

A systematic review of strategies to improve appropriate use of opioids and to reduce opioid use disorder and deaths from prescription opioids

Andrea D. Furlan^{a,b,c}, Nancy Carnide^a, Emma Irvin^a, Dwayne Van Eerd^a, Claire Munhall^a, Jaemin Kim^a, Cathy Meng Fei Li^b, Abdul Hamad^c, Quenby Mahood^a, and Sara MacDonald^a

^aInstitute for Work & Health, Toronto, Ontario, Canada; ^bUniversity of Toronto, Toronto, Ontario, Canada; ^cUniversity Health Network, Toronto, Ontario, Canada

ABSTRACT

Background: Abuse of prescription opioids is a serious problem in North America.

Aims: The aim of this study was to conduct a systematic review of peer-reviewed and grey literature to examine existing strategies aimed at improving the appropriate use of prescription opioids and/or reducing the misuse, abuse, and diversion of these drugs.

Methods: The following electronic databases were searched to September 2015 without language restrictions: MEDLINE, EMBASE, PsycINFO, and CINAHL; the grey literature was searched to May 2014. Reference lists of retrieved papers were also searched. Studies were eligible if a strategy was implemented and its impact on at least one of the primary outcomes of interest (appropriate prescription opioid use; misuse, abuse, opioid use disorder, diversion; overdose) was measured. Standardized, prepiloted forms were used for relevance screening, quality appraisal, and data extraction.

Results: A total of 65 studies that assessed 66 distinct strategies were identified. Due to the heterogeneity of the strategies, a qualitative synthesis was conducted. Many studies combined more than one type of strategy and measured various types of outcomes. The strategies with most promising results involved education, clinical practices, collaborations, prescription monitoring programs, public campaigns, opioid substitution programs, and naloxone distribution. We also found strategies that had some unintended consequences after implementation.

Conclusions: Our review identified successful strategies that have been implemented and evaluated in various jurisdictions. There is a need to replicate and disseminate these strategies where the problem of prescription opioid misuse and abuse has taken a toll on society.

RÉSUMÉ

Contexte: L'abus d'opioïdes sur ordonnance est un problème grave en Amérique du Nord.

But: Effectuer une revue systématique de la littérature examinée par des pairs et de la littérature grise afin d'étudier les stratégies existantes pour améliorer l'usage approprié des opioïdes sur ordonnance ou réduire la mauvaise utilisation, l'abus ou le détournement de ces médicaments.

Méthodes: Des recherches ont été effectuées sans aucune restriction de langue dans les bases de données électroniques suivantes : MEDLINE, EMBASE, PsycINFO et CINAHL jusqu'en septembre 2015 et dans la littérature grise jusqu'en mai 2014. Des recherches ont aussi été effectuées dans les listes de références des articles retenus. Les études étaient admissibles si une stratégie avait été mise en oeuvre et que son effet sur au moins un des principaux résultats étudiés (usage approprié des opioïdes sur ordonnance; mauvaise utilisation, abus, trouble de consommation ou détournement des opioïdes; surdose) avait été mesuré. Des formulaires normalisés et préalablement mis à l'essai ont été utilisés pour déterminer la pertinence et évaluer la qualité des études, et en extraire les données.

Résultats: Au total, 65 études évaluant 66 stratégies distinctes ont été répertoriées. En raison de l'hétérogénéité des stratégies, une synthèse qualitative a été effectuée. De nombreuses études combinaient plus d'un type de stratégie et mesuraient divers types de résultats. Les stratégies dont les résultats étaient les plus prometteurs portaient sur l'éducation, les pratiques cliniques, les collaborations, les programmes de surveillance des ordonnances, les campagnes publiques, les programmes de substitution des opioïdes et la distribution de naloxone. Nous avons également trouvé des stratégies qui avaient eu des conséquences imprévues après leur mise en oeuvre.

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CONTACT Andrea D. Furlan  afurlan@iwh.on.ca;  www.iwh.on.ca/twitter@adfurlan  Institute for Work & Health, 481 University Avenue, Suite 800, Toronto, ON M5G 2E9, Canada.

 Supplemental data for this article can be accessed [here](#).

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Conclusions: Notre revue a recensé des stratégies fructueuses mises en oeuvre et évaluées dans diverses juridictions. Ces stratégies doivent être reproduites et diffusées là où le problème de la mauvaise utilisation et de l'abus d'opioïdes sur ordonnance a eu un effet néfaste sur la société.

Introduction

Abuse of prescription opioids is a serious health and safety problem in North America. In the United States, more than 165 000 people died of overdose related to opioid pain medications between 1999 and 2014.¹ In Canada, after a record-breaking year of apparent opioid-related deaths in 2016 (2861 deaths), the Public Health Agency of Canada predicts the number of Canadians that died from opioid overdoses will surpass 4000 by the end of 2017.^{2,3}

Overprescribing of opioids by health care professionals has been implicated as the root cause of the current epidemic. In Canada, there were more than 21.5 million opioid prescriptions filled in 2016 alone, with an increasing proportion of strong opioids among all opioids dispensed.⁴ On the other hand, the Position Statement from the Canadian Pain Society recognizes that essential tools for managing moderate to severe pain involves pharmacotherapy, which may include opioids among other analgesics, in combination with physical and psychological approaches.⁵ It seems that the underlying cause for overprescribing of opioids is poor understanding and management of acute and chronic pain itself,⁶ and it has been suggested that opioid prescribing is a surrogate for inadequate pain management resources.⁷

An area that has not been the subject of many systematic reviews relates to strategies to promote the appropriate use of prescription opioids and reduce their harms, including abuse, opioid use disorder, and diversion. The knowledge users interested in this topic are not limited to health care professionals but rather are representatives of diverse groups within our communities, including public health, prevention services, government, law enforcement, regulators, and insurance payers, all of whom are interested in programs, strategies, policies, and regulations to solve the problem of inappropriate opioid use. A few recent systematic reviews have synthesized the evidence for narrow and specific types of strategies, including primary care delivery models for treating opioid use disorders,⁸ supervised dosing versus off-site consumption of opioid substitution treatment,⁹ community overdose prevention and naloxone distribution programs,¹⁰⁻¹³ clinical strategies for reducing aberrant drug-related behavior (e.g., treatment agreements, urine drug testing),^{14,15} and prescription opioid policies (namely, guidelines and legislation).¹⁶

Our goal was to conduct a comprehensive systematic review to more broadly identify existing strategies, programs, policies, and practices aimed at improving the appropriate use of prescription opioids and/or reducing the misuse, abuse, and deaths related to these drugs, with a focus on strategies that can be implemented in North America, the epicenter of the current crisis.

Methods

We followed the PRISMA checklist, and the methods for this review have been previously published in Prospero.¹⁷

The research question addressed in this review included the following components:

What: What are the existing strategies, programs, policies and practices aimed at (1) improving the appropriate use of prescription opioids and/or (2) reducing the misuse, abuse, and diversion of these drugs? *Misuse* was defined as taking a medication in a manner or dose other than prescribed; taking someone else's prescription, even if for a legitimate medical complaint such as pain; or taking a medication to feel euphoria (i.e., to get high). The term *nonmedical use* of prescription drugs also refers to these categories of misuse.¹⁸

Who: There are many organizations and agencies with a keen interest in promoting the appropriate use of and/or reduction of inappropriate use of opioids. However, given limited resources and time to conduct this review, we narrowed the sources of material to four major sectors: (1) health-related professions and regulatory authorities; (2) government, public health/health promotion agencies, prevention and treatment organizations; (3) insurance organizations, including workers' compensation; and (4) law enforcement agencies. Therefore, we excluded materials produced by military organizations, the pharmaceutical industry, or for-profit organizations. In addition, we excluded Internet-based or media-related strategies.

