PMPs. PMP usage is higher among prescribers than among pharmacists, and varies according to medical specialty, being lowest among pediatricians. Accessibility and timeliness, both technical aspects of the PMPs, seemed to be a major barrier for use. Interventions aimed at increasing the use of PMPs either through education or point-of-care intervention have been shown to be effective, although most studies were conducted in a hospital setting and not in the community-based setting. States with mandatory PMPs demonstrate a greater usage than in those with optional usage (64).

Table 4. *Results of studies that evaluated the effectiveness of interventions to prevent opioid-related harms.*

	Positive	Negative	Variable	Not available	Total
Implementation	33 (91.6%)	2 (5.6%)	1 (2.8%)	0	**36**
Effectiveness	46 (88.5%)	4 (7.7%)	1 (1.9%)	1 (1.9%)	**52**
Impact	19 (82.6%)	3 (13.0%)	0	1 (4.3%)	**23**

Concerns that PMPs may restrict the appropriate prescription of controlled substances remain inconclusive as no consistent "chilling" effect was observed on the overall prescription rates of opioids. However, channeling has been observed whereby a decrease in Schedule II opioid prescriptions was associated with an increase in Schedule III products, which are less scrutinized. Furthermore, studies have focused on the overall prescription rate of opioids, without considering indication and appropriateness based on clinical guidelines for pain management. In addition, some states and insurance carriers have implemented MED (Morphine Equivalent Dosage) restrictions. Some major pharmacy chains have begun to restrict filling prescriptions that direct a dosage above a set of MED. This may vary from 50 MED to 100 MED depending upon the insurer, pharmacy, utilization review treatment guidelines, or other source. In time, more data will be available about the impact of such practices based upon utilization of a PMP.

Beyond implementation, the findings on the impact of interventions on abuse and overdose-death are conflicting. This could be due to the phenomenon of "channeling" described above and the illicit market (63). Illicit fentanyl and heroin use have been recently shown to hold a strong influence on the opioid epidemic (11). These findings are consistent with those of a recent systematic review that focused on US PMPs only, whereby it was concluded that evidence regarding the effect of PMPs on overdoses is insufficient (65). Furthermore, evaluative studies on PMPs are ecological studies, which are limited by the absence of patient-level data. To correlate pre-post implementation data on opioid prescriptions with those on opioid-related harms at the population level is not a robust design to make inferences on the effect of an intervention, especially in the absence of a parallel comparison group (66).

Our review should be interpreted considering the following limitations. Although no formal assessment of publication bias was done, the large number of published studies presenting positive results compared to those with negative results lends support to the presence of such bias. Secondly, this review was limited to English and French publications. There is a possibility that many local initiatives, such as those in Europe, may be published in local languages, and

Table 5. *Outcomes used for the evaluation of interventions to prevent opioid-related harms.*

Type of Outcomes	Total
Process/Implementation	
Attitude towards program	9 (12.5)
Knowledge and awareness of program	6 (8.3)
Perception regarding impact	2 (2.8)
Perception regarding opioids	2 (2.8)
Satisfaction	3 (4.2)
Use/Exposure to intervention	22 (30.6)
Intention to use intervention	2 (2.8)
Barriers and facilitators of program use	10 (13.9)
Outcome/Effectiveness	
Adherence to guidelines	2 (2.8)
Knowledge and awareness of appropriate opioid prescribing	7 (9.7)
Nbr. Dentist emergency or follow-up consultations and procedures	1 (1.4)
Nbr. Dispensing pharmacies	3 (4.2)
Nbr. Pharmacy interventions	1 (1.4)
Nbr. Patients on chronic opioids	3 (4.2)
Nbr. Patients on high dose	3 (4.2)
Nbr. Prescribers	5 (6.9)
Opioid prescription behaviour	10 (13.9)
Opioid prescription rate	22 (30.6)
Type of opioid	7 (9.7)
Self-rated competence for opioid prescription	1 (1.4)
Opioid utilization	14 (19.4)
Pain management practices	3 (4.2)
Prescription of non-opioid analgesics (acetaminophen)	4 (5.6)
Quality of health care delivery	1 (1.4)
Responses to suspected 'doctor shopping' or diversion	7 (9.7)
Urine drug test	3 (4.2)
Use of Addiction Treatment	1 (1.4)
Impact	
Abuse	7 (9.7)
Emergency department involving opioids	3 (4.2)
Illicit Use	2 (2.8)
Substance Use	1 (1.4)
Misuse	3 (4.2)
Diversion	4 (5.6)
Overdose Death	7 (9.7)
Opioid-associated severe/fatal adverse drug reaction (ADR)	1 (1.4)
Mental health visits	1 (1.4)
Health care utilization	2 (2.8)

therefore excluded from this review. This may partly explain the geographical distribution of interventions observed.

Conclusion

The goal of reducing or preventing opioid-related harms in the population while preserving the highest standards of pain care is not supported by evidence so far. Data on the impact of interventions targeting the prescription of opioids are limited. Although PMPs have been shown to be associated with a reduction in prescription rates of opioids, their impact on appropriateness of use according to clinical guidelines, restriction of access to patients in need, abuse, and overdose is inconsistent. We found that studies conducted at the population level using aggregate data do not address the full spectrum of factors associated with the opioid epidemic, including misuse, legal, and illegal use. Our review suggests that existing interventions have not addressed important determinants of inappropriate opioid prescribing and usage. A well-described theoretical framework would be the backdrop against which targeted interventions or policies may be developed.

Author Contributions

Drs. Moride, Castillon, and Ms. Lemieux-Uresandi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Moride, Bernartsky, and Moura designed the study protocol. Drs. Moride, Castillon, and Ms. Lemieux-Uresandi managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Drs. Pilote, Bernartsky, and Ms. Faure provided revision of intellectual content and final approval of the manuscript.

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