Where: We were interested in materials that are particularly applicable to the current Canadian context.

When: In North America, abuse of prescription opioids began to rise with the introduction of

Oxycontin in 1996.^{19,20} Therefore, we focused on studies published in the 20 years after the release of Oxycontin.

Searches

To identify peer-reviewed publications, we searched the following electronic bibliographic databases from inception to September 2015 with no language restrictions: MEDLINE, EMBASE, PsycINFO, and CINAHL. All search strategies were developed by the research team in consultation with the knowledge users group and executed by an experienced librarian. The search strategies were adapted from the P.I.C.O. structure (Patient, Intervention, Comparison, and Outcomes) of reviews of effects of interventions. The controlled vocabulary differs significantly across peer-reviewed databases. Therefore, search terms were customized for each database. The search strategies are shown in Appendix 1.

It was also anticipated many relevant studies would not be published in peer-reviewed journals. We addressed this gap by also systematically searching the grey literature. The grey literature is a rich source of material that is not controlled by commercial publishing but offers advantages of usually being more current, free, relevant, unique, and on nonmainstream topics or aspects.²¹ For grey literature, Canadian websites for the following groups were searched (Appendix 2): regulatory authorities for health-related professionals (e.g., colleges for physicians, pharmacists, and nurses), government (federal and provincial), public health and health promotion agencies, prevention and treatment organizations, workers' compensation boards, private insurance companies, and law enforcement agencies. There were no language restrictions. However, for feasibility, only materials uploaded, updated, or available in the previous 20 years were searched.

Eligibility criteria

The following primary opioid-related outcomes were considered eligible for inclusion:

- (1) Appropriate prescription of opioids for pain measured by pain intensity or functional improvement, number of high-dose opioid prescriptions, intermittent use of long-acting opioids, combination with benzodiazepines, appropriate education provided to patient, appropriate selection of patients for opioids, and appropriate monitoring of patients on opioids.

- (2) Misuse, abuse, opioid use disorder, and diversion of prescription opioids.
- (3) Fatal or nonfatal opioid-related overdoses.

A secondary outcome of interest was unintended consequences of the implemented strategy. These could be adverse consequences to participants (e.g., being harassed by the police because they were carrying naloxone; additional burden on the clinical staff) or to society (e.g., shifting the opioid crisis to a neighbor region where the strategy had not been implemented).

Only studies with empirical data evaluating the effectiveness of strategies on our outcomes of interest were included in this review. These could be quantitative (observational or experimental), qualitative, or mixed-method studies. For grey literature, we included data evaluations, foundation reports, government reports, grantee publications, noncommercially published conference papers, reports, special reports, and working papers, committee reports, testimony, and conference proceedings.

All strategies that have been developed, implemented, and evaluated in North America, Europe, and Australia/New Zealand were eligible for inclusion. Strategies that have been implemented outside of these regions were only included if they were applicable or useful to the opioid-related issues in Canada (i.e., if the country had trends in prescription opioid use and misuse similar to those in Canada and/or the country has a health care system similar to Canada).

Relevancy screening

Titles and/or abstracts of the studies retrieved were screened independently by rotating pairs of reviewers using the full set of inclusion/exclusion criteria and a standardized, prepiloted form using Distiller SR software. The full text of studies meeting all criteria or where there was uncertainty were retrieved and assessed for relevancy by rotating pairs of reviewers. Any disagreements were resolved through discussion with reviewer pairs and a third reviewer was consulted when consensus could not be reached.

Data extraction

A standardized, prepiloted form was used to extract data from the included studies for evidence synthesis. Data were extracted according to the variables that have been agreed upon by the team members for all papers included in this review, which included country, settings, target population, group that developed the strategy, components of the strategy, duration, outcomes,

and results. During the process of data extraction, we met regularly to resolve issues related to locating the data in the text, establishing the nature and type of the data, ascertaining reliability of data extraction, and checking data extraction in preparation for analysis.

Quality appraisal

To assess the quality of each included study, we first applied a classification by methodological design:

- Group A: Evidence from randomized studies.
- Group B: Evidence from controlled experimental studies without randomization or from epidemiological studies (cross-sectional, cohort, or case-control analytic studies).
- Group C: Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments or qualitative statements could be included here.

Second, a critical appraisal checklist was used to assess risk of selection, performance, detection, attrition, and reporting bias in each study (Appendix 3). The risk of bias assessments was entered in RevMan software version 5.3.²²

Data analysis and synthesis

Empirical data included both quantitative and qualitative evaluations of the impact of the strategy on any of the outcomes described above. Quantitative data were analyzed as differences between groups (for studies in groups A and B) or within groups (for studies in group C). We calculated standardized effect sizes of interventions that yielded statistically significant results: Cohen's d for main differences,²³ Cohen's d from t statistics,²⁴ Cohen's d from F test,²⁵ Cohen's h for differences in proportion,²⁶ Hedge's g from t statistics when sample size was less than 30,²⁷ and logit d from odds ratio.^{26,28,29} (Appendix 4).

For studies with multiple outcomes, we reported the measured outcome with the largest effect size for each of the three outcomes of interest. The effect size was expressed as a negative or positive value, indicating that the intervention either had a smaller or greater effect than the control, respectively. The effect sizes were grouped into categories of no (0–0.19), small (0.20–0.49), medium (0.50–0.79), or large (0.8 or larger) effect.³⁰ In the graphical representations, no effect was assigned a value of 0, small was assigned 1, medium 2, and large 3. When the

data were only reported as a qualitative statement, we assigned its impact factor (0, 1, 2, or 3) based on similar studies from which we had calculated the effect size. The association between number of contents in each strategy and the impact factor was calculated using correlation coefficient for each outcome. Rather than a meta-analysis, we conducted a narrative synthesis to describe the interventions and a quantitative analysis to assess the impact of each intervention.

Results

The searches of electronic databases yielded 5169 titles and abstracts and searches of the grey literature yielded 72 studies (Figure 1). A total of 557 full texts were obtained from the electronic databases and grey literature. Of these, 65 met the inclusion criteria and were included: 9 randomized trials^{31–39} and 56 nonrandomized studies.^{40–95} One study described two strategies and provided separate results.³⁸ The characteristics of population, strategies, outcomes, and unintended consequences are shown in Appendix 5. The target population for the strategies was grouped into three groups: (1) patients and opioid users, (2) health care providers, and (3) the general public.

Critical appraisal of the studies

Overall, randomized trials and nonrandomized studies had significant methodological shortcomings. Among the nine randomized trials, the most common types of bias were performance (blinding of participants and personnel) and detection bias (blinding of outcome assessment; Figure 2). There was a potential for selection bias in approximately half of the trials due to unclear methods of randomization and allocation concealment. One study had a high risk of attrition bias due to a 39% drop out rate³¹ and one study had a high risk of bias due to potential for conflict of interest.³² There was no indication of reporting bias in any of the trials included.

Among the 56 nonrandomized studies, the most frequent methodological flaws were lack of a separate control group, lack of description of how groups were formed, lack of description of pre-intervention characteristics, lack of examination of whether important differences existed between the remaining and dropout participants, lack of documentation of participation (compliance with the intervention), poor reporting of main outcomes measurements at baseline, lack of adjustments for pre-intervention differences, and statistical methods of analysis that were not optimal

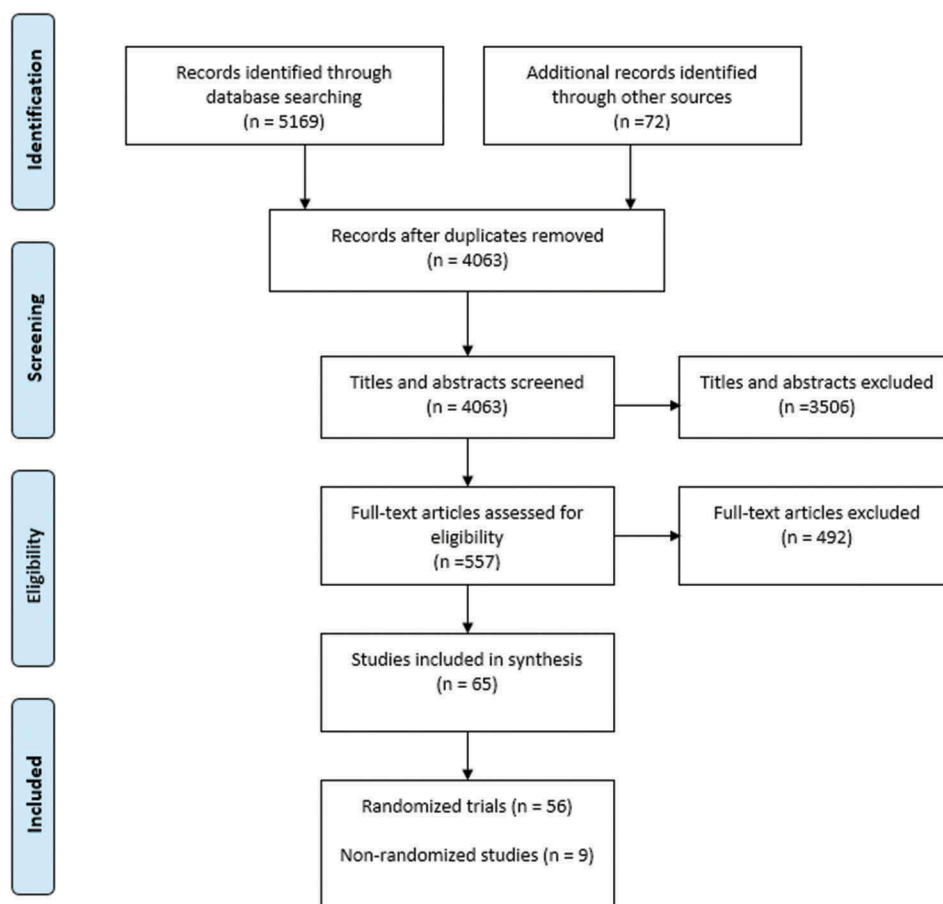


Figure 1. PRISMA flow diagram.

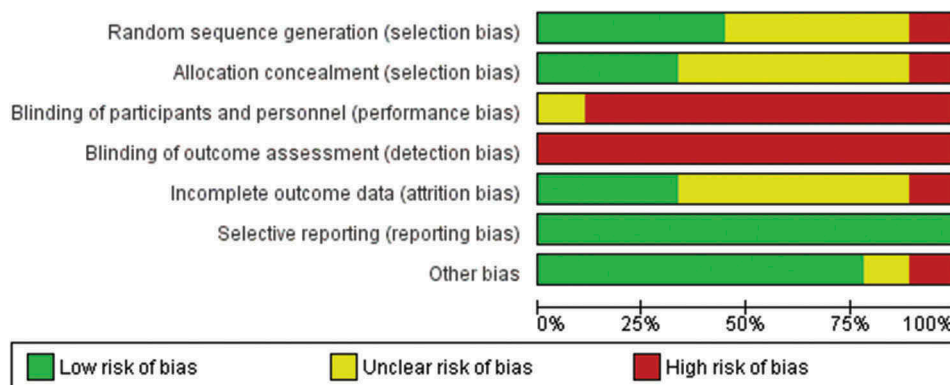


Figure 2. Risk of bias summary of randomized controlled trials.

(Figure 3). The majority of studies had a clear research question, a clear description of the strategy (or intervention process), a clear documentation of the effects of the intervention on some of the exposure parameters, and length of follow-up of 3 months or greater. For some methodological indicators, most studies lacked clear description and therefore the judgments were “unclear”: whether participation rate was at least 50%, whether loss to follow-up was less than 35%, whether

the analysis considered the participants in the groups they were originally allocated, and whether there was a direct between-group comparison or not.

Target population of the strategies

Forty-eight strategies were aimed at only one target group, 15 were aimed at two target groups, and three were aimed at all three target groups of interest

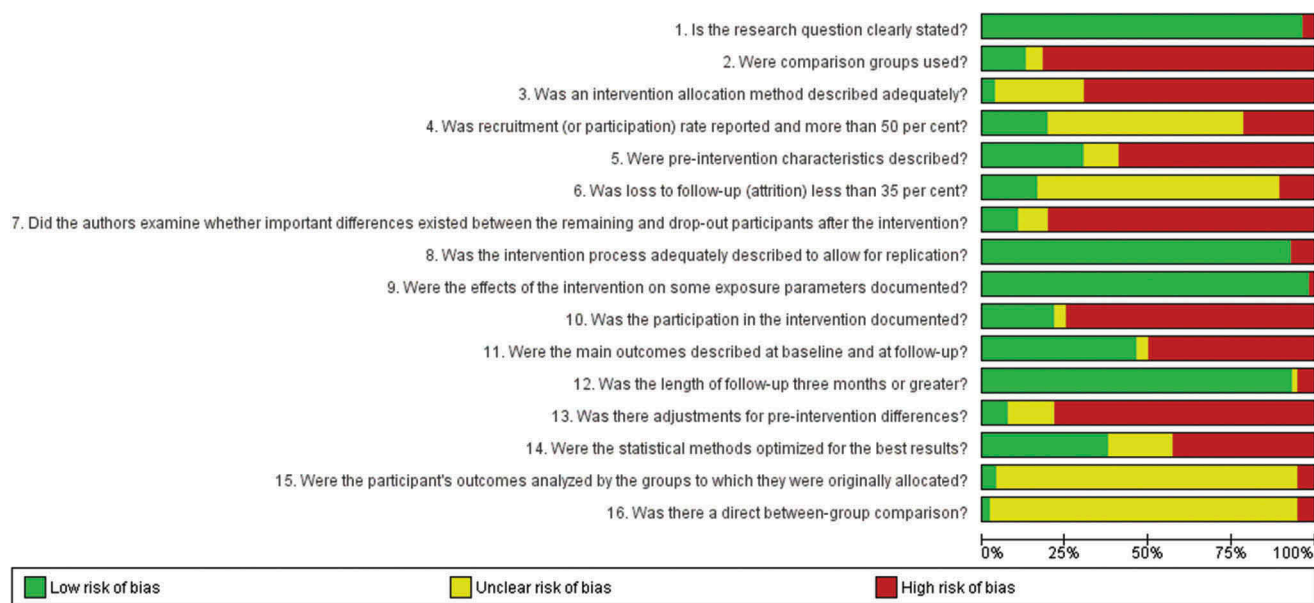


Figure 3. Risk of bias summary of nonrandomized studies.

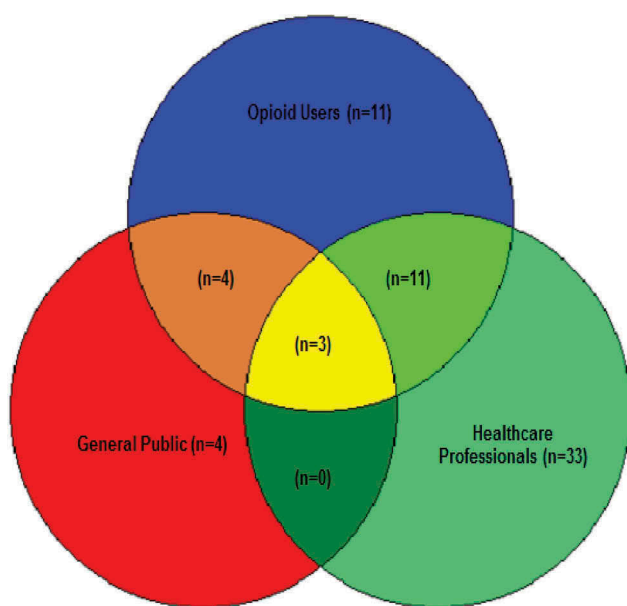


Figure 4. Target populations.

(Figure 4). The most common target group was health care professionals: as a single target in 33 strategies and combined with opioid users in 11 strategies.

Content of the strategies

The content of the strategies was categorized into educational, clinical practice, naloxone distribution, opioid substitution therapies, prescription monitoring, campaigns to return unused opioids (take-back programs), regulations, policies, and public campaigns. A strategy could have more than one type of content: one

strategy had five contents,⁷⁷ 3 strategies had four,^{44,67,81} 13 strategies had three,^{37,41,43,48,51,53,60,63,66,70,76,79,85} 29 strategies had two,^{31,32,34,38–40,42,45,46,49,52,55,59,62,65,69,72–74,80,82–84,87,88,91,93,94} and 20 strategies had a single content.^{33,35,37,47,50,54,56–58,61,63,68,71,78,86,89,90,92,95,96} The association between the number of contents and the impact factors was small for all three outcomes of interest: 0.32 for appropriate use, 0.08 for misuse, and 0.14 for overdose. The contents of each strategy are explained below:

- Education. These strategies involved formal teaching to improve knowledge or training to impart specific skills. Examples of educational strategies were attending a workshop or a continuing medical educational event.⁶⁵ Thirty-five strategies involved education.^{31,32,34,35,37–39,41–44,48,49,52,53,55,60,63,65,67,70,72,74,76,77,79,81,82,85,88,90,91,93,94,97}
- Clinical practice. These strategies involved changes in how health care was delivered, such as implementation of recommendations from clinical practice guidelines,⁸⁷ using a tool to improve opioid prescribing,⁸⁶ implementing urine drug tests,⁸⁵ or using disease management programs.⁴⁶ Thirty-two strategies involved clinical practice changes.^{32–34,39,40,42–46,48,51,56,57,61,65–67,69,72,74,77–80,85–88,91,92,95,97}
- Reversal of overdose with naloxone involved distribution of naloxone to caregivers or bystanders with the potential to reverse an opioid-related overdose. An example was an intervention that included not only distribution of naloxone but

also an educational campaign to identify high-risk individuals.⁵⁵ Nine strategies involved naloxone distribution.^{41,52,53,55,60,63,76,82,93}

- Opioid substitution therapies were carried out by healthcare professionals who prescribe methadone or buprenorphine for opioid use disorder and dependence. This type of strategy was usually combined with clinical or educational strategies.^{43,80} Six strategies involved opioid substitution therapies.^{43,51,69,77,80,89}
- Take-back program involved reducing the amount of unused opioids in households and preventing diversion by providing drop-boxes and incentives for safe disposal of the medications. Only one study was included.⁶²
- Prescription monitoring or review programs (PMPs) are strategies that use an electronic system to keep track of opioid prescriptions by physicians or opioid dispensing by pharmacists. They were usually combined with education,⁴⁴ changes in clinical practices,⁴⁸ or regulations.⁷⁰ Eighteen strategies involved PMPs.^{31,40,41,44,48,50,54,58,64,66,67,70,73,77,81,83,84,87}
- Regulations and policies are strategies that use legislation or policies to correct or incentivize certain behaviors. It could be the sole content of a strategy⁴⁷ or it could be combined with education,⁴⁹ prescription monitoring program,⁷³ or public campaigns.⁸¹ Sixteen strategies involved regulations or policies.^{47,49,53,59,60,62,63,66,68,70,71,73,75,81,83,84,96}
- Community or public health campaigns included strategies aimed at prevention or public health strategies. Seven strategies (reported in five studies) involved community or public health campaigns.^{37,38,76,81,94}
- Collaborative strategies involved bringing diverse groups of people together to solve a common issue or to improve a situation, such as an interprofessional or multidisciplinary team. Ten strategies included collaboration as a key component of their strategies.^{37,44–46,51,59,67,77,79,85}

Impact of the strategies

Impact on appropriate use of opioids

Twenty-six studies measured the impact of a strategy on improving or ensuring appropriate use of opioids (Table 1). The impact factors ranged from –2 to 3. The only strategy with a negative impact involved a comparison of a PMP between two states in the United States.⁶⁴ Researchers found that in suspected diversion

or doctor shopping, the health care providers using PMPs were 53% less likely to discuss the concerns with the patient and 73% less likely to state to the patient that they were out of stock of the medication. Eight strategies had no effect on appropriate use of opioids,^{54,58,59,65,66,74,79,84} seven strategies had a small positive effect,^{32,33,42,46,70,77,89} six strategies had a moderate positive effect,^{39,43,48,80,85,88} and four strategies had a large positive effect, which included (1) Project Lazarus, a community activation and coalition-building, monitoring, and surveillance data, prevention of overdoses, and use of rescue medication for reversing overdoses and evaluation of the program⁴¹; (2) implementation of a treatment agreement developed with cooperation of anesthesiologists, psychologists, nurses, rehabilitation specialists, and clinical pharmacists⁴⁵; (3) a clinic-wide strategy including opioid prescribing policies and protocols, guidelines to address depression and substance abuse screening, drug selection, dose titration, urine toxicology testing, review of the PMP database and agreement violations, in addition to a monthly meeting with a multidisciplinary committee to review protocols and discuss cases and provider education⁶⁷; and (4) a multifaceted education initiative regarding pethidine, tramadol, and morphine prescriptions consisting of in-services and feedback by clinical pharmacists, literature discussion, and posters.⁹¹

Impact on misuse, abuse, opioid use disorder (addiction), and diversion

Forty studies measured the impact of the strategy on outcomes of misuse, abuse, opioid use disorder, and/or diversion (Table 1). The impact factors ranged from –1 to 3. The only strategy with a negative impact on this outcome was a 1-h educational group session on the nature, theories, and treatment of pain provided by a clinical psychologist for new patients. The aim of the intervention was to reduce violations of the opioid treatment agreement. The results showed that those who attended the educational session were 1.8 times more likely to be discharged due to violation of the treatment agreement, and the explanation was that participants in the educational session could perceive a false sense of privilege because they had participated in their care beyond a typical first physician office visit.⁹⁰ Sixteen strategies had no effect on this outcome,^{31,33,35,37,38,47,52,59,61,66,71,73,75,83,86,89} 10 strategies had a small positive effect,^{37,38,56,62,65,77,78,85,87,92} six strategies (seven studies) had a moderate positive effect,^{34,40,44,58,80,95,97} and seven had a large positive effect, which included (1) a standard protocol for buprenorphine with naloxone for patients with low-

Table 1. Outcomes, effect sizes, and impact factors.

Study	Measured outcome	Category of outcome	Derived effect size measure	Effect size	Impact factor
Lamb et al. 2007	Pain ratings	Appropriate use	Extrapolation ^a	—	0 ^b
Wiedemer et al. 2007	Resolution of aberrant behaviors	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	0.57	2
Bujold et al. 2012	Narcotics confiscated	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	0.75	2
Cochella and Bateman 2012	Prescribing long-acting opioids for acute pain	Appropriate use	Cohen's <i>h^{c,d}</i>	0.61	2
Cochella and Bateman 2012	Overdose deaths	Overdose and deaths	Cohen's <i>h^c</i>	0.21	1
Dormuth et al. 2012	Inappropriate opioid prescriptions	Appropriate use	Cohen's <i>d</i> from mean difference	0.03	0
Mandhankanti et al. 2006	Opioid prescription abuse	Misuse, abuse, and addiction	Logit <i>d</i>	0.43	1
Gonzalez and Kolbasovsky 2012	Number of opioid prescriptions	Misuse, abuse, and addiction	Cohen's <i>d</i> from mean difference	0.16	0
Spoth et al. 2013	Lifetime narcotic misuse	Misuse, abuse, and addiction	Cohen's <i>d</i> from <i>t</i> statistic (independent)	0.30	1
Thomas et al. 2013	Prescription alterations	Misuse, abuse, and addiction	Cohen's <i>d</i> from <i>t</i> statistic (correlated)	0.29	1
Pade et al. 2012	Change in pain scores	Appropriate use	Cohen's <i>d</i> from <i>t</i> statistic (correlated)	0.68	2
Pade et al. 2012	Percentage of patients relapsed	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	0.66	2
Stover 2010	Social functioning perception	Appropriate use	Cohen's <i>d</i> from <i>t</i> statistic (independent)	0.26	1
Stover 2010	Reduction in cravings	Appropriate use	Not statistically significant	—	0
Wheeler et al. 2012	Overdose reversal	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	0.28	1
Piper et al. 2007	Number of drug users alive	Overdose and death	Cohen's <i>h^c</i>	0.89	3
Albert et al. 2011	Opioid prescriptions	Overdose and death	Cohen's <i>h</i>	1.62	3
Albert et al. 2011	Overdose	Appropriate use	Cohen's <i>h</i>	0.01	0
Walley et al. 2013	Overdose reversal	Overdose and death	Cohen's <i>d</i> from mean difference	0.01	0
Cicero et al. 2005	Tramadol abuse rates	Misuse, abuse, and addiction	Not statistically significant	—	0 ^b
Ablaiheid et al. 2014	Opioid prescriptions	Misuse, abuse, and addiction	Hedge's <i>g</i> from <i>t</i> statistic (correlated)	0.54	2
Schlicher 2015	Opioid prescriptions	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	0.32	1
Andrews et al. 2013	Intermittent hydromorphone use	Appropriate use	Cohen's <i>h^c</i>	0.49	1
Barry et al. 2015	Pain interference	Appropriate use	Cohen's <i>d</i> from mean differences	0.67	2
Barry et al. 2015	Urinary opioids	Appropriate use	Cohen's <i>d</i> from mean differences	1.13	3
Davis 2015	Overdose reversals	Overdose and death	Extrapolation ^e	—	0
DiPaula and Menachery 2015	Urinary opioids	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	1.03	3
Dwyer et al. 2013	Performed rescue measures	Overdose and death	Cohen's <i>d</i> from <i>t</i> statistic (independent)	0.57	2
Fulton-Kehoe et al. 2015	Methadone poisoning	Overdose and death	Extrapolation ^f	-1.27	-3
Furlan et al. 2014	Patients referred to methadone treatment	Appropriate use	Logit <i>d^c</i>	0.18	0
Furlan et al. 2014	Reduction of pentazocine PO	Misuse, abuse, and addiction	Cohen's <i>h</i>	0.54	2
Green et al. 2013	Prescribers discussing concerns with patients	Appropriate use	Logit <i>d</i>	-0.40	-2
Green et al. 2013	Using PMP	Misuse, abuse, and addiction	Logit <i>d</i>	1.78	3
Green et al. 2015	Deaths	Overdose and death	Cohen's <i>d</i> from mean differences	1.87	3
Gugelmann et al. 2013	Pain complaints	Appropriate use	Logit <i>d</i>	0.07	0
Gugelmann et al. 2013	Discharged with opioids	Misuse, abuse, and addiction	Logit <i>d</i>	0.31	1
Johnson et al. 2014	High-volume oxycodone providers	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	1.57	3
Johnson et al. 2014	Death rates from opioids	Overdose and death	Logit <i>d</i>	0.18	0
Kanate et al. 2015	Medical evaluations	Overdose and death	Cohen's <i>h</i>	1.16	3
Katzman et al. 2014	Morphine equivalents of opioids dispensed	Appropriate use	Cohen's <i>h^c</i>	0.20	1
Katzman et al. 2014	Deaths	Overdose and death	Cohen's <i>h</i>	0.00	0
Keast et al. 2015 ⁹	Average number of opioid prescription claims per member	Misuse, abuse, and addiction	Extrapolation ^a	—	0
Keast et al. 2015	Mortality rates	Overdose and death	Cohen's <i>h</i>	0.00	0
Ketcham et al. 2014	Number of ER visits per opioid user	Misuse, abuse, and addiction	Cohen's <i>d</i> from mean differences ^h	3.26	3
Kim et al. 2014	Number of opioid pills	Misuse, abuse, and addiction	Cohen's <i>d</i> from mean differences ^h	0.07	0
Kunins 2015/Larochelle et al. 2015	Milligrams of opioids	Misuse, abuse, and addiction	Cohen's <i>d</i> from mean differences	0.00	0
Kunins 2015/Larochelle et al. 2015	Overdose from prescription opioids	Overdose and death	Cohen's <i>d</i> from mean differences	0.02	0
Paone et al. 2015	High-dose opioid prescriptions	Misuse, abuse, and addiction	Cohen's <i>h</i>	1.02	3
Paone et al. 2015	Mortality	Overdose and death	Cohen's <i>h</i>	1.14	3
Saitz et al. 2014	Self-reported opioid misuse	Misuse, abuse, and addiction	Not statistically significant	—	0
Saitz et al. 2014	Drug use consequences	Overdose and death	Not statistically significant	—	0
Sandoo et al. 2011	Prescription of inappropriate drugs	Misuse, abuse, and addiction	Cohen's <i>h</i>	0.15	0
Summers et al. 2014	Violated treatment agreement	Misuse, abuse, and addiction	Logit <i>d^c</i>	-0.32	-1

(Continued)

Table 1. (Continued).

Study	Measured outcome	Category of outcome	Derived effect size measure	Effect size	Impact factor
James et al. 2014	ED patients on extremely high opioid dose (>1000/mg MEQ)	Appropriate use	Logit <i>d</i>	0.96	3
Husk et al. 2014	Percentage of ED patients not receiving opioids	Appropriate use	Cohen's <i>h</i>	0.06	0
Husk et al. 2014	Opioid prescriptions	Misuse, abuse, and addiction	Logit <i>d</i>	0.04	0
Saenger et al. 2013	Urinary drug screens completed	Appropriate use	Cohen's <i>h</i>	0.57	2
Saenger et al. 2013	Monthly prescription refills	Misuse, abuse, and addiction	Cohen's <i>h^a</i>	0.36	1
Gray et al. 2015	Units of opioid disposals	Misuse, abuse, and addiction	Extrapolation ^a	—	1
Gray et al. 2015 ^b	Deaths from overdose	Overdose and death	Cohen's <i>h</i>	0.32	1
Ringwalt et al. 2015	Incidence of opioid prescriptions	Appropriate use	Logit <i>d</i>	0.08	0
Garcia et al. 2014	Average daily dose of opioids	Appropriate use	Extrapolation	—	0 ^c
Garcia et al. 2014	Number of opioid users	Misuse, abuse, and addiction	Logit <i>d</i>	0.11	0
Leece et al. 2013	Naloxone administration	Overdose and death	Cohen's <i>h^c</i>	0.17	0
Delcher et al. 2015	Deaths from oxycodone	Overdose and death	Cohen's <i>d</i> from mean differences ^k	0.26	1
Naliboff et al. 2011	Pain ratings	Appropriate use	Cohen's <i>d</i> from mean differences	0.40	1
Naliboff et al. 2011	Patients discharged due to opioid misuse	Misuse, abuse, and addiction	Not statistically significant	—	0
Reifler et al. 2012	Intentional opioid exposures	Misuse, abuse, and addiction	Cohen's <i>h</i>	0.19	0
Franklin et al. 2012	Workers on 120 mg/day MEQ	Misuse, abuse, and addiction	Cohen's <i>h^c</i>	0.40	1
Franklin et al. 2012	Opioid-related deaths	Overdose and death	Cohen's <i>h^c</i>	0.52	2
Taylor et al. 2007	Patients on pethidine	Appropriate use	Logit <i>d</i>	0.82	3
Doe-Simkins et al. 2014	Opioid use within last 30 days	Misuse, abuse, and addiction	Not statistically significant	—	0
Doe-Simkins et al. 2014	Actions taken during overdose	Overdose and death	Not statistically significant	—	0
Doe-Simkins et al. 2009	Successful rescues	Overdose and death	Cohen's <i>h^c</i>	0.22	1
Gaston et al. 2009	Appropriate actions in case of overdose	Overdose and death	Cohen's <i>d</i> from <i>t</i> statistic (correlated)	1.39	3
McCarty et al. 2004	Positive attitude toward buprenorphine	Appropriate use	Not statistically significant	—	0
Srivastava et al. 2012	Physician difficulty with dosing	Appropriate use	Cohen's <i>d</i> from <i>t</i> statistic (correlated)	0.54	2
Sullivan 2006	Methadone prescriptions	Appropriate use	Cohen's <i>d</i> from <i>F</i> test	0.63	2
Otto et al. 2009/Zahradnik et al. 2009	Defined drug dosage	Misuse, abuse, and addiction	Logit <i>d</i>	0.51	2
Jamison et al. 2010	Average pain ratings	Appropriate use	Cohen's <i>d</i> from mean differences	0.38	1
Jamison et al. 2010	Drug misuse index	Misuse, abuse, and addiction	Logit <i>d</i>	1.14	3
Lofwall et al. 2011	Adherence to maximum dose	Appropriate use	Cohen's <i>h</i>	0.46	1
Lofwall et al. 2011	Percentage of doctors giving 7 days or less of buprenorphine	Misuse, abuse, and addiction	Logit <i>d</i>	0.46	1
Lofwall et al. 2011	Lifetime narcotic misuse	Misuse, abuse, and addiction	Cohen's <i>h</i>	0.44	1
Spoth et al. 2008 (Study I)	Lifetime nonprescribed medication use	Misuse, abuse, and addiction	Cohen's <i>h</i>	0.16	0
Spoth et al. 2008 (Study II)	Lifetime prescription opioid misuse	Misuse, abuse, and addiction	Cohen's <i>h</i>	0.13	0
Spoth et al. 2013 (Study III)	Good response to treatment	Appropriate use	Cohen's <i>h^c</i>	0.89	3
Burchman and Pagel 1995	Pain disability index	Appropriate use	Cohen's <i>d</i> from <i>t</i> statistic (correlated)	0.44	1
Cheiminski et al. 2005	Total opioid consumption	Misuse, abuse, and addiction	Cohen's <i>d</i> from mean differences	0.12	0
Goldberg et al. 2005					

^aExtrapolation was based on interpretation of qualitative data.

^bThe aim of study was to demonstrate noninferiority rather than superiority of the intervention.

^cThe calculation for effect size assumes that the expected change in the control is 50% of the measured intervention change.

^dThe lowest value in the reported range was used to calculate a conservative estimate of the effect size.

^eThe impact factor is assigned comparatively, using other calculated impact factors of similar strategies as a framework.

^fThe relative risk is used an approximation of odds ratio for logit *d*.

^gUnintentional Poisoning Deaths in Oklahoma, https://www.ok.gov/health2/documents/UP_Deaths_2007-2012.pdf.

^hThe pooled standard deviation assumes equal sample size in the comparison groups.

ⁱDrug Overdose Deaths, Tennessee Department of Health, https://www.tn.gov/assets/entities/health/attachments/Drug_Overdose_Deaths_county_level_summary_through_2015_PDF.pdf.

^jThe study showed mixed results.

^kThe standard deviation of the intervention group was used as an approximation of the pooled standard deviation.

^lPO = by mouth; PMP = prescription monitoring program; ER = emergency room; ED = emergency department.

back pain and opioid use disorder⁴³; (2) a collaborative practice, with prescription of buprenorphine and naloxone, plus weekly urine drug testing⁵¹; (3) a prescription monitoring program with easy access at the point of care⁶⁴; (4) a structured cognitive behavioral training program for prevention of substance misuse³²; (5) a law enforcement change in the state of Florida⁶⁸; (6) a recidivism program with staff education for high emergency department users⁷²; and (7) a public health initiative involving clinical practice guidelines, media, town halls, public campaigns, and announcements.⁸¹

Impact on overdose and deaths

Twenty-two studies measured the impact of the strategy on outcomes of overdose and death (Table 1). The impact factors ranged from -3 to 3. The strategy with the largest negative impact included the implementation of an opioid dosing guideline (maximum 120 morphine equivalents per day) where there was a marked increase in mortality due to methadone.⁵⁷ Ten strategies had a negligible or no impact on overdoses and deaths.^{35,41,49,52,68,70,75,76,81,93} Five strategies had a small positive effect,^{48,50,53,62,94} two had a moderate positive effect,^{55,56} and four had a large positive effect,^{60,63,69,82} which included (1) overdose prevention training and naloxone distribution, plus a change in the legal status of naloxone to permit its administration by any member of the public⁶⁰; (2) pharmacy-based naloxone distribution plus education and training⁶³; (3) First Nations healing strategies plus opioid substitution and primary care involvement⁶⁹; and (4) take-home naloxone and training program.⁸²

Most promising strategies by content and target audience

Figure 5a and 5b show the impact of the strategies by content and target population. It suggests that the most promising strategies to improve appropriate use of opioids are (1) educational strategies aimed at health care professionals; (2) clinical strategies aimed at patients, opioid users, and health care professionals; and (3) collaborations. The most promising strategies to reduce misuse, abuse, opioid use disorder, and diversion of opioids are (1) educational strategies aimed at patients, opioid users, and health care providers; (2) clinical strategies aimed at patients, opioid users, and health care providers; (3) PMPs; (4) collaborations; (5) public health; and (6) opioid substitution. The most promising strategies to reduce overdoses and deaths are (1) education aimed at patients and opioid users and (2) naloxone distribution.

Unintended consequences of implemented strategies

Among the 66 strategies described, 19 (29%) had some type of unintended consequence^{41,42,44-46,49,53,57,59,60,68,71,73-75,79,82,84,90} and 4 reported no unintended consequence.^{47,55,64,65} It was unclear in 43 studies whether there were any unintended consequences or not.

Consequences that affected the target population of the strategy were reported, such as patients not receiving necessary prescriptions⁷¹; patients paying for their prescriptions out of their own pockets⁷¹; overdose due to rotation from other opioids to methadone^{57,74}; more overdose by morphine, hydromorphone, and heroine^{68,75}; stolen naloxone kits^{53,60,82}; being harassed by police over possession of naloxone⁸²; stigma associated with carrying a naloxone kit⁶⁰; stigma associated with receiving a prescription for addiction⁷⁹; a paradoxical increase in overdose because suspension of physicians who were prescribing improperly led to patients on withdrawal and overdosing from other sources⁴¹; patients had a false sense of privilege because of participation in an educational session, leading to more opioid abuse⁹⁰; and possible beliefs that naloxone access enables addiction to opioids.⁴⁹

There were consequences to the staff involved in the implementation of strategies: extra burden on the clinical staff (pharmacists and/or physicians)^{42,71}; burden on pharmacy staff who had to assemble intranasal naloxone kits; or risks of needle stick injury to staff who had to assemble intramuscular naloxone.⁴⁹

Societal consequences included shifting the opioid crisis to a neighboring region where the strategy had not been implemented⁴⁴; higher costs⁴⁹; increase in the proportion of prescriptions of opioids^{73,84}; increase in dose of opioids prescribed^{46,59}; shifting from one opioid to another⁵⁹; increase in use of benzodiazepines and barbiturates⁵²; and more patients developing opioid tolerance or filling prescriptions from other sources.⁴⁵ (For details about the unintended consequences reported in each study, see Appendix 5.)

Discussion

Interpretation

We searched the peer-reviewed and grey literature for studies that implemented and evaluated strategies, programs, policies, and practices to improve the appropriate use of opioids and reduce misuse, abuse, opioid use disorder, diversion, overdoses, and deaths related to opioids. We found 65 studies reporting on 66 distinct strategies. Though the majority of the studies were at

◆ Impact on appropriate use
 ◆ Impact on abuse, misuse, addiction
 ◆ Impact on overdose and death

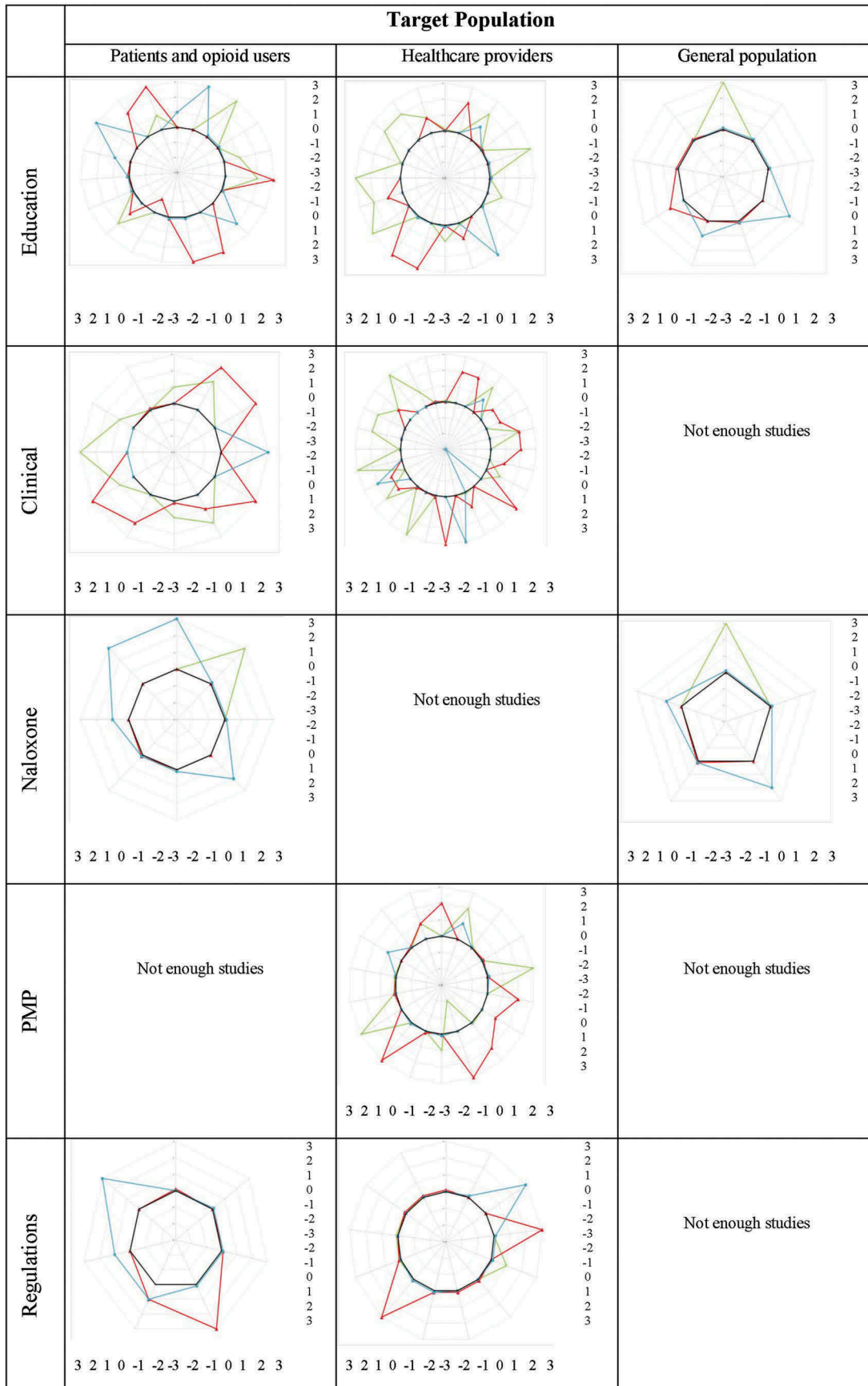


Figure 5. Impact factors by content and target population.

◆ Impact on appropriate use ◆ Impact on abuse, misuse, addiction ◆ Impact on overdose and death

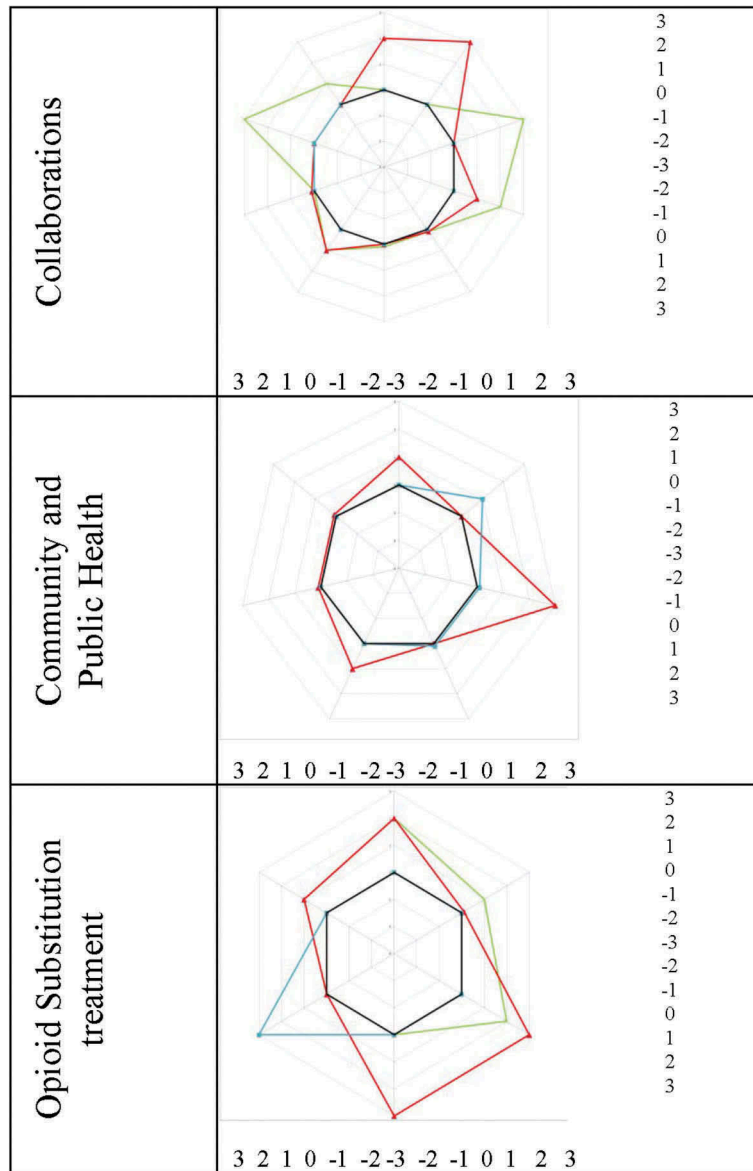


Figure 5. (Continued).

high risk of bias, there is some indication that the most promising strategies involved education, clinical practices, collaborations, PMPs, public campaigns, opioid substitution programs, and naloxone distribution. Twenty-nine percent of strategies reported some sort of unintended consequence.

Significance

Misuse and abuse of opioids have become a widespread problem in Canada, but many areas do not yet have the necessary measures in place to address this. This systematic review benefits from the diversity of strategies

and outcomes that were implemented and evaluated in various jurisdictions similar to the Canadian context. Knowledge users can refer to this systematic review in the planning stages of implementing interventions to improve the appropriate use of prescription opioids and/or reduce the misuse, abuse, and diversion of these drugs. Knowledge users can also appraise the interventions of interest to make contextually appropriate modifications and combine various strategies to achieve the desired effects. As such, this comprehensive compilation of studies provides a concrete foundation for knowledge users to build upon. Lastly, by appraising the quality of the evidence, we highlight the deficits

and need for improvement in this body of literature. We encourage knowledge users to engage with the suggestions for future studies to improve the quality of evidence in this field, while incorporating economic feasibility into the growing body of literature.

Limitations

Limitations of the existing literature

The quality of evidence in this body of literature contains many methodological flaws. The majority of studies are observational in nature, with only nine randomized controlled trials among the 65 studies. In addition, most grey literature publications did not provide empirical data. Another limitation was that a minority of studies reported unintended consequences associated with the strategies.

Limitations of the methods used in this review

One limitation of our review is that the literature search was last updated in September 2015. Since then, there have been publications of studies that could potentially be included in this review. We updated the electronic searches up to March 2018 and there were 1427 titles and abstracts. After screening by two authors, there were 182 remaining titles and abstracts that could potentially meet the inclusion criteria for this current review. Another limitation is using assumptions to calculate an effect size (ES). Fourteen studies did not have a separate control for comparison, and this was particularly common in studies on regulation changes. In an effort to avoid overestimating the ES, we assumed the expected change in the control to be 50% of the measured intervention change in these 14 studies. Another limitation is that the impact factor was extrapolated when studies were qualitative in nature or did not provide sufficient data to calculate an ES; this was applied to four studies. Extrapolation relied on both clinical expertise and the completed framework of impact factors as a reference, which introduced some degree of subjectivity into the analysis. Lastly, studies could not be combined for best evidence synthesis or meta-analysis due to distinct differences in the strategies, populations, or outcomes between each study.

Strengths

This review examined a full spectrum of strategies that were implemented and empirically evaluated to tackle the opioid crisis in North America and to maintain the appropriate use of opioids in improving pain and function among patients with chronic pain. Few systematic reviews in this field have conducted comprehensive

grey literature searches. In doing this, we compiled a comprehensive repository of relevant publications that included peer-reviewed articles and empirical evidence from grey literature. We conducted a narrative synthesis to describe the interventions and a quantitative analysis to assess the effectiveness of each intervention, and we were able to calculate effect sizes and map these strategies using radar charts to visualize the data and make conclusions about the most promising strategies. In addition, we produced a framework that stratifies each intervention by impact factor and type of outcome assessed. This unique framework emphasizes the importance of both elements; for example, even a small impact on overdose and death holds remarkable significance. Decision makers can prioritize the categories of outcome according to their objectives and use the impact factors to determine relative effectiveness of an intervention for a particular outcome. Our study capitalizes on the heterogeneity of interventions, populations, and outcomes found in the literature, so that decision makers can appraise the various interventions in context and tailor their modifications accordingly.

Similar studies

Strategies and interventions to address the sweeping opioid crisis have been the subject of several narrative reviews,^{98–101} providing a broad overview of existing strategies, as well as drawing attention to more novel interventions. Narrative syntheses, however, lack comprehensive and systematic literature search strategies and, thus are prone to publication bias.

We are aware of a handful of recent systematic reviews that have synthesized the evidence for specific types of strategies, including primary care delivery models for treating opioid use disorders,⁸ supervised dosing versus off-site consumption of opioid substitution treatment,⁹ community overdose prevention and naloxone distribution programs,^{10–13} supervised consumption sites,^{102,103} clinical strategies for reducing aberrant drug-related behavior (e.g., treatment agreements, urine drug testing),^{14,15} and prescription opioid policies (namely, guidelines and legislation).¹⁶ Consistent across four reviews was the finding that naloxone and overdose prevention programs are associated with a reduction in overdose mortality and increased odds of recovery.^{10–13} A recent scoping review also found mixed evidence for the effectiveness of prescription drug monitoring programs.¹⁰⁴ These findings are consistent with the findings of our review.

However, most of these prior reviews employed restrictive search strategies and/or had inadequate or nonexistent quality appraisal. Only one review considered some degree of grey literature.⁹

Only one published systematic review, to our knowledge, has considered the effectiveness of a broad range of strategies.¹⁰⁵ Haegerich and colleagues examined the impact of state policy and systems-level interventions on prescriber and patient behavior and health outcomes (e.g., overdoses), finding low-quality evidence of positive effects for PMPs, insurer strategies, pain clinic legislation, clinical guidelines, and naloxone distribution.¹⁰⁵ There was also little evidence of effect for safe storage and disposal strategies and patient education. The review by Haegerich et al.,¹⁰⁵ though comprehensive in scope, also had limitations, including limiting searches to Medline, searches up to 2014, including only English-language studies, and primarily relying on studies from the United States.

Future research

Many promising strategies have already been implemented in the past couple of years in North America, such as naloxone distribution. There is a need to conduct empirical studies of more novel interventions. We found many publications that described various novel strategies, but they were excluded because they lacked an empirical measure to assess the impact on any of the outcomes of interest. A list of the excluded studies can be obtained upon request.

Future studies should aim at high methodological standards. In nonexperimental studies where randomization and separate control groups are not possible, it would be ideal to conduct interrupted time series or controlled before and after as the study design. Interrupted time series and controlled before and after are particularly useful in the context of public health interventions. Nonexperimental or observational studies should also discuss concurrent interventions or policy changes that may affect the population or region of interest. If no other concomitant interventions were introduced, studies should report either the measured outcome at the pre-intervention time point or the literature value that is relevant to the population or region of interest. Rather than only reporting the final change in the outcomes, we recommend that future studies report the measured outcomes at both the pre- and post-intervention time points. Studies should also report the sample size or population size, so that it is possible to calculate the variance of the effect sizes. Lastly, we recommend that future studies include a cost-benefit analysis of an intervention, so that decision makers and policymakers can better assess the relative cost-effectiveness and feasibility of the interventions.

Conclusions

This broad-scope systematic review found some promising strategies to tackle the opioid crisis in North America. The content of these strategies included education, clinical practice changes, naloxone distribution, PMPs, regulations, collaborations, public health, and opioid substitution treatments. The most common target population of these strategies was health care professionals, followed by patients/opioid users and the general public. Twenty-nine percent of the strategies described some type of unintended consequence, which affected the target population, the health care professionals involved in the implementation of the strategy, or the public in general. There is a need for high-quality studies in this area to assess the impact of novel strategies on various outcomes, including appropriate use of opioids and reduction of misuse, abuse, opioid use disorder, diversion, overdoses, and deaths related to opioids.

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Declaration of interest statement

The authors have no conflict of interests to declare.

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